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CLINICAL DECISION RULES APPLIED TO DIABETIC FOOT ULCERATION

~ Prediction, prognosis and prevention ~

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Título: Clinical Decision Rules Applied to Diabetic Foot Ulceration - Prediction, prognosis and prevention

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And finally as my words are not sufficient: Father this Thesis is also for you… If you could see me…

"Father is to take me to a long walk / Showing me how everywhere gets beautiful flowers
Father, wish we could turn back to the time I/ Never thought that you will not see me grow
Only if you could see/ Everything I turn out to be/ Only if you could see me
Everything you taught me to be/ Everything you...
Father I remember all you told me/ Pushing me to always follow what I dream of
Father it's been years since I stop crying/ Never thought that in my heart you will brow
I could dream of/ Many lifetimes/ 'Could have been with you/ Like in old times
I could have grown up/ With you near me
'Could have been there/ All only if you could see
Only if you could see/ Everything I turn out to be
I could have drown/ In my eyes' tears
All those years hoping/ You wouldn't disappear"

Yael Naïm

THESIS OUTLINE

This Thesis was structured in the following described manner.

In the *Abstract* a summary of the Thesis was presented.

In *Chapter 1, Rationale*, it was explained the motivations behind this Thesis conduction and the relevance of diabetic foot ulcer (DFU) prediction, prognosis and for the creation of a combined stratification classification system.

In *Chapter 2, the Aims* of this Thesis were exposed.

In Chapter 3, Background, (*section 3.1*) it was made a description of the methods for clinical decision rules' (a specific type of stratification classification systems) development, validation and updating. Diabetes mellitus (DM) and its foot-related complications [namely DFU and lower extremity amputation (LEA)] epidemiology and costs at individual and societal levels (*section 3.2*) and a brief pathophysiological path for their development were described (*section 3.3*). Also, a sum up of the up-to-date recommendations for DFU and consequent LEA prevention as well as the European quality of diabetic foot care were presented (*section 3.4*).

Chapter 4, DFU prediction, includes 1 submitted and 3 published original studies. Firstly, we assessed the available evidence concerning risk stratification classification systems (*section 4.1*) and individual predictive variables (*section 4.2*) for DFU development risk assessment. Next, we retrospectively validated all the available systems in a consecutive series of patients with DM without an active DFU in a Hospital setting (*section 4.3*) to understand if any system outperformed the remaining, evaluate the refinement pertinence and allow sample size calculation for further studies. Last, using all these results, we prospectively validated all of the systems in a multicentre context, evaluating the systems' and their composing variables' prognostic accuracy (*section 4.4*).

Chapter 5, DFU prognosis, includes 3 published original studies where we conducted similar steps to those described in the previous chapter: classification systems (*section 5.1*) identification by systematic review, and prospective validation of all the available systems for DFU prognosis estimation (*section 5.3)* in a consecutive series of patients with DM and active DFU. In addition, the quality of diabetic foot care in a Portuguese diabetic foot clinic was assessed (*section 5.2*).

We also included 1 published original study proposing a unified classification system, in *Chapter 6*, having as foundation a classification proved valid for DFU development prediction (in Chapter 4) that, with the inclusion of additional DFU characterization variables (identified in Chapter 5), could also accurately predict LEA (the poorest DFU prognostic) in patients with active DFU.

In *Chapter 7* general conclusions of this Thesis and future research were presented.

FINANCIAL SUPPORT AND LIST OF PUBLICATIONS

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CORE PAPERS

The 8 papers described below are the core structure of this Thesis (7 were already published and 1 is under submission). They are listed by order of appearance on the Thesis.

(**Ao abrigo do Art.º 8º do Decreto-Lei n.º 388/70, fazem parte desta dissertação os seguintes trabalhos publicados ou em publicação**)

Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M.
RISK STRATIFICATION SYSTEMS FOR DIABETIC FOOT ULCERS: A SYSTEMATIC REVIEW.
Diabetologia 2011; 54(5): 1190-1199.
Erratum in: Diabetologia 2011; 54(6): 1585.
Journal impact factor: 6.2 (9th percentile; 12/131)
Number of citations: 31

Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M.
PREDICTIVE FACTORS FOR DIABETIC FOOT ULCERATION: A SYSTEMATIC REVIEW.
Diabetes Metab Res Rev, 2012; 28 (7): 574-600.
Journal impact factor: 3.1 (47th percentile; 61/131)
Number of citations: 29

Monteiro-Soares M, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M.
VALIDATION AND COMPARISON OF CURRENTLY AVAILABLE SYSTEMS FOR PATIENTS' WITH DIABETES STRATIFICATION BY RISK OF FOOT ULCER DEVELOPMENT.
Eur J Endocrinol, 2011; 167(3): 401-407.
Journal impact factor: 3.9 (25th percentile; 33/131)
Number of citations: 6

Monteiro-Soares M, Mota A, Pereira da Silva C, Bral T, Pinheiro-Torres S, Morgado A, Couceiro R, Ribeiro R, Dias V, Moreira M, Mourão P, Oliveira MJ, Paixão-Dias V, Dinis-Ribeiro M.
DIABETIC FOOT ULCER DEVELOPMENT RISK CLASSIFICATIONS' VALIDATION: A MULTICENTRE PROSPECTIVE COHORT STUDY
Submitted.

Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. *CLASSIFICATION SYSTEMS FOR DIABETIC FOOT ULCERS' HEALING PREDICTION: A SYSTEMATIC REVIEW AND META-ANALYSIS*
Diabetes Metab Res Rev, 2014, 30(7): 610-22.
Journal impact factor: 3.1 (47th percentile; 61/131)
Number of citations: 6

Monteiro-Soares M, Dinis-Ribeiro M.
PORTUGAL MEETS EURODIALE: BETTER LATE THAN NEVER.
Diabetes Res Clin Pract, 2014, 106(3): e83-5
Journal impact factor: 3.0 (48th percentile; 63/128)
Number of citations: 0

Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Dinis-Ribeiro M.
LOWER LIMB AMPUTATION FOLLOWING FOOT ULCERS IN PATIENTS WITH DIABETES: CLASSIFICATION SYSTEMS, EXTERNAL VALIDATION AND COMPARATIVE ANALYSIS.
Diabetes Metab Res Rev, 2015, 31: 515-529.
Journal impact factor: 3.1 (47th percentile; 61/131)
Number of citations: 2

Monteiro-Soares M, Dinis-Ribeiro M.
A NEW DIABETIC FOOT RISK ASSESSMENT TOOL: DIAFORA
Diabetes Metab Res Rev, 2016, 32: 429-435.
Journal impact factor: 3.1 (47th percentile; 61/131)
Number of citations: 1

Some of the articles were first presented as poster or oral communications in national or international Symposiums. In addition, during the duration of this Thesis conduction the Candidate was also a co-author of the chapter 20: "Peripheral arterial disease, foot ulcers, lower extremity amputations, and diabetes" in Diabetes in America, 3rd Edition (under publication process) and author of other papers and presentations concerning the same subject – diabetic foot ulcers prediction, prognosis and also prevention. Although these studies were not part of the Thesis core structure they were important to improve the researcher's knowledge on the field and/or to present the results to the community. They are listed in the Candidate's Curriculum Vitae.

RESUMO

INTRODUÇÃO

O grupo de patologias denominada de Pé Diabético, principalmente a úlcera e a amputação podológica, têm um grande impacto a nível de recursos financeiros e humanos do Sistema Nacional de Saúde, assim como na qualidade de vida dos utentes. Deste modo, as recomendações existentes sublinham a importância da sua prevenção através de diversas medidas, com especial ênfase na identificação e referenciação para clínicas especializadas dos utentes com Diabetes mellitus (DM) e em risco de desenvolvimento de complicações podológicas.

No entanto, as decisões relativas à prevenção e tratamento destas complicações (por exemplo, o nível de cuidados, periodicidade das consultas, necessidade de intervenções educativas ou médicas, avaliação da eficácia do tratamento, etc.) são frequentemente realizadas tendo por base classificações com uma estrutura variada com rara avaliação da sua validade e reprodutibilidade. Deste modo, nenhuma classificação foi universalmente adoptada como referência para a estratificação por grau de risco de desenvolvimento de complicações a nível podológico dos utentes com DM na prática clínica.

OBJECTIVOS

Este projecto teve como objectivo último aumentar o nível da evidência disponível sobre como classificar o Pé do utente com DM e propor um sistema unificado que permita estratificar estes indivíduos pelo seu risco de úlcera e amputação assim como promover o uso, pelos profissionais de Saúde, de uma classificação simples, clinicamente plausível e baseada na evidência.

Para concretizar tal, vários passos foram definidos dentro de cada secção com os seguintes objectivos:

1. Para a predição de úlcera:
   - 1.1 identificar as classificações e variáveis existentes para a predição deste desfecho clínico, através de revisões sistemáticas, e
   - 1.2 validar e comparar as classificações existentes numa série consecutiva de sujeitos com DM sem úlcera activa.
2. Para o prognóstico de úlcera:
   - 2.1 identificar as classificações e as variáveis existentes para a predição de mau prognóstico de úlcera (i. e., amputação), através de revisões sistemáticas,
   - 2.2 validar e comparar as classificações existentes para a determinação do prognóstico de úlcera numa série consecutiva de sujeitos com DM e úlcera activa.
3. Criar uma classificação unificada que possa ser utilizada para predizer ambos os desfechos clínicos em estudo (úlcera e amputação), tendo por base o resultado das etapas anteriores.

MÉTODOS

Para cada desfecho clínico desenvolvemos revisões sistemáticas em diversas bases de dados e incluindo estudos que analisassem o valor preditivo e/ou validade de variáveis independentes e classificações associadas com o desenvolvimento de úlcera podológica, em sujeitos sem lesão activa, e associadas com a ocorrência de amputação, nos sujeitos com úlcera presente. Métodos de meta-análise foram aplicados, sempre que possível.

A validação das diversas classificações existentes para a estratificação dos sujeitos com DM pelo seu risco de desenvolver uma úlcera a nível podológico foi conduzida sob a forma de estudo de coorte inicialmente num centro único e de forma retrospectiva e posteriormente em contexto multicêntrico e de forma prospectiva.

Para o primeiro estudo, foram incluídos todos os sujeitos com DM e sem úlcera activa que recorreram à consulta de Podologia do Centro Hospitalar de Vila Nova de Gaia/ Espinho EPE (CHVNG), de Janeiro de 2008 a Dezembro de 2010 (n=364).

Para o segundo, foram incluídos todos os sujeitos que recorreram à mesma consulta, de Dezembro de 2010 a Dezembro de 2012; assim como às consultas de rastreio na Unidade de Saúde Familiar (USF) Aquae Flaviae, de Julho de 2013 a Setembro de 2014; e na USF de Santo André de Canidelo, de Março a Setembro de 2014 (n= 446). Os participantes foram seguidos até o desenvolvimento de úlcera, morte ou até 1 ano.

De seguida, um estudo de coorte retrospectivo foi desenvolvido incluindo todos os sujeitos observados como primeiras consultas de Pé Diabético do CHVNG, de Janeiro de 2011 a Dezembro de 2013 (n=950 consultas, 813 sujeitos). Os dados para a caracterização do pedido de referenciação, dos sujeitos e subsequente resultado clínico foram colhidos e comparados com os reportados pelo consórcio Europeu Eurodiale de forma a melhor contextualizar os resultados dos estudos seguintes.

A validação dos sistemas de classificação utilizados para a estimativa de prognóstico de úlcera e consequente necessidade de amputação foi realizada como um estudo de coorte prospectivo unicêntrico, incluindo todos os sujeitos com DM e úlcera activa a nível podológico que recorreram à consulta de Pé Diabético do CHVNG, entre Janeiro de 2010 e Março de 2013 (n=293). Os participantes foram seguidos até cicatrização, amputação ou por pelo menos 3 meses.

Nos estudos de validação a associação entre as variáveis e classificações com o desfecho clínico foi analisada e as diversas medidas de validade diagnóstica/ prognóstica foram calculadas (nomeadamente, sensibilidade, especificidade, *likelihood ratios*, valores preditivos e área sobre a curva ROC). Os respectivos intervalos de confiança a 95% foram comparados entre as classificações de forma a detectar diferenças estatisticamente significativas.

Finalmente, uma classificação refinada e unificada foi desenvolvida, utilizando os dados recolhidos nos estudos anteriores, técnicas de regressão logística e recalculando as respectivas medidas de validade diagnóstica/prognóstica e os seus intervalos de confiança a 95%, dando especial ênfase à área sob a curva ROC.

RESULTADOS

Na primeira revisão sistemática verificamos que existem 5 classificações para a predição de desenvolvimento de úlcera que foram propostas ou validadas em 13 estudos, nomeadamente da Universidade do Texas, do Grupo Internacional de Trabalho em Pé Diabético (conhecida como IWGDF), da Rede de Guidelines Intercolegial Escocesa (SIGN), da Associação Americana de Diabetes (ADA) e de Boyko e colegas.

Observamos que 5 variáveis foram incluídas em praticamente todos os sistemas: neuropatia diabética periférica (NDP), doença arterial periférica (DAP), deformidade podológica e história prévia de úlcera ou amputação. O número de factores predictivos incluídos assim como o número de grupos de risco variou de 4 a 8 e de 2 a 6, respectivamente.

A descrição de medidas de validade foi escassa e a validação externa tinha ocorrido apenas para a classificação de Boyko e colegas.

Na segunda revisão sistemática, identificamos mais de 100 variáveis preditivas analisadas em 71 estudos. As variáveis mais frequentemente analisadas foram a idade, o género, duração da diabetes, índice de massa corporal, hemoglobina glicada e NDP. A maioria das restantes variáveis foram avaliadas em 2 ou menos estudos.

As variáveis mais comumente incluídas nas classificações de risco (NDP, DAP, deformidade podológica e complicação podológica prévia) demonstraram estar consistentemente associadas com a ocorrência de úlcera em diversos estudos.

Em ambas as revisões a prevalência de úlcera descrita em cada um dos estudos incluídos variou substancialmente. Métodos meta-analíticos não foram possíveis de ser aplicados.

Na validação retrospectiva das classificações utilizadas para a predição de desenvolvimento de úlcera verificamos que, na nossa coorte, existe uma associação entre a idade, duração da diabetes, deformidade podológica, DAP, NDP e história prévia de úlcera ou amputação com a ocorrência do desfecho clínico em estudo. Verificou-se também uma associação entre os diferentes grupos de risco de todas as classificações e o desenvolvimento de úlcera.

As várias classificações apresentaram valores robustos de validade (principalmente valores preditivos negativos) sem diferenças estatisticamente significativas entre elas. No entanto, o valor preditivo positivo foi em todos os casos inferior a 30%, os *likelihood ratios* positivos a 4 e os negativos superiores a 0.1 – o que representa um importante potencial de optimização.

Os resultados do estudo de validação prospectiva multicêntrica foram de encontro ao estudo anterior, isto é, as diferentes classificações apresentaram valores substanciais de validade diagnóstica e não se verificaram diferenças significativas entre elas, apesar de ter um tamanho amostral superior. Globalmente, as classificações demonstraram ser válidas e comparáveis para a maioria das medidas e pontos de corte. Os valores preditivos positivos foram inferiores a 40% na maioria dos cenários, mas os valores preditivos negativos foram sempre superiores a 90%. Para todas as classificações a área sob a curva ROC foi igual ou superior a 0.75. Verificaram-se diferenças nas características dos sujeitos assim como na validade das classificações entre o contexto hospitalar e o de cuidados de saúde primários.

No que diz respeito à predição de amputação, foram encontrados 8 sistemas para a descrição e 7 para a estimativa de prognóstico de úlceras podológicas em indivíduos com DM. A prevalência da amputação variou entre 6 e 33%.

Tal como com as classificações para a predição de desenvolvimento de úlcera, o número de factores preditivos incluídos variou substancialmente (de 1 a 9). As variáveis mais frequentemente incluídas foram a presença de DAP (n=12), infecção (n= 10) e profundidade da úlcera (n=10). As classificações de Meggit-Wagner, S(AD)SAD e da Universidade do Texas foram as mais validadas, enquanto que as restantes 10 classificações foram apenas derivadas ou validadas uma vez.

De novo, as medidas de validade foram escassamente reportadas com apenas 5 estudos apresentando-as e 8 permitindo o seu cálculo. A sensibilidade das classificações variou de 38 a 100%, especificidade de 30 a 88%, valores preditivos negativos foram sempre superiores a 80% enquanto que os positivos foram sempre inferiores a 60%. Apenas dois estudos descreveram a área sob a curva ROC apresentando valores de 0.66 e 0.80.

Meta-análise foi possível apenas para a validade das variáveis incluídas. Os valores agregados de validade variaram entre 0.65 (para a presença de gangrena) e 0.74 (para a presença de infecção).

O principal motivo de referenciação para a nossa consulta foi a presença de úlcera activa (70%). Em comparação com a população dos estudos do Eurodiale, a nossa amostra era ligeiramente mais velha, com úlceras mais profundas e graves e mais frequentemente localizadas a nível digital. Relativamente ao desfecho clínico ocorreu cicatrização, amputação major e morte numa proporção similar, mas menos amputações minor e hospitalizações.

Na validação simultânea das classificações existentes para a caracterização de úlcera ou avaliação do seu prognóstico verificamos que todas se encontram associadas com o risco de amputação. As classificações apresentaram tipicamente sensibilidades superiores a 80%, *likelihood ratios* negativos inferiores a 0.5 para os grupos de alto risco; a área sob a curva ROC variou entre 0.56 e 0.83 e os *likelihood ratios* positivos entre 1.0 e 5.9. Não ocorreram diferenças estatisticamente significativas entres os sistemas.

Após tudo isto, consideramos pertinente o refinamento das classificações existentes e propor uma nova classificação (designada de DIAFORA) com uma particularidade: esta classificação é composta por 2 partes e pretende predizer 2 objectivos clínicos.

Após as nossas revisões sistemáticas para identificar as classificações existentes para a predição e para o prognóstico de úlcera, constatou-se que as variáveis mais frequentemente usadas para prever o desenvolvimento de úlceras também estavam incluídas em diversas classificações para prever amputações. As variáveis em questão seriam a presença de NDP, DAP, deformidade podológica e história prévia de úlcera ou amputação.

De facto, este grupo de 4 variáveis corresponde a uma das classificações mais utilizadas para identificar sujeitos com DM e pé em risco: a classificação do IWGDF. Esta classificação provou ter uma validade equiparável às restantes, quer no estudo multicêntrico prospectivo, quer no retrospectivo. Assim consideramos que a primeira parte da DIAFORA deveria ser composta pela classificação IWGDF e deveria ser a ferramenta de eleição para indivíduos sem úlcera activa quando se pretende determinar o risco de a desenvolverem.

Após o aparecimento de úlcera, devem ser adicionadas 4 variáveis de modo a prever a ocorrência de amputação. Esta segunda parte da classificação DIAFORA é composta por variáveis de

caracterização da úlcera (a presença de múltiplas úlceras, infecção, gangrena e atingimento ósseo). A seleção destas variáveis decorreu de uma análise por regressão logística.

Portanto, a primeira parte da DIAFORA já tinha sido validada para prever o desenvolvimento de úlceras em artigos prévios. Ao aplicar a DIAFORA no seu todo, observamos que esta classificação é válida para prever a ocorrência de amputações. Para a predição de ocorrência de amputação, como *score*, a DIAFORA apresentou uma área sob a curva ROC de 0.91 e sob a forma de categorias de risco de 0.89. O grupo de alto risco apresentou um *likelihood ratio* positivo de 5 e um valor preditivo positivo de 58.

Quando comparada com as outras classificações existentes, esta classificação apresentou valores de validade diagnóstica iguais ou superiores às restantes em termos de predição de amputação em indivíduos com úlcera.

CONCLUSÕES

Consideramos que a criação de um sistema unificado para estratificação de indivíduos com DM de acordo com o risco de desenvolverem úlceras ou amputação podológicas, que seja simples, baseado em evidência e clinicamente relevante irá promover a sua adopção e utilização pelos profissionais de saúde. Pretende-se ainda que a utilização seja padronizada quer na prática clínica diária, quer na investigação. Para atingir este objectivo e criar a DIAFORA, foi necessário primeiramente retirar várias conclusões.

Apesar da importância da identificação do pé em risco de ulceração e amputação, concluímos que as classificações existentes para ambos os desfechos clínicos apresentam um baixo nível de evidência por falta de estudos de validação, bem como de estudos de análise de reprodutibilidade. Assim, pela primeira vez, realizamos uma validação externa de todas as classificações em simultâneo para a predição de úlcera e de amputação numa coorte de indivíduos sem e outra com úlcera activa, respectivamente. Deste modo as classificações usadas para cada um dos desfechos clínicos foram comparadas directamente para identificar a mais válida assim como analisar a pertinência da sua melhoria.

De um modo geral a validade dos sistemas era boa, sem diferenças estatisticamente significativas entre as classificações, pelo que nenhuma pôde ser considerada como a melhor.

Além disso, os baixos valores preditivos positivos e de *lilkelihood ratio*, tornaram pertinente melhorar as classificações e a criação de um sistema unificado. A DIAFORA apresenta uma estrutura facilmente memorizável e com procedimentos simples para a recolha de variáveis. Mostrou ainda ter uma validade igual ou superior na predição de amputação em indivíduos com úlcera, em relação às classificações já existentes, o que comprova o seu valor para uso na prática clínica.

Salientamos que os resultados clínicos da consulta multidisciplinar de Pé Diabético onde decorreram a maioria dos estudos que compõem esta Tese são semelhantes aos descritos a nível Europeu pelo consórcio Eurodiale. Consideramos por isso que os nossos resultados são generalizáveis aos centros de Pé Diabético europeus.

Apesar destes progressos, consideramos essencial desenvolver mais investigação no sentido de clarificar se a estratificação de risco no Pé Diabético aplicada à prática clínica tem um verdadeiro impacto na prevenção das complicações e validando externamente a nossa classificação DIAFORA.

ABSTRACT

RATIONALE

Diabetic foot complications, namely ulcer (DFU) and amputation (LEA), have a great impact in National Health Systems' financial and human resources as well as in patients' quality of life. Thus, available recommendations highlight the importance of their prevention by the application of diverse measures, especially the identification and referral to specialized centres of patients with DM at risk of foot complications development.

However, everyday decisions linked to the prevention and treatment of these complications (for example, health institution level of care, appointments periodicity, need for educational or medical intervention, treatment efficacy assessment, etc.) are based on classifications rarely validated or with their accuracy compared. Not surprisingly, no single classification for the stratification of subjects by their risk of foot complications has been adopted as gold-standard for clinical practice.

PURPOSE AND AIMS

This research had as ultimate purpose to increase the level of available evidence on how to classify the diabetic foot and propose a unified system to stratify subjects with diabetes according to their risk of DFU and LEA and to promote the use and adoption, by the healthcare professionals, of a simple, clinically plausible and evidence-based classification system.

To achieve this, several steps were defined within each main section with the following aims:

1. For the DFU prediction,
   1.1 to retrieve, through systematic review, all the stratification systems created and variables assessed for the DFU development prediction in subjects with DM but without active DFU, and
   1.2 to validate all the available systems for DFU development prediction in a consecutive series of patients without active DFU;
2. for the DFU prognosis,
   2.1 to retrieve, through systematic review, all the stratification systems created and variables assessed for the LEA prediction in subjects with DM and active DFU, and
   2.2 to validate all the available systems for DFU prognostic assessment in a consecutive series of patients with active DFU; and finally
3. to create a unified system that can be used to predict both outcomes (DFU and LEA), based on the previous stages' results.

METHODS

For each outcome we have started by conducting systematic reviews in diverse databases including studies that analysed the predictive value and/or accuracy of independent variables and classification systems for DFU development prediction, in subjects with DM without an active lesion, and LEA occurrence prediction, in those with an active lesion. Meta-analysis methods were applied, whenever possible.

Validation of different classification systems available to stratify patients by their risk of DFU development was performed in a single centre retrospective study and latter in a multicentre prospective cohort study.

For the first, all subjects with DM but without an active foot lesion that had a Podiatry appointment in Centro Hospitalar de Vila Nova de Gaia/ Espinho EPE (CHVNG), from January 2008 to December 2010, were included (n=364).

For the second, we included all subjects recurring to the same appointment, from December 2010 to December 2012; as well as those undergoing podiatric screening in the Aquae Flaviae, from July 2013 to September 2014; and Santo André de Canidelo, from March to September 2014, Family Health Units (n= 446). Subjects were followed until DFU development or for 1 year.

Next, a retrospective cohort study including all subjects observed as first appointments in CHVNG Diabetic Foot Clinic, between January 2011 and December 2013, was conducted (n=950; 813 subjects). Variables characterizing referral request, subjects and clinical outcome were collected and compared to the ones reported by the European consortium – Eurodiale in order to better contextualize the following studies' results.

Validation of the classification systems used for DFU prognostic and consequent necessity for LEA was conducted as a single centre prospective cohort study, including all subjects with DM and an active lesion recurring to the CHVNG Diabetic Foot Clinic, between January 2010 and March 2013 (n=293). Subjects were followed until healing, LEA or at least 3 months.

In all validation studies, component variables' and classifications' association with outcome was evaluated and different diagnostic/prognostic accuracy measures were calculated [namely, sensitivity, specificity, likelihood ratios, predictive values (PV) and area under the receiver operating characteristic curve (AUC)]. The measures' respective 95% confidence intervals (CI) were compared between classifications in order to detect statistically significant differences.

Finally, a refined and unified classification that can be used to predict both outcome was developed using the data collected in the previously described studies as well as logistic regression techniques, and by recalculating the respective diagnostic/prognostic accuracy measures, especially AUC, and their 95% CI.

RESULTS

With the first systematic review, we identified 5 different stratification systems for the DFU development risk prediction that were proposed or validated in 13 studies; namely University of Texas, International Working Group on Diabetic Foot (IWGDF), Scottish Intercollegiate Guideline Network (SIGN), American Diabetes Association (ADA), and Boyko and colleagues.

We observed that 5 variables were included in almost all the systems: diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), foot deformity, and previous DFU and LEA. The number of variables included and of risk groups ranged from 4 to 8 and from 2 to 6, respectively.

Accuracy measures reporting was unusual in these studies and external validation had been conducted only for the Boyko et al classification.

In the second systematic review, we identified more than 100 predictive variables assessed in 71 studies for the DFU development prediction. The variables most frequently assessed were age, gender, diabetes duration, body mass index, glycated haemoglobin and DPN. The majority of the identified variables were assessed by only two or fewer studies.

The most commonly included variables in the stratification systems (DPN, PAD, foot deformity and previous foot complications) demonstrated to be consistently associated with DFU in several studies.

In both reviews the DFU prevalence reported in each of the included studies varied greatly.

Meta-analysis was not possible to be conducted.

In the retrospective validation of the systems used for DFU prediction we found that age, diabetes duration, foot deformity, PAD, DPN, previous DFU and LEA were associated with DFU occurrence. There was also an association between the different systems' risk groups and outcome occurrence.

The diverse systems presented good accuracy values (mainly negative PV) and no statistically significance differences were found. Nevertheless, positive PV were all under 30%, positive LR inferior to 4 and negative LR were superior to 0.1. This represents an important potential for optimization.

The multicentre prospective study results are in line to the previous one. The available classifications presented high accuracy values and no significant differences were observed, even with a higher sample size.

Globally the classifications were highly valid and comparable for most of the measures and cut-offs. Positive predictive values (PV) were inferior to 40% in the majority of the scenarios but negative PV were always superior to 90%. For all classifications the AUC was equal or superior to 0.75.

Differences were found between characteristics of the participants and classifications' validity according to the setting.

On the subject of the prediction of LEA we found 8 systems for the description and 7 for the prognostic assessment of DFU that were addressed in 25 studies. LEA prevalence ranged from 6 to 33%.

As with DFU development prediction systems, the number of included variables fluctuated widely (from 1 to 9). The most frequently included were the presence of PAD (n=12), infection at the ulcer site (n=10) and its depth (n=10). The Meggitt–Wagner, S(AD)SAD and Texas University Classification systems were the most extensively validated, whereas the remaining 10 classifications were just derived or validated only once.

Once more, accuracy measures were scarcely reported with just 5 studies describing them and 8 allowing their calculation. Systems' sensitivity ranged from 38 to 100%, specificity 30 to 88%, negative PV were always over 80%, while positive PV were under 60%. Only two studies reported AUC values, presenting values of 0.66 and 0.80.

Meta-analysis was only possible for the composing variables' accuracy. Pooled accuracy ranged from 0.65 (for gangrene) to 0.74 (for infection).

The main referral reason to our centre was the presence of an active DFU (70%). Comparing to the population included in the Eurodiale studies, our sample was slightly older, with deeper and more severe ulcers and more frequently located at the toes. Concerning clinical outcome we had similar healing, major amputation and death rates, but less minor amputations and hospitalization.

Simultaneously validating the systems available for DFU characterization and/or prognostic assessment we verified that all were associated with LEA. Systems typically presented sensitivity values superior to 80% and negative LR inferior to 0.5 for the highest risk group; AUC ranged from 0.56 to 0.83 and positive LR from 1.0 to 5.9. No significant differences were found between systems.

Finally, we have considered as pertinent the refinement of the existing classifications and to create a new classification (named DIAFORA) with some particularities: this classification has two parts and two purposes.

In our systematic reviews to identify the existing classifications for DFU prediction and for prognostic assessment, we have observed that the variables most frequently used for DFU development prediction; namely the presence of DPN, PAD, foot deformity and previous DFU or LEA; were also included in several classifications to predict LEA occurrence. In fact, this group of four variables corresponds to one of the most disseminated classifications to identify the diabetic foot at risk: the IWGDF classification. This classification proved to be equally valid in comparison to the remaining, both in our retrospective as in our prospective multicentre studies. So, we considered that the first part of the DIAFORA should be composed by the IWGDF classification and should be the selected tool to be used in subjects without active DFU to estimate their risk of developing one.

Once a DFU has developed, four variables should be added, in order to accurately predict LEA occurrence. This second part of the DIAFORA classification is composed by DFU characterization variables (the presence of multiple DFU, infection, gangrene and bone affection) that were selected by logistic regression analysis.

So, the first part proved to be valid for DFU development prediction in our first studies, and, when using DIAFORA in its entirety, we observed that this classification was valid for LEA occurrence prediction. As a continuous score DIAFORA had an AUC of 0.91 and as risk categories of 0.89 for LEA prediction. The high-risk group presented a positive LR of 5 and positive PV of 58. This classification presented similar or superior diagnostic accuracy measures for LEA prediction in DFU patients when compared with the existing ones.

CONCLUSIONS

We considered that the creation of a unified system, to stratify subjects with DM according to their risk of DFU and LEA, which is evidence-based, simple and clinically plausible would promote the adoption and use, by healthcare professionals, of a standardized classification in daily clinical care and research conduction. To achieve this major goal and create the DIAFORA tool several conclusions were previously needed to be made.

Despite the importance of an adequate identification of the foot at risk, for both DFU and LEA prediction, we concluded, in our systematic reviews, that the available literature presented a low evidence level due to a lack of validation studies, describing accuracy measures, as well as reliability assessment studies. Thus we have, for the first time, externally validated all the available classifications for each outcome simultaneously in the same cohorts of subjects, one without and one with an active DFU, respectively. This way, the classifications used for each one of the outcomes were directly compared to identify the most valid and their pertinence for refinement.

In general, the systems' accuracy was good, without significant statistical differences among them, meaning that no classification outperformed the remaining and none could be selected as the "best one".

Furthermore, low positive PV and LR values made pertinent the classifications' refinement and the proposal of a unified system: DIAFORA. Our classification, in addition, to an easy to remember structure and the comprehensive manner for the selection of the variables to include, showed an equal or superior accuracy for LEA prediction in individuals with a DFU when compared to those available, which makes it valuable for clinical use.

We highlight that the clinical results of the specialized diabetic foot clinic, where the majority of this Thesis' studies were developed, were similar to those described at European level by the Eurodiale consortium. Therefore, we think that our results are generalizable for specialized diabetic foot centres around Europe.

Despite all these progresses we consider essential future research clarifying if the diabetic foot risk stratification by itself, with clinical practice decisions in accordance, has a true impact on diabetic foot complications' prevention and externally validating DIAFORA.

ACRONYMS AND ABBREVIATIONS

1st	First
3rd	Third
5th	Fifth
α	Intercept
β	Slope
ABI	Ankle–Brachial Index
ADA	American Diabetes Association
AOFAS	American Orthopaedic Foot and Ankle Society
ARR	Absolute Risk Reduction
AUC	Area Under the receiver operating characteristic Curve
BMI	Body Mass Index
CDC	Centers for Disease Control
CDR	Clinical Decision Rules
CHS	Curative Health Services wound grade scale
CI	Confidence Interval
Cm2	Squared centimeter
CONSORT	Consolidated Standards for Reporting Trials
CRF	Case-Report Form
CRP	C-Reactive Protein
DAM	Diagnostic Accuracy Measure
DEPA	Depth of the ulcer, Extent of bacterial colonization, Phase of ulcer and Association aetiology classification system

DFU	Diabetic Foot Ulcer
DIAFORA	DIAbetic FOot Risk Assessment
DM	Diabetes Mellitus
DN	Diabetic Neuropathy
DPN	Diabetic Peripheral Neuropathy
DUSS	Diabetic Ulcer Severity Score
EASD	European Association for the Study of Diabetes
EPE	Entidade Pública Empresarial
EQ-5d	EuroQoL quality of life questionnaire
ESRD	End-Stage Renal Disease
EPV	Events per Variable
GRADE	Grading of Recommendations Assessment Development and Evaluation
HbA1c	Glycated haemoglobin
HR	Hazard Ratio
HrR-QoL	Health Related Quality of Life
Hz	Hertz
IBM	International Business Machines corporation
ICER	Incremental Cost Effectiveness Ratio
IDF	International Diabetes Federation
IDSA	Infectious Disease Society of America
IQR	Interquartile range
IWGDF	International Working Group on Diabetic Foot
l	Litre
LE	Lower Extremity

LEA	Lower Extremity Amputation
LR	Likelihood Ratio
mg	milligrams
mmHg	Millimetres of mercury
MNCV	Motor Nerve Conduction Velocity
MTPJ	Metatarsophalangeal Joint
NA	Not Applicable
NDS	Neuropathy Disability Score
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NNT	Number Needed to Treat
NPV	Negative Predictive Value
OR	Odds Ratio
PAD	Peripheral Arterial Disease
PEDIS	Perfusion, Extent, Depth/tissue loss, Infection, Sensation classification system
PI	Prognostic Index
PODUS	Prediction Of Diabetic Foot Ulcerations
PPP	Peak Plantar Pressure
PPV	Positive Predictive Value
PVD	Peripheral Vascular Disease
ReDFU	Diabetic Foot Ulcer Recurrence
RCT	Randomized Controlled Trial
RG	Risk Groups
ROC	Receiver Operating Characteristic

RR	Relative Risk
RRR	Relative Risk Reduction
S(AD)SAD	Size (Area, Depth), Sepsis, Arteriopathy, Denervation system
SEWSS	Saint Elian Wound Score System
SIGN	Scottish Intercollegiate Guideline Network
SINBAD	Site, Ischemia, Neuropathy, Bacterial infection, and Depth
SPSS	Statistical Package for Social Sciences
SR	Systematic Review
STARD	Standards for the Reporting of Diagnostic Accuracy Studies
STROBE	Strengthening of the Reporting of Observational Studies in Epidemiology
SWM	Semmes–Weinstein Monofilament
TCC	Total Contact Casting
TRIPOD	Transparent Reporting of multivariate prediction model for Individual Prognosis Or Diagnosis
TUC	Texas University Classification
USD	United States Dollars
UT	University of Texas
UTFRS	University of Texas Foot Risk Stratification
VPT	Vibration Perception Threshold
WHO	World Health Organization
WHS	Wound Healing Society

CHAPTER 1: RATIONALE

DIABETES MELLITUS RELATED COMPLICATIONS: THE IMPACT ON THE FOOT

Diabetes mellitus (DM) is one of the most frequent metabolic disorders [1,2]. Located in the North of Portugal, the Porto metropolitan area presents a global prevalence of 13.9%, including subjects with known and unknown diabetes, one of the highest in the country [3]. Moreover, the constant and significant rise of DM prevalence combined with insufficient health care resources will increase even further the need for improvement in the ability to prevent and treat DM-related complications [4].

There are seven most common complications described as related to DM. They are metabolic, retinopathy, nephropathy, cerebrovascular, cardiovascular, neuropathy and peripheral arterial disease (PAD) [5]. Once established, diabetic peripheral neuropathy (DPN) and PAD lead to alterations on lower extremities' sensitivity and blood flow which highly increase the risk of diabetic foot ulcer (DFU) development and lower extremity amputations (LEA) occurrence in subjects with DM [6].

A DFU occurrence represents high costs for the National Health Systems and has a great impact on patients' life, namely through the form of persisting pain, impaired mobility, limited social activities and relationships, and respective family [7,8].

Additionally, a systematic review with meta-analysis, including eight studies, reported that DFU was associated with an increased risk of all-cause mortality [relative risk (RR) of 1.89, 95% confidence interval (CI) 1.60-2.23), fatal myocardial infarction (2.22, 95% CI 1.09-4.53) and fatal stroke (1.41, 95% CI 0.61-3.24)] [9]. In fact, a study concluded that having a DFU increases the risk of mortality independently of age, gender, visual and physical impairment, diabetes duration, the number of diabetes-related complication and LEA history [10].

Not surprisingly, current guidelines emphasise the need for early identification of feet at risk; education of the patient and family; the use of adequate footwear; direct and sustained follow-up; prompt treatment of non-ulcerative lesions [11] and adequate DFU classification and treatment [6]. However, it was reported that costs used for DFU treatment are 10 times higher than those used for DFU prevention [12]. In addition, authors considered that if adequate DFU treatment would prevent 20% of hospitalization and LEA this would decrease in 22 million € treatment costs. But, if 50% of the DFU were prevented by adequate preventive care a total of 88 million € would be saved.

DIABETIC FOOT COMPLICATIONS' PREVENTION: THE IMPORTANCE OF SCREENING

Although structured podiatric care should be available to all diabetic patients, with the existing resource limitation such is impossible and so foot problems' treatment and prevention are frequently inadequate. Therefore, those in most need should be adequately identified and given priority. Prognostic stratification systems incorporating associated risk factors quick, easy and inexpensive to collect through foot examination or simple anamnesis are the most effective way for risk assessment and consequent resource allocation [4,13,14].

Screening is defined as the use of rapid tests to identify certain condition or disease in subjects without signals of its existence. It is appropriate to conduct it if the health condition is serious; the natural history is understood; the condition is detectable in preclinical stage; available screening techniques are cheap, safe, reliable and valid; early treatment is more effective than late; treatment is safe and acceptable; facilities are adequate for diagnosis and treatment, and screening programs can improve outcomes and justify costs [15].

Diabetic foot screening fulfils all the described requisites. However, some authors affirmed that diabetic foot examinations in general practice and in hospitalized patients are both uncommon and unsatisfactory [16,17]. This may be partly due to patients' limited understanding of this condition potential impact, limited access to appropriate healthcare; professionals' lack of time and/or training [16], inaccurate comprehension of which variables to incorporate in regular screening [18] and the belief that intervention is unlikely to have a considerable impact on clinical outcome [19].

Diabetic foot risk stratification is a component of diabetic foot screening, meaning, while the first describes the quantification of the risk an individual has of developing an outcome, the second starts with risk stratification but involves the application of subsequent effective interventions to prevent or manage the clinical condition at an initial stage [20].

Stratification classification systems, in the form of clinical decision rules (CDR), are an essential tool for classifying patients with DM without DFU, according to their cumulative risk of DFU occurrence, and deciding allocation of scarce resources, that represent everyday reality for healthcare services.

In the diabetic foot context, an adequate stratification system must be easy to use but also accurate in identifying patients at higher risk of developing a DFU consequently assisting health professionals in detecting patients for whom the most specialised care, orthotic resources, structured educational programmes and more frequent examinations should be provided [14]. Doing so may diminish the unreasonably high level of foot-related morbidity and costs [14].

Despite their importance, no review had been conducted in order to define and describe all the available stratification systems. In addition, experts stated that no system had been unanimously adopted [6] and so their implementation in clinical practice is still currently scarce [4].

Therefore, we have considered that evidence was lacking identifying and validating the available systems and variables that can be used to predict DFU development. Studies intending to improve the evidence level around the identification of the diabetic foot at risk, to promote the use of a standardized foot assessment in daily clinical practice and consequently reduce DFU occurrence were needed to be conducted.

LOWER EXTREMITY AMPUTATION IMPACT AND PREDICTION

On the other extreme of the diabetic foot disease spectrum, several studies concluded that subjects after a major LEA reported a poorer quality of life when compared to those with other DM-related complications, including end-stage renal disease (ESRD) or blindness [16]. A recent study observed that patients after a major LEA presented a mortality rate comparable to patients with systemic malignant disease, with median survival rates of 40–55 months [21].

It was reported that once a DFU occurs it will take, on average, 3-4 months to heal, in those subjects that the DFU heals 25% will present a re-ulceration, but 25% will require a LEA [7]. In the population with DM, LEAs are 15 to 40 times more frequent than in persons without DM [1,22]. DFU is the major predisposing factor for non-traumatic LEA, preceding about 85% of them [6,22]. Furthermore, after a LEA the risk of an additional one is of 50% in 5 years and the mortality rate is of about 70% [17,22].

A stratification system for DFU prognostic assessment, highlighting the most predictive factors for LEA, is an essential decision-making tool in daily clinical practice, facilitating clinical decisions and communication among different health professionals, standardizing the prognostic estimation itself [23-26] and the DFU treatment efficacy and allowing specialized centres audit and comparison [26,27].

However, it is not unusual to find patients with DFU without their feet ever examined (including in hospital care) [19,28]. Some patients, even with a LEA performed in the same institution, are still found not to attend to the respective clinic [29]. Likewise, DFU treatment is frequently focused exclusively on the wound itself and not taking in consideration the underlying contributing factors [30].

A study reported that the definitive care referral was delayed in more than one third of patients with infection or gangrene and that it was due to an underestimation of severity and poor ischemia's detection [31]. As a result, it often occurs that the access to specialized care of patients in need is being denied due to clinics' overbook with less urgent patients [4].

Again, we considered that evidence was lacking around the identification and validation of classification systems and independent variables used for LEA prediction. There is also still an insufficient use of classifications to improve DFU development and LEA occurrence risk assessment in daily clinical care. So, we supposed that the creation of an easy and intuitive classification, with two distinct parts; the first part consisting on a classification proved valid for DFU occurrence prediction and the second on DFU characterization variables, which could be used for the prediction of both outcomes; would be pertinent to improve clinicians' adherence.

For all this, this Thesis will address DFU prediction and prognosis classification systems for stratifying subjects by their risk of DFU and LEA, respectively, and intends to improve knowledge and quality of care on diabetic foot.

REFERENCES

1. Fard AS, Esmaelzadeh M, Larijani B. Assessment and treatment of diabetic foot ulcer. J Clin Pract 2007;61:1931-8.
2. Khanolkar MP, Bain SC, Stephens JW. The diabetic foot. Q J Med 2008;101:685-95.
3. Diabetes Od. Diabetes: Factos e Números 2009. 2009.
4. Leese GP, Reid F, McAlpine R, et al. Stratification of foot ulcer risk in patients with diabetes: a population-based study. Int J Clin Pract 2006;60:541-5.
5. Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. The American journal of managed care 2008;14:15-23.
6. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45:1-66.
7. Basu S, Hadley J, Tan RM, Williams J, Shearman CP. Is there enough information about foot care among patients with diabetes? The international journal of lower extremity wounds 2004;3:64-8.
8. Prompers L, Huijberts M, Apelqvist J, et al. Optimal organization of health care in diabetic foot disease: introduction to the Eurodiale study. The international journal of lower extremity wounds 2007;6:11-7.
9. Brownrigg JR, Davey J, Holt PJ, et al. The association of ulceration of the foot with cardiovascular and all-cause mortality in patients with diabetes: a meta-analysis. Diabetologia 2012;55:2906-12.
10. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, et al. The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. Journal of diabetes and its complications 2014;28:632-8.
11. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K, International Working Group on the Diabetic Foot (IWGDF). Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev 2016;32:7-15.
12. Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metab Res Rev 2016;32 Suppl 1:195-200.
13. Leese GP, Cochrane L, Mackie ADR, Stang D, Brown K, Green V. Measuring the accuracy of different ways to identify the 'at-risk' foot in routine clinical practice. Diabet Med 2011;28:747-54.
14. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol 2014;70:1.e-18.
15. Wilson JM, Jungner G. Principles and practice of screening for disease. Geneva: World Health Organization (WHO); 1968.
16. Barshes NR, Sigireddi M, Wrobel JS, et al. The system of care for the diabetic foot: objectives, outcomes, and opportunities. Diabet Foot Ankle 2013;4:1-12.
17. Morbach S, Lutale JK, Viswanathan V, et al. Regional differences in risk factors and clinical presentation of diabetic foot lesions. Diabet Med 2004;21:91-5.
18. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med 1998;158:157-62.
19. W J. New guidelines for the management of the diabetic foot in hospitals: so far so good… but will we get Cinderella to the ball? Diabet Med 2012;29:2-4.
20. Ozdemir BA, Brownrigg J, Patel N, Jones KG, Thompson MM, Hinchliffe RJ. Population-based screening for the prevention of lower extremity complications in diabetes. Diabetes Metab Res Rev 2013;29:173-82.
21. Hoffmann M, Kujath P, Flemming A, et al. Survival of diabetes patients with major amputation is comparable to malignant disease. Diabetes & vascular disease research 2015;12:265-71.
22. Brem H, Sheehan P, Rosenberg HJ, Schneider JS, Boulton AJ. Evidence-based protocol for diabetic foot ulcers. Plastic and reconstructive surgery 2006;117:193S-209S; discussion 10S-11S.

23. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. Arch Intern Med 1998;158:289-92.
24. Armstrong DG, Peters EJ. Classification of wounds of the diabetic foot. Current diabetes reports 2001;1:233-8.
25. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. Diabetes Care 2001;24:84-8.
26. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. Diabetes Metab Res Rev 2004;20 Suppl 1:S90-5.
27. Abbas ZG, Lutale JK, Game FL, Jeffcoate WJ. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. Diabet Med 2008;25:134-7.
28. Lavery LA, Wunderlich RP, Tredwell JL. Disease management for the diabetic foot: effectiveness of a diabetic foot prevention program to reduce amputations and hospitalizations. Diabetes research and clinical practice 2005;70:31-7.
29. van Houtum WH. Barriers to implementing foot care. Diabetes Metab Res Rev 2012;28 Suppl 1:112-5.
30. King LB. Impact of a preventive program on amputation rates in the diabetic population. Journal of wound, ostomy, and continence nursing : official publication of The Wound, Ostomy and Continence Nurses Society / WOCN 2008;35:479-82; quiz 83-4.
31. Mills JL, Beckett WC, Taylor SM. The diabetic foot: consequences of delayed treatment and referral. South Med J 1991;84:970-4.

CHAPTER 2: AIMS

The final goal of this project was to improve knowledge and quality of evidence on the DFU development and LEA occurrence prediction. As final goal we intend to propose an easy to collect and apply prognostic stratification system valid both for DFU development prediction (in patients without DFU) as well as for DFU poor prognosis (namely LEA occurrence), by adding a few DFU characterization variables. To achieve this ultimate objective several steps were necessary.

In order to describe in detail this process, our research was divided into 3 main sections:

1. For the **DFU Prediction** we aimed to
    a. retrieve, through systematic reviews, all the stratification systems created and variables assessed for the DFU development prediction with DM but *without active DFU*, and
    b. validate and compare all the available systems for DFU development prediction in a consecutive series of patients *without active DFU*.

2. For the **DFU Prognosis** our main goals were to
    a. retrieve, through systematic reviews, all the stratification systems created and variables assessed for the LEA prediction in subjects with DM and *active DFU*, and
    b. validate and compare all the available systems for DFU worst prognosis prediction (meaning LEA) in a consecutive series of patients with *active DFU*.

3. At the end of these sections we intend to
    a. propose a unified system proved valid for DFU development prediction (retrieved from section 1) that, with the inclusion of additional DFU characterization variables (retrieved from section 2), can also accurately predict LEA in patients with active DFU.

CHAPTER 3: BACKGROUND

3.1 CLINICAL DECISION RULES

DEFINITION

Health professionals and policy makers have the need to make predictions on several aspects of health care and services [1]. However, in clinical practice, we observe variability among patients' characteristics; clinical conditions' causes, presentation, and natural history; and also impact of treatment. So, a single variable is seldom sufficient to adequately estimate the patients' probability to have or to develop a given clinical condition, and health professionals tend to use multiple predictors to do it [2].

A multivariable approach for the prognostic studies' design and analysis is needed to identify the most important group(s) of predictive variables and give outcome probabilities for each group, as also to create tools to estimate such probabilities and classify subjects by their risk of developing the outcome of interest. Such tools are defined as prognostic or prediction models, risk scores, prediction or clinical decision rules [2,3].

Although the methods that will be described in this section were not always applied for the creation of the tools that we will study in this Thesis, systems to stratify subjects by their risk of outcome development we have considered these systems also as clinical decision rules.

We have made such decision based on these risk stratification systems' or classifications' clinical purpose, meaning, to improve prognostic estimation by the use of a group of predictive variables and to group subjects with a similar probability to develop such outcome.

This Thesis focus is on the prediction of diabetic foot outcomes (namely DFU and LEA), so we have considered that a chapter concisely explaining how such risk classification tools are developed and should be assessed, was considered to be of paramount importance.

A clinical decision rule (CDR) is created with the purpose of accurately estimating the probability of a particular clinical outcome to be present (diagnostic context) or occur in the future (prognostic context), and therefore can be applied both in healthy or in ill subjects [1,4].

A CDR should include the "best" predictor variables, be the smallest possible, easy to use in practice and, above all, accurate and generalizable. The predictive probability can be extracted and depicted in several ways.

Using logistic regression, the formula for the prognostic index (PI) corresponds to the sum score by adding our model curve intercept (α) and each combination of the regression coefficients (β) with the predictive variables (α+ β*predictive variable); the score chart uses rounded values of the regression coefficients (for example by multiplying each one for 10) and presents a final score that is calculated by adding each predictive variable related value and a constant; and the nomogram, uses the same principle of the score chart but uses a visual graphic aid [1,3,4].

Derivation (or development)

In this stage, the multivariable prognostic model (CDR) is created, by identifying the most important predictive variables and assigning relative weights to each one [4,5].

Before starting this stage one must select the clinically relevant predictive variables for possible inclusion in the CDR and the procedure to use with possible missing data. Then, make data handling decisions, define the strategy for selecting the most important variables and the procedure to use with continuous variables and measures [5].

The statistical methods more commonly used to develop CDR are logistic and Cox regression (when time to event is considered) [4], as they allow probability' estimation of a particular outcome.

In order to detect which variables should be included in the multivariate analysis (pre-selection screening), some authors consider that they should be identified based on physiological plausibility, clinical reasoning, opinion of experts and previous studies' results [1,4,5]; others prefer to include only those that were associated with the outcome in the univariate analysis (although this is not considered as the most recommended) [1,4].

Concerning missing values, some statistical techniques (namely multiple imputation) can be used. An influence on the assumptions can occur and increase with the number of missing data, as they are rarely random. If all subjects with missing values are not considered it can lead to a loss of statistical power as well as to incorrect CDR's and predictive variables' estimates. When less than 5% of observations are missing, a complete case analysis may be considered reasonable [5].

There are several strategies to select the predictive variables that should be tested to be included in the CDR.

The full model approach consists on including all the considered pertinent predictive variables in the CDR. Some authors consider that this method avoids overfitting and selection bias. However, the full model is frequently difficult to define as several preliminary choices must be made and it is impractical to include all candidates [5].

The backward approach, the most commonly recommended technique, begins with all the candidate variables. A significance level, often 1, 5 or 10%, is considered beforehand. Analysis starts with all candidate variables in the model. Hypothesis tests are sequentially applied to identify if a given variable should be removed from the model [4,5]. The variable with the highest p value is excluded in each round and the model is rerun each time.

The forward method can also be used, however it tends to lose more variables. This method uses the opposite logic. Analysis starts with no variables in the model. Hypothesis tests are sequentially applied to identify if a given variables should be included in the model [4,5]. The variable with the highest predictive variable is included in each round and the model is rerun each time.

The advantage of these selection methods is the fact that they are easy to do, using the same variables and selection criteria the results are the same, and they allow to develop smaller models [6].

However, we should bear in mind that, by using different methods, the final model is different (especially when more candidate predictive variables are tested), regression coefficients can be overestimated [especially when the events per variable problem (EPV) occurs, meaning, there are less than 10 events per predictive variable tested [2,4]] and the distinction between "true" and "false" predictive values is hard.

In each stage of the CDR development one should assess the final model calibration and discrimination ability (procedures will be described latter in this section).

Validation

The validation process determines to what extent the CDR is adequate or optimistic, by comparing the values of calibration and discrimination of the CDR derivation set to a different one [4]. Preferably, using a prospective cohort design, in each participant the CDR's predictive variables and the outcome are collected and the CDR's performance is quantified [7]. A poor performance of the CDR can be due to design or methodologic limitations during the derivation process, the lack of inclusion of an important predictive variable in the CDR and/or the existence of substantial differences between the derivation and validation settings [4,8].

The *internal validation* is conducted in the same setting and with similar subjects in which the CDR was derived [4]. The quality (performance) of the CDR is always better in the derivation dataset than in a new one, even when the new samples are derived from the same population [3,4]. When the derivation sample is small, this optimism is even more pronounced [3,5].

One of the recommended methods used for internal validation is *cross-validation* [4]. In this technique, the available sample is randomly divided in distinct sets: one for the CDR development and the remaining to test it. This procedure is conducted repeatedly and the performance estimate corresponds to the average value [3,4].

Another recommended method is *bootstrapping* [1,4]. In this technique we randomly select subjects from our dataset, one by one, but each time the subjects stays in the sample set (so he can be selected several times) [1,4]. This procedure is repeated until we achieve the desired sample size and replicate to have several bootstrap samples (usually 250, and at least 100) [4]. We simulate that we are making the prediction rule in comparable "new" datasets. We then determine the optimism of our CDR on calibration and discrimination and calculate the shrinkage factor [1,4]. To do so, we apply our prediction model to all bootstrap samples. Due to the correlation between our sample and the bootstrap samples, the CDR will have higher regression coefficients and AUC. We then apply the CDR on the original sample set. The difference observed between each bootstrap sample and our original sample set is the average overestimation value, the value we need to correct (the shrinkage factor). We can then "adjust" our original CDR [1,4].

Non-random splitting by clinical centre reduces the sample similarities, which may be considered as preferable [8].

Temporal validation is considered as an intermediate between internal and external validation and corresponds to a sample splitting by time. There will be several similarities between the two sets.

However, this is a prospective evaluation of the CDR, independent from the original dataset and derivation process [8].

In this type of validation, the calibration and discrimination values of the CDR derivation set will be compared to another from a more recent time period from the same setting [8].

In the *external validation* we are quantifying the CDR's optimism and testing the CDR's generalizability by applying it to a new dataset [3,4,8].

In this stage, we assess if the performance of the CDR in this new dataset from a different setting, through calibration and discrimination measures, is similar to the one reported in the derivation process [4,8] or in the previously described validation methods.

The CDR is optimized for our dataset as regression techniques use, techniques that minimize errors for that dataset. There are several factors that can change the CDR calibration in a new dataset during the validation process, such as different prevalence of outcome, predictive variables' distribution, data collection, etc. In addition, a regression coefficients overestimation (overfitting) could have occurred and a correction (shrinkage) must be conducted, or new variable(s) need to be included [8].

Study designs used for derivation and validation

Several study designs can be used for CDR's derivation and validation, depending on its purpose.

For a diagnostic CDR, the most commonly used design is a cross-sectional study, in which the predictive variables are collected (derivation) or the CDR applied (validation) in a group of patients suspected of having the outcome condition [1,4]. There is usually a time interval between the collection of the predictive variables or the application of the CDR and the reference standard application to detect the presence of outcome. The reference standard is the method considered as the accepted best available method to determine the presence or absence of the outcome of interest [1,4,9]. Ideally, the same reference standard should be applied to all participants [1,4,9].

The time interval should be as short as possible to impede further disease evolution or the beginning of treatments [4]. Due to the existence of this period, it is unclear if this study methodology is a clear cross-sectional or a diagnostic cohort study [4].

The outcome collection should be blind for the presence or absence of the predictive variables, and vice-versa [4,9].

For a prognostic CDR, the most frequent design is a prospective or retrospective cohort study [4,10]. Subjects with specific characteristics are included in the study, predictive variables are collected and then they are followed over a specific period of time and outcome occurrence or absence is registered [4].

A prospective design, with a consecutive inclusion [9], is preferable, due to the possibility of controlling the measurement of all the pertinent predictive variables and outcome(s) and the use of the most adequate methods to do so [4].

Individual participant data from multiple original studies, large data sets from national or international surveys or registries, and meta-analytic techniques are becoming more commonly used to develop or validate CDR [4].

Sample size for derivation studies should be calculated considering the need of at least 10 outcome EPV and/or the precision required for CDR diagnostic accuracy measures [1,4]. For validation studies, it is considered that sample size should include a minimum of 100 events and 100 non-events and/or the precision required for CDR performance measures [4].

Measures used for derivation and validation

Calibration is defined as the agreement between the predicted probabilities of the studied outcome and the observed outcomes in our sample [3,4]. This CDR property is usually assessed through the calibration in the curve, the Hosmer and Lemeshow test, and the calibration in the large.

The *calibration curve* can be used both in the derivation and validation processes and arranges the predicted probabilities from low to high by, usually, making groups of deciles of predicted probabilities [1,2]. The predicted probability in each decile is compared to the observed probability, meaning, the observed outcome divided by the total number of subjects in that group.

This can be depicted in a scatter plot (calibration plot) with the predicted probabilities plotted compared to the observed probabilities [3,5,8]. The optimal calibration curve shows a 45º line, an intercept (α) of 0 and a slope (β) of 1, and a correlation coefficient of 1. The observed and the predicted probabilities always agree [1,3,5]. When this slope is smaller than 1 it means that optimism occurred, the predictions are too extreme, that is, the estimates for low probabilities are too low and for high probabilities too high [1,3]. On the other hand, if this slope is larger than 1, it indicates that probabilities are not extreme enough [1,3].

When the slope is different than 1 and simultaneously the intercept is different from 0, the interpretation is difficult as both are related. This is commonly observed in external validation studies and indicates that patient characteristics that were not included in the CDR had a different distribution in the development when compared to the validation sample [1,3].

The *Hosmer and Lemeshow test* evaluates the same thing as the calibration curve, this is, the goodness of fit [1,5,8]. However, both should be always used, as they complement each other. This test sums all the differences between the predicted and the observed probabilities of each group (for example, predicted probabilities percentiles, prediction intervals or covariate patterns) and follows a X^2 distribution [1,3,8]. The null hypothesis of this test is that there is agreement between these two values, therefore with a p value superior to 0.05 we cannot reject it, and so consider that there is goodness of fit. However, there is no accepted value range (but the higher the better), the test is sensitive to the choice of groups, has poor power to identify miss-calibration in small samples, and is over sensitive in large samples (that is, even small disagreements between predicted probabilities and observed frequencies originate a statistical significant test value) [1,3,5].

The *calibration in the large* is used when validating the CDR in a new patient database and evaluates how different is the sum of all the predicted probabilities when compared to the number of observed outcomes [1,3]. Differences (mis-calibration) can be due to very different observed outcomes or problems in our CDR generalizability. Optimism of the CDR, using this measure, is represented by

a higher value of the sum of the predicted probabilities when compared to the number of observed outcomes [3].

Another measure is the *absolute difference* between the predicted and the observed probabilities [3].

Discrimination evaluates how well the CDR distinguishes between people who actually have the outcome and those who do not [4]. A model with high discrimination usually represents a larger model, with a high number of included variables, and therefore gives a lower calibration. On the other hand, a model with high calibration is more commonly a smaller model, with few variables included, and present lower discrimination [1]. A good CDR should have in consideration the best equilibrium between these two properties.

This CDR's property can be assessed graphically by visualising the validation plot, this is, a boxplot with the predicted probabilities distributions per outcome value (absent and present), analysing the R^2 value or the receiver operating characteristic (ROC) curve, or numerically through concordance-statistic (c-statistic), the area under the ROC curve (AUC), and accuracy measures (namely, sensitivity, specificity, predictive values and likelihood ratios) when applying cut-offs [3,5,8].

In the case of a discriminative CDR, the *validation plot* will show a spread of the predicted probabilities distribution that is wide and distant from the mean probability [3]. This is a very informative tool, although there is no quantification of the discrimination [3].

The R^2 evaluates the amount of explained variation of the risk by the CDR and corresponds to the square of the correlation between the observed and the predicted probability [1,2,4,5].

The *c-statistic* represents the chance of a patient that will have or has the outcome condition to have a higher expected probability when compared to a patient that will not or does not have the outcome condition [2]. This measure is mainly used to assess the presence of optimism. When there is a substantial decrease of this value in a new dataset, optimism is considered to be present [3]. However, this value also depends on the predicted probabilities distribution. For samples with more homogeneous predicted probabilities, meaning, without extreme values, the c-statistic value will be lower [3].

For binary outcomes, the c-statistic is equal to the AUC [3,4]. ROC curve and respective AUC are not very responsive, meaning, the inclusion of a new variable does not make substantial changes and so it is hard to test potential improvements [5].

The *ROC curve* is a plot of true-positive (sensitivity) versus false positive rate (1-specificity) for each value or cut-off points of the predicted probability. The AUC gives the probability that a subject with the outcome has a higher predicted probability when compared to one without, for a random pair of subjects, consisting of one with and the other without the outcome [1]. A value of 0.5 is considered as a useless CDR and a value near 1 as perfect discrimination [3].

Sensitivity is the proportion of subjects with the disease that were adequately identified by the CDR as having the disease. Specificity is the proportion of subjects without the disease that were adequately identified by the CDR as not having the disease [1,11].

Positive predictive value (PPV) is the proportion of subjects that were classified as having the disease by the CDR (positive) that in fact have the disease. Negative predictive value (NPV) is the proportion of subjects that were classified as not having the disease by the CDR (negative) that in fact did not have the disease [11].

Likelihood ratios show the probability of having a specific CDR result in those that have the disease in comparison to those that do not have it [11]. Positive likelihood ratio (LR+) is the probability of having the disease in those classified as positive by the CDR, in comparison to (meaning, divided by) the probability of not having the disease in those classified as positive by the CDR, this is, specificity divided by 1-specificity [11]. The higher the value, the best the discrimination is. On the other hand, negative likelihood ratio (LR-) is the probability of having the disease in those classified as negative by the CDR in comparison to (meaning, divided by) the probability of not having the disease in those classified as negative by the CDR, this is, 1-specificity divided by specificity [11]. The lower the value, the best the discrimination is.

Refinement (or Updating)

Developing a new CDR for each time period, context, institution or country may look tempting. However it diminishes the results' generalizability, makes it hard to decide which one to select for our context, and overfitting is more probable (due to the need of larger samples for derivation) [4].

It is preferable, if necessary, to improve calibration by changing only the intercept or both the intercept and the slope and/or discrimination by considering the inclusion of a new variable on the CDR [4,7].

The refined CDR's discrimination can be compared to the original one by several methods: R^2, comparing AUC, integrated discrimination improvement, and reclassification tables.

Using the R^2 it is possible to compare the amount of explained variation of the risk by the original CDR with the new version. However, it is hard to clinically interpret its value [4].

The *AUC value* evaluates the CDR's discrimination [11]. We can analyse if the refined CDR has a statistically significant higher AUC by comparing its 95% confidence interval (CI) with the one from the original CDR [11]. However, we cannot understand if the change of the AUC will be clinically relevant.

The *integrated discrimination improvement* corresponds to the difference between the predicted probabilities in those with or that developed the outcome in comparison to those who did not [4].

The *reclassification method* evaluates if there is a shift of the subjects to an appropriate risk category after adding a new relevant predictor. It is calculated how many subjects in which the outcome occurred were reclassified from low to a high risk category (desirable) and from high risk to a low risk category. In the same way it is calculated how many subjects in which the outcome did not occurred were reclassified from a high to a low risk category (desirable) and from a low to a high risk category [4].

The net reclassification improvement is calculated by subtracting the number of subjects in which a desirable reclassification occurred to the number of subjects in which reclassification was occurred in a undesirable direction [4].

After updating the CDR, the new version must be validated in a new setting.

Clinical impact

Calibration and discrimination assess the CDR's performance over the complete range of predicted probabilities, but considering that all values are equally relevant [3]. It can be appropriate to predefine what will be considered as an acceptable calibration and discrimination. And if such values are achieved, the CDR may be considered as suitable for clinical practice. Although it is unclear what should be considered as satisfactory, prognostic estimations will be required and even moderate performances may be translated on an improvement of health professionals' own assessments [8].

CDRs are intended to be used in new populations, contexts, countries and time periods. However, it is common to observe that CDRs developed in secondary care settings usually have a diminished performance when applied in the primary care setting [4,7]. This occurs due to a different case-mix, this is, a different outcome or predictive variables' distribution that can lead to a different predictive variable – outcome association [4]. A validation on different contexts should be performed before application in clinical practice [7]. So, for an optimized usability of the CDR, there should be a clear definition of the predictive variables and outcome, collected through methods that are reproducible and available in clinical practice [7].

Real clinical impact is measured by assessing if the CDR will be helpful to the clinician in decision making, whether to request tests or decide treatment strategies [2,3,7], and is independent of calibration and discrimination of the CDR.

In a clinical impact study it is quantified the effect of the CDR on health professionals' behaviour (measured by decision modifications), patient (measured namely by pain, quality of life, satisfaction) or clinical outcomes (measured namely by number of events, risk measures), and/or cost-effectiveness [measured namely by incremental cost effectiveness ratio (ICER)] in comparison to standard care [4,7]. For such studies, a control group is required and a randomized controlled trial (RCT) is the preferred design [4,7]. Randomization can be done by patient, by health professional, or by centre. The last is considered as the best method, because it avoids contamination between groups [7].

Another possible design is a before and after study, with the same health professionals and centres. However, temporal changes in clinical methods can affect the results [7].

An intermediate method between validation and clinical impact assessment are modelling techniques or Markov chain models, evaluating the potential gains of using the CDR on clinical practice [7].

REPORTING: THE TRIPOD STATEMENT

In 2015, a group of specialists developed the TRIPOD guideline: Transparent Reporting of multivariate prediction model for Individual Prognosis Or Diagnosis. This checklist addresses the reporting requirements for the development and validation of CDR for prognosis and diagnosis in all health topics using any kind of predictive variables [4].

This statement was created based on a systematic search, on several databases, identifying articles where recommendations were made for reporting multivariable prediction models and their development and validation methodological aspects [4].

After reviewing the included articles, a total of 129 possible checklist items were identified and compiled in a list of 76 candidate items [4].

A total of 24 experts, including statisticians, epidemiologists, methodologists, healthcare professionals and journal editors, had a 3-day meeting for a consensus on whether retain, merge with another, or delete each item. A total of 22 items were considered as essential for CDR's development and validation studies' reporting [4] (see Figure 1).

This checklist was not used during the majority of this Thesis studies' conduction, as this checklist was published after their conduction.

Section	Topic	Der	Val	Item
TITLE AND ABSTRACT	*Title*	✓	✓	Identify the study as developing and/or validating a multivariable prediction model, the target population and the outcome to be predicted
	Abstract	✓	✓	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results and conclusions
INTRODUCTION	*Background*	✓	✓	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models
	Objectives	✓	✓	Specify the objectives, including whether the study describes the development or validation of the model, or both
METHODS	*Source of data*	✓	✓	Describe the study design or source of data (e.g. randomized trial, cohort or registry data), separately for the development and validation data sets, if applicable
		✓	✓	Specify the key study dates, including start of accrual, end of accrual and, if applicable, end of follow-up
	Participants	✓	✓	Specify key elements of the study setting (e.g. primary care, secondary care, general population) including number and location of centres
		✓	✓	Describe eligibility criteria for participants
		✓	✓	Give details of treatments received, if relevant
	Outcome	✓	✓	Clearly define the outcome that is predicted by the prediction model, including how and when assessed
		✓	✓	Report any actions to blind assessment of the outcome to be predicted
	Predictors	✓	✓	Clearly define all predictors used in developing the multivariable prediction model, including how and when they were measured
		✓	✓	Report any actions to blind assessment of predictors for the outcome and other predictors
	Sample size	✓	✓	Explain how the study size was arrived at
	Missing data	✓	✓	Describe how missing data were handled (e.g. complete-case analysis, single imputation, multiple imputation) with details of any imputation method
	Statistical analysis	✓		Describe how predictors were handled in the analyses
		✓		Specify type of model, all model-building procedures (including any predictor selection) and method for internal validation
			✓	For validation, describe how the predictions were calculated

		✓	✓	Specify all measures used to assess model performance and, if relevant, to compare multiple models
			✓	Describe any model updating (e.g. recalibration) arising from the validation, if done
	Risk groups	✓	✓	Provide details on how risk groups were created, if done
	Development versus validation		✓	For validation, identify any differences from the development data in setting, eligibility criteria, outcome and predictors
RESULTS	*Participants*	✓	✓	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful
		✓	✓	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome
			✓	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome)
	Model development	✓		Specify the number of participants and outcome events in each analysis
		✓		If done, report the unadjusted association between each candidate predictor and outcome
	Model specification	✓		Present the full prediction model to allow predictions for individuals (i.e. all regression coefficients, and model intercept or baseline survival at a given time point)
		✓		Explain how to use the prediction model
	Model performance	✓	✓	Report performance measures (with confidence intervals) for the prediction model
	Model updating		✓	If done, report the results from any model updating (i.e. model specification, model performance)
DISCUSSION	*Limitations*	✓	✓	Discuss any limitations of the study (such as non-representative sample, few events per predictor, missing data)
	Interpretation		✓	For validation, discuss the results with reference to performance in the development data and any other validation data
		✓	✓	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence
	Implications	✓	✓	Discuss the potential clinical use of the model and implications for future research
OTHER INFORMATION	*Supplementary information*	✓	✓	Provide information about the availability of supplementary resources, such as study protocol, web calculator, and data sets
	Funding	✓	✓	Give the source of funding and the role of the funders for the present study

Der: Derivation, Val: Validation

Table 1. TRIPOD statement checklist (adapted from reference number [4])

REFERENCES

1. Steyerberg EW. Clinical prediction models: a practical approach to development, validation and updating. New York, USA: Springer Science+Business Media, LLC; 2009.
2. Moons KG, Royston P, Vergouwe Y, Grobbee DE, Altman DG. Prognosis and prognostic research: what, why, and how? BMJ 2009;338:1317-20.
3. Vergouwe Y, Steyerberg EW, Eijkemans MJ, Habbema DF. Validity of Prognostic Models: When Is A Model Clinically Useful? Seminars in Urologic Oncology 2002;20:96-107.
4. Moons KG, Altman DG, Reistma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Inter Med 2015;162:W1-W73.
5. Royston P, Moons KG, Altman DG, Vergouwe Y. Prognosis and prognostic research: developing a prognostic model. BMJ 2008;338:1373-7.
6. van Houtum WH. Barriers to implementing foot care. Diabetes Metab Res Rev 2012;28 Suppl 1:112-5.
7. Moons KG, Altman DG, Vergouwe Y, Royston P. Prognosis and prognostic research: application and impact of prognostic models in clinical practice. BMJ 2008;338:1487-90.
8. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2008;338:1432-5.
9. Cook CE. Potential pitfalls of clinical prediction rules. The Journal of manual & manipulative therapy 2008;16:69-71.
10. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes Metab Res Rev 2014;30:610-22.
11. Fritz JM, Wainner RS. Examining diagnostic tests: an evidence-based perspective. Physical therapy 2001;81:1546-64.

3.2 DIABETES MELLITUS AND DIABETIC FOOT EPIDEMIOLOGY AND COSTS

In 2015, DM global prevalence was of 8.8%, affecting 415 million people. More than 320 million were on their working age (20-64 years). It is estimated that in 2040 this prevalence will increase to 10.4%, affecting 642 million individuals, due to its rise in every country worldwide [1].

Diabetes' prevalence in Europe, in 2015, is slightly higher when compared to the global one (9.1 vs 8.8%), representing a population of 60 million people. In 2040, it is expected to rise to a prevalence of 10.7% and affect up to 71 million people [1]. The European country with the highest DM prevalence was Turkey (12.8%), and the countries with higher number of habitants with diabetes are the Russian Federation, Germany and Turkey [1]. Portugal presented a prevalence of 9.9%, which is higher when compared to the global and Europe reported values [1].

In 2013, Portugal also had a higher mean DM related expenditure [2250 vs 1437 United States Dollars (USD)] [2]. That year the country had 7982 deaths caused by DM [2]. Furthermore, it was reported that, in 2012, 4683 years of life were lost due to DM in subjects under 70 years [3].

DM was responsible for more than 10% of hospitalizations, in 2014, in Portugal [3]. Circulatory system diseases were the most common cause (22%) and 1863 were directly related to diabetic foot [3].

Worldwide, 5.0 million subjects aged between 20 and 79 years died, in 2015, due to reasons attributed to DM, which represents a 14.5% global prevalence of all-cause mortality among people in this age group. Every 6 seconds a person died due to DM. This magnitude is even higher when compared to the combination of deaths due to human immunodeficiency virus/acquired immune deficiency syndrome or acquired immunodeficiency syndrome, tuberculosis and malaria (3.6 million subjects), which are considered as major public health priorities [1].

In 2013, 1 in 10 deaths in adults (n=619 000) in the Europe Region was DM related. However only 10% were individuals under 50 years, which may indicate the existence of responsive health systems along with the age distribution of the population [2].

That year, it was estimated that more than 25% of the global healthcare budget in the Europe region was spent on DM, representing a cost of more than 147 billion USD. Norway was the country that spent more money with DM (on average 10.368 USD per person and Tajiskitan the less amount (87 USD) [2].

In 2015, there was a global health expenditure from 673 up to 1197 billion USD related to DM care, which represents an investment of 1662 to 2886 USD per person with DM [1]. The majority of global health expenditures for DM were spent on the United States of America, China and Germany [1].

Epidemiologists reported that, in people with diabetes, 20-25% of all hospital admission days are diabetic foot related [4]. This considerable proportion may be explained by the fact that subjects with DM are described to have a 15 to 46 times higher risk of LEA in comparison to those without DM,

and the risk of a new LEA varies from 9 to 17% after 1 year and 25 to 68% after 3 to 5 years [4]. After 5 years of an LEA occurrence the survival rate decreases to values around 40 to 70% [4].

Despite the LEA epidemiology importance, the last global study was published in 2000, including subjects undergoing LEA from July 1995 to June 1997 from 10 centres with populations greater than 200 000 in Japan, Spain, Italy, North America and England. The highest LEA observed rates occurred in the Navajo population (43.9 per 100 000 people per year for first LEA in men) and the lowest in Madrid (2.8 per 100 000 per year). DM was linked with 25 to 90% of LEA [5].

In 2014, there were 825 minor LEA and 560 major LEA during hospitalization in Portugal. The global and the major LEA number in this year were the lowest since the beginning of the National Diabetes Observatory, in 2005 [3].

Due to differences in health organization and variable number of multidisciplinary teams for diabetic foot care, we observe a great variability in the rate of minor and major LEA by 100 000 habitants. The lowest occurred in the North region (6.0 and 4.4, respectively) and the highest in Alentejo region (15.1 and 7.8, respectively) [3].

The impact of diabetic foot on subjects' quality of life is immense. Limited studies have addressed this topic and attempted to derive utility values of health states involving DFU and LEA.

A recent systematic review [6], including studies from EU5 countries (Spain, Italy, France, England and Germany), identified 6 studies reporting quality of life (QoL) data in patients with diabetic foot complications. In this review the authors stated that those subjects with DFU presented a lower mean score on all the eight SF-36 domains, especially in what concerns physical capacity. In the same way, those subjects with non-healed and recurrent DFU showed lower values when compared to those with healed DFU, as well as those that underwent a LEA compared to those that did not.

Another study, estimating utility values for health states observed amongst diabetic foot patients, reported values ranging from 0.31 for patients with feet or leg amputated to 0.84 in those without an active or previous DFU [7].

Moreover, diabetic foot complications represent a major economic burden. Several authors reported that there is a disproportionate increase in the cost according to the condition severity. For example, it was reported that the annual care cost for subjects with DFU, compared to those without, is 5.4 higher in the first year after the DFU occurrence and 2.8 in the second and that the cost of the most severe DFU treatment is 8 times higher when compared to the less severe [8].

Considering the costs associated with diabetic foot care, it was estimated, in one study from the United States of America, that for subjects with DM and DPN it would be of around 11 billion USD and extrapolated that for those with PAD would be of around 17 billion USD, which is similar to the annual costs for breast and colorectal cancer in that country [9].

Other study demonstrated that diabetic foot complications represent an economic and resource utilization burden similar to cancer, depression, lung disease and musculoskeletal diseases' treatment [6]. Several studies, showed that severe DFU and LEA imply a higher per patient average cost when compared to other DM related comorbidities, such as non-fatal myocardial infarction, heart failure, ischemic heart disease and eye disease [6].

DFU treatment cost analysis are more frequently conducted by industrialized countries, such as United States of America, Sweden and The Netherlands. For these countries, the direct cost estimates (in 2010-adjusted USD) have been reported to vary from 3096 USD for a DFU categorized as Wagner

1 to 107 900 USD when a LEA is required. In addition, the reported cost only considered direct costs and rarely the cost to the patient [10]. Data addressing diabetic foot prevalence and costs in Europe will be further presented in section 3.4 of this Thesis: diabetic foot care in Europe. So far no study was conducted in Portugal assessing the diabetic foot prevention and treatment related costs.

Despite all these facts, authors believe that the diabetic foot clinical outcome can be greatly improved by prompt referral for specialized assessment and treatment [11]. In 2012, only 69.4% of the population with diagnosed DM had a register of diabetic foot screening in the Portuguese National Health System [3].

Several authors consider that an organized multidisciplinary approach for the high risk patients, including extensive patient education, early assessment and aggressive therapies such as revascularization procedures and advanced wound-healing techniques, is markedly economically and clinically beneficial by reducing LEA and length of hospital stay [4,8].

A Dutch study reported that the mean total lifetime cost of treating a patient with intensive glycaemic control and/or optimal foot care ranged from 4 088 to 4 386 USD. The incremental cost per quality adjusted life year gained for patients under both interventions was under 25 000 USD for a preventive foot care leading to a decrease in LEA rate superior to 10% [12].

Using data from the year 2000, a study from Austria reported that an intensified (specialized diabetic foot clinic) versus a standard DFU treatment (general practitioners' clinics) reduced the direct costs in 28.9% per patient, per year in a grade A DFU (no infection or PAD), classified according to the Texas classification, and up to 49.7% in grade D (with infection and PAD) due to LEA rates [13].

An Irish Hospital created a Diabetic Foot Clinic with a multidisciplinary team and concluded that the number of major LEA reduced from 12 in the 2 years before the clinic (2006-2008) to 7 in the 2 years after the clinic creation (2008-2010). This reduction represented an overall saving of 111 063€ per year after, even after costing diabetic foot clinic related activity [14].

The Pan American Health Organization studied which were the health service interventions in diabetic foot care that were cost-saving and concluded that the most effective were the education of patients with DM on recognizing and treating minor foot injuries (expected reduction of 72% of LEA), the use of appropriate footwear (expected reduction of 53% of LEA), and improve the access to knowledgeable health care personnel (expected reduction of 47% of LEA) [4].

REFERENCES

1. Federation ID. IDF Diabetes Atlas. 7th ed. http://www.diabetesatlas.org/: International Diabetes Federation; 2015:1-144.
2. Federation ID. IDF Diabetes Atlas. http://www.diabetesatlas.org/: International Diabetes Federation; 2014:1-160.
3. Diabetes Od. Diabetes: Factos e Números O ano de 2014. 2015.
4. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol 2014;70:1.e-18.
5. Global Lower Extremity Amputation Study Group. Epidemiology of lower extremity amputation in centres in Europe, North America and East Asia. The Global Lower Extremity Amputation Study Group. The British journal of surgery 2000;87:328-37.
6. van Acker K, Leger P, Hartemann A, Chawla A, Siddiqui MK. Burden of diabetic foot disorders, guidelines for management and disparities in implementation in Europe: a systematic literature review. Diabetes Metab Res Rev 2014;30:635-45.
7. Redekop WK, Stolk EA, Kok E, Lovas K, Kalo Z, Busschbach JJ. Diabetic foot ulcers and amputations: estimates of health utility for use in cost-effectiveness analyses of new treatments. Diabetes & metabolism 2004;30:549-56.
8. Driver VR, Fabbi M, Lavery LA, Gibbons G. The costs of diabetic foot: the economic case for the limb salvage team. Journal of the American Podiatric Medical Association 2010;100:335-41.
9. Barshes NR, Sigireddi M, Wrobel JS, et al. The system of care for the diabetic foot: objectives, outcomes, and opportunities. Diabet Foot Ankle 2013;4:1-12.
10. Cavanagh P, Attinger C, Abbas Z, Bal A, Rojas N, Xu ZR. Cost of treating diabetic foot ulcers in five different countries. Diabetes Metab Res Rev 2012;28 Suppl 1:107-11.
11. Jeffcoate W. Stratification of foot risk predicts the incidence of new foot disease, but do we yet knowt that the adoption of routine screening reduces it? Diabetologia 2011;54:991-3.
12. Ortegon MM, Redekop WK, Niessen LW. Cost-effectiveness of prevention and treatment of the diabetic foot: a Markov analysis. Diabetes Care 2004;27:901-7.
13. Habacher W, Rakovac I, Gorzer E, et al. A model to analyse costs and benefit of intensified diabetic foot care in Austria. Journal of evaluation in clinical practice 2007;13:906-12.
14. Nason GJ, Strapp H, Kiernan C, et al. The cost utility of a multi-disciplinary foot protection clinic (MDFPC) in an Irish hospital setting. Irish journal of medical science 2013;182:41-5.

3.3 DIABETIC FOOT PATHOPHYSIOLOGY

Diabetic foot screening, through foot examination and identification of those at higher risk of developing complications, is commonly underdone both in inpatient and outpatient settings, due to asymptomatic nature of DM, a lack of knowledge of routine practice procedures and of time in usually busy clinics [1,2]. The best way to overcome these barriers is by explaining the diabetic foot pathophysiology in a comprehensive but simple way and by emphasizing the importance to DFU prevention.

Many authors consider that DFU pathophysiology is very similar in the majority of the patients. They usually arise from the presence of two or more risk factors: DPN, PAD and/or trauma [1,3-8]. DPN diminishes the patient's sensitivity and leads to biomechanical and sweat control alterations, which causes minor trauma, less skin resistance and an unawareness of the callus and DFU occurrence [1,9]. PAD can cause skin frailty which, in the presence of trauma (minor or major), increases the risk of DFU and impairs healing [9].

Trauma, DPN and PAD *per se* can be responsible for DFU occurrence, maintenance, and aggravation and increased infection susceptibility, which leads to more severe DFU (See Figure 1).

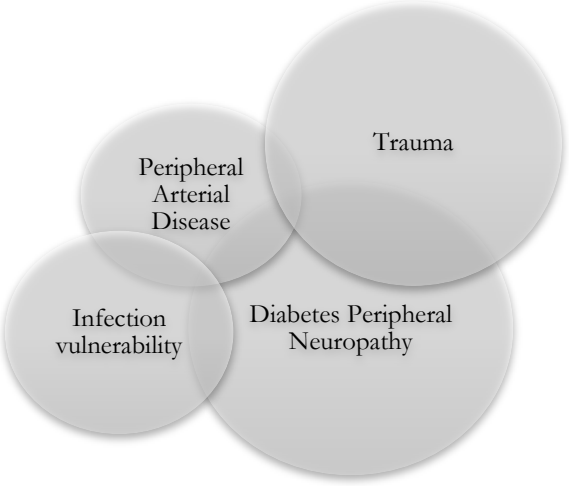

Figure 1. Main factors responsible for DFU development and maintenance

DIABETIC PERIPHERAL NEUROPATHY (DPN)

Peripheral neuropathy is highly prevalent in individuals with DM, and leads to signs and symptoms of motor, autonomic and sensory neuropathy components [1,5-7,9,10]. It is estimated that 70 to 80% of individuals with DM present alterations in their motor nerve conduction velocity or in their electromyography results, even in early stages of DM [5]. Many mechanisms have been proposed to explain this susceptibility, namely nitric oxid blocking and the Maillard reaction [1].

The first mechanism corresponds to a cellular damage and consequent endothelial dysfunction due to maintained hyperglycaemia that inhibits nitric oxide production (a potent vasodilator) and disrupts the endothelium-regulated vascular function, also causing platelet aggregation, altered intimal growth, and inflammation and atherothrombosis processes. This microangiopathy, affecting the peripheral nerves supply, leads to DPN [1].

The second mechanism, the Maillard reaction, consists on an interaction between reducing sugars and amino groups of biomolecules that produce advanced glycation end-products, which, along with lipoproteins, have an important role in the pathogenesis of atherosclerosis [1,5].

Other discussed mechanism corresponds to an alternative metabolic route for the activated glycose in the presence of hyperglycaemia and insulin deficit that leads to sorbitol accumulation in the nervous system cells and polyols formation, which is linked to a neurologic dysfunction secondary to demyelination, axonal degeneration, Schwann cells' hyperplasia and hypertrophy and ganglionic deterioration in the autonomic system [5].

However, several other DM/ metabolic syndrome-related factors seem to be linked with DPN in addition to hyperglycaemia, such as insulin resistance, blood pressure and lipid profile, as well as autoimmune and genetic factors [5].

DPN has a great impact on the subjects' foot shape, biomechanics and sensation.

Motor neuropathy causes foot deformity and limited joint mobility, by affecting both intrinsic foot and leg muscles, which create points with abnormal foot pressure and hyperkeratotic areas [1,5,6,9,10].

Autonomic neuropathy corresponds to a damage of the sympathetic nervous system, causing arteriovenous shunting, leading to vasodilation of the foot small arteries [6], precapillary sphincter malfunction [7], endothelial dysfunction [10] and also alterations in the foot sweat regulation which can cause anhidrosis with dry skin and fissures [1,5-7,10].

Sensory neuropathy diminishes or even eliminates the deep sensation, namely the ability to feel the feet and toes' positions, as well as the superficial sensation, this is, the ability to feel pain (and so to perceive injury), pressure, temperature and proprioception [5,9]. The combination of high pressure points with undetected repetitive injuries causes local tissue damage, inflammation, tissue death and, at the end, DFU occurrence [1,5,8-10].

In addition, DPN may affect neuropeptides' production that are crucial to an adequate wound healing, as they stimulate cell chemotaxis, growth factor production and cells proliferation, as well as modulation of immune defence mechanisms, namely leukocyte infiltration [1].

It is important to emphasize that, despite the potential loss of protective sensation, neuropathic pain is characterized by one or more of the following symptoms that greatly decrease the patients' quality of life: burning, stabbing, shooting, stinging, hyperesthesia and allodynia [1].

PERIPHERAL ARTERIAL AND VASCULAR DISEASE

Ischemic feet present a very fragile skin, which means that a little amount of friction and trauma can lead to skin breakdown [1]. On the other hand, the lack of oxygen and nutrients can lead to cutaneous necrosis [5]. Once there is a solution of continuity, infection may settle and, along with a poor blood supply, a severe DFU can occur. In that way, it was reported that ischemia is present in up to 90% of the individuals with DM that require a major LEA [1].

PAD is linked to dyslipidemia, insulin resistance, hyperglycaemia, arterial hypertension, collagen glycosylation and coagulation mechanism modifications leading to the atherogenic process. This atherosclerosis most frequently settles in the femoral, popliteal and tibial arteries [5].

Although PAD is a macrovascular diabetes-related complication, microvascular dysfunction is also commonly and concomitantly present. This condition also decreases perfusion in the foot of individuals with DM by inducing arteriovenous shunting, precapillary sphincter failure, microvascular

sclerosis, capillary leakage, venous pooling, low oxygen transcutaneous pressure, alterations in hormonal activity as well as the inflammatory process in the vessels [1,5,7,10].

There are 3 main factors that can explain these alterations: endothelial and smooth muscle cell dysfunction and nerve-axon reflex [6].

It is also frequent to find both PAD and DPN in the same subject. For that reason it is usual to examine subjects with DM and severe PAD that do not present severe rest pain or claudication. Thus, several authors have discussed the role of genetic factors in the diabetic foot complications occurrence [3] and the presence of reduced expression of endothelial nitric oxide synthase both in DPN and PAD [6].

TRAUMA

In most cases an internal or an external trauma is the major precipitant factor for the DFU development. DPN or PAD usually do not directly lead to DFU.

As described before, motor neuropathy causes biomechanical modifications in the foot that, together with sweat alterations, lead to the high pressure points and the formation of hyperkeratosis, which increases local pressure even more, which is sustained due to loss of the protective sensation [1,5,6,8,10]. This is described as internal trauma and usually occurs in the toes and plantar surface of the foot [6]. Hyperkeratotic areas, when not removed and without pressure relief techniques, injure the surrounding tissues, create a blister and/or haemorrhage that can evolve to a DFU [1,5,6,8,10].

The most frequent causes of external trauma are ill-fitting shoes that result in a low but continuous increase in the foot pressure, and direct trauma (mechanical, chemical or thermic) [1,5].

INFECTION VULNERABILITY

In subjects with diabetes there is a susceptibility to infection, due to altered leukocyte and immune functions (characterized by defects on leukocyte chemotaxis, low phagocytosis and bactericidal capacity, impaired cell migration, elevated matrix metalloproteinases, etc.), and decrease in host resistance, leading to a loss of the human innate barrier. It is therefore common to find fungal infections in the skin and nails of individuals with diabetes. This is also associated to a higher risk of bacterial infections [1].

As above explained, a handful of clinical factors are the main responsible for DFU development, even if very complex and intertwined mechanisms are also the reason behind DFU chronicity and consequent LEA. Throughout this Thesis it will be emphasized the identification of common pathways for both outcomes (See Figure 2). Individual predictive factors will be discussed in detail in chapters 4.1 and 5.1.

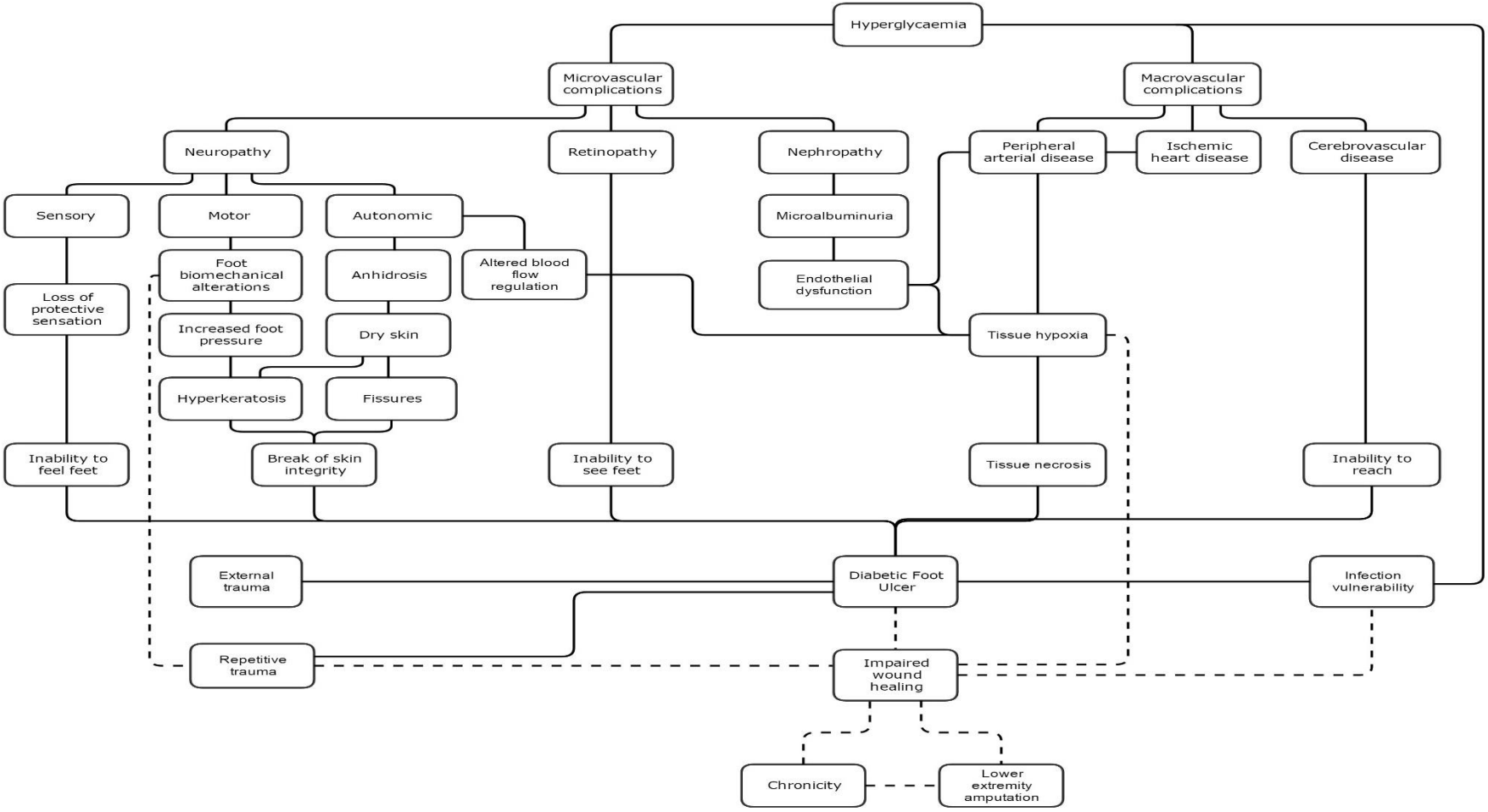

Figure 2. Diabetic foot ulcer development and maintenance and lower extremity amputation main pathways

In full lines the pathways to diabetic foot ulcer development (DFU) and in dashed lines to DFU chronicity and lower extremity amputation (LEA). As one can observe, individual or a combination of several pathways can be involved in DFU development, chronicity and consequent LEA.

REFERENCES

1. Alavi A, Sibbald RG, Mayer D, et al. Diabetic foot ulcers: Part I. Pathophysiology and prevention. J Am Acad Dermatol 2014;70:1.e-18.
2. Leese GP, Reid F, McAlpine R, et al. Stratification of foot ulcer risk in patients with diabetes: a population-based study. Int J Clin Pract 2006;60:541-5.
3. Apelqvist J. Diagnostics and treatment of the diabetic foot. Endocrine 2012;41:384-97.
4. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev 2016;32 Suppl 1:2-6.
5. Castro G, Liceaga G, Arrioja A, et al. Guía clínica basada en evidencia para el manejo del pie diabético. Medicina Interna de México 2009;25:483-526.
6. Dinh TL, Veves A. A review of the mechanisms implicated in the pathogenesis of the diabetic foot. The international journal of lower extremity wounds 2005;4:154-9.
7. Lepantalo M, Apelqvist J, Setacci C, et al. Chapter V: Diabetic foot. European journal of vascular and endovascular surgery : the official journal of the European Society for Vascular Surgery 2011;42 Suppl 2:S60-74.
8. Barshes NR, Sigireddi M, Wrobel JS, et al. The system of care for the diabetic foot: objectives, outcomes, and opportunities. Diabet Foot Ankle 2013;4:1-12.
9. Schaper NC, Van Netten JJ, Apelqvist J, Lipsky BA, Bakker K, International Working Group on the Diabetic Foot (IWGDF). Prevention and management of foot problems in diabetes: a Summary Guidance for Daily Practice 2015, based on the IWGDF Guidance Documents. Diabetes Metab Res Rev 2016;32:7-15.
10. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45:1-66.

3.4 DIABETIC FOOT RECOMMENDATIONS AND QUALITY OF CARE

RECOMMENDATIONS

An effort has been made by many societies throughout the years to improve the diabetic foot care quality by publishing guidelines on that topic, namely the American Diabetes Association (ADA) [1-3], American College of Foot and Ankle Surgeons [4], American Orthopaedic Foot and Ankle Society (AOFAS) [5], Infectious Diseases Society of America (IDSA) [6], International Working Group on Diabetic Foot (IWGDF), National Institute for Health and Care Excellence (NICE) [7], SIGN [8] and Wound Healing Society (WHS) [9].

The IWGDF has a special role in the creation of the most important guidelines in this area, through the International Consensus on the Diabetic Foot [10]. This group was created in 1996, in Malvern, and in 2000 became a Consultative Section of the International Diabetes Federation (IDF) [10].

Due to the level of dissemination of these guidelines around the world, the quality of the methods used and the present partnership with the major DM and global health institutes [ADA, European Association for the Study of Diabetes (EASD) and World Health Organization (WHO)], we have decided to focus and describe the recommendations published by this group.

The first guidelines published by this group, in 1999, addressed recommendations for the management and prevention of the diabetic foot [10] and were translated into 26 languages, with a distribution of more than 100,000 copies worldwide [11].

In this document it was stressed that an adequate foot complications' prevention should be grounded on 5 key elements [10]:

1. *Identification of the at-risk foot*
   An annual evaluation should be performed to identify signs or symptoms of foot deformity, DPN, PAD, previous DFU or LEA, and subjects should be assigned to one of four risk categories (0 – no DPN, 1 - DPN, 2 – DPN with PAD and/or foot deformity, 3 – DPN and history of DFU or LEA).
2. *Regular inspection and examination of the at-risk foot*
   Foot examination should be conducted annually in those patients categorized as grade 0, every 6 months for those as grade 1, 3 to 6 months for those as grade 2 and every 1-3 months for those as grade 3. Such examination should include clinical background characterization, foot and footwear examination.
3. *Education of patient, family and healthcare providers*
   Patients and their caregivers should be educated about foot care in a structured and repeated way in order to increase their foot care knowledge, awareness, self-care behaviours and motivation. Tools must be provided to allow them to identify potential foot problems and act accordingly.

4. *Routine wearing of appropriate footwear*

   People with diabetes should be encouraged to use adequate footwear in what concerns type and size. Patients with DPN should have access to appropriate footwear without economic limitations.

5. *Treatment of pre-ulcerative signs*

   When any pre-ulcerative sign is observed, it should be treated until full resolution. This includes: removing abundant callus; protecting blisters, or draining them if necessary; treating ingrown or thickened nails; and, prescribing antifungal treatment for fungal infections.

Diabetic foot care management should provide resources and staffing to educate the people with DM and respective caregivers, perform annual foot examination, apply measures to prevent DFU development, provide adequate DFU treatment, conduct regular audits and be divided into 3 level institutions [10]:

Level 1: General practitioner, podiatrist, and diabetic nurse;
Level 2: Diabetologist, surgeon (general, orthopaedic, or foot), vascular surgeon, endovascular interventionist, podiatrist and diabetic nurse, in collaboration with a shoe-maker, orthotist or prosthetist; and
Level 3: A level 2 foot centre that is specialized in diabetic foot care, with multiple experts from several disciplines working together, each specialised in this area, and that acts as a tertiary reference centre.

In Portugal, the National Health System published, since 2001, 3 normative documents with recommendations for adequate diabetic foot care. These documents are based on the previously described IWGDF recommendations and emphasise the same 5 key elements and 3 levels of diabetic foot care management [12-14]. In 2010, for the first time, quality evaluation and surveillance indicators for diabetic foot care were presented [13]. At this moment, a new and more complete normative is being conducted for the DFU prevention and treatment. The Candidate is a member of this normative Scientific Committee.

The IWGDF recommendations have started to be based on expert opinion (representatives of more than 100 countries around the world and from the majority of disciplines involved in diabetic foot care), due to a lack of scientific evidence. From 2007 on they are based on systematic reviews of the literature [11].

Since the first document, they have been updated 4 times (2003, 2007, 2011, 2015). The most recent IWGDF recommendations have been launched in May 2015, and were developed in association with ADA, EASD and WHO [11]. The document has been officially endorsed by the IDF [11]. The organization decided to change the name from guidelines to guidance and recommendations documents. They were based in systematic reviews of the literature and used the Grading of Recommendations Assessment Development and Evaluation (GRADE) system. This system allows the formulation of recommendation having in consideration both the available evidence quality level (based on risk of bias, effect size and expert opinion), as well as its strength (based on the quality of evidence, balance between benefits and harms, patient values and preferences and costs) [15].

More than 80 000 articles were reviewed by 5 working groups composed by 149 specialists and corresponding members [16]. The guidance documents focused on 5 topics:

1. Prevention of foot ulcers in at-risk patients with diabetes,
2. Footwear and offloading to prevent and heal foot ulcers in diabetes,

3. Diagnosis, prognosis and management of peripheral artery disease in patients with foot ulcers in diabetes,
4. Diagnosis and management of foot infections in persons with diabetes, and
5. Interventions to enhance healing of chronic ulcers of the foot in diabetes.

This section will give emphasis to the first topic as it is more directly linked with this Thesis theme and the Candidate was a member of the respective working group.

The guidance document on the prevention of foot ulcers [17,18] focused only on at-risk patients with diabetes, this is, those without an active DFU but with DPN, with or without foot deformity or PAD, or previous DFU or LEA. Three groups of interventions were defined and a systematic review was conducted separately:

1. Care: included improvements in care, namely podiatry, chiropody, multidisciplinary and integrated care, screening techniques and interventions to promote health care professionals knowledge,
2. Self-management: comprised interventions used to increase patients' self-management, namely patient education, foot home monitoring and lifestyle interventions, and
3. Medical: addressed interventions conducted in hospital context (for example surgery and therapeutic footwear).

For the first group of interventions, 3061 articles were identified, for the second were 2641, and the third were 2973. An additional 556 trials were retrieved using a trial registries search. In the end, 74 studies were included for qualitative analysis, but only 30 were controlled (19 randomized and 11 non-randomized) [18]. The risk of bias was scored as very low (n=3), low (n=11) or high (n=17), according to the SIGN guidelines [18].

At the end of this process 13 recommendations were presented separately for outcomes of first DFU, first/recurrent DFU, and recurrent DFU [17].

Although foot screening to identify a person with diabetes at risk of DFU is considered as paramount, no study was found assessing its impact on DFU prevention, as well as identifying the recommended periodicity, or the best signs or symptoms to screen for.

Experts strongly recommended that an annual feet examination should be conducted in all people with DM to look for signs or symptoms of DPN and PAD (*Recommendation 1*). In those with DPN, experts strongly recommended to screen also for history of previous DFU or LEA, PAD, foot deformity, pre-ulcerative signs, poor foot hygiene and inadequate footwear (*Recommendation 2*).

In the presence of pre-ulcerative signs it was strongly advised to treat them, including callus, blisters, ingrown or thickened nails, haemorrhage and fungal infections (*Recommendation 3*). However, its effectiveness has been never directly evaluated.

It was highly recommended that to protect their feet, the at-risk patient with DM should not walk barefoot, in socks, or in thin-soled standard slippers at home or outside (*Recommendation 4*), although, no evidence was found on this topic.

Again, no evidence was retrieved, but experts considered that instruction for patients to daily inspect their feet and inside their shoes, wash their feet, avoid chemical agents or plasters to remove callus, use emollients to lubricate dry skin and cut toe nails straight across could likely help prevent DFU (*Recommendation 5*).

Regarding footwear, it was strongly recommended, based on few RCT with high risk of bias, that subjects should wear properly fitting footwear and, when a foot deformity or a pre-ulcerative sign is present, therapeutic shoes, custom-made insoles or toe orthosis prescription should be considered (*Recommendation 6*).

Conversely, with a moderate level of evidence, experts strongly recommended that therapeutic footwear, with demonstrated effective plantar pressure relief, should be prescribed and patients encouraged to wear them in order to prevent recurrent plantar DFU (*Recommendation 7*).

Although it was proved that those patients who follow the advice given in education programmes are at lower risk of developing a first DFU, no evidence was found on the actual impact on DFU risk of foot self-care education. Thus, experts advised, with weak strength, that education should be provided aiming to improve foot care knowledge and behaviour, and patient adherence encouraged (*Recommendation 8*).

For the DFU recurrence prevention, the value of integrated foot care, consisting minimally on professional foot care, patient education and footwear provision was assessed in a few articles. Experts strongly recommended that it should be delivered to patients at risk and repeated or re-evaluated once every one to three months (*Recommendation 9*).

The other topic, in addition to footwear, that was classified has having a moderate level of evidence, was the impact of home monitoring foot skin temperature in DFU development and recurrence prevention. However, it was a weak recommendation as this technique may represent a daily burden to the patients and false-positive outcomes may unnecessarily stress patients. In addition, for now, cost-effectiveness was not evaluated. The idea behind this is for patients to monitor foot skin temperatures at home to identify early signs of inflammation and resolve with the care provider its cause (*Recommendation 10*).

Digital flexor tenotomy should be considered to prevent a toe DFU in case of conservative treatment failure in patients with foot deformity and pre-DFU sign or an active DFU (*Recommendation 11*). This is a weak recommendation based on low quality evidence, namely retrospective case series.

Based on few RCTs, but with the same strength and level of evidence that the previous recommendation, experts recommended that Achilles tendon lengthening, joint arthroplasty, metatarsal head resection or osteotomy should be considered when conservative treatment has failed in patients with an active DFU (*Recommendation 12*).

Due to a lack of adequately conducted studies and the existence of several non-surgical interventions, the use of nerve decompression to prevent DFU was not recommended (*Recommendation 13*).

While conducting the systematic review and building the guidance document, experts found some key controversies. For example, although DPN is considered one of the most important risk factors for DFU development, research on its prevention or treatment is very limited.

The screening topic, on whom, how, when and with which periodicity subjects should be re-evaluated, has a great lack of solid data. The authors consider that it is crucial to better define the patients that will benefit most from preventive interventions.

There is also a great lack of cost and cost-effectiveness studies for all the interventions included in the guidance document.

More controlled trials adequately describing the integrated foot care approach provided are necessary as well as studies assessing the development, evaluation and implementation of methods to improve patients' adherence to diabetic foot care.

QUALITY OF CARE: THE EURODIALE CONSORTIUM

The Eurodiale consortium was created in 1999 and included health professionals from 14 centres located in 10 European countries: Belgium, Czech Republic, Denmark, Germany, Italy, Slovenia, Spain, Sweden, Netherlands and United Kingdom [19].

They aimed to conduct a multicentre prospective observational study to 1) characterize the patients and respective DFU, 2) describe the current clinical outcomes and 3) identify the respective predictive factors, 4) understand the differences in management strategies among centres, 5) current resource use and associated costs, as well as 6) factors related to low health-related quality of life in subjects with DFU. Such analysis resulted in the publication of one dissertation [20] and 12 articles [19,21-31].

The group has designed the study in a way to allow data collection during daily clinical practice and recruited a cohort as much unselected as possible to allow the best characterization of the "normal" European patient with a DFU [23]. That we know of, there are no more studies auditing the diabetic foot care quality in Europe.

Patients' inclusion and data collection

They have consecutively included subjects with an active DFU presenting for the first time within a 12 months period in any of the above mentioned diabetic foot centres from September 1st 2003 to October 1st 2004, both inpatients as outpatients. Participants were excluded if their life expectancy was inferior to 12 months, were not willing or able to return to the clinic at least once a month or to give informed consent [19].

Follow-up visits were conducted every 4 weeks until healing, major LEA or for a maximum of 1 year [19].

A total of 80 items were collected at baseline, using a standardized entry case-report form (CRF), by the multidisciplinary members that were previously trained and audited, describing individual and disease-specific factors that could influence management strategies and outcome [19]. Health related quality of life (HR-QoL) was assessed at the first and last visits by the application of the EuroQoL quality of life questionnaire (EQ-5d) [19].

Sample characterization

A total of 1232 subjects were included in the study, with a mean number of included patients by centre of 88 (range 40-125). The majority of the cases were referred by general practitioners or were self-referrals (63%) [19].

At the moment of entry in the study, subjects' mean age was 65 years, 64% were men, 70% had DM for more than 10 years, 32% presented a comorbidity and 27% were hospitalized [19]. So, the characteristic participants were elderly male with global poor health status and dependent of others for their daily activities. Almost one third of the subjects presented a disabling comorbidity such as severe visual impairment, heart failure or angina, ESRD or poor mobility [21].

A total of 144 subjects were lost to follow up due to non-compliance (n=24), impossibility to follow the patient (n=25) or care transferred to other specialists (n=29) or other indeterminate reasons (n=66) [26]. At baseline, these subjects were marginally older with more frequent history of heart failure and deeper DFU of longer duration [26].

PAD was diagnosed in 49% of the individuals, being possibly underestimated due to falsely high ankle-brachial index (ABI) values, and DPN in 86%. Additionally, the majority of DFU were infected (58%). Infection was more frequent in subjects with PAD [23].

DFU were more commonly located at the toes (55%), affecting tissue below the subcutis (45%), between 1 and 5 cm^2 (52%) and between 1 week and 3 months of duration (57%) [23].

Healing prediction: independent variables and risk score

After 1 year of follow-up, 77% of the participants had their DFU healed (with or without minor LEA), 12% were still under treatment, 5% had a major LEA and 6% died [26]. The majority of the subjects had a (neuro-)ischemic DFU (55%) [24].

It was found that individuals with both PAD and infection had more frequently deep and non-plantar DFU. Higher age and the presence of comorbidities were also associated with more severe DFUs [23]. Moreover, patients with PAD presented higher rates of major LEA and mortality [26].

So, in their next article, the group analysed if the prognostic predictors differed among patients with and without PAD. The potential predictive factors were selected through a literature review, expert opinion and suitability for clinical practice collection [26].

The variables associated with low healing probabilities were older age, male sex, larger DFU, heart failure, inability to stand or walk without help, ESRD, DPN and PAD. In those patients with PAD, DPN was not associated with poorer outcome, and an interaction with infection was observed. In fact, those with PAD and infection had a distinctly higher risk of major LEA, when compared to those with PAD or infection alone [26].

The Eurodiale consortium has also derived a risk-scoring rule for the prediction of non-healing DFU as, after 1 year of follow-up, 23% of the subjects remained with unhealed DFU [20]. Such rule was derived and internally validated by using a random bootstrap samples (with replacement) technique.

Such model consisted on a sum of:

- 2 points for each decade of life,
- 5 points if the subject was of the male gender,
- 7 points for a DFU between 1 and 5cm^2 or 12 points if larger than 5cm^2,
- 4 points for history of heart failure,
- 6 points for inability to stand or walk without help,

- 8 points for ESRD,
- 3 points for DPN and
- 5 points for PAD.

This score presented an area under the receiver operating characteristic curve (AUC) of 0.72 [95% CI 0.69-0.75) and, a cut-off of 30 points presented a sensitivity of 63%, specificity of 72%, positive predictive value (PPV) of 40% and negative predictive value (NPV) of 87% [20].

To understand the impact of DFU location on the chance of healing, an analysis was made including the 1000 patients for which information concerning the specific location of the ulcer was available [22]. The authors observed that subjects with digital DFU were older and that these ulcers were smaller and of shorter duration. DFUs located at the heel were the largest, and occurred in a higher number of patients that were unable to stand or walk without help. Plantar DFUs were smaller than non-plantar, less frequently infected, and present in patients that less frequently suffered from diabetes-related comorbidities [22].

In fact, DFU location had an important impact on outcome. Heel ulcers took more time to heal, in median, and had a lower number of healed DFUs, when compared to those located at the toe or midfoot. This difference was maintained even in the multivariate Cox regression analysis. In addition, subjects with heel DFUs also presented higher mortality [22].

In the same way, non-plantar DFU also took longer and were less likely to heal, when compared to plantar, but such difference was not observed in the multivariate analysis [22].

Differences in management strategies

When comparing the clinical outcomes among the different centres it was observed that the rate of observed healing (including those that underwent minor LEA) varied between 66 and 86%, non-healing from 4 to 19%, major LEA from 0 to 13% and death from 3 to 19%, after 1 year of follow-up. The authors reported that these variation could not be explained just by participants' characteristics differences. For example, it was observed that the centres with better outcomes used significantly more revascularization and surgical procedures [20].

As the group has defined healing including those subjects that underwent minor LEA (meaning, those occurring below and excluding the ankle level) they have decided to assess differences in minor LEA rate and their determinants in the included European countries [30].

After the 1 year follow up, minor LEA was conducted in 18% (n=194) of the participants: 55% toe, 34% ray and 11% midfoot amputations. The risk factors associated with its occurrence, in the univariate analysis, were: male gender, increased depth and size, longer existing, and infected DFU, foot oedema and PAD. Using logistic regression for multivariate analysis, the identified independently associated variables were: male gender, DFU depth, infection and PAD [30].

This score was transformed into a rule by calculating a disease severity score, for each patient, based on the size of the logistic regression coefficients. It is calculated as follows:

- 18 points if deep ulcer
- 6 points if PAD
- 5 points if infected DFU
- 2 points if male.

The AUC of this rule was of 0.77 (95% CI 0.75-0.79) for the prediction of minor LEA.

Rates of minor LEA occurrence varied from 2.4 up to 34%, showing a marked difference. However, the mean subjects' disease severity score also varied greatly. A strong correlation was found between these 2 scores [30].

For all this, one of the articles [24] aimed to determine the patient-related factors and barriers influencing diabetic foot management strategies. Multivariable models were created to identify which participants' characteristics predicted the use of total contact casting (TCC) or alternative casting techniques in those with plantar fore- or mid-foot DFU and the use of vascular imaging techniques in those with severe limb ischemia, non-healing DFU after 1 year of follow-up or undergoing major LEA.

Also, for all episodes that subjects with a neuropathic plantar forefoot DFU were not treated with casting techniques and those with severe limb ischemia that did not underwent angiography/revascularization, the respective CRFs were checked and reasons for not following the current consensus documents were obtained [24].

The group observed that more than one quarter of the subjects (27%) had been treated for more than 3 months in another institution before being referred to the participating diabetic foot clinic, varying from 6 to 55% between centres. Most commonly these subjects were being treated in primary care institutions (44%); in 35% of the cases a general practitioner and in 12% a chiropodist/podiatrist was involved in the DFU care [24].

Although 41% of the subjects were already treated with offloading at baseline, only in 56% the treating physician considered it to be adequately relieving the pressure at the DFU site. So, inadequate or inexistent offloading was observed in 77% of the included subjects, independently of the DFU duration [24].

During follow-up, 35% of the participants were treated with some kind of offloading technique, varying from 0 to 68% between countries and centres [24].

Male gender, DFU size and employed status was independently associated with TCC application in subjects with forefoot or midfoot DFU [24].

The reported reasons for underusing casting were: reimbursement policies, lack of qualified staff, acceptance by healthcare professionals and by patients [24].

In what concerns vascular investigation, at baseline, it had been conducted in 53% of the subjects with (neuro-) ischemic DFU with a duration superior to 3 months. This percentage was significantly lower in those subjects previously treated in primary care centres [24].

During follow-up 98% of the subjects with PAD underwent functional vascular assessment, through transcutaneous oxygen pressure, ankle and/or toe pressure, and 41% vascular imaging, by duplex, conventional angiography and/or magnetic resonance angiography. The last percentage varied from 14 to 86% between countries and centres [24].

Vascular imaging was conducted only in 40% of the individuals with chronic DFU that did not heal after 1 year of follow-up or that undergone major LEA. The predictors for vascular imaging in these subjects and in those with severe limb ischemia were presence of infection and rest pain [24].

Reported reasons for the underuse of vascular procedures were the presence of a non-functional leg, spontaneous DFU healing, very poor health status of the patient and professional beliefs [24].

Resource utilization and costs associated with DFU treatment

In 2008, the group reported on resource utilization and costs associated with DFU treatment. For such analysis they have stratified patients by their disease severity according to the Texas University classification (TUC) [25], and only included countries with, at least, 80 participants to guarantee data representativeness and reliability.

Unit costs, from the entry date up to the date of the final visit, for all kind of DFU care resources were retrieved, using a specific unit cost form, from 7 out of the 10 participating countries. These forms questioned about cost with diagnostic and interventional procedures, off-loading, antibiotic therapy, hospitalisation, management by clinical specialists, topical treatment and indirect costs (related to loss of production) [25].

According to the TUC classification, the costs associated with treating a DFU ranged from 4.514€ for the group A (no infection or PAD) up to 16.835€ for the group D (with both infection and PAD) [25].

The most common diagnostic test used was microbiology, while for offloading techniques were temporary footwear and orthopaedic shoes. Costs associated with hospitalization were the highest use of financial resources in all outcome groups. The highest total costs were observed in the subjects who had undergone major LEA (25.222€) and lower in those with healed DFU (7.722€) [25], highlighting the importance of prevention.

Health-related quality of life in subjects with DFU

Regarding the HR-QoL, no information was obtained in 84 subjects and some EQ-5D domains were missing in another 60 subjects. These patients presented no differences when compared to the 1088 that completed the questionnaire [28].

Overall, participants reported a low HR-QoL, with frequent report of mobility limitation (68%), moderate or severe pain/discomfort (85%), some degree of anxiety/depression (41%) but only 29% referred self-care problems [28].

Inability to walk or stand without help was identified as the most important driver of HR-QoL, followed by DFU size, C-reactive protein (CRP) and severe PAD. Clinical factors associated with poor outcome (namely, infection, PAD and DPN) had a major impact only in the pain/discomfort domain [28].

DFU recurrence prediction

After this 1 year follow-up multicentre cohort study, one of the participants' medical centres decided to assess the risk factors for recurrence of DFU after healing during a 3 year follow-up period including the patients from the original Eurodiale study that had a healed DFU [31].

From the original 120 patients, 93 had their DFU healed but only 73 remained alive and accepted to participate in the study. Only 59 patients were regularly monitored for their foot status in the study foot clinic. Additionally, 14 subjects were followed at other local foot or surgical clinics. The same form, used in the Eurodiale study, was applied to collect data [31].

During follow-up, the majority of the patients' DFU recurred (58%). The recurrence was more common after the first year of follow-up (40%). There was no difference in DFU recurrence between the subjects monitored in the study foot clinic compared to those followed in the other clinics [31].

The identified independent predictors of DFU recurrence, through multivariate stepwise logistic regression, were plantar location, osteomyelitis, HbA1c superior to 7.5% and CRP superior to 5 mg/l. This model identified with 90.5% sensitivity and 55% specificity the predicted probability of DFU recurrence [31].

REFERENCES

1. Assocation AD. Consensus Development Conference on Diabetic Foot Wound Care: 7-8 April 1999, Boston, Massachusetts. American Diabetes Association. Diabetes Care 1999;22:1354-60.
2. American Diabetes Association. Preventive foot care in people with diabetes. American Diabetes Association. Foot & ankle international 2000;21:76-7.
3. Boulton AJ, Armstrong DG, Albert SF, et al. Comprehensive foot examination and risk assessment: a report of the task force of the foot care interest group of the American Diabetes Association, with endorsement by the American Association of Clinical Endocrinologists. Diabetes Care 2008;31:1679-85.
4. Frykberg RG, Zgonis T, Armstrong DG, et al. Diabetic foot disorders: a clinical practice guideline (2006 revision). J Foot Ankle Surg 2006;45:1-66.
5. Pinzur MS, Slovenkai MP, Trepman E, Shields NN. Guidelines for diabetic foot care: recommendations endorsed by the Diabetes Committee of the American Orthopaedic Foot and Ankle Society. Foot & ankle international 2005;26:113-9.
6. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 infectious diseases society of america clinical practice guideline for the diagnosis and treatment of diabetic foot infections. Journal of the American Podiatric Medical Association 2013;103:2-7.
7. NICE CfCPa. Diabetic Foot Problems: Inpatient Management of Diabetic Foot Problems. 2011.
8. Network SIG. SIGN 50: A guideline developers' handbook. SIGN publication 2001;50.
9. Braun L, Kim PJ, Margolis D, Peters EJ, Lavery LA. What's new in the literature: An update of new research since the original WHS diabetic foot ulcer guidelines in 2006. Wound Repair and Regeneration 2014;22:594-604.
10. Bakker K, Schaper NC. The development of global consensus guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev 2012;28 Suppl 1:116-8.
11. International Working Group on the Diabetic Foot (IWGDF). 2015.
12. Castanheira JL. Pé Diabético - Programa de Controlo da Diabetes Mellitus. In: Saúde DGd, ed.2001.
13. George F. Pé Diabético - Programa Nacional de Prevenção e Controlo da Diabetes. In: Saúde DGd, ed.2010.
14. F G. Organização de cuidados, prevenção e tratamento do Pé Diabético. In: Saúde DGd, ed.2011.
15. Guyatt GH, Oxman AD, Schunemann HJ, Tugwell P, Knottnerus A. GRADE guidelines: a new series of articles in the Journal of Clinical Epidemiology. Journal of clinical epidemiology 2011;64:380-2.
16. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev 2016;32 Suppl 1:2-6.
17. Bus SA, van Netten JJ, Lavery LA, et al. IWGDF guidance on the prevention of foot ulcers in at-risk patients with diabetes. Diabetes Metab Res Rev 2016;32 Suppl 1:16-24.
18. van Netten JJ, Price PE, Lavery LA, et al. Prevention of foot ulcers in the at-risk patient with diabetes: a systematic review. Diabetes Metab Res Rev 2016;32 Suppl 1:84-98.
19. Prompers L, Huijberts M, Apelqvist J, et al. Optimal organization of health care in diabetic foot disease: introduction to the Eurodiale study. The international journal of lower extremity wounds 2007;6:11-7.
20. Prompers L. Diabetic foot disease in European perspective: Results from the Eurodiale study. Maastricht: Universiteit Maastricht; 2008.
21. Akhtar S, Schaper N, Apelqvist J, Jude E. A review of the Eurodiale studies: what lessons for diabetic foot care? Current diabetes reports 2011;11:302-9.
22. Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC. Diabetic foot disease: impact of ulcer location on ulcer healing. Diabetes Metab Res Rev 2013;29:377-83.
23. Prompers L, Huijberts M, Apelqvist J, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50:18-25.

24. Prompers L, Huijberts M, Apelqvist J, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med 2008;25:700-7.
25. Prompers L, Huijberts M, Schaper N, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia 2008;51:1826-34.
26. Prompers L, Schaper N, Apelqvist J, et al. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51:747-55.
27. Schaper NC. Lessons from Eurodiale. Diabetes Metab Res Rev 2012;28 Suppl 1:21-6.
28. Siersma V, Thorsen H, Holstein PE, et al. Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. Diabet Med 2013;30:1382-7.
29. Siersma V, Thorsen H, Holstein PE, et al. Health-related quality of life predicts major amputation and death, but not healing, in people with diabetes presenting with foot ulcers: the Eurodiale study. Diabetes Care 2014;37:694-700.
30. van Battum P, Schaper N, Prompers L, et al. Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. Diabet Med 2011;28:199-205.
31. Dubsky M, Jirkovska A, Bem R, et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. International wound journal 2013;10:555-61.

CHAPTER 4: DIABETIC FOOT ULCER PREDICTION

4.1 RISK STRATIFICATION SYSTEMS FOR DIABETIC FOOT ULCERS: A SYSTEMATIC REVIEW

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ARTICLE

Risk stratification systems for diabetic foot ulcers: a systematic review

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Abstract
Aims/hypothesis Several risk stratification systems have been proposed for predicting development of diabetic foot ulcer. However, little has been published that assesses their similarities and disparities, diagnostic accuracy and evidence level. Consequently, we conducted a systematic review of the existing stratification systems.
Methods We searched the MEDLINE database for studies (published until April 2010) describing the creation and validation of risk stratification systems for prediction of diabetic foot ulcer development.
Results We included 13 studies describing or evaluating the following different risk degree stratification systems: University of Texas; International Working Group on Diabetic Foot; Scottish Intercollegiate Guideline Network (SIGN); American Diabetes Association; and Boyko and colleagues. We confirmed that five variables were included in almost all the systems: diabetic neuropathy, peripheral vascular disease, foot deformity, and previous foot ulcer and amputation. The number of variables included ranged from four to eight and the number of risk groups from two to six. Only four studies reported or allowed the calculation of diagnostic accuracy measures. The SIGN system showed some higher diagnostic accuracy values, particularly positive likelihood ratio, while predictive ability was confirmed through external validation only in the system of Boyko et al.
Conclusions/interpretation Foot ulcer risk stratification systems are a much needed tool for screening patients with diabetes. The core variables of various systems are very similar, but the number of included variables in each model and risk groups varied greatly. Overall, the quality of evidence for these systems is low, as little validation of their predictive ability has been done.

Keywords Clinical prediction rules · Diabetes · Diabetic foot · Diagnostic accuracy · Foot ulcer · Podiatry · Stratification systems · Systematic review

Abbreviations

ABI	Ankle–brachial index
AUC	Area under the receiver operating characteristic curve
IWGDF	International Working Group on Diabetic Foot
PVD	Peripheral vascular disease
ROC	Receiver operating characteristic curve
STARD	Standards for the Reporting of Diagnostic Accuracy Studies
SIGN	Scottish Intercollegiate Guideline Network
STROBE	Strengthening of the Reporting of Observational Studies in Epidemiology

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SWM	Semmes–Weinstein monofilament
UTFRS	University of Texas Foot Risk Stratification
VPT	Vibration perception threshold

Introduction

Diabetes mellitus is one of the most frequent metabolic disorders [1, 2], achieving an epidemic magnitude [2], of nearly 3% prevalence worldwide [3], with an expected increment to more than 4% in 2030 [3, 4]. This significant rise combined with insufficient healthcare resources will make it increasingly necessary to further improve prevention and treatment of diabetic foot complications [5].

In diabetic populations, amputations are 15 [3, 6] to 40 [1] times more frequent than in persons without diabetes. Foot ulcer is the major predisposing factor for non-traumatic foot amputations [4], preceding about 85% of them [4, 7]. Furthermore, after a lower limb amputation the risk of additional amputations is 50% in 5 years; the mortality rate is about 70% [8].

It has been reported that an effective evidence-based prevention programme (with early detection and control of independent risk factors for foot ulceration), patient and carer education, foot ulcer treatment by a multidisciplinary team and periodic surveillance can diminish the amputation rate by 49% to 85% [9]. Hence, various studies have concluded that amputation is always more expensive than its prevention [10]. Therefore, it is crucial to define a standardised and efficient approach to prevention of foot ulceration and consequently amputation [2]. The first step should be the correct identification of degree of risk for foot ulceration in all patients [11–13].

At present, numerous stratification systems using different methods have been proposed for this purpose [9, 14], but there are few validation studies [15], leading to the problem of how to select the best system for widespread implementation. Our aim was to conduct a systematic review of the existing risk stratification systems for the development of diabetic foot ulcer in order to compare them with regard to selection of variables, development of prediction model, diagnostic accuracy measures, validation and generalisability. Additionally we aimed to better understand the potential for this decision tool to impact clinical care.

Methods

To conduct this systematic review, we carried out a sensitive search in MEDLINE database (PubMed) for studies that were published up to 15 April 2010 and analysed diabetic foot ulcer risk stratification systems. The query used is shown in Fig. 1.

This search retrieved 2,275 studies. These were considered further if they met the following selection criteria: (1) publication date up to and including 15 April 2010; (2) published in the following languages: English, French, Italian, Spanish or Portuguese; (3) type of study: reviews, randomised controlled trials or cohort, case–control and cross-sectional studies; (4) studies that described the creation of or evaluated diabetic foot ulcer risk degree stratification systems; and (5) results that described the creation or modification (by the same group) and/or evaluated the effectiveness of one or several diabetic foot ulcer risk degree stratification systems.

Initially, articles were masked as to the identities of the authors, institutions and journals, and then selected by assessing their pertinence on the basis of titles and abstracts (when available) by two investigators (M. Monteiro-Soares, J. Ribeiro), who worked independently and were blinded to each other's assessments. In this phase the most common cause for exclusion was an article's theme.

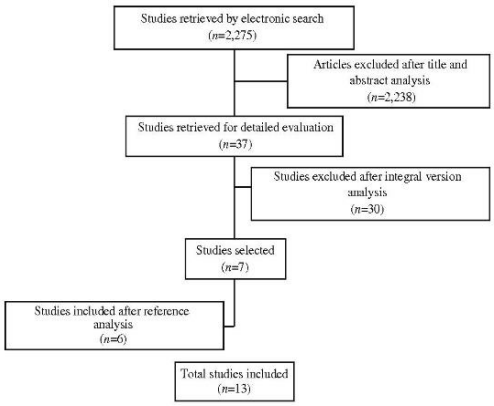

Fig. 1 Systematic review: flow diagram of article selection process. Studies were retrieved using the following query: ("Diabetic Foot/blood"[Mesh] OR "Diabetic Foot/classification"[Mesh] OR "Diabetic Foot/complications"[Mesh] OR "Diabetic Foot/diagnosis"[Mesh] OR "Diabetic Foot/epidemiology"[Mesh] OR "Diabetic Foot/etiology"[Mesh] OR "Diabetic Foot/mortality"[Mesh] OR "Diabetic Foot/pathology"[Mesh] OR "Diabetic Foot/physiopathology"[Mesh] OR "Diabetic Foot/prevention and control"[Mesh] OR "Diabetic Foot/radiography"[Mesh] OR "Diabetic Foot/radionuclide imaging"[Mesh] OR "Diabetic Foot/surgery"[Mesh] OR "Diabetic Foot/ultrasonography"[Mesh] OR "Diabetic Foot/urine"[Mesh] OR (diabetes AND ulcer AND lesion)) AND ((predict*[tiab] OR predictive value of tests [mh] OR scor*[tiab] OR observ*[tiab] OR observer variation[mh]) OR (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]) OR (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading: noexp]) OR (cohort OR case-control OR prospective OR "risk factor" OR screening))

In a second phase, the previously chosen articles (n=37) were examined in their entirety (with the respective reference list) and selected for inclusion for this review by the same two investigators who had performed the initial review, again acting independently and blinded. As in every stage, divergence was resolved by the decision of a third investigator (I. Ribeiro). At the end of this stage, seven articles were included in this systematic review.

Finally, after analysing the reference list of all the selected articles and relevant reviews that had been excluded, new articles were found. These were subjected to the first and second phases, and included or excluded from the study. This procedure was repeated until no new article was found through the reference list analysis, resulting in the inclusion of six more articles. In conclusion, 13 studies were included in this review (Fig. 1).

The review of title and/or abstract led to disagreements between the two reviewers in 36 cases, making for 98% inter-observer agreement and a kappa value of 0.61. The same occurred in the selection of papers reviewed in their entirety, where the two reviewers disagreed on the inclusion of four studies for 95% inter-observer agreement and a kappa value of 0.9.

Once article selection was completed, the following data were collected from each article using a checklist created for this review: (1) article identification: title, author(s), publication date, journal; (2) outcome definition; (3) methods: study design, setting, period(s) of data collection, inclusion and exclusion criteria, sources and methods of participant selection, sample size, clinical factors analysed, diagnostic tests analysed, potential bias; (4) results: study participant characteristics, outcome prevalence, method of statistical analysis, risk categorisation diagnostic accuracy measures; and (5) quality assessment. The articles' quality was assessed (by M. Monteiro-Soares) through the number of items fulfilled in the corresponding checklist, selected according to type of study, i.e. the Strengthening of the Reporting of Observational Studies in Epidemiology [STROBE] checklist for observational studies and the Standards for the Reporting of Diagnostic Accuracy Studies [STARD] checklist for diagnostic accuracy studies) [16, 17]. Both checklists have multiple components per item, which caused difficulties in scoring. We therefore stipulated that total completion of an item should score 1 point, partial completion 1/2 point and null completion 0 points.

Results

Foot ulcer risk stratification systems identified

We retrieved five stratification systems, discussed in 13 papers (Table 1): (1) University of Texas Foot Risk Stratification (UTFRS, n=1) [18]; (2) International Working Group on Diabetic Foot (IWGDF, n=4) [9, 14, 19, 20]; (3) Scottish Intercollegiate Guideline Network (SIGN) Risk Assessment (n=2) [6, 21]; (4) American Diabetes Association (ADA, n=4) [11, 12, 22, 23]; and (5) Boyko et al. model (n=2) [24, 25].

Examining Table 2, which lists the variables included in each stratification system, we observed that the majority had identical core variables, namely: diabetic neuropathy, peripheral vascular disease (PVD), foot deformity, previous ulcer and previous lower extremity amputation. On the other hand, data collection procedures differed greatly between studies for diagnosis of diabetic neuropathy and PVD.

The number of variables included varied from four [18] to eight [21] and the number of risk groups varied from two in the original ADA system [22, 23] to six in the IWGDF system modified by Lavery et al. [20] (Table 3).

The Leese et al. study had the biggest sample size [21], while the Boyko et al. study [24] had the longest follow-up (Table 1).

It was only possible to analyse or calculate diagnostic accuracy measures (sensitivity, specificity, predictive values) in three studies [18, 21, 25] (Table 4). In the studies where diagnostic accuracy measures or crude data were not displayed, they were calculated by or requested from the authors [18, 20, 24], respectively. Unfortunately, it was not possible to obtain these data. In the Boyko and colleagues study [24], only the area under the receiver operating characteristic curve (AUC) and cut-off values were available, which did not allow direct comparison with the effectiveness of other stratification systems.

Using the STROBE checklist, the Peters et al., Boyko et al. and Monteiro-Soares et al. studies had the best scores (all with 18 points out of 22) [19, 24, 25]. For studies where diagnostic accuracy measures were reported the STARD checklist was also applied. The Leese et al. and Boyko et al. studies had 15 items, while Monteiro-Soares et al. had 20 (out of 25) [21, 24, 25].

Only with the SIGN system was reliability assessed through the kappa value for inter-observer agreement calculation [21]. No validity testing of the ADA system has ever been performed, while the SIGN and UTFRS systems have been validated once [18, 21]. The IWGDF system suffered modifications twice and its validation was performed accordingly [19, 20]. The Boyko et al. system was the only one externally validated [24, 25]. Conversely, the IWGDF was the only group that applied worldwide dissemination techniques (manuals and CD distribution, website creation and others) for the system described in Apelqvist et al. articles [9, 14].

Table 1 Stratification systems: characterisation and classification of studies

Study [ref.]	Stratification	Creation method	Step	Sample size (*n*)	Mean follow-up (months)	Ulcer prevalence (%)	STROBE score
Lavery et al. [18]	UTRFS	Logistic regression model	Derivation	225	Cross-sectional	34	13
Apelqvist et al. [9]	IWGDF	International consensus	Description	NA	NA	NA	NA
Peters et al. [19]	IWGDF	International consensus	Modification proposal, evaluation	213	30	25	18
Lavery et al. [20]	IWGDF	International consensus	Modification proposal, evaluation	1,666	27	15	12
Apelqvist et al. [14]	IWGDF	International consensus	Description	NA	NA	NA	NA
SIGN [6]	SIGN	Literature review	Description	NA	NA	NA	NA
Leese et al. [21]	SIGN	Literature review	Modification proposal, evaluation	3,526	20	5	15[a]
Mayfield et al. [22]	ADA	Literature review	Description	NA	NA	NA	NA
Mayfield et al. [23]	ADA	Literature review	Description	NA	NA	NA	NA
Boulton et al. [11]	ADA	Literature review	Modification proposal	NA	NA	NA	NA
Boulton et al. [12]	ADA	Literature review	Modification proposal	NA	NA	NA	NA
Boyko et al. [24]	Boyko	Logistic regression model	Derivation	1,285	40	17	18[a]
Monteiro-Soares et al. [25]	Boyko	Logistic regression model	External validation, optimisation proposal	360	25	26	18[b]

For the construction of this table, studies were ordered by stratification system (through their creation date) and within each one chronologically by publication date

[a] With STARD checklist 15 points;

[b] With STARD checklist 20 points

NA, not applicable

Foot ulcer risk stratification systems: data synthesis

The UTFRS system This system was described for the first and only time in 1998, by Lavery and colleagues, in a cross-sectional case–control study that enrolled 213 participants with diabetes: 76 cases with an existing or recently healed (<4 weeks) foot ulcer and 149 (controls) without active or previous foot ulcer. This study was performed in the setting with the highest foot ulcer prevalence (34%) [18].

First, the association between foot ulceration and several variables was evaluated through univariate analysis. Next, they analysed the cumulative risk associated with the significant variables more frequently available in daily practice: diabetic neuropathy, foot deformity and ulcer or lower extremity amputation history. This resulted in the stratification system presented in Table 3 (very similar to that proposed in 2000 by the IWGDF). For each added variable the cumulative risk increased. For category 1 the OR for foot ulceration was 1.7 (95% CI 0.7–4.3), for category 2 it was 12.1 (95% CI 5.2–28.3) and for category 3 it was 36.4 (95% CI 16.1–82.3) in comparison with category 0 (reference category) [18]. Despite the use of logistic regression, no score for a risk group calculation was created.

A vibration perception threshold (VPT) >25 V, using a biothesiometer, indicated diabetic neuropathy. No foot ulcer definition was provided.

It was not possible to calculate any diagnostic accuracy measures due to a lack of cross-tabulation with the number of cases and controls in each risk stratification group; it was also not possible to retrieve these data from the article's first author.

The IWGDF system This stratification system was created through consensus involving 45 expert clinicians and researchers from 23 countries [9, 19]. Although there is an 8 year interval between them, both papers by Apelqvist and colleagues [9, 14] are very similar. They recommend use of the 10 g Semmes–Weinstein monofilament (SWM),

Table 2 Variables included in the diverse stratification systems

Stratification	Variables										
	DN	PVD	Foot deformity	Previous ulcer	Previous amputation	Visual impairment	Physical impairment	Callus	HbA_{1c}	Tinea pedis	Onychomycosis
UTFRS	O		O	O	O						
IWGDF	O/R	O/R	O/R	O/R	O/R						
SIGN	O/R	O/R	O/R	O/R	O/R	O/R	O/R	O/R			
ADA	O/R	O/R	O/R	O/R	O/R						
Boyko et al.	O/R			O/R	O/R	O/R			O/R	O/R	O/R

DN, diabetic neuropathy; O, present in the original stratification; R, present in the revised stratification

tuning fork and/or cotton wisp for detection of diabetic neuropathy [9, 14]. However, to our knowledge, no study has analysed the cotton wisp's diagnostic ability. Moreover, use of three tests simultaneously or alone presents different accuracy values.

This stratification system has never been validated in its original form for the prediction of foot ulcer development. In 2001, its effectiveness was evaluated, but by this time small modifications had been effected [19]. In a prospective cohort study with 213 participants followed for a mean period of 30 months, this stratification system (Table 1) was evaluated for prediction of diabetic foot ulceration, i.e. skin lesions distal to the ankle [19].

With the stratification system, there was a statistically significant increase in frequency of ulceration and amputation ($p<0.001$, χ^2 test) in the higher risk groups. Individuals in group 3 (higher risk) were 34.1 (95% CI 11.0–105.8) times more prone to foot ulcer occurrence during the follow-up period [19]. Although these results indicate good effectiveness, no diagnostic accuracy measures were reported, although it would have been possible to calculate them (Table 4).

Diabetic neuropathy was defined as one or more insensitive sites to the 10 g SWM or a VPT >25 V. An ankle–brachial index (ABI) inferior to 0.8 or any non-palpable pedal pulsation was defined as PVD [19]. The biothesiometer is not commonly available due to its cost. However, the authors stressed that a 128 Hz tuning fork can be used as an alternative, alleging good correlation, based on a single study [19].

Peters and colleagues proposed a subdivision in group 3, separating patients with history of foot ulceration from those with history of lower-extremity amputation [19]. In 2008, Lavery and colleagues included this modification in the stratification system and also proposed a subdivision for group 2 (Table 3). This prospective cohort study included 1666 consecutive participants followed for an average of 27 months [20]. An increase in the group risk was associated with more foot ulcerations ($p<0.001$, χ^2 test for association and trend) and more complications were observed in group 2B than in 2A ($p<0.001$). This did not occur when comparing group 1 with 2A or group 3A with 3B [20]. No diagnostic accuracy measures were presented in the paper and due to a lack of data, it was impossible to determine them.

Foot ulcer was defined as a full-thickness wound involving the foot or ankle. Diabetic neuropathy was assessed using the 10 g SWM and the biothesiometer [20]. Although the authors did not describe how the diagnosis was established in this paper, they referred to another article where details of the diagnosis are given [26]. One non-palpable foot pulse combined with an ABI inferior to 0.8 indicated PVD [20].

The SIGN system This stratification system was created at the same time as that from the IWGDF through an evidence-based systematic review performed by a multidisciplinary group (Table 3) [6].

It has never been validated in its originally conceived form. In 2006, Leese and colleagues validated it with slight modifications in a prospective cohort study in a community setting (foot ulcer prevalence of 5%). In sum, individuals with no risk factors were considered at low risk of foot ulcer occurrence; those with one risk factor were at moderate risk; and individuals with two or more risk factors or with foot ulcer history were at high risk [21].

In this study, diabetic neuropathy was detected through the 10 g SWM. Inability to feel the monofilament on more than one of ten pre-defined sites was ranked as altered sensation. This study was the only one in this review to assess inter-observer agreement of a stratification system in 50 participants by two healthcare professionals, resulting in a kappa value of 0.95. The main quality of this stratification system is to identify individuals at very low risk of developing a foot ulcer. Thus patients in the low-risk group had a 99.6% probability of not developing a foot ulcer during follow-up [21].

The ADA system This system was created through a literature review. Initially, some variables were recognised

Table 3 Foot ulcer risk stratification system risk group description

UTRFS		IWGDF						SIGN				ADA			
Lavery et al. [18]		Apelqvist et al. [9, 14]		Peters et al. [19]		Lavery et al. [20]		SIGN [6]		Leese et al. [21]		Mayfield et al. [22, 23]		Boulton et al. [11, 12]	
RG	Definition	RG	Definition	RG	Definition	RG	Definition	RG	Definition	RG	Definition	RG	Definition	RG	Definition
0	Without DN	0	Without DN	0	Without DN	0	Without DN or PVD	Low	No PVD, previous FU or FD and no VI	Low	No PVD, no DN, no FD, no PI and no VI	Low	No risk of FU	0	No risk of foot ulcer
1	DN	1	DN	1	DN but without FD or PVD	1	DN but without FD or PVD							1	DN and/or FD
2	DN and FD	2	DN and/or FD or PVD; and/or history of FU or LEA	2	DN and with FD or PVD	2A	DN and FD, no PVD	Medium	DN or PVD or significant VI or PI	Medium	DN or PVD or FD or VI or PI			2	PVD and/or DN
						2B	PVD								
3	DN and FD and history of LEA	3	History of FU or LEA	3	History of FU or LEA	3A	History of foot ulcer	High	History of FU (due to DN/PVD) or previous LEA or PVD and DN or callus with risk factor (DN, PVD, FD)	High	History of FU or LEA or PVD and DN or one of above, with callus or deformity	High	DN, altered biomechanics, evidence of increased pressure, FD, PVD, history of FU or LEA and/or severe nail pathology	3	History of FU or LEA
						3B	LEA								

In this table, the Boyko et al. system was not included due to the fact that patient's risk group attribution depends on a score calculation with multiple possible variable combinations and not in a static number of risk factors being present

DN, diabetic neuropathy; FD, foot deformity; FU, foot ulcer; LEA, lower extremity amputation; PI, physical impairment; RG, risk group; SIGN, SIGN risk assessment; VI, visual impairment

Table 4 Diagnostic accuracy measures for each foot ulcer risk stratification system

Stratification system	Measures						
	Risk group	Sensitivity (95% CI)	Specificity (95% CI)	LR+ (95% CI)	LR− (95% CI)	PPV (95% CI)	Accuracy (95% CI)
UTRFS [18]		NP	NP	NP	NP	NP	NP
IWGDF: Apelqvist et al. [9]		NA	NA	NA	NA	NA	NA
IWGDF: Peters et al. [19]	3	74 (62–86)	86 (81–92)	5.35 (3.52–8.14)	0.30 (0.19–0.47)	64 (58–70)	83 (78–88)
IWGDF: Peters et al. [19]	3+2	87 (78–96)	58 (51–66)	2.10 (1.70–2.59)	0.22 (0.11–0.45)	NA	66 (59–72)
IWGDF: Lavery et al. [20]		NP	NP	NP	NP	NP	NP
IWGDF: Apelqvist et al. [14]		NA	NA	NA	NA	NA	NA
SIGN [6]		NA	NA	NA	NA	NA	NA
SIGN: Leese et al. [21]	High risk	84 (79–90)	90 (89–91)	8.41 (7.45–9.49)	0.17 (0.12–0.25)	31 (29–33)	90 (89–91)
SIGN: Leese et al. [21]	High+moderate risk	95 (92–98)	67 (65–68)	2.87 (2.70–3.04)	0.07 (0.04–0.14)	NA	68 (67–70)
ADA [11, 12, 22, 23]		NA	NA	NA	NA	NA	NA
Boyko et al. [24]	ROC	NP	NP	NP	NP	NP	81
Monteiro-Soares et al. [25]	Highest risk	61 (51–70)	87 (83–91)	4.7 (3.33–6.76)	0.45 (0.35–058)	62 (57–67)	80 (76–84)
Monteiro-Soares et al. [25]	Highest+next-to-highest risk	84 (75–90)	70 (65–75)	2.83 (2.34–3.47)	0.23 (0.14–0.36)	NA	74 (69–79)
Monteiro-Soares et al. [25]	Highest+next-to-highest+next-to-lowest risk	95 (88–98)	50 (44–56)	1.88 (1.65–2.13)	0.10 (0.05–0.25)	NA	61 (56–66)
Monteiro-Soares et al. [25]	ROC	NA	NA	NA	NA	NA	83 (78–88)

LR−, negative likelihood ratio; LR+, positive likelihood ratio; NA, not applicable; NP, not possible to calculate with the available data; PPV, positive predictive value

as related to foot ulcer development (namely diabetic neuropathy, PVD, foot deformity, and foot ulcer or amputation history) and anyone presenting with any of these conditions was considered to be at high risk [22, 23]. In 2008, a modification was proposed. Using the same variables, Boulton and colleagues, proposed a stratification system that graded by estimated cumulative risk [11, 12] (Table 3).

Diabetic neuropathy screening was recommended using the 10 g SWM and one of the following other tests: 128 Hz tuning fork, pinprick sensation, ankle reflex or VPT. An abnormal result in one or more tests suggested loss of protective sensation. Absence of the posterior tibial and/or dorsalis pedis pulses indicated PVD [11, 12].

This stratification system has been described in four articles. However, the two articles by Mayfield et al. [22, 23] are identical, as are the two by Boulton and colleagues [11, 12]. None of the ADA stratification systems were validated for prediction of ulcer development [19].

The Boyko et al. system This stratification system was developed in a study that prospectively followed 1285 veterans (98% men) over more than 3 years, with re-evaluations at 12 to 18 months, with a view to evaluating the 'individual and combined effects of commonly available clinical information in the prediction of diabetic foot ulcer occurrence' [24]. Several available and pertinent variables were assessed at baseline. Using a Cox proportional hazards regression model, the association between baseline variables and foot ulcer occurrence was evaluated through univariate and multivariate analysis, resulting in the following risk score equation, where a one (1) was inserted when the characteristic in parentheses was present: score=HbA_{1c}×0.0975+0.7101×(diabetic neuropathy)+0.3888×(poor vision)−0.3206×(tinea pedis)+0.4579×(onychomycosis)+0.7784×(history of foot ulcer)+0.943×(history of lower limb amputation) [24].

According to the resultant score, participants were stratified into the following risk groups: (1) lowest risk (score<1.48); (2) next-to-lowest risk (score 1.48 to ≤1.99);

(3) next-to-highest risk (score 2.00 to ≤2.61); and (4) highest risk (score≥2.62).

This was the only study that included HbA_{1c} as a predictive variable and assessed the stratification system's ability to predict foot ulcer occurrence through a receiver operating curve (ROC) at 1 and 5 years from the start of follow-up, resulting in AUCs of 0.81 and 0.76 respectively [24].

Analysing the ROC curve at 1 year, it can be seen that a specificity of 86% corresponded to a sensitivity of 60%, while 80% sensitivity corresponded to 60% specificity [24]. However, it was not possible to calculate any other diagnostic accuracy measures for the different groups or the AUC confidence intervals, due to lack of data.

Foot ulcer was defined as a full-thickness skin defect that needed more than 14 days to heal. Diabetic neuropathy was diagnosed by applying a 10 g SWM to nine sites in each foot. Insensitivity in one or more sites indicated altered sensation. In this stratification system, PVD was not included [24].

The Boyko et al. stratification system, as originally proposed, was externally validated in a 2010 retrospective cohort study including 360 participants [25]. They were followed for 25 months (mean) and 26% developed an ulcer (using the same definition as in the study of Boyko et al. [24]). Inability to feel the 10 g SWM at one or more of eight points (four in each foot) was considered to indicate diabetic neuropathy [25].

In univariate analysis, six of the seven variables included in the Boyko model were also significantly associated with foot ulcer development in the external validation study [25]. Tinea pedis, as in the Boyko et al. study [24], showed a statistically significant association only in multivariate analysis [25]. Diagnostic accuracy measures were described, and the resulting AUC and respective confidence intervals (AUC 0.83; 95% CI 0.78–0.88) [25] included the value reported by Boyko and colleagues [24] (Table 4). Additionally, an increase in the group risk was associated with a higher risk of foot ulcer development ($p<0.001$ χ^2 test for association and trend). This study also demonstrated that the model proposed by Boyko et al., which had been originally developed in a predominantly male population, was equally accurate in both sexes; it also reported that including a variable referring to footwear could improve this model's accuracy, although not to a statistically significant degree (AUC 0.88, 95% CI 0.84–0.91) [25].

Discussion

Stratification systems are an essential tool for classifying patients according to a cumulative risk of foot ulcer development and consequently allowing the limited existing medical care resources to be distributed to those at most need [4, 18, 21]. Doing so may diminish the unreasonably high level of foot-related morbidity [11, 12]. However, no system has been unanimously adopted [4] and their implementation in clinical practice is scarce [21]. Consequently we felt the necessity to perform a systematic review in order to understand whether and how these systems could facilitate clinicians' and researchers' choice when it comes to future implementation and development.

Overall, we retrieved five stratification systems, but it was only possible to determine the effectiveness of three of them through diagnostic accuracy measures [19, 21, 25].

The UTRFS stratification system derivation study [18] is a cross-sectional case–control study and therefore has a very low evidence level and some possible bias. We believe that having as an outcome the presence of or recently healed ulcer (without definition) could introduce selection as well as information bias, due to the absence of blinding to presence of the condition. In addition, there are concerns about adequacy of sample size (taking in consideration the reported appropriated number of subjects for each predictive variable's detection) [27]. This study assessed, in univariate analysis, the association between 27 different variables and ulceration in a sample of 213 participants [18].

We reviewed four articles related to the IWGDF stratification system, two describing it [9, 14] and two evaluating its effectiveness [19, 20]. However, each study presents modifications (without reported statistical justification), suggesting that this stratification scheme is still under development. In addition, only one study allowed the calculation of diagnostic accuracy measures and ulcer definition, and diagnosis of diabetic neuropathy and of PVD was somewhat different in each study. As with the UTFRS system, the use of ABI and the biothesiometer is somewhat difficult in daily practice due to its cost and/or need of trained professionals. In the study by Peters et al. [19], patients with a diabetic foot ulcer that directly led to amputation were excluded in order to reduce selection bias, since these patients had a priori a higher risk of amputation.

The SIGN stratification system was validated in a prospective cohort of 3,526 participants in a community setting [21]. It is based on eight easy to use and inexpensive measurements and has great value in detecting patients who will not develop a foot ulcer. The ADA stratification system was never validated for foot ulcer development, only for amputations [19]. However, the variables included are the same as those in the IWGDF system.

The system derived by Boyko et al. [24], along with the UTFRS system [18], were created through multivariate regression modelling instead of literature review and/or consensus. The Boyko group, along with the SIGN group, sought to include only variables that are easy to collect and commonly available in daily clinical care.

The system of Boyko et al. was also the only one assigning a specific score to the presence of each variable associated with foot ulcer development, which allows an impact evaluation of each variable (vs a group of variables) on overall risk. Additionally, no other system has been externally validated using the same variables as the original study, or reported their results in terms of AUC, which is considered the best way to determine a model's discriminatory ability [28]. On the other hand, score calculation is somewhat complicated without the use of data processing (e.g. a personal digital assistant or personal computer), which may make implementation more difficult in daily practice.

The Boyko et al. study [24] was also the only one to include the time factor in their analysis, assessing the stratification system at 1 and 5 years. A limitation of the Boyko et al. study is that participants were mainly men. However, in the subsequent study by Monteiro-Soares et al. [25], the system had no statistical differences by sex in subgroup analysis of foot ulcer risk prediction. Limitations of this later study are its retrospective design and patient recruitment from a high-risk setting. Nevertheless, the Boyko et al. model was equally valid in both distinct contexts.

Comparison of the IWGDF stratification system [19] with that proposed by the SIGN group [21] shows that the latter presents a significantly higher positive likelihood ratio for prediction of foot ulcer development in the high- and moderate-risk groups, and significantly higher accuracy in the high-risk group. In the other diagnostic accuracy measures, no statistically significant difference occurred (Table 4). Comparing the Boyko et al. system [24], validated by Monteiro-Soares et al. [25], with that proposed by the IWGDF [19] revealed no statistical differences. However, comparison of it with the SIGN system [21] revealed that several measures are significantly inferior. Nevertheless, it should be noted that there was a difference in the number of groups and also that these results were retrieved from three different populations with varied foot ulcer prevalence (from 5% [21] to 34% [20]), context and participants characteristics.

These differences in foot ulcer prevalence and/or incidence across studies should be kept in mind when assessing the comparative value of different foot complication prediction systems. Prediction rules developed in persons at high risk such as those under the care of a foot specialist might have less value in lower risk patients receiving care in primary care or diabetes clinic settings.

Our systematic review has a number of strengths and weaknesses. One of the latter is that quality assessment, data analysis and extraction were performed by one reviewer only (M. Monteiro-Soares). Additionally, this reviewer was not blinded to authors or institutions for this phase of the review. Strengths include review of articles for fulfilment of inclusion criteria by two reviewers blinded to identity of authors and institutions, with a third serving as tie breaker.

Although a serious problem for diabetes patients and their healthcare providers, the best method for assessment of risk stratification is not immediately apparent and comparatively little research has been performed on this topic compared with other serious micro- and macrovascular complications of diabetes. The question of which system one should choose to apply to one's specific setting cannot, we believe, be answered clearly at present. This deficiency could be remedied with further testing of existing risk classification systems, with a view to assessing predictive ability overall and in well-defined patient subgroups. In addition, further expansion of such systems would be justified using other easy-to-measure characteristics that have been overlooked in existing research on this subject. Such research will require multi-centre collaboration based on a common protocol, much as is the case with research now being conducted on prediction of cardiovascular disease outcomes [29].

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

References

1. Fard AS, Esmaelzadeh M, Larijani B (2007) Assessment and treatment of diabetic foot ulcer. Int J Clin Pract 61:1931–1938
2. Khanolkar MP, Bain SC, Stephens JW (2008) The diabetic foot. Q J Med 101:685–695
3. Wild S, Roglic G, Green A, Sicree R, King H (2004) Global prevalence of diabetes: estimates for the year 2000 and projections for 2030. Diab Care 27:1047–1053
4. Frykberg RG, Zgnois T, Armstrong DG et al (2006) Diabetic foot disorders: a clinical practice guideline (2006 revision). J Foot Ankle Surg 45(Suppl 5):S1–S66
5. Leese G, Schofield C, McMurray B et al (2007) Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. Diab Care 30:2064–2069
6. [No authors listed] (2001) Scottish Intercollegiate Guideline Network (SIGN) Guideline 55: The management of Diabetes. Edinburgh. SIGN, Royal College of Physicians Edinburgh. Available from www.sign.ac.uk/guidelines/index.html, accessed 10 October 2008
7. Boulton AJ (2004) The diabetic foot: from art to science. The 18th Camillo Golgi Lecture. Diabetologia 47:1343–1353
8. Larsson J, Agardh CD, Apelqvist J, Stenström A (1998) Long-term prognosis after healed amputation in patients with diabetes. Clin Orthop Relat Res 350:149–158
9. Apelqvist J, Bakker K, van Houtum WH, for the International Working Group on Diabetic Foot et al (2000) International consensus and practical guidelines on the management and the prevention of the diabetic foot. Diabetes Metab Res Rev 16(Suppl 1):S84–S92

10. Boulton AJ, Meneses P, Ennis W (1999) Diabetic foot ulcers: a framework for prevention and care. Wound Repair Regen 7:7–16
11. Boulton AJ, Armstrong DG, Albert SF et al (2008) Comprehensive foot examination and risk assessment—a report of the Task Force of the Foot Care Interest Group of the American Diabetes Association with endorsement by the American Diabetes Association of Clinical Endocrinologists. Diab Care 31:1679–1685
12. Boulton AJ, Armstrong DG, Albert SF et al (2008) Comprehensive foot examination and risk assessment. Endocr Pract 14:576–583
13. Helfand AE, Hirt PR (1994) Caring for the diabetic: assessing the risk in the diabetic foot. N J Med 91:256–258
14. Apelqvist J, Bakker K, van Houtum WH, Schaper NC, International Working Group on the Diabetic Foot (IWGDF) Editorial Board (2008) Practical guidelines on the management and prevention of the diabetic foot—based upon the International Consensus on the Diabetic Foot (2007). Diabetes Metab Res Rev 24(Suppl 1):S18–S187
15. Bower VM, Hobbs M (2009) Validation of the basic foot screening checklist. A population screening tool for identifying foot ulcer risk in people with diabetes mellitus. J Am Podiatr Med Assoc 99:339–347
16. Vandenbrouke JP, von Elm E, Altman DG, STROBE initiative et al (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Ann Intern Med 147:W163–W194
17. Bossuyt PM, Reistma JB, Bruns DE et al (2003) The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. Ann Intern Med 138:W1–W12
18. Lavery LA, Armstrong DG, Vela SA, Quebedeaux TL, Fleischli JG (1998) Practical criteria for screening patients at high risk for diabetic foot ulceration. Arch Intern Med 158:157–162
19. Peters EJ, Lavery LA, International Working Group on the Diabetic Foot (2001) Effectiveness of the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diab Care 24:1442–1447
20. Lavery LA, Peters EJ, William JR, Murdoch DP, Hudson A, and International Working Group on the Diabetic Foot (2008) Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. Diab Care 31:154–156
21. Leese GP, Reed F, Green V et al (2006) Stratification of foot ulcer risk in patients with diabetes: a population based study. Int J Clin Pract 60:541–545
22. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pagach LM (2003) Preventive foot care in people with diabetes—American Diabetes Association. Diab Care 26(Suppl 1):S78–S79
23. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pagach LM, American Diabetes Association (2004) Preventive foot care in diabetes: American Diabetes Association. Diab Care 27(Suppl 1): S63–S64
24. Boyko EJ, Ahroni JH, Cohen V et al (2006) Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. Diab Care 29:1202–1207
25. Monteiro-Soares M, Dinis-Ribeiro M (2010) External validation and optimisation of a model for predicting foot ulcers in patients with diabetes. Diabetologia 53:1525–1533
26. Armstrong DG, Hussain SK, Middleton J et al (1998) Vibration perception threshold: are multiple sites of testing superior to single site testing on diabetic foot examination? Ostomy Wound Manage 44:70–74
27. Stiell IG, Wells GA (1999) Methodological standards for development of clinical decision rules in emergency medicine. Ann Emerg Med 33:437–447
28. Reynolds T (2001) Disease prediction models aim to guide medical decision making. Ann Intern Med 135:637–640
29. Bhatt DL, Eagle KA, Ohman M et al (2010) Comparative determinants of 4-year cardiovascular event rates in stable outpatients at risk of or with atherothrombosis. JAMA 304:E1–E8

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ERRATUM

Erratum to: Risk stratification systems for diabetic foot ulcers: a systematic review

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Erratum to: Diabetologia
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Unfortunately there was a mistake in Table 3 of this paper. The column containing the foot ulcer risk stratification system description for Apelqvist et al. should not have contained a third risk group or definition ('History of FU or LEA').

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4.2 PREDICTIVE FACTORS FOR DIABETIC FOOT ULCERATION: A SYSTEMATIC REVIEW

DIABETES/METABOLISM RESEARCH AND REVIEWS
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REVIEW ARTICLE

Predictive factors for diabetic foot ulceration: a systematic review

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Summary

Improving ability to predict and prevent diabetic foot ulceration is imperative because of the high personal and financial costs of this complication. We therefore conducted a systematic review in order to identify all studies of factors associated with DFU and assess whether available DFU risk stratification systems incorporate those factors of highest potential value.

We performed a search in PubMed for studies published through April 2011 that analysed the association between independent variables and DFU. Articles were selected by two investigators-independently and blind to each other. Divergences were solved by a third investigator.

A total of 71 studies were included that evaluated the association between diabetic foot ulceration and more than 100 independent variables. The variables most frequently assessed were age, gender, diabetes duration, BMI, HbA_{1c} and neuropathy. Diabetic foot ulceration prevalence varied greatly among studies. The majority of the identified variables were assessed by only two or fewer studies. Diabetic neuropathy, peripheral vascular disease, foot deformity and previous diabetic foot ulceration or lower extremity amputation – which are the most common variables included in risk stratification systems – were consistently associated with diabetic foot ulceration development.

Existing diabetic foot ulceration risk stratification systems often include variables shown repeatedly in the literature to be strongly predictive of this outcome. Improvement of these risk classification systems though is impaired because of deficiencies noted, including a great lack of standardization in outcome definition and variable selection and measurement. Copyright © 2012 John Wiley & Sons, Ltd.

Keywords diabetic foot; prediction; risk variables; systematic review

Abbreviations ABI, ankle-brachial index; BMI, body mass index; CDC, Centers for Disease Control; CONSORT, Consolidated Standards for Reporting Trials; DFU, diabetic foot ulcer; DN, diabetic neuropathy; HbA_{1c}, glycated haemoglobin; LE, lower extremity; MNCV, motor nerve conduction velocity; MTPJ, metatarsophalangeal joint; PPP, peak plantar pressure; PVD, peripheral vascular disease; RCT, randomized controlled trial; SR, systematic review; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; SWM, Semmes–Weinstein monofilament; VPT, vibration perception threshold

Introduction

Diabetes mellitus prevalence is rising constantly, having already achieved an epidemic level worldwide [1]. This rise in prevalence will also be expected to lead to an increasing number of persons who develop complications of this metabolic disorder unless effective preventive measures are instituted.

Diabetic foot ulceration is an event with a great impact in an individual's life that also represents a significant burden to the healthcare system and society [2].

Additionally, diabetic patients with a DFU history have increased risk of re-ulceration [3] and LE amputation as well as higher mortality [4]. Hence, its prevention is of major importance.

The first step to achieve the goal of DFU prevention should be the appropriate foot screening and risk stratification given that it allows a more effective allocation of the limited resources available for prevention and treatment of this complication [5]. However, although progress has been made on methods to predict persons at highest risk for DFU, current systems still would benefit from measures to improve the accuracy of classification [6].

We recently performed a study [7] with the main goal of identifying all the available DFU risk stratification systems. We observed that none has been based on an SR to choose the best predictive variables to include in such systems. Consequently, we have conducted this study in order to fill that gap. This SR has, therefore, two main goals: (i) to identify all the pertinent variables associated with DFU and subsequently (ii) to evaluate whether existing DFU risk stratification systems include the most pertinent variables and might potentially benefit from considering other variables for inclusion.

Material and methods

Search strategy and study selection

To conduct this SR, we performed a search in MEDLINE database (PubMed) for all studies ever published through April 2011 (including) that reported potential DFU predictive factors, using a query strategy described in Figure 1.

This search retrieved 2569 articles. They were included in the SR if they fulfilled the following selection criteria: (i) *Theme*: studies that evaluated the association between variables (clinical data or diagnostic tests results) and DFU; (ii) *Type of study*: RCT or cohort, case–control, cross-sectional or epidemiological studies; (iii) *Results*: studies must conclude if there is or is not a statistically significant relationship between independent variables and DFU; and (iv) published in the following *languages*: English, French, Italian, Spanish or Portuguese.

Initially, articles were selected by assessing their pertinence through their titles and abstracts (when available) by two investigators (MMS and JR), independent and blind to each other. In this phase, the majority of the exclusions were due to studies' theme, which included osteomyelitis, diabetic foot infection, DFU treatment, DN diagnosis and Charcot neuro-osteoarthropathy (CN). In a second phase, the previously chosen articles ($n = 160$) were examined in their entirety and selected by the two investigators separately and blinded to each other's decision. In this phase, the majority of the exclusions were due to the type of study and the impossibility to conclude if there was or was not a statistically significant relationship between variables and DFU through the reported results. At this stage, 61 articles were included. Finally, after analysing the reference list of all the selected articles and relevant reviews that were excluded, new articles were found. These were subjected to the first and second phases. This procedure was repeated until there was no new article found, which resulted in the inclusion of seven additional articles. Three additional articles, not detected

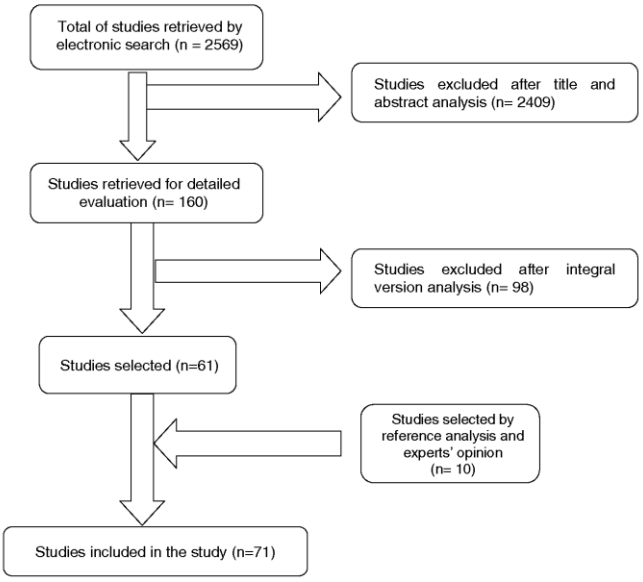

Figure 1. Flow diagram of articles selection process through the systematic review

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by our procedure, were included, taking into consideration the suggestions of the expert reviewers.

In every stage, divergence was solved by the decision of a third investigator (IR).

In conclusion, a total of 71 studies were included (Figure 1).

Data extraction

Once the article selection was completed, the following data were collected from each article: (i) *Article identification*: title, author(s) and publication date; (ii) *Methods*: study design, sources and methods of participants' selection, inclusion and exclusion criteria, sample size, period (s) of data collection, follow-up, setting, clinical factors and/or diagnostic tests analysed, and potential bias; (iii) *Outcome definition*; (iv) *Results*: study participants' characteristics, outcome's prevalence, method of statistical analysis, list of variables and degree of statistical significance in predicting the outcome's development (Tables 1–5).

Criterion for a statistically significant association between variables and DFU was defined as $p < 0.05$ or in studies in which the association was reported only through risk measures (relative risk, odds ratio or hazard ratio), a 95% confidence interval that did not include 1.

Quality assessment

One author (MMS) assessed article quality through the number of items that fulfilled the corresponding checklist according to the type of study (STROBE for observational studies [8] or CONSORT for RCT [9]). The STROBE checklist has several paragraphs in each item, which caused difficulties in scoring. Therefore, we stipulated that the total completion of an item scored 1 point, the partial completion scored ½ point and the null completion 0 point.

Studies were retrieved using the following query: ("Diabetic Foot/blood"[[Mesh] OR "Diabetic Foot/classification"[Mesh] OR "Diabetic Foot/complications"[Mesh] OR "Diabetic Foot/diagnosis"[Mesh] OR "Diabetic Foot/epidemiology"[Mesh] OR "Diabetic Foot/etiology"[Mesh] OR "Diabetic Foot/mortality"[Mesh] OR "Diabetic Foot/pathology"[Mesh] OR "Diabetic Foot/physiopathology"[Mesh] OR "Diabetic Foot/prevention and control"[Mesh] OR "Diabetic Foot/radiography"[Mesh] OR "Diabetic Foot/radionuclide imaging"[Mesh] OR "Diabetic Foot/surgery"[Mesh] OR "Diabetic Foot/ultrasonography"[Mesh] OR "Diabetic Foot/urine"[Mesh] OR (diabetes AND ulcer AND lesion)) AND ((predict*[tiab] OR predictive value of tests[mh] OR scor*[tiab] OR observ*[tiab] OR observer variation[mh]) OR (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH:noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]) OR (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic*[MeSH:noexp] OR diagnosis,differential[MeSH:noexp] OR diagnosis[Subheading:noexp]) OR (cohort OR case–control OR prospective OR "risk factor" OR screening))

Results

Study descriptions

From the 71 included studies, 24 studies evaluated the association of specific variables with DFU development [6,10–32] (Table 1), 14 studies with DFU recurrence or re-ulceration [2,33–45] (Table 2), 15 studies with active or recently healed DFU [46–60] (Table 3), 8 studies with active or past DFU history [61–68] (Table 4) and 10 studies with DFU history [69–78] (Table 5).

According with study category and reporting quality, 63 were observational, with a score in the STROBE checklist [8] varying from 7 [43] to 21 [29] (out of 22), and 8 were RCTs, with a score in the CONSORT checklist [9] varying from 13 [37] to 17 [33] (out of 22).

Predictive variables: data synthesis

Demographic factors (Table 6)

Age. Its association with DFU has been widely evaluated ($n = 42$), although results are somewhat contradictory. For the prediction of DFU development, only five [10,14,22,25,29] (out of 12) showed an association: Armstrong *et al.* [10], in an RCT, verified that younger patients were at higher risk, while four cohort studies [14,22,25,29] with consecutive patient selection concluded the opposite (older patients presented a higher risk). For the prediction of DFU recurrence or re-ulceration, only Gonzalez *et al.* [2] demonstrated an association (lower age associated with higher risk). Only two studies [53,58] found an association between age and active or recently healed DFU, with lower age representing higher risk. In opposition, two studies [61,65] concluded that for an active or past DFU history, a higher age represented a higher risk. Of the four studies [70,73–75] that reported an association between age and DFU history, only one concluded that those with more than 75 years had greater risk [73].

Gender. We identified 34 studies assessing gender's association with DFU. Only 10 found statistically significant associations: three cohort studies [14,16,20] for DFU development, one cohort study for DFU recurrence or re-ulceration [44], two cross-sectional [50,51] and two case–control [58,59] studies for active or recently healed DFU, one cross-sectional study for active or past DFU history [61] and one cross-sectional study for DFU history [78]. All reported an increased risk for the male gender.

Marital status or cohabiting. Only six studies evaluated its association with DFU. Abbott *et al.* [14] reported that

Table 1. Characterization and classification for the prediction of foot ulcer development according to type and quality of study

Study	Participants' characterization					Mean follow-up (months)	Setting	Outcome		Items present CONSORT or STROBE
	Sample size	Male gender (%)	Mean age (years)	Type 2 diabetes (%)	Diabetes duration (years)			Prevalence (%)	Definition	
Randomized controlled trials										
Armstrong *et al.* [10]	225	>95	>68	NR	>12	18	Veterans medical centre	8.4[a]	NR	17
Lavery *et al.* [11]	85	51	>55		>13	6	University centre	9.0[a]		15
Armstrong *et al.* [12]	70[b]	97	70		12	12	NR	5.7[a]		14
Prospective cohort studies										
Boyko *et al.* [13]	749 [c]	98	63	94	11	44	Veterans medical centre	11.0[a,c]	Full-thickness skin defect >14 days for healing	19.5
Abbott *et al.* [14]	6663	54	61	NR	9	24	Multicentre (general practitioners, diabetes centres, hospitals)	4.0[a]	Full-thickness skin break > Wagner 1 stage distal to malleoli	19
Williams *et al.* [15]	3474	52	64		9	49	Multicentre (primary care clinics)	8.4/1000 person-years	Break skin extending through dermis to deeper tissue distal to malleoli >30 days	18.5
Boyko *et al.* [6]	1285	98	62	95	>10	41	Veterans medical centre	17.0[a]	Full-thickness skin defect >14 days for healing	18
Monteiro-Soares *et al.* [16]	360	45	65	98	15	25	Hospital (DF clinic)	26.0[a]		
Kästenbauer *et al.* [17]	187	55	>57	NR	>10	43	Diabetes centre	5.0	Full-thickness skin lesion	
Ledoux *et al.* [18]	398 [c]	77	62		[e]	24	Multicentre (Veterans Health Care System and Group Health Cooperative)	3.5[a]	NR	17.5
Suico *et al.* [19]	253	19	60		10	12	General internal medicine practice	20.9[a]	Wounds ≥1.2 in the Seattle Wound Classification	15.5
Pham *et al.* [20]	248	51	58	80	14	30	Multicentre (foot centre, foot care clinic, university, college)	29.4[a]	NR	15
Armstrong *et al.* [21]	100	95	69	NR	14	8	NR	8.0[a]		
Abbott *et al.* [22]	1035	75	60	75	NR	12	Multicentre	7.2	Full-thickness skin lesion requiring hospital treatment	14.5
Lavery *et al.* [23]	1666	50	69	NR	11	24	Outpatient clinic	15.8[a]	NR	14
Caselli *et al.* [24]	248	46	>50	77	>8	30	Multicentre (foot centre, foot care clinic, university, college)	29.4[a]		
Monami *et al.* [25]	1945	43	64	NR	11	49	Diabetes centre	4.0[a]	ICD codes 707 or 440.23	13
Armstrong *et al.* [26]	1588	50	69		11	24	NR	NR	Full-thickness wounds	
Murray *et al.* [27]	63	68	>52	60	17	16	Multicentre (diabetes centre and DF clinic)	9.5[a]	Ulcer on plantar surface of foot not associated with external trauma[d]	

Table 1. (Continued)

Study	Participants' characterization					Mean follow-up (months)	Setting	Outcome		Items present CONSORT or STROBE
	Sample size	Male gender (%)	Mean age (years)	Type 2 diabetes (%)	Diabetes duration (years)			Prevalence (%)	Definition	
Chantelau *et al.* [28]	41	62	59	74	17	25	DF clinic	59.0[a]	NR	12
Retrospective cohort studies										
Margolis *et al.* [29]	125933	47	65	NR	NR	26	Multicentre (general medical practices)	2.1[a]	NR	21
Prospective case–control studies										
Carrington *et al.* [30]	169	65	>53	51	>18	72	Diabetes centre	37.3[a]	Full-thickness skin break	14
Calle-Pascual *et al.* [31]	318	45	68	NR	9	55	Outpatient clinic	10.0[a]	NR	13
McGill *et al.* [32]	472	73	59	94	>9	24	Diabetes centre	6.0[a]		12

DF, diabetic foot; NR, not reported.
[a]Not all patients were free of active, recently healed or past foot ulcer history.
[b]Only high risk population.
[c]Analysis of affected foot.
[d]Foot intrinsic ulcers (authors' term).
[e]Forty-four per cent of the subjects have more than 10 years of diabetes duration.

living alone represented a higher DFU development risk. On the other hand, for the prediction of an active or recently healed or DFU history, two cross-sectional studies found no association with being married [49,70] and one with being divorced [62]. Iversen *et al.* [73] observed no association between DFU history and being single or alone, while the CDC study [74] reported that those married or cohabiting were less likely to have a history of DFU.

Ethnicity. Only six studies assessed its association with DFU. Three studies [6,14,70] found no statistically significant difference in DFU development or history for Caucasian subjects in comparison with other ethnicities. Conversely, Frykberg *et al.* [61] reported that Caucasians presented a higher prevalence of active or past DFU history when compared with both Black and Hispanic subjects. Olmos *et al.* [48] (for the prediction of active or recently healed DFU) verified no difference between Caucasian and Black subjects, but Ndip *et al.* [54,55] verified for the same outcome a higher prevalence in Caucasian subjects in comparison with Black subjects. Abbott *et al.* [66] observed an extremely lower active or DFU history prevalence in Asians compared with Europeans or African Caribbean, and the CDC [74] observed higher DFU history prevalence in Caucasian subjects in comparison with Black subjects, but not with Hispanic subjects.

Education degree, cognitive function and social status. From the eight studies retrieved, none reported an association between education degree level and any of the outcomes [16,43,48,49,51,70,73,74]. Kloos *et al.* [40] found no association between cognitive function or social status and DFU recurrence or re-ulceration.

Others demographic factors. Only one study [49] evaluated the association between religion, living area, occupations and economic status with active or recently healed DFU, and no association was found.

Depression. One study [15] observed a higher risk of DFU development in those participants with depression and in those using anti-depressants. One study [2] verified an association between depression and DFU recurrence or re-ulceration, while the other [40] did not observe an association with depression diagnosis or anti-depressant use.

Physical impairment. Only one study [16] analysed its association with DFU development, reporting statistical significance only in univariate analysis.

Lifestyle and metabolic syndrome (Table 7)

Smoking habits. We retrieved 17 studies evaluating its association with DFU; however, only two studies presented statistically significant results showing a higher prevalence of active or past DFU history in current smokers [63,65].

Alcohol habits. Daily alcohol intake was significantly associated with DFU development in one study [17]. Regarding DFU recurrence or re-ulceration and active and recently healed DFU, respectively, no study found an

Table 2. Studies' characterization and classification for the prediction of foot ulcer recurrence or re-ulceration according to type and quality of study

Study	Participants' characterization					Mean follow-up (months)	Setting	Outcome		Items present CONSORT or STROBE
	Sample size	Male (%)	Mean age (years)	Type 2 diabetes (%)	Diabetes duration (years)			Prevalence (%)	Definition	
Randomized controlled trials										
Lincoln *et al.* [33]	172	67	NR	77	NR	12	Multicentre (DF clinics)	41.0	NR	19
Lavery *et al.* [34]	173	54	>64	95	>13	15	NR	22.5		17
Reiber *et al.* [35]	400	77	62	93	NR	24	Multicentre (Veterans Health Care System and Group Health Cooperative)	16.0	Cutaneous erosion ≥ dermis to deeper tissue or other cuts not healing within 30 days	16
Plank *et al.* [36]	91	75	>64	97	>14	13	Diabetic foot clinic	47.5	NR	14
Uccioli *et al.* [37]	69	62	>60	75	>17	12	Multicentre (two teaching hospitals)	43.0	Ulceration at same or ≠ site of previous ulcer or in contralateral foot	13
Prospective cohort studies										
Gonzalez *et al.* [2]	333	71	62	73	17	≈18	Diabetes centre	19.0	Full-thickness skin break distal to malleoli	18
Lemaster *et al.* [38]	400	77	62.5	NR	[a]	24	Multicentre (Veterans Health Care System and Group Health Cooperative)	15.5	Cutaneous erosion ≥ dermis to deeper tissue or other cuts not healing within 30 days	17.5
Dargis *et al.* [39]	145	48	>59	79	>14		Multicentre (outpatient clinics)	47.6	Ulcers at previous ulcer site	16
Kloos *et al.* [40]	56	70	65	100	16	12	Diabetes centre	48.0	NR	12.5
Busch *et al.* [41]	92	53	>62	91	>12	Up to 42	General practice-based diabetes clinic	40.0	Partial or complete disruption of the skin (Wagner 1–2)	11.5
Faglia *et al.* [42]	88	73	63	NR	17	78	Diabetic foot clinic	26.0	Ulceration at same or ≠ site of previous ulcer or in contralateral foot	10
Peters *et al.* [43]	81	77	>53	95	[b]	32		60.5	NR	7
Retrospective cohort studies										
Diouri *et al.* [44]	90	60	56	76	5	NR	Hospital	46.6	Ulcer development 30 days after cicatrization on same site or in contralateral limb	14
Cross-sectional case–control studies										
Chantelau *et al.* [45]	51	59	63	71	20	48	Diabetic foot clinic	67.0	NR	13

DF, diabetic foot; NR, not reported.
[a]Twelve per cent of the subjects have more than 25 years of diabetes duration.
[b]Sixty-seven per cent of the subjects have more than 10 years of diabetes duration.

Table 3. Characterization and classification for the prediction of active or recently healed foot ulcer according to type and quality of study

Study	Participants' characterization					Mean follow-up (months)	Setting	Outcome		Items present STROBE
	Sample size	Male (%)	Mean age (years)	Type 2 diabetes (%)	Diabetes duration (years)			Prevalence (%)	Definition	
Prospective cohort studies										
Litzelman *et al.*, [46]	352	19	61	NR	10	12	General medicine practice	18.0	Wounds ≥ 1.2 in Seattle Wound Classification	17
Litzelman *et al.* [47]										16
Retrospective case–control studies										
Olmos *et al.* [48]	199	46	>58	100	>12	12	Teaching hospital (diabetic clinic)	7.0	Wounds ≥ 1.2 in Seattle Wound Classification in the prior 12 months	13
Cross-sectional case–control studies										
Sriussadaporn *et al.* [49]	165	24	>57	100	>9	Cross-sectional	Hospital (diabetic clinic)	33.3	Skin full-thickness disruption below mid-calf with ≥1 of the following: >14 days, severe infection, necrosis or suggested MAC gangrene	16
Armstrong *et al.* [50]	219	46	>52	NR			Multicentre (diabetes institute and university)	32.0	NR[a]	15
Lavery *et al.* [51]	225	94	>52	47				34.0	NR	13
Armstrong *et al.* [52]	115	40	>51	>10	>10		NR	26.0		12
Sauseng *et al.* [53]	43	NR	>57	93	>14		NR	46.5		
Cross-sectional studies										
Ndip *et al.* [54]	326	61	>59	78	>19	Cross-sectional	Multicentre (diabetes centre and dialysis units)	11	NR	16
Ndip *et al.* [55]	466	53	60	87	20		Multicentre (dialysis therapy centres)	38	NR	15
Porcúncula *et al.* [56]	32	69	57,5	17	NR		Diabetes centre	56.3	NR	
González *et al.* [57]	198	47	>67	100	>12		Multicentre (teaching hospital and primary care centres)	44.9	Grades 1 and 2 of Wagner's classification	14
Armstrong *et al.* [58]	143	67	64	NR	>16		Diabetic foot centre	31.0	NR	
Tentolouris *et al.* [59]	379	56	>60	94	>10		NR	46.9		11.5
Tentolouris *et al.* [60]	90	51	>59	82	>8		Hospital (diabetes and foot clinics)	33.3		

MAC, medial arterial calcification; NR, not reported.
[a]Neuropathic ulcers

Table 4. Characterization and classification for the prediction of active or past foot ulcer history according to type and quality of study

Study	Participants' characterization					Mean follow-up (months)	Setting	Outcome		Items present STROBE
	Sample size	Male (%)	Mean age (years)	Type 2 diabetes (%)	Diabetes duration (years)			Prevalence (%)	Definition	
Cross-sectional case–control studies										
Frykberg *et al.* [61]	251	50	59	80	14	Cross-sectional	Multicentre (DF clinics)	39.4	NR	15.5
Bresäter *et al.* [62]	82	100	>69	NR	>8		Population based	34.0		14.5
de Sonaville *et al.* [63]	609	43	65		4		Multicentre (first level medical care offices)	14.0	(Pre) ulcer (Wagner stage ≥ 0) or if any level LEA	14
Jirkovská *et al.* [64]	322	NR	>66	93	13		Multicentre (Community diabetes clinics)	13.7	Wagner grades 1 to 4	
Guerrero-Romero *et al.* [65]	670	33	>55	100	>8		Multicentre (first level medical care offices)	16.4	NR	13.5
Cross-sectional studies										
Abbott *et al.* [66]	15646	54	>55	90	>5	Cross-sectional	Population based	5.1	Full-thickness skin break at least to Wagner 1	15.5
Miranda-Palma *et al.* [67]	93	56	NR	93	NR		Hospital	57.0	Complete break of skin distal to malleoli	14
Saltzman *et al.* [68]	92	NR	>49	74	>11			51.0	Nonlinear break ≥ dermal layer on foot plantar aspect	13

DF, diabetic foot; NR, not reported, LEA, lower extremity amputation.

Table 5. Characterization and classification for the prediction of foot ulcer history according to type and quality of study

Study	Participants' characterization					Mean follow-up (months)	Setting	Outcome		Items present STROBE
	Sample size	Male (%)	Mean age (years)	Type 2 diabetes (%)	Diabetes duration (years)			Prevalence (%)	Definition	
Retrospective case–control studies										
Bennett *et al.* [69]	77	70	>58	55	>15	12	Multicentre (hospitals)	35.0	NR	13
Cross-sectional case–control studies										
McNeely *et al.* [70]	368	97	>60	>13	>13	Cross-sectional	Veterans medical centre	12.5	Wounds ≥2 in the Seattle Wound Classification	17
Gullifford *et al.* [71]	2106	30	>60[a]	NR	>8[a]		Multicentre (health centres)	12.2	NR	14
Boulton *et al.* [72]	135	NR	>52		>10		Hospital	64.0	Open lesion present below the level of the malleolus	12
Cross-sectional studies										
Iversen *et al.* [73]	1494	51	66[a]	82	6[a]	Cross-sectional	Population based	10.4	Foot ulcer that required ≥3 weeks to heal	18
Control Disease Center [74]	NR	NR	NR	NR	NR			11.8	Sores or irritations on the feet that took >4 weeks to heal	17.5
Lott *et al.* [75]	38[b]	69	>63		15		Multicentre (diabetes centre and health system)	57.9	NR	16
Jayasinghe *et al.* [76]	94	34	>54		9		Multicentre (two teaching hospitals)	48.0	Slowly healing ulcers in tips or pulp of the toes, plantar aspect of the MTT heads or heals	14
Maluf *et al.* [77]	22	64	>55	73	>9		Multicentre (outpatient clinics and community health fairs)	50.0	Wagner grades 2 or higher	13
Papanas *et al.* [78]	109	59	>52	NR			Multicentre (hospital diabetes centre and outpatient department)	36.0	Break in the skin, >3 mm in diameter extending to all layers, attributable to neuropathy	12

MTT, metatarsal; NR, not reported.
[a]Median.
[b]Only patients with diabetic peripheral neuropathy.

Table 6. Strength of association between participants' characterization variables and foot ulceration: systematic review results summary

Variables	Outcomes								
	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Demographic factors										
Age (continuous)	+++	[14,22]	+++	[2]	+	[53,58]	+	[61,65]	+	[70,75]
	+	[10,25,29]			−	[50,48,49,54,56,57,59]			−	[69,71–73,77,78]
	−	[16–18,20,27,32]	−	[37,40,42–44]			−	[62–64]		
	−	[6]			−−	[58]			−−	[74]
Age (categorical in years)	NA		−− CO: 60	[43]	NA		+ CO: 60	[65]	++ CO: 75	[73]
									+ CO: 65	[74]
Gender	+++	[16,20]	+	[44]	+++	[51]	+	[61]	+	[78]
	+	[14]	−	[2,40,42,43]	+	[50,58,59]	−	[63,65]	−	[69–71,74,75,77]
	−	[18,20,27,29,30]			−	[48,49,54,56,57,60]			−−	[73]
Marital status	+	[14]	NA		−	[49]	−	[62]	+	[74]
									−	[70,73]
Ethnicity	−	[6,14]	NA		+	[54,55]	+	[61,66]	+	[74]
					−	[48]			−	[70]
Education degree	−	[16]	−	[43]	−	[48,49,51]	NA		−	[70,73,74]
Low social status	NA		−	[40]	NA		NA		NA	
Cognitive function	NA		−	[40]	NA		NA		NA	
Depression	+	[15]	+	[2]	NA		NA		NA	
Antidepressive use	+	[15]	NA		NA		NA		NA	
Depression diagnosis or antidepressive use	NA		−	[40]	NA		NA		NA	
Physical impairment	+	[16]	NA		NA		NA		NA	

CDC, Control Disease Center; CO, cut-off; DFU, diabetic foot ulcer; NA, not assessed; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; −−, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; −, variable with no statistically significant association with the outcome only in univariate analysis.

Table 7. Strength of association between lifestyle and metabolic syndrome variables and foot ulceration: systematic review results summary

	Outcomes									
	DFU development		Recurrence or re-ulceration		Active or recently healed DFU		Active or past DFU history		DFU history	
Variables		References		References		References		References		References
Smoking habits (continuous)		NA	–	[43]		NA		NA	–	[70]
Smoking habits (categorical)	–	[6,16,19,29]	–	[10,40,43]	–	[48,49,51,57,60]	+++	[63]	––	[73]
							+	[65]		
Alcohol habits (continuous)	+++	[17]		NA		NA		NA		NA
Alcohol habits (categorical)		NA	–	[40,43]	–	[49,51]	+	[62]	–	[70]
							–	[63]		
Physical inactivity		NA		NA		NA		NA	+	[73]
Metabolic syndrome		NA		NA	–	[57]		NA		NA
Height	+	[13]		NA	+	[56]	+	[62]	+	[73]
Weight	+	[13,17]	–	[40]		NA	–	[62]		NA
	–	[6]								
BMI (continuous)	+	[30]	–	[40,42,43]	+	[58]	–	[61–63,65]	+	[70]
	–	[18,20]			–	[50,48,49,51,53,56,57]			–	[69,72,75,77,78]
									––	[73]
BMI (categorical)		NA		NA		NA		NA	+	[74]
Waist		NA		NA	–	[56,57]		NA	–	[73]
Dislipidemy		NA	–	[42]	–	[56]		NA		NA
Triglycerides		NA		NA	–	[47,49,56,57]		NA	–	[73]
Total cholesterol	–	[25]	–	[43]	+	[56]		NA		NA
					–	[47,49,57,60]				
HDL	–	[19]		NA	+++	[46,47]	–	[63]		NA
					–	[49,57,60]				
LDL		NA		NA	–	[56]		NA		NA
Hypertension history	+	[29]	–	[42]	–	[49,56]	+	[65]	–	[73]
Mean blood pressure		NA		NA	–	[47]		NA		NA
Systolic blood pressure	+	[25,30]	–	[40]	–	[48,49,56,57,60]	–	[63,65]		NA
Diastolic blood pressure		NA	–	[40]	–	[48,49,56,57,60]	–	[63,65]		NA

CDC, Control Disease Center; DFU, diabetic foot ulcer; HDL, high density lipoprotein; LDL, low density lipoprotein; NA, not assessed; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; ––, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; –, variable with no statistically significant association with the outcome only in univariate analysis.

association. Bresäter *et al.* [62] observed that alcohol users showed a higher prevalence of active or past DFU history.

Physical inactivity. Only Iversen *et al.* [73] assessed its impact with DFU history prevalence, finding an association.

Metabolic syndrome. One study [57], using the ATP III criteria, did not find it to be associated with active or recently healed DFU.

Height. The association between height and DFU was assessed in four studies, in which it was considered as statistically significant with greater height associated with high risk [13,56,62,73].

Weight. Only five studies evaluated its association with DFU, of which two [13,17] reported that those with higher weight were at greater risk of DFU development. In the study of Boyko *et al.* [6], such association was not observed, but two other studies observed a high risk of DFU recurrence or re-ulceration [40] and greater prevalence of active or past DFU history [62] with higher weight.

Body mass index. From the 25 studies that analysed its association with DFU, only four reported it to be statistically significant. They reported that those with higher BMI values were at greater risk of DFU development [30] and active or recently healed DFU [60]. Likewise, McNeely *et al.* [70] and the CDC [71] verified higher prevalence of DFU history in those subjects with greater BMI.

Waist circumference. None of the three studies [56,57,73] found an association with active or recently healed DFU or DFU history.

Dyslipidemia. None of the two retrieved studies [42,54] reported an association with DFU recurrence or re-ulceration and active or recently healed DFU, respectively.

Triglycerides. None of the five studies that evaluated its association with active or recently healed DFU [47,49,56,57] and DFU history [70] reported a statistically significant association.

Total cholesterol. Only one study evaluated its association with DFU development [25] and one other with DFU recurrence or re-ulceration [43] and concluded that the association was not statistically significant. Its association with active or recently healed DFU was assessed by three studies, but only one [56] observed a statistically significant association.

High density lipoprotein. Its association with DFU was evaluated in seven studies. Only two studies, performed in the same population and by the same authors, reported that subjects with higher values showed a greater risk of having an active or recently healed DFU [46,47].

Low density lipoprotein. In the only identified study, it was not associated with active or recently healed DFU [56].

Other laboratory analyses. One study [56] did not find an association of C reactive protein, interleukins 6 and 10 or tumour necrosis factor with active or recently healed DFU. One other study reported that those with active or recently healed DFU presented higher values of apo-b and homocysteine [57].

Hypertension history. One study observed an association with DFU development [29] and another with active or past DFU history [65]. Conversely, the other four identified studies did not observe an association with the other outcomes [42,49,56,73].

Mean blood pressure. Only one study assessed its association with active or recently healed DFU [47], reporting it to be not statistically significant.

Systolic blood pressure. From the nine retrieved studies analysing its association with DFU, only two studies [25,30] reported statistical significance for DFU development prediction.

Diastolic blood pressure. None of the studies ($n = 8$) reported an association with DFU.

Diabetes characteristics and control (Table 8)

Diabetes type. From the 18 retrieved studies, only one study reported that subjects with diabetes type 1 presented higher prevalence of active or past DFU history [59] and another of DFU history [73].

Diabetes treatment. In all the studies (7 out of 16) where an association was reported, treatment with insulin was associated with an increased risk for DFU (whether development [6,13], active or past DFU [60,61] or DFU history [68,73,74]). No association was observed with DFU recurrence or re-ulceration and active or recently healed DFU [40,42,44,48,60].

Diabetes duration. Several studies (25 out of 45) reported an association between longer diabetes' duration and the riskof DFU (whether development [6,13,14,20,25,29,32], active or recently healed [50,51,53,54,59,60], active or past [61–63,65] or DFU history [71–74,77]). For the prediction of DFU recurrence or re-ulceration [2,37,40,42–44], such an association was not observed.

Blood sugar monitoring. The two identified studies did not find an association with DFU recurrence [44] or history [74].

Fasting blood glucose. A higher value was directly associated with DFU development in one study [13], but not with active or recently healed DFU [47,54] or with DFU history [70,71]. Regarding active or past DFU detection, one study [60] found a statistical significant association in opposition to two other studies that did not [63,65].

Glycated haemoglobin. The majority of the studies evaluating its association with DFU development showed that higher values indicated a higher risk [6,13,16,25,29,30]. Similar associations were seen in some of the studies using as

Table 8. Strength of association between diabetes characterization and control variables and foot ulceration: systematic review results summary

	Outcomes									
	DFU development		Recurrence or re-ulceration		Active or recently healed DFU		Active or past DFU history		DFU history	
Variables		References		References		References		References		References
Diabetes type	–	[13,20,27,30]	–	[44,43]	–	[51,53,59,60]	+	[61]	+	[73]
	– –	[16]					–	[64]	–	[69,70,75,77]
Diabetes treatment	+	[6,13]	–	[40,42,44]	–	[48,60]	+	[62,63]	++	[73]
									+	[71,74]
	–	[16,30]					–	[64]	–	[70]
Diabetes duration (continuous)	+	[6,13,14,20,25,29,32] [16,17,27]	–	[2,37,40,42,44]	+	[50,53,54,59,60] [48,49,51,56–58]	+	[61–63]	+	[71–73,77]
	–				–		–	[64]	–	[69,70,75,78]
Diabetes duration (categorical in years)	– CO: 10	[18]	– – CO: 10	[43]	+++ CO: 10	[51]	++ CO: 5	[63]	++ CO 10	[73]
							+ CO: 10	[65]	+ CO 5	[74]
Blood sugar monitoring		NA				NA	NA			[74]
Fasting blood glucose	+	[13]		[44]			+	[62]		[70,71]
			NA		–	[47,56]	–	[63,65]	–	
HbA_{1c} (continuous)	+++	[16]		[43,44]	+++	[57]	+	[62]	+	[73]
	+	[6,13,25,30]			+	[49,56,59,60]				
	–	[17,32]			–	[47,48,53,54]	–	[63]	–	[69,72,75,78]
HbA_{1c} (categorical)	+ CO: 7	[29]	NA		– CO 9	[51]	NA		NA	

CDC, Control Disease Center; CO, cut-off; DFU, diabetic foot ulcer; NA, not assessed; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; – –, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; –, variable with no statistically significant association with the outcome only in univariate analysis.

outcome active or recently healed DFU [49,56,57,59,60], active or past DFU history [60] and DFU history [73], but by no studies that examined DFU recurrence or re-ulceration [43,44].

Macro-vascular complications (Table 9)

Any macro-vascular complications. A significant association with DFU history was found in one study [73], but not with DFU recurrence or re-ulceration in another [2].

Cardiovascular complications.
Stroke. An association with DFU development [16] and recurrence or re-ulceration [42] was not found. Regarding DFU history, one study [73] achieved statistical significance, while another did not [70].
Myocardial infarction. Only one study (out of four) [29] reported an association with DFU development.
Angina Pectoris. Only one study [73] evaluated its association with DFU history but did not achieve statistical significance.
Cardiac autonomic neuropathy. Only one study [60] evaluated its association with active or recently healed DFU but did not achieve statistical significance.

Micro-vascular complications (Table 9)

Any micro-vascular complications. Its association with DFU history was observed in one study [73], but not with DFU recurrence or re-ulceration in another [40].

Nephropathy. Half of the studies analysing its association with DFU development [14,29] and with active or recently healed DFU [51] achieved statistical significance, while the five studies having as outcome DFU recurrence or re-ulceration [2,40,42–44] and one DFU history [70] did not.

End-stage renal disease. Only four studies evaluated its association with DFU, verifying that those with this condition were at higher risk for DFU development [29] and active or recently healed DFU [51,54], but not for DFU recurrence or re-ulceration [40].

Microalbuminuria. Only four studies appraised its impact in DFU risk. It was reported to be associated with active or past DFU history [65] and DFU history [73], but not with DFU recurrence or re-ulceration [42] and active or recently healed DFU [51].

Macroalbuminuria. Both studies [51,57] evaluating its association with active or recently healed DFU reported a statistically significant association. However, the only study [25] having DFU development as outcome did not confirm this association.

Serum creatinine. It was reported to be associated with DFU development [13] and active or recently healed DFU [49,57] in one and two studies, respectively. In contrast, this association was not reported in other two studies with active or recently healed DFU [48,56] and in one study with DFU history [70].

Urea. Only one study evaluated its association with active or recently healed foot ulcer, achieving statistical significance [49].

Retinopathy. The studies assessing its association with DFU development [16,25] reported statistical significance. For the presence of active or recently healed DFU, three studies (out of four) [49,51,55] reported an association, while only one (out of four) [2] reported it for the prediction of DFU recurrence or re-ulceration. One study [70] concluded that those with retinopathy showed higher prevalence of DFU history, while another [73] did not.

Visual aciuty. From the four retrieved studies [6,13,14,16], all of them observed that those with poor vision had significantly higher risk for DFU development. For the risk of active or recently healed DFU, one study [49] showed statistical significance, while another [51] did not.

Laser photocoagulation. Boyko *et al.* in 1999 and 2006 [6,13] concluded that those subjects that have undergone this treatment had a higher risk for DFU development (but only in univariate analysis), while in another study [16], such an association was not verified.

Diabetic neuropathy (Table 10)

Nueropathy diagnosed by clinicians. It was significantly associated with DFU development in all three identified studies [13,15,25]. Conversely, in all three studies of DFU recurrence or re-ulceration prediction, this association was not observed [40,43,44].

Nueropathy symptoms. In four studies (out of five), its presence was significantly associated with DFU development [13], active or recently healed DFU [51,52] and DFU history [71]. Armstrong *et al.* [52] reported that the presence of one or more symptoms (numbness, burning or tingling) had a sensitivity of approximately 100% to detect active or recently healed DFU.

Vibration perception threshold at hallux. Porciúncula *et al.* [54] demonstrated no association with active or recently healed DFU.

Vibration perception threshold at malleoli. All the studies that evaluated its association with DFU development [17,20,22,24,30,32], active or recently healed DFU [51,52,56,60], active or past DFU [61,64,67] and DFU history [69,72,75,77,78] achieved statistical significance. In contrast, only one study (out of three) for the prediction of foot ulcer recurrence or re-ulceration observed an association [2]. When a cut-off was used, 25 V was the most frequently chosen threshold. With this cut-off, one study [52] reported a sensitivity of 90% and specificity of 85% for active or recently healed DFU, another [67] 92% and 39%, respectively, for the detection of active or past DFU and still another [20] of 86% and 56%, respectively, for the prediction of DFU development.

Altered achilles tendon reflex. The retrieved studies observed an association with DFU development [13,14,32]

Table 9. Strength of association between macro and micro-vascular complications and foot ulceration: systematic review results summary

Variables	Outcomes								
	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Any macro-vascular complication	NA		—	[2]	NA		NA		+++	[73]
Stroke	—	[16]	—	[42]	NA		NA		+	[73]
									—	[70]
Myocardial infarction	+	[29]	NA		NA		NA		—	[70,71]
	—	[16]								
Angina pectoris	NA		NA		NA		NA		—	[73]
Cardiac autonomic neuropathy	NA		NA		—	[60]	NA		NA	
Any micro-vascular complication	NA		—	[40]	NA		NA		+++	[73]
Nephropathy	+	[14,29]	—	[2,40,42–44]	+	[51]	NA		—	[70]
	—	[16,25]			—	[60]				
ESRD	+	[29]	—	[40]	+++	[54]	NA		NA	
					+	[51]				
Microalbuminuria	NA		—	[42]	—	[51]	+	[65]	+	[73]
Macroalbuminuria	—	[25]	NA		+++	[57]	NA		NA	
					+	[51]				
Serum creatinine	+	[13]	NA	+	[49,57]	NA	—	[70]		
				—	[48,56]					
Urea	NA		NA		+	[49]	NA		NA	
Retinopathy	+	[16,25]	+++	[2]	+	[49,51,55]	NA		+	[70]
			—	[40,42,43]	—	[54,60]			—	[73]
Visual acuity	+++	[6,13,16]	NA		+++	[49]	NA		NA	
	+	[14]			—	[51]				
Laser photocoagulation	+	[6,13]	NA		NA		NA		NA	
	—	[16]								

DFU, diabetic foot ulcer; ESRD, end-stage renal disease; NA, not assessed: +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; —, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; –, variable with no statistically significant association with the outcome only in univariate analysis.

Table 10. Strength of association between diabetic neuropathy and foot ulceration: systematic review results summary

Variables	Outcomes									
	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Clinical diagnosis	+	[13,15,25]	–	[40,43,44]	NA		NA		NA	
Neuropathy symptoms	+	[13]	NA		+++	[51]	NA		+	[71]
	–	[16]			+	[52]				
VPT hallux	NA		NA		–	[56]	NA		NA	
VPT malleoli (continuous)	+++	[17,22]	–	[42,43]	+++	[60]	+	[61,64,67]	+	[69,72,75,77,78]
	++	[24]			+	[56]				
	+	[20,30]			–	[51,53]				
VPT malleoli (categorical in volts)	+++ CO: 25	[20]	+++ CO: 25	[2]	+++ CO: 25	[51,60]	+++ CO: 25	[61]	NA	
	+ CO: 30	[32]			+ CO 25	[52]				
Achilles reflex	+	[13,14,32]	NA		–	[56]	–	[63]	+	[70]
Deep tendon reflex	NA		NA		+	[56]	+	[63]		
SWM	+++ CO: 1/9	[6,13]	+ CO: 1/NR	[38]	+++ CO: 1/6	[60]	+++ CO 2/3	[61]	+ CO 1/4	[70]
	CO 1/4	[16]			+ CO: score 0–6	[48]				
	CO: Hallux 10 g	[20]								
	CO NR	[19]			CO: 1/6	[57]	CO 2/8	[63]		
	+ CO: 1/2	[32]			CO 1–4/20	[52]	+ CO 1/2	[68]		
	CO: 1/3	[14]			CO: NR	[47]	CO 1/4	[64]		
	CO: NR	[18,29]			– CO: 2/6	[56]	CO 1–4/8	[67]		
Tuning Fork	+	[13,14]	NA		NA		+	[63,67]	+	[70]
Neurotip	+	[14]	NA		NA		NA		NA	
Ball-bearing score	NA		NA		NA		NA			[79]
NDS	+++	[20]	+++	[2]	+++	[59]	+	[67]	+	NA
	+	[14]			+	[57]				
	+	[14]			+	[57,59]				
NSS	+	[14]		NA	+	[57,59]		NA	+	[71]
	–	[20]			–	[60]				
MNSS	+++	[22]		NA		NA		NA		NA
Thermal sensitivity	+	[14,30]		NA	+	[47]		NA	+	[78]
Dry, non-sweating feet		NA		NA	–	[47]	+++	[63]		NA
							+	[62]		
Neuropad		NA		NA	+++	[59]		NA		NA
Absent hair		NA		NA		NA	+			NA
SSEPS		NA		NA	+	[49]		NA		NA
MNCV	+			NA	+	[48,53]		NA		NA
SSR		NA	[17,30]	NA	+++	[60]		NA		NA

CO, cut-off; DFU, diabetic foot ulcer; MNCV, motor nerve conduction velocity; NA, not assessed; NDS, neuropathy disability score; NR, not reported; NSS, neuropathy symptoms score; SSEPS, short-latency somatosensory evoked potentials; SSR, sympathetic skin response; SWM, Semmes–Weinstein monofilament; VPT, vibration perception threshold; +++, variable with statistically significant association with the outcome in both univariate analyses; ++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; +, variable with statistically significant association with the outcome only in univariate analysis; –, variable with no statistically significant association with the outcome in univariate analysis.

and DFU history [70], but not with active or recently healed DFU [56] or with active or past DFU history [63].

Altered deep tendon reflex. It was considered to be associated with active or recently healed DFU [56] and active or past DFU history [63] in the two identified studies.

Altered SWM perception. All the 22 studies appraising its association with DFU demonstrated statistical significance, except for one [56]. However, its definition varied greatly among each study, and there is no selected standard method (number and locations of application and diagnostic cut-off) [64,67,79,80], which has a great impact in test reproducibility [80] and diagnostic accuracy reporting [20,52,67,68]. Olmos *et al.* [48] conducted a study to select the most appropriate SWM size to predict active or past DFU and concluded that the 10 g (5.07 size) was the best at risk discrimination.

Altered tuning fork perception. It was associated in all the retrieved studies with DFU development [13,14], active or past DFU history [63,67] and DFU history [70].

Altered neurotip perception. Only Abbott *et al.* [14] assessed the association between pain sensation abnormalities, using a Neurotip™ (Owen Mumford, UK), and DFU development, reporting a statistically significant result.

Ball-bearing score. A score defined as the number of the smallest ball-bearing felt by the patient was significantly associated with a history of neuropathic DFU in one study [78] in which it was reported to have a k value of 0.811 (95% confidence interval 0.710–0.972).

Neuropathy disability score. It was associated with DFU in all of the retrieved six studies [2,14,20,57,59,67], with a score >5 showing a 92% sensitivity and a 53% specificity for active or past DFU history detection [67], and a 92% sensitivity and 43% specificity for DFU development prediction [20].

Neuropathy symptoms score. From the retrieved studies, four (out of six) reported an association with DFU development [14], active or recently healed DFU [57,59] and history of DFU [71].

Michigan neuropathy screening score. Only Abbott *et al.* [22] evaluated its association with DFU development, verifying a statistically significant association in univariate and multivariate analyses.

Altered thermal sensitivity. It was significantly associated with DFU in all of the four identified studies [14,30,47,78].

Dry, non-sweating feet. The only study evaluating the association between this variable and active or recently healed DFU did not observe a statistically significant association [47]. On the other hand, its presence was significantly associated with a higher risk for active or past DFU history [62,63].

Neuropad. Only Tentolouris *et al.* [59] evaluated this test result's association with active or recently healed DFU, verifying statistical significance in both univariate and multivariate analyses.

Absent lower limb hair. One study [62] assessed its association with active or past DFU history, observing a statistically significant association.

Short-latency somatosensory evoked potentials. It was concluded that those subjects with abnormal short-latency somatosensory evoked potentials presented a higher risk for active or recently healed DFU [49].

Motor nerve conduction velocity. All of the identified studies concluded that it was associated with DFU development [17,30] and active or recently healed DFU [48,53].

Sympathetic skin response. The only identified study [60] reported an association with active or recently healed DFU.

Trauma and foot care habits (Table 11)

Rigid toe deformity. It was associated with an increased risk for DFU development [13,14,18], active or recently healed DFU [51] and active or past DFU history [63] in all the retrieved studies, but not with DFU recurrence or re-ulceration [43]. In one study [62], the subjects with hammer toes did not show an increased active or past DFU history prevalence.

Hallux limitus/rigidus. Hallux rigidus presence was associated with DFU development [13,18] but not with DFU recurrence or re-ulceration [43]. An association between DFU development and hallux limitus presence was reported in two (out of three) studies [13,16].

Hallux abductus valgus. It was associated with DFU development [18] but not with active or past DFU history [62].

Pes cavus and planus. Only one study evaluated the association between pes cavus or pes planus with DFU development [18] and reported no statistically significant association.

Charcot neuro-osteoarthropathy. It was significantly associated with DFU development [13] and active or past DFU history [62], but not with DFU recurrence and re-ulceration [40,43].

Abnormal foot shape. All the retrieved studies ($n = 4$) reported an association with DFU development [6,13,16,18]. However, foot deformity was not associated with active or recently healed DFU [54].

Sub-tarsal joint mobility. It was associated with DFU development [18,20], active or recently healed DFU [51], active or past DFU history [61] and DFU history [69,72] in all the studies, but not with DFU recurrence or re-ulceration [43].

Table 11. Strength of association between foot characteristics and care habits and foot ulceration: systematic review results summary

Variables	Outcomes									
	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Rigid toe deformity	+++	[14]	−	[43]	+	[51]	+	[63]	NA	
	+	[13,18]					−	[62]		
Hallux rigidus	+	[13,18]	−	[43]	NA		NA		NA	
Hallux limitus	+++	[16]	NA		NA		NA		NA	
	+	[13]								
	−	[6]								
HAV	+	[18]	NA		NA		−	[62]	NA	
Pes cavus and planus	−	[18]	NA		NA		NA		NA	
Charcot neuro-osteoarthropathy	+	[13]	−	[40,43]	NA		+	[62]	NA	
Abnormal foot shape	+	[6,13,16,18]	NA		−	[54]	NA		NA	[69,72]
STJ mobility	+	[18,20]	−	[43]	+	[51]	+	[61]	+	
First MPJ mobility	+	[13,20]	NA		NA		+	[61]	NA	
Oedema	+	[6,13]	NA		−	[47]	−	[63]	NA	
	−	[16]								
Redness	NA		NA		NA		+	[62]	NA	
Fissures	NA		NA		NA		−	[62]	NA	
Tinea pedis	++	[6,16]	NA		−	[47]	NA		NA	
Onychomycosis	+++	[6]	NA		−	[47]	−	[62]	NA	
	++	[16]								
Therapeutic nail lacquer	−	[12]	NA		NA		NA		NA	
Nail care	−	[16]	NA		−	[47]	−	[60]	+	[71]
Moisturized skin	+++	[19]	NA		NA		NA		NA	
	−	[16]								
Other foot care habits	−	[19]	NA		NA		NA		NA	
Foot care score	NA		+	[2]	++	[49]	NA		NA	
Footwear										
Use time	NA		NA		NA		NA		+	[76]
Barefoot	−	[19]	NA		−	[54]	NA		+	[76]
								[71,77]		
Quality	+++	[16]	NA		+	[46]	−	[61]	NA	
	+	[14]								
Therapeutic footwear	+	[13,28]	+	[37,41]	+	[54]	NA		+	[77]
			−	[35,40]						
Compliance	NA		+	[45]	+	[55]	NA		NA	
Regularity of use	+	[28]	NA		NA		NA		NA	

First MPJ, first metatarso-phalangic joint; DFU, diabetic foot ulcer; HAV, hallux abductus valgus; STJ, subtalar joint; NA, not assessed; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; −−, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; −, variable with no statistically significant association with the outcome only in univariate analysis.

First MTPJ mobility. All the studies concluded that limited first MTPJ mobility increased the risk for DFU development [13,20] and active or past DFU history [61].

Oedema. It was associated with DFU development in two studies (out of three) [6,13], but not with active or recently healed [47] or active or past DFU history [63] in all the studies.

Foot redness. It was associated with active or past DFU history [62] in the only study assessing it.

Skin fissures on the feet. It was not associated with active or past DFU history [62] in the only study retrieved.

Tinea pedis. It significantly decreased the DFU development risk in two studies [6,16] but only in their multivariate analysis. However, for the presence of active or recently healed DFU [47], no association was found.

Onychomycosis. It was significantly associated with DFU development [6,16] but not with active or recently healed DFU [47] or with active or past DFU history [62].

Therapeutic nail lacquer. Armstrong *et al.* [12], in an RCT, concluded that it was not associated with a decrease in the risk of DFU development.

Foot self-care habits.
Nail care. The presence of ingrown nails was not associated with a higher risk for active or past DFU history [62] and active or recently healed DFU [47], as well as the presence of improperly trimmed nails [47]. On the other hand, Gulliford *et al.* [71] concluded that those subjects who receive nail care from friends or relatives showed a higher prevalence of DFU history. Poor nail care at baseline was not associated with DFU development [16].
Moisturized skin. The irregular application of lubricant as treatment for dry skin of the feet was associated with a higher risk of DFU development [19] in one study, but an insufficiently moisturized skin at baseline was not associated with DFU development in another [16].
Other foot care habits. Several other self-foot care behaviours demonstrated no association with DFU development (washing, foot problem reporting, sock use, soaking feet, footwear inspection, toe drying, foot inspection and testing water temperature) [19].
Foot care score. It was concluded that subjects with higher foot care score had a lower risk for DFU recurrence or re-ulceration [2] and active or recently healed DFU [49].

Footwear.
Use time. In one study [76], it was observed that a group of subjects who wore footwear for less than 10 h had a higher DFU history prevalence.
Barefoot. Walking barefoot inside the house was not associated with an increase in DFU development risk [19], active or recently healed DFU [54] or DFU history [71]. Not wearing footwear outside the house was not associated with DFU development [19] but was with DFU history [71]. In one study [76], subjects who walked barefoot regularly had a significantly higher DFU history prevalence, while in another, no such association was observed [77].
Quality. One study [46] that assessed several shoe-related characteristics reported that only appropriate size (length and width), new shoe acquisition in the last 6 months and special shoe recommendation were significantly associated with active or recently healed DFU (at a 0.2 p level). Only special shoe recommendation maintained significance in the multivariate analysis. In another study, the use of very poor quality footwear was not associated with active or past DFU history [63]. Abbott *et al.* [14] proposed a footwear risk categorization that was associated with DFU development. Such a classification was significantly associated with DFU development also in another study [16].
Therapeutic. In five studies (out of eight), the use of therapeutic footwear was associated with a smaller risk of DFU development [13,28], recurrence or re-ulceration [41], active or recently healed DFU [54] and DFU history [77]. A significant difference in risk was not achieved in one RCT [35] and one cohort study [40] assessing the impact of therapeutic footwear in DFU recurrence. In another RCT, the risk of foot ulcer recurrence was significantly lower in persons with prior ulcer randomized to therapeutic or usual footwear [37]. Of concern in the interpretation of this difference is the extremely high foot ulcer recurrence rate in the usual care group of 58.3%, raising concerns about the validity of the randomization method that was not described and the generalizability of these findings. However, it is important to stress that in both RCTs, patients with severe foot deformity (such as CN) were excluded.
Compliance and regularity. In one study [28], subjects that wore regularly the provided therapeutic shoes were at lower risk for DFU development after 25 months follow-up. In another study [45], greater compliance with the provided therapeutic shoes diminished significantly the risk for DFU recurrence. Failure to wear bespoke footwear was associated with higher active or recently healed DFU in the Ndip *et al.* study [55].

Pressure, shear stress and activity (Table 12)

Callus. Its presence at baseline was significantly associated with active or past DFU history [62] and DFU development in one study (out of three) [27].

Number of callus. It had no significant impact in the risk of DFU development [27] in the only identified study.

Peak plantar pressure. All the identified studies showed that subjects with greater PPP values presented a higher risk for DFU development [17,20,23,24,27], active or recently healed DFU [50,51], active or past DFU history [61] and DFU history [69,75]. However, it had no impact in the prediction of DFU recurrence or re-ulceration [43]. Caselli *et al.* [24] found a statistically significant association with the forefoot peak pressure and a forefoot/rearfoot ratio (F/R R) superior to 2.

Table 12. Strength of association between foot pressure, shear stress and activity and foot ulceration: systematic review results summary

	Outcomes									
Variables	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Callus present	+	[27]	NA		NA		+	[62]	NA	
	−	[6,16]								
Number of callus	−	[27]	NA		NA		NA		NA	
PPP (continuous)	+	[17,23]	−	[43]	+	[50,51]	+	[61]	+	[69,75]
PPP (categorical)	+++ CO: 6 kg/cm2	[20,24]	− CO: 70 N/cm2	[43]	+++ CO: 65 N/cm2	[51]	+++ CO: 6 kg/cm2	[61]	NA	
	+ CO: 10 kg/cm2	[27]								
	CO: 87.5 N/cm2	[23]								
PPG	NA		NA	[38]	NA		NA		+	[75]
Daily activity	+	[21]	+		NA		NA		+	[77]
Activity variability	+	[21]	NA		NA		NA		NA	

CO, cut-off; DFU, diabetic foot ulcer; NA, not assessed; PPG, peak plantar gradient; PPP, peak plantar pressure; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; −−, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; −, variable with no statistically significant association with the outcome only in univariate analysis.

Peak pressure gradient. In a study [75] including only subjects with DN, those with greater values presented with higher DFU history prevalence.

Other pressure measures. An association with pressure time integral, peak maximal shear stress and depth at the forefoot was not found in one study [75]. Sauseng *et al.* [53] showed that the maximum plantar pressure, the plantar loading over time and the relative contact time under the first metatarsal head were significantly higher in the subjects with a neuropathic plantar DFU.

Average daily activity. All studies reported that smaller average daily activity indicated higher risk for DFU development [21], DFU recurrence or re-ulceration [38] and DFU history [77].

Activity variability coefficient. The only study identified [21] reported that those subjects with higher activity variability presented an increased risk for DFU development.

Peripheral vascular disease (Table 13)
All reports demonstrated a statistically significant association with DFU development [13–16,25]. For DFU recurrence or re-ulceration prediction, only one study (out of three) [43] reported that those with any pedal pulse missing or ABI inferior to 0.8 had a significantly higher risk. With active or recently healed DFU, an association was not observed in one study [57], but it was in the other two of the three studies performed [54,55].

Foot palpable pulses. Although an association between the intensity or presence/absence of palpable pedal pulses and DFU was reported in the majority of the retrieved studies (five out of six) [14,20,32,61,63], the PVD diagnosis definition varied among studies.

Le vascular study. Olmos *et al.* [48] reported that subjects in whom an LE vascular study was performed showed higher prevalence of active or past DFU history.

Peripheral vascular surgery. Its association with DFU development [13] and active or recently healed DFU [51] was reported, but not with DFU recurrence or re-ulceration [42,44] nor with DFU history [70].

Claudication. In three different studies [6,13,16], it was concluded that those subjects presenting with claudication at a distance inferior to one block had higher risk for DFU development. The remaining studies did not find an association with this or the other outcomes [32,42,51].

Hallux-brachial index. Only one study evaluated this procedure and observed that subjects with values <0.7 demonstrated a higher risk for active or recently healed DFU [56].

Ankle-brachial index. For the prediction of DFU development, one study [32] found no association with this variable, while another [13] reported a statistically significant association. All the studies evaluating the association between ABI and DFU recurrence or re-ulceration [42,43] and DFU history [70,77] did not find a

Table 13. Strength of association between peripheral vascular disease and foot ulceration: systematic review results summary

	Outcomes											
	DFU development			Recurrence or re-ulceration		Active or recently healed DFU		Active or past DFU history		DFU history		
Variables		References			References		References		References			References
Peripheral vascular disease	+	[13–16,25]		+++	[43]		[54,55]		NA	NA		
					[40,44]		[59]					
Foot palpable pulses	+	[14,20,32]			NA		[51]	+	[61,63]	NA		
Vascular study	NA				NA	+	[48]		NA	NA		
Vascular surgery	+ +	[13]			[42,44]	+	[51]		NA			[70]
Claudication	+	[6,13,16]			[42]		[51]		NA	NA		
		[32]										
Hallux-brachial index		NA			NA	+ CO: 0.7	[56]		NA	NA		
ABI (continuous)	+	[13]			[42,43]	+	[57]	+	[61,63,64]			[70,77]
		[32]					[49–51,59]					
ABI (categorical)		NA			NA	− CO: 0.8	[51]		NA	NA		
						CO: 0.9	[56]					
TcPO2 (continuous)	+	[13]			[42,43]		[50,51]		NA	NA		
TcPO2 (categorical)	NA				NA	NA			NA	+ CO: 30 mmHg		[70]

ABI, ankle-brachial index; CO, cut-off; NA, not assessed; DFU, diabetic foot ulcer; TcPO2, transcutaneous oxygen pressure; ++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; −−, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; −, variable with no statistically significant association with the outcome only in univariate analysis.

statistically significant association. One (out of five) and all of the studies having as outcome active or recently healed DFU [55] and active or past DFU history [61,63,64], respectively, demonstrated an inverse correlation between ABI value and risk for these outcomes.

Transcutaneous oxygen pressure. The only study assessing its association with DFU development concluded that those subjects with lower values presented a significantly higher risk [13]. This association did not reach statistical significance for DFU recurrence or re-ulceration [42,43] nor for active or recently healed DFU [50,51]. McNeely *et al.* [70] observed that subjects with a transcutaneous oxygen pressure < 30 mmHg had a higher prevalence of active DFU.

Previous foot complications (Table 14)

Previous foot ulcer. All studies ($n = 10$) showed an association with DFU development [6,13,14,16,20,25,27,29,30,32], with active or recently healed DFU [54,55] and DFU recurrence in two (out of three) studies [2,44]. However, in one study [40], the number of previous DFUs was not associated with a higher risk of DFU recurrence.

Previous ulcer in the hallux. Peters *et al.* [43] concluded that those with a DFU history over the plantar surface of the hallux showed a higher risk for DFU recurrence or re-ulceration.

Previous le amputation. It was statistically associated with DFU development [6,13,14,16,29,32], active or recently healed [51] and active or past history [62] in all the retrieved studies. On the other, for the prediction of DFU recurrence or re-ulceration, no study identified a statistically significant association [42–44]. Regarding DFU history, two studies (out of three) observed a higher prevalence in those subjects with a previous LE amputation history [71,73].

Preventive measures (Table 15)

Foot education programme. Calle-Pascual *et al.*, in a study including only subjects with DN (based on an NDS ≥6), observed that those completing the educational programme had a significantly lower risk of DFU development [31]. However, subjects with PVD were excluded. Another study [14] showed a higher risk for DFU development in those subjects that ever had foot care advice. Conversely, in an RCT [33], an educational intervention had no effect on the prevention of DFU recurrence.

Podiatric/chiropodist care. An RCT [36] observed that subjects with monthly chiropodist care had a lower risk of DFU recurrence and, in the McGill *et al.* study [32], with DFU development. Kloos *et al.* [40] did not observe an association between podiatric care and DFU recurrence as well as Ndip *et al.* with active or recently healed DFU [54].

Multidisciplinary team. An RCT [39] showed a lower risk for DFU recurrence or re-ulceration in a group receiving multidisciplinary care for 2 years. All the included subjects

Table 14. Strength of association between previous foot complications and foot ulceration: systematic review results summary

	Outcomes								
Variables	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Previous foot ulcer	+++	[6,13,14,16]	+++	[2]	+++	[54,55]	NA		NA	
			+	[44]						
	+	[20,25,27,29,30,32]	−	[42]						
Previous hallux ulcer		NA	+	[43]	NA		NA		NA	
Number previous ulcers		NA	−	[40]	NA		NA		NA	
Previous LE amputation	+++	[6,13]	−	[40,42–44]	+++	[51]	+	[62]	+	[71,73]
	+	[14,16,29,32]							−	[70]

DFU, diabetic foot ulcer; LE, lower extremity; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; —, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; −, variable with no statistically significant association with the outcome only in univariate analysis.

Table 15. Strength of association between preventive measures and foot ulceration: systematic review results summary

	Outcomes									
Variables	DFU development	References	Recurrence or re-ulceration	References	Active or recently healed DFU	References	Active or past DFU history	References	DFU history	References
Foot education	+	[14,31]	−	[33]		NA		NA		NA
Podiatric/chiropodist care	+	[32]	+	[36]	−	[54]		NA		NA
			−	[40]						
Multidisciplinary team		NA	+	[39]		NA		NA		NA
Diabetes education		NA	−	[40]		NA		NA	−	[70,74]
Dermal thermometry	+	[10,11]	+	[34]	+	[58]		NA		NA
	−	[26]								

CDC, Control Disease Center; DFU, diabetic foot ulcer; +++, variable with statistically significant association with the outcome in both univariate and multivariate analyses; ++, variable with statistically significant association with the outcome only in multivariate analysis; +, variable with statistically significant association with the outcome only in univariate analysis; —, variable with no statistically significant association with the outcome in both univariate and multivariate analyses; −, variable with no statistically significant association with the outcome only in univariate analysis.

had a previous neuropathic DFU and no PVD, CN or previous LE amputation history.

Diabetes management education. In all the three retrieved studies, it had no statistically significant association with DFU recurrence [40] or DFU history [70,74].

Dermal thermometry. In two studies [10,11], the daily use of self-administered infrared temperature sensors significantly reduced the risk of DFU development in comparison with standard care. Lavery *et al.* [34] performed an RCT distributing patients into three groups: standard therapy, structured foot exam twice a day and structured foot exam twice a day plus digital infrared thermometry. The latter group demonstrated a significant decrease in DFU recurrence in comparison with the standard therapy and regular foot exam group. In another study [58], subjects with active or recently healed neuropathic DFU had a significantly higher skin temperature. However, Armstrong *et al.* [26] concluded that as a one-time screening tool, the baseline skin temperature did not predict DFU development in a 2-year prospective cohort study.

Discussion

Various studies affirmed that diabetic foot examinations in general practice and in hospitalized patients are uncommon and unsatisfactory [79,80]. This may be partly due to an inaccurate comprehension of which variables to incorporate for regular screening. We believe that an SR producing a list of all the possible predictors for DFU is essential as a starting point.

We found that there is considerable evidence available (71 studies) about the association between independent variables and DFU development, but with several drawbacks.

The reported frequency of DFU development in the retrieved studies varies greatly. Only three studies included exclusively patients with no active, recently healed or past DFU history. In these studies, the outcome incidence ranged from 5.0% [17] to 7.2% [22].

In the remaining studies (where not all patients were free of active, recently healed or past DFU history), DFU rate varied from 2.1% [29] to 59.0% [28]. DFU recurred in 15.5% [38] to 60.5% [43] of the patients. The DFU history prevalence ranged from 10.4% [73] in a Norwegian community-based study to 48% [76] in an Indian hospital-based study. For this analysis, case–control studies were excluded because of the fact that their prevalence value is 'artificial' because of the selection of a limited number of controls often in a pre-specified ratio that leads to a distortion of prevalence from the source population that gives rise to the research subjects.

The most frequently assessed variables were age, gender, BMI, diabetes duration, HbA_{1c}, VPT at malleoli and SWM.

Of the more than 100 variables assessed, visual acuity ($n = 4$); DN measured by clinical diagnosis ($n = 3$), VPT at the malleoli ($n = 7$), altered Achilles reflex ($n = 3$) or insensitivity to the SWM ($n = 9$); rigid toe deformity ($n = 3$) and abnormal foot shape ($n = 4$); PPP ($n = 6$); PVD; ($n = 5$); lack of palpable foot pulses ($n = 3$); previous DFU ($n = 10$) and LE amputation ($n = 6$) were significantly and consistently associated with DFU development in all the retrieved studies, and numerically in at least three studies.

For those risk factors for DFU development (Table 1) considered in five or more studies, those predictive in the majority of studies (three or more) include higher diabetes duration, HbA_{1c}, DPN diagnosed through VPT at malleoli and SWM, higher PPP, PVD, previous foot ulcer and LE amputation; those unrelated in all studies include diabetes type; and those predictive of uncertain value include higher age and male gender. For those risk factors for DFU recurrence (Table 2) considered in five or more studies, no variable was considered as predictive in the majority of studies (three or more), and those unrelated in almost all studies include age, gender, diabetes duration and nephropathy. In general, risk factors considered in four or fewer studies are of uncertain significance with the exception of height, DPN diagnosed through tuning fork, NDS, thermal sensitivity or MNCV, first MPJ mobility and daily activity due to predictive ability in all conducted studies or large cumulative study sample size. Education degree was never associated with any of the outcomes. The preventive interventions described for the prevention of DFU and tested in RCTs include the following: nail-lacquer application, therapeutic footwear use and compliance, foot education, podiatric care and dermal thermometry. Nail-lacquer application resulted ineffective for DFU development prevention [12] as foot education for DFU recurrence [33]. Conversely, podiatric care reduced the DFU recurrence risk [36], and dermal thermometry, both DFU development and recurrence risk [10,11,34]. Therapeutic footwear impact in DFU recurrence risk was contradictory [35,37].

We must emphasize that all of the available DFU risk stratification systems previously reviewed by our group include variables that are demonstrated here to significantly predict DFU development. For some, the evidence is not as compelling, as physical impairment association was only assessed in one study [16] and tinea pedis in two [6,16]. But these variables were statistically significantly associated with prediction of DFU although not in three or more investigations as were those variables described in the previous paragraph. High HbA_{1c} value was considered as associated with DFU development in six [6,13,16,25,29,30] out of eight studies. Therefore, we conclude that all the variables included in the DFU risk systems previously reviewed by us are substantiated by the available evidence as predictive variables.

Regarding the pertinence of the inclusion of some other variables resultant from this SR for DFU development prediction, only diabetes duration and claudication show some predictive potential and are not included in the risk stratification systems that we previously reviewed. Although significant association was found in seven and three studies, respectively, it did not occur in all studies.

Only previous DFU was significantly associated with DFU recurrence in more than one study. However, one must highlight that only 14 studies had this outcome. Moreover, their sample size ranged from 51 to 400 (median 160) that in some studies may have contributed to the fact that no variable achieved a statistically significant association with this outcome because of inadequate power [33,37,40].

Some variables were studied by more than two studies and never found to be associated with DFU such as education degree, waist size, triglycerides and diastolic blood pressure.

In fact, it was rather unexpected that there is no sufficient evidence supporting the effect of metabolic syndrome components (such as waist circumference, lipids and triglycerides) and related conditions on DFU occurrence. These results are in contraposition with the latest DISTANCE [81] and FIELD [82] studies having LE amputation as outcome and thus did not meet our entry criteria for inclusion in this SR. In the included studies in our review, the only metabolic syndrome components evaluated as predictors of DFU occurrence were weight and BMI and were found to be statistically significant in two [13,17] out of three studies and one [30] out of three, respectively.

We must emphasize that the association between each predictive variable and DFU development was assessed only by two or fewer studies in 76% of the cases, with foot ulcer recurrence or re-ulceration in 90%, with active or recently healed DFU in 85%, with active or past DFU in 92% and with DFU history in 91% of the cases. This underlines the striking necessity of more research in this field on measurements that are readily accessible to clinical investigators and may prove valuable in predicting these foot outcomes and characteristics.

Almost half of the retrieved studies were RCTs or well conducted prospective cohort studies, which represents a reasonably high evidence level, and the reporting quality, assessed through the respective checklists, was moderate. In the observational studies, evaluated using the STROBE checklist, a higher disparity was verified across the range of studies (from 7 up to 21 points).

One of the most important results of this SR is that a DFU definition is absent in 41% of the retrieved studies and that the remaining studies presented around 20 different definitions.

Several variables (e.g. foot pulses, VPT, SWM or PPP) presented different cut-offs, which creates difficulties in analysis, standardization and interpretation, and can be considered as a shortcoming.

These different definitions, cut-offs and results demonstrate that there is still much work to be carried out to develop a universal language for DFU prediction and research standardization. One of the ex-libris and more important variables with this setback is SWM. One SR, evaluating this test diagnostic accuracy for DN (using MNCV as gold standard), concluded that little can be said because of a lack of methodologically adequate studies and called for future research to be performed to define the best procedure and threshold [83]. Another article [84] even affirms that in the included studies, the selection of the number and sites of application seemed arbitrary.

In addition, one can observe a great void in DFU prevention research – an extremely important thematic. Fewer than 10 studies evaluated the association between DFU development and therapeutic footwear, foot or diabetes education, podiatrist/chiropodist care, multidisciplinary team care, diabetes education and dermal thermometry altogether.

Regarding the use of low-risk or therapeutic footwear, all four studies assessing this variable showed a reduced DFU development rate in such patients [13,14,16,28]. Consequently, we believe that facilitating patients' adequate footwear acquisition and selection may lead to benefits in terms of risk reduction. However, further research (namely RCT) is desirable, and we must highpoint that an impact in recurrence rate was not consistently observed [35,37,40].

Although foot self-care habits such as inspection of feet or footwear, use of moisturizing cream and checking bath water temperature are encouraged by clinical providers and diabetes educators, no sufficient evidence is available that demonstrates a resulting lower risk of DFU associated with these behaviours. Limited data are available, though, on the efficacy of these practices, with several having been evaluated in only one study.

Dermal thermometry seems to be a valid and important DFU preventive tool. However, again, further research is required.

This SR identified several modifiable risk variables that, if addressed, may reduce foot complications, including good glycaemic control (assessed by HbA_{1c}), adequate footwear and insole provision for abnormal foot shape management, PPP reduction, and onychomycosis treatment. Other potentially modifiable risk factors have been investigated but did not appear consistently related to foot ulceration. BMI and waist circumference are related to multiple metabolic abnormalities, yet the former was unrelated to foot ulcer in most studies, while the latter was unrelated in all studies. A possible explanation for these findings is that the majority of persons with type 2 diabetes are overweight or obese, and thus, there is a limited range of BMI and waist circumference values in the normal range, thereby preventing detection of associations. Lipid abnormalities were also investigated, although these were addressed by a small number of studies (five of fewer), with no associations noted between total triglycerides, cholesterol and LDL-cholesterol. Paradoxically, higher HDL-cholesterol was reported to be associated with higher foot ulcer risk. A potential explanation for these findings is treatment effect aimed at lowering triglycerides and LDL-cholesterol, and raising HDL-cholesterol, thereby masking any association between their levels and DFU.

A limitation of this study is the fact that the quality assessment, data analysis and extraction were performed only by one reviewer (MMS).

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A previous meta-analysis [85] on the prediction of DFU included 16 studies. While the authors included only studies where all subjects were free of active DFU at baseline, we attempted a more comprehensive treatment of this subject considering that for now a meta-analysis cannot effectively translate all the evidence available because of variations in outcome selection and definition, variable measurement techniques, different cut-off values and study methodology disparities. Although studies including participants with active, recently healed or previous DFU may prevent blinding as to the presence of the outcome, we believe that their results should be reported in order to give us a 'better picture' of the research performed in this field and what missing elements may need to be addressed.

There are several statistically significant predictors of DFU that are readily available to clinicians that involve no more than a questionnaire, observation of the foot, application of one or more DN tests and palpation of pedal pulses. In general, the status of research on DFU predictors could be greatly improved with standardization of methods for measurements, application of a consistent definition for DFU, higher quality study designs and sufficient sample size to avoid missing clinically important associations. More attention to these issues might generate better knowledge leading to improved classification of persons with diabetes as to their risk of DFU and other complications.

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Conflict of interest

The authors have nothing to disclose.

References

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005; **366**: 1719–1724.
2. Gonzalez JS, Vileikyte L, Ulbrecht JS, *et al*. Depression predicts first but not recurrent diabetic foot ulcers. *Diabetologia* 2010; **53**: 2241–2248.
3. Ghanassia E, Villon L, Thuan dit Dieudonne J, Boegner C, Avignon A, Sultan A. Diabetic patients hospitalized for diabetic foot ulcers: a 6.5 years follow-up study. *Diabetes Care* 2008; **31**: 1288–1292.
4. Boyko EJ, Ahroni JH, Smith DG, Davignon D. Increased mortality rate associated with diabetic foot ulcer. *Diabet Med* 1996; **13**: 967–972.
5. Boulton AJ, Armstrong DG, Albert SF, *et al*. Comprehensive foot examination and risk assessment. *Endocr Pract* 2008; **14**(5): 576–583.
6. Boyko EJ, Ahroni JH, Cohen V, *et al*. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care* 2006; **29**(6): 1202–1207.
7. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. *Diabetologia* 2011; **54**(5): 1190–1199.
8. von Elm E, Altman DG, Egger M, *et al*. STROBE initiative. The Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med* 2007; **4**(10): e296.
9. Altman DG, Schulz KF, Moher D, *et al*. The Revised CONSORT Statement for Reporting Randomized Trials: explanation and elaboration. *Ann Inter Med* 2001; **134**: 663–694.
10. Armstrong DG, Holtz-Neiderer K, Wendel C, Mohler MJ, Kimbriel HR, Lavery LA. Skin temperature monitoring reduces the risk for diabetic foot ulceration in high-risk patients. *Am J Med* 2007; **120**: 1042–1046.
11. Lavery LA, Higgins KR, Lanctot DR, *et al*. Home monitoring of foot skin temperatures to prevent ulceration. *Diabetes Care* 2004; **27**(11): 2642–2647.
12. Armstrong DG, Holtz K, Wu S. Can the use of a topical antifungal nail lacquer reduce risk for diabetic foot ulceration? Results from a randomized controlled pilot study. *Int Wound J* 2005; **2**: 166–170.
13. Boyko EJ, Ahroni JH, Stensel V, *et al*. A prospective study of risk factors for diabetic foot ulcer. *The Seattle Diabetic Foot Study. Diabetes Care* 1999; **22**(7): 1036–1042.
14. Abbott CA, Carrington AL, Ashe H, *et al*. The North-West Diabetes Foot Care study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabet Med* 2002; **19**(5): 377–384.
15. Williams LH, Rutter CM, Katon WJ, *et al*. Depression and incident diabetic foot ulcers: a prospective cohort study. *Am J Med* 2010; **123**: 748–754.
16. Monteiro-Soares M, Dinis-Ribeiro M. External validation and optimisation of a model predicting foot ulcers in patients with diabetes. *Diabetologia* 2010; **53**: 1525–1533.
17. Kästenbauer T, Sauseng S, Sokol G, Auinger M, Irsigler K. A prospective study of predictors for foot ulceration in type 2 diabetes. *J Am Podriatr Med Assoc* 2001; **91**(7): 343–350.
18. Ledoux WR, Shofer JB, Smith DG, *et al*. Relationship between foot type, foot deformity, and ulcer occurrence in the high-risk diabetic foot. *J Rehab Res & Dev* 2005; **42**(5): 665–672.
19. Suico JG, Marriott DJ, Vinicor F, Litzelman DK. Behaviors predicting foot lesions in patients with non-insulin-dependent diabetes mellitus. *J Gen Int Med* 1998; **13**(7): 482–484.
20. Pham H, Armstrong DG, Harvey C, *et al*. Screening techniques to identify people at high risk for diabetic foot ulceration. *Diabetes Care* 2000; **23**: 606–611.
21. Armstrong DG, Lavery LA, Holtz-Neiderer K, *et al*. Variability in activity may precede diabetic foot ulceration. *Diabetes Care* 2004; **27**: 1980–1984.
22. Abbott CA, Vileikyte L, Williamson S, Carrington AL, Boulton AJ. Multicenter study of the incidence of and predictive risk factors for diabetic neuropathic ulceration. *Diabetes Care* 1998; **21**(7): 1071–1075.
23. Lavery LA, Armstrong DG, Wunderlich RP, Tredwell J, Boulton AJ. Predictive value of foot pressure assessment as part of a population-based diabetes disease management program. *Diabetes Care* 2003; **26**(4): 1069–1073.
24. Caselli A, Pham H, Giurini JM, Armstrong DG, Veves A. The forefoot-to-rearfoot plantar pressure ratio is increased in severe diabetic neuropathy and can predict foot ulceration. *Diabetes Care* 2002; **25**(6): 1066–1071.
25. Monami M, Vivarelli M, Desideri CM, *et al*. Pulse pressure and prediction of incident foot ulcers in type 2 diabetes. *Diabetes Care* 2009; **32**: 897–899.
26. Armstrong DG, Lavery LA, Wunderlich RP, Boulton AJ. Skin temperature as a one-time screening tool do not predict future diabetic foot complications. *J Am Podiatr Med Assoc* 2003; **93**(6): 443–447.
27. Murray HJ, Young MJ, Hollis S, Boulton AJ. The association between callus

formation, high pressures and neuropathy in diabetic foot ulceration. *Diabet Med* 1996; **13**: 979–982.
28. Chantelau E, Kushner T, Spraul M. How effective is cushioned therapeutic footwear in protecting diabetic feet? A clinical study. *Diabet Med* 1990; **7**: 355–359.
29. Margolis DJ, Hofstad O, Feldman HI. Association between renal failure and foot ulcer or lower extremity amputation in patients with diabetes. *Diabetes Care* 2008; **31**(7): 1331–1336.
30. Carrington AL, Shaw JE, Van Schie CH, *et al*. Can motor nerve conduction velocity predict foot problems in diabetic subjects over a 6-year outcome period? *Diabetes Care* 2002; **25**(11): 2010–2015.
31. Calle-Pascual AL, Durán A, Benedí A, *et al*. Reduction in foot ulcer incidence: relation to compliance with a prophylactic foot care program. *Diabetes Care* 2001; **24**(2): 405–407.
32. McGill M, Molyneaux L, Yue DK. Which diabetic patients should receive podiatry care? An objective analysis. *Inter Med J* 2005; **35**: 451–456.
33. Lincoln NB, Radford KA, Game FL, Jeffcoate WJ. Education for secondary prevention of foot ulcers in people with diabetes: a randomised controlled trial. *Diabetologia* 2008; **51**(11): 1954–1961.
34. Lavery LA, Higgins KR, Lanctot DR, *et al*. Preventing diabetic foot ulcer recurrence in high-risk patients. *Diabetes Care* 2007; **30**: 14–20.
35. Reiber GE, Smith DG, Wallace C, *et al*. Effect of therapeutic footwear on foot reulceration in patients with diabetes: a randomized controlled trial. *JAMA* 2002; **287**: 2552–2558.
36. Plank J, Haas W, Rakovac I, *et al*. Evaluation of the impact of chiropodist care in the secondary prevention of foot ulcerations in diabetic subjects. *Diabetes Care* 2003; **26**(6): 1691–1695.
37. Uccioli L, Faglia E, Monticone G, *et al*. Manufactured shoes in the prevention of diabetic foot ulcers. *Diabetes Care* 1995; **10**: 1376–1378.
38. Lemaster JW, Reiber GE, Smith DG, Heagerty PJ, Wallace C. Daily weight-bearing activity does not increase the risk of diabetic foot ulcers. *Med Sci Sports Exerc* 2003; **35**(7): 1093–1099.
39. Dargis V, Pantelejeva O, Jonushaite A, Vileikyte L, Boulton AJ. Benefits of a multidisciplinary approach in the management of recurrent diabetic foot ulceration in Lithuania. *Diabetes Care* 1999; **22**: 1428–1431.
40. Kloos C, Hagen F, Lindloh C, Braun A, *et al*. Cognitive function is not associated with recurrent foot ulcers in patients with diabetes and neuropathy. *Diabetes Care* 2010; **32**: 894–896.
41. Busch K, Chantelau E. Effectiveness of a new brand of stock "diabetic" shoes to protect against diabetic foot ulcer relapse: a prospective cohort study. *Diabet Med* 2003; **20**: 665–669.
42. Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993. *Diabetes Care* 2001; **24**: 78–83.
43. Peters EJ, Armstrong DG, Lavery LA. Risk factors for recurrent diabetic foot ulcers. *Diabetes Care* 2007; **30**(8): 2077–2079.
44. Diouri A, Slaoui Z, Chadli A, *et al*. Étude de la fréquence et des facteurs favorisant les récidives des ulcères de pied chez les patients diabétiques. *Ann Endocrinol* 2002; **63**(6): 491–496.
45. Chantelau E, Haage P. An audit of cushioned diabetic footwear: relation to patient compliance. *Diabet Med* 1994; **11**: 114–116.
46. Litzelman DK, Marriott DJ, Vinicor F. The role of footwear in the prevention of foot lesions in patients with NIDDM. Conventional wisdom or evidence-based practice? *Diabetes Care* 1997a; **20**(2): 156–162.
47. Litzelman DK, Marriott DJ, Vinicor F. Independent physiological predictors of foot lesions in patients with NIDDM. *Diabetes Care* 1997b; **20**(8): 1273–1278.
48. Olmos PR, Cataland S, O'Dorisio TM, *et al*. The Semmes–Weinstein monofilament as a potential predictor of foot ulceration in patients with noninsulin-dependent diabetes. *Am J Med Sci* 1995; **309**(2): 76–82.
49. Sriussadaporn S, Mekanandha P, Vannasaeng S, *et al*. Factors associated with diabetic foot ulceration in Thailand: a case–control study. *Diabet Med* 1997; **14**(1): 50–56.
50. Armstrong DG, Peters EJ, Athanasiou KA, Lavery LA. Is there a critical level of plantar foot pressure to identify patients at risk for neuropathic foot ulceration? *J Foot Ankle Surg* 1998a; **37**(4): 303–307.
51. Lavery LA, Armsrong DG, Vela SA, Quebedeaux TL, Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. *Arch Intern Med* 1998; **158**: 157–162.
52. Armstrong DG, Lavery LA, Vela SA, Quebedeaux TL, Fleischli JG. Choosing a practical screening instrument to identify patients at risk for diabetic foot ulceration. *Arch Inter Med* 1998b; **158**: 289–292.
53. Sauseng S, Kästenbauer T, Sokol G, Irsigler K. Estimation of risk for plantar foot ulceration in diabetic patients with neuropathy. *Diab Nutr Metab* 1999; **12**: 189–193.
54. Ndip A, Rutter M, Vileikyte L, *et al*. Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 and 5 chronic kidney disease. *Diabetes Care* 2010; **33**: 1811–1816.
55. Ndip A, Lavery LA, LaFontaine J, *et al*. High levels of foot ulceration and amputation risk in a multirracial cohort of diabetic patients on dialysis therapy. *Diabetes Care* 2010; **33**: 878–880.
56. Porciúncula MV, Rolim LC, Garofolo L, Ferreira SR. Análise de fatores associados à ulceração de extremidades em indivíduos diabéticos com neuropatia periférica. *Arq Bras Endocrinol Metab* 2007; **51**(7): 1134–1142.
57. González R, Pedro T, Real JT, *et al*. Plasma homocysteine levels are associated with ulceration of the foot in patients with type 2 diabetes mellitus. *Diabetes Metab Res Rev* 2010; **26**: 115–120.
58. Armstrong DG, Lavery LA, Liswood PJ, Todd WF, Tredwell JA. Infrared dermal thermometry for the high-risk diabetic foot. *Phys Ther* 1997; 77(2): 169–177.
59. Tentolouris N, Voulgari C, Liatis S, *et al*. Moisture status of the skin of the feet assessed by the visual test neuropad correlates with foot ulceration in diabetes. *Diabetes Care* 2010; **33**: 1112–1114.
60. Tentolouris N, Marinou K, Kokotis P, Karanti A, Diakoumopoulou E, Katsilambros N. Sudomotor dysfunction is associated with foot ulceration in diabetes. *Diabet Med* 2009; **26**: 302–305.
61. Frykberg RG, Lavery LA, Pham H, *et al*. Role of neuropathy and high foot pressures in diabetic foot ulceration. *Diabetes Care* 1998; **21**: 1714–1719.
62. Bresäter LE, Welin L, Romanus B. Foot pathology and risk factors for diabetic foot disease in elderly men. *Diab Res & Clin Pract* 1996; **32**: 103–109.
63. de Sonnaville JJ, Colly LP, Wijkel D, Heine RJ. The prevalence and determinants of foot ulceration in type II diabetic patients in a primary health care setting. *Diab Res & Clin Pract* 1997; **35**: 149–156.
64. Jirkovská A, Boucek P, Wosková V, Bartos V, Skibová J, *et al*. Identification of patients at risk for diabetic foot: a comparison of standardized noninvasive testing with routine practice at community diabetes clinics. *J Diab Compl* 2001; **15**: 63–68.
65. Guerrero-Romero F, Rodríguez-Morán M. Relationship of microalbuminuria with the diabetic foot ulcers in type II diabetes. *J Diab Compl* 1998; **12**(4): 193–196.
66. Abbott CA, Garrott AP, Carrington AL, *et al*. Foot ulcer risk is lower in South-Asian and African-Caribbean compared with European diabetic patients in the UK. *Diabetes Care* 2005; **28**: 1869–1875.
67. Miranda-Palma B, Sosenko JM, Bowker JH, Mizel MS, Boulton AJ. A comparison of the monofilament with other testing modalities for foot ulcer susceptibility. *Diab Res Clin Pract* 2005; **70**: 8–12.
68. Saltzman CL, Rashid R, Hayes A, *et al*. 4.5-gram monofilament sensation beneath both first metatarsal heads indicates protective foot sensation in diabetic patients. *J Bone & Joint Surg* 2004; **86**(4): 717–723.
69. Bennett PJ, Stocks AE, Whittam DJ. Analysis of risk factors for neuropathic foot ulceration in diabetes mellitus. *J Am Podiatr Med Assoc* 1996; **86**(3): 112–116.
70. McNeely MJ, Boyko EJ, Ahroni JH, *et al*. The independent contributions of diabetic neuropathy and vasculopathy in foot ulceration: how great are the risks? *Diabetes Care* 1995; **18**(2): 216–219.
71. Gulliford MC, Mahabir D. Diabetic foot disease and foot care in a Caribbean community. *Diab Res Clin Pract* 2002; **56**: 35–40.
72. Boulton AJ, Kubrusly DB, Bowker JH, *et al*. Impaired vibratory perception and diabetic foot ulceration. *Diabet Med* 1986; **3**: 335–337.
73. Iversen MM, Mifdtjell K, Ostbye T, *et al*. History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trondelag Health Study. *Scand J Public Health* 2008; **36**(1): 62–68.
74. Control Disease Center (CDC). History of foot ulcer among persons with diabetes – United States 2000–2002. *MMWR* 2003; **52**(45): 1098–1102.

75. Lott DJ, Zou D, Mueller MJ. Pressure gradient and subsurface shear stress on the neuropathic forefoot. *Clin Biomech* 2008; **23**: 342–348.
76. Jayasinghe SA, Atukorala I, Gunethilleke B, *et al*. Is walking barefoot a risk factor for diabetic foot disease in developing countries? *Rural Remote Health* 2007; **7**: 692–698.
77. Maluf KS, Mueller MJ. Comparison of physical activity and cumulative plantar tissue stress among subjects with and without diabetes mellitus and a history of recurrent plantar ulcers. *Clin Biomech* 2003; **18**: 567–575.
78. Papanas N, Gries A, Maltezos E, Zick R. The steel ball-bearing test: a new test for evaluating protective sensation in the diabetic foot. *Diabetologia* 2006; **49**: 739–743.
79. Boulton AJ, Meneses P, Ennis WJ. Diabetic foot ulcers: a framework for prevention and care. *Wound Rep Reg* 1999; **7**: 7–16.
80. Morbach S. *Diagnosis, Treatment and Prevention of the Diabetic Foot Syndrome*. Paul Hartmann AG: Germany, 2003. ISBN 3-929870-29-0.
81. Callaghan BC, Feldman E, Liu J, Kerber K, Pop-Busui R, Moffet H, Karter AJ. Triglycerides and amputation risk in patients with diabetes: ten-year follow-up in the DISTANCE study. *Diabetes Care* 2011; **34**(3): 635–640.
82. Rajamani K, Colman PG, Li LP, Best JD, *et al*. Effect of fenofibrate on amputation events in people with type 2 diabetes mellitus (FIELD study): a prespecified analysis of a randomised controlled trial. *Lancet* 2009; **373**(9677): 1780–1788.
83. Dros J, Wewerinke A, Bindels PK, van Weert HC. Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. *Ann Fam Med* 2009; **7**(6): 555–558.
84. Feng Y, Schlösser FJ, Sumpio BE. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. *J Vasc Surg* 2009; **50**(3): 675–682.
85. Crawford F, Inkster M, Kleijnen J, Fahey T. Predicting foot ulcers in patients with diabetes: a systematic review and meta-analysis. *Q J Med* 2007; **100**: 65–68.

4.3 (RETROSPECTIVE) VALIDATION AND COMPARISON OF CURRENTLY AVAILABLE SYSTEMS FOR PATIENTS' WITH DIABETES STRATIFICATION BY RISK OF FOOT ULCER DEVELOPMENT

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CLINICAL STUDY

Validation and comparison of currently available stratification systems for patients with diabetes by risk of foot ulcer development

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Abstract

Aims/hypothesis: There are five systems to stratify the risk for the development of a diabetic foot ulcer (DFU). This study aimed to prospectively validate all of them in the same cohort of participants to allow their direct comparison.

Methods: A retrospective cohort study was conducted on all patients with diabetes but without an active DFU attending our podiatry section ($n=364$) from January 2008 to December 2010. Participants' characteristics and all variables composing the stratification systems were assessed at baseline. Follow-up was performed for 1 year or until DFU occurred.

Results: Participants had a mean age of 64 years; 99.7% had type 2 diabetes and 48.6% were male. Median follow-up was 12 months (1–12) during which 33 subjects (9.1%) developed a DFU. Age, diabetes duration, foot deformity, peripheral vascular disease, diabetic peripheral neuropathy, previous DFU, and previous lower extremity amputation were associated with DFU occurrence. All systems presented greater DFU occurrence frequency as the risk group was higher (χ^2, $P<0.001$) and showed good diagnostic accuracy values, especially negative predictive value ($\geq 95\%$) and area under the receiver operating curve (≥ 0.73). The lowest performance concerned positive predictive value ($\leq 29.5\%$).

Conclusions/interpretation: All the currently available stratification systems show high accuracy to detect which patients will develop a DFU with no significant differences among them. Therefore, for diabetic foot screening and resource allocation, it would be desirable to have a single unified system, combining the available systems, prospectively validated in a multicenter context and testing the inclusion of novel predictive variables' pertinence.

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Introduction

Diabetes-related foot complications, namely diabetic foot ulcers (DFUs) and lower extremity amputation (LEA), are very prevalent worldwide (1). Therefore, they have a great impact on health economy and available resource allocation, as well as on patients' quality of life. Additionally, we are observing a constant and pronounced increase in diabetes prevalence, which represents a number of patients exceedingly superior to the available resources (2). In fact, economical cuts in preventive diabetic care are being proposed and implemented internationally. More than ever, an appropriate stratification of patients by their risk of developing a DFU is crucial for resource allocation, as well as prevention of complications (3, 4).

Although five stratification systems were developed, namely the University of Texas (UT) (5), American Diabetes Association (ADA) (6), International Working Group on the Diabetic Foot (IWGDF) (7), Scottish Intercollegiate Grouping Network (SIGN) systems (8), and the Seattle risk score (9), to date no system has been collectively adopted (10) and their use in clinical practice is still scarce (8).

A systematic review (4), performed to retrieve all the available stratification systems created and their validation studies, showed that: i) although their core variables are very similar, the procedures for selection of variables and risk group stratification varies considerably; ii) some were never externally validated; iii) their prognostic accuracy was not reported; and iv) they were never validated simultaneously in the same cohort.

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Therefore, in that systematic review, the authors could not choose which system to apply in daily practice (4). Hence, we have conducted this retrospective cohort study in order to validate and compare all the available systems in terms of structure and validity at 1 year in the same cohort of patients.

Materials and methods

Type of study and selection of participants

A retrospective cohort study was conducted on all patients with diabetes attending the podiatry section of our Diabetic Foot Clinic, from January 2008 to December 2010. Patients were excluded if they had an active DFU, complete inability to walk, any data missing, and/or a follow-up period of less than 1 year.

This study was approved by the Ethics Committee of our institution and no adverse events occurred due to its conduction.

Data collection

At baseline (the first podiatric appointment), patients' characterization variables and those included in all the available systems were assessed and registered by two podiatrists with extensive experience in diabetic foot care (more than 8 years). Variables were collected from the patients' clinical files until the end of December 2011, and all the systems were applied at that moment. Consequently, investigators were blinded to the systems' stratification during data assessment and collection.

The characterization variables are of age, gender, diabetes duration, type and treatment, previous myocardial infarction and/or stroke, hypertension, nephropathy, and retinopathy (and respective laser treatment). These were collected through a structured interview including the presence of claudication and DFU (5, 6, 7, 8, 9) and/or LEA (5, 6, 7, 8, 9) history.

HbA1c value (9) was collected through blood sample analysis, and we used the one closest to the first appointment (with <3 months). Visual impairment (8, 9) and physical impairment (8) were assessed through questionnaires during interviews and subjective analysis and were defined as patients' inability to see or reach their own feet (8) respectively.

Diabetic peripheral neuropathy (DPN) diagnosis varied according to the system used. For the UT system (5), we used the 128 Hz tuning fork sensitivity, at the distal phalanx of the hallux (instead of the biothesiometer); for the SIGN system (8) and Seattle risk score (9), the Semmes–Weinstein monofilament; for the ADA (6) and IWGDF (7) systems, an altered monofilament and/or tuning fork sensation was considered to evaluate the presence of DPN. Monofilament touch perception was tested at the pulp of the hallux, 1st, 3rd, and 5th metatarsal heads in each foot. Absent sensation at one or more sites was considered as the presence of DPN (11).

Regarding the peripheral vascular disease (PVD) diagnosis, although definition variation also occurred (6, 7, 8), it was assessed through direct pulse palpation. One non-palpable foot pulse was considered as PVD for the ADA and IWGDF systems, conversely for the SIGN system was the inability to feel both pulses in one foot. In the UT system and Seattle risk score, the PVD diagnosis is not included. The presence of foot deformity (5, 6, 7, 8), callus (8), edema, onychomycosis, and *tinea pedis* (9) was identified through foot examination.

Follow-up ended as the first DFU occurred in any foot or after 1 year. Participants were reevaluated in variable intervals (from 1 to 6 months), according to podiatrists' clinical evaluation. However, patients were instructed to contact or return to our clinic if any complication developed before the next scheduled appointment. DFU development was defined as a full-thickness defect distal to the malleoli requiring more than 14 days to heal (9).

Statistical analysis

For the association between characterization and systems' composing variables with DFU occurrence, we used Student's *t*-test for continuous variables for independent samples (as all presented a normal distribution), and for categorical variables, we applied the χ^2 or Fisher's exact test, when applicable. Significance was defined as $P<0.05$. In those cases presenting an association, a P value between 0.05 and 0.1, odds ratio (OR), and respective 95% confidence intervals (95% CIs) were calculated in addition to the Cramer's V statistic (φ_c) for categorical variables – this index varies from 0 to 1, ranging from no association between variables to complete association respectively – and for continuous variables, Cohen's d statistic (d) – in which a 0.2 value is interpreted as a small effect size, 0.5 as medium, and 0.8 as large.

Participants were stratified according to each system categories. Sensitivity, specificity, likelihood ratios (LRs), predictive values, and area under the receiver operating curve (AUC) with 95% CI were calculated. All statistical analysis was performed using IBM SPSS version 19.0 (Chicago, IL, USA).

Results

Description of participants

In this study, 364 subjects were included. Median follow-up was 12 (range 1–12) months during which 33 participants (9.1%) developed a DFU. The mean age of the sample was 64 (19–94) years, 48.6% were male, 99.7% had type 2 diabetes, 41.5% used insulin, and the mean diabetes duration was 17 (1–52) years.

Association of variables with DFU development

Of the former variables, only age and diabetes duration were significantly associated with DFU occurrence (Table 1). The association between DFU risk stratification system variables and the outcome is also described in Table 1. Foot deformity, PVD diagnosis (through different definitions), DPN diagnosis (through different definitions), previous DFU, and previous LEA were highly associated with DFU development ($P<0.001$). We stress that the HbA1c value ($P=0.10$; OR 1.21 (95% CI 0.91–1.60); $d=0.3$), the presence of retinopathy ($P=0.05$, OR 2.07 (95% CI 1.00–4.28), $\varphi_c=0.1$), laser photocoagulation ($P=0.10$, OR 1.80 (95% CI 0.87–3.74), $\varphi_c=0.08$) and visual impairment ($P=0.08$, OR 1.90 (95% CI 0.92–3.92), $\varphi_c=0.09$), callus ($P=0.09$, OR 1.84 (95% CI 0.90–3.78), $\varphi_c=0.09$), and claudication ($P=0.10$, OR 1.92 (95% CI 0.87–4.25), $\varphi_c=0.09$) presented a P value ≤ 0.1, which also represents a potential predictive value, but with small effect size.

For all the systems, DFU occurrence increased as the risk group got higher (χ^2 for association and trend, $P<0.001$; Table 2). For this analysis, some of the categories had to be grouped due to low expected values (<5).

Accuracy of the DFU risk stratification systems

Analyzing Table 3, one observes that in the highest risk group, the UT system presented the lowest sensitivity and the SIGN system the lowest specificity and positive

Table 1 Association of the collected variables with the outcome.

Variables	All (n=364)	No DFU occurrence (n=331)	DFU occurrence (n=33)	*P* value
Characterization variables				
Age (mean (S.D.))	65 (10.6)	64 (10.4)	69 (11.7)	**0.01**[a]
Male (%)	177 (48.6)	158 (47.7)	19 (57.6)	0.28[c]
Type 2 diabetes (%)	363 (99.7)	330 (99.7)	33 (100)	1.00[b]
Insulin use (%)	151 (41.5)	137 (41.4)	14 (42.4)	0.91[c]
Diabetes duration (mean (S.D.))	17 (10.7)	16.6 (10.6)	21 (11.3)	**0.04**[a]
Reportable myocardial infarction history (%)	35 (9.6)	31 (9.4)	4 (12.1)	0.54[b]
Reportable stroke history (%)	68 (18.7)	60 (18.1)	8 (24.2)	0.39[c]
Reportable hypertension history (%)	229 (62.9)	205 (61.9)	24 (72.7)	0.22[c]
Nephropathy (%)	40 (11.0)	36 (10.9)	4 (12.1)	0.77[b]
Retinopathy (%)	150 (41.2)	131 (39.6)	19 (57.6)	*0.05*[c]
Laser photocoagulation (%)	110 (30.2)	96 (29.0)	14 (42.4)	*0.10*[c]
Foot edema (%)	93 (25.5)	84 (25.4)	9 (27.3)	0.81[c]
Claudication presence (%)	71 (19.5)	61 (18.4)	10 (30.3)	*0.10*[c]
DFU risk stratification systems' composing variables				
HbA1c (mean (S.D.))	7.5 (1.6)	7.5 (1.6)	8.2 (1.6)	*0.1*[a]
Visual impairment (%)	157 (43.1)	138 (41.7)	19 (57.6)	*0.08*[c]
Physical impairment (%)	83 (22.8)	72 (21.8)	11 (33.3)	*0.13*[c]
Callus (%)	128 (35.2)	112 (33.8)	16 (48.5)	*0.09*[c]
Foot deformity (%)	259 (71.2)	230 (69.5)	29 (87.9)	**0.03**[c]
Onychomycosis (%)	208 (57.1)	185 (55.9)	23 (69.7)	0.13[c]
Tinea pedis (%)	18 (4.9)	17 (5.1)	1 (3.0)	1.00[b]
Right foot pulses (n(%))				
0	76 (20.9)	62 (18.7)	14 (42.4)	
1	33 (9.1)	28 (8.5)	5 (15.2)	**0.001**[c,d]
2	255 (70.1)	241 (72.8)	14 (42.4)	
Left foot pulses (n(%))				
0	72 (19.8)	57 (17.2)	15 (45.5)	
1	37 (10.2)	31 (9.4)	6 (18.2)	**<0.001**[c,d]
2	255 (70.1)	243 (73.4)	12 (36.4)	
Total foot pulses (n(%))				
0–1	73 (20.0)	59 (17.8)	14 (42.4)	
2–3	43 (11.8)	36 (10.9)	7 (21.2)	**<0.001**[c,d]
4	248 (68.1)	236 (71.3)	12 (36.4)	
SWM sensitivity altered (%)	151 (41.5)	128 (38.7)	23 (69.7)	**0.001**[c]
Tuning fork sensitivity altered (%)	119 (32.7)	96 (29.0)	23 (69.7)	**0.001**[c]
SWM and/or tuning fork sensitivity altered (%)	183 (50.3)	155 (46.8)	28 (84.8)	**<0.001**[c]
Previous DFU (%)	128 (35.2)	98 (29.6)	30 (90.9)	**<0.001**[c]
Previous LEA (%)	38 (10.4)	24 (7.3)	14 (42.4)	**<0.001**[b]

P values in bold are $P<0.05$ and values in italic are $P\leq 0.1$.
[a]Students' *t*-test.
[b]Fisher's exact test.
[c]χ^2 for association.
[d]χ^2 for trend.

Table 2 DFU risk stratification systems' classification distribution.

UT system			ADA system			IWGDF system			SIGN system			Boyko *et al.* system		
RG	Subjects (*n*)	DFU frequency (*n* (%))	RG	Subjects (*n*)	DFU frequency (*n* (%))	RG	Subjects (*n*)	DFU frequency (*n* (%))	RG	Subjects (*n*)	DFU frequency (*n* (%))	RG	Subjects (*n*)	DFU frequency (*n* (%))
0	227	9 (4)	0	43	0 (0)	0	127	0 (0)	Low	29	0 (0)	Lowest	147	2 (1)
1	26	3 (12)	1	142	0 (0)	1	21	0 (0)	Medium	141	0 (0)	Next-to-lowest	88	3 (3)
2	41	2 (5)	2	51	3 (6)	2A	44	1 (2)				Next-to-highest	51	5 (10)
						2B	46	3 (7)						
3	70	19 (27)	3	128	30 (23)	3A	87	14 (16)	High	194	33 (100)	Highest	78	23 (30)
						3B	39	15 (39)						

ADA, American Diabetes Association; DFU, diabetic foot ulcer; IWGDF, International Working Group on the Diabetic Foot; RG, risk group; SIGN, Scottish Intercollegiate Guidelines Network; UT, University of Texas.

LR. The UT system and the Seattle risk scores presented the highest specificity values.

When assembling the highest and high/medium risk groups, the SIGN system presented the lowest specificity and positive predictive values (PPV) and the ADA system the lowest positive LR. Once again, the UT system and the Seattle risk score had the highest specificity values. When assembling the highest and medium/low risk groups, the ADA system presented the lowest positive LR and the UT system the highest specificity value.

Regarding the systems' diagnostic accuracy, the respective AUC values were 0.73 (95% CI 0.63–0.83) for the UT system, 0.83 (95% CI 0.79–0.88) for the ADA system, 0.86 (95% CI 0.81–0.91) for the IWGDF system, 0.75 (95% CI 0.68–0.82) for the SIGN system, and 0.82 (95% CI 0.75–0.89) for the Seattle risk score (Fig. 1). All classification systems presented high AUC values and no statistical differences were found between them.

Discussion

There are several risk stratification systems developed for the detection of diabetic patients at higher risk of DFU occurrence (4), and it has been evidenced that they are more sensitive than any individual predictive variable (2). This study was the first where all the DFU risk stratification systems were retrospectively validated in the same cohort. Until now, the ADA and UT were never validated and respective diagnostic accuracy measures reported, and the IWGDF and SIGN were never externally validated.

Additionally, for all the systems (except Seattle risk score), the AUC value was never reported. This measure is considered, for some authors, the best way to determine a system's discriminatory ability (12).

Our data support the predictive value of the stratification systems' main variables such as PVD, DPN, and previous foot complications. All the remaining composing variables of the systems, except for *tinea pedis* and physical impairment, presented a potential predictive value ($P \leq 0.1$) but did not achieve statistical significance. One must highlight that, in the two studies assessing the predictive value of *tinea pedis* for DFU development, statistical significance was only observed in the multivariate analysis (3, 9). Of the collected variables not included in any of the studied systems, only older age and diabetes duration were associated with DFU development.

Also, our results suggest that all the available systems are equally and highly accurate. All systems presented AUC values higher than 0.73 and a trend was observed for increased DFU occurrence in higher risk groups.

We have observed that all the systems, using as cutoff any of the risk groups, presented a PPV value $< 30\%$. This can be interpreted by classifying the subjects as

Table 3 DFU risk stratification systems' classification diagnostic accuracy measures.

	ADA system			IWGDF system			UT system			SIGN system			Seattle risk score		
DAM	RG	Value (%)	95% CI	RG	Value (%)	95% CI	RG	Value (%)	95% CI	RG	Value (%)	95% CI	RG	Value (%)	95% CI
Sens	3	90.9	81.1–100.0	3A+3B	87.9	76.7–99.0	3	57.6	40.7–74.4	High	100.0	NC	Highest	69.7	54.0–85.4
Spe		70.4	65.5–75.3		70.7	65.8–75.6		84.6	80.7–88.5		51.4	46.0–56.7		83.4	79.4–87.4
PPV		23.4	16.1–30.8		23.0	15.7–30.4		27.1	16.7–37.6		17.0	11.7–22.3		29.5	19.4–39.6
NPV		98.7	97.3–100.0		98.3	96.7–100.0		95.2	92.8–97.7		100.0	NC		96.5	94.4–98.6
LR+		3.1	2.5–3.7		3.0	2.4–3.7		3.7	2.5–5.5		2.1	1.8–2.3		4.2	3.0–5.8
LR−		0.1	0.04–0.4		0.2	0.07–0.4		0.5	0.3–0.7		NC	NC		0.4	0.2–0.6
Sens	2+3	100.0	NC	2A+2B+3A+3B	100.0	NC	2+3	63.6	47.2–80.1	High+medium	100.0	NC	Highest+next-to-highest	84.9	72.6–97.1
Spe		55.9	50.5–61.2		44.7	39.4–50.1		72.8	68.0–77.6		8.7	5.7–11.8		69.5	64.5–74.5
PPV		18.4	12.8–24.1		15.3	10.5–20.1		18.9	11.6–26.2		9.9	6.1–12.2		21.7	14.6–28.8
NPV		100.0	NC		100.0	NC		95.3	92.6–97.9		100.0	NC		97.9	96.0–99.7
LR+		2.3	2.0–2.6		1.8	1.6–1.9		2.3	1.7–3.2		1.1	1.0–1.1		2.8	2.2–3.5
LR−		NC	NC		NC	NC		0.5	0.3–0.8		NC	NC		0.2	0.1–0.5
Sens	1+2+3	100.0	NC	1+2A+2B+3A+3B	100.0	NC	1+2+3	72.7	57.5–87.9				Highest+next-to-highest+next-to-lowest	93.9	85.8–100.0
Spe		13.0	9.0–16.6		38.4	33.1–43.6		65.9	60.8–71.0					43.8	38.5–49.2
PPV		10.3	7.0–13.6		13.9	9.5–18.3		17.5	11.1–23.9					14.3	9.6–18.9
NPV		100.0	NC		100.0	NC		96.0	93.5–98.6					98.6	96.8–100.0
LR+		1.1	1.1–1.2		1.6	1.5–1.8		2.1	1.6–2.8					1.7	1.5–1.9
LR−		NC	NC		NC	NC		0.4	0.2–0.7					0.1	0.04–0.5

DAM, diagnostic accuracy measure; Sens, sensitivity; Spe, specificity; PPV, positive predictive value; NPV, negative predictive value; LR+, positive likelihood ratio; LR−, negative likelihood ratio; ADA, American Diabetes Association; RG, risk groups; 95% CI, 95% confidence interval; NC, non-calculable; IWGDF, International Working Group on Diabetic Foot; UT, University of Texas; SIGN, Scottish Intercollegiate Guideline Network.

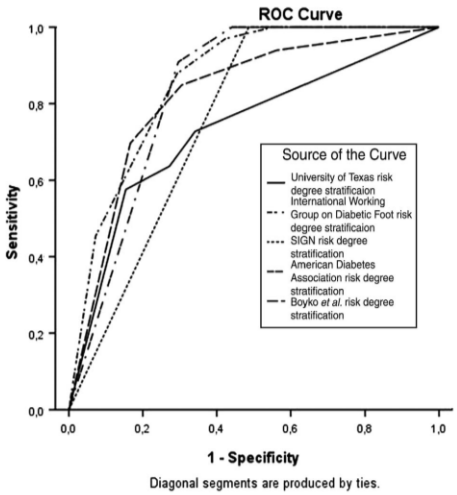

Figure 1 Classification systems' diagnostic accuracy. ROC, receiver operating curve; straight line, University of Texas system; dashed and dotted line, International Working Group on Diabetic Foot system; double dashed and dotted line, American Diabetes Association system; continuous dashed line, Scottish Intercollegiate Guidelines Network system; discontinuous dashed line, Boyko *et al.* system.

being at risk, and that more than 70% will not develop a DFU, which represents a high cost (especially for tertiary institutions). We believe that it is essential to develop strategies to improve this situation.

Conversely, for the highest risk group or combining the medium with the highest risk group, excellent negative predictive values were obtained in all the systems, and also in most of the systems' sensitivity values. This means that almost all the patients developing a DFU are predicted by the systems. Therefore, we suggest that those in lower risk groups be followed in the primary care setting.

When comparing the systems with each other we observed that the UT system presented the highest specificity values (only similar to the Seattle risk score) but for the highest risk and the lowest sensitivity. The SIGN system presented the lowest specificity and positive LR in the highest risk group and in the medium plus high-risk group the lowest specificity and PPV.

Comparing the results of this study with the systems' validation studies, we observed that the IWGDF presented lower specificity and PPV values in comparison with the study by Peters *et al.* (13). The SIGN system presented lower specificity and PPV in comparison with one study from Leese *et al.* (8) and also lower positive LR when compared with a different study by Leese *et al.* (2). The Seattle risk score was externally validated in the same setting (3), and therefore, no differences were found. Regarding the ADA and UT systems, that we are aware of, no diagnostic accuracy measures were ever reported.

The differences described may be justified by the following limitations. This study was conducted in a tertiary referral center and therefore presents a possible bias – a high prevalence of DFU occurrence (9.1%) when compared with other DFU risk stratification systems' validation studies, such as the one performed by Leese *et al.* (8) in a community setting (5%). Conversely, all the remaining derivation or validation studies (2, 3, 5, 7, 9, 13) presented higher frequency (9.5–34%). Our study population was composed mainly of elderly subjects (mean age greater than 65 years) with type 2 diabetes (99.7%), which may affect our results' generalizability.

For each variable's prognostic value analyzed, one should include 10–15 subjects (14), which represents a required sample size of 280–450. We enrolled 364 participants, a number containing all the patients available during the study conduction period but not achieving the superior limit for an adequate sample size. Therefore, we have considered that those variables presenting a P value less than or equal to 0.1 presented a potential predictive value. However, for all the variables in this condition, a small effect size was observed.

We believe that a DFU risk stratification system should be equally easy to apply in all sorts of settings and performed using only commonly available material. Therefore, we have chosen to perform the PVD diagnosis only through pulse palpation as proposed by Leese *et al.* (8). Additionally, we have decided, for the DPN diagnosis, to apply the tuning fork in spite of the biothesiometer as proposed by Peters *et al.* (13). Despite these modifications and using all the different definitions proposed, these two variables were highly associated with DFU development ($P<0.001$). This corroborates our systematic review results: DPN and PVD clinical collection methods seem relatively unimportant (4, 15). Although several authors have described the foot pulse palpation to have low sensitivity (16, 17), the SWM application procedure does not have consensus (18, 19) and the tuning fork has low reliability (19); several studies have shown that these simple methods can be implemented for both community (2, 8, 15, 19, 20) and high risk (3, 4) setting diabetic foot screening, independently of the variables collection method.

Patients with diabetes should have their feet checked at least once per year (2, 6, 10). However, to our knowledge, no foot reclassification periodicity was ever suggested. Therefore, we decided to implement a 1-year follow-up period. Another limitation was the fact that reliability of variables and systems was not assessed due to the retrospective character of this study.

In conclusion, although the selection of which system to apply is still unclear, this study shows that all these systems include pertinent variables, are easy to apply, present a high accuracy, and therefore are valuable tools to apply in our clinical practice.

Nevertheless, further validation studies should be performed on larger samples and in different settings with a longer follow-up period. Additionally, there is a great need to assess the reliability of the systems and their components, the impact of time in the systems' validity and to consequently propose the most efficient foot examination reevaluation periodicity.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Author contribution statement

M Monteiro-Soares was responsible for data collection and article writing; A Vaz-Carneiro, S Sampaio, and M Dinis-Ribeiro were responsible for the statistical analysis and text editing and revision.

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References

1 Boulton AJ, Vileikyte L, Ragnarson-Tennvall G & Apelqvist J. The global burden of diabetic foot disease. *Lancet* 2005 **366** 1719–1724. (doi:10.1016/S0140-6736(05)67698-2)

2 Leese GP, Cochrane L, Mackie AD, Stang D, Brown K & Green V. Measuring the accuracy of different ways to identify the "at-risk" foot in routine clinical practice. *Diabetic Medicine* 2011 **28** 747–754. (doi:10.1111/j.1464-5491.2011.03297.x)

3 Monteiro-Soares M & Dinis-Ribeiro M. External validation and optimisation of a model for predicting foot ulcers in patients with diabetes. *Diabetologia* 2010 **53** 1525–1533. (doi:10.1007/s00125-010-1731-y)

4 Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I & Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. *Diabetologia* 2011 **54** 1190–1199. (doi:10.1007/s00125-010-2030-3)

5 Lavery LA, Armstrong DG, Vela SA, Quebedaux TL & Fleischli JG. Practical criteria for screening patients at high risk for diabetic foot ulceration. *Archives of Internal Medicine* 1998 **158** 157–162. (doi:10.1001/archinte.158.2.157)

6 Boulton AJ, Armstrong DG, Albert SF, Frykberg RG, Hellman R, Kirkman MS, Lavery LA, LeMaster JW, Mills JL Sr, Mueller MJ, Sheehan P, Wukich DK & Task Force of the Foot Care Interest Group of the American Diabetes Association. Comprehensive foot examination and risk assessment. *Endocrine Practice* 2008 **14** 576–583.

7 Lavery LA, Peters EJ, William JR, Murdoch DP, Hudson A & International Working Group on the Diabetic Foot. Reevaluating the way we classify the diabetic foot: restructuring the diabetic foot risk classification of the International Working Group on the Diabetic Foot. *Diabetes Care* 2008 **31** 154–156. (doi:10.2337/dc07-1302)

8 Leese GP, Reed F, Green V, McAlpine R, Cunningham S, Emslie-Smith AM, Morris AD, McMurray B & Connacher AC. Stratification of foot ulcer risk in patients with diabetes: a population based study. *International Journal of Clinical Practice* 2006 **60** 541–545. (doi:10.1111/j.1368-5031.2006.00899.x)

9 Boyko EJ, Ahroni JH, Cohen V, Nelson KM & Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care* 2006 **29** 1202–1207. (doi:10.2337/dc05-2031)

10 Frykberg RG, Zgonis T, Armstrong DG, Driver VR, Giurini JM, Kravitz SR, Landsman AS, Lavery LA, Moore JC, Schuberth JM, Wukich DK, Andersen C, Vanore JV & American College of Foot and Ankle Surgeons. Diabetic foot disorders. A clinical practice guideline (2006 revision). *Journal of Foot and Ankle Surgery* 2006 **45** (5 Suppl) S1–S66.

11 Smieja M, Hunt DL, Edelman D, Etchells E, Cornuz J, Sime DL & for the International Cooperative Group for Clinical Examination Research. Clinical examination for the detection of protective sensation in the feet of the diabetic patients. *Journal of General Internal Medicine* 1999 **14** 418–424. (doi:10.1046/j.1525-1497.1999.05208.x)

12 Reynolds T. Disease prediction models aim to guide medical decision making. *Annals of Internal Medicine* 2001 **135** 637–640.

13 Peters EJ, Lavery LA & International Working Group on the Diabetic Foot. Effectiveness of the diabetic foot risk classification system of the International Working Group on the Diabetic Foot. *Diabetes Care* 2001 **24** 1442–1447. (doi:10.2337/diacare.24.8.1442)

14 Stiell IG. Clinical decision rules in the emergency department. *CMAJ: Canadian Medical Association Journal* 2000 **163** 1465–1466.

15 Jeffcoate WJ. Stratification of foot risk predicts the incidence of new foot disease, but do we yet know that the adoption of routine screening reduces it? *Diabetologia* 2011 **54** 991–993. (doi:10.1007/s00125-011-2075-y)

16 Lundin M, Wiksten JP, Peräkylä T, Lindfors O, Savolainen H, Skyttä J & Lepäntalo M. Distal pulse palpation: is it reliable? *World Journal of Surgery* 1999 **23** 252–255. (doi:10.1007/PL00013177)

17 Rollins DL, Kalakuntla V & Wilson A. Arterial revascularization in patients with diabetes: an overview. *Journal for Vascular Ultrasound* 2006 **30** 221–227.

18 Feng Y, Schlösser FJ & Sumpio B. The Semmes Weinstein monofilament examination as a screening tool for diabetic peripheral neuropathy. *Journal of Vascular Surgery* 2009 **50** 675–682. (doi:10.1016/j.jvs.2009.05.017)

19 Dros J, Wewerinke A, Bindels PJ & van Weert HC. Accuracy of monofilament testing to diagnose peripheral neuropathy: a systematic review. *Annals of Family Medicine* 2009 **7** 555–558. (doi:10.1370/afm.1016)

20 Abbott CA, Carrington AL, Ashe H, Bath S, Every LC, Griffiths J, Hann AW, Hussein A, Jackson N, Johnson KE, Ryder CH, Torkington R, Van Ross ER, Whalley AM, Widdows P, Williamson S, Boulton AJ & North-West Diabetes Foot Care Study. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. *Diabetic Medicine* 2002 **19** 377–384. (doi:10.1046/j.1464-5491.2002.00698.x)

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4.4 (PROSPECTIVE AND MULTICENTRE) VALIDATION AND COMPARISON OF CURRENTLY AVAILABLE SYSTEMS FOR PATIENTS' WITH DIABETES STRATIFICATION BY RISK OF FOOT ULCER DEVELOPMENT

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INTRODUCTION

Diabetic foot is a multifactorial condition. Understanding how each one of the clinical factors involved affects the morbidity risk allows a more comprehensive and rational vision of this problem, thus, increasing the efficacy of diabetic foot complications' prevention and treatment [1].

In the last guidance document from the International Working Group on Diabetic Foot (IWGDF) it was observed that there is a scarcity of robust data concerning how, whom, and when diabetic foot screening should be conducted [2].

A total of five classifications used to stratify subjects by their risk of developing a diabetic foot ulcer (DFU) were identified in a systematic review (SR) [3]. These classifications were developed or validated in high or low risk settings, and no multicentre study was ever conducted. All these classifications were validated and compared in a retrospective cohort study conducted in a Hospital Diabetic Foot Clinic [4]. In this study, no significant statistical differences were observed between classifications. Moreover, even in the highest risk groups all positive predictive values (PPV) were under 30% and moderate likelihood ratios (LR) were achieved.

Other SR [5] observed that the association of more than 100 predictive variables with DFU was tested in 71 studies. However, each variable's association with DFU development was assessed only by two or fewer studies in about 80% of the cases. This underlined the striking need for more research about measurements readily accessible to clinical investigators that may prove valuable in predicting foot outcomes.

For all this, our study main goals were to validate the available DFU development risk classifications, assess the predictive value of the included variables, and compare the classifications' accuracy between hospital and primary care settings.

As secondary objectives, we intended to assess the improvement in foot self-care habits, their impact on DFU risk and to identify which subjects that will adhere to adequate foot self-care habits.

METHODS

Type of study and selection of participants

A multicentre prospective cohort study was conducted. Subjects with diabetes and without active DFU, that underwent diabetic foot screening in different settings; namely the Centro Hospitalar de Vila Nova de Gaia EPE (a tertiary Hospital) Diabetic Foot Clinic, from December 2010 to December 2012; the Unidade de Saúde Familiar Aquae Flaviae, from July 2013 to September 2014; and Unidade de Saúde Familiar Santo André de Canidelo, from March to September 2014 (the last are both primary care institutions); were consecutively included.

Those subjects unable to walk and/or to respond adequately to foot examination tests were excluded.

Analysing the results from a retrospective cohort study comparing all the available risk classifications [4], we observed that the diagnostic accuracy measures ranged from 9.9% (a PPV value) up to 100% [for sensitivity, specificity and negative predictive values (NPV) in several cases].

So, for sample size calculation we considered that if we wished to detect a two-sided difference of 15% on the 45% specificity value [4] (the scenario that would require a larger sample size) between the two settings, for a 95% confidence interval (CI) and a power of 80%, a sample of 186 participants, for each setting, was proposed. Allowing a potential loss to follow up of approximately 20% we considered pertinent to include 223 subjects per setting, this is, a total of 446 participants.

This study was approved by the Comissão Nacional de Protecção de Dados (Data Protection National Committee) and the Ethical Committees from the Administração Regional de Saúde do Norte (North Regional Health Administration) and from each institution where it was performed. No adverse event occurred due to the study conduction.

Data collection

The risk classifications to be validated in this study, selected through a SR [3], were the American Diabetes Association (ADA), International Working Group on the Diabetic Foot (IWGDF), and Scottish Intercollegiate Grouping Network (SIGN) classifications, the Seattle risk score (both in its original and refined version) and the University of Texas Foot Risk System (UTFRS).

However, since this SR publication, and that we are aware of, another system to predict DFU development was developed that was called PODUS (Prediction Of Diabetic Foot Ulcerations). This classification was created using an individual participant data meta-analysis and was also applied in our study [6]. This classification considered subjects to be at high risk when there was history of DFU and as medium risk those with absent sensation to the Semmes-Weinstein monofilament (SWM) and/or with an absent pedal pulse in one or both feet.

At baseline, we collected demographic and clinical characterization variables, all the variables included in the classifications and others considered as pertinent in another SR [5] that was conducted to identify DFU occurrence predictive factors.

Data was recorded using a case-report form previously created and discussed with all the health professionals that participated in the variables' collection. In addition, a manual was developed and several formation sessions were performed to standardize data collection, to improve its consistency.

Variables were collected and registered by several professionals, namely general practitioners and nurses in the primary health care institutions and a podiatrist in the Hospital setting, with a variable number of years of experience on diabetic foot (from less than 1 up to 7 years).

Demographic and clinical characterization variables, history of previous DFU, visual and physical impairment (according to the SIGN definition [1] were obtained through clinical interview. A recent glycated haemoglobin (HbA1c) value, within 3 months, was collected through clinical file consult.

The presence of foot deformity, hyperkeratosis, tinea pedis, onychomycosis, and history of previous LEA and foot self-care habits were collected through foot examination. Previous lower extremity amputation (LEA) level was considered as the one with higher level.

Diabetic peripheral neuropathy (DPN) was diagnosed through a SWM and a tuning fork using the procedure described in the IWGDF recommendations [7]. Peripheral arterial disease (PAD) was considered present in the absence of at least one of the two foot pulses in one or both feet [8].

Footwear was categorised as low, medium or high risk using the classification proposed by Abbott et al [8]. In this classification, subjects using more often trainers, lace-ups, boots (low heel), extra depth/surgical shoes are categorized as at low risk of developing DFU; subjects wearing "slip-ons"/casual shoes, bar or buckle fastened shoes or slippers as at medium risk and those using open-toe sandals, high-heeled shoes or flip-flops as at high risk.

Measures were registered per individual, this is, when a variable occurred in one or both feet it was considered as present.

DFU was defined as a full-thickness skin defect distal to the malleoli [7].

Participants were followed for one year or until outcome occurred (DFU) or death. Subjects were re-assessed in variable intervals (from 1 to 6 months), according to the IWGDF recommendations [7] and health professionals' clinical judgement, and a reinforcement of adequate foot self-care habits was made. Participants were also instructed to return to the clinic if any foot complication appeared before the next scheduled appointment.

A participant was considered as lost to follow up when he or she missed the scheduled appointment(s) and did not return before the 1 year follow up. When this occurred, the subjects' clinical electronic file and the National Health Platform was consulted to identify if a DFU or death occurred in another institution.

Statistical analysis

Differences between settings and univariate association between variables and DFU occurrence assessment of improvement and prediction of adherence to adequate foot self-care habits were identified using statistical tests for two independent samples, such as the student's t test or the Mann-

Whitney test for continuous variables and X2 or Fisher's exact test for categorical variables. Statistical significance was considered when the p value was inferior to 0.05.

For each DFU risk classification, prognostic accuracy measures were calculated, namely sensitivity, specificity, likelihood ratios, predictive values and area under the receiver operating curve (AUC) and respective 95% CI. Statistical differences between classifications were assessed by comparing prognostic accuracy measures values and respective 95% CI. Statistical significance was considered when there was no overlap between the compared 95% CI.

RESULTS

In a median follow up of 12 months (1 to 12), a total of 32 subjects (7%) developed a DFU, 3 (0.7%) required a minor LEA, 4 (0.9%) a major LEA, 18 (4%) died and 61 (14%) were lost to follow-up. The majority of the events occurred in subjects followed in the hospital setting, this is, 91% of the DFU (n=29), 100% of the minor LEA (n=3), 75% of the major LEA (n=3), 89% of death (n=16) and 77% of the lost to follow-up (n=47).

Sample characterization

A total of 446 subjects were included, 223 from each setting (hospital and primary care). Participants had a mean age of 65 years, body mass index of 29 and a diabetes (DM) duration of 13 years. The majority were male (52%), lived with a companion (91%), had type 2 DM (99%) and used only oral anti-diabetic drugs for glycaemic control (69%) (See Table 1).

No missing data occurred.

In the primary care setting, subjects were significantly more commonly female, lived alone, had lower mean DM duration and HbA1c values, used less frequently insulin and presented less frequently any of the DM-related complications. All of the variables included in the available classifications were significantly less prevalent in the primary care, except for tinea pedis (See Table 1).

Variables associated with DFU occurrence

Analysing Table 1, we can observe that except for tinea pedis and low risk footwear all the variables included in the available classification systems were associated with a higher risk of DFU development at 1 year, in our univariate analysis. Higher DM duration, insulin use, and the presence of more than 1 DPN symptom and pain in rest also presented a statistically significant association with outcome.

Classifications validity for DFU prediction

Using the complete sample, meaning subjects from both the hospital and primary care setting, we observed that no statistically significant differences occurred between classifications on sensitivity, PPV, NPV and negative likelihood ratio when assembling the medium and high risk groups and the low, medium and high risk groups (See Table 2). NPV and negative likelihood ratios were not different between classifications when using only the high risk group as cut-off.

In the high risk group, the Seattle (both the original and the refined version) and the UTFRS classifications had lower sensitivity but higher specificity. The SIGN classification presented lower

specificity, PPV and positive LR. In this risk group PPV were less than 40% for almost all classifications.

Assembling the medium and high risk groups, the IWGDF, PODUS and SIGN classifications presented lower specificity and positive LR. In these risk groups PPV were inferior to 26% in all classifications.

Uniting the low, medium and high risk groups, the Seattle classification in its original version showed the higher specificity and positive LR, while the refined version presented the lower specificity.

The observed likelihood ratios are expected to have a moderate impact on the DFU risk development likelihood. In the high risk group positive LR were usually between 5 and 10 and the low risk group negative LR typically ranged from 0.1 to 0.2.

Observing Table 3, no differences in the AUC of the classifications were found and all presented values equal or superior to 0.75.

Comparing the classifications' accuracy between hospital and primary care setting (See Table 2), we observe that, for all cut-offs, sensitivity and positive LR are lower in the primary care setting, while specificity and negative LR are higher. NPV are similar, and superior to 90%, in both contexts using any of the cut-offs and classifications.

In what concerns AUC (See Table 3), no differences between classifications were found considering the complete sample, hospital or primary care setting. In the primary care setting, AUC values tended to be lower (without statistical significance).

Foot self-care habits

At baseline, participants had less frequently an adequate foot skin moisturizing but wore more frequently a low risk footwear in the hospital setting, when compared to the primary care setting (See Table 1).

The presence of adequate foot self-care habits at baseline did not have an impact on the prevention of DFU development at 1 year (See Table 1). In fact, those in which a DFU developed were more prone to adhere to each of the 3 studied parameters.

So, we studied the impact of the presence of these habits, at baseline, on DFU recurrence. When including only subjects with history of previous DFU in our analysis, baseline adherence to each one or ≥2 foot self-care habits did not achieved a statistical significant association with the risk of outcome development (results not shown). However, those in which a DFU developed were less prone to adhere to each of the 3 studied parameters.

After 1 year of follow-up a statistically significant improvement in adherence to adequate skin moisturizing, nail care and footwear was observed, when evaluating the total sample or the hospital setting. In the primary care setting, there was not a significant improvement only in adherence to adequate nail care (See Table 4).

Assessing Table 5, we found that those with previous DFU history tended to adhere more frequently to an adequate skin moisturizing after 1 year of follow-up; those with lower age presented more frequently adequate nail care; and that male gender, higher DM duration, insulin use, presence of retinopathy, hyperkeratosis and history of previous DFU and LEA were associated with the use of low risk footwear.

DISCUSSION

The selection and application of an adequate classification to stratify subjects by their risk of DFU development is crucial for a good clinical practice.

This is the first study prospectively validating all the available classifications in a multicentre context, comparing the classifications' accuracy among them and between the primary care and the hospital setting.

In agreement with our previous study [4], this article concluded that the available classifications are equally and highly valid. Therefore one should select which one to apply according to practicability and characteristics of each setting.

Sensitivity and specificity values varied between classifications and cut-off used.

In all the classifications and for any cut-off, NPV were always superior to 90%. So, one subject classified as low risk has a low chance of developing a DFU and should be followed in the primary care setting. However, PPV were typically under 40%, which may represent a burden for the high risk setting, due to the high number of subjects that will be followed in that context but will not develop a DFU.

Assessing the classifications' LR, we can observe that to be classified as at high or low risk will have a moderate impact on the subjects' likelihood of developing a DFU, by increasing or reducing it, respectively.

AUC values for the complete sample were generally superior to 0.80, which highlights the high validity of the classifications. The lowest values corresponded to the SIGN and UTFRS classifications. However, without presenting a statistical significant difference.

There were differences in subjects' characteristics and the classifications' accuracy when comparing the primary care to the hospital setting.

Subjects lived alone more frequently in the primary care setting, which was expected as more lived in a rural setting.

This study was conducted in an Hospital and a primary care institution (USF Santo André de Canidelo) located in a city in the North Coast of Portugal, but also in a primary institution in a rural region in the interior of the North of Portugal (USF Aquae Flaviae). Our country is considered to be one the most affected countries in the European Union by the population desertification. This process is defined by the migration flux from rural areas at the interior to urban areas at the coast line and affects one third of the national territory. This phenomena leads to family disaggregation, as those that migrate are usually the active population, and to interior regions with more poverty and aged population. So, aged people from rural areas that have lost his/her spouse tend to live more commonly alone due to the fact that their descendants have moved to another region.

Also, subjects in this context had better glycaemic control and less DM-related complication, which was also anticipated. Subjects with more severe complications are usually followed in hospital context.

Classifications tended to have lower accuracy measures in the primary care setting. We believe this occurred for many reasons that we will enunciate next in detail. PPV values are affected by the outcome prevalence and in the primary setting DFU occurred in 3 subjects, representing 1% of these subjects.

Independently of the classification used, 75% of the subjects followed in the primary care centres that developed a DFU were categorized as being at medium or low risk. This could be due to the existence of less experienced professionals that could have missed to diagnose DPN and/or PAD in such subjects. Despite the sessions that were conducted in order to improve the standardization and quality of such procedures, these variables seem to be experience dependent.

All the variables included in the classifications, were significantly associated with a higher risk of DFU, except for tinea pedis. DPN symptoms, pain in rest and diabetes duration were also a predictor of DFU development. These results are in accordance to the previous SR [3] and retrospective cohort study [4]. On the other hand, DPN and PAD are already included in the available classifications, so, no great improvement in their accuracy is expected. Diabetes duration association should be tested in multivariate analysis to overcome a potential confounding effect.

Although nephropathy is considered to be an important variable for DFU risk prediction [9,10], in this study no association was found. Nevertheless, in our study it was collected as reported nephropathy and the presence of end-stage renal disease was not collected separately.

Adherence to foot self-care habits at baseline had no significant impact on DFU development risk at 1 year. We consider that in order to detect an effect of these habits on DFU prevention a longer follow-up would be needed.

Adequate moisturizing of the skin was more frequent on subjects that developed a DFU. This association was linked to the fact that those at higher risk tended to adhere more to foot self-care habits. Furthermore this association was not observed when including only subjects with previous DFU on the analysis.

After 1 year of follow-up and education of the participants, an improvement in adherence to all of the studied foot self-care habits was observed. The awareness of the magnitude of improvement of adherence to foot self-care habits with the surveillance and educational reinforcement during the periodical appointments is important to understand the baseline value to which specific educational interventions should be compared to.

It is important to understand which individuals will adhere more easily to the prescribed habits to better personalize their education.

We observed, as anticipated, that older people had less frequently an adequate nail care. The use of low risk footwear was more prevalent in male subjects, with higher DM duration, using insulin, with retinopathy, hyperkeratosis and previous foot complications. Female subjects are more resistant to change footwear due to aesthetic reasons. We consider that a special reinforcement on this care is given to those with longer disease duration, DM-related complications and biomechanical alterations. In addition, in the hospital setting some of the subjects classified as at high risk with biomechanical alterations can have therapeutic footwear free of charge.

This study has some limitations. Namely, the number of DFU in the primary care setting was very low, which greatly affects the diagnostic accuracy measures precision and diminished the PPV values.

Some of the researchers had very low experience on diabetic foot and no reliability assessment was conducted for the predictive variables detection, the classifications application or outcome recognition. This may had an indeterminate effect on the estimated measures. However, by including health professionals with different levels of experience we intended to better portray the reality of clinical care in this topic.

The presence of the predictive variables collection and the classifications' application was made and registered before outcome development. So, researchers were not blind to baseline characteristics when assessing DFU occurrence. This can lead to an overestimation of the estimated measures.

There were differences in each institution's participants' inclusion period due to the time needed to recruit the institutions, to receive ethical consent and to each institution's logistics.

Some decisions were made in order to facilitate results' analysis. When indeterminate results occurred, it was considered as the presence of such variable in the individual.

In line with a previous study [4], we have simplified the DPN and PAD diagnosis by replacing vibration perception threshold test by the tuning fork and using only foot pulses to detect the last. This may have underestimated the classifications' accuracy measures. Nonetheless, it simplifies the classifications' application and therefore their use in clinical practice.

Our results are applicable for all clinical settings. However, our sample was constituted by subjects with a mean of 65 years and mainly with type 2 DM (99%), which may impair our results' generalizability. Then again, this reflects the majority of diabetic foot clinics' population.

In the primary care setting the outcome prevalence was of 7% and in the hospital setting of 13%. Studies published for the prediction o DFU development with 1 year of follow-up [3] reported prevalence values of 5.7 (without setting reported), 7.2 (in a multicentre study) and 20.9% (in a general internal medicine practice). So, for both settings we had low prevalence values and could not achieve the 100 events that are recommended for prediction models validation [11].

As main strengths our study presents its prospective and multicentre design, including all type of health professionals that work on this topic and with different experience levels. The number of participants was based on an appropriate sample size calculation.

No missing data occurred and a comparison of the diagnostic accuracy measures between classifications and settings was possible.

The STARD [12] and STROBE [13] checklists were used to improve reporting.

We have used a 1 year follow up in accordance to the guidelines, in which a reclassification of diabetic foot risk is proposed [2].

We have studied the impact of foot self-care habits impact on DFU risk, improvement after 1 year of follow-up and variables' associated with such adherence. This is a topic for which evidence is considered both crucial and scarce [2].

In conclusion, all the available classifications used to stratify individuals with DM by their risk of DFU development showed high and similar accuracy in this external prospective multicentre validation study. The follow up of subjects considered to be at low risk in primary care institutions and at medium and high risk in hospital institutions is considered as reasonable.

The variables included in the classifications were considered as pertinent. DM duration was considered as associated with DFU development, in univariate analysis, and is not currently included in any classification.

Foot self-care habits adherence at baseline had no impact on DFU risk development reduction at 1 year. Those at higher risk tended to adhered more frequently to such habits.

A significant improvement on these habits adherence was detected during diabetic foot surveillance appointments. Nail care should be reinforced and provided specially to older people. The aesthetics of low risk footwear should be considered when prescribing them to females. Education on the importance of adequate footwear to subjects with more recent diagnosis of DM, without DM-related and foot complication should be emphasized.

Further studies addressing the accuracy of the available classifications in the primary care setting and the impact of adherence to foot self-care habits on DFU risk at long term are needed.

Table 1. Differences between settings and association of the baseline variables with DFU and recurrence of DFU

Variables	All (n=446)	Hospital setting (n=223)	Community setting (n=223)	p-value	DFU (n=32)	No DFU (n=414)	p-value
Subject characterization							
Age (in years) [mean (SD)]	65 (11)	65 (10)	65 (10)	0.7[a]	68 (12)	65 (11)	0.1[a]
Male gender [n (%)]	233 (52)	128 (57)	105 (47)	**0.03**[b]	19 (59)	214 (52)	0.4[b]
Body mass index [mean (SD)]	29 (5)	29 (6)	29 (5)	0.9[a]	28 (5)	29 (5)	0.09[a]
Lives alone [n (%)]	39 (9)	12 (5)	27 (12)	**0.01**[b]	3 (9)	36 (9)	0.9[c]
Diabetes characterization and comorbidities							
Type 2 diabetes [n (%)]	443 (99)	223 (100)	220 (99)	0.08[c]	32 (100)	411 (99)	0.6[c]
Diabetes duration (in years) [mean (SD)]	13 (10)	16 (11)	9 (8)	**<0.001**[a]	18 (11)	12 (10)	**0.01**[a]
Insulin use [n (%)]	136 (31)	106 (48)	30 (14)	**<0.001**[b]	18 (56)	118 (29)	**0.001**[b]
Reported hypertension [n (%)]	343 (77)	166 (74)	177 (79)	0.2[b]	23 (72)	320 (77)	0.5[b]
Reported myocardial infarction [n (%)]	30 (7)	26 (12)	4 (2)	**<0.001**[b]	4 (12)	26 (7)	0.2[c]
Reported history of stroke [n (%)]	50 (11)	39 (18)	11 (5)	**<0.001**[b]	7 (22)	43 (11)	0.05[c]
Reported retinopathy [n (%)]	111 (25)	90 (40)	21 (10)	**<0.001**[b]	8 (25)	103 (25)	1.0[b]
Reported nephropathy [n (%)]	58 (13)	45 (20)	12 (6)	**<0.001**[b]	5 (16)	53 (13)	0.7[b]
Variables included in the classifications							
HbA1c (in %) [mean (SD)]	7.3 (1.6)	8.0 (1.6)	6.8 (1.4)	**<0.001** [a]	8.4 (1.8)	7.2 (1.6)	**0.001**[a]
Visual impairment [n (%)]	159 (36)	115 (52)	44 (20)	**<0.001**[b]	17 (53)	142 (24)	**0.03**[b]
Physical impairment [n (%)]	124 (28)	91 (41)	33 (15)	**<0.001**[b]	17 (53)	107 (26)	**0.001**[b]
Foot deformity [n (%)]	250 (56)	184 (83)	66 (30)	**<0.001**[b]	30 (94)	220 (53)	**<0.001**[b]
Onychomycosis [n (%)]	211 (47)	132 (59)	79 (35)	**<0.001**[b]	22 (69)	189 (46)	**0.01**[b]
Tinea pedis [n (%)]	34 (8)	10 (4)	24 (11)	**0.01**[b]	2 (6)	32 (8)	0.8[c]
SWM sensitivity altered [n (%)]	137 (31)	88 (40)	49 (22)	**<0.001**[b]	19 (59)	118 (29)	**<0.001**[b]
TFS altered [n (%)]	135 (30)	79 (35)	56 (25)	**0.02**[b]	23 (72)	112 (27)	**<0.001**[b]
DPN [n (%)]	194 (44)	108 (48)	86 (39)	**0.04**[b]	24 (75)	170 (41)	**<0.001**[b]
PAD [n (%)]	86 (19)	62 (28)	24 (11)	**<0.001**[b]	18 (56)	68 (16)	**<0.001**[b]
History of DFU [n (%)]	77 (17)	75 (34)	2 (1)	**<0.001**[b]	23 (72)	54 (13)	**0.001**[b]
History of LEA [n (%)]	26 (6)	24 (11)	2 (1)	**<0.001**[b]	12 (38)	14 (3)	**0.001**[c]
Low risk footwear [n (%)]	193 (43)	117 (52)	76 (34)	**<0.001**[b]	14 (44)	179 (43)	1.0[b]
Other foot characterization variables not included in the classifications							
More than 1 symptom of DPN [n (%)]	120 (27)	92 (41)	28 (13)	**<0.001**[b]	17 (53)	103 (25)	**0.005**[b]
Oedema [n (%)]	100 (22)	73 (33)	27 (12)	**<0.001**[b]	8 (25)	92 (22)	0.7[b]
Hyperkeratosis [n (%)]	142 (32)	40 (18)	102 (46)	**<0.001**[b]	6 (19)	136 (33)	0.2[b]
Pain in rest [n (%)]	39 (9)	15 (7)	24 (11)	0.1[b]	6 (19)	33 (8)	**0.04**[c]
Claudication [n (%)]	49 (11)	31 (14)	18 (8)	0.05[b]	4 (13)	45 (11)	0.8[c]
Adequate skin moisturizing [n (%)]	249 (56)	126 (56)	123 (55)	0.8[b]	24 (75)	225 (54)	**0.03**[b]
Adequate nail care [n (%)]	354 (79)	162 (73)	192 (86)	**0.002**[b]	26 (81)	328 (79)	0.8[b]

DFU: Diabetic Foot Ulcer; DPN: Diabetic Peripheral Neuropathy; PAD: Peripheral Arterial Disease; reDFU: DFU recurrence; SD: Standard Deviation; SWM: Semmes-Weinstein Monofilament; TFS: Tuning Fork Sensation

[a]: student's t test for independent samples; [b]: Fisher's exact test; [c]: X^2 test

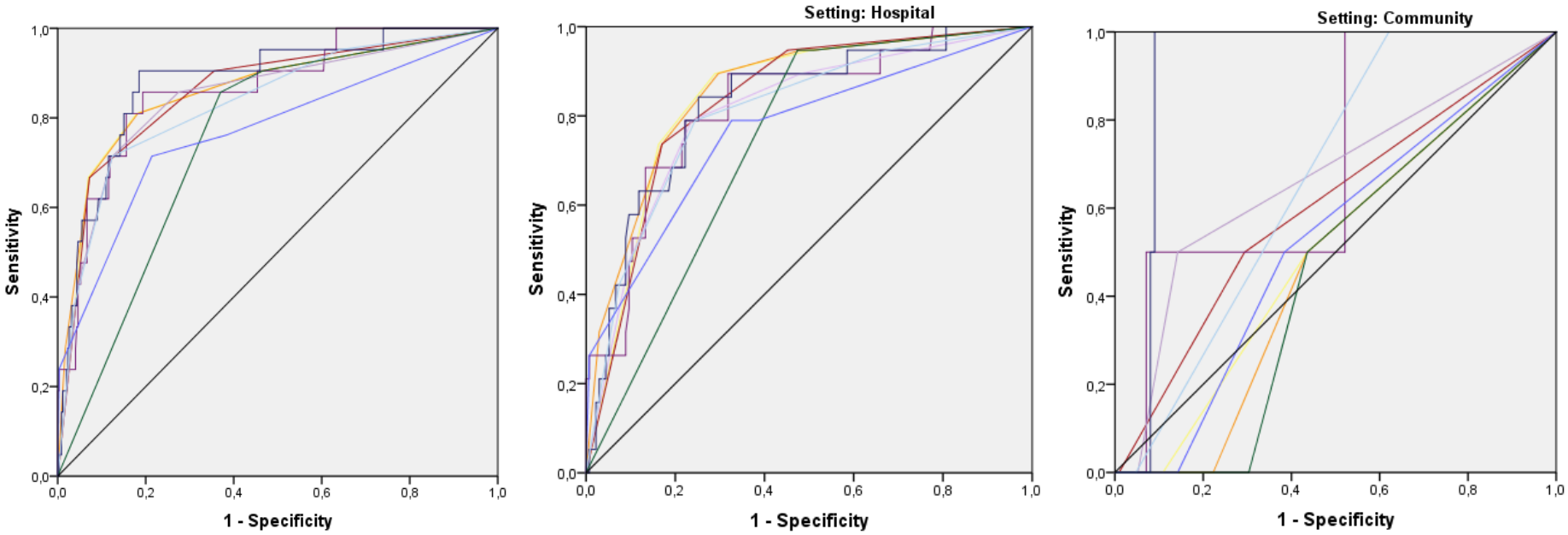
Table 2. Diagnostic accuracy measures (in percentages) of the classification systems for DFU development prediction at 1 year in the total sample, the hospital and community setting

DAM	ADA			IWGDF			PODUS			Seattle			Seattle refined			SIGN			UTFRS		
	RG	Value	95% CI	RG	Value	95% CI	RG	Value	95% CI	RG	Value	95% CI	RG	Value	95% CI	RG	Value	95% CI	RG	Value	95% CI
All																					
Sens	3	72	56-87	3A+	72	56-87	High	72	56-87	Highest	43	22-64	Highest	38	17-59	High	91	81-100	3	31	15-47
Spe		87	84-90	3B	87	84-90		87	84-90		95	93-98		96	94-98		58	53-63		98	97-100
PPV		30	20-41		30	20-40		30	20-40		36	18-55		38	17-59		14	10-19		59	35-82
NPV		98	96-99		98	96-99		98	96-99		97	95-98		96	94-98		99	97-100		95	93-97
LR+		5.6	4.0-7.8		5.5	4.0-7.6		5.5	4.0-7.7		9.3	4.7-18.5		10.2	4.7-21.8		2.2	1.8-2.5		18.5	7.5-45.3
LR-		0.3	0.2-0.6		0.3	0.2-0.6		0.3	0.2-0.6		0.6	0.4-0.9		0.6	0.5-0.9		0.2	0.05-0.5		0.7	0.6-0.9
Sens	3+2	84	72-97	3A+	91	81-100	High+	91	81-100	Highest	71	52-91	Highest	71	52-91	High+	94	85-100	3+2	72	56-87
Spe		77	72-81	3B+	62	58-67	Med	60	55-65	+	88	84-91	+	88	84-91	Med	50	45-54		74	70-79
PPV		22	15-29	2A+	16	10-21		15	10-20	Next-to-	26	15-37	Next-to-	26	15-37		13	8-17		18	11-24
NPV		98	97-100	2B	99	98-100		99	97-100	Highest	98	97-100	Highest	98	97-100		99	98-100		97	95-99
LR+		3.6	2.9-4.5		2.4	2.0-2.8		2.3	1.9-2.7		5.8	3.9-8.5		5.8	3.9-8.5		1.9	1.6-2.1		2.8	2.1-3.7
LR-		0.2	0.09-0.5		0.2	0.05-0.4		0.2	0.05-0.5		0.3	0.2-0.6		0.3	0.2-0.6		0.1	0.03-0.5		0.4	0.2-0.7
Sens	3+2+1	94	85-100	3A+	94	85-100				Highest + Next-to-Highest + Next-to- Lowest	86	71-100	Highest + Next-to- Highest	95	86-100				3+2+1	75	60-90
Spe		50	45-55	3B+	50	45-54					73	68-77		36	31-41					59	54-64
PPV		13	8-17	2A+	13	8-17					16	9-23		8	5-12					12	8-17
NPV		99	97-100	2B+	99	98-100					99	98-100		99	98-100					97	95-99
LR+		1.9	1.7-2.1	1	1.9	1.6-2.1					3.1	2.5-4.0		1.5	1.3-1.7					1.8	1.4-2.3
LR-		0.1	0.03-0.5		0.1	0.03-0.5					0.2	0.07-0.6		0.1	0.02-0.9					0.4	0.2-0.8
Hospital Setting																					
Sens	3	79	65-94	3A+	79	65-94	High	79	65-94	Highest	47	25-70	Highest	42	20-64	High	97	90-100	3	34	17-52
Spe		74	68-80	3B	73	67-79		73	67-79		90	86-95		93	88-97		45	38-52		96	94-99
PPV		31	21-42		31	20-41		31	20-41		41	20-61		44	21-67		21	14-28		59	35-82
NPV		96	93-99		96	93-99		96	93-99		92	88-97		92	87-97		99	97-100		91	87-95
LR+		3.0	2.2-4.1		2.9	2.2-4.0		3.0	2.2-4.0		5.0	2.5-10.0		5.7	2.6-12.7		1.8	1.5-2.0		9.6	3.9-23.1
LR-		0.3	0.1-0.6		0.3	0.1-0.6		0.3	0.1-0.6		0.6	0.4-0.9		0.6	0.4-0.9		0.08	0.01-0.5		0.7	0.5-0.9
Sens	3+2	93	84-100	3A+	97	90-100	High+	97	90-100	Highest +	79	61-97	Highest +	79	61-97	High+	97	90-100	3+2	76	60-91
Spe		63	56-70	3B+	55	48-62	Med	48	41-55		76	69-84		76	69-83	Med	42	35-49		61	54-68
PPV		27	19-36	2A+	25	17-32		22	15-29	Next-to-	32	19-45	Next-to-	31	17-44		20	13-26		23	14-31
NPV		98	96-100	2B	99	97-100		99	97-100	Highest	96	93-100	Highest	96	93-100		99	97-100		94	90-98
LR+		2.5	2.0-3.1		2.2	1.8-2.6		1.9	1.6-2.2		3.4	2.3-4.9		3.3	2.2-4.7		1.7	1.4-1.9		2.0	1.5-2.6

LR-		0.1	0.03-0.4		0.06	0.009-0.4		0.07	0.01-0.5		0.3	0.1-0.7		0.3	0.1-0.7		0.08	0.01-0.6		0.4	0.2-0.8
Sens	3+2	97	90-100	3A+	97	90-100				Highest	89	76-100	Highest	95	85-100				3+2	76	60-91
Spe	+1	42	35-49	3B+	58	51-65				+ Next-to-	52	44-61	+ Next-	32	24-40				+1	56	49-63
PPV		20	13-27	2A+	25	17-32				Highest	21	12-30	to-	16	9-23					20	13-28
NPV		99	96-100	2B+	99	97-100				+ Next-	97	94-100	Highest	98	93-100					94	90-98
LR+		1.7	1.5-1.9	1	2.3	1.9-2.8				to- Lowest	1.9	1.5-2.4	+ Next-	1.4	1.2-1.6					1.7	1.3-2.2
LR-		0.08	0.01-0.6		0.06	0.009-0.4					0.2	0.05-0.8	to- Lowest	0.2	0.02-1.11					0.4	0.2-0.8
Community setting																					
Sens	3	0	NA	3A+	0	NA	High	0	NA	Highest	0	NA	Highest	0	NA	High	33	0-87	3		
Spe		99	98-100	3B	99	98-100		99	98-100		99	97-100		99	97-100		70	64-76			
PPV		0	NA		0	NA		0	NA		0	NA		0	NA		1	0-4		n=0	
NPV		99	97-100		99	97-100		99	97-100		99	98-100		99	97-100		99	97-100		NA	
LR+		NA	NA		NA	NA		NA	NA		NA	NA		NA	NA		1.1	0.2-5.5			
LR-		1.0	1.0-1.0		1.0	1.0-1.0		1.0	1.0-1.0		1.0	1.0-1.0		1.0	1.0-1.0		1.0	0.4-2.1			
Sens	3+2	0	NA	3A+	33	0-87	High+	33	0-87	Highest	0	NA	Highest	0	NA	High+	67	13-100	3+2	33	0-87
Spe		89	84-93	3B+	78	72-83	Med	70	64-76	+	95	92-98	+	95	92-98	Med	56	50-63		70	63-76
PPV		0	NA	2A+	2	0-6		2	0-6	Next-to-	0	NA	Next-to-	0	NA		2	0-5		1	0-3
NPV		98	97-100	2B	99	97-100		99	97-100	Highest	99	98-100	Highest	99	98-100		99	98-100		99	96-100
LR+		NA	NA		1.5	0.3-7.6		1.1	0.2-5.7		NA	NA		NA	NA		1.5	0.7-3.4		1.1	0.2-5.5
LR-		1.1	1.1-1.2		0.9	0.4-1.9		0.9	0.4-2.1		1.1	1.0-1.1		1.0	1.0-1.1		0.6	0.1-2.9		1.0	0.4-2.1
Sens	3+2	67	13-100	3A+	67	13-100				Highest	50	0-100	Highest	100	NA				3+2	67	13-100
Spe	+1	56	50-63	3B+	56	50-63				+ Next-to-	86	81-90	+ Next-	38	31-44				+1	62	55-68
PPV		2	0-5	2A+	2	0-5				Highest	3	0-9	to-	2	0-4					2	0-6
NPV		99	98-100	2B+	99	98-100				+ Next-	99	98-100	Highest	100	NA					99	98-100
LR+		1.5	0.7-3.4	1	1.5	0.7-3.4				to- Lowest	3.5	0.8-14.6	+ Next-	1.6	1.5-1.8					1.7	0.8-4.0
LR-		0.6	0.1-2.9		0.6	0.1-2.9					0.6	0.1-2.3	to- Lowest	NA	NA					0.5	0.1-2.7

ADA: American Diabetes Association; CI: Confidence Interval; DAM: Diagnostic Accuracy Measure; IWGDF: International Working Group on the Diabetic Foot; Med: Medium; NA: Not Applicable; PODUS: Prediction Of Diabetic Foot Ulcerations; RG: Risk Group; SIGN: Scottish Intercollegiate Grouping Network; UTFRS: University of Texas Foot Risk System

Figure 1. Area Under the Receiver Operating Characteristic Curve of the classification systems for DFU development prediction at 1 year in the total sample (figure on the left), the hospital (figure in the middle) and community setting (figure in the right)



Yellow line: American Diabetes Association; Orange line: International Working Group on Diabetic Foot; Burgundy line: PODUS (prediction of diabetic foot ulcerations); Purple line: Seattle score; Lilac line: Seattle categories; Dark blue line: Seattle score; Light blue line: Seattle refined categories; Green line: Scottish Intercollegiate Guidelines Network; Violet line: University of Texas

Table 3. Area Under the Receiver Operating Characteristic Curve of the classification systems for DFU development prediction at 1 year in the total sample, the hospital and community setting

Classification	All		Hospital setting		Community setting	
	AUC	**95% CI**	**AUC**	**95% CI**	**AUC**	**95% CI**
ADA	0.86	0.76-0.95	0.84	0.76-0.93	0.51	0.14-0.87
IWGDF	0.86	0.77-0.96	0.86	0.77-0.94	0.48	0.15-0.80
PODUS	0.86	0.77-0.95	0.83	0.75-0.92	0.60	0.19-1.00
Seattle (continuous)	0.86	0.78-0.95	0.82	0.72-0.92	0.70	0.39-1.00
Seattle (categorical)	0.85	0.75-0.94	0.81	0.70-0.92	0.67	0.26-1.00
Seattle Refined (continuous)	0.88	0.81-0.96	0.83	0.73-0.93	0.92	0.88-0.95
Seattle Refined (categorical)	0.84	0.74-0.93	0.81	0.70-0.91	0.67	0.43-0.90
SIGN	0.75	0.66-0.84	0.74	0.64-0.83	0.46	0.16-0.75
UTFRS	0.77	0.65-0.89	0.77	0.64-0.89	0.52	0.17-0.88

ADA: American Diabetes Association; CI: Confidence Interval; IWGDF: International Working Group on the Diabetic Foot; PODUS: Prediction Of Diabetic Foot Ulcerations; SIGN: Scottish Intercollegiate Grouping Network; UTFRS: University of Texas Foot Risk System

Table 4. Improvement of foot self-care habits after 1 year of follow up

	Adequate skin moisturizing			Adequate nail care			Low risk footwear		
	Baseline	**After 1 year**	**p-value**	**Baseline**	**After 1 year**	**p-value**	**Baseline**	**After 1 year**	**p-value**
Total sample [n (%)]	249 (56)	240 (72)	**<0.001**[a]	354 (79)	298 (89)	**<0.001**[a]	193 (43)	178 (53)	**0.006**[a]
Hospital setting [n (%)]	126 (56)	95 (72)	**<0.001**[a]	162 (73)	113 (86)	**<0.001**[a]	117 (52)	80 (61)	**0.04**[a]
Community setting [n (%)]	123 (55)	145 (72)	**0.002**[a]	192 (86)	185 (91)	0.3[a]	76 (34)	98 (48)	**0.006**[a]

[a]: Fisher's exact test; [b]: X^2 test

Table 5. Variables associated with good foot self-care habits after 1 year of follow up

Variables	Adequate skin moisturizing			Adequate nail care			Low risk footwear		
	Yes (n=240)	No (n=95)	p-value	Yes (n=298)	No (n=37)	p-value	Yes (n=178)	No (n=157)	p-value
Subject characterization									
Age (in years) [mean (SD)]	65 (10)	66 (10)	0.7[a]	65 (10)	70 (9)	**0.006**[a]	65 (10)	65 (11)	0.6[a]
Male gender [n (%)]	120 (50)	48 (50)	0.9[b]	148 (50)	20 (54)	0.4[b]	103 (58)	64 (41)	**0.004**[b]
Body mass index [mean (SD)]	30 (6)	29 (5)	0.4[a]	29 (6)	29 (5)	0.9[a]	30 (5)	29 (6)	0.9[a]
Lives alone [n (%)]	22 (9)	7 (7)	0.8[b]	26 (9)	3 (8)	1.0[b]	14 (8)	15 (10)	0.6[b]
Diabetes characterization and comorbidities									
Type 2 diabetes [n (%)]	238 (99)	91 (96)	0.2[b]	296 (99)	33 (89)	0.3[b]	176 (99)	152 (97)	1.0[b]
Diabetes duration (in years) [mean (SD)]	12 (11)	12 (9)	1.0[a]	11 (10)	14 (10)	0.1[a]	13 (10)	7 (2)	**0.03**[a]
Insulin use [n (%)]	63 (26)	23 (24)	0.9[b]	77 (26)	9 (24)	1.0[b]	55 (31)	30 (19)	**0.03**[b]
Reported hypertension [n (%)]	187 (78)	70 (74)	0.6[b]	230 (77)	27 (73)	1.0[b]	135 (76)	121 (77)	0.5[b]
Reported myocardial infarction [n (%)]	12 (5)	5 (5)	0.8[b]	15 (5)	2 (5)	0.7[b]	12 (7)	5 (3)	0.2[b]
Reported history of stroke [n (%)]	24 (10)	9 (9)	1.0[b]	30 (10)	3 (8)	1.0[b]	17 (10)	16 (10)	0.9[b]
Reported retinopathy [n (%)]	46 (19)	20 (21)	0.6[b]	59 (20)	7 (19)	0.8[b]	44 (25)	21 (13)	**0.01**[b]
Reported nephropathy [n (%)]	23 (10)	10 (11)	0.7[b]	32 (11)	1 (3)	0.2[b]	20 (11)	12 (8)	0.4[b]
Variables included in the classifications									
HbA1c (in %) [mean (SD)]	6.9 (1.4)	7.2 (1.6)	0.2[a]	7.2 (1.6)	7.0 (1.5)	0.5[a]	7.2 (1.7)	7.1 (1.4)	0.4[a]
Visual impairment [n (%)]	75 (31)	27 (28)	0.7[b]	88 (30)	14 (38)	0.2[b]	62 (35)	39 (25)	0.07[b]
Physical impairment [n (%)]	53 (22)	23 (24)	0.7[b]	69 (23)	7 (19)	0.8[b]	46 (26)	29 (18)	0.1[b]
Foot deformity [n (%)]	122 (51)	41 (43)	0.3[b]	145 (49)	18 (49)	0.7[b]	96 (54)	67 (43)	0.08[b]
Onychomycosis [n (%)]	105 (44)	36 (38)	0.5[b]	122 (41)	19 (51)	0.1[b]	83 (47)	58 (37)	0.1[b]
Tinea pedis [n (%)]	19 (8)	11 (12)	0.3[b]	24 (8)	6 (16)	0.1[b]	16 (9)	14 (9)	1.0[b]
SWM sensitivity altered [n (%)]	66 (28)	29 (31)	0.6[b]	86 (29)	9 (24)	0.8[b]	58 (33)	36 (23)	0.09[b]
TFS altered [n (%)]	68 (28)	20 (21)	0.2[b]	78 (26)	10 (27)	0.7[b]	48 (27)	39 (25)	0.8[b]
DPN [n (%)]	98 (41)	39 (41)	0.9[b]	122 (41)	15 (41)	0.7[b]	78 (44)	58 (37)	0.3[b]
PAD [n (%)]	36 (15)	14 (15)	0.2[b]	43 (14)	7 (19)	0.5[b]	32 (18)	18 (11)	0.3[b]
History of DFU [n (%)]	32 (13)	5 (5)	*0.05*[b]	35 (12)	2 (5)	0.4[b]	30 (17)	7 (4)	**<0.001**[b]
History of LEA [n (%)]	11 (5)	1 (1)	0.2[b]	12 (4)	0 (0)	0.6[b]	11 (6)	1 (1)	**0.007**[b]
Other foot characterization variables not included in the classifications									
More than 1 symptom of DPN [n (%)]	225 (94)	75 (79)	0.4[b]	281 (94)	34 (92)	0.3[b]	170 (96)	144 (92)	0.6[b]
Oedema [n (%)]	38 (16)	23 (24)	0.08[b]	52 (17)	9 (24)	0.2[b]	37 (21)	24 (15)	0.3[b]
Hyperkeratosis [n (%)]	79 (33)	36 (38)	0.5[b]	104 (35)	11 (30)	0.5[b]	64 (36)	51 (32)	**0.02**[b]
Pain in rest [n (%)]	20 (8)	10 (10)	0.5[b]	26 (9)	4 (11)	0.5[b]	15 (8)	14 (9)	0.8[b]
Claudication [n (%)]	23 (10)	9 (9)	1.0[b]	28 (9)	4 (11)	0.6[b]	19 (11)	13 (8)	0.6[b]

DFU: Diabetic Foot Ulcer; DPN: Diabetic Peripheral Neuropathy; PAD: Peripheral Arterial Disease; SD: Standard Deviation; SWM: Semmes-Weinstein Monofilament; TFS: Tuning Fork Sensation

[a]: student's t test for independent samples; [b]: Fisher's exact test; [c]: X^2 test

REFERENCES

1. Leese GP, Reid F, McAlpine R, et al. Stratification of foot ulcer risk in patients with diabetes: a population-based study. Int J Clin Pract 2006;60:541-5.
2. Bus SA, van Netten JJ, Lavery LA, et al. IWGDF guidance on the prevention of foot ulcers in at-risk patients with diabetes. Diabetes Metab Res Rev 2016;32 Suppl 1:16-24.
3. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia 2011;54:1190-9.
4. Monteiro-Soares M, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Validation and comparison of currently available stratification systems for patients with diabetes by risk of foot ulcer development. European journal of endocrinology / European Federation of Endocrine Societies 2012;167:401-7.
5. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev 2012;28:574-600.
6. Crawford F, Cezard G, Chappell FM, et al. A systematic review and individual patient data meta-analysis of prognostic factors for foot ulceration in people with diabetes: the international research collaboration for the prediction of diabetic foot ulcerations (PODUS). Health technology assessment (Winchester, England) 2015;19:1-210.
7. Bakker K, Apelqvist J, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot 2011. Diabetes Metab Res Rev 2012;28 Suppl 1:225-31.
8. Abbott CA, Carrington AL, Ashe H, et al. The North-West Diabetes Foot Care Study: incidence of, and risk factors for, new diabetic foot ulceration in a community-based patient cohort. Diabet Med 2002;19:377-84.
9. Ndip A, Rutter MK, Vileikyte L, et al. Dialysis treatment is an independent risk factor for foot ulceration in patients with diabetes and stage 4 or 5 chronic kidney disease. Diabetes Care 2010;33:1811-6.
10. Otte J, van Netten JJ, Woittiez AJ. The association of chronic kidney disease and dialysis treatment with foot ulceration and major amputation. Journal of vascular surgery 2015;62:406-11.
11. Moons KG, Altman DG, Reistma JB, et al. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): explanation and elaboration. Ann Inter Med 2015;162:W1-W73.
12. Bossuyt PM, Reitsma JB, Bruns DE, et al. STARD 2015: an updated list of essential items for reporting diagnostic accuracy studies. Bmj 2015;351:h5527.
13. Vandenbroucke JP, von Elm E, Altman DG, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Annals of internal medicine 2007;147:W163-94.

CHAPTER 5: DIABETIC FOOT ULCER PROGNOSIS

5.1 CLASSIFICATION SYSTEMS FOR LOWER EXTREMITY AMPUTATION PREDICTION IN SUBJECTS WITH ACTIVE DIABETIC FOOT ULCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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RESEARCH ARTICLE

Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis

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Abstract

Aim We aimed to systematically review the available systems used to classify diabetic foot ulcers (DFUs) in order to synthesize their methodological qualitative issues and accuracy to predict lower extremity amputation (LEA), as this may represent a critical point in these patients' care.

Material and Methods Two investigators searched, in EBSCO, ISI, PubMed and SCOPUS databases, and independently selected studies published until May 2013 and reporting prognostic accuracy and/or reliability of specific systems for patients with DFU in order to predict LEA.

Results We included 25 studies reporting a prevalence of LEA between 6% and 78%. Eight different DFU descriptions and seven prognostic stratification classification systems were addressed with a variable (1–9) number of factors included, being the presence of peripheral arterial disease ($n = 12$) or infection at the ulcer site ($n = 10$) or its (ulcer) depth ($n = 10$) the most frequently included. The Meggitt–Wagner, S(AD)SAD and Texas University Classification systems were the most extensively validated, whereas ten classifications were derived or validated only once. Reliability was reported in a single study, and accuracy measures were reported in five studies with another eight allowing their calculation. Meta-analysis was only possible for the composing variables' accuracy. Pooled accuracy ranged from 0.65 (for gangrene) to 0.74 (for infection).

Conclusion There are numerous classification systems for DFU outcome prediction, but only few studies evaluated their reliability or external validity. Studies rarely validated several systems simultaneously and only a few reported accuracy measures. Further studies assessing reliability and accuracy of the available systems and their composing variables are needed. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords clinical prediction rules; diabetic foot; diagnostic accuracy; foot ulcer; classification systems; systematic review

Abbreviations: AUC, area under the receiver operating characteristic curve; CHS, Curative Health Services wound grade scale; CI, confidence interval; DEPA, Depth of the Ulcer, Extent of Bacterial Colonization, Phase of Ulcer and Association Aetiology classification system; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; DUSS, Diabetic Ulcer Severity Score;

IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; LEA, lower extremity amputation; LR, likelihood ratio; NPV, negative predictive value; PAD, peripheral arterial disease; PEDIS, Perfusion, Extent, Depth/Tissue Loss, Infection, Sensation classification system; PPV, positive predictive value; S(AD)SAD, Size (Area, Depth), Sepsis, Arteriopathy, Denervation system; SEWSS, Saint Elian Wound Score System; SIGN, Scottish Intercollegiate Guidelines Network classification; SINBAD, Site, Ischaemia, Neuropathy, Bacterial Infection and Depth; STARD, Standards for the Reporting of Diagnostic Accuracy studies; STROBE, Strengthening of the Reporting of Observational Studies in Epidemiology; SWM, Semmes–Weinstein monofilament; TUC, Texas University Classification

Introduction

Diabetes mellitus is one of the most frequent metabolic disorders, achieving an epidemic magnitude of 8.4% prevalence worldwide, affecting 371 million people, and with an increasing number around the world [1]. Foot disease is one of the most serious, costly and frightening complications [2–5], presenting a threat to the patients' well-being and survival [6]. There is a 15–40 times higher risk of lower extremity amputation (LEA) in patients with diabetes when compared with those without [3,7], with an incidence of LEA of the contralateral member superior to 50% in the three following years [4]. Furthermore, the 6-year mortality after a minor LEA is 35% and, after a major LEA, may be up to 75% [8].

Diabetic foot ulcer (DFU) is the major predisposing factor for non-traumatic LEA in patients with diabetes, preceding about 85% of them [4]. It was reported that the presence of neuropathy, foot deformity, ischaemia and infection is the main cause for DFU occurrence and subsequent amputation [9–12]. DFU classification systems are an essential tool for assessing and selecting treatment and for improving communication among different healthcare professionals. They also facilitate standardization of prognostic estimation itself [10,11,13,14] and the audition and comparison of specialized centres [11,15]. Furthermore, they are crucial to identify which patients will need specialized care and those who can maintain treatment in primary care.

Therefore, a single or simplified classification system of DFUs, highlighting the most accurate predictive factors for LEA, could represent a relevant tool for decision-making in our daily clinical practice, as well as for research planning. Nevertheless, despite high morbidity and consequent costs, no prognostic system has yet been accepted as the gold standard [4]. Therefore, we aimed to systematically review the available systems used to classify patients suffering from diabetes-related foot ulcer in order to synthesize their methodological qualitative issues and accuracy to predict LEA.

Methods

Search strategy and study selection

In order to identify all the available DFU classification systems, we conducted a sensible search in MEDLINE (PubMed), EBSCO, SCOPUS and ISI databases for studies published up to 31 May 2013, in English, French, Italian, Spanish or Portuguese. For the MEDLINE search, we used the query shown in Figure 1 and, for the other databases, the terms *diabetic foot ulcer*, *prognostic* and *classification* in combination using the AND or OR Boolean operators.

This search retrieved 3389 studies. The following selection criteria were applied: (1) *publication date*: up to and including 31 May 2013; (2) *study design*: randomized controlled trials, and cohort and case–control studies; (3) *population*: subjects with diabetes and active DFU, excluding those studies that enrolled subjects with post-LEA wounds in their analysis; (4) *prognostic factors*: DFU description or prognostic stratification classification systems; (5) *outcome*: LEA occurrence; and (6) *measures*: prognostic accuracy and/or reliability.

Initially, the articles' pertinence was assessed on the basis of their titles and abstracts (when available). Afterwards, the full text versions of the selected articles ($n = 39$) were evaluated applying the selection criteria described earlier. In the end, 25 studies remained. In both stages, selection was conducted by two investigators (MMS and DMM), working independently and blindly to each other. Divergence was resolved by consensus.

Analysis of the articles' reference list and relevant reviews did not identify any new article [4,13,16,17].

Data extraction and quality assessment

The following data were collected from each of the included articles: (1) *article identification*: title, author(s), publication date and journal; (2) *methods*: study design, setting, period(s) of data collection, inclusion and exclusion criteria, sources and methods of participant selection, sample size, independent variables and DFU description or prognostic stratification classification systems analysed, and potential biases; (3) *results*: study participant characteristics, outcome prevalence (minor, major or total LEA), statistical analysis, variables' association with outcome, reliability measures, prognostic accuracy measures or data that allowed their calculation; and (5) *quality assessment*.

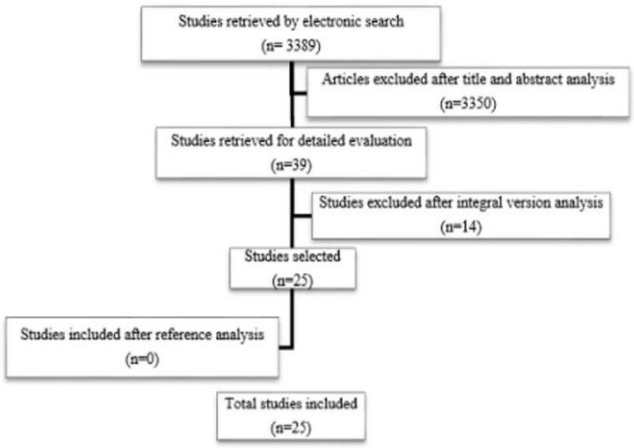

Figure 1. Systematic review flow diagram of article selection process. Used query for articles' identification in Medline database: ***("Diabetic Foot"[Mesh] OR (diabetes AND ulcer AND lesion)) AND ((predict*[tiab] OR predictive value of tests[mh] OR scor*[tiab] OR observ*[tiab] OR observer variation[mh]) OR (incidence[MeSH:noexp] OR mortality[MeSH Terms] OR follow up studies[MeSH: noexp] OR prognos*[Text Word] OR predict*[Text Word] OR course*[Text Word]) OR (sensitiv*[Title/Abstract] OR sensitivity and specificity[MeSH Terms] OR diagnos*[Title/Abstract] OR diagnosis[MeSH:noexp] OR diagnostic * [MeSH:noexp] OR diagnosis,differential [MeSH:noexp] OR diagnosis[Subheading:noexp]) OR (cohort OR case-control OR prospective OR "risk factor" OR screening OR Classification[Mesh]OR scoring[tiab]))***

Studies' reporting quality was assessed (by MMS) through the number of items fulfilled in the Strengthening of the Reporting of Observational Studies in Epidemiology (STROBE) checklist [18] and the Standards for the Reporting of Diagnostic Accuracy studies (STARD) [19], when pertinent. For both checklists, we considered that total completion of an item should score 1 point, partial completion ½ point and null completion 0 points.

When not reported, but possible, we calculated the classifications' prognostic accuracy measures [sensitivity, specificity, positive and negative likelihood ratios (LRs), positive predictive value (PPV) and negative predictive value (NPV)] and respective 95% confidence intervals (CIs). For that purpose, we used cut-offs proposed in the studies or, alternatively, those that achieved the optimal balance between sensitivity and specificity. When mortality was reported, such individuals were removed from the analysis.

Because of a lack of reported or calculable prognostic accuracy measures for each classification system, no meta-analysis was performed. However, it was possible for some systems' composing variables. In such cases, meta-analysis was performed using the Meta-DiSc software (version 1.4) in order to calculate pooled diagnostic accuracy measures [sensitivity, specificity, LR and area under the receiver operating characteristic curve (AUC)], the respective 95% CIs and heterogeneity statistics. Heterogeneity tests were conducted (chi-square test-based Q-statistic and I^2-statistic), and as we assumed that the observed estimate could vary across studies because of differences in the setting and participants' characteristics, a random effects model (DerSimonian and Laird method) was used [20].

Results

Studies description

We retrieved 15 classification systems, assessed in 25 articles (Table 1).

In this section, we will describe all the retrieved classifications ordered by date of creation. Those based on a previous one were assembled in the same group. The same order was used in Tables 1–3.

We have divided the available systems in DFU description, when no specific prognostic was proposed ($n = 7$) (descriptions), or in prognostic stratification classification, when subjects were grouped according to their risk of outcome occurrence ($n = 8$) (classification systems' formal assessment). Results in Tables 1–3 will be separated according to that.

The number of included variables for the classification varied from 1 (the classification proposed by the IDSA–IWGDF focused on infection) [21] to 9 (SEWSS classification) [22]. The most frequent included variables were

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Table 1. Diabetic foot ulcer classification systems: derivation and/or validation studies' characterization (ordered by year of creation and group of variables' included)

Step	Study (ref)	Study type	Sample size (*n*)	Mean follow-up (months)	Setting	LEA (prevalence)		Prognostic accuracy measures reported	Reliability measures reported	STROBE
						Minor	Major			
DFU DESCRIPTION CLASSIFICATION SYSTEMS										
Meggitt–Wagner										
Multicentre validation	Oyibo *et al.* [14]	Prospective cohort	194	NR	Two multicentre DF centres		15.0			13.5
External validation	Abbas *et al.* [15]		252	36[a]	Multidisciplinary service		15.5	x	x	15
	Parisi *et al.* [36]	Retrospective cohort	105	NR	Diabetology centre	12.2	0.0			
	Faglia *et al.* [39]		115		Multidisciplinary DF clinic		33.3			14.5
	Sun *et al.* [37]		789			22.9	19.9			14
	Al-Tawfiq and Johndrow [33]		62		Medical Services Organization		19.0			13
	Gul *et al.* [24]		200	>2.8	Diabetology Institute		24.0			12
	Apelqvist *et al.* [34]		314	NR	Internal Medicine Department	0.0	25.0			11.5
	Van Acker *et al.* [31]		121		Multidisciplinary DF clinic		11.9			
TUC										
Multicentre validation	Oyibo *et al.* [14]	Prospective cohort	194	NR	Two multicentre DF centres		15.0	x	x	13.5
External validation	Abbas *et al.* [15]		252	36[a]	Multidisciplinary service		15.5			15
	Parisi *et al.* [36]		105	NR	Diabetology centre	12.2	0.0			
	Ali *et al.* [32]		214	16.3			27.5			14.5
	Gul *et al.* [24]	Retrospective cohort	200	>2.8			24.0			12
Internal validation	Armstrong *et al.* [10]		360	All 6 months	Multidisciplinary tertiary care DF clinic	21.6	7.0			15
S(AD)SAD										
External validation	Treece *et al.* [38]	Prospective cohort	300	NR	Hospitalar multidisciplinary DF clinic	7.3	2.7	x	x	15
	Abbas *et al.* [15]		252	36[a]	Multidisciplinary service		15.5			
	Parisi *et al.* [36]		105	NR		12.2	0			
	Chipchase *et al.* [35]		97	NR (total 47)	Hospitalar specialist unit	0.0	7.1	✓		14[b]
	Ince *et al.* [25]		449	Up to 12	Multidisciplinary DF clinic		31.7	x		13
PEDIS										
External validation	Abbas *et al.* [15]	Prospective cohort	252	36[a]	Specialist multidisciplinary service		15.5	x	x	15
SINBAD										
Derivation and multicentre validation	Ince *et al.* [40]	Retrospective cohort	449 891	>1	Four multicentre specialist DF centres		8.0–19.0	x	x	13
SEWSS										
Validation	Martínez-De Jesús [22]	Prospective cohort	235	12	Specialist DF centre	10.6	3.4	x	✓	15.5
CHS										
Multicentre validation	Margolis *et al.* [28]	Retrospective cohort	31.106	All 4.7	Curative Health Services		NR	✓	x	18
	Margolis *et al.* [30]		24.616	NR		3.8	2.9	x		17
	Margolis *et al.* [29]		19.280[c] 8350	All 4.7			6.4	✓		15.5[d]
PROGNOSTIC STRATIFICATION CLASSIFICATION SYSTEMS										
Levine and O'Neal										
External validation	Watts *et al.* [23]	Case–control	137	NR	HMO		NA	x	x	11
Van Acker/Peter										
Internal validation	Van Acker *et al.* [31]	Retrospective cohort	121	NR	Multidisciplinary DF clinic		11.9	x	x	11.5

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Margolis *et al.*											
Derivation	Margolis *et al.* [29]	Retrospective cohort	19.280	All 4.7	Curative Health Services	6.4		✓	x	15.5[d]
Validation			8350							
DEPA										
Validation	Younes and Albsoul [12]	Prospective cohort	84	5	University Hospital	15.5		x	x	12
DUSS										
Derivation	Beckert *et al.* [9]	Prospective cohort	1000	2.3[a]	Outpatient wound care unit	9.9	2.6	x	x	14
SIGN										
Validation	Leese *et al.* [26]	Retrospective cohort	198	3[a]	Specialist DF clinic	3.6	8.1	x	x	15
IDSA–IWGDF										
Validation	Lavery *et al.* [21]	Prospective cohort	247	27.2	Multidisciplinary DF clinic	48.1	29.6	x	x	11
Lipsky *et al.*										
Derivation	Lipsky *et al.* [27]	Retrospective cohort	2230	NR	Acute care hospitals		20.8	✓	x	14.5[e]
Multicentre validation			788				23.2			

Within each classification, studies were ordered by evidence level (by decreasing order); this is, first by study type, second by methodological quality (assessed by the STROBE checklist) and third by sample size.
CHS, Curative Health Services wound grade scale; DF, diabetic foot; HMO, Health Maintenance Organization; IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; LEA, lower extremity amputation; NA. not applicable; NR, not reported; SEWSS, Saint Elian Wound Score System; TUC, Texas University Classification.
[a]Median.
[b]STARD: 12 points.
[c]Not all with active ulcer at baseline.
[d]STARD: 15 points.
[e]STARD: 12 points.

peripheral arterial disease (PAD) ($n = 12$), DFU depth ($n = 10$) and infection ($n = 10$), whereas the least frequent included variables were patient related [such as visual ($n = 2$) or physical impairment ($n = 1$) and nephropathy ($n = 2$)] (Table 2).

Variables included in the DFU description systems were more similar than those composing the prognostic stratification systems.

Only one case–control study [23] was retrieved; the remaining studies were retrospective ($n = 9$) [10,24–31] or prospective ($n = 15$) [8,9,12,14,15,21,22,25,32–38] cohort studies. In the case–control study [23], a random selection of patients with and without diabetes-related LEA was performed, whereas in all cohort studies, selection was made by consecutive inclusion.

The most validated classifications were the Meggitt–Wagner ($n = 9$), S(AD)SAD ($n = 5$) and TUC ($n = 5$). The CHS [28,30], Lipsky *et al.* [27] and the SINBAD [25] classifications were multicentre, validated by the research teams that built them.

Several classifications were validated only once: DEPA [12], IDSA–IWGDF [21], Levine and O'Neal [23], Lipsky *et al.* [27], Margolis *et al.* [29], PEDIS [15], SEWSS [22], SIGN [26], SINBAD [25] and Van Acker/Peter [31]; and the DUSS score was only derived and never externally validated [9].

Regarding reporting quality, the STROBE score varied from 11 [21,23] to 18 [28] (out of 22), and the STARD score from 12 [27,35] to 15 [29] (out of 25).

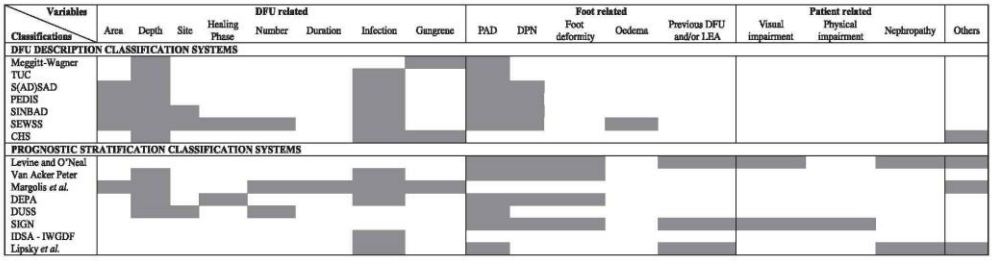
Diabetes-related LEA prevalence varied from 6.4 [29], in a wound care multicentre study, to 77.7 [21], in a diabetes management programme's foot clinic.

Description of classifications

Meggitt–Wagner

This classification system comprises 6 different groups: (0) intact skin, (1) superficial DFU, (2) DFU reaching tendon, joint or bone, (3) Grade 2 plus infection, (4) gangrene of portion or all forefoot and (5) gangrene or dysvascularity of the entire foot. However, several limitations are apparent to clinicians. This system is considered to be very simplistic and linear, lacking specificity of DFU description, with the majority being classified as grade 2 or 3 in clinical practice [15]. This is the most frequently used and validated system [14,15,24,31,33,34,36,37,39], in different settings, where an association between grade and LEA risk was consistently observed. No study reported prognostic accuracy measures, but it was possible to calculate them in some studies [14,24,34,37] (Table 3). The study of Al-Tawfiq *et al.* [33] reported that all patients who underwent diabetes-related LEA were classified as grade 4 or 5 [33] (corresponding to a 100% sensitivity). Unfortunately, we were unable to calculate any other measures.

Table 2. Variables included in the various diabetic foot ulcer classification systems (ordered by year of creation and group of variables' included)



We have decided to group variables according to a clinical logic from local to global prognostic factors: diabetic foot ulcer characterization variables, foot characterization variables and patient related.

CHS, Curative Health Services wound grade scale; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; LEA, lower extremity amputation; PAD, peripheral arterial disease; SWESS, Saint Elian Wound Score System; TUC, Texas University Classification.

Levine and O'Neal

Only one case–control study [23] validated this classification, and full description was not retrievable. It stratifies subjects into three groups according to the presence or absence of SWM diminished sensation, foot deformity, diabetes duration superior to 10 years, PAD, smoking or coronary heart disease, nephropathy or retinopathy and previous DFU history. Association between risk grade and LEA was observed in both univariate and multivariate analyses [23]. It was possible to calculate all prognostic accuracy measures (described in Table 3).

TUC

This system represents the first bi-dimensional system creating a 16-square matrix, using partly depth (grade) and partly presence of ischaemia and/or infection (stage) to assess the subjects' diabetes-related foot ulcer [10]. However, it is regarded as somewhat complex to use in daily clinical care [16]. It was validated by six different studies that consistently reported an association of stage and grade with outcome (i.e. LEA occurrence) [10,14,15,24,32,36]. No study reported prognostic accuracy measures, but all measures were calculable in three of them [14,15,24,32] (Table 3). In the study of Armstrong *et al.*, it was reported that all subjects classified as grade II stage D or grade III stages C and D required LEA, in comparison with grade 0 or I stage A or B, where it occurred in less than 13%.

Van Acker/Peter

This classification is based upon the TUC system and categorizes subjects in a 25-square matrix according to the type of lesion (grade) and foot pathology (stage) [31]. Through shades of grey, it gives a visual DFU prognostic estimate according to its stage and grade. This classification was validated once [31] and presented a good correlation with the Meggitt–Wagner. It was described that 70% of LEA occurred in stage D or E. No prognostic accuracy measures were reported or calculable.

S(AD)SAD

This classification uses an acronym in order to facilitate memorization. It selects only easy-to-collect variables without requiring special techniques to allow its use in a busy clinical practice. Each composing variable [area, depth, infection, diabetic peripheral neuropathy (DPN) and PAD] can be graded between 0 and 3 points, which are then used to obtain a total score [36]. Because of the high number of variables and irregular structure, it is considered hard to remember [15]. It was validated by five studies [15,25,35,36,38], but the association between variables and outcome occurrence (diabetes-related LEA) was not consensual. The study of Chipchase *et al.* [35] included only patients with heel DFU. In the study of Abbas *et al.* [15], DPN diagnosis was modified and considered simply as being present or absent, and a high drop-out rate (22.7%) was reported. Only one study described a good agreement between two clinicians in a separate small sample; however, results were not given [38]. Just the study of Parisi *et al.* [36] reported prognostic accuracy measures for healing prediction using a score of ≤ 9 as cut-off.

PEDIS

This system was created by the IWGDF, by expert consensus, for research purposes. Nevertheless, it was used for a clinical audit study in 14 European centres [15]. It is composed of the same five variables as the S(AD)SAD classification. In the single study validating PEDIS, all variables were related to the healing rate [15]. However, it is a fairly complex classification. Because its development aimed to improve communication between centres worldwide (including developing countries), each variable can be collected using different procedures and materials (depending on their availability), but it does not allow a straightforward prognostication. Because each included variable is graded and no final risk classification is proposed, there were no diagnostic/prognostic accuracy reports.

Table 3. Diabetic foot ulcer classification systems' prognostic accuracy measures for lower extremity amputation prediction

PAM classifications	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	LR+ (95% CI)	LR− (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
DFU DESCRIPTION CLASSIFICATION SYSTEMS						
Meggitt–Wagner (grade ≥ 3)						
Gul *et al.* [24]	49.0 (35.0–63.0)	78.2 (71.6–84.7)	2.2 (1.5–3.4)	0.7 (0.5–0.9)	42.1 (29.3–54.9)	82.5 (76.3–88.7)
Apelqvist *et al.* [34]	97.4 (93.9–100.0)	85.8 (80.9–90.7)	6.9 (4.9–9.7)	0.03 (0.008–0.1)	72.8 (64.2–81.4)	98.8 (97.2–100.0)
Sun *et al.* [37]	88.8 (85.4–92.1)	65.0 (60.6–69.4)	2.5 (2.2–2.9)	0.2 (0.1–0.2)	65.5 (61.2–69.9)	88.5 (85.1–91.2)
Oyibo *et al.* [14]	45.2 (27.6–62.7)	85.2 (79.8–90.7)	3.1 (1.8–5.2)	0.6 (0.5–0.9)	36.8 (21.5–52.2)	89.1 (84.2–94.0)
S(AD)SAD (score > 9)						
Parisi *et al.* [36]	52.2 (25.1–84.0)	87.5 (81.0–95.0)	4.5 (2.0–10.0)	0.5 (0.3–1.0)	37.5 (13.8–61.2)	93.6 (88.2–99.0)
CHS (grade ≥ 3)						
Margolis *et al.* [29] (derivation set)[a]	37.6 (36.6–38.5)	79.5 (78.7–80.4)	1.8 (1.7–1.9)	0.8 (0.8–0.8)	67.3 (66.1–68.5)	53.2 (52.3–54.0)
Margolis *et al.* [29] (validation set)[a]	38.7 (37.2–40.1)	80.1 (78.8–81.3)	1.9 (1.8–2.1)	0.8 (0.7–0.8)	68.6 (66.8–70.5)	53.6 (52.4–54.9)
Margolis *et al.* [30]	62.5 (60.2–64.8)	72.6 (72.0–73.2)	2.3 (2.2–2.4)	0.5 (0.5–0.6)	14.0 (13.3–14.9)	96.4 (96.2–96.7)
Margolis *et al.* [28][a]	67.4		Not reported nor calculable			
DEPA (score ≥ 7)						
Younes and Albsoul [12]	100 (NA)	49.2 (37.1–61.4)	2.0 (1.6–2.5)	NA	36.5 (23.5–49.6)	100 (NA)
PROGNOSTIC STRATIFICATION CLASSIFICATION SYSTEMS						
Levine and O'Neal (high)						
Watts *et al.* [23]	63.0 (44.8–81.2)	70.9 (62.4–79.4)	2.2 (1.4–3.3)	0.5 (0.3–0.9)	34.7 (21.4–48.0)	88.6 (82.0–95.3)
SIGN (high-risk group)						
Leese *et al.* [26]	92.3 (82.1–100.0)	30.8 (23.9–37.7)	1.3 (1.1–1.5)	0.2 (0.06–1.0)	16.8 (10.7–23.0)	96.4 (91.4–100.0)
IDSA–IWGDF (group ≥ moderate infection)						
Lavery *et al.* [21]	90.0 (81.7–98.3)	82.7 (77.5–88.0)	5.2 (3.8–7.2)	0.1 (0.05–0.3)	57.0 (46.0–67.9)	97.0 (94.5–99.6)
Lipsky *et al.* (score ≥ 12)						
Lipsky *et al.* [27]	79.4 (73.5–85.2)	56.2 (52.2–60.2)	1.8 (1.6–2.0)	0.4 (0.3–0.5)	35.5 (30.9–40.2)	89.9 (86.9–92.3)

Within each classification, studies were ordered by evidence level (by decreasing order); this is, first by study type, second by methodological quality (assessed by the STROBE checklist) and third by sample size. Prognostic accuracy measures for the Texas University, PEDIS, SINBAD, Saint Elian Wound Score System, Van Acker/Peter, Margolis *et al.* and DUSS classifications were not described because of the lack of reporting and impossibility to calculate using the available data.

[a]Non-healing DFU at 20 weeks as outcome.

CHS, Curative Health Services wound grade scale; CI, confidence interval; IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NA, not applicable; NPV, negative predictive value; PAM, prognostic accuracy measure, PPV, positive predictive value.

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SINBAD

This score is a reformulation of the S(AD)SAD system, including the same variables, into a score (ranging from 0 to 6) resulting into a four-risk grade classification. We have retrieved only one study validating this system in different continents and, therefore, multiple ethnic groups [40]. However, depending on the country, different variables were significantly associated with the outcome. Additionally, no prognostic accuracy measures were reported or calculable.

SEWSS

This system evolved from the PEDIS classification, with the inclusion of five more variables (addressing the subjects' diabetes-related foot ulcer location, topographic aspect, number of affected zones, healing phase and foot oedema). A total of ten variables are scored from 1 to 3 and result in three simple grades (mild, moderate or severe) for different outcome prognoses [22]. It was validated only once [22], but no prognostic accuracy measures were reported (or calculable). Regarding reproducibility, a kappa value of 0.8 was reported. In this study, it was observed that a higher grade had greater LEA rates.

CHS

Developed by the Curative Health Services, it has six grades describing depth, abscess or osteomyelitis and necrotic tissue presence. It was validated thrice by the same group in all the CHS wound care facilities for the neuropathic DFU healing prediction at the 20th week of care [28–30]. In the 2002 study [28], a grade 6 presented a 91.5% sensitivity for the detection of wounds that had not healed, whereas a grade 3 or higher presented a sensitivity of 67.4%. No other measures were reported or possible to calculate, and a potential selection and information bias was reported. In the 2003 study [29], the CHS classification was optimized (see next classification), in a derivation and validation set. For both, all prognostic accuracy measures were calculable. In the 2005 study [30], an AUC of 0.80 was reported, and all measures were possible to calculate and are described in Table 3. All studies showed an association between CHS classification and non-healing/LEA in both univariate and multivariate analyses.

Margolis et al.

In 2003, Margolis *et al.* derived and validated, in the same sample, four prediction models (using from three to six variables) for the neuropathic DFU healing prediction [29], including the CHS classification as foundation. The simplest model gives 1 point to each included variable presence (wound older than 2 months, wound larger than 2 cm^2 and CHS equal or superior to 3). This model presented an AUC value of 0.66 (95% CI 0.64–0.67), for predicting non-healing DFU at 20 weeks as well as an excellent internal validity. The remaining models had values from 0.66 to 0.70. No other prognostic accuracy measure was reported or possible to calculate.

DEPA

This score rates from 1 to 3 points the patients' diabetes-related ulcer depth, extent of bacterial colonization, phase and associated aetiology, with a total ranging from 3 to 12 [12]. Subject is considered at low risk of LEA with a score inferior to 6, moderate between 7 and 9, and high between 10 and 12 or with a DFU with wet gangrene. The use of an acronym and only four easy-to-collect variables is an advantage for clinical implementation. Besides this classification, only SEWSS also includes the DFU healing status. However, some authors consider scoring as particularly subjective [16]. In the internal validation prospective study [12], 84 consecutive participants were included. All subjects with a DEPA score inferior to 6 achieved complete closure in less than 10 weeks in contrast with all those with a score of 11 or 12 that required LEA. All prognostic accuracy measures were possible to calculate and are described in Table 3. The authors do not support its use for heel DFU classification.

DUSS

This score categorizes the subjects' DFU from 0 to 4 points attributing each point to the presence of ischaemia, bone involvement, ulcer not localized at the toes and multiple ulcers [9]. Only one derivation study assessed those variables that significantly reduced the chances for healing [9]. No accuracy measures were reported or calculable.

SIGN

This system was developed for the DFU occurrence prediction [41], but in 2007, it was also validated for the DFU outcome prediction [26]. The authors reported that subjects classified as high risk were less likely to heal. Although no prognostic accuracy measures were reported, they were calculable and are described in Table 3.

IDSA–IWGDF

This classification was developed through IDSA and IWGDF expert consensus and divides the patients' DFU infection severity into categories. Only one study validated its prognostic accuracy [21], disclosing a trend between its groups and risk for LEA. This study presented the highest LEA rate. All prognostic accuracy measures were possible to calculate and are described in Table 3.

Lipsky et al.

Lipsky *et al.* derived and validated a new scoring system for LEA risk prediction – in a multicentric retrospective cohort study [27], including hospitalized patients due to infected foot ulcer. The derivation cohort was composed of 2230 participants, and the classification was created using regression analysis and comparing the predicted

with the observed probability of LEA. The final model and score calculation consisted on 0.1372 × (chronic renal disease or creatinine >3 mg/dL) + 0.1988 × (male sex) + 0.2830 × (temperature <96 or >100.5 °F) + 0.5477 × (age ≥50 years) + 0.5168 × (infected ulcer *versus* cellulitis) + 0.5020 × (LEA history) + 0.6203 × (albumin <2.8 g/dL) + 0.7485 × (PAD history) + 0.9596 × (white blood cell count ≥11) + 1.3845 × (surgical site *versus* cellulitis) + 1.6418 × (transferred from other acute care facility). According to the score, five classifications groups were created. Some prognostic accuracy measures were reported, and the remaining measures were computable and are described in Table 3. It was also reported that the derived model presented a good calibration in the validation cohort. Authors reported potential selection bias.

Formal assessment of classification systems and prognostic accuracy of composing variables

At least one classification prognostic accuracy measure was reported in five studies [27–29,35,36] and calculable in eight more [10,12,21,23,30,33,34,37] (Table 3).

The sensitivity values of the classification systems ranged from 37.6%, using the CHS [29], to 100%, using the DEPA score [12]. Regarding the four studies assessing the Meggitt–Wagner classification, two reported values superior to 88% [34,37], and two inferior to 50% [14,24]. Although conducted in the same setting and by the same group, the studies of Margolis *et al.* in 2003 and 2005 present different sensitivity values (around 38% and 62%, respectively).

Concerning specificity, values fluctuated between 30%, using the SIGN system [26], and 87.5%, using the S(AD) SAD score [36]. All reported LRs are expected to have small or minimal effect on the likelihood of disease (depending also on the expectable LEA prevalence). All reported NPV values were superior to 80%, whereas the majority of PPV values were inferior to 60%. In fact, only two of Meggitt–Wagner validation studies reported higher values [34,37] (Table 3). No differences were found between DFU description and prognostic stratification systems' accuracy measures.

Only two studies [29,30] reported an AUC value, presenting values of 0.80 [30] and 0.66 [29], for the CHS validation and optimization attempt, respectively. Reliability was assessed only in one study [22].

Only three studies [23,26,37] reported minor and major LEA rates separately. When assessing the classifications' accuracy for major LEA prediction, we observed that the Meggitt–Wagner [37] and SIGN [26] tended to produce higher sensitivity and NPV values, whereas the remaining study tended to be lower in comparison with global LEA prediction. Conversely, the system of Lipsky *et al.* presented globally higher accuracy values. However, statistical significance was not observed in any of the described cases (Table 4).

In what concerns the classifications' composing variables, we were able to conduct a meta-analysis – as shown in Figure 2.

The most validated variables were the presence of PAD ($n = 10$), and DFU's depth ($n = 8$) and infection ($n = 8$). The least validated variables were DFU's site, healing phase, number and duration, as well as foot deformity, oedema, previous diabetes-related foot complications (namely DFU or LEA), visual or physical impairment and nephropathy, with two or few studies validating their association with LEA.

Almost all variables presented high inconsistency (I^2 superior to 90%) and, therefore, disperse prognostic accuracy values.

Pooled sensitivity values ranged from 11% (for DPN) to 88% (for gangrene), specificity values from 30% (for DPN) to 95% (for gangrene), LR+ from 1.22

Table 4. Diabetic foot ulcer classification systems' prognostic accuracy measures for major lower extremity amputation prediction

PAM Classifications	Sensitivity (%) (95% CI)	Specificity (%) (95% CI)	LR+ (95% CI)	LR- (95% CI)	PPV (%) (95% CI)	NPV (%) (95% CI)
DFU DESCRIPTION CLASSIFICATION SYSTEMS						
Meggitt–Wagner (grade ≥ 3)						
Sun *et al.* [37]	93.6 (89.8–97.4)	50.8 (46.9–54.7)	1.9 (1.7–2.1)	0.1 (0.06–0.2)	32.1 (27.8–36.4)	96.9 (95.1–98.8)
PROGNOSTIC STRATIFICATION CLASSIFICATION SYSTEMS						
SIGN (high-risk group)						
Leese *et al.* [26]	89.5 (75.7–100.0)	29.6 (22.9–36.3)	1.3 (1.1–1.5)	0.4 (0.09–1.3)	11.9 (6.6–17.2)	96.9 (95.1–98.8)
Lipsky *et al.* (score ≥ 12)						
Lipsky *et al.* [27]	100.0 (NA)	74.1 (68.3–79.7)	3.8 (3.1–4.8)	NA	25.3 (15.7–34.9)	97.0 (95.1–98.8)

Within each classification, studies were ordered by evidence level (by decreasing order); this is, first by study type, second by methodological quality (assessed by the STROBE checklist) and third by sample size. Prognostic accuracy measures for the Texas University, S(AD)SAD, PEDIS, SINBAD, Saint Elian Wound Score System, Curative Health Services wound grade scale, Levine and O'Neal, Van Acker/Peter, Margolis *et al.*, DEPA, DUSS and IDSA–IWGDF classifications were not described because of the lack of reporting and impossibility to calculate using the available data.

CI, confidence interval; IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; LR−: negative likelihood ratio; LR+: positive likelihood ratio; NA, not applicable; NPV, negative predictive value; PAM, prognostic accuracy measure; PPV, positive predictive value.

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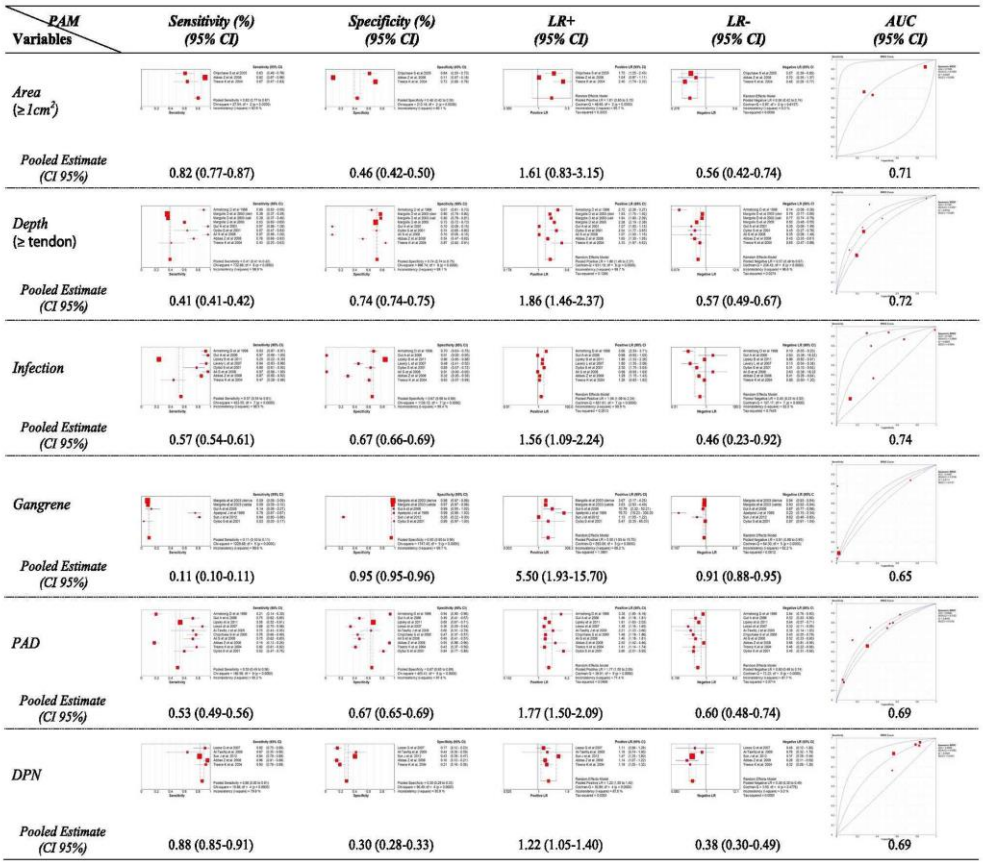

Figure 2. Classifications systems' composing variables' prognostic accuracy (meta-analysis). We have decided to group variables according to a clinical logic from local to global prognostic factors: diabetic foot ulcer characterization variables, foot characterization variables and patient related. Within each variable, studies were ordered by evidence level (by decreasing order); this is, first by study type, second by methodological quality (assessed by the STROBE checklist) and third by sample size. Regarding diabetic foot ulcer site, healing phase, number and duration as well as foot deformity, oedema, previous foot ulcer or amputation, visual or physical impairment and nephropathy's association with lower extremity amputation, meta-analysis was not possible to conduct (two or few studies assessed these variables) and, therefore, was not reported in this table. Legend: CI, confidence interval; cm^2, squared centimetres; DPN, diabetic peripheral neuropathy; LR−, negative likelihood ratio; LR+, positive likelihood ratio; PAD, peripheral arterial disease; PAM, prognostic accuracy measure

(for DPN) to 5.50 (for gangrene), LR− from 0.38 (for DPN) to 0.91 (for gangrene), and AUC from 0.65 (for gangrene) to 0.74 (for infection).

Discussion

A prognostic patients' diabetes-related foot ulcer classification system, highlighting the most accurate predictive factors for healing failure, primarily LEA, is an essential decision-making tool in our daily clinical practice. It should be adequately validated, easy to use, effective to communicate DFU status [10], able to suggest appropriate therapy and predict outcome [24] and allow effective comparison of quality of routine management and treatment strategies [36]. However, and despite the elevated morbidity and consequent costs of DFU and LEA, the existing systems have a poor evidence support and have not been adequately standardized to allow their widespread clinical use.

We identified 15 different systems for patients' diabetes-related foot ulcer classification that were derived and/or validated in 25 studies.

From these, only eight systems provided a clear prognostic stratification. Additionally, only the SIGN system was developed for DFU development risk prediction but also validated for LEA occurrence [26]. Although Peters *et al.* [42] have validated the IWGDF's DFU development risk classification system also for the LEA prediction, not all the included subjects presented DFU at baseline. Thus, their article was excluded from our review.

We chose not to include classifications that were merely described because our main objective was to identify the most pertinent and evidence-supported system(s) for clinical application. We have also excluded studies where only subjects with foot wounds post diabetes-related LEA were enrolled because, in our opinion, such ulcers do not present the same risk as primary lesions.

Contrariwise, we have decided to include simultaneously prognostic stratification as well as DFU description classification systems. Although the last may have not necessarily been designed for the prediction of clinical outcome (but for research, case-mix identification or communication standardization purposes), we believe that, in last instance, their grades will correspond to DFU severity and, therefore, LEA risk. So, their inclusion would present a more comprehensive review of the available evidence.

We have removed from the analysis data specifically concerning subjects in which death occurred during follow-up. The main reasons were the fact that we were not conducting a time-to-event analysis but wished to assess systems' and respective composing variables' association with LEA occurrence and that, in such subjects, we could not know if our outcome would occur or not.

Although it is a more conservative analysis, we may have increased the accuracy measures' estimation CI width.

Although with different presentation and composition, several variables are commonly included (such as patients' diabetes-related foot ulcer area, depth and infection, PAD, DPN and foot deformity). All but one study were cohort studies with moderate to good reporting quality according to STROBE or STARD checklist.

Despite being considered as the first step for a classification system assessment, reliability was evaluated only once.

Only five studies reported prognostic accuracy measures, and although it was possible to calculate them in eight more, data were poorly described and difficult to extract. Only the Meggitt–Wagner, TUC, S(AD)SAD and CHS systems were validated by three or more studies, but because of a lack of prognostic accuracy measures, we were unable to perform a meta-analysis for the classification systems.

Accuracy measures were widely variable. We must highlight that LR for all systems and in all studies presented values with small effect on clinical decision, with PPV values inferior to 73%, and no significant differences were found between DFU description and prognostic stratification systems.

Lower extremity amputation prevalence ranged from 6.4% to 77.7%, which can also explain the great inconsistency in prognostic accuracy of the different systems. This variation may translate substantial differences in clinical decision-making, which can have a great effect mainly on minor LEA rates (due to a more aggressive approach, definition differences, etc.). Therefore, we have also assessed the classifications' accuracy for predicting major LEA. Only three studies allowed measures calculation, and no significant difference was observed. In addition, a great variation in major LEA also occurred, with reported values ranging from 0% to 29.6%.

In the Eurodiale study [43], several crucial aspects of DFU management presented important differences between centres, namely in what concerns referrals, off loading, vascular assessment, infection treatment and overall healthcare organization.

We must also highlight the 20-year interval between the first and last system creation, with all that it implies, namely modifications in the classification needs, in patients' characteristics, and in professionals' and researchers' knowledge as well as therapeutic options.

Because of these considerations, we decided to conduct a meta-analysis for the systems' composing variables' prognostic accuracy. Several authors consider the application of actual systems as somewhat imprecise because of their dependence on clinical examination [15] and collection of variables requiring clinical interpretation [10], which can in part explain the wide variation of the composing variables' prognostic accuracy measures. On the other hand, various systems use roughly the same variable definition, such as perfusion and infection (in the PEDIS and S(AD)SAD systems) and depth (in the Meggitt–Wagner, PEDIS, S(AD)SAD, Texas University and Van Acker/Peter classifications).

In 2010, Karthikesalingam *et al.* [16] published an systematic review of scoring systems, for patients' diabetes-related foot ulcer assessment, including a slightly different set of classification systems due to divergences in search strategy and inclusion criteria. The main differences reside in the fact that we have excluded only described DFU classifications as well as those applied in other than DFU wounds but have retrieved and included more articles.

Our study presents the following strengths: We have used several databases, a broad search and a standardized selection process (conducted by two researchers blind to each other) – which resulted in no new article retrieved from cross-reference analysis. In addition, this is (to our

knowledge) the only study that synthesizes prognostic accuracy measures and performs a meta-analysis of the composing variables' accuracy.

Our limitations include the following: Only one researcher conducted quality assessment, meta-analysis results in the creation of unadjusted estimates, it was performed only for composing variables, and a high discrepancy was observed.

In summary, several systems for the patients' diabetes-related foot ulcer classification were described; they have an acceptable methodological quality but a poor evidence level (due to a lack of validation studies). We observed that, for all the systems where accuracy measures were reported or calculable, LR values are considered to have a poor effect on decision-making (around 1). Classification systems need optimization. Therefore, we have conducted a meta-analysis of the composing variables' accuracy in order to identify the most pertinent. When the meta-analysis was conductable, we observed that all the variables were associated with LEA occurrence. However, once again, high inconsistency was observed, and pooled measures seem to have a small effect on clinical decision. Hence, in our opinion, no classification system is ready for wide application, and no independent predictive variables showed enough accuracy or consistency in order to propose a new classification or optimization of the existing systems.

A future research comparing all the available classifications, using the same procedures to collect data, preferably in different countries, is vital. In addition, we also need a systematic review conducted for identifying all the studies evaluating predicting variables' association with LEA, in order to better understand the markers of outcome and therefore allow an optimization of the existing classifications.

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Conflicts of interest

None declared.

References

1. International Diabetes Federation. Diabetes atlas 2012 update: out now! 2012 Nov 2012 [cited 2012 Dec 2012].
2. Apelqvist J, Bakker K, van Houtum WH, Schaper NC, International Working Group on the Diabetic Foot (IWGDF) Editorial Board. Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) prepared by the International Working Group on the Diabetic Foot. *Diabetes Metab Res Rev* 2008; **24** (Suppl 1): S181–S187.
3. Fard AS, Esmaelzadeh M, Larijani B. Assessment and treatment of diabetic foot ulcer. *Int J Clin Pract* 2007; **61**: 1931–1938.
4. Frykberg RG, Zgonis T, Armstrong DG, *et al.* Diabetic foot disorders: a clinical practice guideline (2006 revision). *J Foot Ankle Surg* 2006; **45**(Suppl 5): S1–S66.
5. Khanolkar MP, Bain SC, Stephens JW. The diabetic foot. *Q J Med* 2008; **101**: 685–695.
6. Jeffcoate WJ. Stratification of foot risk predicts the incidence of new foot disease, but do we yet know that the adoption of routine screening reduces it? *Diabetologia* 2011; **54**(5): 991–993.
7. Mayfield JA, Reiber GE, Sanders LJ, Janisse D, Pogach LM. Preventive foot care in people with diabetes - American Diabetes Association. *Diab Care* 2003; **26** (Suppl 1): S78–S79.
8. Faglia E, Favales F, Morabito A. New ulceration, new major amputation, and survival rates in diabetic subjects hospitalized for foot ulceration from 1990 to 1993. *Diab Care* 2001; **24**(1): 78–83.
9. Beckert S, Witte M, Königsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients. *Diab Care* 2006; **29**(5): 988–992.
10. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diab Care* 1998; **21**(5): 855–859.
11. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev* 2004; **20**(Suppl 1): S90–S95.
12. Younes NA, Albsoul AM. The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers. *J Foot Ankle Surg* 2004; **43**(4): 209–213.
13. Armstrong DG, Peters EJ. Classification of wounds of the diabetic foot. *Curr Diab Rep* 2001; **1**(3): 233–238.
14. Oyibo SO, Jude EB, Tarawneh I, Nguyen HC, Harkless LB, Boulton AJ. A comparison of two diabetic foot ulcer classification systems: the Wagner and the University of Texas wound classification systems. *Diab Care* 2001; **24**(1): 84–88.
15. Abbas ZG, Lutale JK, Game FL, Jeffcoate WJ. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. *Diabet Med* 2008; **25** (2): 134–137.
16. Karthikesalingam A, Holt PJ, Moxey P, Jones KG, Thompson MM, Hinchliffe RJ. A systematic review of scoring systems for diabetic foot ulcers. *Diabet Med* 2010; **27**(5): 544–549.
17. Lavery LA, Armstrong DG, Harkless LB. Classification of diabetic foot wounds - the University of Texas San Antonio diabetic wound classification systems. *Ostomy Wound Manag* 1997; **43** (2): 44–53.
18. Vandenbroucke JP, von Elm E, Altman D, *et al.* STROBE initiative (2007). Strengthening the reporting of observational studies in epidemiology (STROBE): explanation and elaboration. *Ann Intern Med* 2007; **147**: W163–W194.
19. Bossuyt PM, Reitsma JB, Bruns DE, *et al.* The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003; **138**(1): W1–W12.
20. Riley R, Higgins J, Deek J. Interpretation of random effects meta-analyses. *BMJ* 2011; **342**: d549.
21. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of

America's diabetic foot infection classification system. *Clin Infect Dis* 2007; **15**(44): 4.
22. Martínez-De Jesús FR. A checklist system to score healing progress of diabetic foot ulcers. *Int J Low Extrem Wounds* 2010; **9**(2): 74–83.
23. Watts SA, Daly B, Anthony M, McDonald P, Khoury A, Dahar W. The effect of age, gender, risk level and glycosylated hemoglobin in predicting foot amputation in HMO patients with diabetes. *J Am Acad Nurse Pract* 2001; **13**(5): 230–235.
24. Gul A, Basit A, Ali SM, Ahmadani MY, Miyan Z. Role of wound classification in predicting the outcome of diabetic foot ulcer. *J Pak Med Assoc* 2006; **56**(10): 444–447.
25. Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes. *Diabet Med* 2007; **24**(9): 977–981.
26. Leese G, Schofield C, McMurray B, *et al.* Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. *Diab Care* 2007; **30**(8): 2064–2069.
27. Lipsky BA, Weigelt JA, Sun X, Johannes RS, Derby KG, Tabak YP. Developing and validating a risk score for lower-extremity amputation in patients hospitalized for a diabetic foot infection. *Diab Care* 2011; **34**(8): 1695–1700.
28. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: the association of wound size, wound duration, and wound grade on healing. *Diab Care* 2002; **25**(10): 1835–1839.
29. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. *Am J Med* 2003; **115**(8): 627–631.
30. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers and amputation. *Wound Repair Regen* 2005; **13**(3): 230–236.
31. Van Acker K, De Block C, Abrams P, *et al.* The choice of diabetic foot ulcer classification in relation to the final outcome. *Wounds* 2002; **14**: 16–25.
32. Ali SM, Basit A, Fawwad A, Ahmedani MY, Miyan Z, Malik RA. Presentation and outcome of diabetic foot at a tertiary care unit. *Pak J Med Sci* 2008; **24**(5): 651–656.
33. Al-Tawfiq JA, Johndrow JA. Presentation and outcome of diabetic foot ulcers in Saudi Arabian patients. *Adv Skin Wound Care* 2009; **22**(3): 119–121.
34. Apelqvist J, Castenfors J, Larsson J, Stenström A, Agardh CD. Wound classification is more important than site of ulceration in the outcome of diabetic foot ulcers. *Diabet Med* 1989; **6**(6): 526–530.
35. Chipchase SY, Treece KA, Pound N, Game FL, Jeffcoate WJ. Heel ulcers don't heal in diabetes. Or do they? *Diabet Med* 2005; **22**(9): 1258–1262.
36. Parisi MC, Zantut-Wittmann DE, Pavin EJ, Machado H, Nery M, Jeffcoate WJ. Comparison of three systems of classification in predicting the outcome of diabetic foot ulcers in a Brazilian population. *Eur J Endocrinol* 2008; **159** (4): 417–422.
37. Sun JH, Tsai JS, Huang CH, *et al.* Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. *Diabetes Res Clin Pract* 2012; **95**(3): 358–363.
38. Treece KA, Macfarlane RM, Pound N, Game FL, Jeffcoate WJ. Validation of a system of foot ulcer classification in diabetes mellitus. *Diabet Med* 2004; **21** (9): 987–991.
39. Faglia E, Favales F, Aldeghi A, *et al.* Change in major amputation rate in a center dedicated to diabetic foot care during the 1980s: prognostic determinants for major amputation. *J Diabetes Complications* 1998; **12**(2): 96–102.
40. Ince P, Abbas Z, Lutale J. Use of the SINBAD classification system and score in comparing outcome of foot ulcer management on three continents. *Diab Care* 2008; **31**(5): 964–967.
41. Leese GP, Reid F, Green V, *et al.* Stratification of foot ulcer risk in patients with diabetes: a population-based study. *Int J Clin Pract* 2006; **60**(5): 541–545.
42. Peters E, Lavery L. Effectiveness of the diabetic foot risk classification systems of the International Working Group on the Diabetic Foot. *Diab Care* 2001; **24**(8): 1442–1447.
43. Akhtar S, Schape N, Apelqvist J, Jude E. A review of the Eurodiale studies: what lessons for diabetic foot care? *Curr Diab Rep* 2011; **11**: 302–309.

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Erratum

Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2014; **30**(7): 610–622.

The authors wish to bring to the readers' attention the following errors in the aforementioned paper.

In Table 1, in the IDSA-IWGDF classification system validation by Lavery *et al.* [21], the minor LEA prevalence should be 12.6% and major 8%, instead of 48.1 and 29.6%, respectively.

In the discussion section, the authors report that 'Lower extremity amputation prevalence ranged from 6.4% to 77.7%'; this sentence should, instead, read 'Lower extremity amputation prevalence ranged from 6.4% to 42.8%'. Finally, the values stated in the following sentence, 'In addition, a great variation in major LEA also occurred, with reported values ranging from 0% to 29.6%', should instead be '0% to 25%'.

We apologize for this error and any confusion it may have caused.

5.2 QUALITY OF DIABETIC FOOT CARE: PORTUGAL MEETS EURODIALE

DIABETES RESEARCH AND CLINICAL PRACTICE XXX (2014) XXX.E1–XXX.E3

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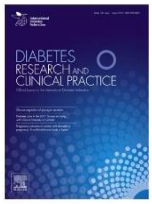

Brief Report

Portugal meets Eurodiale: Better late than never

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ABSTRACT

Understanding the quality of diabetic foot care delivery is essential. The Eurodiale consortium addressed subjects' characteristics, diabetic foot ulcer prognostic predictors and clinical outcomes, in 10 European countries. We analyzed the results of a specialized Portuguese diabetic foot clinic at the light of the ones from Eurodiale.

1. Introduction

Recently, the Portuguese Health Ministry presented guidelines describing which subjects with diabetes should be followed in specialized diabetic foot clinics by their risk of foot complications [1], using the International Working Group on Diabetic Foot Guidelines (IWGDF) classification [2].

Several articles were published by the Eurodiale consortium assessing the quality of diabetic foot care in Europe [3–14], however without including Portugal.

It is essential to appraise diabetic foot clinical management in each country to fully recognize variations between countries and the areas that need improvement, identify barriers in foot care implementation and so adequately direct educational programs as well as mobilize lacking resources. Thus, we aimed to evaluate the quality of care in Portugal, using a Hospital's diabetic foot clinic as an example, and compare these to the Eurodiale results and IWGDF guidelines.

2. Methods

A retrospective cohort study was conducted, analyzing all first appointments scheduled for the Centro Hospitalar de Vila Nova de Gaia/Espinho EPE diabetic foot clinic, between January 2011 and December 2013.

All referral requests and variables were retrieved from the informatics medical registry, between January and March 2014.

We have collected the same parameters reported by the Eurodiale (namely, patient demographics and foot and ulcer

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Abbreviations: DPN, diabetic peripheral neuropathy; HbA1c, glycosylated hemoglobin; IWGDF, International Working Group on Diabetic Foot Guidelines; PAD, peripheral arterial disease; UT, University of Texas.

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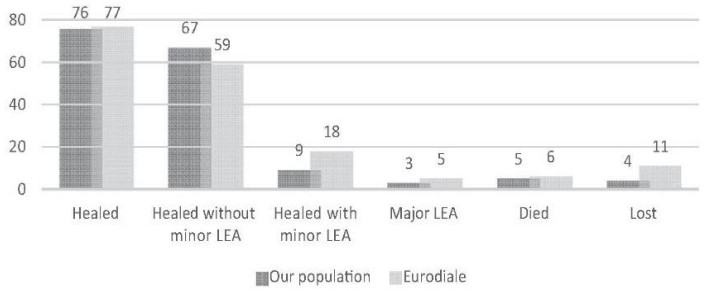

Fig. 1 – Comparison of diabetic foot ulcer outcome between our population and the Eurodiale (in percentage).

characteristics, clinical outcome and major factors influencing it [15]).

Peripheral arterial disease (PAD) was considered present when no pulse was palpable in the foot with the diabetic foot ulcer (DFU). Diabetic peripheral neuropathy (DPN) was diagnosed when there was an abnormal sensation of the Semmes-Weinstein monofilament and/or the tuning fork test. DFU depth, extent and presence of infection was collected in the same way as described by the Eurodiale [6].

Every subject was classified according to the IWGDF classification [2].

DFU was defined as a full-thickness skin defect distal to the malleoli [6]. Such subjects had at least one monthly appointment and were followed until healing, amputation or death occurred or for at least 3 months.

When the required information was missing from the patients' clinical file as well as the national data platform, the subject was excluded from analysis.

Comparisons between groups were made using, for continuous variables, the Student's t test or the Mann–Whitney U test, according to the variable distribution; and for categorical variables, the χ^2 test or Fisher's exact test, when applicable. Statistical significance was defined as $p < 0.05$.

3. Results

3.1. *During the 3-year period, 950 first appointments were scheduled*

Subjects had a mean age of 68 years (±13), 18 years (±11) of disease duration, 55% were male, 99% with type 2 diabetes, presenting a mean glycosylated hemoglobin of 7.7% (±2.1) or 61 mmol/mol (according to the International Federation of Clinical Chemistry) and 55% with HbA1c ≥7.5%. Of those, 67% had a referral request retrievable; 23% from primary health care institutions, 18% and 14% from our hospital's emergency and vascular surgery departments, respectively, and 12% from other departments or Hospitals. In total, 20% of subjects did not have a referral request but were sent to our clinic by other health professional and 13% were self-referrals. A median waiting time until appointment of 14 days [interquartile range (IQR) 7–23] was observed.

Using the IWGDF classification, 70% of the subjects were considered as at high risk of DFU development. After the first two appointments, 20% were discharged and 17% were referred to Podiatry, while 10% failed to attend.

As several of the subjects required to be re-admitted to our clinic, our total of 950 appointments was conducted on 813 patients.

Active DFU was the referral motive in 64% ($n = 606$) of the cases. The subjects had a mean age of 69 (±12) years, 63% were male, 74% had diabetes for over 10 years and 54% with HbA1c ≥ 7.5%.

At the first appointment, 41 cases (7%) were admitted to the hospital, while 105 (17%) healed in less than 3 appointments. Around 65% remained under prolonged treatment in our clinic (i.e. more than 2 appointments) for a median of 120 days (IQR 70–239).

Some of the required information for adequate DFU characterization was missing in 67 subjects. The following analysis was conducted on the remaining 539 participants.

Regarding DFU characterization: 74% were digital, 58% infected, 53% ischemic, 29% necrotic, 64% deep [University of Texas (UT) grade II or III] and 61% severe (UT stage C or D). In the subjects with DFU, neuropathy was diagnosed in 70% of the participants.

Approximately 90% of the hospitalized subjects had an infected DFU.

In patients with PAD, infection was also present in 68% of the subjects, which is significantly higher when compared to those subjects without PAD (48%, $p < 0.001$).

More than one third (38%) of the subjects with both PAD and active DFU underwent a revascularization procedure.

An increase in the UT grade or stage was associated with higher risk of minor and overall LEA.

We had a similar area under the curve [0.65 (95% confidence interval 0.55–0.75)] for the prediction of minor LEA risk score proposed by the Eurodiale consortium [14] that included gender, depth, ischemia and infection.

Data concerning the outcome of all subjects that presented active DFU and comparison to the Eurodiale results are described in Fig. 1.

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4. Discussion

It is important to expand the evidence around the Eurodiale and, so, for the countries not included in such consortium to present their results.

In our study, we observed a lesser rate of general practitioners and self-referrals in comparison to the Eurodiale. The majority of the appointments' request were made by other departments of our hospital.

At our tertiary center, the majority of the subjects were classified as being at high risk of DFU development and therefore adequately referred. On the other hand, 20% were promptly discharged and 10% failed to attend, which implies that almost one third of the appointments were probably not necessary.

An active DFU was the leading reason for referral – this supports that specialized clinics are still scarcely used for adequate DFU development prevention in subjects at high risk.

While 7% of the individuals with active DFU were immediately admitted to the hospital to their case severity, 17% of them healed in less than 3 appointments. So it is more common to receive adequate or premature referrals rather than tardy ones.

In comparison to the Eurodiale, our subjects with active DFU were marginally older, had DFUs deeper, more severe and commonly located at the toes. Our sample presented a similar prevalence of PAD and also of consequent revascularization procedures.

Concerning DFU outcome, we had equal healing, major LEA and death rates, but less minor LEA and hospital admissions. Additionally, the same variables were associated with minor LEA, for except gender and we provided a similar accuracy for the Eurodiale proposed risk score.

All this enables us to conclude that our clinic in Portugal has similar clinical outcomes to those reported in the Eurodiale studies and to observe some aspects that need improvement.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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REFERENCES

[1] Direcção Geral da Saúde. Diagnóstico Sistemático do Pé Diabético; 2011.
[2] Apelqvist J, Bakker K, van Houtum WH, Schaper NC. Practical guidelines on the management and prevention of the diabetic foot: based upon the International Consensus on the Diabetic Foot (2007) Prepared by the International Working Group on the Diabetic Foot. Diabetes Metab Res Rev 2008;24(Suppl. 1):S181–7.
[3] Akhtar S, Schaper N, Apelqvist J, Jude E. A review of the Eurodiale studies: what lessons for diabetic foot care. Curr Diab Rep 2011;11:302–9.
[4] Dubský M, Jirkovská A, Bem R, Fejfarová V, Schaper N, et al. Risk factors for recurrence of diabetic foot ulcers: prospective follow-up analysis in the Eurodiale subgroup. Int Wound J 2013;10:555–61.
[5] Pickwell KM, Siersma VD, Kars M, Holstein PE, Schaper NC. Diabetic foot disease: impact of ulcer location on ulcer healing. Diabetes Metab Res Rev 2013;29:377–83.
[6] Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. Diabetologia 2007;50:18–25.
[7] Prompers L, Huijberts M, Apelqvist J, Jude E, Piaggesi A, Bakker K, et al. Optimal organization of health care in diabetic foot disease: introduction to the Eurodiale study. Int J Low Extrem Wounds 2007;6:11–7.
[8] Prompers L, Huijberts M, Apelqvist J, Piaggesi A, Bakker K, et al. Delivery of care to diabetic patients with foot ulcers in daily practice: results of the Eurodiale Study, a prospective cohort study. Diabet Med 2008;25:700–7.
[9] Prompers L, Huijberts M, Schaper N, Apelqvist J, Piaggesi A, Bakker K, et al. Resource utilisation and costs associated with the treatment of diabetic foot ulcers. Prospective data from the Eurodiale Study. Diabetologia 2008;51:1826–34.
[10] Prompers L, Schaper N, Apelqvist J, Edmonds M, Jude E, Mauricio D. Prediction of outcome in individuals with diabetic foot ulcers: focus on the differences between individuals with and without peripheral arterial disease. The EURODIALE Study. Diabetologia 2008;51:747–55.
[11] Schaper NC. Lessons from Eurodiale. Diabetes Metab Res Rev 2012;28(Suppl. 1):21–6.
[12] Siersma V, Thorsen H, Holstein PE, Kars M, Apelqvist J, Jude E, et al. Importance of factors determining the low health-related quality of life in people presenting with a diabetic foot ulcer: the Eurodiale study. Diabet Med 2013;30:1382–7.
[13] Siersma V, Thorsen H, Holstein PE, Kars M, Apelqvist J, Jude E, et al. Health-related quality of life predicts major amputation and death, but not healing, in people with diabetes presenting with foot ulcers: the eurodiale study. Diabetes Care 2014;37:694–700.
[14] van Battum P, Schaper N, Prompers L, Apelqvist J, Jude E, Piaggesi A, et al. Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. Diabet Med 2011;28:199–205.
[15] Prompers L. Diabetic foot disease in European perspective. Results from the Eurodiale study. Public Health and Primary Care (CAPHRI): Universitaire Pers Maastricht; 2008.

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5.3 Lower limb amputation following foot ulcers in patients with diabetes: classification systems' external validation and comparative analysis

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RESEARCH ARTICLE

Lower-limb amputation following foot ulcers in patients with diabetes: classification systems, external validation and comparative analysis

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Abstract

Background This study aimed to validate and compare the existing systems developed to stratify subjects with diabetic foot ulcers by risk of consequent lower extremity amputation.

Methods We conducted a prospective cohort study on a consecutive series of patients (mean age of 68 years; 64% male) with active ulcer who were attending our Hospital Diabetic Foot Clinic ($n = 293$) from January 2010 to March 2013. At baseline, we collected information on the participants' characteristics and the relevant variables. Afterwards, we assessed the predictive value of each variable and each system's prognostic accuracy for amputation occurrence.

Results During a median follow-up of 91 days (interquartile range of 98), ulcers healed in 62% of the subjects. Major amputation occurred in 7% and minor occurred in 17%. Previous ulcer or amputation, ulcer area, and gangrene were associated with amputation occurrence. Nephropathy, pulses number, ulcer aetiology, depth, and number were associated with risk of amputation. Systems typically presented sensitivity values ≥80% and negative likelihood ratios ≤0.5 for the highest risk group; area under the receiver operating characteristic curve ranged from 0.56 to 0.83 and positive likelihood ratios from 1.0 to 5.9. If one chose only major amputation as an outcome, positive predictive values were lower, and negative predictive values tended to be higher.

Conclusions System stages, grades, scores, and/or prognostics were generally associated with amputation, presenting overall substantial accuracy values. Nevertheless, great improvement is possible. A multicentre study validating and refining the existing systems is needed to improve clinical decision-making in this area. Copyright © 2014 John Wiley & Sons, Ltd.

Keywords clinical prediction rules; diabetic foot; diagnostic accuracy; foot ulcer; classification systems

Abbreviations ABI, ankle–brachial index; ADA, American Diabetes Association; AUC, area under the receiver operating characteristic curve; CHS, Curative Health Services wound grade scale; CI, confidence interval; DEPA, Depth of the ulcer, Extent of bacterial colonization, Phase of ulcer and Association aetiology classification system; DFU, Foot Ulcer in subjects with Diabetes; DPN, diabetic peripheral neuropathy; DUSS, diabetic ulcer severity score; IDSA, Infectious Disease Society of America; IWGDF, International

Working Group on Diabetic Foot; LEA, lower-extremity amputation; LR, likelihood ratio; mmHg, millimetres of mercury; NPV, negative predictive value; OR, odds ratio; PAD, peripheral arterial disease; PEDIS, Perfusion, Extent, Depth/tissue loss, Infection, Sensation classification system; PPV, positive predictive value; S(AD)SAD, Size (Area, Depth), Sepsis, Arteriopathy, Denervation system; SEWSS, Saint Elian Wound Score System; SIGN, Scottish Intercollegiate Guidelines Network classification; SINBAD, Site, Ischemia, Neuropathy, Bacterial infection, and Depth; STARD, Standards for the Reporting of Diagnostic Accuracy studies; SWM, Semmes–Weinstein Monofilament; TUC, Texas University Classification; UT, University of Texas

Introduction

Foot ulcers in subjects with diabetes DFU frequently result in LEA [1] and increase death risk [2]. They lead to considerable costs in terms of disability, loss of productivity and quality of life [3,4]. Therefore, we should identify the most effective ways to reduce the morbi-mortality related to foot complications in subjects with diabetes.

A Eurodiale study reported that referral was delayed in more than one quarter of patients with an infected or necrotic DFU, mainly because of underestimating DFU severity and poor ischemia detection [5]. On the other hand, some authors report that critical patients' access to specialized care is delayed, because clinics are overbooked with less urgent patients [6].

A systematic and standardized prognostic assessment of subjects with an active DFU is vital for various aspects of clinical care, namely, adequate resource allocation, treatment planning and evaluating its effectiveness, inter-professionals' communication and quality of practice auditing [7].

There are 15 different systems that can be used to stratify patients with diabetes and active foot ulcer by their risk of LEA. None has been selected for widespread use, as their evidence level is low. A systematic review concluded that, currently, validation studies are scarce, prognostic accuracy measures are poorly or not at all described, and both overall and major LEA rates are inconsistent [8].

Therefore, we have conducted this study to (1) externally and simultaneously validate, (2) compare all the available systems' accuracy for predicting LEA occurrence in subjects with diabetes and active foot ulcer and (3) discuss the systems' ease of use and the pertinence of the composing variables.

Also, some experts consider that the systems' ability may be different in what concerns LEA at any level or only major LEA prediction. Therefore, we have conducted a subgroup analysis using the last as an outcome. Afterwards, we evaluated if the system's accuracy or the associated predictive variables changed.

Methods

Type of study and selection of participants

We conducted a prospective cohort study, consecutively including all subjects with diabetes and active foot ulcer attending our Diabetic Foot Outpatient Clinic, at a northern Portuguese Public Hospital, from January 2010 to March 2013. Subjects with post-LEA wounds ($n = 17$), *decubitus* ulcers ($n = 14$) or those that were discharged or hospitalized in the first appointment ($n = 137$) were excluded.

Data collection

At baseline (the first appointment), characterization variables and all those included in the available stratification systems were collected through a structured interview and foot examination, performed by one podiatrist (Matilde Monteiro-Soares). At the end of data collection, all systems' classifications and/or score were applied.

All systems available for LEA prediction in subjects with diabetes and active foot ulcer were applied. They were retrieved through a systematic review previously conducted by our group [8]. The systems found were the following: (1) CHS, (2) DEPA scoring system, (3) DUSS, (4) IDSA-IWGDF classification, (5) Margolis *et al.* classification, (6) Meggitt–Wagner classification, (7) SEWSS, (8) SIGN, (9) SINBAD score, (10) TUC and (11) Van Acker–Peter classification [4,9–19]. We excluded the Lipsky *et al.* system [9], because it was derived only for hospitalized patients. PEDIS classification [7] does not allow score or overall risk stratification as it was created to permit audits between centres and therefore was also excluded. S(AD)SAD was excluded because it was modified by the authors into the SINBAD score [10].

Margolis *et al.* [11] proposed several models for non-healing DFU prediction. We selected the one designated as count model (that uses dichotomous variables) for the following reasons: it was easier to apply and did not present a statistically different AUC value in the derivation/internal validation study.

All the subjects' characterization variables (Table 1) were retrieved by clinical questionnaire and confirmed with the patients' medical file. Physical impairment was

Table 1. Variables' association in univariate analysis with lower-extremity amputation occurrence

Variables	All (n = 293)	Non-LEA (n = 225)	LEA (n = 68)	Univariate analysis		Non-major LEA (n = 274)	Major LEA (n = 19)	Univariate analysis	
				p value	OR (95% CI)			p value	OR (95% CI)
Subject characterization									
Age [mean (SD)]	67.6 (11.7)	67.5 (11.6)	67.8 (12.4)	0.8 [a]	1.00 (0.98–1.02)	67.2 (11.8)	72.1 (10.1)	0.08 [a]	1.00 (0.99–1.09)
Male gender [n (%)]	188 (64)	144 (64)	44 (65)	1.0 [b]	1.07 (0.59–1.82)	177 (65)	11 (58)	0.6 [b]	0.75 (0.29–1.94)
Type 2 diabetes [n (%)]	288 (98)	221 (98)	67 (99)	1.0 [b]	1.00 (0.14–11.04)	269 (98)	19 (100)	1.0 [b]	1.00 (NC)
Diabetes duration (in years) [mean (SD)]	18.1 (10.9)	18.0 (11.0)	18.7 (10.8)	0.6 [a]	1.00 (0.98–1.03)	17.8 (10.7)	22.2 (13.3)	0.09 [a]	1.03 (0.99–1.08)
Insulin use [n (%)]	144 (49)	108 (48)	36 (53)	0.5[b]	1.22 (0.71–2.10)	135 (49)	9 (47)	1.0[b]	1.08 (0.43–2.74)
Body mass index [mean (SD)]	27.1 (4.6)	27.1 (4.7)	27.2 (4.5)	1.0 [a]	1.00 (0.94–1.07)	27.1 (4.6)	28.5 (4.5)	0.4 [a]	1.06 (0.94–1.21)
Lives alone [n (%)]	26 (9)	17 (8)	9 (13)	0.1 [a]	1.87 (0.79–4.40)	24 (9)	2 (11)	0.7 [a]	1.23 (0.27–5.63)
Physical impairment [n (%)]	173 (59)	128 (57)	45 (66)	0.2[b]	1.48 (0.84–2.62)	157 (57)	16 (84)	**0.03**[b]	**3.98 (1.13–13.96)**
Visual impairment [n (%)]	194 (66)	143 (64)	51 (75)	0.1[b]	1.72 (0.93–3.17)	181 (66)	13 (68)	1.0[b]	1.11 (0.41–3.02)
Retinopathy [n (%)]	159 (54)	119 (53)	40 (59)	0.4 [b]	1.27 (0.73–2.20)	146 (53)	13 (68)	0.2 [b]	1.90 (0.70–5.14)
Nephropathy [n (%)]	69 (24)	46 (20)	21 (31)	0.02 [b]	**1.99 (1.09–3.61)**	60 (22)	9 (47)	**0.01** [b]	**3.21 (1.25–8.26)**
Hypertension [n (%)]	237 (81)	178 (79)	59 (87)	0.2 [b]	1.73 (0.80–3.74)	221 (81)	16 (84)	1.0 [b]	1.28 (0.36–4.55)
Coronary heart disease [n (%)]	42 (14)	34 (15)	8 (12)	0.6[b]	0.75 (0.33–1.71)	40 (15)	2 (11)	1.0[b]	0.69 (0.15–3.09)
Stroke [n (%)]	59 (20)	46 (20)	13 (19)	0.9[b]	0.92 (0.46–1.83)	56 (20)	3 (16)	0.8[b]	0.73 (0.21–2.59)
DFU foot characterization									
Total foot pulses [n (%)]									
0	149 (51)	93 (41)	56 (82)	<**0.001**[c,d]	**0.30 (0.19–0.46)**	132 (48)	17 (90)	<**0.001**[c,d]	**0.19 (0.06–0.62)**
1	40 (14)	33 (15)	7 (10)			38 (14)	2 (11)		
2	104 (35)	99 (44)	5 (7)			104 (38)	0 (0)		
ABI [mean (SD)] (n = 146)[e]	0.7 (0.3)	0.8 (0.3)	0.7 (0.3)	0.06[a]	0.31 (0.09–1.08)	0.8 (0.3)	0.6 (0.3)	0.09[a]	0.15 (0.02–1.44)
Altered SWM sensation [n (%)] (n = 277)[f]	211 (76)	163 (76)	48 (79)	0.7[b]	1.20 (0.60–2.39)	200 (76)	11 (73)	0.8[b]	0.85 (0.26–2.77)
Altered TFS [n (%)] (n = 273)[g]	174 (64)	132 (62)	42 (69)	0.4[b]	1.34 (0.73–2.46)	163 (63)	11 (73)	0.6[b]	1.60 (0.50–5.17)
Foot deformity [n (%)]	280 (96)	214 (95)	66 (97)	0.7[b]	1.94 (0.47–7.96)	261 (95)	19 (100)	1.0[b]	NC
Oedema [n (%)]									
Absent	183 (62)	140 (62)	43 (63)	0.8 [c,d]	0.96 (0.79–1.18)	171 (62)	12 (63)	0.1/0.7 [c,d]	0.93 (0.65-1.32)
Periwound	3 (1)	2 (1)	1 (2)			3 (1)	0 (0)		
Affected leg	24 (8)	17 (8)	7 (10)			20 (7)	4 (21)		
Bilateral	83 (28)	66 (29)	17 (25)			80 (29)	3 (16)		
Previous DFU [n (%)]	127 (43)	90 (40)	37 (54)	**0.04** [b]	**1.79 (1.04–3.09)**	118 (43)	9 (47)	0.8 [b]	1.19 (0.47–3.02)
Previous LEA [n (%)]	54 (18)	35 (16)	19 (28)	**0.03** [b]	**2.11 (1.11–4.00)**	49 (18)	5 (26)	0.4 [b]	1.64 (0.56–4.77)
DFU characterization									
Aetiology [n (%)]									
DPN	38 (13)	36 (16)	2 (3)			37 (14)	1 (5)		
Deformity	107 (37)	92 (41)	15 (22)	<**0.001**[c,d]	**3.16 (1.89–5.29)**	106 (39)	1 (5)	**0.002/0.001**[c,d]	**4.91 (1.52–15.77)**
PAD	148 (51)	97 (43)	51 (75)			131 (48)	17 (89)		
Area (in cm^2) [median (range)]	4.7 (0.1–283.0)	3.5 (0.1–282.6)	6.3 (0.2–197.8)	<**0.001**[h]	**1.01 (1.00–1.02)**	4.7 (282.5)	18.8 (197.6)	0.06 [h]	7.16 (0.94–54.58)
Depth [n (%)]									
Superficial	106 (36)	99 (44)	7 (10)	<**0.001**[c,d]	**3.52 (2.34–5.29)**	105 (38)	1 (5)	**0.007/0.002**[c,d]	**2.74 (1.39–5.39)**
Tendon or ligament	94 (32)	76 (34)	18 (26)			87 (32)	7 (37)		
Bone	93 (32)	50 (22)	43 (63)			82 (30)	11 (58)		
Duration (in months) [median (range)]	1.0 (0.1–24.0)	1.0 (0.1–24.0)	1.0 (0.2–24.0)	0.1[h]	1.06 (0.95–1.18)	1.0 (23.9)	2.0 (23.5)	0.1[h]	1.09 (0.98–1.22)

(Continues)

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Table 1. (continued)

Variables	All ($n = 293$)	Non-LEA ($n = 225$)	LEA ($n = 68$)	Univariate analysis		Non-major LEA ($n = 274$)	Major LEA ($n = 19$)	Univariate analysis	
				p value	OR (95% CI)			*p* value	OR (95% CI)
Located in toes [*n* (%)]	193 (66)	139 (62)	54 (79)	**0.008**[b]	**2.39 (1.25–4.56)**	180 (66)	13 (68)	1.0[b]	1.25 (0.81–1.94)
Multiple DFUs [*n* (%)]	98 (33)	60 (27)	38 (56)	**<0.001**[b]	**3.48 (1.99–6.11)**	86 (31)	12 (63)	**0.01**[b]	**3.75 (1.43–9.85)**
Two zones or Entire foot affected [*n* (%)]	24 (8)	16 (7)	8 (12)	0.6[b]	1.14 (0.97–1.32)	22 (8)	2 (11)	0.5[b]	1.10 (0.92–1.36)
Infection presence [*n* (%)]									
Absent	124 (42)	106 (47)	16 (24)	**<0.001**[c,d]	**2.17 (1.53–3.07)**	120 (44)	4 (21)	0.2/0.07[c,d]	1.68 (0.94–2.98)
Light	93 (32)	72 (32)	21 (31)			85 (31)	8 (42)		
Moderate	76 (26)	45 (20)	31 (46)			69 (25)	7 (37)		
Severe	0 (0)	0 (0)	0 (0)			0 (0)	0 (0)		
Gangrene presence [*n* (%)]	95 (32)	46 (20)	49 (72)	**<0.001**[b]	**10.04 (5.39–18.67)**	80 (29)	15 (79)	**<0.001**[b]	**9.09 (2.93–28.24)**

LEA, lower-extremity amputation; OR, odds ratio; CI, confidence interval; SD, standard deviation; NC, not calculable; DFU, foot ulcer in subject with diabetes; ABI, ankle–brachial index; SWM, Semmes–Weinstein monofilament; TFS, tuning fork sensation; DPN, diabetic peripheral neuropathy; PAD, peripheral arterial disease.
Bold text indicates statistical significance.
[a]Student's *t*-test for two independent samples.
[b]Fisher's exact test.
[c]χ^2-test for association.
[d]χ^2-test for trend.
[e]147 missing values.
[f]16 missing values.
[g]20 missing values.
[h]Mann–Whitney *U*-test.

defined as inability to reach one's feet [12]. Visual impairment was considered present if the subjects mentioned an impossibility to perform regular foot care and examine her/his feet due to visual inability [12]. Retinopathy and nephropathy were defined as self-reported eye and kidney problems due to diabetes, respectively [20]. Hypertension was diagnosed when there was a registered value of the subjects' systolic blood pressure equal to or above 140 mm Hg and/or diastolic blood pressure equal to or above 90 mm Hg [21] and/or when he/she reported taking medication for this condition.

Each patient was included once in the study. In the presence of multiple DFUs, only the deepest was selected for inclusion. All foot-related measurements (Table 1) were conducted only in the foot with the included DFU.

Foot deformity was defined when there was a foot alteration that increased pressure in one or several sites of the foot and therefore contributed to callus and/or ulcer development.

PAD was diagnosed when only one [13,22] or none [6,7,10,12,14,15] of the pulses was palpated in the *posterior tibial* and *dorsalis pedis* arteries. For better characterization of those with PAD, the ABI was registered when available at first or subsequent appointment and before any additional vascular surgery intervention. Such evaluation was conducted only in subjects with diminished or non-palpable pedal pulses and was conducted in our Vascular Surgery Department.

When the subject was unable to feel the SWM perpendicular application for 2 s at one or more (out of four) applications at non-keratosic points (namely, hallux pulp, first, third and fifth metatarsal heads), it was considered altered sensitivity [30]. Inability to feel the tuning fork vibration at the dorsum of the hallux distal phalanx was considered altered vibration perception [7].

For those systems using the pinprick [16] or Neurotip™ [10], it was replaced by the SWM following authors' recommendations [10,17].

DFU related variables (Table 1) were collected through clinical examination, except for a duration that was retrieved by inquiring the participant and/or consulting the clinical file.

DFU was defined as a full thickness skin defect distal to the *malleoli* requiring more than 14 days to heal [18]. Complete healing was defined as ulcer closure with no further need of any dressing [15].

DFU aetiology [15], used in the DEPA score, was considered to be a neuropathy when such was present (using the SWM), foot deformity if structural biomechanical alterations were associated and PAD if chronic lower-limb ischemia was diagnosed (defined as absence of pulses in the affected foot).

Area was calculated using the elliptical wound measurement [19]. Depth was determined by visual inspection and using a sterile probe [13], if necessary.

Healing phase was categorized as epithelization, granulating (when there was evidence of granulation tissue formation), inflammatory (when the ulcer was hyperaemic with no granulation tissue with a duration less than 2 weeks) or non-healing (when the ulcer was non-granulating and had a duration over 2 weeks) [15,23].

Infection was defined as purulent discharge with another two local signs (warmth, erythema, lymphangitis, lymphadenopathy, oedema or pain) [14] and was classified according to the IDSA-IWGDF classification [24]. A DFU without purulence or any inflammatory sign was considered to be uninfected. A mild infection was defined as a DFU with two or more inflammatory signs or in the presence of cellulitis or erythema extending less than 2 cm peri-DFU and limited to skin or superficial subcutaneous tissues. When a metabolically stable patient had cellulitis extending over 2 cm, lymphangitis, spreading beneath fascia, deep tissue abscess, gangrene and muscle, tendon, joint or bone involvement, infection was classified as moderate. A patient with systemic toxicity or metabolic instability (for example, with fever, chills, tachycardia, hypotension, confusion, vomiting, leukocytosis, acidosis, hyperglycaemia or azotemia) had a severe infection.

Osteomyelitis was diagnosed by probing to bone and confirmed with radiological imaging [25] by an orthopaedist.

DFU re-evaluation was conducted at least once a month. The grading of each system corresponded to the most severe stage of the DFU during follow-up.

Follow-up was performed for at least 3 months or until complete healing, LEA or death occurred.

Toe, ray or transmetatarsal amputation was considered as minor LEA and all the remaining as major LEA. When several levels of LEA occurred, only the highest one was considered.

This study was approved by our Ethics Committee, and no adverse events occurred related to its conduction.

Management guidelines

Our diabetic foot clinic team is composed by endocrinologists, internal medicine doctors, vascular surgeons, orthopaedic surgeons, podiatrists and nurses. This multidisciplinary team works together once a week, while in the remaining days of the week, subjects are followed and treated by the nurses, podiatrists, endocrinologists and/or internal medicine doctors. Optimized blood sugar control and adequate diabetic foot care education were provided to all patients.

Empirical oral antibiotics were administered to all patients with clinical signs of infection (described earlier). When the empiric treatment was not successful, culture and sensitivity analysis was performed. Whenever adequate, sharp debridement was conducted. Healing promoting agents were selected in accordance to the presence of

infection and DFU healing stage. Regular revision was conducted, and its periodicity depended on the applied product and DFU characteristics. In those cases where offloading was necessary, pressure-relieving methods were applied (namely, callus debridement, felted foam/padding, total contact cast and/or orthopaedic surgery). Education on adequate footwear was provided to all patients. Insoles prescription was made whenever pertinent.

Revascularization was considered in all patients with deep DFUs and PAD, diagnosed by diminished palpable pulses and confirmed with the ABI value, except for those extremely debilitated, with severe functional impairment and/or large volume of necrotic tissue.

Some subjects ($n = 14$) also underwent hyperbaric oxygen therapy, on another facility (Pedro Hispano's Hospital), if they had an ischemic DFU, without healing improvement 8 weeks after the revascularization procedure.

The majority of the patients were regularly treated in their primary health care centres and had an appointment in our clinic for evaluation and treatment at most once a week and at least once a month.

Criteria for minor LEA were DFU reaching to the bone, presenting osteomyelitis and gangrene. In those cases in which PAD was also present, revascularization was firstly considered and conducted whenever adequate. Whenever the resultant blood flow was compatible with the minor LEA, wound healing was the level preferred. However, when the total restoration of the blood flow was not possible, major LEA was proposed.

Statistical analysis

For the continuous variables description, we have used the mean plus the standard deviation, when the variable was normally distributed, or otherwise, the median and range. For the analysis of association between subjects in which LEA occurred or not and continuous variables, we used the Student's *t*-test or the Mann–Whitney *U*-test, according to the distribution of the variable. For categorical variables, we used the χ^2-test or Fisher's exact test, when applicable.

Statistical analysis was conducted using IBM SPSS version 20.0 (Chicago, IL, USA).

A value of p inferior to 0.05 was considered as statistically significant.

Multivariate analysis was conducted using logistic regression, using a backward approach. So OR and respective 95% CIs were calculated.

Missing or indeterminate values were excluded from the analysis.

Participants were stratified according to stratification system categories. For all systems, sensitivity, specificity, LRs, predictive values and AUC and respective 95% CI were calculated. For that, we have used cut-offs proposed in the available derivation and/ or validation studies or those achieving the optimal equilibrium between sensitivity and specificity [8].

We chose to report the described accuracy measures as they all provide essential information to understand the impact of each classification in decision-making [26]. Sensitivity and specificity correspond to the true positive and true negative proportion rates, respectively. However, they have a difficult interpretation in the clinic as they give us the probability of the test being correct given that the condition is present or absent. On the other hand, predictive values seem to be more useful as they provide us the probability of the result being correct given the test result (positive or negative). Thus, these measures are highly prevalence dependent. LRs reflect a combination of information, using the sensitivity and specificity values to create a ratio. Positive LR (LR+) indicates the increase in odds favouring the condition given a positive test result, while negative LR (LR−) indicates the change in odds favouring the condition given a negative test result.

A test's accuracy relies on how well it can separate the subjects with condition from those without condition and can also be measured by the AUC. A receiver operating characteristic curve graph illustrates the trade-off relation between true positives and false positives. In a different context from the diagnostic tests, Ling and co-workers have proved empirically and formally that AUC is more discriminating and consistent than accuracy [27].

A subgroup analysis having only major LEA as an outcome was conducted.

Results

Characterization of participants

We included 293 subjects. The mean age of the sample was 67.6 years (±11.7), diabetes duration 18.1 years (±10.9) and body mass index 27.1 (±4.6); 64.2% was male subjects, 98.3% had type 2 diabetes and 49.1% used insulin.

During a median follow-up of 91 days (percentile 25% of 49 days and 75% of 147 days), DFU healed in 62.1% ($n = 182$) of the subjects and persisted unhealed in 6.5% ($n = 19$). A total of 16.7% ($n = 49$) of the individuals suffered minor LEA and 6.5% ($n = 19$) major LEA. Death occurred in 5.1% ($n = 15$) of the subjects, and 3.1% ($n = 9$) was lost to follow-up. In three subjects after a minor LEA procedure, a major LEA was further required (and the last was considered as an outcome).

Association of variables with LEA occurrence

Within the patients' characterization variables, only the presence of nephropathy was associated with the overall LEA (minor, midfoot or major) and major LEA. The presence of physical impairment increased specifically the risk of major LEA [OR 3.98 (95% CI 1.13–13.96)] (Table 1).

Within foot characterization variables, subjects with lower number of foot pulses ($p < 0.001$) and those with previous DFU or LEA presented higher risk of the overall LEA ($p < 0.05$). Adequate perfusion diagnosed by foot pulses palpation was related to a lower risk of major LEA [OR 0.19 (95% CI 0.02–0.62)]. However, those with or without such outcome occurrences presented similar rates of previous foot complications ($p > 0.05$).

All DFU characterization variables were highly associated with the overall LEA risk ($p < 0.001$), except for duration and number of affected zones.

Only aetiology, depth, number and gangrene were predictive of major LEA (Table 1).

Excluding those with non-healing DFU, dead or those that were lost during follow-up, we observed that the association between variables and the overall LEA was maintained, except for the previous ABI value that gained statistical significance.

In multivariate analysis, the total number of foot pulses, previous DFU, multiple DFUs, infection and gangrene maintained their significant association with LEA occurrence ($p < 0.05$) (Table 2). Only gangrene continued associated with major LEA when adjusting to the remaining variables that presented statistical significance in the univariate analysis (Tables 1 and 3).

In 50 patients with diminished or absent foot pulses, ABI was not available. In several participants, we were not able to diagnose DPN using the tuning fork ($n = 20$) or the SWM ($n = 16$).

Only 12 of the included patients were, at baseline, in other healing phases than chronic, i.e. non-healing for more than 15 days. During follow-up, all DFUs became chronic.

Table 2. Variables' associated with lower-extremity amputation occurrence in multivariate analysis, using logistic regression

Variables	*p* value	OR (95% CI)
DFU foot characterization		
Absence of palpable foot pulses	0.001	3.74 (1.75–8.02)
Previous DFU	0.02	2.34 (1.17–4.68)
DFU characterization		
Multiple DFUs	0.01	2.46 (1.23–4.91)
Infection presence	0.003	3.16 (1.48–6.75)
Gangrene presence	<0.001	7.85 (3.91–15.76)

OR, odds ratio; CI, confidence interval; DFU, foot ulcer in subject with diabetes.

Table 3. Gangrene association with major lower-extremity amputation occurrence in multivariate analysis, using logistic regression to adjust to other pertinent variables

Variables	*p* value	OR (95% CI)
Subject characterization		
Physical impairment	0.09	3.18 (0.84–12.06)
Nephropathy	0.1	2.19 (0.77–6.23)
DFU foot characterization		
Absence of palpable foot pulses	0.2	2.74 (0.50–14.97)
DFU characterization		
Aetiology (PAD)	0.2	3.21 (0.60–17.19)
Depth (Bone)	0.3	1.75 (0.61–4.96)
Multiple DFUs	0.2	2.08 (0.72–5.99)
Gangrene presence	**0.02**	4.40 (1.34–14.46)

OR, odds ratio; CI, confidence interval; DFU, foot ulcer in subject with diabetes; PAD, peripheral arterial disease.
Bold text indicates statistical significance.

Accuracy of the systems used to stratify subjects with diabetes and active DFU by their risk of LEA occurrence

All the classifications' stages, grades or overall prognostic were highly associated with the overall LEA occurrence (all $p < 0.001$, except for SIGN with $p < 0.05$). The IDSA-IWGDF and SIGN systems were not significantly associated with major LEA (Table 4). We observed no change in the association significance when excluding those with non-healing DFU, dead or lost during follow-up from analysis.

Doubts arouse when applying the CHS system. In eight subjects, DFU was superficial, corresponding to grade 1 (partial thickness involving only dermis and epidermis) but presented necrosis (that would correspond to grade 5 but requires tendon, ligament or joint exposition) [11]. Consequently, they were classified as indeterminate.

Regarding systems' accuracy, both the overall LEA and only major LEA (Table 5), the CHS, DEPA, Meggitt–Wagner and SIGN classifications tended to present the highest sensitivity when using only the higher risk groups, while all LEA were correctly detected using the DEPA, SEWSS and SIGN highest + high-risk groups. All major LEA were also accurately identified by the Margolis *et al.* system, when using this last cut-off.

Specificity was superior to 74% in all the systems' highest risk groups but significantly superior in the SEWSS system both for the overall LEA and major LEA. For the overall LEA detection, the LR+ was higher than 2.5 in all systems, when using this cut-off, significantly decreasing to values between 1.0 and 2.9 when changing it to highest + high-risk groups. For the major LEA detection, LR+ values tended to be smaller than the overall LEA but similarly diminished even more when widening the cut-off.

Conversely, LR− was inferior or equal to 0.3 in the majority of the systems when using the highest + high-risk groups but superior or equal to 0.4 for the highest risk groups (up to 0.9) for both outcomes.

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Table 4. Association of foot ulcer classification systems for subjects with diabetes risk stratification with lower-extremity amputation occurrence

Variables	All ($n = 293$)	Non-LEA ($n = 225$)	LEA ($n = 68$)	Univariate analysis		Non-major LEA ($n = 274$)	Major LEA ($n = 19$)	Univariate analysis	
				p value	OR (95% CI)			*p* value	OR (95% CI)
CHS [*n* (%)] ($n = 281$)[a]									
1	63 (22)	60 (28)	3 (5)	**<0.001** [b,c]	**2.71 (2.02–3.63)**	62 (24)	1 (5)	**<0.001** [b,c]	**2.37 (1.45–3.88)**
2–3	97 (35)	91 (42)	6 (9)			95 (36)	2 (11)		
4–6	121 (43)	65 (30)	56 (86)			105 (40)	16 (84)		
DEPA score [mean (SD)] ($n = 289$)[d]	8.8 (1.8)	8.4 (1.7)	10.0 (1.3)	**<0.001**[e]	**1.87 (1.53–2.30)**	8.7 (1.7)	10.1 (1.4)	**0.001**[e]	**1.68 (1.21–2.33)**
DEPA risk groups [*n* (%)] ($n = 289$)[d]									
Low	34 (12)	33 (15)	1 (1)	**<0.001** [b,c]	**5.17 (3.00–8.92)**	34 (13)	0 (0)	**0.02** [b,c]	**3.31 (1.37–8.00)**
Medium	153 (53)	130 (59)	23 (33)			146 (54)	7 (37)		
High	102 (35)	57 (26)	45 (65)			90 (33)	12 (63)		
DUSS score [mean (SD)] ($n = 292$)[f]	1.5 (1.0)	1.3 (0.9)	2.2 (0.8)	**<0.001**[e]	**2.90 (2.06–4.08)**	1.4 (1.0)	2.4 (0.9)	**<0.001**[e]	**2.83 (1.65–4.83)**
DUSS risk groups [*n* (%)] ($n = 292$)[f]									
0	47 (16)	47 (21)	0 (0)	**<0.001** [b,c]		47 (17)	0 (0)	**<0.001** [b,c]	
1–2	198 (68)	152 (68)	46 (68)			187 (69)	11 (58)		
3–4	47 (16)	25 (11)	22 (32)			39 (14)	8 (42)		
IDSA-IWGDF [*n* (%)]									
Absent	124 (42)	108 (48)	16 (24)	**<0.001** [b,c]	**2.17 (1.53–3.07)**	120 (44)	4 (21)	0.2 [b]/0.07 [c]	1.68 (0.94–2.98)
Light	93 (32)	72 (32)	21 (31)			85 (31)	8 (42)		
Moderate	76 (26)	45 (20)	31 (46)			69 (25)	7 (37)		
Severe	0 (0)	0 (0)	0 (0)			0 (0)	0 (0)		
Margolis *et al.* [*n* (%)] ($n = 281$)[a]									
0–1	103 (37)	100 (46)	3 (5)	**<0.001** [b,c]	**3.83 (2.47–5.95)**	103 (39)	0 (0)	0.01 [b]/**0.002** [c]	**2.79 (1.42–5.46)**
2–3	178 (63)	116 (54)	62 (95)			159 (61)	19 (100)		
Meggitt–Wagner [*n* (%)]									
0–2	154 (53)	145 (64)	9 (13)	**<0.001** [b,c]	**3.08 (2.24–4.25)**	152 (55)	3 (16)	**<0.001** [b,c]	**2.68 (1.52–4.73)**
3–4	139 (47)	80 (36)	59 (87)			122 (45)	16 (84)		
SEWSS score [mean (SD)] ($n = 277$)[g]	15.0 (2.8)	14.5 (2.7)	16.8 (2.4)	**<0.001**[e]	**1.41 (1.24–1.60)**	14.9 (2.8)	17.1 (2.3)	**0.003**[e]	**1.33 (1.09–1.61)**
SEWSS risk groups [*n* (%)] ($n = 277$)[g]									
Mild	14 (5)	13 (6)	0 (0)	**0.003**[b]/0.001[c]	**7.73 (2.02–29.59)**	33 (13)	0 (0)	**0.04**[b]/**0.03** [c]	**6.29 (1.29–30.82)**
Moderate	255 (92)	200 (93)	56 (92)			223 (83)	13 (87)		
Severe	8 (3)	3 (1)	5 (8)			6 (2)	2 (13)		
SIGN [*n* (%)] ($n = 291$)[h]									
Low	26 (9)	2 (1)	0 (0)	**0.02** [b] **/0.005** [c]	**6.12 (1.45–25.78)**	2 (1)	0 (0)	0.2 [b] /0.09 [c]	NC
Medium	36 (12)	34 (15)	2 (3)			36 (13)	0 (0)		
High	253 (87)	187 (84)	66 (97)			234 (86)	19 (100)		
SINBAD score [mean (SD)] ($n = 277$)[g]	3.4 (1.3)	3.1 (1.2)	4.3 (0.9)	**<0.001**[e]	**2.78 (1.99–3.91)**	3.3 (1.2)	4.6 (0.7)	**<0.001**[e]	**3.42 (1.74–6.73)**
SINBAD risk groups [*n* (%)] ($n = 277$)[g]									
0–1	21 (8)	21 (10)	4 (7)	**<0.001** [b,c]		21 (8)	0 (0)	**0.002** [b]/**<0.001** [c]	
2–3	116 (42)	106 (49)	9 (15)			115 (44)	1 (7)		
4–6	140 (51)	89 (41)	51 (84)			126 (48)	14 (93)		

TUC grade [*n* (%)]										
0–I	100 (34)	94 (42)	6 (9)	**<0.001** [b,c]	**3.64 (2.39–5.54)**	99 (36)	1 (5)	**0.03** [b]**/0.003** [c]	**2.63 (1.33–5.20)**
II–III	193 (66)	131 (58)	62 (91)			175 (64)	18 (95)		
TUC stage [*n* (%)] ($n = 292$)[f]										
A–B	112 (38)	110 (49)	2 (3)	**<0.001** [b,c]	**3.83 (2.51–5.86)**	112 (41)	0 (0)	**<0.001** [b,c]	**8.00 (2.13–30.05)**
C–D	180 (62)	114 (51)	66 (97)			161 (59)	19 (100)		
Van Acker–Peter grade [*n* (%)]										
1–2	107 (37)	99 (44)	8 (12)	**<0.001** [b,c]	**1.91 (1.55–2.35)**	106 (39)	1 (5)	**0.04** [b]**/0.002** [c]	**1.66 (1.18–2.34)**
3–5	186 (63)	126 (56)	60 (88)			168 (61)	18 (95)		
Van Acker–Peter stage [*n* (%)] ($n = 275$)[i]										
A–B	114 (41)	102 (48)	7 (11)	**<0.001** [b,c]	**1.90 (1.47–2.46)**	108 (42)	1 (6)	**0.07** [b]**/0.004** [c]	**2.04 (1.16–3.57)**
C–E	161 (59)	112 (52)	54 (89)			151 (58)	15 (94)		
Van Acker–Peter risk groups [*n* (%)] ($n = 275$)[i]										
Low–medium	138 (50)	131 (61)	7 (11)	**<0.001** [b,c]	**3.77 (2.52–5.64)**	137 (53)	1 (6)	**0.003** [b]**/0.001** [c]	**2.91 (1.52–5.57)**
High–highest	137 (50)	83 (39)	54 (89)			122 (47)	15 (94)		

Univariate analysis was conducted using all the categories, and thus, odds ratios correspond to the increase of one risk group.
LEA, lower-extremity amputation; OR, odds ratio; CI, confidence interval; CHS, Curative Health Services wound grade scale; DEPA, Depth of the Ulcer, Extent of bacterial colonization, Phase of ulcer and Association aetiology; SD, standard deviation; DUSS, diabetic ulcer severity score; IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; SEWSS, Saint Elian Wound Score System; SIGN, Scottish Intercollegiate Guidelines Network; NC, not calculable; SINBAD, Site, Ischemia, Neuropathy, Bacterial infection, and Depth; TUC, Texas University Classification.
Bold text indicates statistical significance.
[a]12 missing values.
[b]χ^2-test for association.
[c]χ^2-test for trend.
[d]3 missing values.
[e]Student's *t*-test for two independent samples.
[f]1 missing values.
[g]16 missing values.
[h]2 missing values.
[i]18 missing value.

Table 5. Accuracy of the systems used to stratify subjects with diabetes and active diabetic foot ulcer by their risk of lower-extremity amputation occurrence

	LEA						Major LEA					
PAM system	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR− (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR− (95% CI)	PPV % (95% CI)	NPV % (95% CI)
CHS (5–6) [b]	71 (59–82)	82 (77–87)	4.0 (2.9–5.6)	0.4 (0.2–0.5)	55 (44–65)	90 (86–94)	79 (61–97)	74 (68–79)	3.0 (2.2–4.1)	0.3 (0.1–0.7)	18 (10–26)	98 (96–100)
DEPA (high)	66 (54–77)	74 (68–80)	2.6 (1.9–3.4)	0.5 (0.3–0.6)	44 (34–54)	88 (83–92)	63 (41–85)	67 (61–72)	1.9 (1.3–2.8)	0.6 (0.3–1.0)	12 (6–18)	96 (94–99)
DUSS (3 + 4)	32 (22–45)	89 (84–93)	2.9 (1.8–4.8)	0.8 (0.6–0.9)	47 (33–61)	81 (76–86)	42 (20–64)	86 (82–90)	2.9 (1.6–5.4)	0.7 (0.5–1.0)	17 (6–28)	96 (93–98)
IDSA-IWGDF (severe) Margolis *et al.* (3)	51 (38–63)	85 (80–90)	Not applicable [a] 3.4 (2.3–5.1)	0.6 (0.5–0.8)	52 (39–64)	85 (80–90)	42 (20–64)	78 (73–83)	Not applicable [a] 1.9 (1.1–3.4)	0.7 (0.5–1.1)	13 (4–21)	95 (92–98)
Meggitt–Wagner (4)	72 (60–82)	79 (73–84)	3.5 (2.6–4.7)	0.4 (0.2–0.5)	52 (42–62)	90 (86–94)	79 (61–97)	71 (65–76)	2.7 (2.0–3.6)	0.3 (0.1–0.7)	16 (8–23)	98 (96–100)
SEWSS (severe)	8 (3–18)	99 (96–100)	5.9 (1.5–24.1)	0.9 (0.9–1.0)	63 (29–96)	79 (74–84)	13 (0–31)	98 (96–99)	5.4 (1.2–24.4)	0.9 (0.7–1.1)	25 (0–55)	95 (92–98)
SIGN (high)	97 (90–100)	16 (12–22)	1.2 (1.1–1.2)	0.2 (0.05–0.7)	26 (21–32)	95 (88–100)	100 (NC)	14 (10–18)	1.2 (1.1–1.2)	NC	8 (4–10)	100 (NC)
SINBAD (5 + 6)	49 (36–62)	88 (83–92)	4.0 (2.6–6.4)	0.6 (0.5–0.7)	54 (41–67)	86 (81–91)	60 (35–85)	82 (77–87)	3.3 (2.1–5.4)	0.5 (0.3–0.9)	16 (6–26)	97 (95–99)
TUC (3C + 3D)	54 (42–65)	82 (78–88)	3.2 (2.3–4.6)	0.6 (0.4–0.7)	53 (42–63)	84 (79–89)	58 (36–80)	75 (70–80)	2.3 (1.5–3.5)	0.6 (0.3–0.9)	14 (6–21)	96 (94–99)
Van Acker–Peter (highest)	39 (27–53)	89 (84–93)	3.7 (2.2–6.0)	0.7 (0.6–0.8)	51 (37–65)	84 (79–89)	38 (14–61)	84 (80–89)	2.4 (1.2–4.7)	0.7 (0.5–1.1)	13 (3–22)	96 (93–98)
CHS (4–6) [b]	82 (73–91)	71 (65–77)	2.9 (2.3–3.6)	0.2 (0.1–0.4)	46 (37–55)	93 (89–97)	79 (61–97)	74 (68–79)	3.0 (2.2–4.1)	0.3 (0.1–0.7)	18 (10–26)	98 (96–100)
DEPA (medium + high)	100 (NC)	15 (11–21)	1.2 (1.1–1.3)	NC	27 (21–32)	100 (NC)	100 (NC)	13 (9–17)	1.1 (1.1–1.2)	NC	7 (4–11)	100 (NC)
DUSS (2–4)	81 (70–89)	63 (56–69)	2.2 (1.8–2.7)	0.3 (0.2–0.5)	40 (32–48)	92 (87–96)	84 (68–100)	56 (50–62)	1.9 (1.5–2.4)	0.3 (0.1–0.8)	12 (6–17)	98 (96–100)
IDSA-IWGDF (moderate + severe)	76 (65–86)	60 (50–69)	1.5 (1.2–1.8)	0.5 (0.3–0.8)	31 (24–38)	87 (81–93)	37 (15–59)	75 (70–80)	1.5 (0.8–2.7)	0.8 (0.6–1.2)	9 (3–16)	95 (91–98)
Margolis *et al.* (2 + 3)	95 (87–99)	48 (41–55)	1.7 (1.5–2.0)	0.1 (0.03–0.3)	35 (28–42)	97 (93–100)	100 (NC)	37 (31–43)	1.6 (1.5–1.8)	NC	11 (6–15)	100 (NC)
Meggitt–Wagner (3 + 4)	86 (76–94)	65 (58–71)	2.5 (2.0–3.0)	0.2 (0.1–0.4)	43 (35–51)	94 (90–98)	84 (68–100)	55 (49–61)	1.9 (1.5–2.4)	0.3 (0.1–0.8)	12 (6–17)	98 (96–100)
SEWSS (moderate + severe)	100 (NC)	6 (4–11)	1.1 (1.0–1.1)	NC	23 (18–28)	100 (NC)	100 (NC)	5 (3–8)	1.0 (0.7–1.11)	NC	5 (3–9)	100 (NC)
SIGN (medium + high)	100 (NC)	1 (0–3)	1.0 (1.0–1.0)	NC	24 (19–28)	100 (NC)	100 (NC)	1 (0–2)	1.0 (1.0–1.1)	NC	7 (4–9)	100 (NC)
SINBAD (4–6)	75 (65–85)	60 (54–67)	1.9 (1.5–2.3)	0.4 (0.3–0.6)	36 (28–44)	89 (84–94)	100 (NC)	52 (46–58)	2.1 (1.8–2.4)	NC	13 (8–19)	100 (NC)
TUC (2B–3D)	91 (82–97)	46 (39–53)	1.7 (1.5–1.9)	0.2 (0.09–0.4)	34 (27–41)	95 (90–99)	95 (85–100)	37 (32–43)	1.5 (1.3–1.7)	0.1 (0.02–0.9)	10 (5–14)	99 (97–100)
Van Acker–Peter (high + highest)	89 (78–95)	61 (54–68)	2.3 (1.9–2.8)	0.2 (0.09–0.4)	39 (31–48)	95 (91–98)	94 (82–100)	53 (47–59)	2.0 (1.7–2.4)	0.1 (0.02–0.8)	11 (6–16)	99 (98–100)

LEA, lower-extremity amputation; CI, confidence interval; LR+, positive likelihood ratio; LR−, negative likelihood ratio; PPV, positive predictive value; NPV, negative predictive value; PAM, prognostic accuracy measure; CHS, Curative Health Services wound grade scale; DEPA, Depth of the Ulcer, Extent of bacterial colonization, Phase of ulcer and Association aetiology; DUSS, diabetic ulcer severity score; IDSA, Infectious Disease Society of America; IWGDF, International Working Group on Diabetic Foot; SEWSS, Saint Elian Wound Score System; SIGN, Scottish Intercollegiate Guidelines Network; NC, not calculable; SINBAD, Site, Ischemia, Neuropathy, Bacterial infection, and Depth; TUC, Texas University Classification.

[a] No subject was classified as being in the severe risk group.

[b] ,8 indeterminate results.

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Positive predictive values ranged from 21% to 65%, which implies a proportion of false positives from 35% to 79%, while NPVs were superior to 80%, regardless the cut-off used for the overall LEA prediction. No significant differences were observed between systems in these measures.

However, in general, PPVs were significantly inferior (in all cases, inferior to 25%), and NPVs were significantly superior (always superior to 95%) for major LEA prediction.

AUC values were superior to 0.72 in almost all the systems for both outcomes. The SIGN (AUC of 0.56) and SEWSS (AUC of 0.57) risk groups presented the lowest AUC when compared with all the other systems (Figure 1). For the overall LEA identification, such difference was statistically significant but not for the major LEA prediction (Figure 2). No other differences were observed when the remaining systems were compared with each other.

Discussion

We conducted a prospective cohort study, consecutively including 293 subjects with diabetes and active foot ulcer attending our Hospital's Diabetic Foot clinic. To the best of our knowledge, this is the first study where all the available systems were externally validated for the LEA occurrence prediction, in the same cohort of patients, allowing their accuracy comparison. We must, however, point that some of the systems were created to predict (non-)healing and others for audit purposes.

Participants were followed for a median of 91 days, during which 23.2% required an LEA (16.7% minor and 6.5% major). This outcome rate is within the average reported values [5,9,13–17,19,22,23,25].

As additional strengths, this study presents its prospective design and the use of the STARD checklist [28] for adequate reporting.

We observed that, although in univariate analysis several variables were associated with LEA occurrence, only the total number of foot pulses, previous DFU, multiple DFUs, infection and gangrene maintained their significant association with the overall LEA occurrence. Only gangrene was significantly associated with major LEA (adjusting to the remaining variables).

Peripheral arterial disease and infection are included in almost all the systems; previous DFU is included only by SIGN; DFU number by DUSS, Margolis *et al.* and SEWSS; and gangrene by CHS, Margolis *et al.* and Meggitt–Wagner.

We observed that no major LEA occurred in subjects in which both pedal pulses were palpable, as expected. However, minor LEA was required in four of them as they presented necrotic, moderately infected and reaching to the bone DFUs.

Only one subject presented with a superficial DFU underwent major LEA due to absence of palpable pulses, an ABI of 0.36 and impossibility to conduct an adequate revascu-

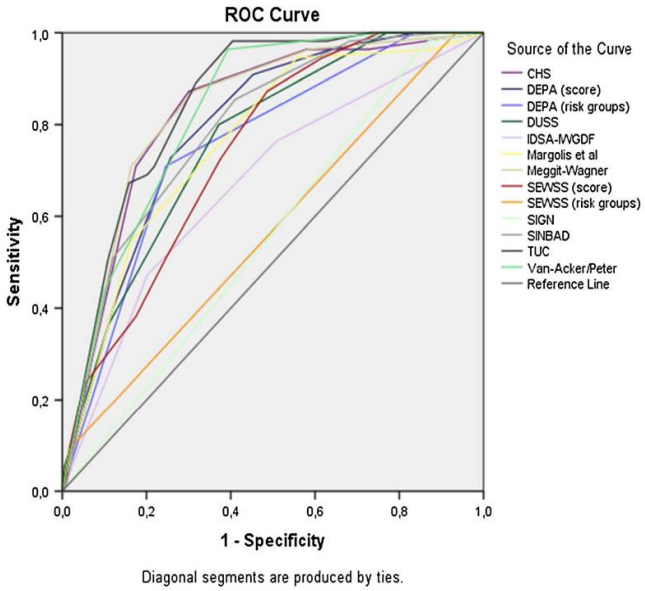

Figure 1. Risk stratification systems' receiver operating characteristic curve for lower-extremity amputation occurrence

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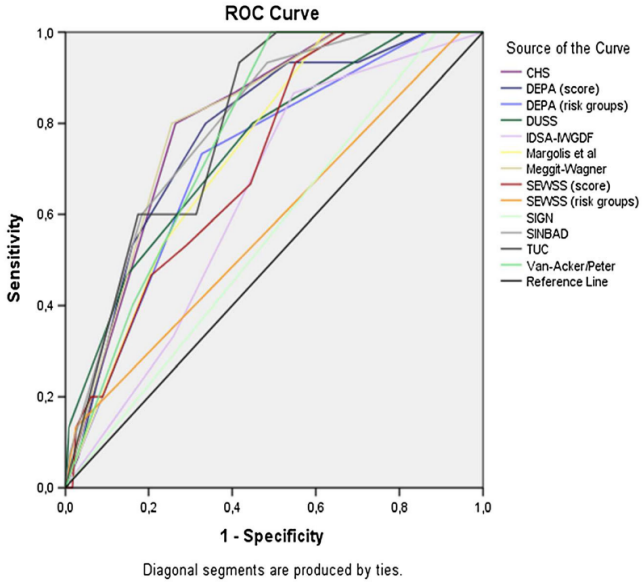

Figure 2. Risk stratification systems' receiver operating characteristic curve for major lower-extremity amputation occurrence

larization. In addition, seven individuals with DFU reaching to the tendon or ligament also required a major LEA. In all those cases, pedal pulses were not palpable, ABI ranged from 0.33 to 0.79, adequate revascularization was not viable and both infection and gangrene were present. Minor LEA was conducted in 17 patients with superficial DFU or reaching to the tendon or ligament as they were concomitantly ischemic (no pedal pulse was palpable) and necrotic.

We must highlight that the grade of infection, classified according to the IDSA-IWGDF system, was not associated with a higher risk of major LEA. No subject presented severe infection, but several presented moderate infection (26%). Such results point that our team is effective in controlling infection locally.

The authors decided to grade the DFU at its most severe moment instead of at baseline. We considered this procedure to give a more accurate image of the systems' ability to predict the necessity of LEA. If they exist to support our clinical decision in our daily practice, which is based on the last DFU evaluation and on the highest risk situation, the same should occur with the systems.

It may be considered that the results can be confounded by the treatment chosen by our team, adherence to the prescribed treatment by the primary health care centres or to the adequate diabetic foot care habits and offloading by the patient. However, we have observed that only 23 subjects (8%) got worse before outcome occurred (healing or LEA). Therefore, we do not believe that this decision may have a major impact on our results.

Having this in mind, for the overall LEA prediction, when using the highest risk cut-off, the available DFU classification systems presented high NPV and specificity. The only system presenting lower values (SIGN) had 16% specificity. Conversely, sensitivity, LR and PPV values produced only the modest values. In this case, the SIGN system presented the highest sensitivity (97%).

When including the highest + high-risk groups, we observed that there was an improvement in sensitivity and NPV (achieving 100% in the DEPA, SEWSS and SIGN systems for both measures) as well as LR− (although still presenting values between 0.1 and 0.3). Contrariwise, specificity, LR+ and PPV diminished their values when changing the cut-off. In six systems, specificity was lower than 50%, LR+ between 1.0 and 1.5 and in all, PPV was inferior to 46%.

AUC values were superior to 0.74 in almost all the systems, except for SIGN and SEWSS (presenting significantly lower values).

Comparing our results with those retrieved from the available literature [8], we observed that, using the same cut-offs, specificity was lower in the SIGN system; specificity and LR+ were lower in the DEPA system and specificity, LR+, LR−, PPV and NPV were lower in the IDSA-IWGDF system. Contrariwise, sensitivity was higher in the CHS system, while no differences were observed for the Meggitt–Wagner system.

When assessing only major LEA prediction ability, we conclude that the systems' accuracy is very similar to the

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one presented for the overall LEA prediction. PPVs were higher, and NPV tended to be lower, in part because of the lower prevalence of major LEA compared with the overall LEA.

In our systematic review [8], we were able only to calculate prognostic accuracy measures for major LEA in two studies. The one assessing the Meggitt–Wagner [29] presented lower specificity and the one evaluating the SIGN system [12] higher specificity, in comparison with this study results.

That we are aware of, there is no available information regarding the remaining systems' accuracy [8]. So, this is the first time that prognostic accuracy measures are reported or calculable for several of the existing systems, namely, DUSS, SEWSS, SINBAD, TUC and Van Acker–Peter.

For the interpretation of these data, several factors must be considered. We have decided to exclude post-LEA and *decubitus* wounds, as we consider them to have a different prognosis or pathophysiology than the primary wound, respectively.

PAD was diagnosed only through palpable foot pulses, as it is easier to collect; the majority of the systems do not use ABI (DEPA, DUSS, SINBAD and SIGN) or uses it only as a complementary test (SEWSS, Texas). Various articles validating some of the available systems also used only foot pulses palpation, claiming the same reasons we described [22,24] and also because of the number of ABI missing values as it was measured only in subjects with diminished or non-palpable pedal pulses.

Pinprick and Neurotip ™ were replaced by the SWM, having in consideration the authors' recommendations. Although they may affect several systems' accuracy, it can improve our results' generalizability as such tests are not so commonly used.

The authors have decided to exclude the cases with missing values from univariate analysis. Only three variables presented the missing values: ABI (147 missing values), SWM (16 missing values) and tuning fork (20 missing values) sensation tests.

The reasons for the high number of ABI missing values have already been addressed in Methods and Discussion Section. We have observed that those requiring an LEA [global ($p < 0.001$) or major ($p = 0.04$)] had less missing values. As it is expected that those at lower risk of LEA present higher ABI values, it would be likely that, if we had the values for all the samples, the association could become statistically significant.

There was no difference in the missingness rate of the DPN tests between those requiring LEA and those who did not ($p = 0.06$ for the SWM and $p = 0.3$ for the tuning fork). On the other hand, those requiring major LEA had a higher number of missing values for both tests ($p = 0.01$ for the SWM and $p = 0.03$ for the tuning fork). This occurred because such missing values were due to the impossibility to conduct the tests in patients that were too debilitated or with their feet severely affected in multiple sites. As the number of missing values is under 20 and for both tests the OR 95% CI is so wide, in the univariate analysis, we do not expect that this situation has an impact on the association significance level.

Only nine participants were lost (3.1%) to follow-up; however, we confirmed that no LEA or death was registered in our institutions' clinical file and in the national data platform. Therefore, it is highly probably that the respective DFU healed meanwhile. In addition, when excluding them, as well as those that have died, no major differences were observed in our results.

Our results' generalizability may be affected by the single-centre design and eventually small sample size, high number of patients that presented type 2 diabetes ($n = 288$) and a chronic DFU ($n = 281$) at baseline. On the other hand, we believe that this may also reflect what generally occurs in specialized diabetic foot clinics worldwide.

Regarding the sample size, we must highlight that when taking in consideration that for a worst-case scenario (a proportion of 50%), with a margin of error of 0.6% and a significance of 0.05, a total of 267 subjects would be required. Therefore, we may assume that we have included an adequate number of subjects.

Several specialists in the diabetic foot area consider that the prediction of the overall LEA and major LEA cannot be compared. On the other hand, they also consider minor LEA as a therapeutic procedure, based on highly subjective and variable criteria and should not be classified as an outcome.

However, our systematic review [8] concluded that major LEA is also widely variable, with a prevalence ranging from 0% up to 29.6%.

In this study, we also observed that the systems' accuracy was comparable between the outcomes. Only the PPV was higher, and NPV tended to be lower. Such PPV differences represent that for each 100 subjects considered at high risk, around 10–20 will require a major LEA, 30–40 will require a minor LEA and up to 40–50 will heal.

Despite the fact that using the systems for predicting the overall LEA represents an increase of costs and resources, it is more adequate to apply the systems for this global outcome. Until they can be more discriminative, we should aim to refer to specialized care all those subjects that present medium or high risk of LEA, according to any of the assessed classifications. In addition, the systems and their categories that accurately predicted both outcomes (overall and major LEA) were the same.

In our diabetic foot clinic, we observed that major LEA was conducted mainly in physically limited patients with multiple ischemic and necrotic wounds.

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Being the first study where such comparison was possible and taking into account that the different systems presented similar accuracy, the authors considered important to discuss their characteristics and ease of use.

The CHS system [11] has six grades describing depth, abscess or osteomyelitis and necrotic tissue. However, in 12 subjects, DFU was superficial but presented necrosis and had to be classified as indeterminate. The same occurred with the Margolis system as it includes the CHS system plus DFU duration and area. The DEPA and DUSS systems score four easy-to-collect variables and, in that way, categorize subjects by their risk of LEA. Although the first uses an acronym and rates each variable from 1 to 3, the second dichotomized all variables' classification (absence *versus* presence) and therefore is easier to use. The IDSA-IWGDF was created only to characterize the subject's degree of infection. The Meggitt–Wagner classification is the most widely used. If, for the one hand, it uses few easy-to-collect variables, on the other hand, it is considered as too simplistic and linear [8]. The SEWSS system is the most complex and difficult to apply as it uses ten variables that are scored from 1 to 3. The SIGN system uses six easily available and easy-to-collect variables and is the only one that was developed for DFU development and validated for LEA occurrence risk prediction. The SINBAD systems evolved from the S(AD)SAD classification that was considered by some authors as hard to remember [8]. It scores the six included variables from 0 to 3 and results in a four-risk grade classification. Both TUC and Van Acker–Peter systems use a square matrix, as the second (including five variables and creating 25 squares) was based on the first (including three variables and creating 16 squares).

In our opinion, the systems that use fewer easy-to-use dichomotic variables, such as DEPA, DUSS, Meggitt–Wagner and SIGN, are better for implementation in daily clinical care. However, contrariwise to some authors, we considered the application of the square matrix systems (TUC and Van Acker–Peter) also as straightforward and visually informative of the subjects' risk of LEA. The SIGN system has the advantage of being accurate to predict the two most important outcomes in the foot of individuals with diabetes: DFU development and LEA risk.

We conclude that all the available systems present similar and substantial accuracy and also that their main variables are associated with LEA occurrence. However, such association is not maintained for all in the multivariate analysis. PAD, previous DFU, multiple DFUs, infection and gangrene seem to be the most important predictive variables.

Furthermore, despite the association between outcome and the systems' stages, grades and prognostic, we observed merely fair PPVs and LRs. Therefore, we believe that systems' accuracy should be improved before selecting and implementing the 'best' one.

In order to accomplish that, future research, particularly multicenter studies, is needed to validate and refine the existing systems.

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Conflicts of interest

The authors have no conflicts of interest.

References

1. Apelqvist J, Bakker K, van Houtum WH, *et al.* Practical guidelines on the management and prevention of the diabetic foot. *Diabetes Metab Res Rev* 2008; **24** (Suppl 1): S181–S187.
2. Martins-Mendes D, Monteiro-Soares M, Boyko EJ, *et al.* The independent contribution of diabetic foot ulcer on lower extremity amputation and mortality risk. *J Diabetes Complications* 2014; **28**(5): 632–638.
3. Basu S, Hadley J, Tan RM, Williams J, Shearman CP. Is there enough information about foot care among patients with diabetes? *Int J Low ExtremWounds* 2004; **3**: 64–68.
4. Boulton AJ, Meneses P, Ennis WJ. Diabetic foot ulcers: a framework for prevention and care. *Wound Rep Reg* 1999; **7**: 7–16.
5. Prompers L, Huijberts M, Apelqvist J, *et al.* Optimal organization of health care in diabetic foot disease: introduction to the Eurodiale study. *Int J Low ExtremWounds* 2007; **6**: 11–17.
6. Leese GP, Reid F, Green V, *et al.* Stratification of foot ulcer risk patient with diabetes: a population-based study. *Int J Clin Pract* 2006; **60**(5): 541–545.
7. Schaper NC. Diabetic foot ulcer classification system for research purposes: a progress report on criteria for including patients in research studies. *Diabetes Metab Res Rev* 2004; **20**(S1): S90–S95.
8. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2014; **30**(7): 610–622.
9. Lipsky BA, Weigelt JA, Sun X, Johannes RS, Derby KG, Tabak YP. Developing and validating a risk score for lower-extremity amputation in patients hospitalized for a diabetic foot infection. *Diabetes Care* 2011; **34**(8): 1695–1700.
10. Ince P, Kendrick D, Game F, Jeffcoate W. The association between baseline characteristics and the outcome of foot lesions in a UK population with diabetes. *Diabet Med* 2007; **24**(9): 977–981.

11. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. *Am J Med* 2003; **115**(8): 627–631.
12. Leese G, Schofield C, McMurray B, *et al.* Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. *Diabetes Care* 2007; **30**(8): 2064–2069.
13. Abbas ZG, Lutale JK, Game FL, Jeffcoate WJ. Comparison of four systems of classification of diabetic foot ulcers in Tanzania. *Diabet Med* 2008; **25**(2): 134–137.
14. Beckert S, Witte M, Wicke C, Königsrainer A, Coerper S. A new wound-based severity score for diabetic foot ulcers: a prospective analysis of 1,000 patients. *Diabetes Care* 2006; **29**(5): 988–992.
15. Younes NA, Albsoul AM. The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers. *J Foot Ankle Surg* 2004; **43**(4): 209–213.
16. Treece KA, Macfarlane RM, Pound N, Game FL, Jeffcoate WJ. Validation of a system of foot ulcer classification in diabetes mellitus. *Diabet Med* 2004; **21**(9): 987–991.
17. Chipchase SY, Treece KA, Pound N, Game FL, Jeffcoate WJ. Heel ulcers don't heal in diabetes or do they? *Diabet Med* 2005; **22**(9): 1258–1262.
18. Boyko EJ, Ahroni JH, Cohen V, Nelson KM, Heagerty PJ. Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care* 2006; **29**: 1202–1207.
19. Shaw J, Hughes CM, Lagan KM, Bell PM, Stevenson MR. An evaluation of three wound measurement techniques in diabetic foot wounds. *Diabetes Care* 2007; **30**(10): 2641–2642.
20. Iversen MM, Midthjell K, Østbye T, *et al.* History of and factors associated with diabetic foot ulcers in Norway: the Nord-Trøndelag Health Study. *Scand J Public Health* 2008; **36**(1): 62–68.
21. World Health Organization. A global brief on hypertension: silent killer, global public health crisis, 2013. Available at: http://apps.who.int/iris/bitstream/10665/79059/1/WHO_DCO_WHD_2013.2_eng.pdf. Last access in: 15 September 2014.
22. Armstrong DG, Lavery LA, Harkless LB. Validation of a diabetic wound classification system. The contribution of depth, infection, and ischemia to risk of amputation. *Diabetes Care* 1998; **21**(5): 855–859.
23. Martínez-de JF. A checklist system to score healing progress of diabetic foot ulcers. *Int J Low Extrem Wounds* 2010; **9**(2): 74–83.
24. Lavery LA, Armstrong DG, Murdoch DP, Peters EJ, Lipsky BA. Validation of the Infectious Diseases Society of America's diabetic foot infection classification system. *Clin Infect Dis* 2007; **44**(4): 562–565.
25. Ali S, Basit A, Fawwad A, Ahmedani M, Miyan Z, Malik R. Presentation and outcome of diabetic foot at a tertiary care unit. *Pak J Med Sci* 2008; **24**(5): 651–656.
26. Fritz JM, Wainner RS. Examining diagnostic tests: an evidence-based perspective. *Phys Ther* 2001; **81**(9): 1546–1564.
27. Ling CX, Huang J, Zhang H. AUC: a statistically consistent and more discriminating measure than accuracy. *Proc. 18th Int'l Joint Conf. Artificial Intelligence (IJCAI)* 2003: 329–341.
28. Bossuyt PM, Reitsma JB, Bruns DE, *et al.* Standards for reporting of diagnostic accuracy. The STARD statement for reporting studies of diagnostic accuracy: explanation and elaboration. *Ann Intern Med* 2003; **138**(1): W1–W12.
29. Sun JH, Tsai JS, Huang CH, *et al.* Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. *Diabetes Res Clin Pract* 2012; **95**(3): 358–363.
30. Smieja M, Hunt D, Edelman D, *et al.* Clinical examination for the detection of protective sensation in the feet of the diabetic patients. *J Gen Int Med* 1999; **14**: 418–424.

CHAPTER 6. A NEW DIABETIC FOOT RISK ASSESSMENT TOOL: DIAFORA

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RESEARCH ARTICLE

A new diabetic foot risk assessment tool: DIAFORA

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Abstract

Aims This study aimed to derive a new model to classify subjects with diabetes and active diabetic foot ulcer by their risk of lower extremity amputation.

Methods A prospective cohort study was conducted that included all subjects with diabetic foot ulcer attending our Hospital Diabetic Foot Clinic from 2010 to 2013. Variables were collected at baseline. Subjects were followed up until healing, lower extremity amputation, death or for at least 3 months. Logistic regression was used to derive the new model, and the area under the receiver operating characteristic curve was assessed to propose the model with the greatest discrimination.

Results A total of 293 participants were included and followed for a median of 91 days. In 23.2% amputation was required, 5.1% died and 3.1% were lost. Our final model included the variables most commonly used in clinical practice for diabetic foot risk assessment (presence of neuropathy, foot deformity, peripheral arterial disease and previous foot complications) in addition to multiple diabetic foot ulcer, infection, gangrene and bone involvement. This model had an area under the receiver operating characteristic curve of 0.91 [95% confidence interval (CI) 0.87–0.95] and as classification of 0.89 (95% CI 0.84–0.93) for lower extremity amputation prediction. The high-risk group presented a positive likelihood ratio of 5 (95% CI 3–8) and predictive value of 58 (46–71). Only one minor lower extremity amputation occurred in the low-risk group.

Conclusions We propose a new classification: diabetic foot risk assessment (DIAFORA). This classification was equally or more accurate for lower extremity amputation prediction in diabetic foot ulcer patients when compared with the existing ones. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords diabetic foot; foot ulcer; amputation; risk

Abbreviations AUC, area under the receiver operating characteristic curve; CI, confidence interval; DIAFORA, diabetic foot risk assessment; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; IWGDF, International Working Group on Diabetic Foot; LEA, lower extremity amputation; LR, likelihood ratio; PAD, peripheral arterial disease; ROC, receiver operating characteristic

Introduction

An accurate assessment of the risk of diabetic foot complications is essential to guide daily clinical practice. Currently, there are 5 classification systems for diabetic foot ulcer development (DFU) [1] and 15 for lower extremity

amputation prediction (LEA) [2]. However, they have been scarcely validated, which has impaired the selection and adoption of such classifications by health professionals worldwide.

In the two existing studies [3,4] comparing each kind of classification among themselves, no statistically significant differences were observed, and opportunities for improvement were reported, especially with regard to low positive predictive values.

Furthermore, several classifications used for LEA prediction include foot-related variables that are present in the majority of DFU development risk classifications [namely, diabetic peripheral neuropathy (DPN), peripheral arterial disease (PAD), foot deformity and previous DFU or LEA].

Therefore, we aimed to derive a new model to classify subjects with diabetes and active DFU by their risk of LEA (DIAFORA – diabetic foot risk assessment) providing equal or higher validity in comparison with those currently available. To improve the utility of the new classification for health professionals, we consider it more useful to select as core variables those that are already included in the most commonly used DFU development risk classifications [namely, by the International Working Group on Diabetic Foot (IWGDF)]. In that way, the first part of the new classification can be used to predict DFU development in those subjects without an active DFU, as it is currently carried out in clinical practice, and in its full form to predict LEA in those with DFU.

Methods

For the new classification (DIAFORA) derivation, we have used a prospective cohort study that was already described previously [4]. In sum, we have consecutively included all subjects with active DFU that attended, from January 2010 to March 2013, our public Hospital Diabetic Foot Clinic and were followed up until healing, amputation or death occurred or for at least 3 months. Exclusion criteria were non-healing post-LEA wounds, decubitus ulcers or having been discharged from the outpatient clinic at the first appointment.

The collection of the variables required, identified through previously published systematic reviews [1,2], was conducted at baseline by one podiatrist (Matilde Monteiro-Soares) specialized in diabetic foot complications through a structured interview and foot examination.

All foot-related measurements were conducted only in the foot with the included DFU. PAD was defined as the absence of foot palpable pulses [5], DPN as inability to feel Semmes–Weinstein monofilament in one or more (out of four) pre-specified non-keratotic points [6] and/or the tuning fork at the dorsal side of the distal phalanx of the hallux [7] and foot deformity as a biomechanical alteration that increases pressure in any point of the foot.

DFU characterization, its depth, extent and presence of infection was collected as reported by the Eurodiale consortium [8]. Bone involvement was assessed by visual inspection and/or using a sterile probe [4] and, if necessary, X-ray evaluation. DFU aetiology was categorized according to the DEPA classification as DPN, deformity or PAD [9].

For the LEA prediction models' derivation, we selected the four foot-related variables that were most commonly included in the DFU development risk classifications (DPN, PAD, foot deformity and previous DFU or LEA) [2]. To decide which DFU-related variables to include, a multivariate analysis predicting the presence of LEA as the dependent variable was conducted using logistic regression, with a backward stepwise approach. For inclusion in the new model, significance was defined as a p-value inferior to 0.1 in the univariate analysis (please see [4]).

The final model was selected through area under the receiver operating characteristic (ROC) curve (AUC) analysis, and risk groups were created by assessing the AUC that provided maximum discrimination. We considered that the creation of three risk groups would be clinically relevant: low, medium and high risk. The required two cut-offs (to create the three risk groups) were defined using visual assessment of the ROC curve and of the respective sensitivity and specificity coordinates. We have selected the two points that for the maximum sensitivity provided the better specificity and produced the respective ROC curve. In sum, the first cut-off point value presented a sensitivity of 100% and the highest specificity value, and the second cut-off point value presented a specificity superior to 90% and the highest sensitivity value.

Prognostic accuracy measures, namely, sensitivity, specificity, likelihood ratios (LR), predictive values and AUC and respective 95% confidence intervals (CI), were calculated. Significant statistical differences between our model's score in its continuous and group risk categories form and between our model and the available classifications were conducted by comparing the respective 95% CI. We considered that a statistically significant difference occurred whenever there was no overlap between 95% CI.

Statistical analysis was conducted using IBM SPSS version 20.0 (Chicago, IL, USA).

Management guidelines were described in our previous article (please see [4]).

This study was approved by our Ethics Committee, and no adverse events occurred related to its conduction.

Results

We included a cohort of 293 subjects, followed up for a median of 91 days, with a mean age of 67.6 years (±11.7), diabetes duration 18.1 years (±10.9) and body mass index of 27.1 (±4.6). The majority were men (64.2%) and had type 2 diabetes (94.1%). Amputation occurred in 23.2% (16.7% minor and 6.5% major), death in 5.1% and 3.1% were lost (for full description, please see [4]).

The DFU characterization variables that, in addition to the foot characterization variables, created a more valid and simple model were the presence of multiple DFU, infection and gangrene and bone involvement. We have selected these variables taking into consideration the results of our previous study [4]. In our sample, DFU aetiology and duration, area, bone involvement and the presence of multiple DFU, gangrene and infection were associated with LEA in our univariate analysis. Including all these variables in the multivariate analysis, DFU area and duration lost statistical significance and so were excluded from the final model. As DFU aetiology corresponds to the presence of DPN, foot deformity or PAD, we have also excluded them from our final model as these variables were already included separately in the first part of the model. We have dichotomized the number of DFU into one or multiple and depth into with or without bone involvement in order to simplify the model. However, we tested these modifications by recalculating the resulting model's AUC score and observed that it did not significantly diminish its accuracy for LEA prediction by assessing the respective 95% CI.

Using the logistic regression coefficients, we propose the following model score calculation for the prediction of LEA in subjects with active DFU: DIAFORA score = 0.75 (neuropathy present) + 0.21 (foot deformity present) + 1.43 (peripheral arterial disease present) + 0.68 (previous DFU or LEA) + 0.70 (multiple DFU) + 0.81 (infection present) + 2.00 (gangrene present) + 1.37 (DFU involving bone). By assessing the best-fit coordinates, as explained in the Methods section, we propose that those subjects with a value under 3.08 should be classified as low risk, between 3.08 and 5.12 as medium risk and over 5.12 as high risk. These risk groups and diagnostic accuracy measures are described in Table 1.

When assessing DIAFORA classification diagnostic accuracy measures and the respective 95% CI, using only major LEA as the outcome versus all levels of LEA, the highest risk group was associated with higher negative predictive values and lower positive predictive values. When assembling the highest and medium risk groups, a lower positive predictive value was observed. For the remaining measures, no significant statistical differences were found (Table 1).

The new model showed an AUC of 0.91 (95% CI 0.87–0.95) in its continuous form and the risk groups classification form of 0.89 (95% CI 0.84–0.93) for LEA prediction and, only for major LEA, of 0.86 (95% CI 0.79–0.92) and 0.82 (95% CI 0.75–0.89), respectively (Figure 1). These values were similar or superior (38%) to the ones reported for the existing scores and classifications [4].

Using a similar method to the one described by the Eurodiale consortium for the creation of a model for the minor LEA prediction [10], we have transformed our model into a simple and easily applicable rule by multiplying each logistic regression coefficient by 5 and rounding to the nearest integer. This resulted in the following prediction rule:

DIAFORA rule = 4 points (if neuropathy present) + 1 point (if foot deformity present) + 7 points (if peripheral arterial disease present) + 3 points (if previous DFU or LEA) + 4 points (if multiple DFU) + 4 points (if infection present) + 10 points (if gangrene present) + 7 points (if DFU affects bone). Using these values, we propose that

Table 1. DIAFORA classification diagnostic accuracy measures

Risk group	Patients *n* (%)	LEA *n* (%)	Risk group	Sensitivity % (95% CI)	Specificity % (95% CI)	LR+ (95% CI)	LR– (95% CI)	PPV % (95% CI)	NPV % (95% CI)
Minor + Major LEA									
High	60 (22)	35 (58)	High	57 (45–70)	88 (84–93)	5 (3–8)	0.5 (0.4–0.6)	58 (46–71)	88 (84–92)
Medium	78 (28)	25 (32)	High + Medium	98 (95–100)	64 (57–70)	3 (2–3)	0.03 (0.004–0.2)	44 (35–52)	99 (98–100)
Low	138 (50)	1 (0.7)							
Major LEA only									
High	60 (22)	9 (15)	High	60 (35–85)	80 (76–85)	3 (2–5)	0.5 (0.3–0.9)	15 (6–24)	97 (95–99)
Medium	78 (28)	6 (8)	High + Medium	100 (NC)	53 (47–59)	2 (2–2)	NC	11 (6–17)	100 (NC)
Low	138 (53)	0 (0)							

DIAFORA, diabetic foot risk assessment; CI, confidence interval; LEA, lower extremity amputation; LR–, negative likelihood ratio; LR+, positive likelihood ratio; NC, not calculable; NPV, negative predictive value; PPV, positive predictive value.

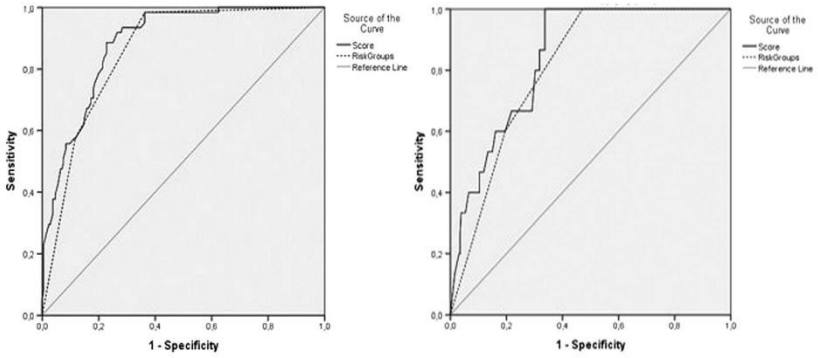

Figure 1. Diabetic foot risk assessment (DIAFORA) area under the receiver operating characteristic curve for lower extremity amputation (LEA) (left) and major LEA (right) prediction. DIAFORA classification presents an area under the receiver operating characteristic curve of 0.91 [95% confidence interval (CI) 0.87–0.95] in its continuous form and the risk groups classification form of 0.89 (95% CI 0.84–0.93) for LEA prediction (figure in the left) and, only for major LEA (figure in the right), of 0.86 (95% CI 0.79–0.92) and 0.82 (95% CI 0.75–0.89), respectively.

those subjects with less than 15 points should be classified as low risk, between 15 and 25 as medium risk and over 25 as high risk. This rule showed an AUC of 0.87 (95% CI 0.82–0.93) for LEA and of 0.82 (95% CI 0.73–0.90) for major LEA prediction. Thus, no significant differences were found between the accuracy of the model both in its continuous score and classification form and this prediction rule.

To facilitate clinicians' and/or researchers' use of the DIAFORA tool, in Table 2, instructions on how to apply this prediction rule are reported, and in Table 3, clinical cases with different severity are described.

Discussion

Taking into consideration the results of our group's previous systematic reviews [1,2] and validation studies [3,4], we believe that diabetic foot risk assessment has great potential for improvement. And so, before creating a new classification, we considered refining one of the existing classifications for the LEA prediction.

In 2007, Leese *et al.* observed that their DFU risk classification also predicted DFU healing [11]. However, in our validation study [4], it did not demonstrate the best accuracy.

Table 2. DIAFORA prediction rule instructions

Foot related			DFU related		
Variables	Definition	Points	Variables	Definition	Points
DPN	Inability to feel SWM at ≥1 of 4 points (hallux pulp, first, third and fifth MTT heads)	4	Multiple DFU	Presence of ≥1 DFU	4
Foot deformity	Foot alteration increasing pressure in ≥1 sites of the foot	1	Infection	Purulent discharge with another two local signs (warmth, erythema, lymphangitis, lymphadenopathy, oedema or pain)	4
PAD	≤1 palpable pedal pulse (posterior tibial and dorsalis pedis arteries)	7	Gangrene	Presence of necrosis (dry or wet)	10
Previous DFU or LEA	History of previous DFU or LEA	3	Bone involvement	Bone exposure identified through visual inspection, touch with sterile probe and/or bone affection identified through X-ray	7
Risk groups					
Less than 15 points	Low risk of LEA	Between 15 and 25 points	Medium risk of LEA	More than 25 points	High risk of LEA

DIAFORA, diabetic foot risk assessment; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; LEA, lower extremity amputation; MTT, metatarsal; PAD, peripheral arterial disease; SWM, Semmes–Weinstein monofilament.
The variables should be collected in the foot with the active DFU. Definitions were fully reported in Reference [4].

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Table 3. DIAFORA prediction rule applied to three clinical cases

Low LEA risk case scenario (<15 points)		Medium LEA risk case scenario (15–25 points)		High LEA risk case scenario (>25 points)	
Description	Points	Description	Points	Description	Points
DPN present	4	DPN absent	0	DPN present	4
Foot deformity present	1	Foot deformity absent	0	Foot deformity present	1
PAD absent	0	PAD present	7	PAD absent	0
Previous DFU or LEA absent	0	Previous DFU or LEA present	3	Previous DFU or LEA absent	0
Multiple DFU absent	0	Multiple DFU absent	0	Multiple DFU present	4
Infection present	4	Infection absent	0	Infection present	4
Gangrene absent	0	Gangrene present	10	Gangrene present	10
Bone involvement absent	0	Bone involvement absent	0	Bone involvement present	7
	Total: 9		Total: 20		Total: 30

DIAFORA, diabetic foot risk assessment; DFU, diabetic foot ulcer; DPN, diabetic peripheral neuropathy; LEA, lower extremity amputation; PAD, peripheral arterial disease.

We therefore created a new system composed of two parts: one including the main DFU prediction variables (DPN, PAD, foot deformity and previous DFU or LEA) and another including DFU features.

In this way, we have demonstrated improved clinical use of a standardized classification in daily clinical practice for LEA risk assessment.

To develop this new classification, we have used the same cohort in which we have validated all the available DFU classifications [4], which allowed us to directly compare their accuracy values.

Although it is a high-risk context (Hospital Diabetic Foot Clinic), our LEA prevalence (23.2%: 16.7% minor and 6.5% major) was considered to be within the values reported in the available literature [4] and similar to those from Eurodiale (23%: 18% minor and 5% major) [12]. Additionally, subjects containing the whole spectrum of severity of DFU were included, as this model, in its complete form, is to be used for LEA prediction in those with an active DFU. According to our classification, 50% of the subjects were at low risk of requiring a LEA, 28% at medium risk and only 22% at high risk.

The new classification, DIAFORA, included four foot and four DFU features. For the first part, we have chosen to include the variables already used by the IWGDF and American Diabetes Association to facilitate the adoption of this tool by health professionals in their clinical practice [1,3]. While for the last, because of a lack of consensus [2], we decided to use statistical methods to identify the most pertinent from those already included in the available systems. They were multiple DFU, infection, gangrene and bone involvement. Such variables are easy to collect and are already empirically used by clinicians to estimate DFU prognosis. The presence of multiple DFU and gangrene are included in three of the 15 available DFU classification systems and both infection and depth in 11 [2].

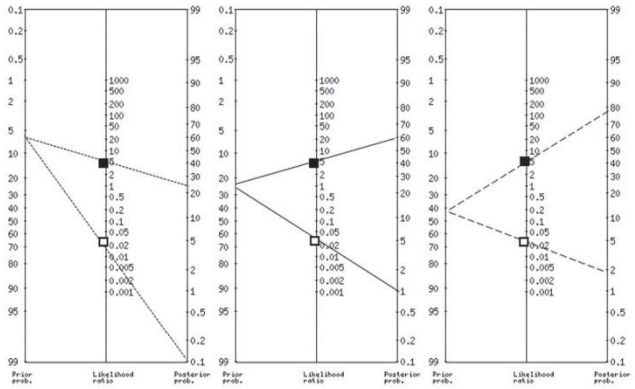
Conversely, we would like to underscore that multiple DFU, gangrene and bone involvement were present in around 35% of our sample and infection in 58% [4]. The prevalence of these conditions is expected to be much lower in a primary care context, where only less severe DFU are treated, and so statistically significant associations between these variables and LEA are expected to be more difficult to detect because of a lower number of exposures and outcomes.

Analysing its accuracy, we observed that our model in the continuous score form presented an AUC of 0.91, while when creating the group risk categories, it dropped slightly to 0.89, without a major modification when having only major LEA as outcome. To facilitate the use in daily clinical practice we have transformed our model into a clinical prediction rule, using a point system, that was equally valid.

The DIAFORA high-risk group, when compared with the other available classifications [4], presented significantly lower sensitivity than the Scottish Intercollegiate Guidelines Network classification and significantly lower specificity than the Saint Elian Wound Score System, regardless of having all types or just major LEA as outcome. When changing the cut-off for highest + medium risk groups, the new classification had lower specificity when compared with the Curative Health Services wound grade scale and Infectious Disease Society of America/IWGDF infection classifications, but only for major LEA prediction. For the remaining measures, the DIAFORA classification showed an equal (in 81% of the cases) or significantly higher values (in 17%).

Because of clinical limitations and our choice to assess only variables already used by the available LEA risk prediction classifications, some pertinent variables were not evaluated, namely, glycated haemoglobin and plantar pressure.

Despite its potential value, we aimed to assess if this tool would be useful in different contexts. We assessed its impact on LEA probability estimation using our study prevalence as well as high, representing a specialized diabetic foot clinic context, and low values, representing a community context, reported in our previous systematic review [2].



■ Positive likelihood ratio for the high risk group, □ Negative likelihood ratio for the low risk group, DIAFORA: Diabetic Foot Risk Assessment; LEA: Lower Extremity Amputation

Figure 2. Diabetic foot risk assessment (DIAFORA) classification impact on the probability of lower extremity amputation (LEA) assessment, through Fagan's Nomogran, in low (left), our cohort (middle) and high-risk (right) contexts. On the picture of the left, we can observe that in a community risk context (LEA prevalence of 6%), being classified as high risk with the DIAFORA tool raises the LEA probability to 25% and as low risk drops to 0.2%, thus using DIAFORA LEA is excluded as a potential outcome. In our cohort (LEA prevalence of 23%), those categorized as being at high risk of LEA present a probability of 60% to require LEA and those as low risk of 1% (picture in the middle). At the other extreme, in a diabetic foot centre risk context (LEA prevalence of 43%), being graded as high risk with our classification increases the LEA probability to 79% and as low risk diminishes to 2%. With this, LEA is most probable if DIAFORA is positive and has less than 2% chance of occurring if it is negative.

Using the DIAFORA tool in our cohort, when subjects were classified as high risk (which presents a positive LR of 5), their pre-classification probability of LEA was 23%, but their post-classification probability rose to almost 60%. Conversely, when classified as low risk (which presents a negative LR of 0.03), it dropped to 1% (Figure 2).

Even when changing the prevalence value, one can observe that this classification is potentially useful in a majority of clinical settings.

For example, using the community context prevalence (6.4%) [13], we observe that those classified as low risk tend to have a null probability of requiring a LEA (0.2%). On the other hand, in a diabetic foot centre prevalence context (42.8%) [14], those categorized at high risk will most likely undergo a LEA, as the post-classification probability of LEA increases to 79%, and still, those considered as low risk present a post-classification probability of LEA of 2%.

Those considered at low risk can be safely followed up in primary care institutions. In our cohort, only one of the subjects in this category had to undergo a minor LEA and none a major LEA. Conversely, those classified as high risk should be rapidly referred to specialized diabetic foot clinics. In our study, the majority of the subjects (58%) required a LEA when included in this risk category.

As limitations, we acknowledge the existence of missing values for Semmes–Weinstein monofilament ($n = 16$) and tuning fork ($n = 20$) sensation tests and potential limited generalizability of our results (owing to the single-centre design in a high-risk context, high number of patients with type 2 diabetes and chronic DFU).

Although at least 3 months of follow-up can be considered as short, we must highlight that only 6.5% ($n = 19$) of the subjects persisted with their DFU unhealed after a median follow-up of 133 days (range 89–747 days).

In sum, we were able to create a new classification (DIAFORA) that uses 8 easy to collect variables, having in its foundation the IWGDF diabetic foot risk classification, which is accurate in predicting LEA occurrence. Our model demonstrates similar or greater accuracy measures when compared with those from the existing DFU classifications and proved to be useful in improving risk assessment in a variety of clinical settings (primary, secondary and tertiary).

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Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. *Diabetologia* 2011; **54**(5): 1190–9.
2. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. *Diabetes Metab Res Rev* 2014; **30**(7): 610–22.
3. Monteiro-Soares M, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Validation and comparison of currently available stratification systems for patients with diabetes by risk of foot ulcer development. *Eur J Endocrinol* 2012; **167**(3): 401–7.
4. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Dinis-Ribeiro M. Lower limb amputation following foot ulcers in patients with diabetes: classification systems' external validation and comparative analysis. *Diabetes Metab Res Rev* 2015; **31**(5): 515–529.
5. Leese GP, Reid F, Green V, *et al.* Stratification of foot ulcer risk in patients with diabetes: a population-based study. *Int J Clin Pract* 2006; **60**(5): 541–5.
6. Smieja M, Hunt DL, Edelman D, Etchells E, Cornuz J, Simel DL. Clinical examination for the detection of protective sensation in the feet of diabetic patients. International Cooperative Group for Clinical Examination Research. *J Gen Intern Med* 1999; **14**(7): 418–24.
7. Bakker K, Apelqvist J, Schaper NC. International Working Group on Diabetic Foot Editorial Board. Practical guidelines on the management and prevention of the diabetic foot 2011. *Diabetes Metab Res Rev* 2012; **28**(Suppl 1): 225–31.
8. Prompers L, Huijberts M, Apelqvist J, *et al.* High prevalence of ischaemia, infection and serious comorbidity in patients with diabetic foot disease in Europe. Baseline results from the Eurodiale study. *Diabetologia* 2007; **50**(1): 18–25.
9. Younes NA1, Albsoul AM. The DEPA scoring system and its correlation with the healing rate of diabetic foot ulcers. *J Foot Ankle Surg* 2004; **43**(4): 209–13.
10. van Battum P, Schaper N, Prompers L, *et al.* Differences in minor amputation rate in diabetic foot disease throughout Europe are in part explained by differences in disease severity at presentation. *Diabet Med* 2011 Feb; **28**(2): 199–205.
11. Leese G, Schofield C, McMurray B, *et al.* Scottish foot ulcer risk score predicts foot ulcer healing in a regional specialist foot clinic. *Diabetes Care* 2007; **30**(8): 2064–9.
12. Akhtar S, Schaper N, Apelqvist J, Jude E. A review of the Eurodiale studies: what lessons for diabetic foot care? *Curr Diab Rep* 2011; **11**(4): 302–9.
13. Margolis DJ, Allen-Taylor L, Hoffstad O, Berlin JA. Diabetic neuropathic foot ulcers: predicting which ones will not heal. *Am J Med* 2003; **115**(8): 627–631.
14. Sun JH, Tsai JS, Huang CH, *et al.* Risk factors for lower extremity amputation in diabetic foot disease categorized by Wagner classification. *Diabetes Res Clin Pract* 2012; **95**(3): 358–363.

CHAPTER 7: CONCLUSIONS AND FUTURE RESEARCH

This Thesis addresses the prediction of diabetic foot complications (DFU and LEA). Although an adequate stratification of subjects by their risk of these outcomes to occur is the pillar stone for a correct and rational allocation of human and economic resources in clinical practice, until now, no classification or stratification system has been widely adopted for none of both outcomes.

Furthermore, despite its importance, research on diabetic foot and respective funding are still scarce. For example, between 2002 and 2011 the National Institutes of Health (NIH) funded a total of 22.531 projects in diabetes from which only 33 (0.15%) were on DFU, corresponding to a 7.161.363.871 United States Dollars (USD) and 11.851.468 USD (0.17%) funding, respectively [1]. In the same way, between 2010 and 2011 the Diabetes UK received 402 grant applications, from which only 15 were diabetic foot related and only one of these was funded [1].

MAIN FINDINGS

With our research, we believe to have achieved our purpose of increasing the available evidence on this topic, by identifying the predictive variables and systems created for DFU and LEA prediction and externally validating such systems.

Diabetic foot ulcer prediction

In our first systematic review with the aim of identifying the available evidence on DFU risk stratifications systems (or classifications) [2], we concluded that 5 systems had been published until that time: ADA, IWGDF, SIGN, Seattle System from Boyko et al and University of Texas. The articles addressing this topic were scarce (n=13), for some of the systems accuracy measures were not possible to retrieve and external validation was never conducted.

DFU prevalence ranged from 5% (community setting) up to 34% (high risk/ hospital setting) and classifications had diverse structures and included a different number and type of variables. It was possible to determine accuracy measures in 4 studies only for 3 out of the 5 classifications.

On the other hand, DPN, PAD, foot deformity and previous DFU and LEA were included in the majority of the systems and accuracy measures were similar and robust.

We must highlight that just 2 of the classifications were developed using multivariate regression techniques (UT and Boyko et al). The Boyko et al (or Seattle classification) was the only classification that underwent external validation, reported AUC value and assessed the impact of time on the classification's accuracy.

The IWGDF classification is the most disseminated classification and it is even included in the National Health Systems' recommendations documents on diabetic foot in some countries, such as Portugal. However, further external validation is necessary and includes ABI and VPT measurements for the identification of PAD and DPN, respectively, which are not easily collected in all clinical contexts.

The Boyko et al system requires a spreadsheet to conduct the necessary calculus and the cut-off values are hard to memorize.

The SIGN classification, uses only easy to collect variables and has an easy classification system, with subjects with no risk factor being classified as low risk, with one risk factor as moderate risk and with two or more as high risk. However, this classification includes the higher number of variables (n=8).

For all this, it was not possible to select the "best" classification system to be used in all or in each setting.

While reviewing all the predictive factors associated with DFU [3], we have included 71 studies studying more than 100 variables. Again, DFU prevalence varied greatly. For first DFU development it ranged from 5.0 to 7.2%; DFU recurrence from 15.5 to 60.5%; and DFU history prevalence from 10.4%, in a Norwegian community based study, up to 48.0%, in an Indian hospital based study.

In this study [2], we have observed that risk factors for DFU development, assessed in five or more studies, considered as predictive in the majority of studies (3 or more) included higher diabetes duration, HbA1c, DPN diagnosed through VPT at malleoli and SWM, higher PPP, PAD, previous DFU and LEA; as unrelated in all studies included diabetes type; and as predictive of uncertain value included higher age and male gender.

In general, risk factors considered in four or fewer studies were of uncertain significance with the exception of height, DPN diagnosed through tuning fork, NDS, thermal sensitivity or MNCV, first MTPJ mobility and daily activity due to predictive ability in all the studies or large cumulative study sample size. Education degree was never associated with any of the outcomes.

We emphasize that all of the available DFU risk stratification systems previously reviewed by our group included variables that were demonstrated to significantly predict DFU development (DPN, PAD, foot deformity and previous foot complications). For some the evidence was not as compelling, as for example physical impairment (included in the SIGN classification) and tinea pedis (included in the Boyko et al classification). High HbA1c value (included in the Boyko et al classification) was considered to be associated with DFU development in various studies, although not in all.

Only previous DFU was significantly associated with DFU recurrence in more than one study. However, generally studies' sample sizes were insufficient to detect association between variables.

We have also concluded that several important predictive variables' collection procedure; namely for SWM perception, PAD diagnoses through pulses palpation, PPP and footwear risk classification; in what concerns cut-off definition is widely variable. This is of paramount importance as the SWM and pulses palpation are included in almost all the DFU development risk classifications.

In addition, the association between each predictive variable and DFU development was assessed only by two or fewer studies in 76% of the cases and with DFU recurrence or re-ulceration in 90%. This underlined the striking necessity for more research on measurements that are readily accessible to clinical investigators and may prove valuable in predicting these foot outcomes.

In what concerns DFU development or recurrence prevention measures the available evidence is almost inexistent, with 6 studies published assessing the prevention of DFU development and 5 of recurrence; and include education, clinical care and dermal thermometry. Furthermore, only one study was conducted assessing the impact of foot self-care habits on DFU development prevention. These results highlight the fact that several clinical decisions (selection of team elements, type of care provided, advices given and reinforced in each appointment) are not evidence-based.

There is some reassurance that the variables used for the identification of the foot at risk are adequate, although their collection is still not sufficiently standardized. But, with our first systematic review [2], due to a low evidence level, we could not select which system to apply in clinical care. As for predictive variables few of them had compelling evidence stating their association with a high risk of DFU [3].

After retrieving all the available evidence around this topic, we considered pertinent to conduct a retrospective cohort study validating simultaneously all the existing diabetic foot risk stratification classification systems [4]. This study helped to understand the classification systems' performance in a high risk setting, to evaluate the independent variables predictive value and to allow future studies' sample size calculation.

Foot deformity, PAD, DPN and previous diabetic foot complications were again associated with higher DFU development risk. All the classifications were highly and equally accurate, especially sensitivity, specificity, NPV and AUC. PPV values were under 30% for all classifications. Some differences were observed between the accuracy values found in our study when compared to the studies included in our systematic review for which such measures were available.

However, several questions remained, namely if the systems would be equally valid also in the primary care context, if using an higher sample size any statistical significant difference would be found between systems and if it would be relevant to include new predictive variables. For all this we considered pertinent to prospectively validate all the classification systems in a multicentre context, to assess differences on participants' characteristics and classifications' performance according to the institution of origin and to test the relevance of including new predictive variables (*submitted for publication*).

Both in the retrospective [4] as in the prospective multicentre validation (*submitted for publication*) of the available systems, we concluded that the systems were comparable and valid to classify subjects by their risk of DFU at 1 year. High AUC, NPV, sensitivity and specificity values and moderate LR were observed. Only PPV values were considered to be modest (under 30-40%). This implies that 60 to 70% of the subjects categorized at high risk of DFU development will not develop one. This can occur due to several reasons, namely the prevention techniques' effectivity or misclassification, and, in both cases, a high level of resources are being spent unnecessarily.

Differences were found on subjects' characteristics and systems' accuracy when comparing the hospital with the primary care setting. It is needed to further study the impact of the setting on the systems' accuracy and understand if such variation is just prevalence dependent.

At 1 year, an improvement on adherence to foot self-care habits was observed in both contexts. However, adherence at baseline was not associated with a reduction on DFU development risk. A study with longer follow-up should be conducted.

Our results did not support the need to include any variable to improve diagnostic accuracy of any classification and none of the classifications outperformed the remaining.

In addition, it is described [5-7] that subjects should have their risk of DFU development reclassified each year. However, there is no evidence substantiating this periodicity. Studies with longer follow up should be conducted in order to identify any significant loss of the systems' accuracy as well as to quantify the annual progression from each risk group to another.

Diabetic foot ulcer prognosis

In our systematic review with the aim of identifying the available evidence on LEA risk stratification systems (or classifications) [8], we concluded that 15 had been published (8 systems for the description and 7 for the prognostic assessment of active DFU), assessed on 25 articles.

As in the DFU prediction, we observed that outcome prevalence was highly variable (6.4 to 33.3%) and that the classifications had different structures.

DFU area, depth, infection, PAD, DPN and foot deformity were the most commonly included variables. DFU area, depth, infection, gangrene, PAD and DPN were the most studied predictive variables and for which meta-analysis was possible to conduct. DPN and DFU area presented the highest sensitivity; gangrene the highest specificity, and positive and negative LR. Pooled AUC values were similar and ranged from 0.65 to 0.74.

Foot deformity, PAD and DPN are included in almost all classifications used both for DFU development and LEA prediction. DFU depth, the presence of infection and gangrene are the most commonly used variables for DFU characterization in daily practice, even when no specific classification is being used. Our data supports the collection of such variables and the selection of a classification that includes them.

The most frequently validated classifications were the Meggit-Wagner, S(AD)SAD and TUC. However, all of them have several clinical use limitations. The Meggit-Wagner is considered to be too simple and lacking on DFU description details. The S(AD)SAD classification, although it includes just easy to collect variables, it has a complex and hard to remember structure. The TUC classification is the only one with a bi-dimensional structure and includes depth, ischemia and infection. However, area is not included and some authors considered it difficult to use in daily clinical care.

Accuracy measures were highly variable and not always possible to extract. There is a lack of external validation studies for the available systems. Reported LR for all systems were usually below 5, from 1.3 to 6.9, and are expected to have little to moderate effect on clinical decision.

We were not able to distinguish any classification performance and select the one that should be widely implemented.

The Eurodiale consortium published a group of studies conducted in 10 European countries evaluating the DFU care, namely clinical outcome, patients' characteristics and quality of life and barriers to adequate care delivery [9]. To contextualize our classification systems' validation results, we considered imperative to understand the quality of diabetic foot care in Portugal [10]. So, we performed a cohort study assessing the clinical outcome of all patients scheduled for a specialized diabetic foot clinic, the setting in which the majority of the studies were conducted, and compared the results to the ones reported by the Eurodiale consortium.

In comparison to the Eurodiale studies, our sample was slightly older, with deeper and more severe DFU and frequently located at the toes. Despite this, we had similar healing, major LEA and mortality rates, but inferior rates of minor LEA and hospitalization. So, we consider that the results of the next study are generalizable to Europe.

Due to the need of improving the classifications' evidence level and to allow, for the first time, a direct comparison, we have conducted a prospective cohort study simultaneously validating all the identified classification systems and assessed the pertinence of the included predictive variables [11].

In this study, we verified that all systems were associated with LEA, had equivalent and good accuracy measures values, especially high NPV and specificity. However, once more, PPV were considered to be small (under 30%) and sensitivity and LR were only modest.

When comparing the results in our cohort to those retrieved in our systematic review, some differences were observed. Several systems (SIGN, DEPA and IDSA-IWGDF) underperformed in our cohort, particularly in what concerns specificity values. For the DUSS, SWESS, SINBAD, TUC and van Acker-Peter systems this was the first time that diagnostic accuracy measures were reported.

In this study we have confirmed that the majority of the most commonly used variables for the DFU development risk assessment (namely, deformity, PAD and previous foot complications) were associated with LEA prediction in those subjects with active DFU, in the univariate analysis. PAD and previous DFU were associated with LEA occurrence even in the multivariate analysis.

However, it was not possible to select the "best" system to use in clinical practice and potential for enhancement was detected.

DIAFORA

This last study, is the epitome and integrates the results of all the previous ones.

In the first systematic review and validation studies we have concluded that no DFU development risk classification could be selected has the best one for dissemination and clinical adoption. On the other hand, the IWGDF has been widely disseminated and is in fact included in the Health ministry guidelines for adequate diabetic foot care in several countries, in which Portugal is included (since 2011).

As for LEA risk prediction, several classifications exists but adoption in clinical practice is very scarce and both our systematic review and validation study could not identify which one should be selected. We have also observed that room for improvement existed. Thus, we have considered that the creation of a new classification easy to use, to memorize and with properties that could improve adherence would be pertinent.

We have observed in our studies that DPN, PAD, foot deformity and previous foot complications were frequently associated and included both in classifications to predict DFU development as well as LEA occurrence.

So, using the same cohort of participants [12] in which the previous study was conducted, we were able to create a classification system composed by two sections, named DIAFORA.

The first section, is intended to be used on subjects without DFU and includes DPN, PAD, foot deformity and previous DFU (the same to say the IWGDF classification).

Once DFU occurred, the addition of DFU characterization variables (such as, multiple DFU, infection, gangrene and bone affection) makes the classification system full version adequate to predict LEA occurrence.

We consider that this group of variables, besides statistical significance, is also pathophysiologically reasonable. The DFU development most common pathway results from the

presence of two or more of these risk factors: DPN, PAD and/or trauma. Trauma can be external, direct or indirect (for example caused by ill-fitting shoes), or internal, caused by foot deformity.

A DFU history implies that several of these factors are present and so the risk of a new occurrence is higher. When such DFU requires a LEA, biomechanical changes will also occur and high pressure points will exist.

Such factors are also linked to a poor DFU prognosis. The presence of DPN, by diminishing the pain, may delay the patient search for the health professionals and adequate treatment. Furthermore, the presence of DPN is associated with changes in neuropeptides production and thus to an inadequate healing. PAD diminishes the tissue perfusion and alters the inflammatory process. Several factors also link the presence of DPN and PAD to each other.

The presence of a DFU in a foot deformity site will increase the pressure, and adequate offloading techniques are needed to stop the continuous lesion of the tissues and enable healing.

As for DFU characterization variables, tissue necrosis and gangrene are linked to the presence of PAD and infection. The adequate removal of inviable tissue can lead *per se* to the necessity of a LEA.

The treatment of infection in the diabetic foot, especially when severe and/or in the presence of PAD, can be very difficult and lead to cellulitis, abscess and/or osteomyelitis that can quickly spread to the leg and require an emergency LEA. When in the presence of DPN, it is common that patients will only detect the presence of their DFU when the infection signs are visible and has already spread throughout the tissues.

When a DFU reaches the bone, it has usually a long duration and represents an open gateway for infection and osteomyelitis that destroys greatly the bone structure and consequently alters the toe or foot biomechanics. When in the presence of PAD, osteomyelitis' conservative treatment is very challenging and frequently LEA is required to clean the infected bone and surrounding tissues.

Multiple DFU usually occur in subjects with PAD, DPN and/or global health debilitation. They also represent several opportunities for infection to install by the presence of several sites with skin breakdown as well as by the possibility of inter-contamination. Furthermore, it impairs the effectivity of local offloading techniques in active subjects.

Besides the reasonability of the included variables, DIAFORA had a comparable or higher accuracy measures' values when compared to the existing ones. The results showed that, using the DIAFORA system, those subjects classified as low risk can be safely followed in primary care institutions and those as medium or high risk should be urgently sent to specialized care.

We consider that our DIAFORA classification has some advantages. For example, we believe that the fact that it is composed by a classification that is already used for the identification of diabetic foot at risk worldwide, and by four additional variables, that are currently empirically used by the majority of the clinicians in daily practice, is expected to help memorization and adoption.

In addition, we have chosen to use only easy to conduct data collection procedures and to transform the score in a round point system that can be straightforwardly calculated to facilitate application in clinical practice.

MAIN LIMITATIONS

This Thesis has some limitations. Studies evaluating the reliability of predictive variables and stratification systems for both outcomes were very limited. We have already developed a protocol to overcome this lack of evidence and the respective study is under ethical approval to be performed on a Hospital setting. However, we could not conduct them during this Thesis execution.

The fact that almost all the studies were conducted in a high risk setting results' generalisability may be reduced and participants' characteristics may be more homogeneous which may alter the classifications' accuracy.

For both outcomes, we have chosen to simplify the DPN and PAD diagnosis (by using the tuning fork instead of the VPT, for the first; and by using just foot pulses palpation, for the second) to standardize these variables' collection and to better mimic the instruments available in most clinical settings. In the future, it is important to address the real impact of these modifications on the systems' accuracy measures and understand if these procedures implications significantly decrease their validity.

On the other hand, the cut-off for DPN diagnosis using the SWM (number of locations where to apply) and for PAD using foot pulses palpation (number of absent pulses) is still not standardized. Further studies are needed addressing this topic.

Additionally, although diabetic foot risk assessment is considered to be important for the respective complications' prevention, we still do not know how effective they really are. A recent systematic review [13], assessing the effect of diabetic foot screening, was able to retrieve only 2 RCTs and 4 before and after studies addressing this topic. Several authors reported that, there is insufficient evidence to support foot screening as an effective intervention in the DM population [13,14].

FUTURE RESEARCH

Research assessing the true impact of diabetic foot screening, based on risk stratification conducted by any of the available systems, on reducing DFU and LEA and improving resources utilization is indispensable.

In sum, the following research questions are still to be answered:

- Are the variables included in the DFU and LEA prediction systems reliable?
- Which are the best procedures to screen for DPN, PAD and high foot pressure?
- Which is the best group of variables to predict DFU recurrence?
- Which is the best group of variables to predict LEA occurrence?
- Do the available classifications systems for DFU and LEA prediction will have significantly different accuracy measures when validated in different settings and countries?
- Is it possible to improve the systems' accuracy, especially PPV and LR?
- Does DIAFORA classification presents equal accuracy in other contexts?
- Which is the best periodicity to conduct diabetic foot risk assessment?
- Which is the impact of diabetic foot screening on DFU and LEA reduction?
- Is diabetic foot screening and prevention techniques cost-effective?

REFERENCES

1. Armstrong DG, Kanda VA, Lavery LA, Marston W, Mills JL, Boulton AJ. Mind the gap: disparity between research funding and costs of care for diabetic foot ulcers. Diabetes Care 2013;36:1815-7.
2. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Risk stratification systems for diabetic foot ulcers: a systematic review. Diabetologia 2011;54:1190-9.
3. Monteiro-Soares M, Boyko EJ, Ribeiro J, Ribeiro I, Dinis-Ribeiro M. Predictive factors for diabetic foot ulceration: a systematic review. Diabetes Metab Res Rev 2012;28:574-600.
4. Monteiro-Soares M, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Validation and comparison of currently available stratification systems for patients with diabetes by risk of foot ulcer development. European journal of endocrinology / European Federation of Endocrine Societies 2012;167:401-7.
5. American Diabetes Association. Preventive foot care in people with diabetes. American Diabetes Association. Foot & ankle international 2000;21:76-7.
6. Bakker K, Apelqvist J, Lipsky BA, Van Netten JJ. The 2015 IWGDF guidance documents on prevention and management of foot problems in diabetes: development of an evidence-based global consensus. Diabetes Metab Res Rev 2016;32 Suppl 1:2-6.
7. Leese GP, Reid F, McAlpine R, et al. Stratification of foot ulcer risk in patients with diabetes: a population-based study. Int J Clin Pract 2006;60:541-5.
8. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Sampaio S, Dinis-Ribeiro M. Classification systems for lower extremity amputation prediction in subjects with active diabetic foot ulcer: a systematic review and meta-analysis. Diabetes Metab Res Rev 2014;30:610-22.
9. Akhtar S, Schaper N, Apelqvist J, Jude E. A review of the Eurodiale studies: what lessons for diabetic foot care? Current diabetes reports 2011;11:302-9.
10. Monteiro-Soares M, Dinis-Ribeiro M. Portugal meets Eurodiale: better late than never. Diabetes research and clinical practice 2014;106:e83-5.
11. Monteiro-Soares M, Martins-Mendes D, Vaz-Carneiro A, Dinis-Ribeiro M. Lower-limb amputation following foot ulcers in patients with diabetes: classification systems, external validation and comparative analysis. Diabetes Metab Res Rev 2015;31:515-29.
12. Monteiro-Soares M, Dinis-Ribeiro M. A new diabetic foot risk assessment tool: DIAFORA. Diabetes Metab Res Rev 2016;32:429-35.
13. Ozdemir BA, Brownrigg J, Patel N, Jones KG, Thompson MM, Hinchliffe RJ. Population-based screening for the prevention of lower extremity complications in diabetes. Diabetes Metab Res Rev 2013;29:173-82.
14. Bus SA, van Netten JJ. A shift in priority in diabetic foot care and research: 75% of foot ulcers are preventable. Diabetes Metab Res Rev 2016;32 Suppl 1:195-200.

ATTACHMENTS

ETHICAL PERMISSIONS

PERMISSION FROM THE CENTRO HOSPITALAR DE VILA NOVA DE GAIA/ ESPINHO EPE ETHICAL COMMITTEE FOR CHAPTER 4.3

COMISSÃO DE ÉTICA DO CHVNG
PROC. Nº 9/2009
Apreciado em Reunião de 8/01/2009
PARECER Nada a opôr; salvaguardar a existência de vícios ocultos. Enviar documento para o Arquivo.
P/la Comissão de Ética Elvira Tavares

Exª Senhora

Presidente da Comissão de Ética

do CHVNG/ Espinho EPE

Nada a opôr.
Deve ser informada a Direcção
Serviço de Endocrinologia. 14/01/09

CHVNG/E, EPE
Dr. Alcino Branco
Director de UGI Medicina
Nº Mecanográfico: 0712

Matilde Filipa Monteiro Soares, a exercer funções como Podologista na Consulta de Pé Diabético, no Serviço de Endocrinologia deste Centro Hospitalar, com o número mecanográfico 9799, vem solicitar a autorização para efectuar a consulta de processos clínicos dos doentes da respectiva consulta para a execução do seguinte estudo: "**Factores preditivos de lesões podológicas no diabético – derivação, validação e refinamento de uma regra de decisão clínica**", no âmbito do Mestrado em Evidência e Decisão em Saúde que se encontra a frequentar na Faculdade de Medicina da Universidade do Porto.

Reunião de C.A. 29/01/09
Deliberação: Autorizado
(Presidente do C.A.)
(Vogal do C.A.)
(Director Clínico)
(Vogal do C.A.)
(Enfermeiro Director)

Pede deferimento,

Vila Nova de Gaia, 07 de Janeiro de 2009

Matilde Filipa Monteiro Soares

Contacto: 965252887

CHVNG/E, EPE
Nº 116/2009
Data 3/2/09
Tipo de documento: Int. Externa
Serviço de Formação, Ensino e Investigação

Anexo 1: Protocolo do estudo supra-citado

Anexo 2: Boyko et al. Prediction of Diabetic Foot Ulcer Occurrence Using Commonly Available Clinical Information. Diabetes Care, 2006, 29:1202–1207

Secretariado do C.A.
Entrada nº 1076
Entrada 7/1/09
Entrada / /
Reunião do C.A.
Doc Nº 082

À Sr-D. M.F.M. Soares
para conhecimento
07-02-09

CHVNG/E, EPE
Dr. Júlio Sampaio
Coordenador Executivo
Nº Mecanográfico: 0706
Dep. de Formação, Ensino e Investigação

PERMISSION FROM THE CENTRO HOSPITALAR DE VILA NOVA DE GAIA/ ESPINHO EPE ETHICAL COMMITTEE FOR CHAPTER 4.4

CENTRO HOSPITALAR
VILA NOVA DE GAIA|ESPINHO

Exma. Sr.ª

Dr.ª Matilde Filipa Monteiro Soares
Podologista Consulta Pé Diabético
Serviço de Endocrinologia

N/ Referência	Data
66/2012	8/2/2012

Assunto: ***Resposta a pedido de autorização para a realização do Projeto "Validação, Comparação e análise da reprodutibilidade de sistemas de estratificação por grau de risco do pé do diabético na predição de desenvolvimento de úlcera – um estudo de corte prospectivo"***

Informo Vª Ex.ª que o pedido para a realização do Projeto ***"Validação, Comparação e análise da reprodutibilidade de sistemas de estratificação por grau de risco do pé do diabético na predição de desenvolvimento de úlcera – um estudo de corte prospectivo"***, conforme deliberação do Sr. Director Clínico de 2 de Fevereiro de 2012, está **autorizado**.

Com os melhores cumprimentos,

Vila Nova de Gaia, 8 de Fevereiro de 2012

CHVNG/E, E.P.E.
Dr. JÚLIO SAMPAIO
Responsável pelo Serviço
Nº Mecanográfico 0706
Serv. de Formação, Ensino e Investigação

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NIPC 508 112 156
Capital Estatutário 47.082.000,00 Euros
Registo Comercial nº 508 112 156

Ministério da Saúde

PERMISSION FROM THE DA ARS NORTE I.P ETHICAL COMMITTEE AND CLINICAL INVESTIGATION UNIT FOR CHAPTER 4.4

ARS NORTE
Administração Regional
de Saúde do Norte, I.P.

ADMINISTRAÇÃO REGIONAL DE SAÚDE DO NORTE, IP
EXARADO NA ACTA N. 39
REUNIÃO DE 14/10/2013

COMUNICAÇÃO ☐ INFORMAÇÃO ☐ PARECER ☒ Nº 79 DATA: 2 Out 13

DE: Comissão de Ética para a Saúde da ARS Norte

PARA: Conselho Diretivo da ARS Norte

ASSUNTO: Parecer Nº 75/2013

DELIBERADO AUTORIZAR
14/10/2013

Levo ao conhecimento desse Conselho Diretivo o Parecer nº 75/2013 (sobre o estudo: "Estudo sobre: Predição do desenvolvimento de ulcera a nível podológico em utentes com diabetes"), aprovado na reunião do dia 17 de Setembro de 2013, por unanimidade.

Rui Cernadas
Vice-Presidente do C

Dr. Ponciano Oliveira
Vogal C. D.

José Carlos Pedro
Vogal C. D.

À Consideração Superior

Belinda Neves
Assessora CES/UIC

Rua Santa Catarina, 1288 Tel 220 411 000 arsn@arsnorte.min-saude.pt
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GOVERNO DE PORTUGAL | MINISTÉRIO DA SAÚDE

Comissão de Ética para a Saúde
Administração Regional de Saúde do Norte, IP

PARECER Nº 75/2013

Sobre o estudo T/204 – Estudo sobre "Predição do desenvolvimento de ulcera a nível podológico em utentes com diabetes"

A – Relatório

A Comissão de Ética para a Saúde (CES) da Administração Regional de Saúde do Norte, I.P. (ARSN), iniciou a apreciação do Processo n.º T204, na sequência do pedido de parecer dirigido a esta Comissão, referente ao estudo "Predição do desenvolvimento de úlcera a nível podológico em utentes com diabetes", cuja investigadora é Matilde Filipa Monteiro Soares, aluna do doutoramento na faculdade de medicina do Porto, sob orientação do Professor Mário Dinis Ribeiro e professor António Vaz Carneiro. Estudo a ser implementado no ACES Alto Tâmega e Barroso (USF Aquae Flaviae) e Centro Hospitalar de Vila Nova de Gaia.

1. Fazem parte do processo em análise os seguintes documentos: requerimento à Comissão de Ética, curriculum da investigadora, consentimento informado, declaração do Coordenador da USF do ACES onde se vai realizar o estudo, declaração de entrega de relatório final à CES, declaração do orientador e coorientador do referido estudo, instrumento de recolha de dados, declaração de confidencialidade dos dados e autorização da Comissão Nacional de Proteção de Dados.
2. Trata-se de um estudo observacional analítico longitudinal de coorte prospetivo, cuja população inclui utentes com diabetes aquando a sua primeira consulta de podologia no Centro Hospitalar Vila Nova de Gaia e USF Aquae Flaviae, sendo a amostra constituída por 500 participantes de forma aleatória consecutiva. Foram definidos critérios de exclusão
3. O instrumento de recolha de dados é um formulário elaborado para o efeito e já validado. O procedimento de recolha de dados será realizado por enfermeiro, médico ou podologista na primeira consulta, 4 a 6 meses após e 12 meses após. Será solicitado o consentimento para participarem no estudo imediatamente antes do início da primeira consulta; A análise

estatística será efetuada com recurso ao Programa Stastistic (Program for Social Sciences – SPSS

4. Os objetivos primários deste estudo são: Avaliar a validade das variáveis mais pertinentes para a predição do desenvolvimento de úlcera a nível podológico em utentes com diabetes"; Avaliar e comparar a validade dos diversos sistemas de classificação para a estratificação dos utentes com diabetes por grau de risco de desenvolvimento de úlcera a nível podológico.

   Os objetivos secundários são: Avaliar se existem diferenças entre os fatores preditivos para a predição do desenvolvimento da primeira ulcera vs recorrência de úlcera; Analisar o impacto do contexto (população de alto risco – Centro Hospitalar – vs população baixo risco- Centros de Saúde) na validade dos sistemas classificativos para a estratificação dos utentes com diabetes por grau de risco de desenvolvimento de úlcera a nível podológico"

B – Identificação das questões com eventuais implicações éticas

1. Reconhece-se relevância e pertinência do estudo e interesse prático para a Saúde do cidadão;
2. A confidencialidade dos dados recolhidos, o uso exclusivo para o presente estudo, bem como o anonimato, são estritamente garantidos pela investigadora.
3. Considera-se que a identificação dos participantes no estudo não trará implicações éticas, dado que a recolha de dados é feita pelo médico ou enfermeiro de família do utente, solicitando o consentimento livre e esclarecido para participar no referido estudo.
4. A participação do doente não terá qualquer tipo de incentivo / recompensa ou punição, podendo em qualquer momento, abandonar o estudo, sem que daí resulte qualquer prejuízo ou dano relativamente aos cuidados que lhe são prestados.
5. Foi referido pela investigadora que o instrumento de recolha de dados é da sua autoria e já foi validado.
6. Já solicitou autorização do Centro Hospitalar Vila Nova de Gaia para a realização do estudo na instituição.
7. Assume a destruição da chave de codificação dos dados no final do estudo

C – Conclusões

1. Face ao exposto, a CES delibera que o estudo de investigação em causa pode ser aprovado.

O relator

Mestre Maria Assunção Gomes Magalhães

Aprovado em reunião do dia 17/09/2013, por unanimidade

O Presidente da Comissão de Ética para a Saúde da ARS Norte IP

Professor Doutor Alberto Pinto Hespanhol

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PERMISSION FROM THE COMISSÃO NACIONAL DE PROTECÇÃO DE DADOS FOR CHAPTER 4.4

Proc. N.º: 6607/2013 | 1

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

AUTORIZAÇÃO N.º 5521 /2013

I. Do Pedido

O CIDES – Departamento de Ciência de Informação e da Decisão em Saúde da Faculdade de Medicina da Universidade do Porto notificou à CNPD um tratamento de dados pessoais com a finalidade de elaborar um estudo observacional sobre a "Predição do desenvolvimento de úlcera a nível podológico em utentes com diabetes".

Serão incluídos no estudo aproximadamente quinhentos indivíduos, maiores de idade, diagnosticados com diabetes e que recorram à consulta de Podologia do Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE ou à consulta de rastreio podológico da USF Aquae Flaviae.

A participação no estudo consiste na recolha de dados do processo clínico pelo médico, enfermeiro ou podologista assistente, na avaliação podológica e na realização de testes de diagnóstico não invasivos. Prevê-se a duração do estudo pelo período de um ano, sendo a recolha de dados efetuada no momento da inclusão do participante no estudo, assim como seis e doze meses após essa data.

O profissional de saúde assistente solicitará consentimento informado, cuja declaração arquivará em local de acesso reservado na unidade de saúde.

Os dados serão recolhidos num caderno de recolha de dados em papel e em suporte eletrónico.

No "caderno de recolha de dados" não há identificação nominal do titular, sendo aposto um código de doente. A chave desta codificação só será conhecida do profissional de saúde assistente e da investigadora principal.

Os destinatários serão ainda informados sobre a natureza facultativa da sua participação e garantida confidencialidade no tratamento.

Rua de São Bento, 148-3º • 1200-821 LISBOA
Tel: 213 928 400 Fax: 213 976 832
geral@cnpd.pt www.cnpd.pt

213 928 098
LINHA PRIVACIDADE
Dias úteis das 10 às 13 h
duvidas@cnpd.pt

COMISSÃO NACIONAL
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II. Da Análise

A CNPD já se pronunciou na sua Deliberação n.º 227/2007 sobre o enquadramento legal, os fundamentos de legitimidade, os princípios orientadores para o correto cumprimento da Lei n.º 67/98, de 26 de outubro (Lei de Proteção de Dados – LPD), bem como as condições gerais aplicáveis ao tratamento de dados pessoais para esta finalidade.

No caso em apreço, a notificação enquadra-se no âmbito tipificado por aquela Deliberação.

O fundamento de legitimidade é o consentimento expresso da titular dos dados.

A informação tratada é recolhida de forma lícita (cfr. alínea a) do n.º 1 do artigo 5.º da LPD), para finalidades determinadas, explícitas e legítimas (cfr. alínea b) do mesmo artigo) e não é excessiva.

III. Da Conclusão

Assim, nos termos das disposições conjugadas do n.º 2 do artigo 7.º, n.º 1 do artigo 27.º, alínea a) do n.º 1 do artigo 28.º e artigo 30.º da LPD, com as condições e limites fixados na referida Deliberação n.º 227/2007, que se dão aqui por reproduzidos e que fundamentam esta decisão, a CNPD autoriza o tratamento de dados supra referido, para a elaboração do presente estudo.

Termos do tratamento:
Responsável pelo tratamento: CIDES – Departamento de Ciência de Informação e da Decisão em Saúde da Faculdade de Medicina da Universidade do Porto
Finalidade: Estudo observacional sobre a "Predição do desenvolvimento de úlcera a nível podológico em utentes com diabetes".
Categoria de Dados pessoais tratados: código do participante, dados demográficos (mês e ano de nascimento, género), data da avaliação, dados antropométricos (peso e altura), existência de cuidadores, autonomia física, história clínica da diabetes,

COMISSÃO NACIONAL
DE PROTECÇÃO DE DADOS

doenças concomitantes, avaliação podológica, testes de diagnóstico não invasivos e seguimento aos seis e doze meses após a inclusão no estudo.

Entidades a quem podem ser comunicados: Não há.

Formas de exercício do direito de acesso e retificação: Junto do profissional de saúde assistente.

Interconexões de tratamentos: Não há.

Transferências de dados para países terceiros: Não há.

Prazo de conservação: A chave de codificação dos dados do titular deve ser destruída um mês após o fim do estudo.

Dos termos e condições fixados na Deliberação n.º 227/ 2007 e na presente Autorização decorrem obrigações que o responsável deve cumprir. Deve, igualmente, dar conhecimento dessas condições a todos os intervenientes no circuito de informação.

Lisboa, 30 de julho de 2013

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Exma. Sr.ª

Dr.ª Matilde Filipa Monteiro Soares
Podologista Consulta Pé Diabético
Serviço de Endocrinologia

N/ Referência	Data
442/2012	31/7/2012

Assunto: ***Resposta a pedido de autorização para a realização do Projeto "Análise da qualidade da informação presente nos pedidos de consultas de pé diabético""***

Informo Vª Ex.ª que o pedido para a realização do Projeto ***"Análise da qualidade da informação presente nos pedidos de consultas de pé diabético""***, conforme deliberação do Sr. Director Clínico de 2 de Julho de 2012, está **autorizado**.

Com os melhores cumprimentos,

Vila Nova de Gaia, 31 de Julho de 2012

CHVNG/E, E.P.E.
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Responsável pelo Serviço
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Dr.ª Maria João Oliveira
Directora do Serviço de Endocrinologia

V/ Referência	Data	N/ Referência	Data
		217/2011	08/04/2011

Assunto: Resposta a pedido de recolha prospectiva de dados

Informo Vª Ex.ª que o pedido dos membros constituintes da Consulta de Pé Diabético, para a recolha prospectiva de dados dos utentes para a realização do estudo ***"Validação e comparação de sistemas de classificação de úlceras no pé do diabético na predição de amputação – um estudo de corte prospectivo",*** conforme despacho do Director Clínico, Dr. Raul César Sá de 29-03-2011, está **autorizado**.

Com os melhores cumprimentos,

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