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ORIGINAL ARTICLE
VENOUS DISEASE

EDITOR'S CHOICE

Enhancing identification and treatment of patients with concomitant chronic venous insufficiency and diabetes mellitus

A modified Delphi study from the CODAC (ChrOnic venous disease and Diabetes Advisory Council) group

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ABSTRACT

Background: Chronic venous insufficiency (CVI) and diabetes mellitus (DM) pose significant burdens to patients and healthcare systems. While the two diseases share a number of commonalities in risk factors and pathophysiology, they are often assessed and managed separately. This can lead to a worsening of comorbidities and limitations in a patient's quality of life. This project aims to develop recommendations to enhance the identification and treatment of patients with concomitant CVI and DM.

Methods: Using a modified Delphi method, a panel of experts developed 38 Likert Scale and two multiple choice questions across six key themes. These were used to form an online survey which was disseminated

through a convenience sampling approach to CVI and DM healthcare professionals across Europe, Central America, South America, and the Middle East. The threshold for consensus was set at ≥75%.

Results: A total of 238 responses were received. 27/38 statements attained >90% agreement, nine of 38 attained between 75-90%, and two failed to meet the threshold (<75%). The awareness around the impact of the two diseases was high, but a gap was highlighted in the identification of patients with concomitant CVI and DM.

Conclusions: The high level of agreement shows that healthcare professionals are aware of the gaps in identification and treatment of patients with concomitant CVI and DM, and of the need to approach this as a combined therapy area. An algorithm is proposed to help the identification of at-risk patients and to provide recommendations on the management of patients with concomitant disease.

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Key words: Diabetes mellitus; Venous insufficiency; Consensus.

Chronic venous disease (CVD) and diabetes mellitus (DM) are both highly prevalent conditions globally and represent major challenges to both healthcare systems and wider society.

CVD encompasses a broad spectrum of morphological and functional abnormalities of the venous system.[1] Pathophysiology of CVD is mediated by numerous environmental and hemodynamic risk factors such as increasing age, a family history of CVD, female sex, obesity (Body Mass Index [BMI] >25 kg/m^2), high-impact physical activities, comorbid conditions such as deep vein thrombosis, and a combination of venous reflux and obstruction.[1, 2]

CVD shows a prevalence of up to 84% in adults[1, 3] with a variance of between 2-56% in men and 1-60% in women.[4] In the USA alone, 30 million people are affected at an average direct treatment cost of $3 billion per year.[5] The severity of CVD is measured *via* the presence of specific clinical signs classified on the Clinical, Etiological, Anatomical and Pathophysiological (CEAP) system.[6]

The more severe forms of CVD (C3 to C6) present with signs of advanced functional venous abnormalities (such as edema, skin changes, or venous ulceration) are designated as chronic venous insufficiency (CVI).[6]

Interestingly, an association between CVD/CVI and increased risk of cardiovascular disease and mortality has recently been observed in two different large patient cohorts in Taiwan and Germany, respectively.[7, 8]

Globally, DM is one of the top 10 causes of death in adults, with an estimated four million deaths attributed to the condition in 2017.[5] As of 2019, it was estimated that 463 million people are living with the condition, representing 9.3% of the global adult population.[5] This number is expected to rise to 578 million, around 10% of the adult population, by 2030.[5]

Since 1990, there has been a 130% rise in the global prevalence of DM, and this rise shows a strong association with socioeconomic status, particularly for type 2 DM (T2DM).[9] This may in part be due to a drive to a more sedentary lifestyle and rapid urbanization (where rates are higher than for rural areas).[10]

The costs associated with DM vary greatly across territories. In the UK, an estimated £ 14 billion a year is spent,[11] whereas in Germany DM treatment costs € 43.2 billion a year.[11] An increasing number of affected individuals in Central and South America has led to increased treatment of costs in these regions. Mexico has a diabetic population 12.8 million,[5] leading to costs of $ 778 million per year,[12] whereas in Brazil, the number of affected individuals is estimated at 16.8 million,[5] at a cost of $ 2.15 billion.[13]

While DM is a multifactorial disease with a diverse etiology, there are a number of well-established risk factors associated with T2DM which include: a high BMI and obesity, a lack of physical activity, advancing age, a family history of diabetes, polycystic ovary syndrome, a low birth weight for gestational age, ethnicity, prior gestational diabetes, a genetic predisposition, hypertension, dyslipidemia, drug treatments (including statins and corticosteroids), and lifestyle (including smoking history and a low fiber, high glycemic index diet).[1, 14]

DM adversely affects the microvasculature in multiple

organs, leading to the development of diabetic microvascular complications (DmVC). DmVC is comprised of microangiopathies that can lead to organ dysfunction in the eye (diabetic retinopathy), kidney (diabetic nephropathy) and nerve (diabetic peripheral neuropathy).[15] Studies have shown that there is a high prevalence of DmVC particularly where the use of preventative drugs is suboptimal.[16] It is important to note that even after conventional treatment for T2DM, a residual risk (around 50%) for the development of DmVC still persists.[17]

While it is established that patients with CVI and DM/DmVC share similar lifestyle related risk factors (*e.g.* obesity, family history, and a lack of physical activity), recently it has been recognized that there may be a common pathophysiology linking them (Figure 1).[1]

While historically there has been a limited number of studies examining the prevalence of DM in CVI patients, more recent data suggests that this combined population may be higher than anticipated, leading to calls for greater examination of patients with CVI for the presence of DM.[18, 19]

Prior to this study, a review of the literature was conducted to identify what information was available regarding CVI and DM as a combined treatment approach. This review identified 15 studies that met these criteria (Supplementary Digital Material 1: Supplementary Table I).

The data from these studies indicate that the incidence of DM in patients with CVI is two times higher than in the general population[18] with a prevalence between 10-50%.[1, 18-21] In addition, the presence of DM leads to more severe CVI symptoms.[22] This therefore suggests that there is a need to address both conditions when assessing patients for either one of them.

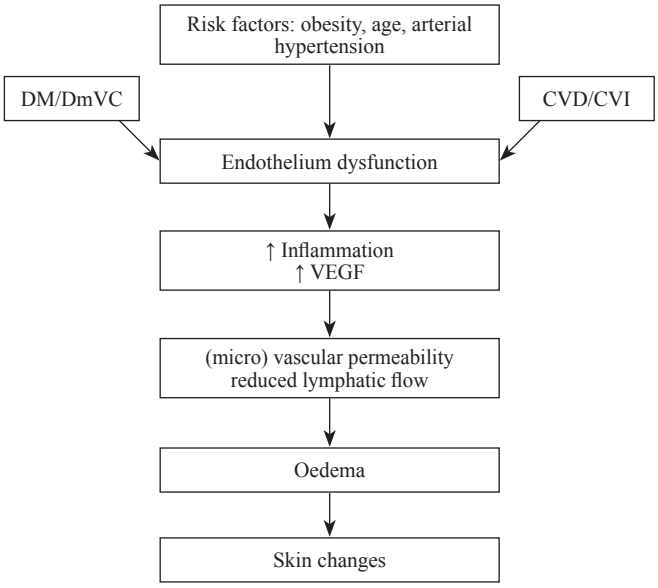

Figure 1.—Commonalities between chronic venous disease and diabetes mellitus/diabetic microangiopathies (modified from Gastaldi *et al.*).[1]
VEGF: vascular endothelial growth factor.

This study aims to examine how the identification and treatment of patients with concomitant CVI and DM can be enhanced. A multinational modified Delphi consensus was employed to determine the strength of opinion held by allied specialist healthcare professionals (HCPs) as to how awareness of these patients could be improved.

Materials and methods

A panel of experts in venous disease and diabetes care from across Europe, Central America, and South America convened in May 2022 to discuss current challenges in identifying and treating patients with concomitant CVI and DM through a facilitator-led group discussion.

Using a modified Delphi methodology guided by an independent facilitator (Triducive Partners Limited), the panelists identified six main domains of focus:

- recognition of the commonalities between chronic venous insufficiency (CVI) and diabetes mellitus (DM);
- impact of chronic venous insufficiency (CVI) and diabetes mellitus (DM) on the patient profile;
- practical steps (assessments) that can be taken to improve identification and outcomes: patients with CVI;
- practical steps (assessments) that can be taken to improve identification and outcomes: patients with DM;
- treatment for concomitant chronic venous insufficiency (CVI) and diabetic microvascular complications;
- future requirements in this area of medicine.

These domains were discussed in detail and 38 Likert Scale statements, along with two multiple choice questions, were developed for testing across a wider group of HCPs in the form of an online survey developed using Microsoft Forms.

The survey was distributed through a convenience sampling method to HCPs working within venous disease and diabetes care across Europe, Central America, South America, and the Middle East.

Stopping criteria were defined as a five-month period to collect responses (July - November 2022) and a minimum target of 150 responses within the pre-defined period. The threshold for consensus agreement was defined as 75%. This was further defined as 'high' at ≥75% and 'very high' at ≥90%.

For the Likert statements, respondents were offered a

four-point scale ('strongly disagree,' 'tend to disagree,' 'tend to agree,' and 'strongly agree') to allow respondents to indicate their level of agreement with each statement. The survey also captured respondents' country, specialty, and years of experience.

Completed surveys were anonymously collated and analyzed by the independent facilitator to produce an arithmetic agreement score for each statement. This information would then be reviewed by the panel of experts and recommendations made accordingly.

A statement of consent was included, and consent was accepted through the completion and submission of the survey.

As this study only sought the anonymous opinions of HCPs and no patient-specific data were captured, ethical approval was not sought.

Results

A total of 238 responses were received within the five-month time period (Figure 2, 3). From these responses, 27 of 38 attained very high agreement, nine of 38 high agreement, and 2 did not meet the established threshold for consensus (Figure 4, Supplementary Digital Material 2: Supplementary Table II). Given that all the established stopping criteria were met, and the very high level of agreement demonstrated, it was agreed that a single round of wider testing was sufficient to establish the opinion of HCPs.

In addition, two multiple choice questions were asked to establish a consensus about the warning signs that should be considered as criteria for assessment in concomitant conditions (Supplementary Digital Material 3: Supplementary Figure 1).

Analysis of these data showed that independently of age, 77% of respondents would assess a patient with CVI for concomitant DM if they presented with a BMI >30 and leg edema, and of this number, 7% would assess patients with a BMI >25 and with signs of leg edema, whereas 18% would assess a patient with BMI >30 even without the presence of edema. Furthermore 12% of respondents would assess a patient if their age was >40, BMI >25 and they presented with leg edema, and 9% would do so if a patient presented with a BMI >25 even without signs of edema (Supplementary Figure 1B).

When asked what signs in a patient with DM that would trigger an investigation for concomitant CVI, 36% of respondents stated that skin changes and leg edema were individually key parameters (Supplementary Figure 1C). However, 63% of respondents agreed that the three parameters of skin changes (including pigmentation, eczema, and varicose veins), leg burden (pain, heaviness, itching or burning sensation, and cramps), and leg edema would be required to trigger an investigation (Figure 5).

Analysis conducted on the demographic data collected highlighted a few key trends. When comparing vascular specialties (vascular surgeons, cardiologists, angiologist, and phlebologists) against diabetes specialties (diabetologist, nephrologists, and endocrinologists) it was found that vascular specialties tended to show a lower level of agreement across the board than the other disciplines, in particular for statements 13 and 27.

Interestingly, diabetologists showed a lower agreement to statement 31 compared to other specialties (Supplementary Digital Material 4: Supplementary Figure 2). This suggests that there may be a gap in knowledge or appreciation of the associations between the two conditions and their management between vascular and diabetes specialties. Indeed, in DM cases, the clinical benefits of GLP-1 receptor agonist (RA) use are mainly demonstrated on the atherosclerotic complications such as myocardial infarc-

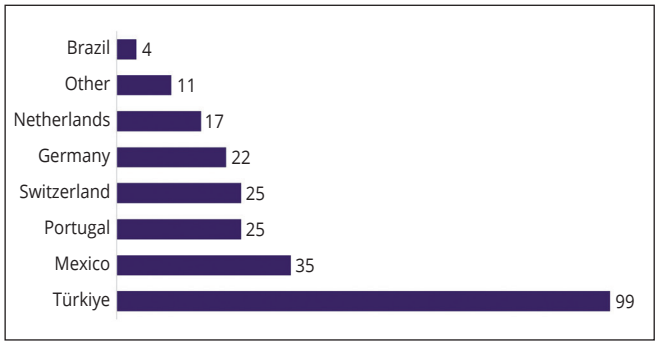

Figure 2.—Responses received by country. Included under "Other" are: Honduras, Ireland, Poland, Greece, Austria, Denmark, France, Qatar, Sweden (2), and Italy.

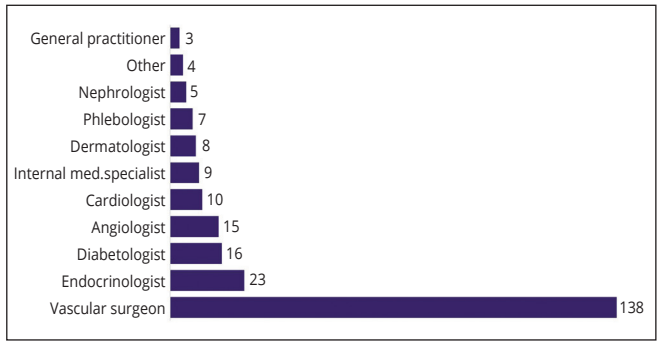

Figure 3.—Respondent reported specialty. Included under Other are: Geriatrician (2), Oncologist, and Hematologist.

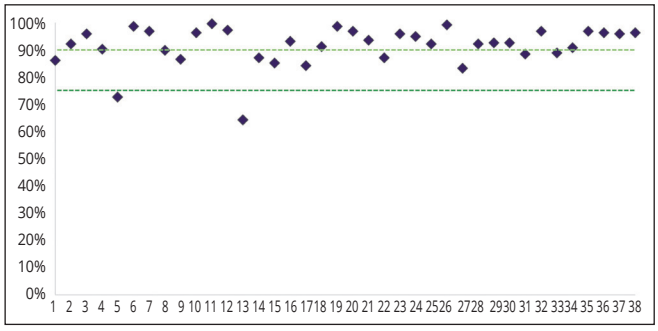

Figure 4.—Combined consensus statement number from 238 responses. The dark green line represents the threshold for consensus (75%), and the light green line represents the threshold for very high agreement (90%).

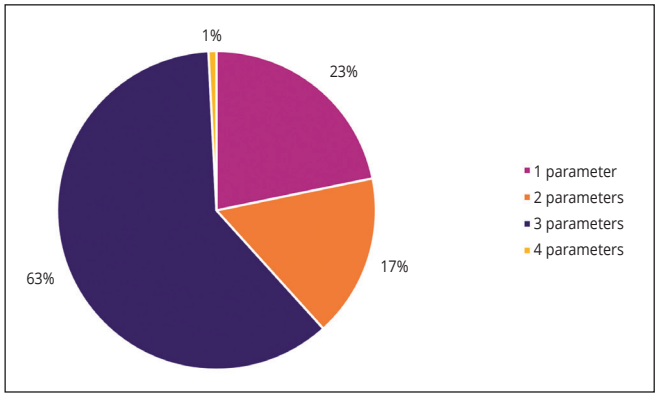

Figure 5.—Number of parameters selected by respondents that would instigate an examination for CVI in a patient with DM. Overall, 63% of respondents determined that three parameters including skin changes (such as pigmentation, eczema, and varicose veins), leg burden (pain, heaviness, itching or burning sensation, and cramps), and leg oedema would be required.

tion and stroke.[23]

This trend was further examined by exploring the data around the type of patient treated. In those respondents who stated that they only treated patients with CVI, the level of agreement displayed was generally lower than all other groups (Supplementary Digital Material 5: Supplementary Figure 3).

Years of experience of the respondents also had an impact on the level of agreement displayed: respondents with 5-10 years of experience showing a lower trend of agreement, compared to respondents with 1-3 years and 3-5 years of experience (Supplementary Digital Material 6: Supplementary Figure 4). This might be reflective of the nature of HCP education and awareness of recent research regarding the commonalities between the conditions.

Respondent country displayed limited variation in level of agreement. Responses from Portugal were lower on average than that of other regions surveyed (Supplementary Digital Material 7: Supplementary Figure 5). However, agreement to certain questions was affected by country with respondents from the Netherlands showing a markedly lower agreement to statement 22 than the next lowest agreement from Portuguese respondents (35% and 80% respectively). When examining the results obtained for statements 33 and 34, German respondents displayed a level of agreement lower than other regions, with both statements not reaching consensus in this area (59% and 73%, respectively).

Discussion

Recognition of the commonalities between CVI and DM

Respondents agreed that both CVI and DM share a number of common risk factors and commonalities regarding pathophysiology and disease progression. The results confirm that respondents believe that these commonalities, particularly microcirculatory changes, are insufficiently understood by the majority of HCPs (Statement 1, 87%). Greater and more in-depth medical education for HCPs is therefore needed, which could be achieved through targeted information campaigns, as well as a greater focus on the links between the diseases at international conferences.

The wording of Statement 5 may have inversely impacted the level of agreement (only 72%) as the two elements (high BMI and leg edema) should not be considered as evidence of co-existing DM in a patient with CVI. However, these factors should be considered as signals for a diabetes screening in patients with CVI, as reported in Statement 15 (86% agreement).

Impact of CVI and DM on the patient profile

As demonstrated by the very high levels of agreement, the impact of the diseases on the patient is well understood by the wider HCP community. However, the low agreement on Statement 13 (64%) reveals that the role of hypertension is less clearly understood by HCPs. This may have been as a result over a lack of clarity in the statement as arterial hypertension is associated with DM, while venous hypertension is associated with CVI. It is unclear from the wider literature what, if any, role arterial hypertension has in CVI/CVD, and this may have contributed to the lower agreement shown.

While hypertension may not affect the development of CVI/DM, it will lead to worsening of symptoms, such

as more severe edema. Further to this, anti-hypertensive drugs may adversely affect patients with edema with the drugs themselves leading to the formation of the edema.

Practical steps (assessments) that can be taken to improve identification and outcomes: patients with CVI

Respondents recognized the importance of routine assessment of patients and the need to assess for concomitant DM if a patient presents with key signs. However, it remains to be clarified how often these parameters are taken in consideration within daily practice as indicators for comorbid diabetes. As described in the results above, the intention of the first multiple choice question (Supplementary Figure 1A, B) was to determine what factors would represent the main signals that would trigger an investigation. The respondents believed that a high BMI (>30 kg/m^2) and leg edema independently of a patient's age were the key factors parameters to examine.

Practical steps (assessments) that can be taken to improve identification and outcomes: patients with DM

There was very high agreement to the statements in this section. However, venous and endothelial dysfunction are not routinely assessed within clinical practice or covered by existing diabetes guidelines. The results of this study highlight the importance to implement this topic in the future recommendations. Patients with DM who present with leg edema, skin changes and leg burden should be examined for the presence of CVI. In addition, any patient presenting with corona phlebectatica should be investigated for concomitant CVI, as this represents a signal of a more serious venous dysfunction secondary to venous hypertension, and it is recognized as a prognostic marker for CVI evolution[6] and when confirmed, CVI should be considered as a significant predictor of all-cause death.[8]

Finally, these results confirm the importance of a regular foot screening in diabetic patients. The pathophysiology of diabetic foot ulcer has neuropathic, vascular, and immune system components.[24] Approximately 50% of adults with DM will be affected by peripheral neuropathy in their lifetime and are at risk for foot ulceration.[25] Early management of diabetic neuropathy and regular foot review may reduce the burden of this serious complication that can lead to amputation.

Treatment for concomitant CVI and diabetic microvascular complications (DmVC)

Addressing CVI and DmVC in a combined approach will represent a new area of medicine and there is therefore a need to clarify what would constitute best practice approaches. The high degree of agreement seen in this topic is encouraging and it provides a platform from which this approach can be developed.

According to the survey results, there are three key statements which can be used as base to create a best practice for the treatment of these patient population:

- lifestyle changes focusing on reducing risk factors, such as obesity and poor diet, may positively affect the progression of both diseases (Statement 26, 99%);
- non-medical treatment, such as compression stockings, may contribute to treat edema, whereas there are still conflicting and debating results on their role in diabetic ulcer,[26] as reflected by the slightly lower level of agreement for Statement 27 (84%);
- pharmacological intervention was recognized to be a pivotal step in treatment of concomitant diseases. While diuretics were not considered as an optimal treatment for both conditions, SGLT-2 inhibitors, GLP-1 RA, and venoactive drugs should be considered in the treatment of patients with both CVI and DmVC. Licensed venoactive drugs with clinical evidence in improving both CVI and DmVC symptoms were deemed as a good option (Statement 34, 91%).

Venoactive drugs are generally prescribed as treatment for CVD and can be classified into two main categories: naturally derived and synthetic drugs. For example, flavonoids belong to the family of natural drugs and includes micronized purified flavonoid fraction, diosmin, rutin, and rutosides. Their efficacy on CVD symptoms has been established in a number of clinical trials and meta-analyses,[27, 28] however their clinical benefit in DmVC is not clearly established.[29]

Calcium dobesilate is a synthetic venoactive drug that has been shown to reduce microvascular permeability, cellular oxidative stress, and inflammation.[30-34] Of particular interest, it is indicated for the treatment of both CVI and microangiopathies and several studies have demonstrated its efficacy in reducing CVI symptoms such as leg pain, heaviness, and edema,[35-37] and also in improving DmVC, such as diabetic retinopathy,[38] nephropathy,[39, 40] and peripheral neuropathy.[41]

Finally, respondents also agree that a combination approach of non-medical and medical treatment should always be considered (Statement 35, 97%), although caution is advised when using compression therapy in patients with cardiac failure or peripheral arterial disease.[1]

Future requirements in this area of medicine

Results show that CVI and DM are not commonly assessed together, and current guidelines do not suggest this

approach.[35, 42] Furthermore, the authors note that CVI is not on the list of complications associated with DM. This represents a key area for improvement to identify these patients earlier and reduce the impact of the disease.

Management algorithm

Given the high level of agreement across the statements tested, and in particular that of Statement 37 (96%) which shows the support from HCPs for the need for a management algorithm, the authors propose the following algorithm by which patients with concomitant CVI and DM may be better identified and treated (Figure 6, 7).[43] This was further refined by the authors proposing additional assessments that could be utilized to confirm patient's comorbidities (Table I).

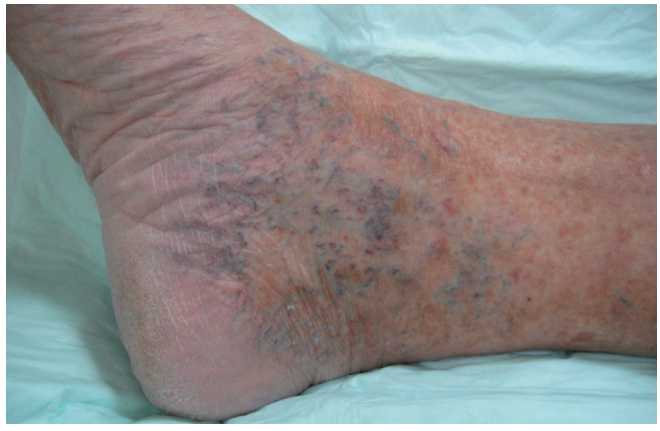

Figure 6.—Clinical presentation of corona phlebectatica (provided with permission by Dr Tim D. Wentel).[43]

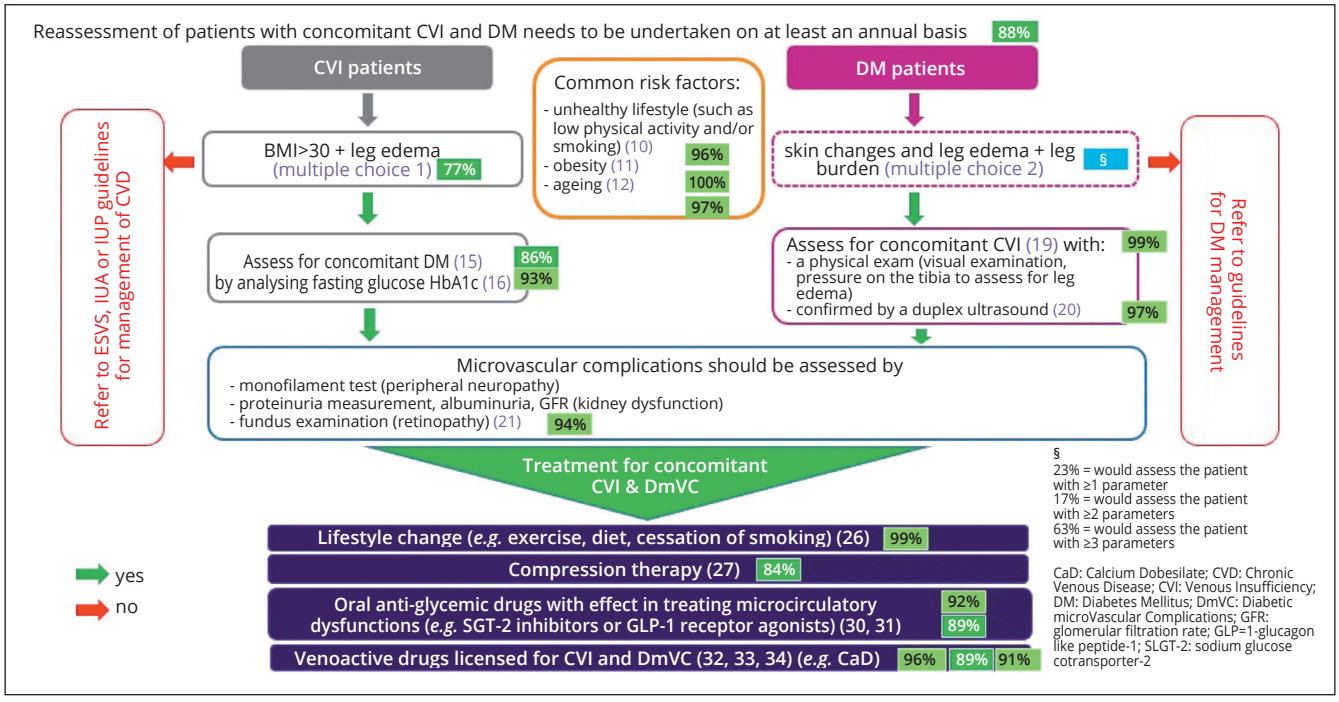

Figure 7.—Proposed algorithm for the identification and treatment of patients with concomitant CVI and DM. Text in purple indicates which consensus statement informed the development of the step, and the green boxes indicate the corresponding agreement attained for those statements Dotted box indicated that the agreement did not reach the threshold of 75%. Guidelines for reference of patients with CVI.[35, 44, 45] Guidelines for reference of patients with DM.[42, 46]

TABLE I.—*Additional assessment criteria for proposed algorithm.*

Condition to be assessed	Additional assessment to be conducted
Hypertension as sign of concomitant DM in CVI patient	A 24 hour blood pressure measurement
Skin changes as a sign of concomitant CVI in a patient with DM	Corona phlebectatica evaluated by visual examination
Microvascular complications	Monofilament test, pallesthesia testing, Ipswich test (peripheral neuropathy), albuminuria measurement and glomerular filtration rate (kidney dysfunction).

Strengths and limitations of the study

The results represent the current state of care for CVI and DM as practiced internationally by experts within the field. The number of responses received during the course of this study provide a very strong foundation from which to develop and recommend the proposed algorithm to improve the identification and treatment of patients with concomitant CVI and DM. The high levels of agreement and similar consensus across specialties suggests a keen understanding of the field and the challenges both HCPs and patients face.

The wording of statements, especially those of 5, 13, and 27 as discussed, may have impacted the resulting level of agreement. More precise phrasing of these statements may produce a more defined answer in any future work.

The limited number of responses from Brazil may have led to an underestimation of the management of the diseases from that country. On the other hand, the large number of responses from Türkiye may have impacted the overall results. However when examining the results without these responses, the same level of agreement emerged (data not shown).

Similarly, the higher number of responses from vascular specialties compared to other disciplines did not change the trend of agreement (data not shown).

Conclusions

This study provides the framework from which improvements can be made in the identification and treatment of patients with concomitant CVI and DM. This has been done by highlighting the areas of agreement held by HCPs working within the field and where gaps in understanding and education around this issue exists. With the strong levels of agreement shown, the proposed algorithm provides a strong basis from which these improvements can be undertaken. The next step that should be undertaken as a result of this study is to test the algorithm within a real-world clinical setting.

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Conflicts of interest
Eberhard Rabe: consultant for Sigvaris International, Mylan, Eurocom; speaker agreements with OM Pharma. Giacomo Gastaldi: consultant for Novo Nordisk, Lilly, Sanofi, Insulet SA, Medtronic, Roche SA; speaker agreements with OM Pharma, Ypsomed SA, Roche SA, Novo Nordisk SA. Juan Rosas-Saucedo: speaker agreements with AstraZeneca, Janssen, Boehringer Ingelheim, Silanes. Daniel Zingg and Alessandra Calabrese: full-time employees of OM Pharma. All other authors declare no conflicts of interest beyond involvement in this study.

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Authors' contributions
Ahmet K. Bozkurt and Marie J. van Rijn contributed equally to this work. Eberhard Rabe and Armando Mansilha gave equal advice and supervision on this work. Giacomo Gastaldi has substantially contributed to the development of the algorithm. Daniel Zingg and Alessandra Calabrese provided technical and logistic support to the project and helped in producing the figure for the algorithm. Neither were involved in data collection or the conclusions of the manuscript. All authors have revised it critically and approved the final version of the manuscript.

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Supplementary data
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