Glucose metabolism in patients with psoriasis

Friis, N. U.; Hoffmann, N.; Gyldenlove, M.; Skov, L.; Vilsbøll, T.; Knop, F. K.; Storgaard, H.

Published in:
British Journal of Dermatology

DOI:
10.1111/bjd.17349

Publication date:
2019

Document version
Publisher's PDF, also known as Version of record

REVIEW ARTICLE

BJD
British Journal of Dermatology

Glucose metabolism in patients with psoriasis*

N.U. Friis,[1] N. Hoffmann,[1] M. Gyldenløve,[2] L. Skov,[2] T. Vilsbøll,[1,3] F.K. Knop[1,3,4] and H. Storgaard[1]

[1]Clinical Metabolic Physiology, Steno Diabetes Center Copenhagen, Gentofte Hospital, Kildegårdsvej 28, DK-2900 Hellerup, Denmark
[2]Department of Dermatology and Allergology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark
[3]Department of Clinical Medicine and [4]Novo Nordisk Foundation Center for Basic Metabolic Research, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Summary

Background Epidemiological studies strongly suggest that psoriasis predisposes to type 2 diabetes. Several theories have been proposed to explain how these disease entities might be pathophysiologically connected.
Objectives Our primary objective was to elucidate whether clinical data support the notion of common pathophysiological denominators in patients with psoriasis and type 2 diabetes, and thus to delineate the association between the two conditions that has arisen on the basis of epidemiological studies.
Methods We reviewed clinical studies investigating parameters of glucose metabolism in patients with psoriasis. The PubMed and Embase databases were searched for studies investigating glucose metabolism in adult patients with psoriasis as a primary or secondary end point. Studies had to include a relevant control group.
Results Twenty-six clinical studies reporting on insulin resistance, glucose tolerance or insulin secretion were eligible for review. The results were widely conflicting, with less than half of the studies showing results suggestive of defective glucose metabolism in patients with psoriasis. In general, the studies suffered from a lack of information regarding possible confounders and patient characteristics. Furthermore, the research methods varied, and in all but one study they might not have been appropriate to detect early and subtle defects in glucose metabolism.
Conclusions The available literature does not unequivocally support common pathophysiological denominators in psoriasis and type 2 diabetes. Well-designed clinical studies are needed to expose potential diabetogenic defects in the glucose metabolism in patients with psoriasis.

Correspondence
Heidi Storgaard.
E-mail: hstorgaard@dadlnet.dk

Accepted for publication
23 October 2018

Funding sources
Kirsten og Freddy Johansens Fond funded a research year for lead author N.U.F.

Conflicts of interest
L.S. has been a paid speaker for AbbVie, Eli Lilly, Novartis and LEO Pharma; has been a consultant or served on advisory boards with AbbVie, Janssen Cilag, Novartis, Eli Lilly, LEO Pharma, UCB, Almirall and Sanofi; has served as an investigator for AbbVie, Janssen Cilag, Boehringer Ingelheim, AstraZeneca, Eli Lilly, Novartis, Regeneron and LEO Pharma; and has received research and educational grants from Pfizer, AbbVie, Novartis, Sanofi, Janssen Cilag and LEO Pharma. H.S. has served on an advisory board for Boehringer Ingelheim Pharmaceuticals. The other authors declare no conflicts of interest.

*Plain language summary available online

DOI 10.1111/bjd.17349

What's already known about this topic?

- Large epidemiological studies have concluded that psoriasis predisposes to type 2 diabetes, and there seems to be a dose–response relationship with severe psoriasis associated with a higher risk of developing type 2 diabetes.
- Several theories of how these diseases might be connected have been proposed.
- These are based mostly on the chronic inflammatory state shared by the two conditions.

What does this study add?

- We reviewed clinical studies investigating glucose metabolism in patients with psoriasis and found that the clinical evidence supporting epidemiology-based hypotheses pathophysiologically connecting psoriasis and type 2 diabetes is inconclusive.
- The methods used were suboptimal and the results ambiguous.
- Well-designed studies are warranted to determine whether psoriasis itself constitutes a prediabetic condition or whether the development of type 2 diabetes in patients with psoriasis comprises an epiphenomenon.

Psoriasis is a multifactorial immune-mediated chronic inflammatory skin disease associated with an extensive range of comorbidities including cardiovascular disease, metabolic syndrome, depression and type 2 diabetes (T2D).[1] Like psoriasis, T2D is a complex disease with a multifactorial aetiology. According to the World Health Organization, the worldwide prevalence of diabetes has doubled since 1980 and shows no signs of regressing.[2]

T2D is characterized by insulin resistance in skeletal muscle and adipose tissue (collectively named peripheral insulin resistance) and in the liver (central or hepatic insulin resistance), as well as impaired insulin secretion from pancreatic beta cells.[3] In the progression from normal glucose tolerance through prediabetes to overt T2D there is initially a phase of normal fasting and postprandial glucose levels maintained by compensatorily increased insulin secretion from pancreatic beta cells.[4] Prediabetes and T2D develop when the beta cells are not capable of secreting enough insulin to keep up with the insulin resistance, resulting in relative insulin deficiency and increasing plasma glucose levels (Fig. 1). Insulin resistance, dysfunction of the insulin-secreting beta cells and impaired glucose tolerance are thus early signs of disturbances in glucose metabolism appearing prior to the development of overt T2D.[4]

Epidemiological studies strongly support an association between psoriasis and T2D,[5–10] and several lines of evidence point to a dose–response effect, with more severe psoriasis associated with a higher risk of T2D.[5,6,9,10] Thus, epidemiological data firmly suggest that psoriasis predisposes to T2D, but the pathophysiological link between psoriasis and T2D is, as yet, poorly understood.

With the epidemiological evidence uniformly pointing to an association between psoriasis and the risk of developing T2D, we set out to provide a critical review of clinical studies examining glucose metabolism in patients with psoriasis. The aim was to investigate whether patients with psoriasis display the well-known early signs of disturbances in glucose metabolism seen in the progression to T2D.

Methods

All studies on adult patients with psoriasis investigating any form of glucose metabolism as primary or secondary end points were taken into consideration. The search for relevant studies was conducted in the PubMed and Embase databases. Search terms were psoriasis, glucose, insulin, insulin resistance, insulin sensitivity, glucose metabolism, homeostasis

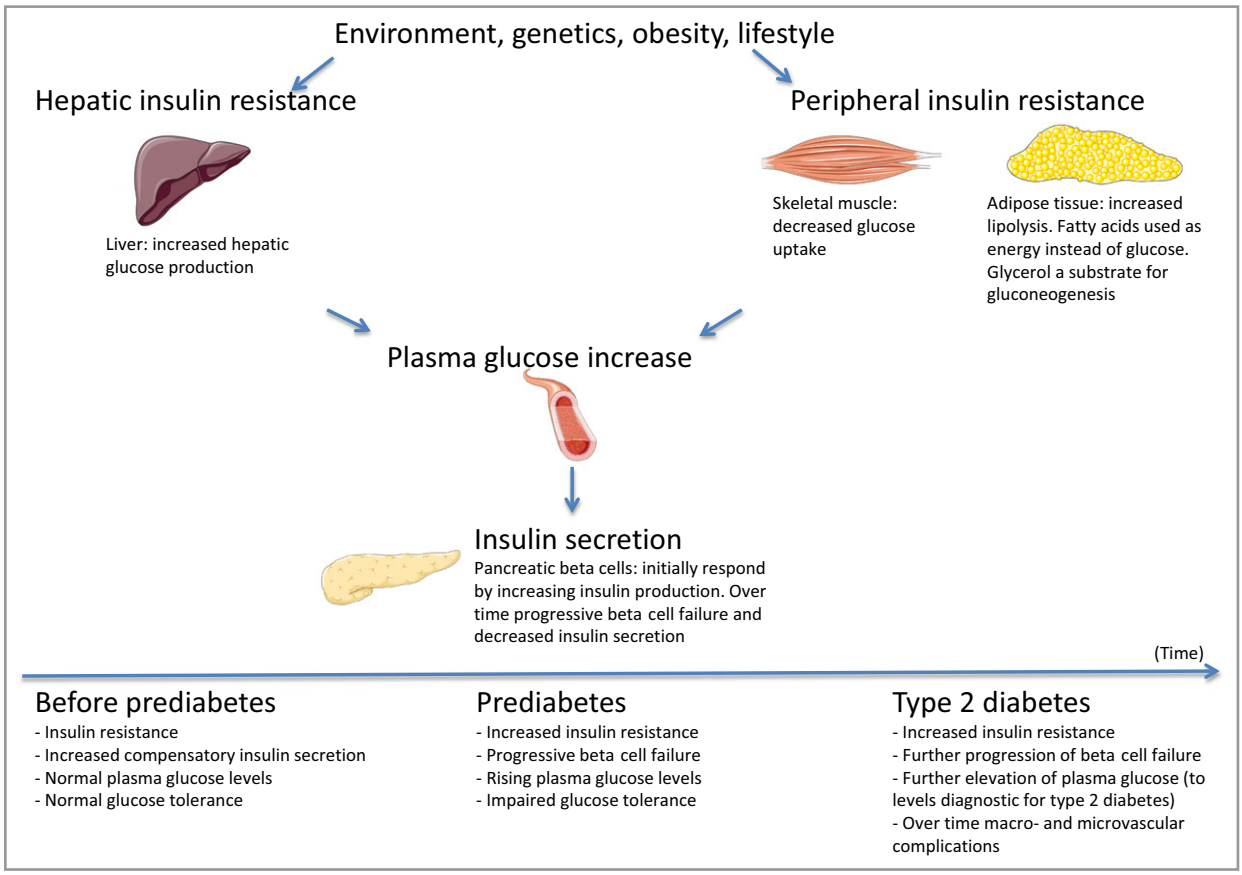

Fig 1. The development of type 2 diabetes. This figure was created using Servier Medical Art, licensed under the Creative Commons Attribution 3·0 Unported License: http://creativecommons.org/licenses/by/3·0.

model assessment, oral glucose tolerance test, clinical study, beta cell and hyperinsulinaemic euglycaemic clamp. All search terms were used in various relevant combinations and in the Medical Subject Headings search builder tool in PubMed. All studies were screened for relevance based on the abstract available. Studies written in a language other than English and studies without a control group of persons without psoriasis were not taken into consideration. Studies that reported only blood-sample values of insulin, glucose and glycated haemoglobin A_{1c} without using methods to study specific aspects of glucose metabolism were also excluded. References in papers already included were examined for relevance. We identified a total of 26 eligible studies, presented in Table S1 (see Supporting Information). The study selection process is illustrated in Figure 2.

Overview of the clinical studies

Insulin resistance

The hyperinsulinaemic euglycaemic clamp is considered the gold standard of measuring whole-body insulin resistance. A standardized amount of insulin is infused continuously (enough to shut down hepatic glucose production) and an adjustable intravenous glucose infusion is used to maintain euglycaemia. The amount of glucose infused during a predefined steady-state period is denoted the M-value and used as a marker of insulin sensitivity (or, reciprocally, insulin resistance).[11] Patients with T2D are typically insulin resistant and thus have a low M-value.[12]

Only one descriptive hyperinsulinaemic euglycaemic clamp study has specifically investigated insulin resistance in patients with psoriasis.[13] This study found that patients with moderate-to-severe psoriasis [Psoriasis Area and Severity Index (PASI) > 8][14] were significantly more insulin resistant than controls matched for age, sex and body mass index (BMI): median (interquartile range) M-value 4·5 (1·6–14·0) vs. 7·4 (2·1–10·8) mg kg^{-1} min^{-1}, P = 0·046. The two groups did not differ regarding habitual physical activity, fasting plasma glucose, glycated haemoglobin A_{1c} and predisposition to T2D.

The hyperinsulinaemic euglycaemic clamp requires significant resources with its advanced set-up, but if done correctly it provides a detailed comparison of insulin resistance between groups. A much simpler but less precise way of investigating insulin resistance is using the homeostasis model assessment (HOMA). The HOMA index is based on a mathematical modelling of fasting plasma glucose and plasma insulin. In the fasting state the glucose level is predominantly controlled by the liver (hepatic glucose production). Hepatic glucose production is sensitive to insulin. Thus, the HOMA index will mainly evaluate hepatic insulin sensitivity or resistance. It is applied in research to estimate both insulin resistance (HOMA-IR) and beta cell function (HOMA-B). Usually,

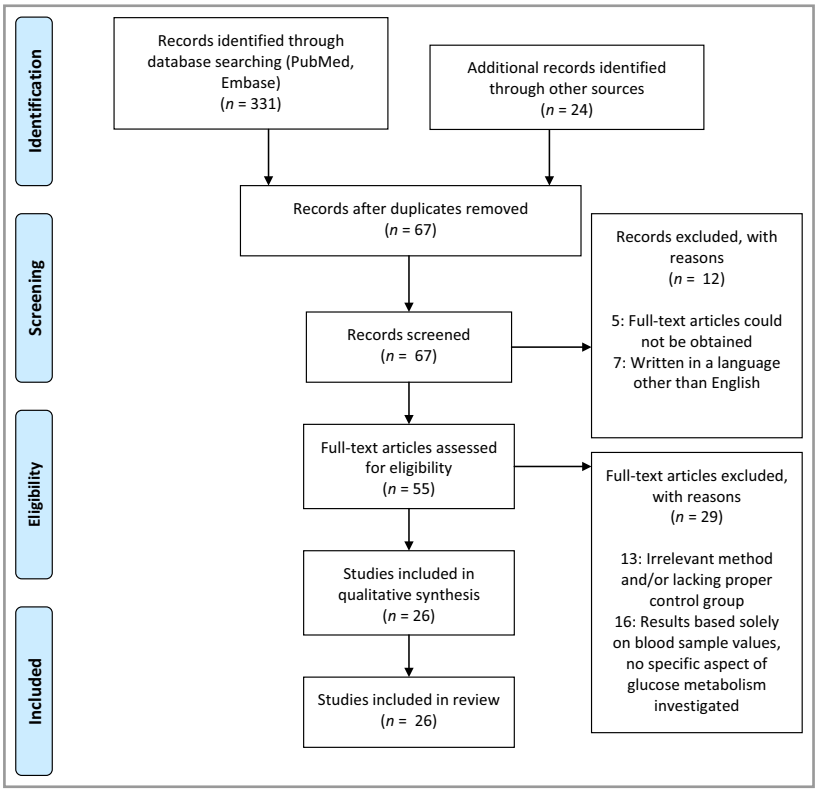

Fig 2. PRISMA flow diagram of the study selection process. From Moher *et al. PLOS Med* 2009; **6**:e1000097.[67]

patients with T2D have higher HOMA-IR and lower HOMA-B values than controls.[15]

In total, 17 studies have investigated insulin resistance in patients with psoriasis compared with controls using HOMA-IR (Table S1; see Supporting Information).[16–32] Eight studies found a higher degree of insulin resistance in patients with psoriasis than in controls.[19,20,22,26,28,29,31,32] Two studies showed inconclusive results[23,27] (marked with a '?' in Table S1) and six studies found no difference between groups.[16–18,21,24,25] One study even reported a significantly decreased HOMA-IR in the patient group.[30] Interestingly, only three[26,29,32] of eight studies matching for BMI[16,21,24–26,29,30,32] showed significantly increased insulin resistance.

As alluded to above, epidemiological studies have revealed a positive correlation between psoriasis disease severity and risk of developing T2D.[5,6,9,10] In five of the HOMA-IR studies mentioned above, the mean PASI of the included patients was high (> 8), reflecting severe disease.[18,20,21,27,29] These studies all found some sign of impaired glucose metabolism, albeit of differing character. Two studies found a significantly higher HOMA-IR in the patients with psoriasis than in controls.[20,29] Two studies showed higher fasting plasma insulin levels or HOMA-B value[18,21] but no difference in HOMA-IR. The last study found that patients with psoriasis more frequently had HOMA-IR > 2·5, were characterized by higher fasting plasma insulin levels and had a higher prevalence of diabetes.[27] Unfortunately, a majority of the studies had no requirement regarding the severity of psoriasis in the inclusion criteria.

As evident from the above results and summarized in Table S1, clinical studies investigating insulin resistance in psoriasis display conflicting results. Notably, the only gold standard hyperinsulinaemic euglycaemic clamp study performed showed a greater degree of insulin resistance in patients with psoriasis than in matched controls.

Glucose tolerance

The oral glucose tolerance test (OGTT) is a dynamic test and closely resembles physiological conditions, with gastric emptying and absorption and release of glucose-regulating hormones all contributing to glucose tolerance. After the patient has fasted overnight, a set amount of glucose is dissolved in water and ingested orally. Blood samples are obtained at specified time points. The fasting or 2-h value of plasma glucose can be used in the diagnosis of diabetes. High levels indicate diabetes, while midrange values classify a person as having impaired fasting glucose (IFG) or impaired glucose tolerance (IGT), which are characteristics of prediabetes.[33]

As illustrated in Table S1 (see Supporting Information), in total, nine studies used the OGTT to investigate glucose metabolism in patients with psoriasis compared with controls.[32,34–41] The results of the OGTTs were presented as the prevalence of IFG, IGT or overt T2D. Only two of the studies[39,40] found significantly higher rates of IGT or T2D in patients with psoriasis. Even though this is only two studies, their results are worth highlighting as these studies were large and they accounted for several risk factors for T2D. Pereira *et al.*[40] studied 77 patients with plaque psoriasis. Patients and controls were matched with regard to BMI, family history of diabetes and smoking. Patients with psoriasis had an odds ratio of 2·63 (95% confidence interval 1·37–5·04, P = 0·003) of having an abnormal glucose metabolism (IFG, IGT or diabetes) compared with controls. Ucak *et al.*[39] examined patients with psoriasis with no previous history of IGT and no family history of diabetes and compared them with age-, sex- and BMI-matched controls. They found that 18·6% of the patients with psoriasis vs. 2·5% of the controls had IGT. The HOMA-IR was also increased in the psoriasis group. The remaining studies found no significant difference regarding IGT or diabetes between the groups.[32,34–38,41]

Similar to the studies investigating insulin resistance, the collated evidence from the OGTT studies reviewed above, and summarized in Table S1, is inconclusive. Only two of the nine studies showed significantly impaired glucose tolerance in patients with psoriasis.

Pancreatic beta cell function

The function of the pancreatic beta cell is a key part of glucose metabolism.[42] It has scarcely been investigated in patients with psoriasis, even though direct measurements of pancreatic beta cell function can be made relatively simply, for example by an intravenous glucose tolerance test.[43] Another simple method is the utilization of the HOMA-B index. Two[21,39] of three studies[16,21,39] using HOMA-B showed increased beta cell function in patients with psoriasis. Other studies[18,38] found significantly elevated insulin levels in patients with psoriasis, but no insulin resistance or impaired glucose tolerance. Despite the scarcity of studies and their limited sizes, current evidence suggests that patients with psoriasis are characterized by hypersecretion of insulin – most likely as a consequence of insulin resistance (see Fig. 1).

Epidemiological studies on the association between psoriasis and type 2 diabetes

As mentioned briefly in the introduction, the evidence from the epidemiological literature has suggested that psoriasis is associated with T2D and, intriguingly, that there exists a dose–response effect with more severe psoriasis associated with a higher risk of T2D.[5,6,9,10] Three comprehensive meta-analyses all found a significant association between psoriasis and the prevalence and/or incidence of diabetes.[6,7,9] However, they all have some notable reservations to consider. There was a sizeable degree of heterogeneity in the studies included. The heterogeneity mainly stemmed from the method of data collection, namely questionnaires, clinical assessment and a billing database. All three studies also commented on the risk of confounding given that most studies lacked information regarding known risk factors of T2D including obesity, physical activity levels and medical history

of diabetes. Lastly, the possibility of bias could not be excluded, especially regarding recall and selection bias in the case–control studies. The epidemiological evidence of an association between the two diseases appears convincing, but it cannot provide an explanation of the mechanism(s) underlying this association.

The pathophysiological link between psoriasis and type 2 diabetes

The exact pathophysiological mechanism(s) linking psoriasis and T2D is unknown. Several theories have been proposed, which include shared genetic variations and risk factors. There is also an emphasis on the proinflammatory cytokines present as a result of the systemic inflammation that occurs in both psoriasis and T2D.[44] Systemic inflammation in severe psoriasis leads to the development of comorbidities such as diabetes and cardiac diseases, which then impact the selection of appropriate systemic therapy.[45] Patients with psoriasis have a deregulated immune system (Fig. 3). Inflammatory myeloid dendritic cells release interleukin (IL)-23 and IL-12, which activate IL-17-producing T cells, T helper (Th)1 cells and Th22 cells.[46] These cells stimulate the production of proinflammatory cytokines including IL-1, IL-6 and tumour necrosis factor (TNF)-α, which, besides playing a pivotal part in the pathogenesis of psoriasis[47] have been shown to interfere with insulin signalling and induce apoptosis in beta cells.[48,49]

Intriguingly, it has been suggested that insulin plays a key role in the differentiation of keratinocytes.[50,51] Insulin resistance in human keratinocytes caused by the proinflammatory cytokine IL-1β could be responsible for the lack of differentiation and uncontrolled proliferation seen in psoriatic plaques.[52] IL-1β has long been known to be involved in the pathogenesis of psoriasis[47] and causes insulin resistance in muscle, adipose tissue and liver cells.[53–55] It may therefore constitute a pathophysiological link between diabetes and psoriasis. These possible mechanisms indicate that the low-grade inflammation present in patients with psoriasis might lead to insulin resistance, an important precursor of T2D (Fig. 3).

Shared gene variants exist in both diseases. Several genetic psoriasis susceptibility loci (PSORS) have been identified. PSORS2, PSORS3 and PSORS4 are associated with susceptibility loci of metabolic diseases including T2D.[56] Through genome-wide association studies a host of single-nucleotide polymorphisms (SNPs) linked to psoriasis have been uncovered.[46] While the function and thus pathophysiological consequence of gene mutations in these susceptibility loci and SNPs are not fully elucidated it has been shown that some of these contribute to the state of chronic inflammation seen in both

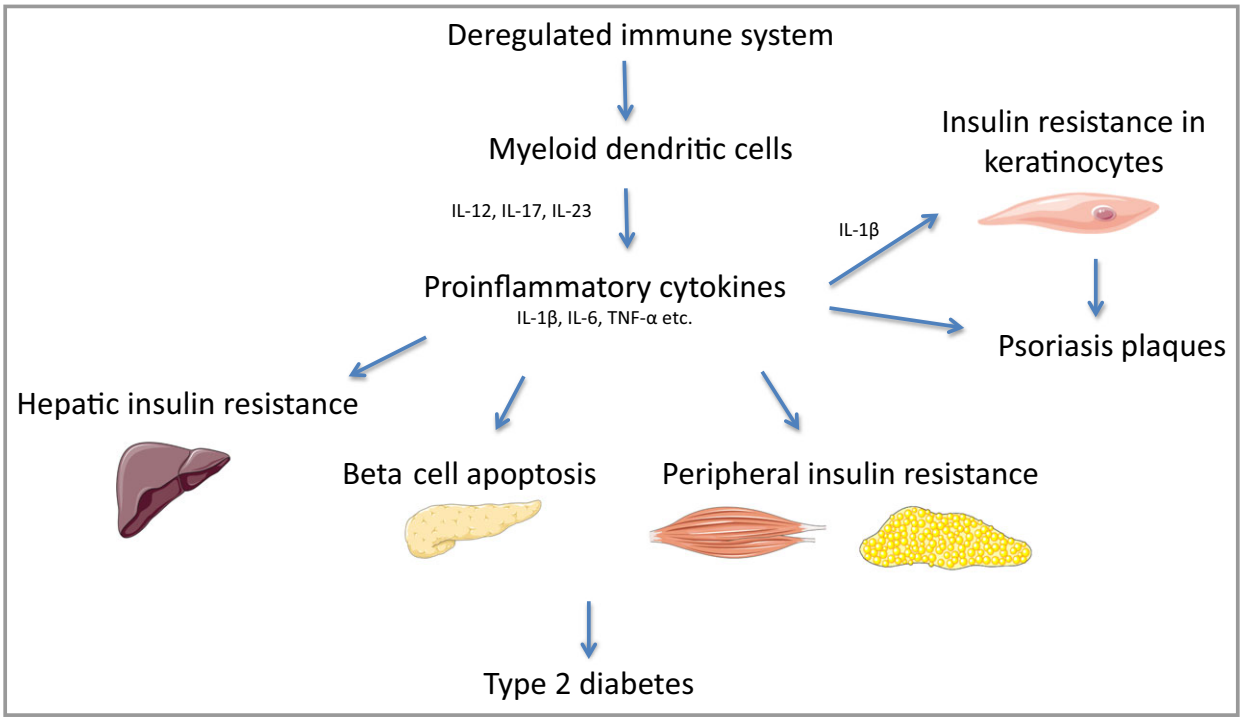

Fig 3. Theoretical role of inflammation in the shared pathogenesis of psoriasis and type 2 diabetes. Overactive myeloid dendritic cells release interleukin (IL)-23 and IL-12, which activate IL-17-producing T cells, T helper (Th)1 cells and Th17 cells. These cells stimulate the production of proinflammatory cytokines including IL-1, IL-6 and tumour necrosis factor (TNF)-α, which interfere with insulin signalling and lead to plaque production. IL-1β might induce plaque psoriasis by inhibiting insulin-dependent keratin differentiation and control of proliferation. This figure was created using Servier Medical Art, licensed under the Creative Commons Attribution 3·0 Unported License: http://creativecommons.org/licenses/by/3·0.

psoriasis and diabetes.[46] For instance, a gene mutation in the caspase recruitment domain-containing protein 14 gene (*CARD14*), located in PSORS2, ultimately leads to recruitment of neutrophils, dendritic cells and T cells, resulting in an increased production of inflammatory cytokines.[46] Another of these shared genetic defects is a mutation in the CDK5 regulatory subunit associated protein 1-like 1 gene (*CDKAL1*), which is thought to inhibit the pancreatic beta cells' response to plasma glucose.[57] Normally, pancreatic beta cells respond directly and proportionally to a rise in plasma glucose by producing and secreting more insulin.

Lastly, the connection between psoriasis and T2D may simply rely on the fact that many independent risk factors for T2D including smoking, inactivity and obesity[1] are more prevalent in patients with psoriasis than in the general population. Also, stigmatizing psoriatic skin lesions can be thought to catalyse an unhealthy, secluded lifestyle increasing the risk of developing T2D. This would make T2D an epiphenomenon to psoriasis.

Comments on the available evidence from clinical studies

A number of clinical studies, including one gold standard hyperinsulinaemic euglycaemic clamp study, point to defective glucose metabolism in patients with psoriasis. This is in line with the evidence derived from epidemiological studies. Studies investigating patients with severe psoriasis were more consistent and generally showed signs of deranged glucose metabolism, which is in agreement with the dose–response relationship observed in epidemiological studies. Nevertheless, the overall evidence from clinical studies in the field is far from convincing.

The OGTT was used as a diagnostic test in some of the included studies determining normal glucose tolerance, IGT and T2D.[32,34–41] It is well known that the OGTT is characterized by a high intraindividual variation in the 2-h plasma glucose concentration, resulting in a low reproducibility of the IGT category in particular. In a study of an elderly white population without a history of diabetes ($n = 555$) the reproducibility of the OGTT performed on two different days was 91% for normal glucose tolerance, 48% for IGT and 78% for T2D.[58] Considerations regarding power calculations and sample size are therefore crucial for the interpretation of OGTT results. Only three of the studies included information on power calculations[13,19,32] and none of these were OGTT studies. Several studies highlighted a small sample size as a limitation to their study,[17,24,27,37,41] while the rest did not address this issue. Therefore, many of the included studies might be too small or underpowered to draw firm conclusions from.

Less than half of the studies showed significant changes in the parameters of glucose metabolism they investigated. Furthermore, only six of 12 BMI-matched studies suggested impaired glucose metabolism in patients with psoriasis. The roles of lifestyle factors such as smoking, alcohol and physical inactivity were rarely taken into account. Furthermore, there was a general lack of information regarding the patient group characteristics, concomitant medication, disease severity and predisposition to T2D. Compared with epidemiological studies, clinical studies should ideally be designed to control for these confounders, but most of the studies identified in this review failed to do so (Table S1; see Supporting Information).

Thus, the increased risk of T2D found in the epidemiological studies might simply be explained by the fact that typical risk factors for T2D are more prevalent in patients with psoriasis. In that case, early lifestyle interventions would reduce the risk of developing T2D to the level of the background population.

There are some important points in favour of a clinically significant association between the two diseases. The hyperinsulinaemic euglycaemic clamp study[13] showed increased insulin resistance in patients with psoriasis. No difference was found in the HOMA-IR index in the same study. This may suggest that HOMA-IR, and maybe the OGTT method as well, are not sensitive enough to discover subtle differences in glucose metabolism between groups. That would explain the conflicting results of the clinical studies reviewed here.

Interestingly, it has been demonstrated that patients with psoriasis have a significantly decreased incretin effect compared with age- and sex-matched controls.[59] Impairment of the incretin effect has been speculated to constitute an early disturbance in glucose metabolism,[60] and the same could be true in patients with psoriasis.

There have also been some crossover effects in the concurrent treatment of the two diseases. Treatment with the anti-TNF-α drugs etanercept and adalimumab, commonly used in the treatment of psoriasis, has been shown to exert positive effects on insulin sensitivity.[61,62] This is in agreement with the theory that inflammatory cytokines are involved in the pathogenesis of both diseases.[47,48] On the other hand, a hyperinsulinaemic euglycaemic clamp study on the positive effect of anti-inflammatory treatment on insulin resistance was cancelled halfway through when no trend was observed.[63] More treatment studies are needed to clarify whether early anti-inflammatory treatment might prevent the development of T2D in patients with psoriasis.

Similar to the studies investigating the effect of anti-inflammatory treatment on insulin resistance, the effects of antidiabetic drugs on psoriasis have been studied on several occasions. Intriguingly, there are a number of reports that treatment with antidiabetic drugs can have positive effects on psoriasis.[64] If that were indeed the case then it would be suggestive of a common pathogenesis. The reports cover different antidiabetic treatments, for example glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase 4 inhibitors, thiazolidinediones and biguanides. However, a relief of psoriasis symptoms due to antidiabetic drugs has been seen mainly in small studies so far.[64] Two randomized placebo-controlled studies with a GLP-1RA[65] and thiazolidinediones[66] failed to show a beneficial effect of antidiabetic drugs on psoriasis.

Finally, important information regarding glucose metabolism in patients with psoriasis is still missing in order to confirm whether psoriasis constitutes a state comparable with prediabetes, and thus can accurately be classified as an individual risk factor for T2D. Prediabetes describes a state where plasma glucose is higher than normal but below the cut-off value for diabetes. All of the mechanisms involved in glucose metabolism may contribute to this elevation of plasma glucose, including but not limited to hepatic insulin resistance, peripheral insulin resistance and beta cell dysfunction resulting in IFG, IGT or both (Fig. 1). As shown in this review these parameters of glucose metabolism have not been investigated extensively enough, in particular regarding hepatic insulin resistance and beta cell function. Uncovering specific pathological changes in glucose metabolism in patients with psoriasis could lead to better preventive strategies and novel treatment targets, improving the general health and quality of life of these patients.

Conclusions

The results of clinical studies investigating glucose metabolism in patients with psoriasis are conflicting and it seems presumptuous to conclude firmly that patients with psoriasis share glucometabolic impairments with people with prediabetes. However, seen in conjunction with the epidemiological literature and the proposed theories of a shared pathophysiology, there is ample basis for further research in this area. New studies using sound methods and elaborate research techniques are needed for further characterization of the glucose metabolism in patients with psoriasis.

References

1 Ryan C, Kirby B. Psoriasis is a systemic disease with multiple cardiovascular and metabolic comorbidities. *Dermatol Clin* 2015; **33**:41–55.

2 World Health Organization. Global report on diabetes. Available at: http://www.who.int/diabetes/global-report/en (last accessed 7 November 2018).

3 Kahn SE, Cooper ME, Del Prato S. Pathophysiology and treatment of type 2 diabetes: perspectives on the past, present and future. *Lancet* 2014; **383**:1068–83.

4 Ramlo-Halsted BA, Edelman SV. The natural history of type 2 diabetes: implications for clinical practice. *Prim Care* 1999; **26**:771–90.

5 Khalid U, Hansen PR, Gislason GH *et al.* Psoriasis and new-onset diabetes. *Diabetes Care* 2013; **36**:2402–7.

6 Coto-Segura P, Eiris-Salvado N, González-Lara L *et al.* Psoriasis, psoriatic arthritis and type 2 diabetes mellitus: a systematic review and meta-analysis. *Br J Dermatol* 2013; **169**:783–93.

7 Cheng J, Kuai D, Zhang L *et al.* Psoriasis increased the risk of diabetes: a meta-analysis. *Arch Dermatol Res* 2012; **304**:119–25.

8 Miller IM, Ellervik C, Yazdanyar S, Jemec GB. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol* 2013; **69**:1014–24.

9 Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and the risk of diabetes mellitus: a systematic review and meta-analysis. *JAMA Dermatol* 2013; **149**:84–91.

10 Wan MT, Shin DB, Hubbard RA *et al.* Psoriasis and the risk of diabetes: a prospective population-based cohort study. *J Am Acad Dermatol* 2018; **78**:315–22.

11 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979; **237**:E214–23.

12 Greenfield MS, Doberne L, Kraemer F *et al.* Assessment of insulin resistance with the insulin suppression test and the euglycemic clamp. *Diabetes* 1981; **30**:387–92.

13 Gyldenløve M, Storgaard H, Holst JJ *et al.* Patients with psoriasis are insulin resistant. *J Am Acad Dermatol* 2015; **72**:599–605.

14 Fredriksson T, Pettersson U. Severe psoriasis – oral therapy with a new retinoid. *Dermatologica* 1978; **157**:238–44.

15 Matthews DR, Hosker JP, Rudenski AS *et al.* Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**:412–19.

16 Reynoso-von Drateln C, Martínez-Abundis E, Balcázar-Muñoz BR *et al.* Lipid profile, insulin secretion, and insulin sensitivity in psoriasis. *J Am Acad Dermatol* 2003; **48**:882–5.

17 Usta M, Turan E, Aral H *et al.* Serum paraoxonase-1 activities and oxidative status in patients with plaque-type psoriasis with/without metabolic syndrome. *J Clin Lab Anal* 2011; **25**:289–95.

18 Arias-Santiago S, Orgaz-Molina J, Castellote-Caballero L *et al.* Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis. *Eur J Dermatol* 2012; **22**:337–44.

19 Mehta NN, Li R, Krishnamoorthy P *et al.* Abnormal lipoprotein particles and cholesterol efflux capacity in patients with psoriasis. *Atherosclerosis* 2012; **224**:218–21.

20 Abdel Hay R, Nour-Edin F, Hegazy R *et al.* Expression of osteopontin genotypes (T-4754-C and A-9138-C) in psoriasis and their relation to metabolic syndrome. *J Dermatol Sci* 2014; **75**:150–3.

21 El Asmi MA, Zidi W, Mebazaa A *et al.* Serum lipid level in Tunisian patients with psoriasis. *Clin Lab* 2014; **60**:1043–7.

22 Shivanand DR, Srikrishna R. Study of insulin resistance and dyslipidemia in psoriasis patients in a tertiary care hospital, south India. *J Krishna Inst Med Sci Univ* 2016; **5**:14–19.

23 Korkmaz S, Korkmaz H. Effect of alterations in apoptotic pathway on development of metabolic syndrome in patients with psoriasis vulgaris. *Br J Dermatol* 2016; **176**:1549–57.

24 Coban M, Tasli L, Turgut S *et al.* Association of adipokines, insulin resistance, hypertension and dyslipidemia in patients with psoriasis vulgaris. *Ann Dermatol* 2016; **28**:74–9.

25 Bulur I, Kaya Erdogan H, Kocatürk E *et al.* The role of irisin in the relationship between psoriasis and insulin resistance. *G Ital Dermatol Venereol* 2018; **153**:477–82.

26 Karadag AS, Yavuz B, Ertugrul DT *et al.* Is psoriasis a pre-atherosclerotic disease? Increased insulin resistance and impaired endothelial function in patients with psoriasis. *Int J Dermatol* 2010; **49**:642–6.

27 Warnecke C, Manousaridi I, Herr R *et al.* Cardiovascular and metabolic risk profile in German patients with moderate and severe psoriasis: a case control study. *Eur J Dermatol* 2011; **21**:761–70.

28 Dhara S, Dasgupta A, Rout JK *et al.* Clinico-biochemical correlation between psoriasis and insulin resistance. *Indian J Clin Biochem* 2015; **30**:99–103.

29 Okan G, Baki AM, Yorulmaz E *et al.* Serum visfatin, fetuin-A, and pentraxin 3 levels in patients with psoriasis and their relation to disease severity. *J Clin Lab Anal* 2016; **30**:284–9.

30 Dogan FB, Cicek D, Aydin S *et al.* Serum preptin and amylin values in psoriasis vulgaris and Behçet's patients. *J Clin Lab Anal* 2016; **30**:165–8.

31 Uysal S, Yilmaz FM, Karatoprak K *et al*. The levels of serum pentraxin3, CRP, fetuin-A, and insulin in patients with psoriasis. *Eur Rev Med Pharmacol Sci* 2014; **18**:3453–8.

32 Albareda M, Ravella A, Castelló M *et al*. Metabolic syndrome and its components in patients with psoriasis. *Springerplus* 2014; **3**:612.

33 Buysschaert M, Medina JL, Bergman M *et al*. Prediabetes and associated disorders. *Endocrine* 2015; **48**:371–93.

34 Beek C. Blood sugar tolerance tests in psoriasis vulgaris. *Dermatologica* 1952; **104**:171–5.

35 Nigam P, Dayal SG, Joshi LD, Samuel KC. Diabetic status in psoriasis. *Indian J Dermatol Venereol Leprol* 1979; **45**:171–4.

36 Sundharam J, Singh R, Agarwal P. Psoriasis and diabetes millitus. *Indian J Dermatol Venereol Leprol* 1980; **46**:158–62.

37 Seishima M, Mori S, Noma A. Serum lipid and apolipoprotein levels in patients with psoriasis. *Br J Dermatol* 1994; **130**:738–42.

38 Brenelli SL, Moraes AM, Monte-Alegre S *et al*. Insulin resistance in psoriasis. *Braz J Med Biol Res* 1995; **28**:297–301.

39 Ucak S, Ekmekci T, Basat O *et al*. Comparison of various insulin sensitivity indices in psoriatic patients and their relationship with type of psoriasis. *J Eur Acad Dermatol Venereol* 2006; **20**:517–22.

40 Pereira RR, Amladi ST, Varthakavi PK. A study of the prevalence of diabetes, insulin resistance, lipid abnormalities, and cardiovascular risk factors in patients with chronic plaque psoriasis. *Indian J Dermatol* 2011; **56**:520–6.

41 Malekzad F, Robati R, Abaei H *et al*. Insulin resistance in psoriasis: a case–control study. *Iran J Dermatol* 2011; **14**:136–9.

42 Hannon TS, Kahn SE, Utzschneider KM *et al*. Review of methods for measuring β-cell function: design considerations from the Restoring Insulin Secretion (RISE) Consortium. *Diabetes Obes Metab* 2018; **20**:14–24.

43 Hahn RG, Ljunggren S, Larsen F, Nyström T. A simple intravenous glucose tolerance test for assessment of insulin sensitivity. *Theor Biol Med Model* 2011; **8**:12.

44 Davidovici BB, Sattar N, Prinz J *et al*. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. *J Invest Dermatol* 2010; **130**:1785–96.

45 Kaushik SB, Lebwohl MG. CME Part I psoriasis: which therapy for which patient. Psoriasis comorbidities and preferred systemic agents. *J Am Acad Dermatol* 2018; https://doi.org/10.1016/j.jaad.2018.06.057.

46 Lowes MA, Suárez-Fariñas M, Krueger JG. Immunology of psoriasis. *Annu Rev Immunol* 2014; **32**:227–55.

47 Nestle FO, Kaplan DH, Barker J. Psoriasis. *N Engl J Med* 2009; **361**:496–509.

48 Mandrup-Poulsen T. Type 2 diabetes mellitus. *Dermatol Clin* 2013; **31**:495–506.

49 Gurzov EN, Ortis F, Cunha DA *et al*. Signaling by IL-1β+IFN-γ and ER stress converge on DP5/Hrk activation: a novel mechanism for pancreatic β-cell apoptosis. *Cell Death Differ* 2009; **16**:1539–50.

50 Wertheimer E, Trebicz M, Eldar T *et al*. Differential roles of insulin receptor and insulin-like growth factor-1 receptor in differentiation of murine skin keratinocytes. *J Invest Dermatol* 2000; **115**:24–9.

51 Wertheimer E, Spravchikov N, Trebicz M *et al*. The regulation of skin proliferation and differentiation in the IR null mouse: implications for skin complications of diabetes. *Endocrinology* 2001; **142**:1234–41.

52 Buerger C, Richter B, Woth K *et al*. Interleukin-1β interferes with epidermal homeostasis through induction of insulin resistance: implications for psoriasis pathogenesis. *J Invest Dermatol* 2012; **132**:2206–14.

53 Jager J, Grémeaux T, Cormont M *et al*. Interleukin-1β-induced insulin resistance in adipocytes through down-regulation of insulin receptor substrate-1 expression. *Endocrinology* 2007; **148**:241–51.

54 Nov O, Kohl A, Lewis EC *et al*. Interleukin-1β may mediate insulin resistance in liver-derived cells in response to adipocyte inflammation. *Endocrinology* 2010; **151**:4247–56.

55 Martins AR, Nachbar RT, Gorjao R *et al*. Mechanisms underlying skeletal muscle insulin resistance induced by fatty acids: importance of the mitochondrial function. *Lipids Health Dis* 2012; **11**:30.

56 Azfar RS, Gelfand JM. Psoriasis and metabolic disease: epidemiology and pathophysiology. *Curr Opin Rheumatol* 2008; **20**:416–22.

57 Steinthorsdottir V, Thorleifsson G, Reynisdottir L *et al*. A variant in *CDKAL1* influences insulin response and risk of type 2 diabetes. *Nat Genet* 2007; **39**:770–5.

58 Mooy JM, Grootenhuis PA, de Vries H *et al*. Intra-individual variation of glucose, specific insulin and proinsulin concentrations measured by two oral glucose tolerance tests in a general Caucasian population: the Hoorn Study. *Diabetologia* 1996; **39**:298–305.

59 Gyldenløve M, Vilsbøll T, Zachariae C *et al*. Impaired incretin effect is an early sign of glucose dysmetabolism in nondiabetic patients with psoriasis. *J Intern Med* 2015; **278**:660–70.

60 Holst JJ, Knop FK, Vilsbøll T *et al*. Loss of incretin effect is a specific, important, and early characteristic of type 2 diabetes. *Diabetes Care* 2011; **34**(Suppl. 2):S251–7.

61 Puig L, Strohal R, Fuiman J *et al*. Cardiometabolic biomarkers in chronic plaque psoriasis before and after etanercept treatment. *J Dermatolog Treat* 2014; **25**:470–81.

62 Pina T, Armesto S, Lopez-Mejias R *et al*. Anti-TNF-α therapy improves insulin sensitivity in non-diabetic patients with psoriasis: a 6-month prospective study. *J Eur Acad Dermatol Venereol* 2015; **29**:1325–30.

63 Kofoed K, Clemmensen A, Mikkelsen UR *et al*. Effects of anti-tumor necrosis factor therapy on body composition and insulin sensitivity in patients with psoriasis. *Arch Dermatol* 2012; **148**:1089–91.

64 Ip W, Kirchhof MG. Glycemic control in the treatment of psoriasis. *Dermatology* 2017; **233**:23–9.

65 Faurschou A, Gyldenløve M, Rohde U *et al*. Lack of effect of the glucagon-like peptide-1 receptor agonist liraglutide on psoriasis in glucose-tolerant patients – a randomized placebo-controlled trial. *J Eur Acad Dermatol Venereol* 2015; **29**:555–9.

66 Ellis CN, Barker JN, Haig AE *et al*. Placebo response in two long-term randomized psoriasis studies that were negative for rosiglitazone. *Am J Clin Dermatol* 2007; **8**:93–102.

67 Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Med* 2009; **6**:e1000097.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Table S1 List of studies investigating glucose metabolism in patients with psoriasis.

Powerpoint S1 Journal Club Slide Set.