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Systemic therapy of psoriasis in diabetic patients

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Abstract

Psoriasis is a chronic inflammatory skin disease affecting 2-3% of worldwide population. Moderate to severe psoriasis is frequently associated with metabolic disorders including diabetes, obesity, dyslipidaemia, metabolic syndrome and non-alcoholic fatty liver disease. In particular, the prevalence of diabetes in patients with psoriasis ranges from 5 to 54%. Most of the studies found that the prevalence of diabetes is higher in patients with moderate to severe psoriasis compared to mild disease. The association between psoriasis and diabetes could be explained considering several factors including a common genetic background, the high prevalence of metabolic risk factors for diabetes in patients with psoriasis as well as unhealthy life-styles such heavy drinking, over-eating and sedentary, which are common in patients with psoriasis. From a clinical prospective, the understanding of the patients in the context of metabolic comorbidities including diabetes is very important to ensure that treatment is tailored to meet the individual patient needs. Indeed, some pharmacological treatments may negatively affect metabolic comorbidities, and have important interactions with drugs that are commonly used to treat them. Non-pharmacological intervention such as diet and physical exercise could both improve the response to treatments for psoriasis and reduce the risk of diabetes and cardiovascular events.

Introduction

Psoriasis is a common chronic inflammatory disorder affecting approximately 2-3% of the general population, depending on ethnicity and geographical area [1]. It can occur at any age, although the majority of cases develop before the age of 50 years and it is uncommon in children. Psoriasis is considered to be an autoimmune disease, and the precise nature of the autoantigens triggering T-cell responses is being elucidated [2]. Psoriasis has a strong genetic component with the majority of the patients having relatives affected [1]. The class I major histocompatibility complex (MHC) allele *HLA-Cw6* is the strongest susceptibility factor for psoriasis. Other genetic predisposing factors include molecules involved in innate and adaptive immunity [3].

Chronic plaque psoriasis is the most common clinical variant of the disease [4] and the extent of skin involvement is widely variable, ranging from a few localized plaques at extensor sites to generalized involvement. Moderate to severe psoriasis is defined if the body surface involvement and/or the Dermatology life Quality Index is greater than 10. Patients with psoriasis, like those with other major medical disorders, have a decreased quality of life as well as a reduced employment and income [5]. Awareness is increasing that psoriasis is more than skin deep and that it is associated with comorbidities including metabolic disorders such as diabetes, obesity and metabolic syndrome.

Chronic plaque psoriasis and diabetes, the epidemiological evidence

The association of psoriasis with insulin-resistance and diabetes was firstly described more than 40 years ago [6]. More recently this association has been confirmed and further investigated in several epidemiological studies and meta-analysis. The prevalence of diabetes in patients with psoriasis ranges from 4.4 to 54% [7]. Most of the studies found that the prevalence of diabetes is higher in patients with moderate to severe psoriasis compared to mild disease [8] (Figure 1).

In a meta-analysis of 44 studies by Coto-Segura P *et al.* the pooled odds ratio for the association between psoriasis and diabetes was 1.76 (95% CI 1.59-1.96). It was reported a "dose effect" in the risk of suffering from diabetes, as patients with severe psoriasis had higher risk compared with the pooled OR (OR 2.10, 95% CI 1.73–2.55 versus OR 1.76, 95% CI 1.59-1.96) [9]. The highest risk was for patients with psoriatic arthritis (OR 2.18, 95% C.I.1.36-3.50) [9]. In another meta-analyses of observational studies (n=27) psoriasis was associated also with an increased incidence of diabetes, other than prevalence. The study found that patients with psoriasis have a 27% increased risk of developing diabetes compared to the general population. In particular, those aged below 60 years and with more severe psoriasis carry the higher risk of developing diabetes [7]. Moreover, a Danish nationwide cohort study (study period 1997–2009) including 52.613 patients with psoriasis found that the incidence rate ratios of new-onset diabetes were increased in patients with psoriasis compared with the general population. Again, the incidence increased with psoriasis severity [10]. On the other hand, a case-control study by Wu *et al.* including 41.289 subjects, found that diabetic patients are at risk of developing psoriasis. The incidence rates of first-time psoriasis in diabetic patients and non-diabetic subjects were 70.2 cases and 42.5 cases per 100.000 person-years, respectively ($p<0.001$). The more severe the diabetes is, the higher the risk for psoriasis [11]. Furthermore, thiazolidinedione use has been associated with slightly lower risk of incident psoriasis (0.87, 95% CI 0.77-0.99) [11].

A large cross-sectional survey (National Health and Nutrition Examination Survey) including 12.737 subjects reported an increased prevalence of obesity and hypertension among patients with psoriasis,

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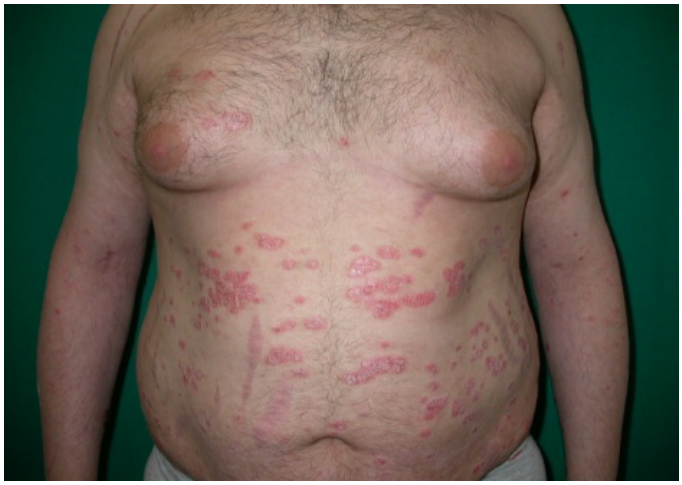

Figure 1. Plaques of psoriasis localised on the trunk of a overweighted patient with diabetes.

whereas it did not confirm an association with diabetes [12]. However, they included only five patients with severe psoriasis in their study.

Patients with moderate to severe psoriasis have an increased prevalence of the metabolic syndrome that is a cluster of metabolic disorders including abdominal obesity, impaired fasting glucose/diabetes, dyslipidaemia and hypertension [13]. In a cross-sectional study, we found that patients with psoriasis had a higher prevalence of metabolic syndrome than those with other inflammatory skin diseases after adjusting for sex and age (30.1% vs. 20.6%, OR: 1.65, 95%C.I. 1.16–2.35) [14]. Non-alcoholic fatty liver disease (NAFLD) is recognized as the hepatic expression of the metabolic syndrome and these conditions have insulin resistance as a common pathophysiological mechanism [15]. We found that the prevalence of NAFLD in patients with chronic plaque psoriasis was greater than in controls (47% *vs*. 28%; p<0.0001) who were matched by age, sex and BMI [16]. Our findings have been also confirmed in a recent Dutch study. NAFLD was diagnosed in 46.2% of patients with psoriasis compared with 33.3% of the controls (p=0.005) [17]. Psoriasis was found associated to NAFLD independently of alcohol consumption, smoking status, presence of metabolic syndrome and serum levels of alanine aminotransferase (adjusted OR 1.7, 95% CI 1.1-2.6) [17]. This is noteworthy as excess liver fat promotes hepatic insulin resistance, and NAFLD is recognized risk factor for diabetes [18,19].

Putative mechanisms of the association between psoriasis and diabetes

The association between psoriasis and diabetes could be explained considering several factors including a common genetic background, the high prevalence of metabolic risk factors for diabetes in patients with psoriasis, the effects of chronic inflammation and insulin resistance as well as an unhealthy life-style such as heavy smoking/drinking, over-eating habit and sedentary life, which are common in patients with psoriasis (Table 1).

It is likely that psoriasis and diabetes share common genetic background. Indeed, Suárez-Fariñas *et al.* [20] identified several genes biologically significant for psoriasis and metabolic disorders, including renin, cytotoxic T-lymphocyte antigen 4 (CTLA4) and Toll like receptor 3 (TLR3). Moreover, genetic variation at IL12B, IL23R and IL23A influences either the risk of psoriasis, its severity as well as type 2 diabetes mellitus [21]. Another study found that patients with psoriasis are enriched for certain common genetic variants (HLA, FUT2, UBE2L3, SH2B3) that predispose to dyslipidaemia, hypertension and cardiovascular risk [22]. The presence of risk factors for diabetes in patients with psoriasis is quite common. Patients with psoriasis are more frequently overweight or obese than the general population, and the severity of psoriasis is correlated to body mass index (BMI) [23,24]. Obesity generally precedes the development of psoriasis and the BMI is correlated to an increased risk of incident psoriasis [25]. Several measures of adiposity, including BMI, waist and hip circumference and waist-hip ratio have been reported as independent risk factors for the development of psoriasis and psoriatic arthritis (PsA) [25]. The relationships between psoriasis and obesity are largely explained by the complex properties of the adipose tissue. Indeed, the adipose tissue is not only a storage fat organ but also an active endocrine organ with many other secretory products, such as free fatty acids, adipocyte-derived hormones and pro-inflammatory adipokines including chemerin, leptin and adiponectin, which are released by macrophages and lymphocytes [26]. Increased chemerin and leptin and reduced adiponectin serum have been reported in patients with psoriasis compared to age, sex and BMI matched controls. [27–29]. Obesity is a strong risk factor for insulin resistance and diabetes [30]. Moreover, psoriatic keratinocytes release pro-inflammatory cytokines including IL-1β that induce insulin resistance and may favour the development of diabetes [26,31]. Indeed, IL-1β is present in high quantities in the tissue fluid collected via micro-dialysis from patients with psoriasis and its levels are reduced under successful anti-psoriatic therapy. IL-1β contributes to diabetes and psoriasis by inducing insulin resistance through p38MAPK (mitogen activated protein kinase), which blocks insulin-dependent differentiation of keratinocytes and drives their proliferation [32]. Buerger *et al*. showed that long-term IL-1β treatment induces insulin resistance in metabolically active tissues. At the same time, IL-1β is able to activate protein kinase B (PKB) via a different set of kinases such as c-Jun N-terminal kinase (JNK) or p38MAPK, which results in induction of cell proliferation. They assume that PKB preferentially induces proliferative pathways, whereas the insulin-dependent and differentiation-inducing functions are shut off by means of insulin resistance [32,33].

The hypothesis that psoriasis itself constitutes a pre-diabetic condition has been suggested by the study of Gyldenløve *et al.* conducted over 32 patients with psoriasis [34]. They found that normal glucose-tolerant psoriatic patients had reduced insulin sensitivity. In this study the gold standard hyperinsulinemic-euglycemic clamp technique was used and psoriatic patients exhibited reduced insulin sensitivity compared with controls. Furthermore, C-peptide and glucagon levels during the hyperinsulinemic-euglycemic clamp tended to be higher in the psoriasis group.

On the other hand, it is also possible that the coexisting metabolic comorbidities might directly contribute to exacerbate psoriatic inflammation through the release of several pro-inflammatory mediators from the liver and/or visceral adipose tissues, such as

Table 1. Putative mechanisms of the association between psoriasis and type 2 diabetes mellitus.

Common genetic background
High prevalence of risk factors for diabetes in patients with psoriasis (i.e. obesity, insulin resistance)
Common inflammatory pathways (i.e. TNF-alpha, IL-1 beta)
Unhealthy life-styles (heavy drinking, over-eating and sedentary)

increased reactive oxygen species, C reactive protein (CRP), IL-6 and other adipokines [29]. Further research is needed to investigate the complex relationship between psoriasis and diabetes at both clinical and molecular level.

Management of patients with moderate to severe psoriasis and diabetes

The association between psoriasis and cardio-metabolic disorders has important clinical implications [35]. In particular, methotrexate [MTX] should be administered with caution for long-term course in the presence of obesity, type 2 diabetes, NAFLD and heavy alcohol intake because of the increased risk of liver fibrosis [36]. In addition, it should be considered that chronic kidney disease that is common in older patients and in patients with diabetes could reduce renal clearance of MTX favouring toxicity [37]. Besides, treatment with MTX is not associated with a reduction in diabetes risk [38] or change in usual anti-diabetic therapy [39]. MTX associated with TNF inhibitors does not affect fasting plasma glucose and Hb-A1C when compared to MTX alone [40].

Cyclosporine can induce or worsen arterial hypertension, interfere with fatty acid metabolism inducing dyslipidaemia and hyperuricaemia [41]. Cyclosporine treatment is significantly associated with the risk of developing diabetes [41]. Then, the drug interaction between cyclosporine and statins, which are commonly used for hypercholesterolemia, could potentially induce rabdomiolysis [42]. Consequently, cyclosporine should be used with caution in psoriatic patients with metabolic syndrome. Moreover, the presence of an established renal disease is a contraindication for cyclosporine.

Acitretin is a vitamin A derivative that has been used to treat psoriasis since the early 1980s. Acitretin therapy is associated with increased risk of hypertriglyceridemia and/or hypercholesterolemia [41]. There is a very limited evidence supporting that acitretin may decrease insulin resistance (IR), Homeostasis Model Assessment IR (HOMA-IR) and adipokines production [43].

PUVA and narrowband UVB therapy are not expected to cause significant changes in metabolic parameters [44], including glycaemia.

TNF-alpha antagonists have represented an important advancement in the therapy of psoriasis as well as many others TNF-related conditions, their use being associated with generally rapid improvement of clinical manifestation. As previously mentioned systemic inflammation link psoriasis to type 2 diabetes mellitus, and in this contest biological therapy with TNF-alpha agents would be expected to show beneficial effects on psoriasis comorbidities. Generally, biological therapies do not negatively affect metabolic parameters as conventional treatments can do. Indeed, Solomon DH *et al.* found that patients with rheumatoid arthritis or psoriasis receiving TNF-inhibitors have lower risk of developing diabetes compared with other disease modifying anti-rheumatic drug [38]. The Author speculated this effect being related to the inhibition of TNF-alpha capable of altering insulin sensitivity [38,45]. Clinically meaningful dyslipidaemia has been rarely reported in patients receiving TNF-alpha antagonists. [46].

A body weight gain could occur in patients treated with TNF-α antagonists [47,48]. Weight changes are induced mainly by fat mass gain in patients with psoriasis receiving TNF-alpha antagonists [47]. Ustekinumab is not associated with weight gain in patients with chronic plaque psoriasis [49]. The effects of TNF-α inhibitors therapy on insulin sensitivity are controversial [50,51]. The effects of anti-TNFs on glycaemic parameters and insulin resistance in patients with psoriasis have been addressed mostly in small studies by means of the HOMA and the Quantitative Insulin Sensitivity Check Index (QUICKI], two widely used non-invasive surrogate markers of insulin resistance and sensitivity, respectively. Several studies evaluating the effects of infliximab on insulin resistance and sensitivity have revealed a decrease in resistance and an increase in sensitivity. It is noteworthy that infliximab treatment may have beneficial effects on insulin sensitivity [52,53]. A randomized, double-blind study in 12 psoriatic patients at high risk of developing type 2 diabetes mellitus failed to see a significant effect of a 2-week treatment with etanercept on insulin secretion and sensitivity [54]. In contrast, a 24-week study in 9 patients with stable active plaque psoriasis treated with etanercept found a significant reduction in insulin plasma levels, with a significant improvement in insulin resistance as suggested by the decrease in the HOMA index [55]. In accordance with that, another study in 40 obese subjects with metabolic syndrome suggested that treatment with etanercept improves insulin sensitivity [56]. In addition, there have been isolated reports of diabetic patients with psoriasis or rheumatoid arthritis who developed unpredictable hypoglycaemia during treatment with etanercept [57,58]. There have been no studies investigating the effects of adalimumab on insulin resistance in psoriatic patients. Only one case report describe a patient with psoriasis, psoriatic spondyloarthritis and type 2 diabetes who developed recurrent hyperglycaemia during adalimumab treatment [59]; when the patient switched to etanercept no hyperglycaemic episodes were noted. Moreover, no significant changes in insulin sensitivity or in the levels of fasting blood glucose were seen in 9 patients with psoriasis after 12 weeks of treatment with adalimumab [60].

Ustekinumab has proven to be highly effective in psoriasis, but its effect on insulin resistance has not been investigated. Long-term use of topical corticosteroids may be associated with significant systemic absorption interfering with insulin sensitivity and optimal control of diabetes [61].

Finally, patients with moderate-to-severe psoriasis are candidate to interventions aimed to reduce their cardiovascular risk including hypo-caloric diet, regular physical activity and smoking cessation. Low calorie diet inducing a moderate weight loss (*i.e.* 5 to 10% of body weight) increases the responsiveness of obese patients to any systemic treatments [62–64]. Smoking habit has been associated to onset and worsening of psoriasis, and smoking cessation can positively affect the disease course [65]. Patients with psoriasis exhibit a decreased level of physical activity, possibly for both psychological and physiological reasons [66]. Regular physical activity may lower the risk of incident psoriasis and have also a beneficial effect on the natural course of the disease influencing the response to therapy as well as metabolic comorbidities [62,67].

Concluding remarks

From a clinical prospective, the understanding of patients with moderate-to-severe psoriasis in the context of metabolic comorbidities is very important to ensure that treatment is tailored to meet the specific individual patient needs. Appropriate patient monitoring and counselling, and therapy selection are important to maximize metabolic safety. In particular, it is important that patients with psoriasis are screened and monitored for diabetes. Studies addressing the effects of systemic treatments on glucose homeostasis in patients with psoriasis were very limited, making it not reasonable to give any formal

recommendations on the most appropriate treatment. However, we may suggest not using cyclosporine as a first line treatment in patients with diabetes since it may reduce insulin sensitivity. In contrast, preliminary evidence suggests that TNF-α inhibitors may be beneficial on insulin resistance on long term. Methotrexate does not affect insulin resistance. Finally, non-pharmacological interventions including hypo-caloric diet, regular physical activity and smoking cessation could be recommended in psoriasis patients with metabolic disorders including obesity and diabetes

Conflict of interest disclosure

- Paolo Gisondi has been a consultant and/or speaker for Abbott, Celgene, Janssen, Leo-pharma, Lilly, Merck Sharp and Dohme, Novartis and Pfizer.
- Gabriele Perazzolli has nothing to declare.
- Micol Del Giglio has been a consultant/investigator for Abbott, Janssen, Novartis and Pfizer.

Giampiero Girolomoni has been principal investigator and/or received personal fee from AbbVie, Almirall, Amgen, Boeringher-Ingelheim, Celgene, Dompè, Galderma, GlaxoSmithKline, Eli-Lilly, Hospira, Janssen, Leo Pharma, Merck Serono, Merck Sharp &Dohme, Mundipharma, Novartis, Otsuka, Pfizer and Shiseido.

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