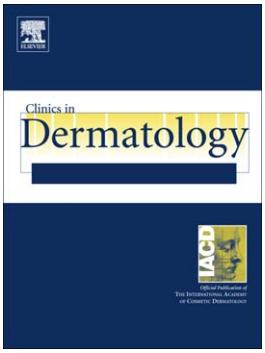

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PII: S0738-081X(17)30159-1
DOI: doi: 10.1016/j.clindermatol.2017.09.005
Reference: CID 7183

To appear in: *Clinics in Dermatology*

Please cite this article as: Gisondi Paolo, Fostini Anna Chiara, Fossà Irene, Girolomoni Giampiero, Targher Giovanni, Psoriasis and the metabolic syndrome, *Clinics in Dermatology* (2017), doi: 10.1016/j.clindermatol.2017.09.005

Psoriasis and the metabolic syndrome

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Running head: psoriasis and metabolic syndrome

Word count: 3816

Tables: 2

Figures: 1

Key words: psoriasis, metabolic syndrome, non-alcoholic fatty liver disease, systemic treatments for psoriasis.

The study was not funded.

Conflicts of interest: Gisondi Paolo served as consultant for AbbVie, Abiogen, Celgene, Eli Lilly, Janssen, Leo Pharma, Merck, Merck Sharp and Dohme, Novartis, Otsuka, Pfizer, and Pierre Fabre. Girolomoni Giampiero served as consultant for AbbVie, Abiogen, Almirall, Amgen, Bayer, Celgene, Eli Lilly, Genzyme, Janssen, Leo Pharma, Merck, Merck Sharp and Dohme, Novartis, Otsuka, Pfizer, Pierre Fabre, Regeneron, Sanofi, and Shiseido.

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Abstract

Chronic plaque psoriasis is an immune-mediated inflammatory skin disease that is strongly associated with the clinical features of the metabolic syndrome (MetS), including abdominal obesity, hypertension, atherogenic dyslipidemia, type 2 diabetes, insulin resistance, and non-alcoholic fatty liver disease. The strength of these associations has been repeatedly confirmed by several observational studies. In particular, the prevalence of MetS in patients with psoriasis ranges from 20 to 50%, with a risk of having MetS that is at least double in psoriatic patients compared to non-psoriatic control individuals. MetS is also more common in patients with severe psoriasis than in those with mild skin disease. Emerging evidence now suggests that psoriasis and MetS share multiple metabolic risk factors, genetic background, and pathogenic pathways. The association between psoriasis and MetS has important clinical implications. Systemic conventional treatments should be used with caution in psoriatic patients with MetS, because they could adversely impact on the coexisting metabolic disorders, especially in the case of their chronic use. Biologics appear to have a different safety profile compared to conventional treatments, so that they are usually more tolerated. Collectively, dermatologists should pay close attention to the early recognition of coexisting metabolic disorders and give appropriate pharmacologica and non-pharmacologic (hypo-caloric diet and regular exercise) recommendations to their patients.

Introduction

Chronic plaque psoriasis is an inflammatory skin disease affecting 2–3% of the general adult population.[1] Psoriasis may have a negative impact on the physical and psychosocial status of patients. About one third of patients have symptoms of arthropathy, which may be very disabling in the more severe cases;[2] moreover, moderate to severe psoriasis is frequently associated with metabolic disorders including obesity, diabetes, dyslipidemia, non-alcoholic fatty liver disease, and MetS.[3] Dermatologists could play an important role in the early recognition and assessment of these comorbidities, selecting appropriate treatments for psoriasis, and giving the correct recommendations on diet and physical activity to patients. We provide an overview on general aspects of MetS and frequency of its association with psoriasis to highlight putative pathogenic links between psoriasis and metabolic disorders, as well as to facilitate the management of psoriasis with pharmacologic treatments and lifestyle interventions.

Definition, epidemiology and principles of management of MetS

MetS is a pathologic condition typically characterized by the combination of various inter-related metabolic disorders that include abdominal obesity, insulin resistance, dysglycemia, atherogenic dyslipidemia, and hypertension. These pathologic conditions co-occur in an individual more often than might be expected by chance. Each component of this syndrome represents a cardiovascular risk factor, and the association of MetS with the increased risk for cardiovascular disease and type 2 diabetes mellitus is now well established.[4-7] At present, however, it is still unclear whether MetS has a single cause, and it appears that it can be precipitated by multiple underlying risk factors. The most important of these underlying risk factors are abdominal obesity and insulin resistance. Other associated conditions can include physical inactivity, aging, hormonal imbalance, and genetic or ethnic predispositions.[4,7] Various diagnostic criteria for MetS have been

proposed by different scientific organizations over the past decade. These clinical definitions for the diagnosis of MetS often share the same risk abnormalities but do differ in the detail and criteria (as summarized in **Table 1**).

It is important to note that many cardiometabolic risk factors that contribute to MetS are acquired and potentially modifiable. The mainstay of management for MetS is lifestyle intervention, which includes a hypocaloric diet, regular physical exercise, smoking cessation, and reduction of daily alcohol intake.[4,8,9] When lifestyle intervention is not sufficient, appropriate pharmacologic interventions to target the individual features of MetS should be used.[4,10] Metformin and glitazones (pioglitazone), by improving hepatic/peripheral insulin sensitivity, are the most widely used pharmacologic agents for the treatment of MetS. Some novel drugs, such as glucagon like peptide-1 (GLP-1) agonists and sodium glucose transporter-2 (SGLT-2) inhibitors, might also be an alternative pharmacologic option, particularly in patients with established type 2 diabetes, because they also may reduce body weight.[10] Lipid-lowering agents, such as statins, are indicated in the presence of dyslipidemia, even in combination with either fibrates or omega-3 fatty acids, principally to treat atherogenic dyslipidaemia (typically characterized by high triglycerides and low HDL-cholesterol levels).[4,10,11] An anti-hypertensive drug therapy with renin-angiotensin-system inhibitors represents a safe and well-tolerated first option in presence of the hypertension.[12] Finally, clinicians should also consider bariatric surgery for patients with severe obesity. Bariatric surgery, as an effective non-pharmacologic treatment to decrease body weight in patients with severe obesity, markedly diminshes all clinical features of MetS (including type 2 diabetes). Although bariatric surgery is undoubtedly effective, limitations to this approach — including complications, patient acceptability, service availability and costs — exist.[13]

Evidence of the association between psoriasis and MetS

Moderate-to-severe psoriasis is often associated with the clinical features of the metabolic disorders[3] (**Figure 1-3**). In particular, two recent meta-analyses have examined the strength of the association between psoriasis and MetS.[3,14] The former meta-analysis included 12 studies, either cross-sectional or case-control, published between 2006 and 2012, all reporting the risk of patients with psoriasis to have MetS compared to the general population by measuring the odds ratios (ORs). Five of the 12 included studies used the NCEP-ATP III revised criteria to diagnose MetS, but the two largest studies used diagnostic codes identified by general practitioners. The main finding of this meta-analysis was the existence of a strong association between psoriasis and MetS with a pooled OR of 2.26 (95% CI, 1.70-3.01).[14]

An update of this meta-analytic study was subsequently published in 2016. It included 17 studies (6 cross-sectional and 11 case-control) published between 2010 and 2016;[3] however, the diagnostic criteria of MetS were quite heterogeneous, including the NCEP-ATP III criteria, the IDF criteria, the South Asian modified-NCEP ATP III criteria or clinical assessments in conjunction with population study questionnaires (self-reporting). Eleven studies reported unadjusted and/or adjusted ORs, whereas six studies provided only prevalence data of MetS. In addition, 14 studies also assessed the association between psoriasis and the individual components of MetS. The main finding of this latter meta-analysis was that the adjusted ORs for the presence of MetS in psoriatic patients ranged between 0.4 and 5.0 and the prevalence of MetS in patients with psoriasis ranged from 20% to 50%.[3] There was a significant association between the severity and extent of psoriasis (Psoriasis Area and Severity Index) and the prevalence of MetS.[15-20] The most comprehensive study included in the meta-analysis showed a significant, graded relationship between psoriasis severity and MetS, with adjusted-ORs of 1.22, 1.56 and

1.98 for mild, moderate and severe psoriasis, respectively.[16] When examining the relationship between psoriasis and the individual components of MetS, a higher prevalence of abdominal obesity (OR range: 2.1-3.8), high blood pressure (OR range: 1.2-2.6), and elevated fasting plasma glucose levels (OR range: 1.2-4.6) were noted in patients with psoriasis when compared to non-psoriatic controls.[3]

Non-alcoholic fatty liver disease (NAFLD) is also recognized as the hepatic manifestation of MetS, and these two pathologic conditions share insulin resistance as a common pathophysiologic mechanism.[21] We found that the prevalence of ultrasound-diagnosed NAFLD was remarkably higher in patients with chronic plaque psoriasis (47% vs. 28%) than in age, sex ,and body mass index-matched control subjects.[22] Similar findings were also reported in a large Dutch study where NAFLD on ultrasound was diagnosed in 46.2% of patients with psoriasis compared with 33.3% of the controls (p=0.005). In addition, psoriasis was found to be closely associated with the presence of NAFLD independently of daily alcohol consumption, smoking history, serum alanine aminotransferase levels, and presence of MetS (adjusted OR 1.7, 95% CI 1.1-2.6).[23] In a recent review, we also confirmed that the prevalence of NAFLD (as diagnosed either by imaging or by histology) was remarkably higher in psoriatic patients (occurring in up to 50% of these patients) than in matched control subjects. Notably, psoriasis was associated with NAFLD even after adjusting for MetS features. Some studies also suggested that psoriatic patients were more likely to have the more advanced forms of NAFLD than non-psoriatic controls and that psoriatic patients with NAFLD have more severe psoriasis than those without NAFLD.[24]

Potential pathogenic mechanisms linking psoriasis and MetS

Detailed discussion of the underlying pathogenic mechanisms linking psoriasis to MetS is beyond the scope of this brief review. To date, the exact underlying pathways that link MetS to psoriasis are complex and not fully understood; however, identification of the pathophysiologic mechanisms linking these two diseases is of clinical importance, because it may offer the promise for novel pharmacologic approaches.

Psoriasis and MetS share multiple inflammatory and cytokine-mediated mechanisms. Both are part of an intriguing network of genetic, clinical, and pathophysiologic features. The mechanisms underlying the association between psoriasis and MetS are multifactorial (involving both genetic and environmental factors) and often overlap with metabolic abnormalities, which frequently coexist in psoriatic patients. In particular, altered transcription in genes biologically significant for psoriasis and metabolic disorders, including renin, cytotoxic T-lymphocyte antigen 4 (CTLA4) and Toll like receptor 3 (TLR3), was identified.[25] We have found a higher prevalence of parental cardiovascular disease and metabolic disorders in patients with psoriasis compared to controls individuals.[26] In general, a chronic pro-inflammatory state typically characterizes both diseases; this pro-inflammatory state may affect each the disease through intertwined and complex mechanisms that are currently under intense investigation.

Psoriasis is a T cell-mediated inflammatory disease characterized by the expansion and activation of Th-1, Th-17 and Th-22 cells, which lead to local over-production of multiple pro-inflammatory mediators by lymphocytes and keratinocytes into the skin of psoriatic patients, including tumor necrosis factor (TNF)-α, interleukin (IL)-6, IL-1, IL- 17, IL-22, IL-23, vascular endothelial growth factor (VEGF), and interferon-γ.[27-29] There is now evidence that these locally overproduced pro-inflammatory mediators can migrate into the systemic circulation, potentially inducing systemic insulin resistance, circulatory endothelial dysfunction, increased oxidative stress, increased angiogenesis, and hypercoagulation, all of which are common features of inflammatory conditions and cardiovascular damage.[30-32]

Abdominal adipose tissue accumulation, which is a key pathogenic factor of MetS, also represents a major source of several proinflammatory cytokines, and adipokines.[33] Activated macrophages and T-cells infiltrate abdominal visceral adipose tissue stimulating adipocytes to release non-esterified fatty acids (NEFA) and secrete a myriad of adipokines and proinflammatory molecules, such as TNF-α, IL-6, leptin, resistin, chemerin, VEGF, procoagulant factors, which can induce a chronic low-grade inflammatory state, thus further contributing to the development of systemic insulin resistance, dysglycaemia, atherogenic dyslipidemia, vascular dysfunction, and NAFLD.[24,33] In addition, accumulating evidence indicates that NAFLD (especially in its more severe forms, i.e. steatohepatitis and advanced fibrosis) exacerbates systemic/hepatic insulin resistance, induces atherogenic dyslipidaemia and releases a series of pro-inflammatory, pro-coagulant, pro-oxidant and pro-fibrogenic mediators (e.g., C-reactive protein, IL-6, fibrinogen, plasminogen activator inhibitor-1, transforming growth factor-β) that play important roles in the pathophysiology of psoriasis. It is conceivable that the release of these mediators from the steatotic and inflamed liver may also adversely influence the severity of psoriasis by increased keratinocyte proliferation, increased inflammation, and up-regulation of various vascular adhesion molecules.[24]

In this context, adiponectin is an adipokine, with anti-inflammatory, insulin-sensitizing and anti-atherogenic properties, whose secretion is decreased by proinflammatory cytokines.[33] Many studies have shown that adiponectin levels are decreased in psoriasis patients,[34,35] and that anti-psoriatic treatments with anti-TNF-α agents may increase adiponectin levels,[36] suggesting that adiponectin might be also partly implicated in the progression of psoriasis. Interestingly, IL-17 production from T-cells, whose role in the pathogenesis of psoriasis has been demonstrated and extensively studied, appears also to be suppressed

by adiponectin.[27,33] A recent experimental study in animal models has suggested the prevention and potential reversibility of MetS after low-dose IL-17 administration.[37]

Systemic treatment of moderate-to-severe psoriasis in patients with MetS

The close association between psoriasis and MetS has important clinical implications. Firstly, all patients with moderate-to-severe psoriasis should have the following variables assessed at baseline and, periodically afterwards, based on the clinical judgment: blood pressure, body mass index, waist circumference, smoking status, and average consumption of alcoholic beverage. In addition, it is advisable to monitor selected biochemical variables, including serum lipids, uric acid, liver enzymes, and fasting glucose levels. Dermatologists should consider that some drugs specific for individual component of MetS might influence psoriasis course. Pioglitazone seems to exert some positive effects on psoriasis outcome, but further study are necessary to define its role.[38] A number of studies have reported a possible psoriasis exacerbation and exposure to antihypertensive drugs, such as beta-blockers, calcium-channel blockers, and ACE inhibitors, although data are controversial.[39,40] Some studies showed a decreased risk for psoriasis in patients under treatment with statins, in particular atorvastatin and simvastatin;[41,42] however, high quality randomized studies have not been conducted.[43]

Dermatologists should be aware of the potential adverse impacts of systemic treatments on metabolic disorders (as summarized in **Table 2**). Indeed, Systemic conventional treatments should be used with caution in psoriatic patients with features of MetS, because they could significantly interfere with metabolic parameters, especially in the case of their continuous and prolonged use.[44] For example, cyclosporine may have a negative impact on metabolic parameters, including serum lipids and glucose as well as it can induce or worsening arterial hypertension. In a large observational study on psoriatic

patients enrolled in the Psocare registry (n=10550), we found that the risk of developing arterial hypertension, diabetes, and hypercholesterolaemia was increased for patients receiving cyclosporine compared to those treated with etanercept after 16-week treatment (OR 3.31 95% CI 2.1–5.3, p<0.001; OR 2.88 95% CI 1.0–8.3, p=0.05; OR 1.34 95% CI 1.0–1.8, p=0.05, respectively).[45]

The potentially diabetogenic effect of treatment with cyclosporine might be related to its inhibition of insulin secretion from pancreatic beta cells, an effect that may be even more pronounced in obese psoriatic patients.[46] Cyclosporine might also induce a renal toxicity that is generally closely related to the daily dose and treatment duration.[45] The presence of established chronic kidney disease (CKD) is a contraindication for cyclosporine use. Cyclosporine might also interact with use of statins, potentially inducing rhabdomyolysis.[47] As previously discussed, NAFLD is commonly associated with both MetS and psoriasis.

The risk of methotrexate-induced liver toxicity is increased in the presence of NAFLD, excessive alcohol consumption, obesity or diabetes.[48] Whether methotrexate could also induce kidney damage is controversial. A study conducted on 28 psoriatic patients treated with low-dose methotrexate (5-25 mg/week) showed the development of kidney failure (defined as glomerular filtration rate ≤30 mL/min/1.73 m^2) in 13 patients (46%), 6 of whom presented with acute kidney failure, while 7 had further deterioration of previously kidney dysfunction.[49] Another study evaluating the impact of the severity of psoriasis, comorbidities and concomitant drugs on the risk of CKD in psoriatic patients, showed no association between methotrexate use and CKD development.[50] Renal clearance is the main pathway for methotrexate elimination; therefore, the administered dose of methotrexate should be lowered according to the reduction of kidney function, in order to avoid a possible rising in serum methotrexate levels.

Similar to cyclosporine, acitretin could induce either hypertriglyceridemia and/or hypercholesterolemia.[51] Few data exist about the influence of acitretin on glucose tolerance. A 3-month treatment with acitretin decreased biomarkers of insulin resistance and adipokines in psoriatic patients (n=35) in a non-controlled clinical trial.[52] In contrast, a 1-month treatment with acitretin induced a mild, transient reduction of insulin sensitivity in a small sample of psoriatic patients (n=10).[53] Generally, biologic therapies do not negatively affect metabolic, liver, or renal function parameters. An improvement in the AST/ALT ratio, C-reactive protein levels, and insulin resistance markers was reported in 89 overweight patients with psoriasis and NAFLD receiving a 24-week treatment with etanercept.[54] A body weight gain may occur in patients treated with anti-TNF-α antagonists,[55-57] mainly due to increased body fat mass. The anti-IL 12/23 monoclonal antibody ustekinumab and the anti-IL-17 secukinumab do not increase significantly body weight in patients with psoriasis.[48,57,58]

The effects of TNF-α antagonists on serum lipid profiles are unclear. Clinically significant dyslipidemia has been occasionally reported in some patients receiving TNF-α antagonists, but this is not a common issue in clinical practice, although plasma lipids monitoring would be indicated in psoriatic patients with metabolic disorders receiving TNF-α antagonists.[45]

The long-term effects of anti-TNF-α treatment on insulin sensitivity are also controversial. Preliminary evidence shows that treatment with etanercept may improve both plasma glucose levels and insulin resistance indices,[59] and that patients with psoriasis or rheumatoid arthritis, receiving TNF-α antagonists, exhibit a lower risk of new-onset type 2 diabetes compared with those receiving other non-biologic disease-modifying anti-rheumatic drugs;[60] however, a randomized, double-blind, study in 12 psoriatic patients at high risk of developing type 2 diabetes did not find any significant effect of a 2-week

treatment with etanercept on insulin secretion and sensitivity.[61] No significant changes both in insulin sensitivity and in fasting plasma glucose levels were observed in 9 psoriatic patients after a 12-week treatment with adalimumab.[62] Effects of ustekinumab or secukinumab on insulin resistance have not been yet investigated. Phototherapy is not expected to induce significant changes in metabolic parameters.[44]

Apremilast is a novel oral, small molecule phosphodiesterase-4 inhibitor, approved for the treatment of chronic plaque psoriasis and psoriatic arthritis. Data from clinical trials show a good safety profile of apremilast on metabolic parameters.[63,64] Abnormal laboratory test results in apremilast-treated patients were rare, transient, and not clinically significant. The dose of apremilast should be reduced to 30 mg once daily in patients with severe CKD. Treatment with apremilast has been also associated with weight loss. The mean observed weight loss in patients treated for up to 52 weeks with apremilast was ~2 kg. A total of 14.3% of patients receiving apremilast had observed weight loss between 5-10% while 5.7% of those receiving apremilast had observed weight loss >10%.[65]

Effects of diet on the severity of chronic plaque psoriasis

The positive impact of body weight reduction in patients with MetS, diabetes, or cardiovascular disease has been well documented.[66] Given the high prevalence of MetS in patients with psoriasis, dermatologists should play a role in the early recognition and assessment of this pathologic condition and treat these patients with the appropriate recommendations on diet and physical activity (and in some cases, also treat them with appropriate pharmacologic interventions). To date, growing evidence indicates that weight loss may be useful in diminshing the severity of psoriasis.[67] In particular, a moderate weight reduction (i.e., about 5% to 10% of body weight) may increase the responsiveness to systemic treatments, including cyclosporine and the biologics, in obese patients.[68-71]

Weight loss intervention could be positively associated with regular physical activity, which is usually poor in psoriatic patients possibly for both physiologic and psychologil reasons.[72] In addition, spontaneous clearing of psoriasis has been also described in severely obese patients after bariatric surgery.[73] We suggest that bariatric surgery should not be discouraged in severely obese patients; however, out of the setting of clinical trials, obese patients may be reluctant to undergo a diet regimen change or to maintain body weight reduction on long term.[74] Changing dietary behaviour is a complex task and changes may not be stable over time.

Conclusions

The association between psoriasis and MetS is clinically relevant, because MetS is a risk factor for cardiovascular diseases. The cardiovascular risk of patients with psoriasis is increased.[75,76] Whether psoriasis itself is an independent cardiovascular risk factor or this is related to the concomitance of many risk factors is open to discussion The link between skin inflammation and metabolic abnormalities is not fully understood; however, accumulating evidences suggest a partially shared pathogenesis, based on the systemic effect of chronic inflammation, genetic background, insulin resistance, and an unhealthy lifestyle.

Dermatologists could play a pivotal role in early identification and prompt referral for assessment and treatment of the individual components of MetS in psoriatic patients. Some drug therapies used in treating MetS may negatively influence the course of psoriasis and vice versa, ie treatment for psoriasis may worsen some metabolic parameters. Individual awareness of a cardiovascular risk and lifestyle education are essential in these patients. Laboratory screening, blood pressure, BMI, and waist circumference measurement are procedures that should be routinely performed during a

dermatologic consultation in order to obtain a complete clinical overview and to ensure that treatment of psoriasis is tailored to meet individual patient needs.[77]

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Legend to the Figure

Figure 1. Chronic plaque psoriasis in a patient with abdominal obesity and metabolic syndrome.

Figure 2. A man with MetS and chronic plaque psoriasis pn the thorax (A) and the abdomen (B)

Figure 3. A woman with MetS and diffuse chronic plaque psoriasis on the back

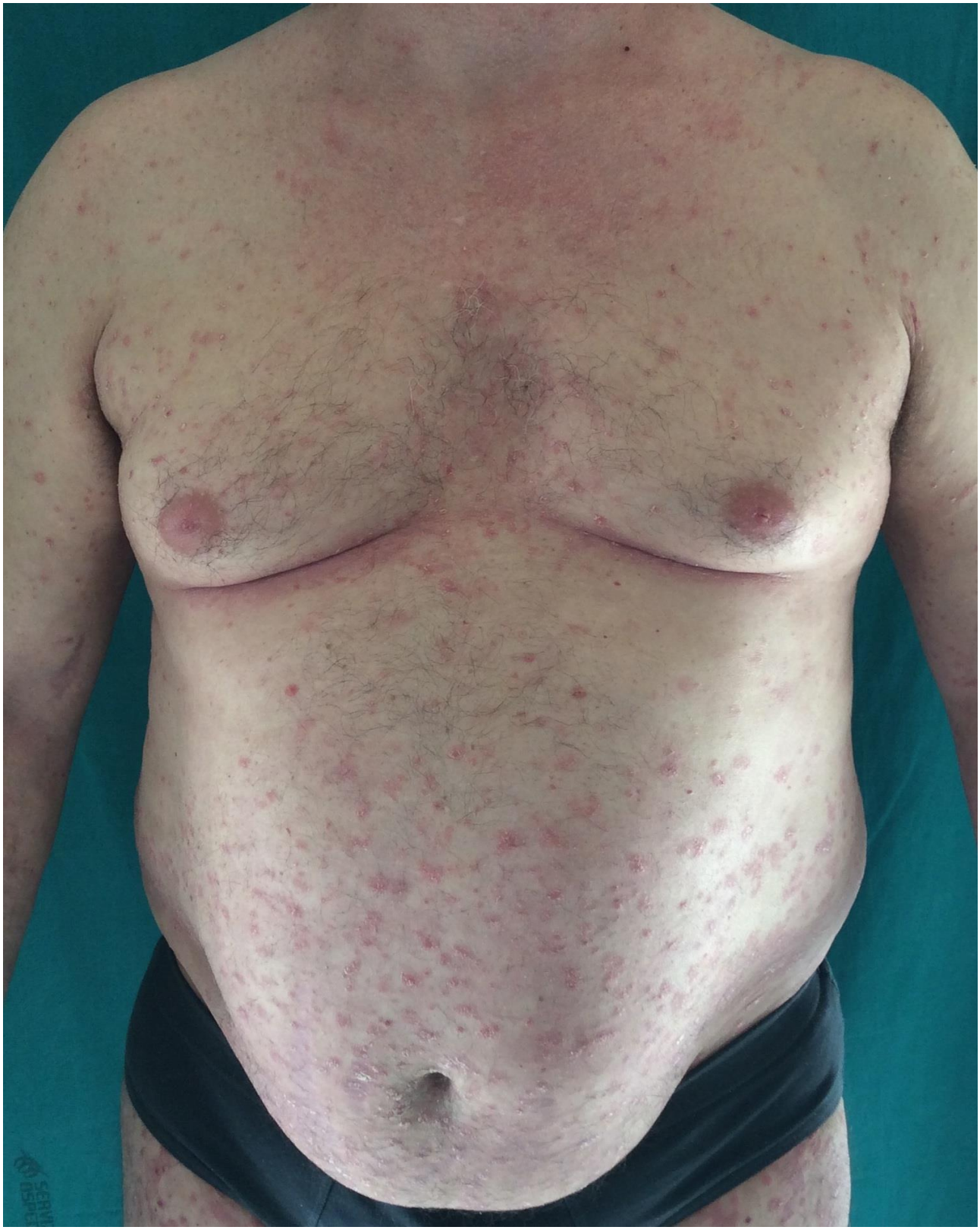

Figure 1

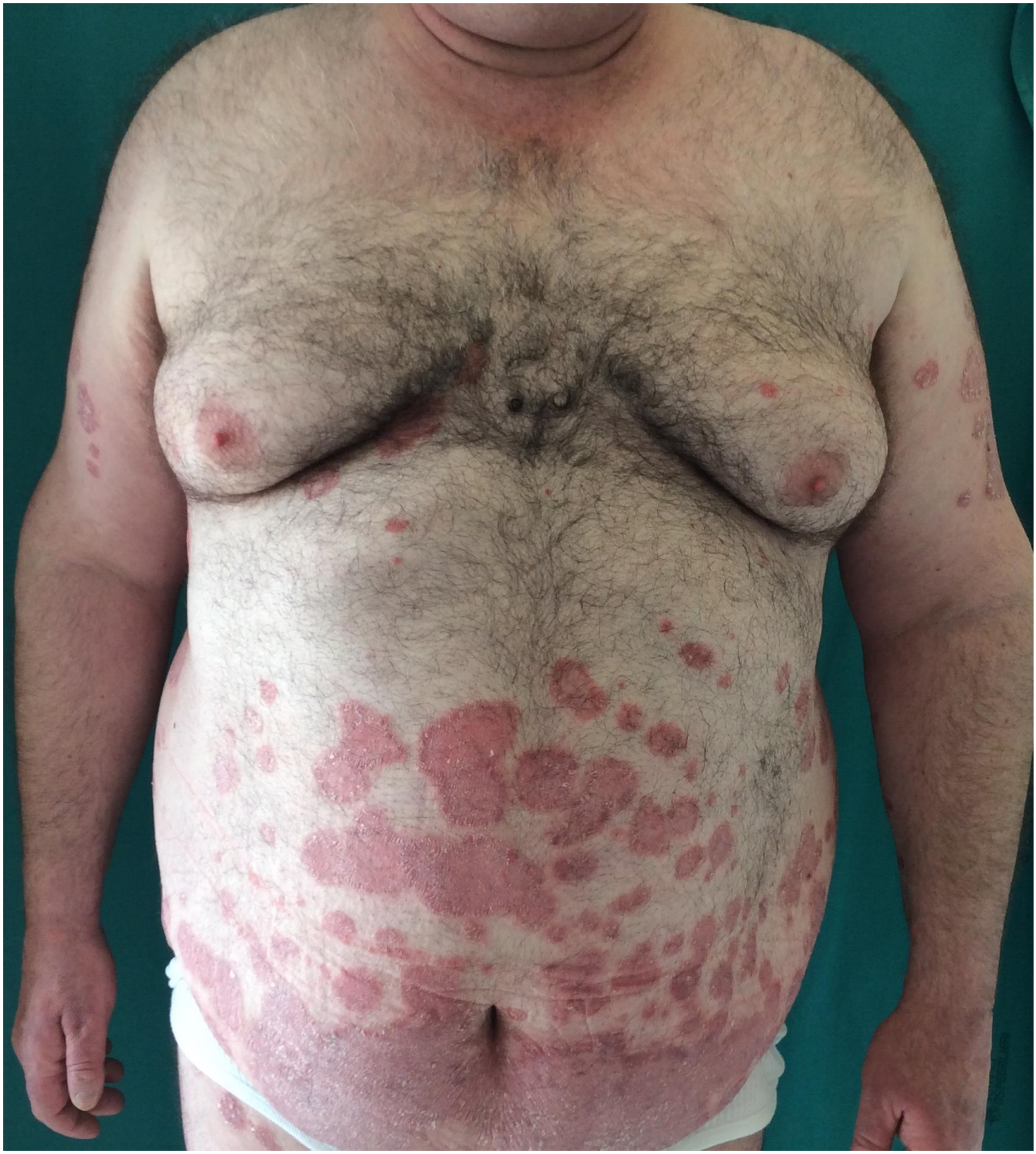

Figure 2A

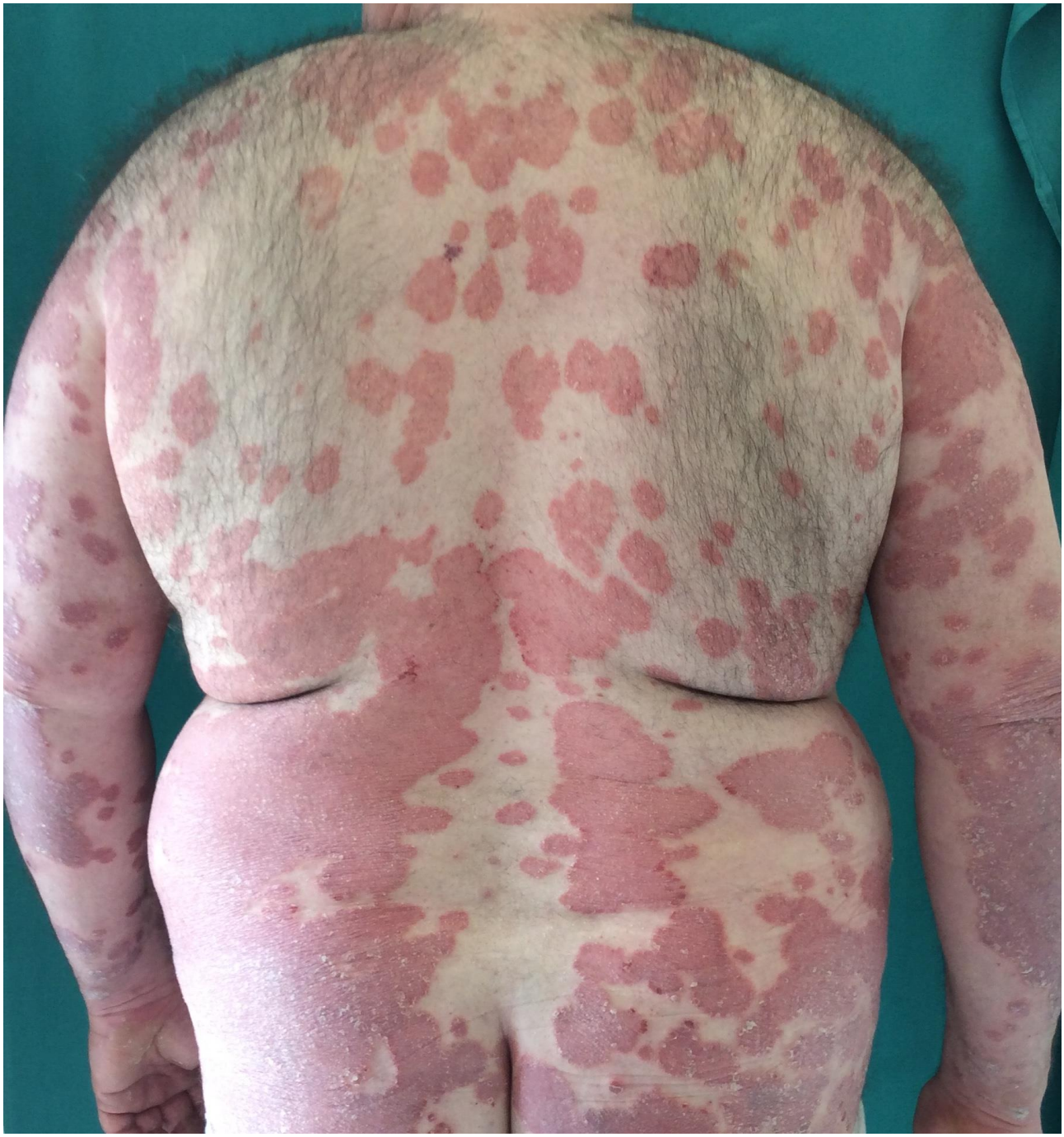

Figure 2B

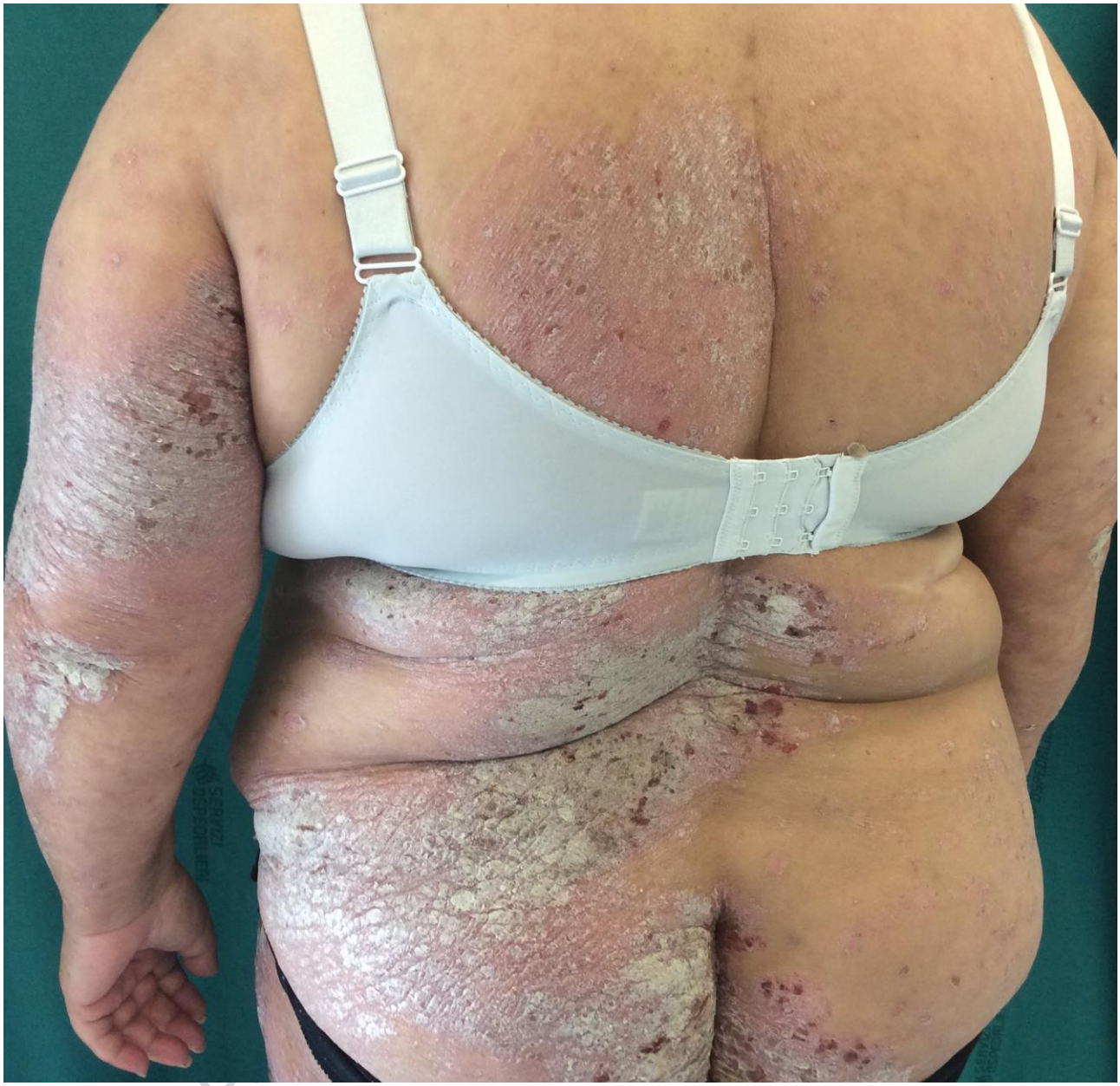

Figure 3

Table 1. Differences between the major criteria for the clinical diagnosis of the metabolic syndrome

WHO, 1998	Type 2 diabetes or impaired glucose tolerance or impaired fasting glycaemia or insulin resistance *and* two or more of the following: - BMI ≥30 kg/m^2 or waist-to-hip ratio >0.90 (men) or >0.85 (women) - Triglycerides ≥1.7 mmol/l (≥150 mg/dl) and/or HDL <0.9 mmol/l (<35 mg/dl) (men) and <1.0 mmol/l (<40 mg/dl) (women) - Blood pressure ≥160/90 mmHg - Albumin excretion rate >20 mcg/min
NCEP-ATP III, 2001	Any three or more of the following 5 risk abnormalities: - Waist circumference ≥102 cm (men) or ≥88 cm (women) - Triglycerides ≥1.7 mmol/l (≥150 mg/dl) - HDL cholesterol <1.0 mmol/l (<40 mg/dl) (men) or <1.3 mmol/l (<50 mg/dl) (women) - Blood pressure ≥130/85 mmHg - Fasting plasma glucose ≥6.1 mmol/l (≥110 mg/dl)
AHA/NHLBI, 2005 (revised ATP III criteria)	Any three or more of the following 5 risk abnormalities: - Waist circumference ≥102 cm (men) or ≥88 cm (women) - Triglycerides ≥1.7 mmol/l (≥150 mg/dl) or drug treatment - HDL cholesterol <1.0 mmol/l (<40 mg/dl) (men) or <1.3 mmol/l (<50 mg/dl) (women) or drug treatment - Blood pressure ≥130/85 mmHg or drug treatment - Fasting plasma glucose ≥5.6 mmol/l (≥100 mg/dl) or drug treatment
International Diabetes Federation (IDF), 2005	Increased waist circumference with population-specific and country-specific criteria (in Europid >94 cm for men or >80 cm for women) *plus* any two or more of the following 4 risk abnormalities: - Triglycerides ≥1.7 mmol/l (≥150 mg/dl) or drug treatment - HDL cholesterol <1.0 mmol/l (<40 mg/dl) (men) or <1.3 mmol/l (<50 mg/dl) (women) or drug treatment - Blood pressure ≥130/85 mmHg or drug treatment - Fasting plasma glucose ≥5.6 mmol/l (≥100 mg/dl) or previously diagnosed type 2 diabetes
IDF/NHBLI/AHA/World Heart Federation/International Atherosclerosis Society/International Association for the Study of Obesity, 2009	Any three or more of the following 5 risk abnormalities: - Increased waist circumference with population-specific and country-specific criteria (in Europid >94 cm for men or >80 cm for women) - Triglycerides ≥1.7 mmol/l (≥150 mg/dl) or drug treatment - HDL cholesterol <1.0 mmol/l (<40 mg/dl) (men) or <1.3 mmol/l (<50 mg/dl) (women) or drug treatment - Blood pressure ≥130/85 mm Hg or drug treatment - Fasting plasma glucose ≥5.6 mmol/l (≥100 mg/dl) or drug treatment

Table 2. Effects of systemic treatments for psoriasis on the components of the metabolic syndrome

	MTX	CsA	Acitretin	Apremilast	Anti-TNF-α	IL-17 inhibitors	Anti-IL12/23
Atherogenic dyslipidaemia	Neutral	Worsening	Worsening	Neutral	Neutral	Neutral	Neutral
Arterial hypertension	Neutral	Worsening	Neutral	Neutral	Neutral	Neutral	Neutral
Obesity	Neutral	Neutral	Neutral	Neutral	Neutral/worsening	Neutral	Neutral
Glucose intolerance/Diabetes	Neutral	Worsening	Neutral	Neutral	Neutral	Neutral	Neutral

MTX, methotrexate; CsA, cyclosporine