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# PSORIASIS: THE LINK WITH THE METABOLIC SYNDROME AND CARDIOVASCULAR DISEASES. A SYSTEMATIC REVIEW

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**Abstract**

The aim of the present study was to conduct a systematic review of psoriasis role both in metabolic syndrome and in cardiovascular diseases. Relevant studies have been identified by computerised studies research on PubMed.

The studies examined included clinical studies, meta-analysis, reviews and guidelines and showed that psoriasis, metabolic syndrome and cardiovascular diseases are closely related. In this study, I will explain how this happens.

**Keywords**: *psoriasis, metabolic syndrome, cardiovascular diseases, nutrition.*

## Introduction

Eating habits in industrialized nations promote diets rich in fact, salt and sugar with an excessive caloric intake that causes the so-called "diseases of progress". Psoriasis is one of them.

In fact psoriasis is a systemic and chronic inflammatory disorder of the skin (1) that causes lesions such as erythema and desquamation on the whole body but in particular on the elbows, knees, scalp and lumbar region of the back (2). Psoriasis is a result of a quick change of skin cells (3) and it affects approximately 2–5% of the population (4) and approximately 125 million people worldwide (5). The pathogenesis of psoriasis is currently under investigation through studies aimed at identifying the genetic susceptibility of psoriasis in order to detect new targets for systemic therapy (6). Indeed, the exact cause of psoriasis is not fully understood, but according to the researchers, it is the result of several factors such as genetics, lifestyle and the immune system (7). As regards the genetic predisposition, some studies have shown a strong genetic association between the HLA-Cw6 allele and psoriasis in various breeds and revealed a concordance of 35-72% in monozygotic twins, compared to a concordance of 12-30% in dizygotic twins (8). As regard lifestyle, the researchers showed that smoking and alcohol are a risk factors for psoriasis (9) and psychological stress have a significant role in triggering psoriasis (10). As regard immune system, the literature showed that the immune system of psoriasis suffers is hyperactive. It creates inflammation within the body, causing spots on the skin. Healthier than normal cells are produced. Those excess cells are pushed onto the skin surface too quickly. Normally, skin cells take about a month to flow through the body while, with psoriasis, it takes day (11). Furthermore, some investigations have led to a renewed understanding of the paths Th-17 and Th-1 involved in Th-1 paths involved in the development of psoriasis (12). In particular, the Th-1 path involving dysregulation and activation of Th-1 inflammatory cells is thought to contribute to obesity and insulin resistance, which may increase the risk of cardiovascular disease (13).

There are different types of psoriasis: (a) psoriasis vulgaris is characterized by patches covered with grey scales whose most frequent locations are the limbs, trunk and scalp, sometimes even the nails. The plates are raised on the skin and have variable dimensions: they can extend for a few centimetres, but it is not uncommon for them to extend very widely (several tens of centimetres). In rare cases they give itching (14); (b) gutted psoriasis is more frequent in children and young people, it occurs with small patches that can affect both the trunk and limbs (15); (c) palm-plantar psoriasis affects almost exclusively the hands and feet but can also affect the nails causing pain in the fingertips and limiting the functionality of the hand (16); (d) pustular psoriasis is a very rare, but particularly severe form characterized by the presence of pustules that can extend to the entire surface of the body (17).

## Methods

In this article we reviewed available literature with a systematic approach. Relevant studies have been identified by computerised studies research on PubMed. We used psoriasis, metabolic syndrome and cardiovascular diseases as keywords. We included in my research reviews, clinical studies, meta-analysis, reviews and guidelines.

## Psoriasis and comorbidity

Psoriasis has a significant impact on the quality of life, both physical and emotional, comparable to other major diseases (18). Dermatologists have shown that it is a disorder with important implications beyond the skin, for example diabetes (19), hypertension (20), dyslipidemia (21), gastrointestinal diseases (22), chronic kidney disease (23), cancer (24), infections (25; 26) mood diseases (27), chronic obstructive pulmonary (28), peptic ulcer (29), sexual dysfunction (30), and obstructive sleep apnea (31). Epidemiological and scientific studies on psoriasis have shown that psoriasis is significantly associated with cardiovascular disease (32) and metabolic syndrome (33), which suggests

that chronic skin inflammation can extend systemic inflammation beyond the skin.

**Psoriasis and metabolic syndrome**

The metabolic syndrome, such as type 2 diabetes and obesity, is composed of an assortment of metabolic abnormalities that increase the risk of developing cardiovascular disease. According to the criteria of National Treatment Cholesterol Education Program Panel for adults III (NCEP ATP III), the metabolic syndrome is diagnosed when : 1) the waist circumference is 102 cm or more in men or women 88 cm; 2) triglycerides 150 mg/dL or more (or to receive drug therapy for hypertriglyceridemia); 3) high-density lipoprotein-cholesterol complex (HDL-C) less than 40 mg/dL in men or less than 50 mg/dL in women (or receiving drug therapy for the reduction of HDL-C); 4) blood pressure 130/85 mm Hg or higher (or on medication for hypertension), 5) glucose on an empty stomach of 100 mg/dL or more (or on medication for hyperglycemia). The prevalence of metabolic syndrome is 35% in the United States (34) and is associated with a higher risk of cardiovascular mortality (35, 36). Although the connection between psoriasis and metabolic syndrome is known, what is trying to be discovered is the precise mechanism of that connection, that is, precise pathogen mechanisms. It is considered that a chronic inflammation and inflammatory mediators are the initiators for the development of metabolic syndrome.

Salihbegovic and colleagues (37) conducted a study of 70 patients (36 males and 34 females) with psoriasis over the age of 18. The criteria the NCEP ATP III were used to diagnose the metabolic syndrome, while the area of psoriasis and the severity index (PASI) were used to detect the severity and spread of psoriasis. The results showed that psoriasis is linked to metabolic syndrome and that there is a positive correlation between the severity of psoriasis and frequency of metabolic syndrome. Instead, Henseler and Christophers (38) conducted a study in which they showed that (50) obesity and type 2 diabetes mellitus are significantly associated with psoriasis in many countries (e.g., Italy, Denmark, Israel, Germany and United Kingdom) and that these results were consistent also with those of patients with psoriasis in eastern countries (e.g., Thailand, Japan, and Korea). Neimann and colleagues (39) have also shown that psoriasis is also comorbid with other components of the metabolic syndrome, such as dyslipidaemia and hypertension. Moreover, patients with severe psoriasis had a greater prevalence of diabetes (39) and obesity (39) than those with mild psoriasis. Furthermore, it is interesting to note that dipeptidyl peptidase-4 inhibitors, a new class of antidiabetic agents, have been shown to improve skin symptoms in some patients with psoriasis (40). Since the topical application of vitamin D3 is effective in the treatment of psoriasis, the level of vitamin D3 (41) and bone mineral density (42) have been evaluated. Patients with low bone mineral density showed a statistically significant mean duration of psoriasis longer than those with better bone density (42).

Also Xin Yu Gui and colleagues (43) conducted a study on 859 psoriasis patients and 1.718 controls. The authors evaluated the prevalence of metabolic syndrome in Chinese patients with psoriasis and controls and they demonstrated that the prevalence of metabolic syndrome is higher in Chinese psoriasis population, which can promote cardiovascular problems.

Cenk Akcali and colleagues (44) found that metabolic syndrome was more frequent in the group of patients with psoriasis than in the control group. In terms of parameters of the metabolic syndrome, hypertension alone was more frequent in patients with psoriasis than in controls. There was no statistically significant difference between patient and control groups for obesity, hypertriglyceridemia, HDL levels or hyperglycemia. Fibrinogen levels were increased and adiponectin levels decreased in the psoriasis group. No difference between groups in homocysteine levels was found.

Finally, Vachatova and colleagues (45) studied the role of selected inflammatory and anti-inflammatory serum markers of psoriatic patients in the pathogenesis of metabolic syndrome and psoriasis, comparing the psoriatic patient group and the control group. The analysis revealed significantly

higher levels of CRP, Lp-PLA2 , leptin and resistance in psoriatic patients in patients with metabolic syndrome compared to the control group. The level of adiponectin was significantly lower in patients with metabolic syndrome and the level of Lp-PLA2 was significantly higher in the group of patients without metabolic syndrome than in controls without metabolic syndrome, demonstrating that the observed inflammatory and anti-inflammatory markers (CRP, adiponectin, leptin, resistance and Lp-PLA2) are involved in both the pathogenesis of metabolic syndrome and psoriasis.

## Psoriasis and cardiovascular diseases

Some studies have reported that psoriasis and cardiovascular diseases are closely related.

Cardiovascular diseases are pathological processes that affect the arterial system as a whole and determine the progressive narrowing of the arteries until they are completely obstructed (46) Therefore, should be considered a single disease that manifests itself clinically in different ways depending on which arterial district is affected. It can have multiple localizations and can be responsible for several diseases: if it affects the coronary arteries it can cause angina pectoris and myocardial infarction, if it affects the cerebrovascular system, for example the carotids, it can cause stroke, if it involves the peripheral arteries of the lower limbs it can be responsible for the so-called "intermittent claudication", like the pain during walking (46).

It is known that patients with psoriasis are more exposed to the risk of cardiovascular disease, particularly those with severe psoriasis at an early age. A study conducted in 2006 on the American population showed that psoriasis is associated with an increased risk of myocardial infarction regardless of classic risk factors such as smoking, diabetes, dyslipidaemia and BMI (47).

Still, a hospital study conducted in Japan analyzed the prevalence of hypertension, dyslipidaemia, psoriasis, coronary heart disease and diabetes mellitus in 113,065 patients, showing that psoriasis was an independent variable associated with coronary heart disease (48). Furthermore, Kothiwala and colleagues conducted a transversal study in hospital on 140 patients with psoriasis and 140 controls at which BMI, blood pressure and screw circumference were measured and both lipid profile and fasting blood sugar level were estimated. The authors highlighted that there was a significantly higher prevalence of subclinical atherosclerosis in patients with psoriasis, thus increasing the risk of cardiovascular disease (49).

Researchers have shown that inflammatory events occurring in the bloodstream as a result of psoriasis injuries can lead to cardiovascular problems and atherosclerosis and that, as a result, by decreasing the inflammatory load, the risk of onset of cardiovascular disease may decrease (50).

Currently, seem to be no specific studies assessing the impact of therapy on cardiovascular risk.

conferred by psoriasis, but there are only studies that have evaluated the association between the use of immunobiological and the incidence of cardiovascular events in patients with psoriasis (51).

Recent literature (51) shows that a possible cause of problems when analyzing the effects of antipsoriatic therapies on comorbidities is the relationship between anti- IL-12/23 immunobiological and possible serious cardiovascular diseases events, leading to the suspension of the study with briakinumab and briakinumab and considerable concern in the prescription of ustekinumab. Again, a study conducted on 2400 patients with psoriasis showed that patients treated with immunobiological agents or MTX, particularly with etanercept showed a significant reduction in cardiovascular risk. (52) .

Ryan et al. evaluated the association between biological therapy for skin psoriasis and cardiovascular disease. The study selected 22 randomized, double-blind, placebo-organized events, with the specific focus of evaluating, among other things, the development of MACE. data showed that when the biologics were divided between anti-TNF-α and anti-IL-12/23, one patient presented MACE in the group receiving anti-TNF-α with respect to one patient in the placebo group,

while 10 patients presented MACE in the group receiving anti-IL12 / 23 and none in the placebo group (53).

The importance of nutrition among psoriasis to metabolic syndrome and cardiovascular diseases. Numerous studies have reported that in a high number of patients, psoriasis is associated with obesity. Recent studies have shown that the prototype of the western nutrition is among the risk factors involved in the psoriasis pathogenesis. In particular, Barrea and collaborators (53) conducted a study aimed to assessing the differences in diet type, anthropometric measurements and cardiovascular risk profile in 41 patients with psoriasis and 41 controls balanced to age and BMI, observing the association between the diet type followed and the severity of psoriasis in patients with psoriasis. The results showed differences in the diet type followed between patients with psoriasis and control group and that these differences were associated with both the severity of psoriasis and the cardio-metabolic risk. In addition, the fatty liver index (FLI) was an early indicator of cardo-metabolic risk in patients with psoriasis and dietary monounsaturated fatty acids (MUFA) were major predictors of the severity of psoriasis. In addition, the association between metabolic syndrome and psoriasis seemed to be independent of the intake of MUFA highlighted that low consumption of MUFA could act as a possible additional mechanism aimed at increasing the site of inflammation of patients with psoriasis.

The ketogenic diet is a nutritional regimen characterized by a reduction in carbohydrates and a relative increase in protein and fat. Recent scientific studies have shown the therapeutic potential of ketogenic diets in many diseases, such as diabetes, polycystic ovary syndrome, acne, neurological diseases, cancer, and the amelioration of respiratory and cardiovascular disease risk factors. A very low-calorie ketogenic diet (VLCKD) has been associated with a significant reduction in visceral adipose tissue and ketone bodies that likely possess anti-inflammatory properties. A 2015 clinical case by Castaldo et al. reported a patient treated with biological therapy who restored his response to the systemic treatment of psoriasis after a 4-week intensive ketogenic low calorie diet based on protein without carbohydrates [54].

This nutritional therapy, that led to rapid weight loss, resulted in a reduction of the inflammation associated with the loss of visceral adipose tissue (which is particularly characteristic of psoriasis patients), responsible for insulin resistance and other metabolic complications.

The same authors evaluated the efficacy of an aggressive weight-loss (WL) program with a ketogenic induction phase as first-line treatment for chronic plaque psoriasis. They reported that in drug-naïve adult overweight patients with stable chronic plaque psoriasis, the ketogenic protocol named Oloproteic Diet appeared to be an effective first-line strategy to reduce disease severity. [55] In another clinical study, 30 psoriasis patients were subjected to a ketogenic nutritional regimen and monitored for 4 weeks by evaluating the clinical data, biochemical and clinical parameters, NMR metabolomic profile, and IL-2, IL-1β, TNF-α, IFN-γ, and IL-4 concentrations before and after the nutritional regimen. The resuls showed that a VLCKD can be considered a successful strategy and therapeutic option to gain an improvement in psoriasis-related dysmetabolism, with significant correction of the full metabolic and inflammatory status. [56]

## Discussion

Although the mechanisms underlying the pathogenesis of psoriasis are not yet fully understood, recent literature has focused on the role of the cutaneous-to-systemic expansion of the inflammatory process, showed that psoriasis may be associated with cardiovascular disease (32) and metabolic syndrome. Psoriasis is an inflammatory disease that not only affects the skin but can also cause metabolic problems and cardiovascular disease. This systematic review shows that the literature on the subject confirms the prevalence of metabolic syndrome patients with psoriasis and that patients with psoriasis are more exposed to the risk of cardiovascular disease. Finally, a study that concurrently considered the psoriasis role in metabolic syndrome and cardiovascular diseases (53), further confirmed that there is a prevalence of

metabolic syndrome and a higher risk of developing cardiovascular diseases in patients with severe psoriasis.

Awareness of these links is crucial to progress in understanding and treating psoriasis and associated comorbidities.

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