

PSORIASIS AND ASSOCIATED CARDIO-METABOLIC COMORBIDITIES

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Abstract: Psoriasis is a chronic inflammatory skin disease with possible systemic damage, more commonly at joints level. Psoriasis associated cardio-metabolic comorbidities recognize the inflammation as the common link in the pathogenesis of this disease. Purpose: Analysis of cardio-metabolic comorbidities associated with psoriasis in a group of patients. Methods: We conducted a retrospective study on 270 patients with psoriasis in the Dermatology Clinic of Sibiu, for a period of 3 years and we identified the cardio-metabolic comorbidities associated with psoriasis. Results: The most common metabolic comorbidities identified in our group of patients were: overweight - 23.33%, obesity - 24.07% of cases, hypercholesterolemia - 32.59%, hyperlipidemia - 26.66%, type 2 diabetes in 25, 18% of the cases. Cardiovascular comorbidities identified in our study were: hypertension - 43.33%, ischemic heart disease - 32.96%, and other cardiovascular diseases in 27.41% of cases. Conclusions: cardio-metabolic pathology associated with psoriasis should be recognized and treated early in order to reduce the complications related to this disease.

INTRODUCTION

Psoriasis is a chronic inflammatory disease of still unknown aetiology, with a prevalence of 1-3% (1), with predominantly cutaneous manifestations under the form of plaques and infiltrative erythematous-squamous placards, but also with systemic damage, especially at joints level. Pathogenically speaking, the involvement of cell-mediated immunity is involved, which led to the introduction of new biologic therapies in psoriasis. An important part in the disease occurrence is played by the genetic factors (LCE3B LCE3C gene deletions, human leukocyte antigen alleles Cw6, B13, Bw17, Bw37, Bw57, DR7).(2)

The occurrence of the disease and of the eruptive episodes is triggered by the environmental factors (stress, streptococcal and staphylococcal bacterial infections, human immunodeficiency virus infection, candidiasis, tobacco and alcohol abuse, trauma, exposure to cold and some medications). Also, the immunological factors involved, through the disruption of immunity mediated by T lymphocytes and increased proinflammatory cytokines and Tumour Necrosis Factor (TNF) - α are leading to the onset of inflammation in the psoriatic disease.

Recent research highlights the aggravating role in psoriasis comorbidities as independent risk factors in disease occurrence. Diabetes mellitus (DM), obesity, dyslipidemia and hypertension (HTA), diseases grouped within the metabolic syndrome are frequently associated with the psoriatic disease and adversely affect both the skin disease and the respective diseases.(1)

Currently, in Romania there is an increasing trend of the incidence of both cardiovascular diseases and those metabolic. In addition, the prevalence of obesity has increased alarmingly, which is reflected in the prevalence of hypertension, type 2 DM, dyslipidemia and the metabolic syndrome.

The inflammatory mechanisms which are common to those producing the proinflammatory cytokines could represent

the common pathogenic link in the development of the cardio-metabolic comorbidities associated with psoriasis. The chronic inflammation mediated by Th1 lymphocytes and by the pro-inflammatory cytokines is a common element, both in the pathogenesis of psoriasis, and of the cardiovascular diseases, atherosclerosis, metabolic syndrome, obesity and diabetes.(3,4)

The patients with psoriasis require careful attention and further investigations in this regard for the early detection of these associated comorbidities, through their interrelations with the cutaneous disease. The two groups of pathologies, when coexisting may worsen each other, both because of the chronic inflammation and because of the possible side effects of the followed treatment. Psoriasis *per se*, as inflammatory disease significantly alters the quality of life of patients, and the cardio-metabolic comorbidities association reduces the life expectancy of these patients by 4 years.(5)

The early diagnosis and treatment of cardio-metabolic comorbidities associated with the psoriatic disease would allow the improvement of the quality of life on one part, and on long-term, it could favourably influence morbidity and mortality from these diseases.

PURPOSE

The purpose of our study was to analyze the metabolic comorbidities associated (overweight obesity, type 2 diabetes, hypercholesterolemia, hyperlipidemia, hypertriglyceridemia, hyperuricemia), respectively the cardiovascular diseases (hypertension, ischemic heart disease, myocardial infarction (MI) and other cardiovascular diseases, the chronic venous pathology and cerebrovascular diseases in a group of patients with psoriasis.

METHODS

We performed a retrospective study on 270 patients with psoriasis in the Dermatology Department of County Clinical Hospital of Sibiu, from January 2010 - January 2013.

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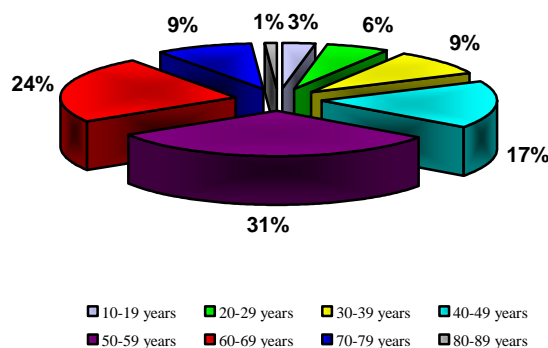
CLINICAL ASPECTS

The diagnosis of psoriasis has been established clinically and histologically, as appropriate. The inclusion criteria were: age between 10 and 90 years old, definite diagnosis of psoriasis, any clinical form of psoriasis. In our group of patients, we analyzed the distribution by gender, age and frequency of the association of psoriasis with each of the above-mentioned comorbidities.

RESULTS

In our study, there was a slight predominance of male gender (54%). There was a higher proportion of patients with psoriasis in the age group of 50-59 years old (31%), followed by the age group of 60-69 years old (24%) and of 40-49 years old (17%) (figure no. 1).

Figure no. 1. Distribution of study group by age groups



The metabolic comorbidities identified in our group of patients were the following: overweight - 63 patients (23.33%), obesity - 65 patients (24.07%), hypercholesterolemia - 88 patients (32.59%), hyperlipidemia - 72 patients (26.66%), hypertriglyceridemia - 32 patients (11.85%), diabetes type 2 - 68 patients (25.18%), hepatic steatosis - 64 patients (23.70%) and hyperuricemia - 48 patients (17.78%) (table no. 1).

It can be observed that 47.40% of our subjects had a BMI >25 kg / m², and 23% of them said they were overweight previous the diagnosis of psoriasis.

Approximately ¾ of our group (71.10%) had a disorder of lipid metabolism, mainly of hypercholesterolemia (32.59%). DM type 2 is a common comorbidity associated with the psoriatic disease. Within our study, 25.18% of the patients with psoriasis had type 2 diabetes, respectively one patient in four presented type 2 diabetes as associated comorbidity. Most subjects in the group having associated type 2 diabetes did not use cortisone topical treatments at the moment of their inclusion in the study, which could influence the carbohydrate metabolism.

Of the 270 patients with psoriasis, the cardiovascular comorbidities identified in our group of patients in the order of frequency were the following: hypertension - 117 patients (43.33%), ischemic heart disease - 89 patients (32.96%), MI in history - 174 patients (27.41%), chronic venous insufficiency - 60 patients (22.22%) (table no. 2), 6.30% of the patients with other cardiovascular diseases.

In the group of patients with psoriasis, the percentage of 27.41% was represented by other associated cardiovascular diseases, respectively dilated cardiomyopathy, carotid artery occlusion due to atherosclerosis, heart failure, conduction disturbances, abnormal heart rhythm, angina and aortic aneurysms.

Table no. 1. The distribution of metabolic comorbidities associated with psoriasis in the study group

No.	Associated cardiovascular and cerebrovascular comorbidities	No. of patients	Frequency %
1.	Hypertension	117	43.33%
2.	Ischemic heart disease	89	32.96%
3.	Acute myocardial infraction	17	6.30%
4.	Other cardiovascular diseases	74	27.41%
5.	Chronic venous insufficiency	60	22.22%
6.	Other cerebrovascular diseases	36	13.33%

Table no. 2. Distribution of cardiovascular and cerebrovascular comorbidities associated with psoriasis in the group of patients

No.	Associated metabolic comorbidities	No. of patients	Frequency %
1.	Overweight	63	23.33%
2.	Obesity	65	24.07%
3.	Hypercholesterolemia	88	32.59%
4.	Hyperlipidemia	72	26.66%
5.	Hypertriglyceridemia	32	11.85%
6.	Diabetes Mellitus type 2	68	25.18%
7.	Hepatic steatosis	64	23.70%
8.	Hyperuricemia	48	17.78%

Cerebrovascular disorders are also more common in the patients with psoriasis. In our study, out of 270 psoriasis patients, 36 patients (13.33%) were diagnosed with a history of strokes and transient ischemic attacks.

DISCUSSIONS

Psoriasis is a chronic inflammatory disease affecting mainly the skin but also the systemic level, especially being associated with psoriatic arthritis and Crohn's disease.

Most cardio-metabolic comorbidities of psoriasis induced by the chronic skin inflammation of skin and/or systemic represents the metabolic syndrome, which includes hypertension, insulin-resistant diabetes mellitus, atherogenic risk dyslipidemia and obesity. Nonalcoholic fatty liver disease is also frequently associated in the same dysmetabolic context. Other comorbidities can be associated, induced by impaired quality of life of patients with anxious syndromes - depression, alcoholism, as well as comorbidities related to treatments, particularly dyslipidemia, nephrotoxicity, hepatotoxicity and skin cancers.

From the pathophysiological point of view, psoriasis is characterized by dermo-epidermal inflammatory phenomena, hyperproliferation and abnormal keratinocyte differentiation.(6) The immunological processes in psoriasis involves the immunity acquired by the overexpressed T helper1 lymphocytes (Th1), which cause the increased release of Interferon (IFN) - γ , TNF- α and interleukin (IL) -2. CD4+ lymphocytes type 17 produce IL17, IL6, IL12 and TNF- α ; CD8 + lymphocytes produce TNF- α and IFN- γ .(7) Innate immunity occurs by the Natural Killer cells, dendritic cells, neutrophils, keratinocytes, proinflammatory cytokines, antimicrobial peptides, receptors for microbial products, and complement regulatory proteins.(8) Proinflammatory cytokines will activate the macrophages, the keratinocytes and other T-lymphocytes leading to hyperproliferation, neovascularization, and amplification of the inflammatory response.(9)

Keratinocytes produce mediators that activate the immune system cells and the dermal endothelial cells with the increase of the expression of antimicrobial peptides, neutrophils,

CLINICAL ASPECTS

macrophages, mast cells, plasma cells and T lymphocytes, thus maintaining a vicious circle.(10) Proinflammatory cytokines contribute to initiating the process of atherogenesis, to the occurrence of hypertension, insulin resistance and type 2 diabetes.(11)

Elevated levels of TNF- α cause keratinocyte hyperproliferation, increased insulin resistance by altering the sensitivity of insulin receptors, and modulate glucose metabolism and adipogenesis.(12) There have also been identified elevated levels of insulin-like growth factor-II in the patients with psoriasis, with a role in keratinocyte hyperproliferation, modulating lipid metabolism, atherosclerosis initiation and modification of the fat mass.(13) In psoriasis, there have been identified elevated levels of vascular-endothelial growth factor (VEGF), which is directly correlated with the severity of the disease, hyperinsulinemia, metabolic syndrome, obesity, coronary artery disease. It plays a part in stimulating the angiogenic status in the activation of the endothelial cells and in vascular intimal hyperplasia.(14)

In our group of patients with psoriasis, the identified metabolic comorbidities were: overweight and obesity (47.40%), dyslipidemia (71.10%), type 2 diabetes (25.18%), hepatic steatosis (23.70%) and hyperuricemia (17.78%).

Given that $\frac{1}{4}$ of psoriasis patients included in the study had type 2 diabetes, periodical glucose monitoring is essential, as well as the compulsory treatment of all forms of diabetes. Thus, psoriasis can be incriminated as an independent risk factor for the occurrence of type 2 diabetes and reversely diabetes as a risk factor for developing psoriasis, especially when there is a predisposing genetic field.

A study conducted on 16 851 patients with psoriasis compared with 48 681 patients without psoriasis showed an increase in the cases of dyslipidemia in the group of patients with psoriasis (hypercholesterolemia, hypertriglyceridemia and decreased HDL-cholesterol).(15) A meta-analysis published by Armstrong et al. has shown that the risk for developing diabetes is increased in the patients with psoriasis, in particular in the severe forms of psoriasis.(16) A study published by Herron et al, on a group of 557 patients with psoriasis has shown that the risk of developing obesity after the onset of psoriasis was higher than before the onset of psoriasis, to this contributing the psychosocial impact of psoriasis on the individual (weight gain by depression, antidepressant medication, social isolation, high-caloric diet, avoiding sports in public spaces).(17)

Through the high impact of obesity on other conditions, including psoriasis, with a decisive role in lowering life expectancy of these patients, a good collaboration between dermatologist-nutritionist is required, adopting effective prophylactic preventive measures on long-term in order to control patients' weight, with favourable effects on inflammation in psoriasis.

Recent studies identified in the patients with psoriasis increased levels of leptin, which correlate with an increased risk of arterial thrombosis and an increase in TNF- α and IL-2, with pro-inflammatory effects.(18)

Two studies conducted on patients with psoriasis (1 127, respectively 581 cases of psoriasis cases vs. control group) showed that in the patients with psoriasis, there were frequently encountered cardiovascular and metabolic comorbidities (hypertension, coronary heart disease, hypercholesterolemia, hyperlipidemia, type 2 diabetes, metabolic syndrome) compared with controls.(11,19)

The cardiovascular comorbidities in our group of patients diagnosed with psoriasis with the following percentages, arterial hypertension (HTA) (43.33%), ischemic heart disease (32.96%), MI (6.40%), other cardiovascular

diseases (27.41%), confirm similar results, although on a smaller group of patients. In addition, we identified the association of psoriasis with cerebrovascular disease in a percentage of 13.33% and chronic venous insufficiency in a percentage of 22.22%.

It should be noted that over half of the cases of psoriasis (55%) were aged between 50 and 69 years old, age group in which there can be found frequent cardiovascular risk factors (smoking, alcohol, obesity, stress) common with psoriasis. The groups of young patients did not show risk factors for hypertension, which shows that these factors may be associated at the same time with the development of psoriatic disease and aging.

The occurrence of hypertension more frequently in the patients with psoriasis could be explained by identifying some elevated levels of angiotensin II (vasoconstrictor and pro-inflammatory effect) and endothelin-1 (one of the sources being keratinocytes, with vasoconstrictor effect).(20)

A study published in 2012 on 56 patients with psoriasis vs. 56 control patients draws the attention on the risk of microvascular coronary dysfunction in the young patients with psoriasis with severe forms of disease without other risk factors or cardiovascular comorbidities.(21)

A cohort study conducted in Denmark for a period of 10 years compared the risk of atrial fibrillation and ischemic stroke in the patients with psoriasis, mild form (36 765 patients) and severe psoriasis (2 793 patients) vs. the control group (4 478 926 individuals). The risk of atrial fibrillation in the patients under 50 years old with mild psoriasis vs. severe psoriasis was of 1.50 vs. 2.98, and the risk of ischemic stroke in the same categories was of 1.97 vs. 2.80. These results support the involvement of psoriasis in increasing cardiovascular risk.(22)

High frequency of cardiovascular comorbidities in patients with psoriasis (both in our study and in the present study) recommends a special attention and a good cooperation between the dermatologist and the cardiologist, with a view to early diagnose and treat the cardiovascular diseases in the patients with this pathology.

The systemic medication used to treat psoriasis can also cause the onset or can worsen certain cardiometabolic comorbidities, the same way as in turn, the therapy used to treat comorbidities (angiotensin-converting enzyme (ACE) inhibitors, beta-blockers) can worsen psoriasis.(23) Psoriasis, on the one hand and the treatment of the disease, on the other hand, are considered independent risk factors for developing different cardiovascular and dysmetabolic comorbidities.

This could be explained by neglecting or abandoning comorbidities therapies by the patients with psoriasis, some cardiovascular and metabolic diseases being present prior to the diagnosis of psoriasis.

Among the systemic therapies, retinoids and cyclosporine may cause dyslipidemia, with secondary cardiovascular risk, while TNF- α inhibitors can cause weight gain, overweight and obesity.

On the other hand, recent research emphasizes the cardioprotective effect of the recommended treatments in psoriasis. Thus, methotrexate reduces cardiovascular risk by 21% and by 18% the risk of acute myocardial infraction (AMI) (24), anti TNF- α decrease the risk of AMI by 55% (25) and lower the insulin requirements.(26)

A common beneficial denominator in the treatment of these disorders is the hygienic-dietary plan of the patients with psoriasis and cardio-metabolic comorbidities, knowing that the diets low in animal fats, hypolipidaemic, hypoglycemic, hypolipidic, in case of obesity or overweight, has a favourable effect on the development of psoriatic disease as well.

CONCLUSIONS

Psoriasis is a chronic inflammatory disease with predominantly skin and joints manifestations, which is often associated with metabolic and cardiovascular diseases. The metabolic syndrome, defined as the association of the following diseases: central obesity, type 1 or 2 diabetes, or impaired glucose tolerance, hypertension, and dyslipidemia with atherogenic risk is an aggravating factor in psoriasis.

Taking into account that the association of psoriasis with these comorbidities and their intrication, proper monitoring of psoriasis and of the associated general pathology is recommended in order to detect the metabolic disorders and the cardiovascular risk factors. Also, the early institution of associated comorbidities treatment is recommended, as well as the development of effective risk factors prevention strategies for both skin pathology and the systemic one with impact on morbidity and mortality by these conditions.

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