Metabolic syndrome in hospitalised psoriatic patients

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UNIVERSITY OF SPLIT

SCHOOL OF MEDICINE

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1. INTRODUCTION

1.1. Psoriasis

1.1.1. Definition and etiology of psoriasis

Psoriasis is a systemic, immune-mediated polygenic skin disorder. Various environmental provoking factors, e.g. trauma, infection or medications can trigger the disease in predisposed individuals. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaque may be localized or widespread in distribution, preferably at the extensor surfaces of the extremities. Histologically, hyperkeratosis, parakeratosis, acanthosis of the epidermis, tortious and dilated vessels, and inflammatory infiltrate composed primarily of lymphocytes are observed. In patients with moderate to severe psoriasis, there is an increased relative risk for metabolic syndrome and atherosclerosis (2).

1.1.2. Epidemiology

The prevalence of psoriasis range from 0.5% - 4.6%, with rates varying between countries and races. It is more often found in persons living at higher latitudes than in lower latitudes and in more Caucasians than in other races (1). Psoriasis can develop at any age, from infancy to the eighth decade of life. Two peaks of onset have been reported, one at 20-30 years of age and a second peak at 50-60 years. Although the age of onset is earlier in women than in men, the natural history is chronic with intermittent remissions (2). The most common type of psoriasis is plaque psoriasis, occurring in more than 80% of cases. Guttate psoriasis occurs in about 10% of patients, and erythrodermic and pustular psoriasis each occur in less than 3% of patients (3). Psoriasis is associated with significant physical and behavioral comorbidities in addition to cutaneous manifestations. Persons with psoriasis have a greater prevalence of different comorbidities across all age groups when compared with those without (4).

1.1.3. Diagnosis

The diagnosis of psoriasis confines almost entirely on characteristic clinical features and rarely depends on histological confirmation. The presence of sharply demarcated, erythematous, scaling plaques on any part of the body should raise suspicion of psoriasis. Pitted fingernails, subungual hyperkeratosis, or other nail changes could aid in diagnosis when other characteristic clinical features are absent. The differential diagnosis is usually limited; some diseases which could mimic psoriasis are seborrheic dermatitis, lichen simplex, lichen planus, tinea corporis and subacute cutaneous lupus erythematous (1).

1.1.4. Clinical features

Psoriasis can present with a wide range of cutaneous manifestations. Different variations may coexist in an individual but the skin lesions all share the same hallmark: erythema, thickening and scale. The size of a lesion may vary from a pinpoint papule to over 20cm dimeter and the outline of the lesion is usually circular, oval or polycyclic. The shape of the lesion due to the Koebner phenomenon reflects the etiology of the trauma. Psoriatic lesions are sometimes surrounded by a pale blanching ring, which is referred to as Woronoff´s ring, in addition to their highly characteristic sharp demarcation. Psoriatic lesions often itch during exacerbations. The indication for an unstable phase of the disease are pinpoint papules surrounding existing psoriatic plaques, as a consequence expanding psoriatic lesions are characterized by an active edge with a more intense erythema. Inflamed lesions may be slightly tender. The involution of a lesion usually begins in its center, which results in annular psoriatic lesions (2).

The most common form of psoriasis is psoriasis vulgaris, which occurs in more than 80% of affected patients. It is characterized by sharply demarcated, erythematous, scaling plaques that typically affect the elbows, knees, scalp, and intergluteal cleft. Some patients develop lesions on the palms and soles before other regions are affected, and frequently it will present with lesions in the genitals. Inverse psoriasis is a form of the disease characterized by erythematous scaling which affects the skin folds, such as the axilla, antecubital fossae, popliteal fossae, and inguinal creases. It is often accompanied by another form such as psoriasis vulgaris. Guttate psoriasis often arises after streptococcal infection and is characterized by sudden development of numerous erythematous scaling papules on the trunk and extremities. Erythrodermic psoriasis is characterized by generalized inflamed erythema and scaling, which affects up to 100% of the body surface area. Patients lose protective functions of the skin, which includes the ability to protect against infections, body temperature control, and prevention of fluid and nutrient loss through the cutaneous surface (2).

Generalized pustular psoriasis or von Zumbusch is defined by development of sterile pustules covering large parts of the trunk and extremities. In severe cases, pustules become convergent forming large lakes of pus. Many of the skin protective functions are lost as in erythrodermic psoriasis, making patients susceptible to infection and loss of fluids and nutrients. Localized forms of pustular psoriasis involving palms and soles are not life-threatening, but are debilitating, since they have difficulty walking or using their hands. One of

the most common sites for psoriasis is the scalp. The lesions often advance onto the periphery of the face, the retroauricular areas and the upper neck. The scales sometimes have an asbestos-like appearance and can be attached for some distance to the scalp hairs. Within the involved areas alopecia can occur (2).

Nail involvement has been reported in 10-80% of psoriatic patients. The fingernails are more often affected than the toe nails. Patients with nail involvement appear to have an increased incidence of psoriatic arthritis. The nail matrix, nail bed and hyponychium are affected. A small parakeratotic focus in the proximal portion of the nail matrix leads to pits in the nails. Leukonychia and loss of transparency are due to involvement of the mid portion of the matrix. Psoriatic changes of the nail bed results in the "oil spot" phenomenon, which reflects exocytosis of leukocytes beneath the nail plate. Splinter hemorrhages are the result of increased capillary fragility, and subungual hyperkeratosis and distal onycholysis are due to parakeratosis of the distal nail bed. Vigorous removal of the distal subungual debris may be an exacerbating factor. Psoriatic arthritis occurs in 5-30% of patients with cutaneous manifestations (2).

In 10-15% the symptoms of psoriatic arthritis appear before skin involvement. It is more common in patients with severe psoriasis. Risk factors for more severe arthritis course include: early presentation, female gender, polyarticular involvement, genetic predisposition and radiographic signs. The most common presentation is the inflammation of the interphalangeal joints-both distal and proximal hands and feet. In contrast to rheumatoid arthritis, the metacarpophalangeal joint is an unusual site for psoriatic arthritis (2).

1.1.5. Histologic features

The histologic findings are elongated dilated capillaries that are close to the skin surface, epidermal acanthosis with cellular infiltrates, and abnormal keratinization with focal parakteratosis. A characteristic coherence is noticed, after the superficial silvery white scale is removed via curettage. Subsequently, a surface membrane is seen, which will disperse as a whole. If the latter is removed, then a wet surface is seen with characteristic pinpoint bleeding. This finding, called Auspitz sign, is the clinical reflection of elongated vessels in the dermal papillae together with thinning of the suprapapillary epidermis (2).

1.1.6. Pathogenesis

Psoriasis is a multifactorial skin disease with a complex pathogenesis. It is linked to many interactive responses between infiltrating leucocytes, resident skin cells, and an array of proinflammatory cytokines, chemokines, and chemical mediators produced in the skin under regulation of the cellular immune system. When the affected skin is compared with unaffected skin, the models which are used to explain the physiopathogenesis reveals differences in cell composition and in inflammatory mediators. Regarding the cell composition, unaffected skin has few immature Langerhans and dendritic cells, few CD4+ lymphocytes and rare CD8+ lymphocytes, in affected skin there is an abundance of these and other cell types (6).

At the onset of the disease and during the episodes of exacerbation, mature dendritic, myeloid and plasmacytoid cells are activated in the epidermis and dermis, producing messengers that stimulate the development of subclasses of T helper and T cytotoxic cells (Th1, Tc1). These T cells secrete mediators (IFN-γ), which induce HLA-DR production in the keratinocytes, reactivating the process, which then contributes to the epidermal and vascular alterations (5). In individuals with a genetic predisposition, external stimuli such as trauma, infections, stress, drugs, and alcohol can trigger an initial episode of psoriasis and activates the innate immune system. Complexes of the antimicrobial peptide LL-37 and host DNA/RNA, are released by keratinocytes after epidermal damage and activate plasmacytoid dendritic cells (pDCs) to produce large amounts of interfernons (IFN) (6).

pDCs are sensors of viral nucleic acid and induce protective immunity, an early key event in the disease development is the production of IFN. IFN initiates the activation and maturation of conventional dendritic cells (cDCs), which are key stimulators of T cells, thereby bridging the gap between innate and adaptive immunity. Another key event is the autoreactive T cells proliferation and migration into the epidermis, which is controlled by the expression of alpha 1 beta 1 integrin on effector T cells. This T-cell expansion and migration into the epidermis initiates the onset of psoriasis and is essential for the development of characteristic epidermal changes. Although the epidermal autoantigen remains unique, T cells show oligoclonal expansion, which indicates a common antigen for autoimmune T cells (6).

In psoriasis, these autoreactive T cells are IFN-gamma-secreting type 1 T helper (Th1) cells and Th17/Th22 cells producing interleukin (IL)-17 and IL-22. Th1 and Th17 cells seem to show concomitant presence in different inflammatory pathologies, but they represent along

with Th22 cells distinctly polarized Th cell types. These cytokines are key mediators linking adaptive immune response and epithelial dysregulation in psoriasis. IL-22 induces hyperproliferation of keratinocytes which leads to typical acanthosis. These cytokines potentially not only cause the typical epidermal changes seen in psoriasis but also lead to a self-sustained feedback loop and chronic progression of the disease (6).

1.1.7. Genetics

Psoriasis is a complex, multifactorial disease, with genetic and environmental factors having an important role in its etiology. Epidemiologic studies have found a strong genetic basis for psoriasis and the heritability is estimated at 60% to 90% which is among the highest for complex genetic diseases (7). Patients with childhood psoriasis report a positive family history in around 70% (8). Histocompatibility antigens (HLA) are surface antigens on human cells and the corresponding chromosomal region is called the major histocompatibility complex (MHC). The association of psoriasis with alleles in the MHC region has been recognized and researched for over three decades and today there are many association studies with HLA alleles (10).

The chromosome 6(p) is shown to be an important region in the pathogenesis of psoriasis. The surface antigen HLA-Cw6, which is located on the short arm (p) of chromosome 6 is strongly associated with more severe and early onset of psoriasis and PSORS1, which is the most important genetic region and it accounts for up to 50% of psoriasis risk (2,9). Other psoriasis susceptibility regions have been identified by genome-wide linkage analysis in different chromosomal locations (10).

1.1.8. Pathology

The initial lesion is a pinhead-sized papule, a superficial perivascular infiltrate of lymphocytes and macrophages that can be obtained in the dermis along with papillary edema and a dilation of capillaries. Mast cell degranulation is a constant feature in eruptive guttate lesions. The keratinocytes have a swollen presentation and a mild epidermal acanthosis without parakeratosis can be seen. Macrophages and lymphocytes appear in the epidermis but neutrophils are not found in the early phase. In an active lesion the histopathologic findings are diagnostic (2).

The capillaries are in the dermis increased, elongated and have a tortuous appearance and at the tops of the papilla edema is seen. There is a compound perivascular infiltrate of lymphocytes, macrophages and neutrophils. Neutrophils and lymphocytes accumulate in the epidermis, which is is acanthotic and spongiotic at these sites. Above these foci, the granular layer is absent and the stratum corneum still contains flattened nuclei. There are two findings that are pathognomonic for psoriasis. First, neutrophil accumulation within a spongiform pustule, which is known as spongiform pustule of Kogoj and second, microabcess of Munro, an accumulation of neutrophil remnants in the stratum corneum surrounded by parakeratosis (2).

As in the active lesion, the stable lesion consists of elongated and tortuous capillaries in the dermis, extending upward into elongated club shaped dermal papillae, a small suprapapillary plate of epidermal cells covers the tip of dermal papillae. A perivascular infiltrate is seen that consists of lymphocytes and macrophages. The psoriatic lesion is heterogenous, consisting of active areas and chronic nonspecific areas. The hyperproliferation of the epidermis has reached its characteristic pattern. The rete ridges are elongated and have a squared-off appearance. The horny layer has parakeratotic foci with an absence of the stratum granulosum. Micropustules of Kogoj and microabscesses of Munro may be seen in some lesions. In pustular psoriasis, accumulation of neutrophils between eosinophilic strands of keratocytes is the predominant feature and accumulations of neutrophils are observed in the stratum corneum, surrounded by parakeratosis (2).

1.1.9. Comorbidities

Epidemiological evidence is increasing and propose that patients may be more adipose compared to individuals without psoriasis (12). That was also shown in a cross sectional study, where obesity was two times more prevalent in psoriatic patients then in the general population (11). Psoriasis is independently associated with diabetes mellitus (DM) (13,14), in a systematic review and meta-analysis it was found, that there is a 59% increased prevalence of DM in psoriasis patients and a 27% increased risk of developing DM among patients with psoriasis (15). Dyslipidemia is present in 27.3% of psoriasis patients (16), it may be present at the onset of psoriasis, suggesting that the lipid abnormalities in psoriasis patients may occur at an earlier age and not just related to obesity (17).

Psoriasis is also independently associated with myocardial infarction (MI), with greatest risk in younger patients with severe psoriasis (18). Patients with severe psoriasis were at increased risk of death from kidney disease, cardiovascular disease (CVD), malignancies, dementia, chronic lower respiratory disease, DM and infection. Mean age of death in patients with psoriasis was in one study 73 years and in patients without psoriasis 79 years (19). The prevalence of smoking is increased in psoriatic patients, as it was shown in a cross-sectional study using the Utah Psoriasis Initiative database. The result was that smoking among psoriatic patients aged 18 years or older was more frequent than that in general Utah population (37% vs 13%; $P<0.001$). After onset of psoriasis 22% of patients started smoking,78% started smoking before the onset of psoriasis, suggesting that smoking may contribute to psoriasis (11).

1.1.10. Treatment

Psoriatic treatment ranges from topical therapies for mild types to phototherapy or systemic therapy for more widespread disease. Topical corticosteroids are the most commonly used treatment, due to their rapid effectiveness and the application in various strengths and formulations. Side-effects include cutaneous atrophy, striae formation, teleangiectasis, and tachyphylaxis. An alternative to topical corticosteroids are vitamin D analogs. Phototherapy or systemic therapy are used, when patients are refractory to topical treatment or if the acute state of illness is too widespread for topical remedies. Sunlight can also have a beneficial effect. PUVA (psoralen and ultraviolet A) is highly effective but it has been associated with squamous cell carcinomas (20). Patients who do not respond to phototherapy can be treated with methotrexate, which side effects include nausea, aphtous stomatitis, and bone marrow toxicity. Retinoids are another class of systemic psoriasis therapy, which are only moderate effective as monotherapy and are associated with numerous mucocutaneous side-effects and teratogenicity. Cyclosporine is a very effective drug but long-term use is associated with nephrotoxicity. Several drugs have been designed to treat psoriasis by targeting specific cells, cytokines, or specific interactions between ligand and receptors (1).

1.3. Metabolic Syndrome

1.3.1. Definition

Metabolic syndrome (MS) is defined as an interconnection between physiological, clinical, biochemical, and metabolic factors that directly increases the risk of cardiovascular disease, and type 2 diabetes mellitus. Insulin resistance, genetic susceptibility, visceral adiposity, elevated blood pressure, dyslipidemia, chronic stress, endothelial dysfunction, and hypercoagulable state are the factors which constitute the syndrome. Chronic inflammation is characterized by production of abnormal adipocytokines such as tumor necrosis factor α, interleukin-1 (IL-1), IL-6, leptin, and adiponectin are known to be associated with insulin resistance and visceral obesity. The development of a proinflammatory state happens due to the interaction between components of the clinical and biological phenotype of the syndrome which progresses to a chronic, subclinical vascular inflammation and results in atherosclerotic processes (21).

1.3.2. Diagnostic criteria

Diagnostic criteria for MS have been established by the International Diabetes Federation (IDF) in 2005. MS was defined using the IDF criteria. Patients with central obesity and two other factors of the following criteria: abdominal obesity (waist circumference ≥ 94 cm in Europid men or >80 cm in Europid women); hypertriglyceridemia (triglycerides ≥1.7 mmol/l) or specific treatment for this lipid abnormality; low levels of HDL-C (<1.03 mmol/l in men or <1.29 mmol/l in women) or specific treatment for this lipid abnormality; high systolic blood pressure (≥130 mmHg) or high diastolic blood pressure (≥ 85mmHg) or receiving drug therapy for hypertension; and high fasting glucose levels (≥5.6 mmol/l) or previously diagnosed DM were defined as having MS (22).

1.3.3. Epidemiology

It is estimated that 20-25 % of the world´s adult population have the MS and it is shown that the prevalence tends to increase with age among both men and women. The factors which are important for the increased prevalence of the MS are obesity and DM and it is known that those persons are three times as likely to have a heart attack or stroke compared to people without the MS (23,24).

1.3.4. Pathophysiology

Factors which constitute the MS are dyslipidemia, glucose intolerance, insulin resistance, visceral obesity, increased blood pressure and other manifestations.

1.3.4.1. Atherogenic dyslipidemia

Dyslipidemias are disorders of lipoprotein metabolism, including lipoprotein overproduction and deficiency. These disorders may be manifested by elevation of the serum total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglyceride (TG) concentrations, and a decrease in the high-density lipoprotein (HDL) cholesterol concentration (25). Dyslipidemia plays a crucial role in the development of cardiovascular diseases, which is the leading cause of death in developed countries. Atherogenic dyslipidemia is a combination of raised triglycerides and low concentration of HDL-c together with elevated apolipoprotein B(ApoB), small dense LDL and small HDL particles (26). Low HDL and high triglyceride levels are a reflection of insulin resistance, and are risk factors for coronary heart disease (27,28). The primary treatment is to change the life style, which includes calorie restriction, changes in dietary composition and increase in physical activity. The IDF recommends drugs as a secondary intervention for atherogenic dyslipidemia which lower TG and LDL and increases the HDL levels. The drugs of choice are fibrates and statins. Fibrates improve all components of atherogenic dyslipidemia and appear to reduce the risk of cardiovascular disease (CVD) (28) in people with MS. On the other hand, statins are known to reduce all ApoB-containing lipoproteins, which is confirmed by several clinical studies (29-31). It is not recommended to prescribe statins and fibrates as a combination due to side effects (21).

1.3.4.2. Insulin resistance

The most accepted hypothesis to describe the pathophysiology of the metabolic syndrome is insulin resistance, which is defined as a defect in insulin action that results in hyperinsulinaemia, necessary to maintain euglycaemia. Insulin resistance develops when target tissue such as skeletal muscle, liver, and adipocytes become less sensitive to insulin, which is produced by the ß cells in the pancreas to promote glucose utilization. Eckel et al. (32) stated that “a major contributor to the development of insulin resistance is an overabundance of circulating fatty acids”. Free fatty acids (FFA) reduce insulin sensitivity in muscle by inhibiting insulin-mediated glucose uptake. Increased level of circulating glucose increases pancreatic insulin secretion resulting in hyperinsulinemia. In the liver, FFA increases the production of

glucose, triglycerides and secretion of very low density lipoproteins (VLDL). The consequence is the reduction in glucose transformation to glycogen and increased lipid accumulation in triglycerides (33). Triglyceride molecules in adipose tissue produces more fatty acids, which could further inhibit the antilipolytic effect of insulin, creating additional lipolysis (34). There is a possibility that drugs that reduce insulin resistance will delay the onset of DM type 2 and decreases the risk of CVD when metabolic syndrome is present (35). The Diabetes Prevention Program (DPP) found that the therapy with metformin or thiazolidinedione will prevent or delay the development of DM (35-37). Other studies have shown that the therapy with acarbose and orlistat can delay the development of DM type 2 in people with impaired glucose tolerance (38,39). Despite that, the most important factor in prevention or delaying the development of diabetes is a healthy life style change.

1.3.4.3. Obesity and increased waist circumference

Physical inactivity and excess food intake are the major cause of obesity worldwide. Central obesity plays a fundamental role in the development of insulin resistance and the metabolic syndrome and is associated with the development of hypertension. Obesity contributes to high level of glucose, high serum cholesterol and low HDL, it is also independently associated with higher CVD risk (40-42). Obesity is not directly dependent on body mass index (BMI) (43) but the accumulation of fat in the abdomen seems to be a more important risk factor (44,45). Accumulated visceral adipose tissue produce and secrete a number of adipocytokines, which are variety of bioactive substances such as leptin, tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), angiotensinogen, and non-esterified fatty acids (NEFA), which induce development of hypertension (46). Central obesity is measured by waist circumference using guidelines which are gender and ethnic-group specific (22).

1.3.4.4. Hypertension

MS is shown to be present in up to one third of all hypertensive patients (47,48). A correlation between increased blood pressure, insulin resistance and visceral obesity is well established (49). The renin-angiotensin system (RAS) plays a central role in blood pressure regulation, by affecting renal function and by modulating vascular tone. The activity of the RAS appears to be regulated by food intake, and overfeeding of rodents has been reported to lead to increased formation of angiotensin II in adipocytes (50), which contributes to the development of hypertension in MS (51). Plasma aldosterone is significantly associated with

the MS and with obesity-related hypertension (51,52). Goodfried TL et al. (53) reported that the best predictor for plasma aldosterone level is abdominal obesity. Possible factors enhancing sympathetic nervous activation in the MS are insulin resistance, increased leptin and non-esterified fatty acids (NEFA). NEFA has been reported to raise heart rate, blood pressure, and α1-adrenoceptor vasoreactivity, while reducing vascular compliance, baroreflex sensitivity and endothelium-dependent vasodilatation (54). Insulin resistance increases plasma leptin levels, and leptin has been shown to increase sympathetic nervous activity, suggesting that leptin-dependent sympathetic nervous activation may contribute to an obesity-associated hypertension (55). Recent evidences suggest that oxidative stress, which is elevated in the MS (56), is associated with sodium retention and salt sensitivity (57). TNF-α stimulates the production of endothelin-1 and angiotensinogen, and it has shown to be positively correlated with systolic blood pressure and insulin resistance (58). IL-6 is a multifunctional cytokine which mediates inflammatory responses, stimulates the central and sympathetic nervous system and induces an increase in plasma angiotensinogen and angiotensin II (59), which contributes to the development of hypertension.

1.4. Metabolic syndrome and psoriasis

The underlying pathophysiology associating psoriasis and MS may link inflammatory pathways and genetic predisposition. Psoriasis is a prototypical Th-1 inflammatory disease characterized by expansion and activation of Th-1 T cells, antigen presenting cells, and Th-1 cytokines. Th-1 also plays an important role in the pathophysiology of obesity, metabolic syndrome, DM, atherosclerosis, and myocardial infarction (MI). Chronic Th-1 and Th-17-mediated inflammation with dysregulation of cytokines, e.g. Tumor Necrosis Factor -α (TNF-α) and interleukin-6 (IL-6), not only stimulates epidermal hyperplasia in psoriasis, but may also antagonize insulin signaling, modify adipokine expression, and mediate obesity and insulin resistance. On the other hand, hyperinsulinemia in MS may enhance psoriasis susceptibility or severity by facilitating chronic inflammation and angiogenesis. Angiogenetic factors such as VEGF produced by immunocytes and keratinocytes in psoriatic skin, promote angiogenesis and endothelial cell activation (60,61).

VEGF is also increased in hyperinsulinemic states such as MS in which adipocytes are its primary source, promoting susceptibility to psoriasis or exacerbate existing psoriasis (62). When looking at individual components of the MS, which tend to be more prevalent in psoriatic

then in non-psoriatic patients, only hypertriglyceridemia and abdominal obesity were more significantly increased, according to Cohen et al. (63). Several cross-sectional studies demonstrated an association of psoriasis and dyslipidemia, which showed increased total cholesterol and triglycerides, decreased HDL, and no alteration in LDL in psoriasis patients compared to controls (64). In a case-control study of 560 psoriasis patients, obesity was found to be an independent risk factor for the development of psoriasis (65). Multiple studies have also found psoriasis to be associated with cardiovascular disease including atherosclerosis and thrombosis (e.g. myocardial infarction) (66,67). Importantly, psoriasis independently predicted coronary artery disease when controlling for cardiovascular risk factors (68).

2. OBJECTIVES

The aim of our study was to evaluate the association between MS and psoriasis in hospitalized psoriatic patients in the period of January 1th 2015 to December 31th 2015 in the Dermatology and Venerology department, University Hospital of Split.

3. MATERIALS AND METHODS

3.1. Subjects

A cross-sectional study was conducted at the department of Dermatology and Venerology, University Hospital of Split, from January 1th 2015 to December 31th 2015. The study research included 49 hospitalised psoriatic patients with plaque psoriasis.
A short structured questionnaire was used to collect data regarding age, gender, family history of psoriasis, joint involvement, age of psoriasis onset, duration of the disease, comorbidities like smoking, alcohol, DM, depression, CVD, MI, skin tumors, hypertension, Inflammatory bowel disease, multiple sclerosis, lymphoma and leukemia.

Anthropometric measures recorded in this study were weight, height and waist circumference. Measures of weight (kilograms) and height (meters) were assessed using a standard physician's scale and a stadiometer, respectively. The waist circumference was measured by placing he measuring tape horizontally around the abdomen at level of the upper part of the hipbone. Blood pressure was recorded as the mean of two measurements after subjects had been sitting for 15 minutes. Glycaemia, trygliceridemia and HDL levels were measured using standard biochemical procedures, after taking a venous blood sample from patients who had fasted overnight for at least 8h.

The median age of patients was 58 (min-max: 22-83 years). We included in our study 25 (51%) men, with a median age of 52 years (min-max: 22-75) and 24 (49%) women with a median age of 61 years (min-max: 26-83).

3.2. Diagnostic criteria for MS

For the definition of the MS we used the guidelines from the International Diabetes Federation (IDF) from 2005. The IDF criteria are race and gender specific of which we used the Europid criteria. The main diagnostic criteria for the MS is central obesity plus two other factors. Central obesity is defined as waist circumference ≥ 94 cm for Europid men and ≥ 80 cm for Europid women. The person has to have raised triglycerides above 1.7 mmol/L, or they have to take specific treatment for this lipid abnormality. The HDL cholesterol has to be bellow 1.03 mmol/L in males, and 1.29 mmol/L in females, or specific treatment for this lipid abnormality has to be taken. The systolic blood pressure has to be above 130 mmHg or diastolic blood pressure above 85 mmHg. Fasting plasma glucose has to be more than 5.6 mmol/L**,** or previously diagnosed DM (22).

3.3. Diagnostic criteria for psoriasis

There are no established diagnostic criteria for cutaneous psoriasis and there is no unified classification for the clinical spectrum of the disease. Histopathological examination and blood tests are generally not valuable tools in making the diagnosis of psoriasis (2). The inclusion criteria for the clinical diagnosis of chronic plaque psoriasis in our psoriatic patients (lasting at least 6 months) was established by experienced dermatologists. The exclusion criteria were other forms of psoriasis (pustular, palmoplantar, pustular palmoplantar).

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3.4. Statistical analysis

The data was entered into Microsoft Excel program for Windows. The data processing was made using the statistical program MedCalc (MedCalc Software, Mariakerke, Belgium). In the statistical analysis we used chi-square test and Mann-Whitney U test for results interpretation. The level of statistical significance is $p<0.05$.

4. RESULTS

In our psoriatic patients the most common investigated risk factor was the increased waist circumference in 46 (94%) patients, in those with and without the MS. The second most common risk factor was the increased systolic blood pressure in 26 (53%) subjects. It is equally represented with or without the metabolic syndrome (Table 1.).

Table 1. The number (%) of patients according to the individual components of the MS

		Metabolic Syndrome	
	Total (n= 49)	Yes (n=23)	No (n=26)
Waist circumference (>94 cm in men; >80 cm in women)	46 (94)	22 (96)	24 (92)
Triglycerides (>1.7 mmol/l)	23 (47)	20 (87)	3 (11)
HDL (<1.03 mmol/l in men; <1.29 mmol/l in women)	22 (45)	15 (65)	7 (27)
Systolic blood pressure (<130 mmHg)	26 (53)	13 (56)	13 (50)
Diastolic blood pressure (<85 mmHg)	21 (43)	9 (39)	12 (46)
Fasting glucose (> 5.6 mmol/l)	19 (39)	16 (70)	3 (11)

The distribution of patients according to the incidence of comorbidities was not statistically significant in relation to gender (z=1.16; p=0.281). The proportion of patients with comorbidities was 75%. The number of patients with MS (47%) was almost equal to the number of patients without MS (53%). The disease duration was marginally higher in women than in men, but not statistically significant (z=1.8; p=0.071) (Table 2.).

Table 2. Comparison of family history, joint involvement, co-morbidities and metabolic syndrome in men and women with psoriasis, as well as the onset of disease and disease duration

		Gender			
		Total	Men (=25)	Women (=24)	p*
Family history (%)	Yes	24 (49)	9 (36)	15 (62)	0.117*
	No	25 (51)	16 (64)	9 (38)	
Joint involvement (%)	Yes	28 (57)	15 (60)	13 (54)	0.902*
	No	21 (43)	10 (40)	11 (46)	
Co-morbidities (%)	Yes	37 (75)	21 (84)	16 (67)	0.281*
	No	12 (25)	4 (16)	8 (33)	
Metabolic syndrome (%)	Yes	23 (47)	12 (48)	11 (46)	0.879*
	No	26 (53)	13 (52)	13 (54)	
Disease onset (years)		35 (7-70)	35 (7-68)	33 (11-70)	0.764**
Disease duration (years)		20 (0-48)	17 (0-43)	21 (0-48)	0.071**

*Chi-squared test
** Mann Whitney U test

The proportion of patients with joint involvement was not statistically significant in relation to MS ($\chi 2$= 0.043; p=0.836). Patients with MS had 1.5 times more co-morbidities than patients without MS ($\chi 2$=4.4; p=0.037). There was no statistically significant difference in patients' age (z =1.45; p=0.146), disease onset (z=1.2; p=0.237) and disease duration (z=0.080; p=0.936) in regard to the MS (Table 3.).

Table 3. Comparison of family history, joint involvement, co-morbidities and metabolic syndrome in regard to the metabolic syndrome, as well as the onset of disease and disease duration

		Metabolic syndrome		
		Yes (=23)	No (=26)	p*
Joint involvement	Yes	14 (61)	14 (54)	0.836*
	No	9 (39)	12 (46)	
Co-morbidities	Yes	21 (91)	16 (61)	0.037*
	No	2 (9)	10 (39)	
Family history	Yes	12 (52)	12 (46)	0.892*
	No	11 (48)	14 (52)	
Patient age (years)		60 (22-83)	54 (26-82)	0.237**
Disease onset (years)		40 (7-60)	32 (11-70)	0.146**
Disease duration (years)		20 (0-43)	20 (0-48)	0.936**

*Chi-squared test
** Mann-Whitney U test

In the study 12 (24%) psoriatic patients had no comorbidities. The most common comorbidity was hypertension, which was present in 23 (46%) patients. The second most common comorbidity was DM, which was present in 10 (20%) patients. Smoking was present in 14 (28%) and other comorbidities were present in 11 (22%) patients (Table 4.).

Table 4. The prevalence of co-morbidities (%) with regard to MS (%)

		Metabolic syndrome		
		Yes (=23)	No (=26)	Total
	No Comorbidities	2 (4.1)	10 (20.4)	12 (24.5)
Co-morbidities				
	Smoking	6 (12.2)	8 (16.3)	14 (28.6)
	Diabetes	8 (16.3)	2 (4.1)	10 (20.4)
	Hypertension	14 (28.6)	9 (18.4)	23 (46.9)
	Other	4 (8.2)	7 (14.3)	11 (22.4)

There was no statistically significant difference in the age of patients with and without co-morbidities (z=0.884; p=0.377). There was no statistically significant difference in the disease onset and duration of patients with and without co-morbidities (z=0.698; p=0.485) (Table 5.).

Table 5. Co-morbidities according to age, disease onset and disease duration

	Co-morbidities		
	Yes (=37)	No (=12)	p*
Age (years)	60 (22-83)	52.5 (26-82)	0.377*
Disease onset (years)	35 (7-68)	32 (11-70)	0.485*
Disease duration (years)	20 (0-47)	20 (0-48)	0.780*

* Mann-Whitney U test

5. DISCUSSION

MS is shown to have a high incidence in psoriatic patients. This could be caused due to certain proinflammatory and immunologic mediators, which are observed in psoriatic plaques and are also found in hypertension, insulin resistance and dyslipidemia which are the individual components of the metabolic syndrome. The MS is associated with an increased risk of cardiovascular disease. Increased free fatty acids and lipid accumulation in certain organs mediate insulin resistance. Atherosclerosis is potentiated by obesity due to its increased role in proinflammatory and prothrombotic response (69). There are other factors influencing the MS in those patients such as dietary habits, levels of physical activity, differences in genetic background, population age and sex and diet. Aging is also an important factor in the genesis of the MS, it is known that with increased age there is an increased risk of developing MS (70). Varies studies demonstrated that neuroendocrine changes play a major role in the pathogenesis of central obesity, insulin resistance and hypertension. These neuroendocrine changes involve disorders of the hypothalamo-pituitary-adrenal (HPA) axis activated after periods of prolonged stress and environmental stress factors (71). It is also found that psychosocial stress has impact on the central HPA axis in psoriatic patients (72). Therefore, psychosocial stress is an important factor in the exacerbation of psoriasis and development of MS.

Our study showed no statistical significant difference in patients age at disease onset ($p=0.674$). The prevalence of psoriasis was marginally higher in women, but without statistical significance. Gupta et al. (73) showed in their study similar results, so we can conclude that age and gender do not play a significant role in the development of psoriasis.

Cumulative evidence showed that incidence of psoriasis is higher in relatives compared to the general population. The probability of inheriting psoriasis has been estimated to be between 60% and 90% (74). However, our study did not demonstrate a higher prevalence of psoriasis in family members. The total number of patients with positive family history (49%) was almost equal to the number of patients who did not have a positive family history family (51%).

In this study 57% of psoriatic patients had joint involvement, which is 1.4 times more than those patients whose had no joint involvement (43%). Our study only included patients with psoriasis vulgaris, which is also the most common type associated with psoriatic arthritis (75). We did not find a statistically significance of joint involvement in relation to gender ($p=0.902$), age, ($p=0.903$) nor a difference in disease duration ($p=0.233$). We can conclude, that joint involvement is a common disability in psoriatic patients.

Several studies reported that psoriatic patients carry an increased risk of developing comorbidities, especially those related to the MS (76). Similarly, our study showed, that 75% of our patients had comorbidities. We did not found any statistical difference according to gender, age, and disease duration. The most common comorbidities were central obesity (94%). Smoking is associated with a higher risk of developing CVD and studies showed that patients with psoriasis are more likely to be smokers. It is also suggested, that smoking may be a risk factor in the development of psoriasis (77). In this study 28% of all our psoriatic patients were smokers and 12% of those had also the MS. We can conclude, that comorbidities are highly prominent in psoriatic patients and they should be better monitored and advised to change their life style.

Our study did not show an increased prevalence of MS in hospitalized psoriatic patients. The number of patients with MS (47%) was almost equal to the number of patients without MS (53%) ($p=0.879$). Similarly, Kim et al. (78) did not demonstrate a statistical significant difference in metabolic syndrome between psoriatic patients and controls ($p=0.2$). Nonetheless, other studies showed a higher prevalence of MS in psoriatic patients. Zindancy et al. (79) found a significantly higher prevalence of MS in psoriatic patients ($p<0.001$) using International Diabetes Federation criteria (IDF), which we also used in our study. Gisondi et al. (80) used the National Cholesterol Education Program (NCEP) ATP III criteria and also demonstrated a statistically significant higher prevalence of MS in psoriatic patients ($p=0.005$).

The occurrence of MS is more common in elderly. Gisondi et al. (80) observed MS in psoriatic patients after 40 years of age. Lakshmi S. et al. (81) showed that MS in psoriatic patients is higher in older population. Kim et al. (78) demonstrated that MS is more common in patients older than 53 years of age. In our study we did not find a statistically significant difference in patients age but the mean age for psoriatic patients with MS was 60 and those without MS was 56 ($p=0.146$).

Gisondi et al. (80) and Sommer at al. (82) reported, that prevalence of MS is related to the duration of the disease. However, our study did not show any difference in disease duration ($p=0.936$) nor in disease onset ($p=0.237$) compared to the MS.

The distribution of patients according to the incidence of MS is not shown to be statistically significant in relation to gender ($p=0.281$). Similarly, Gisondi et al. (80) and Kim

et al. (78) found no gender difference. Other studies such as Mebazaa et al. (83) and Zindancy et al. (79) showed higher prevalence of MS in female psoriatic patients.

Joint involvement was found to be as high as 57% in our psoriatic patients. However, joint involvement had no significant impact on MS ($p=0.836$). Other studies showed a prevalence of 58% in psoriatic arthritis patients in relation to MS (84).

Psoriatic patients had a high prevalence of comorbidities 75%, and those with MS had 1.5 times more co-morbidities than patients without the MS (91%) ($p=0.037$). Systolic blood pressure was increased in 56 % of patients with the MS, 39% had increased diastolic blood pressure and of those had 28% already diagnosed hypertension. The investigation has revealed that 70 % of patients with MS had increased fasting glucose and of those patients 16% had already diagnosed DM. Likewise, other studies were similar associated with those co-morbidities. Cohen et al. (85) showed in a case-control study a higher prevalence of hypertension in psoriatic patients (38.8%; $p<0.001$). Zindancy et al. (79) also demonstrated an increased prevalence of DM and hypertension in their patients. The exact mechanism linking psoriasis with DM and hypertension is still unknown. Nonetheless, Armstrong et al. (86) found that psoriasis and hypertension are independently associated by adjusting one of these factors. Zindanci et al. (79) found normal lipid levels in their study and concluded that hyperlipidemia had no clinical significance in psoriatic patients. However, our study showed 47% of all our psoriatic patients had increased triglycerides level and 45% had low HDL levels. Due to our findings we concluded that high lipids have a significant role in psoriatic patients. Cohen et al. (85) demonstrated as well as we did, that hyperlipidemia is present in psoriatic patients. Increased waist circumference was the most frequent component of our patient with and without the MS. Our study observed that 46 (94%) out of 49 psoriatic patients had increased waist circumference. It is known, that adipokines interact with immune cells and contributing to the inflammatory process and proinflammatory cytokines such as IL-6 and TNF α are found in both adipose tissue and psoriatic tissue (87). Consequently, we can conclude that fat distribution and adipokine production is a relevant concern in psoriasis.

The limitations of our study were that we did not have a control groups and no height measurement of the patients to calculate their BMI index.

6. CONCLUSION

Due to higher incidence of CVD, hypertension, central obesity and insulin resistance in psoriatic patients many studies have been conducted and demonstrated a higher incidence of MS in psoriatic patients. Due to lack of a control group we cannot definitely say that MS is more prevalent in psoriatic patients. However, we found a significant increase in waist circumference, hypertension and hyperlipidemia, which are the main factors of the MS. As general consideration the patient's knowledge about the MS should be increased and all patient with psoriasis should be encouraged to change their life style. The management of psoriasis should be an integrated approach due to its correlation with other co-morbidities.

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8.SUMMARY (ENGLISH)

METABOLIC SYNDROME IN HOSPITALISED PSORIATIC PATIENTS

Backround: Recent studies suggest a link between psoriasis and metabolic syndrome (MS). The aim of our study was to demonstrate the prevalence of MS in our hospitalized psoriatic patients.

Methods: A hospital-based, cross - sectional study with 49 psoriatic patients was conducted from January 1th 2015 to December 31th 2015 in the Dermatology and Venerology department, University Hospital of Split. MS was defined by the International Diabetes Federation (IDF) guidelines.

Results: In this investigation 47% of the hospitalized psoriatic patients had the MS, whereas 53% had not. Gender (p=0.281), disease duration (p=0.936) and disease onset (p=0.237) did not play a statistical significant role in relation to the MS. Similarly, we could not find a higher prevalence of MS in regard to age (p=0.146). Our psoriatic patients had joint involvement in 57% of cases, however we did not show a correlation between joint involvement and the metabolic (p=0.836). Psoriatic patients had a high prevalence of co-morbidities (75%), and it was significantly high (91%) in those psoriatic patients who had the MS (p= 0.037). Systolic blood pressure was increased in 56 % of patients with the MS, 39% had increased diastolic blood pressure and of those had 28% already diagnosed hypertension. In this study 70 % of patients with MS had increased fasting glucose and of those patients 16% had already diagnosed diabetes mellitus. Our study showed a significant correlation between psoriasis and co-morbidities, which are associated with the metabolic syndrome.

Conclusion: MS is prevalent in psoriatic patients. As a general consideration all psoriatic patients should be advised to change their life style, if necessary early treatment should be advised and regularly follow up of patients with increased risk to develop MS. Management of psoriasis should be an integrated approach due to its increased correlation with other co-morbidities.

9. SUMMARY (CROATIAN)

METABOLIČKI SINDROM U HOSPITALIZIRANIH BOLESNIKA S PSORIJAZOM

Cilj: Nedavne studije upućuju na povezanost vulgarne psorijaze i metaboličkog sindroma (MS). Cilj našeg istraživanja bio je istražiti prevalenciju MS u hospitaliziranih bolesnika s psorijazom.

Metode: Od 1. siječnja 2015. do 31. prosinca 2015. provedena je presječena studija sa 49 hospitaliziranih bolesnika sa psorijazom, u Klinici za dermatologiju i venerologiju, Kliničkog bolničkog centra Split. MS je definiran smjernicama International Diabetes Federation (IDF).

Rezultati: U ovom istraživanju 47% hospitaliziranih bolesnika imalo je MS, dok 53% nije. Spol (p=0,281), trajanje bolesti (p=0,936), niti početak bolesti (p=0,237) nisu imali statistički značajnu ulogu u odnosu na MS. U ovoj studiji dob nije imala statističku značajnost (p=0,146) u odnosu na MS. Ispitivani bolesnici imali su zahvaćene zglobove u 57% slučajeva, što se nije pokazalo značajnim u odnosu na MS (p=0,836). Bolesnici sa psorijazom su imali veliku prevalenciju komorbiditeta (75%), a značajno su bili visoki (91%) kod pacijenata koji su imali MS (p = 0,037). U 56% bolesnika sa MS uočeno je povišenje sistoličkog krvnog tlaka, a 39% je imalo porast dijastoličkog krvnog tlaka dok je u 28% već prethodno dijagnosticirana hipertenzija. U ovom istraživanju 70% bolesnika sa MS imalo je povišene vrijednosti glukoze u krvi natašte, a među njima 16% je već imao dijagnosticiran dijabetes. Pokazano je da postoji značajna korelacija između vulgarne psorijaze i komorbiditeta, posebno onih čimbenika koji su povezani sa MS.

Zaključak: MS je prisutan kod bolesnika s psorijazom. Kao opći zaključak, svim bolesnicima sa psorijazom bi trebalo savjetovati promijenu načina života. Preporučuje se rano liječenje i redovno praćenje bolesnika s povećanim rizikom za razvoj metaboličkog sindroma. Liječenje vulgarne psorijaze bi trebalo imati integrirani pristup zbog povećane povezanosti upalnih promjena sa drugim organskim sustavima i posljedične pojave komorbiditeta.

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