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METABOLIC SYNDROME AND INFLAMMATORY CYTOKINES IN PSORIASIS

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Abstract

Obesity negatively affects the pathological states of chronic inflammation, such as Psoriasis and Psoriatic Arthritis. The inflammatory cytokines released by the adipose tissue determine, in addition to inflammation, a condition of insulin resistance, which is also a comorbidity of psoriasis. The state of chronic inflammation unites both psoriasis and obesity. The first is an autoimmune skin disease, where very thick skin layers are evident due to an abnormal proliferation of keratinocytes; obesity, on the other hand, represents one of the possible comorbidities of psoriasis the simultaneous presence in the same subject of two or more diseases.

Keywords: *metabolic syndrome, inflammatory cytokines, obesity, psoriasis, psoriatic arthritis.*

Introduction

The state of chronic inflammation is common to both psoriasis and obesity. The first is an autoimmune skin disease, where very thick skin layers are evident due to an abnormal proliferation of keratinocytes; obesity, on the other hand, appears to be one of the diagnostic parameters of the MetS and, at the same time, represents one of the possible comorbidity of psoriasis. Adipose tissue, normally considered as a source of energy, in conditions of overweight and obesity causes an alteration of cytokines and hormones that it normally secretes, such as adiponectin and leptin. The first, in a normal weight subject, regulates insulin sensitivity, hence it can be deduced that in an obese individual there will be alterations in blood glucose, dictated by insulin resistance that can derive from the unregulated expression of Akt or Phosphoinositide-3 kinases; in fact, the activity of GLUT 4, the classic glucose transporter, will be altered. In addition, there are also alterations in the concentrations of leptin, a hormone of a protein nature that regulates the sense of hunger, thermogenesis, and reproductive hormones. Adipose tissue releases TNF alpha, a cytokine whose blood concentration is high even in patients with psoriasis. This cytokine enhances the condition of insulin resistance as it determines the inhibition of serine phosphorylation of substrate 1 of the insulin receptor (IRS1); therefore it is evident that in psoriatic patients a condition of obesity is not ideal. Conditions of obesity increase the secretion of IL-17 through the activation of an enzyme, called acetyl coenzyme A carboxylase, which mediates the biosynthesis of fatty acids starting from acetyl-CoA to obtain malonyl-CoA it enhances the activity of the ROR gamma t receptor and consequently the differentiation of T lymphocytes into T helper 17, which will produce large quantities of IL-17, common to both disease states. It will therefore be clear that a reduction in body fat could lead to an improvement not only in inflammation caused by obesity, but also in that typical of psoriasis.

Metabolic Syndrome

The Metabolic Syndrome, also known as Syndrome X, has been defined by the World Health Organization (WHO) as a pathological condition involving insulin resistance, abdominal obesity, hypertension and hyperlipidemia.

According to the definition of the WHO, the parameters that allow to diagnose the Metabolic Syndrome are at least three among those listed below:

- Insulin resistance, with fasting blood glucose values> 100 mg/dL
- HDL cholesterol <40 mg/dL in men and <50 mg/dL in women
- Blood concentration of triglycerides> 150 mg/dL
- Waist / hip ratio> 102 cm in men and> 88 cm in women
- Blood pressure> 140/90 mmHg.

Metabolic Syndrome was first described in 1988 and refers to clinical conditions that include the following disorders: central and abdominal obesity, systemic hypertension, insulin resistance (type 2 diabetes mellitus, T2DM), and atherogenic dyslipidemia (particularly hypertriglyceridemia) and reduced blood levels of high-density cholesterol (HDL). It arises from an imbalance between the calories introduced with the diet and energy expenditure, epigenetic changes are sometimes highlighted in genetically predisposed subjects and finally the quality of the foods consumed and the lifestyle can determine the onset of the MetS. It is linked to an atherosclerotic condition, as a response to a chronic inflammatory state and to a malfunction of the vascular endothelium and this leads to a significant increase in cardiovascular risks. In recent decades, a significant increase in the incidence of the Metabolic Syndrome has been highlighted and at the same time the underlying molecular mechanisms have been understood. We focus attention on the adipose tissue, in fact the adipocytes are not all the same; they differ in adipocytes of white, brown and beige adipose tissue. The latter two are morphologically and functionally different from white adipocytes, in fact they have a cytoplasm rich in mitochondria and type 1 uncoupling proteins (UCP1), which enhance the processes of thermogenesis [1].

Adipose tissue is considered active from an endocrine as well as metabolic point of view, determining the secretion of cytokines and hormones that regulate appetite, the sense of satiety and energy metabolism. Leptin and

Adiponectin are the main protein hormones secreted by adipose tissue; the first determines the sense of satiety, the second regulates insulin sensitivity and consequently the correct functionality of pancreatic beta cells [2].

Macrophages residing in adipose tissue play an important role in energy metabolism; the pro-inflammatory ones (M1) promote hepatic steatosis and adipogenesis, the anti-inflammatory ones (M2) increase the secretion of anti-inflammatory cytokines such as IL-10. In a recent study was reported that the presence of M1 macrophages at the level of adipose tissue is mediated by integrin alpha-beta 1; the recall of these is also dictated by the expression of VCAM1, which codes for some adhesion molecules of vascular cells [3]. The presence of M1 macrophages inhibits the function performed by UCP1 proteins. Stress of the Endoplasmic Reticle is another important factor in the onset of the Metabolic Syndrome. From experiments on mice, Shan et al. have shown that the stress on the endoplasmic reticulum induced by a high-fat diet depends on the activity of the enzyme IRE1 alpha, which requires inositol. The deficiency of IRE1 prevented conditions of obesity, insulin resistance and hepatic steatosis induced by a diet rich in fatty acids [3].

The Mediterranean diet is the ideal to follow to avoid obesity conditions and consequently the onset of the Metabolic Syndrome. In the PREDIMED (Prevenciòn con Dieta Mediterranea) studyit was noted that one gram of extra virgin olive oil, taken as a supplement to the normal Western-style diet, significantly reduced blood pressure values and reduced blood pressure [4]. Incidence of MetS: the foods that have reduced the incidence ofSyndrome, we find, in addition to extra virgin olive oil, capsaicin, rosemary, curcumin, luteolin, cinnamon, etc [5-7]. Some food polyphenols, taken in high doses, can favorably influence the onset of the Metabolic Syndrome[8]. Cheng etal. showed that a low-calorie, low-protein, low-carbohydrate but high-fatty acid diet allowed pancreatic beta cells to enhance their function and reversal was noted in mouse models of the T1D and T2D phenotypes [9]. Instead, soy isoflavone, hesperidin, citrus-based products, and quercetin have improved lipid metabolism and cocoa has improved hypertension and blood glucose values. Green tea significantly reduced the Body Mass Index and waist circumference [10]. Cheng etal. showed that a low-calorie, low-protein, low-carbohydrate but high-fatty acid diet allowed pancreatic beta cells to enhance their function and reversal was noted in mouse models. of the T1D and T2D phenotypes [9].

Adipokines and immune response cells

In the current century, obesity is considered a chronic multifactorial disease and is the result of the interaction that exists between genetics and the environment around us; men and women of all ages and social conditions are affected equally. Obesity causes excessive accumulation of fat, which is harmful to health, especially at the visceral level [11]. In the blood there is a high concentration of proinflammatory cytokines including tumor necrosis factor alpha (TNF alpha), interleukin 6 (IL-6) and acute phase proteins such as C reactive protein (PCR).

Adipocytes are the protagonists of inflammatory activity. Adipose tissue is normally considered to be an energy store; in case of obesity, it communicates with the whole body through the secretion of proinflammatory adipokines, with prothrombotic activity and with vasoactive function; these include TNF alpha, IL-6, leptin and the plasminogen activator inhibitor [12,13].

In obese subjects, a drastic reduction in adiponectin, an anti-inflammatory cytokine, was shown. In fact, following the inflammatory stimulus, the macrophages are attracted to the adipose tissue and, once trapped between the adipocytes, the macrophages themselves determine the secretion of cytokines; hence there is primary inflammation [14]. In advanced obesity, macrophages converge on necrotic adipocytes, resulting in the formation of crown structures (CLS). The number of macrophages increases significantly in the adipose tissue of an obese subject, compared to those found in the fat of a normal weight subject [15]At the same time, adipose tissue also contains a large number of T cells; in particular, there is an increase in CD8 cells. CD8+ initiates inflammation by determining the activation and migration of monocytes/macrophages and promoting their differentiation into mature macrophages. Therefore, CD8+ cells propagate the inflammatory state, determining insulin resistance and metabolic

alterations typical of the Metabolic Syndrome [16]. In a normal weight subject, however, the response of T helper 2 and T reg limits the inflammatory state through the secretion of an anti-inflammatory interleukin, or IL-10. In the obese subject, however, a predominant function of CD8+ and T helper 1 is noted, with enhancement of the inflammatory state [17,18]. Consequently, these cytokines determine the production of inflammatory proteins in the liver and this promotes the low-grade systemic inflammation observed in the obese [14]. We remind you that cytokines enhance the lipolytic activity or the release of free fatty acids into the blood stream by the adipose tissue. Free fatty acids play an important role if we consider the relationship between chronic inflammation and the activity of adipose tissue itself, in fact they cause an increase in oxidative stress and therefore alter vascular activity. In obese subjects, the distribution of adipose tissue is purely localized at the visceral level, compared to the peripheral distribution of fat. In fact, the adipocytes of visceral fat have a higher metabolic activity than the peripheral ones and therefore cause a notable release of cytokines and fatty acids; from here we can deduce the pronounced inflammatory state in subjects with visceral obesity [19].

Psoriasis and inflammatory state.

The state of chronic inflammation is also present in psoriasis. Psoriasis is a chronic autoimmune disease on genetic and multifactorial bases that affects skin, adnexa and joints, mucosa and submucosa [20]. Psoriasis affects 2-5% of the population. Hyperproliferative keratinocytes (KCs), neutrophils, inflammatory dendritic cells (DCs), T cells and mast cells are the mediators that allow the formation and development of psoriatic plaques which, from a clinical point of view, are erythematous and squamous and they are found mainly in the scalp, lumbosacral area, knees, elbows and in the folds of the body with symmetrical distribution and can even develop in the lesion sites (Koebner phenomenon). Current studies have shown the possibility of evaluating some biological markers to detect psoriasis, to evaluate prognosis and response to treatment. Those conducted by Yadav et al. focus attention on the biomarkers that are involved in psoriasis [21]. The transcription signal transducer and activator (STAT) performs relevant functions in the pathogenesis of psoriasis as it modulates biological functions related to immune pathways such as cell division, cell growth and apoptosis, in fact the intracellular signaling pathways JAK / STAT control inflammatory reactions of psoriasis. The STAT transcriptional proteins (STAT1, STAT2, STAT3, STAT4, STAT5A STAT5B and STAT6) determine the expression of different cytokines and are involved in the nuclear transmission of extracellular signals. In psoriasis STAT1 seems to have a significant importance since its activity (regulated by the hyperphosphorylation of TAT1) occurs in the skin, STAT3 determines the activation of T lymphocytes and keratinotics, finally STAT 2 is also characteristic of psoriatic lesions [22-25]. Speaking of psoriasis we must outline how there are high levels of interferon gamma produced by Th1 lymphocytes and there are also high levels of interleukin 17 A (IL 17 A) produced by Th17. Obesity and psoriasis have common pathophysiological mechanisms expressed in terms of a low degree of chronic inflammation; in fact, obesity also affects the response to the treatment of the autoimmune disease. By evaluating the inflammatory state typical of obesity, a connection with other pathological conditions is denoted to determine what is the metabolic syndrome, which is one of the comorbidities of psoriasis [26]. The common cytokines in the inflammatory state of obesity and psoriasis are IL-1, IL-6, TNF alpha and a reduction in adiponectin. These cytokines are the basis of the evolution of psoriasis and that is why the treatment based on methotrexate and anti-TNFalpha could reduce the risk of comorbidities. It is therefore deduced that TNF alpha is one of the cytokines that determines an incidence of risk of cardiovascular diseases in patients with psoriasis. The cytokines most involved in the inflammatory state dictated by Psoriasis are Il-1 beta and TNF alpha; there are monoclonal antibodies directed on proteins or cell receptors, examples of antibodies to TNF alpha are Certolixumab and, Infliximab, Adalimumab Golimumab; other drugs are Ustekinumab, Secukinumab. Normally these drugs are administered subcutaneously and the main side effect is systemic immunosuppression which determines greater susceptibility to infections. In addition to phototherapy and the classic biological treatment, there are also pharmacological

treatments that basically have two different objectives: either to enhance the immune response or to normalize the activity of keratinocytes. It is obvious that in psoriasis there is hyperproliferation of keratinocytes and this allows us to distinguish a skin with psoriasis from a normal one[27].

Relationship between obesity and psoriasis: diagnostic parameters.

Debbaneh et al. conducting an observational and clinical literature review study on how weight loss could lead to improved PASI [28], paved the way for Naldi et al. on the conduct of a randomized and controlled study on 303 patients, for a total of 20 weeks of diet and physical activity interventions for obese or overweight patients with psoriasis [29].

Carrying out constant physical exercise and an adequate diet have made it possible to highlight a significant improvement in the PASI score (i.e. the evaluation of psoriasis in terms of surface extension), also inhibiting the oxidative stress phenomena that enhance inflammation due to psoriasis [30].

The doctors' task would be to encourage patients to lead a lifestyle as healthy as possible, improving the quality of the foods they consume and practicing sports to keep their body weight under control.

In further studies, an association was found between BMI and obesity [31,32].

When a systemic drug therapy is undertaken, such as that with cyclosporine or methotrexate, it is necessary to evaluate, if present, the concomitant condition of obesity. In fact, it is necessary to regularly dose the liver and kidney enzymes, it should be considered, in fact, that the aforementioned drugs have numerous side effects, especially at the level of kidney and liver [33]. Rui et al. estimated decreases in blood levels of interleukin 17 and interleukin 6 in patients with psoriasis and with metabolic syndrome after 10 sessions with NB-UVB treatment compared to patients without metabolic syndrome (P lower of 0.05) [34]. Obviously, patients with psoriasis and metabolic syndrome showed a much milder improvement than patients with psoriasis alone who used this treatment. Psoriatic patients with metabolic syndrome showed a mild reduction in the following systemic biomarkers: interleukin 17, interleukin 6 and TNF alpha compared to patients without metabolic syndrome; from this it could be deduced that patients belonging to the first type would need a longer treatment to be effective on the treatment of psoriatic plaques. Since 2004, drugs obtained through recombinant DNA technology have been on the market that target cytokines, the interface of proteins or block lymphocytes in precise steps during the pathogenesis of psoriasis itself [35,36].

An important biomarker is Wnt5a, which determines the regeneration of cutaneous and intestinal tissues. It has two different receptor subtypes, which are named fzd3 and fzd5, both of which are fundamental in the cellular differentiation process and are located at the level of the hair bulbs. Obviously, alterations of Wnt5a and fzd5 determine an abnormal keratinocytic turnover and therefore there are the typical histomorphological characteristics of a skin with psoriasis.

Another crucial factor in psoriasis is the tumor protein or p53/ tp53 which is a phosphoprotein that regulates the cell cycle; it is localized in the layers of the psoriatic skin and this determines its involvement in the pathology.

Let's now analyze the enzymatic biomarkers, in particular we evaluate the epidermal exfoliation that is then followed by hyperproliferation. Phospholipase C (PLC) is involved in the formation of the stratum corneum and in the differentiation of keratinocytes; in the same way, Psoriasin (S100A7) and Koebnerisin (S100A15) regulate tissue functions and are involved in innate immunity, in the maturation of epidermal cells and in the genesis of epithelial tumors [37].

Ekman et al. highlight how IL-22 is involved in the differentiation of keratinocytes and the role of cytokines in the skin of patients with psoriasis has been evaluated, in fact a large concentration of this cytokine has been found at the level of plaques psoriasis which and moreover high levels of IL-22 were also found in the blood level [38].

Role of interleukin 17 in the genesis of Psoriasis and the inflammatory state IL-17 in Psoriasis.

Psoriasis is a chronic inflammatory disease which, if we consider the US population alone, affects a percentage equal to 3% (i.e. about 7 million people) [39,40].

The disease has an epigenetic basis and occurs when a series of cytokines that normally regulate the state of proliferation of keratinocytes are produced in an anomalous way [41].

Dendritic cells, together with keratinocytes and T cells, determine the production of many proinflammatory cytokines, including chemokines. Dendritic cells (DCs) produce high levels of IL-23 which activates Th17 to produce IL-17A and IL-17F which have effects on abnormal proliferation of keratinocytes. These cytokines, together with tumor necrosis factor (TNF alpha), determine a state of chronic inflammation where there is constant activation of T cells [42,43].

Psoriasis and Obesity have in common a state of chronic inflammation; we said previously that in an obese subject, the same adipose tissue determines the production of cytokines defined as adipokines, where there is a marked reduction in adiponectin and an increase in leptin. This state is defined as prothrombotic and further stimulates the production of cytokines such as TNF alpha, IL-6, the inhibitor of the activator of plasminogen and fibrinogen.

Pharmacological therapies for the treatment of psoriasis have shown an incidence of subjects to increase their body weight, probably due to changes in the glucose-dependent insulinotropic polypeptide, ghrelin, leprin and metabolism [44,45].

The more an individual's condition of obesity increases, the more IL-6 and TNF alpha will be secreted, resulting in metabolic alterations regarding insulin resistance and lipid metabolism.

Studies conducted on adipocytes *in vitro* with anti-IL-17 drugs have shown a significant reduction in their maturation [46,47].

Interleukin 17 induces the expression of IL-6 in preadipocytes and fibroblasts, and also determines resistance to insulin [47].

The factors that determine the release of interleukin 17:

- Increased production of IL-6 at the level of adipocytes and macrophages at the level of visceral fat. High concentrations of IL-6 stimulate STAT 3 and Retinoid receptors by increasing the differentiation of T cells into Th 17, which secrete IL-17.
- Serum concentrations of Amyloid A (acute phase response protein), with increased secretion of IL-23 [48].
- TNF-alpha production [49].

Adiponectin, which normally regulates insulin sensitivity, also regulates skin inflammation, in particular psoriasis, linked to the secretion of IL-17 [50].

Studies conducted on mice with adiponectin deficiency show inflammation of the skin, calling up the lymphocytes and causing their differentiation to give IL-17. Through the analysis of this study it will be shown that in patients suffering from psoriasis there is a reduced concentration of adiponectin [51,52].

This cytokine, in fact, suppresses the production of IL-17, positively modulating the inhibition of the pathogenesis of psoriasis.

The inflammation of psoriasis is not limited to the skin but extends to the systemic level; in fact, there, the large release of pro-inflammatory cytokines can lead to insulin resistance and atherosclerosis.

We speak of the aforementioned "March Psoriasis" which leads patients suffering from the disease to develop the Metabolic Syndrome. [50]

Systemic inflammation exacerbated by obesity and the Metabolic Syndrome, in turn, can lead to enhancing the inflammatory state of the skin through the bloodstream [53].

In vitro, adiponectin inhibits the production of TNF-alpha, IL-6 and IL-12 secreted by Th1 and inhibits the secretion of IL-6 also by keratinocyteo [54].

Conclusions

Obesity is a problem that affects an increasingly large slice of the world population; the inflammatory state that derives from it should not be underestimated and it is also a parameter to be constantly monitored when dealing with patients suffering from autoimmune diseases such as Psoriasis and Psoriatic Arthritis.

The lack of regulation in the release of proinflammatory hormones and cytokines by adipose tissue confirms this.

Through the studies on mice reported in this thesis it has been shown that reductions in adiponectin predispose a psoriatic subject to have a significant release of IL-17, a cytokine found in psoriatic plaques and at the blood level.

The confirmation of this occurs thanks to the analyzes carried out on mice after injections of anti-IL-17 A antibodies such as Secukinumab; in fact the cytokine concentration is considerably reduced after this pharmacological treatment.

Therefore a weight reduction in obese subjects could determine an advantageous aspect, as a comorbidity of psoriasis; in addition to reducing the concentration of proinflammatory cytokines, in this way it will also be possible to re-establish the metabolic parameters and consequently reduce the cardiovascular risk strictly connected to the Metabolic Syndrome.

The alterations of adiponectin (cytokine that regulates insulin sensitivity), are altered in an obese subject and it has been shown, starting from the mouse models mentioned above, that intraperitoneal injections of adiponectin reduce the secretion of IL-17 and at the same time improve exacerbation of autoimmune disease in terms of skin extension of the plaque, calculated by the PASI score.

Finally, to avoid a condition of overt inflammation, the ideal would be to lead a correct lifestyle, with adequate nutrition and of relevant importance, it would also be practicing physical exercise, in order to reduce metabolic alterations and consequently reduce comorbidity of psoriasis.

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