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Obesity, Insulin Resistance and Dysregulation of the mTOR Signalling Pathway in Hidradenitis Suppurativa

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Abstract

BACKGROUND: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by recurrent painful nodules, abscesses, and draining tunnels, with a predilection for intertriginous regions.

AIM: We aimed to review dysregulation of mTOR signalling pathway based on the latest relevant scientific studies.

METHODS: This literature review explores the association between HS, obesity, insulin resistance, and the dysregulation of mTOR signalling pathway. Additionally, research investigating the effects of therapeutic strategies, such as metformin and its influence on clinical outcomes in HS patients, was analyzed.

RESULTS: Obesity is considered a predisposing factor for the development of insulin resistance and type 2 diabetes, both of which influence the IHS4 (International Hidradenitis Suppurativa Severity Score System) score in HS patients. The prevalence of insulin resistance among HS patients is 43.4%. Studies have shown that metformin significantly reduces inflammatory cytokines, chemokines, and the expression of genes associated with glycolytic processes. In vitro analyses suggest that these effects are mediated through the modulations of the NLRP3 inflammasome and mTOR signalling pathway.

CONCLUSION: A holistic approach to HS treatment, including the management of obesity and insulin resistance, significantly improves disease progression. The use of metformin as an adjunct therapy in standard treatment protocols has the potential to improve IHS4 scores in obese patients.

Introduction

Hidradenitis suppurativa (HS) is a chronic, inflammatory and often severe skin disease that affects the hair follicles. HS usually presents after puberty with painful, deep, inflamed lesions in areas containing apocrine glands, most commonly under the armpits, inguinal and anogenital regions. The disease is recurrent, with at least two manifestations within a six-month period or with one or more chronic lesions lasting more than three months [1], [2].

The most commonly used scores for HS diagnosis and monitoring are Hurley (Hurley I, II and III) and IHS4 (International Hidradenitis Suppurativa Severity Score System). IHS4 score is obtained by the sum of the number of nodules (multiplied by 1), the number of abscesses (multiplied by 2) and the number of draining tunnels (multiplied by 4). A total score of 3 or less indicates mild disease, 4-10 moderate disease, and 11 or more severe disease [3]. The Sartorius score is also commonly used [4]. Recent studies have defined three stages in the pathogenesis of the disease: non-inflammatory, acute inflammation, and chronic inflammation [5].

The association of obesity and metabolic disorders with HS is well known. Both conditions lead to a chronic low-intensity systemic inflammation, so it is not clear whether the inflammation caused by metabolic disorders leads to the initiation of HS or whether the systemic inflammation in HS leads to the manifestation of metabolic disorders. This literature review aims to evaluate the metabolic disorders present in HS patients, the impaired metabolic molecular mechanisms that are directly correlated with the severity of the disease, as well as the therapeutic effects of metformin as a direct regulator of insulin

resistance, which underlies all these metabolic disorders.

Risk factors for the development of hidradenitis suppurativa in the Republic of North Macedonia

In 2023, a study was conducted in the Republic of North Macedonia, Skopje, which demonstrated a prevalence of HS of 0.84%, in a population of 598 participants [6]. The study later became part of a meta-analysis that included data from 23 countries on 6 continents with a total of 22,743 participants. This meta-analysis showed a global prevalence of HS of 0.99%, ranging from 0.67 – 1.46%, a finding that justifies the increased interest in this disease [7].

Although there are studies that indicate a genetic predisposition to the disease, two main risk factors that influence the development and course of HS have emerged, namely smoking and obesity. The presence of HS is more common in obese people compared to the general population, and losing more than 15% of body weight is associated with a significant reduction in the severity of the disease [8].

The interest in studying the prevalence of obesity in the Republic of North Macedonia is increasing. A cross-sectional study was conducted in 2022 which analyzed the prevalence of overweight and obesity in 1034 healthy children aged 6 to 13 years in the Republic of North Macedonia. The results showed that 57% of the children were of normal weight, 19.5% were obese, and 13.5% were overweight. The study showed a worrying increase in the rate of overweight and obesity, especially among the groups of children aged 6-7 and 8-9 years, where the rates increased from 17.9% to 25.4% for obesity and from 5.8% to 12% for overweight. The Global Atlas of Childhood Obesity predicts that the rate of obesity in children aged 5 to 19 in North Macedonia will increase up to 52.5% by 2030 [9].

Increased body weight in childhood leads to the early development of insulin resistance, metabolic syndrome and type 2 diabetes mellitus. Statistical analysis regarding the prevalence of diabetes in the Republic of North Macedonia is presented in a retrospective study, based on adult population data from the State Statistical Office for the period 2015-2019. The results showed a constant increase in the number of patients with diabetes. The number of registered patients increased from 103,480 in 2015 to 124,450 in 2019, showing an increase of 20.3%. The majority (95%) of these patients are diagnosed with type 2 diabetes (T2DM), while only 4.1% have type 1 diabetes (T1DM), indicating that T2DM is the dominant form of diabetes among the population. The prevalence increased from 5.66% in 2015 to 7.2% in 2019, showing an increase of 1.54% (an increase of 27%). This indicates a significant increase in the population diagnosed with T2DM [10].

Although there is evidence that the rising prevalence of childhood overweight and obesity increases the risk of developing type 2 diabetes later in life, nationally representative epidemiological data in the Republic of North Macedonia specifically linking childhood obesity with subsequent diabetes are currently lacking. Given the known associations between obesity and inflammatory skin disorders, it is relevant to explore whether similar trends exist for hidradenitis suppurativa (HS). However, there is currently a lack of epidemiological data assessing the prevalence or temporal trends of HS in the country.

Insulin resistance in hidradenitis suppurativa

Obesity is the most common cause of insulin resistance (IR). IR is defined as a decreased sensitivity of cells to insulin, resulting in reduced glucose uptake by muscle cells, increased glucose production by the liver, and increased lipolysis in the adipose tissue. This leads to increased insulin secretion and hyperinsulinemia, to maintain the normal functions of insulin. Insulin resistance is closely related to metabolic syndrome; in fact, it is one of its criteria. Other criteria that define metabolic syndrome include central obesity, hypertension and dyslipidemia [11].

In everyday practice, IR can be determined by several methods, the most accurate of which is the “hyperinsulinemic-euglycemic clamp” method, while the most commonly used is the homeostatic model assessment for insulin resistance (HOMA-IR) due to its simplicity of implementation [12]. HOMA-IR is determined by the product of the fasting glucose level and the fasting insulin level, divided by a constant (normalizing factor) [13].

Another method for assessing insulin resistance, which is widely used, is the triglyceride-glucose (TyG) index [14]. This index is considered superior to HOMA-IR for predicting metabolic syndrome and IR [15], because the first parameter whose concentration increases as a result of IR and cellular metabolic burden is the level of circulating triglycerides, which are predominately carried by chylomicrons and very low density lipoproteins (VLDL). In conditions of hyperglycemia and IR, VLDL production and chylomicron release increase, which leads to an increase in serum triglyceride levels. On the other hand, in IR and type 2 DM, increased hepatic gluconeogenesis leads to increased hepatic glucose production, thus increasing blood glucose levels. The association between increased triglyceride and glucose levels in insulin resistance is the basis for using both parameters (included in the TyG index) for assessment of various abnormalities associated with impaired insulin sensitivity [14].

IR (via HOMA-IR) is an independent risk factor for the development of metabolic dysfunction-associated steatohepatitis (MASH, formerly named as nonalcoholic fatty liver disease). In fact, HOMA-IR is a

potential indicator of the risk of developing MASH in non-diabetic and non-obese patients and can be used in the diagnosis of the disease and as a screening method [16]. There is a strong association between MASH and HS, namely patients with hidradenitis suppurativa have a significantly higher prevalence of MASH (57.6%) compared to those without HS (31.7%), regardless of the presence of traditional metabolic risk factors such as age, body weight, hypertension and elevated levels of circulating transaminases [17], [18].

IR and type 2 DM are among the most common comorbidities in patients with HS [19]. Patients with HS have a higher risk of developing IR compared to healthy individuals, as 43.4% of HS patients have IR compared to only 16.4% in the control group [20]. The prevalence of type 2 DM in patients with HS is significantly higher than in healthy individuals (39% vs 19%) [21]. In addition, HS is associated with other metabolic disorders, including hypertriglyceridemia (OR 1.67, 95% CI 1.14–2.47, P =0.009), low values of high-density lipoprotein (HDL) (OR 2.48, 95% CI 1.49–4.16, P <0.001), diabetes (OR 2.85, 95% CI 1.34–6.08, P =0.007), and metabolic syndrome (OR 2.22, 95% CI 1.62–3.06, P <0.001) [22].

HS patients exhibit heterogeneity of metabolic disorders, but essentially all of them are based on dysregulation of the mTOR signalling pathway that govern the metabolic processes at the cellular level.

mTOR signalling pathway, metabolic disorders, and hidradenitis suppurativa

mTOR or mammalian target of rapamycin is a 289 kDa serine/threonine protein kinase that belongs to the phosphatidylinositol 3-kinase (PI3K)-related protein kinase family. mTOR consists of two distinct multi-protein complexes known as mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). These complexes differ in their structure, sensitivity to rapamycin, and specific functions. The mTOR pathway integrates a diverse set of signals, such as signals from growth factors and nutritional status, and determines the direction in which eukaryotic cells will grow, depending on whether it activates anabolic or catabolic processes. mTORC1 is sensitive to nutrients (amino acids, glucose), energy (ATP levels), and growth factors (insulin, IGF-1) and controls protein synthesis, lipid metabolism, and autophagy. mTORC2 responds mainly to growth factors and regulates cytoskeletal organization, cell survival, and insulin signalization. Given the central role of this pathway in maintaining cellular and systemic homeostasis, dysregulation of mTOR signalling has been linked to metabolic disorders, neurodegenerative diseases, cancer, and aging [23], [24].

Liu and Sabatini (2020) describe the role of mTOR signalling in the development of IR. Obesity, caused by overfeeding, creates a large and harmful energy imbalance in the body. This leads to a continuous excess of hormones, cytokines, and nutrients, disrupting the metabolic cycles responsible for cellular homeostasis, placing mTORC1 in a persistently active state. Under these conditions, constitutive mTORC1 signalling activates S6K1 and Grb10 to uncouple the insulin/IGF-1 receptor from downstream effectors of the PI3K pathway, leading to a reduced physiological response to insulin. In addition, PI3K inhibition suppresses the mTORC2-Akt axis, which blocks glucose uptake and promotes gluconeogenesis, further increasing glycemic load and exacerbating ectopic fat deposition and glucose intolerance [25].

Accordingly, medications that counteract these mechanisms may be beneficial in reducing body weight and improving insulin sensitivity and type 2 diabetes mellitus. Metformin finds its application in this area as an already well-known and widely used drug for type 2 DM, by effectively suppressing mTORC1 through both AMPK-dependent and AMPK-independent mechanisms, depending on the dose, and thereby improving insulin sensitivity [26].

Meta inflammation and hidradenitis suppurativa

Meta inflammation is a term first introduced by Gökhan S. Hotamisligil, and it refers to chronic, low-grade systemic inflammation driven by metabolic disorders. Meta inflammation is characterized by only a moderate increase in circulating proinflammatory factors and the absence of clinical signs of inflammation (subclinical inflammation). The main factors that drive this inflammation are excessive fat deposition, insulin resistance and impaired immune signalling (chronic inflammation) [27].

Meta inflammation affects the metabolic organs, with a main emphasis on adipose tissue. Adipose tissue is a histologically diverse structure composed of mature adipocytes, preadipocytes and a stromal-vascular component that includes vascular endothelial cells and various immune cells from the innate and adaptive immune systems. Functionally, adipose tissue serves as an energy store, an endocrine organ, and an important factor in immunological regulation [28].

Under conditions of continuous excessive food intake, changes occur in the number and activity of almost all resident immune cells in the adipose tissue. Additionally, various subsets of immune cells are recruited. The imbalance in immunological phenotypes leads to the development of local inflammation and the release of biologically active components that enter systemic circulation [29].

Macrophages and lymphocytes represent the most abundant immune populations in the white adipose tissue. Depending on the degree of obesity, adipose tissue macrophages (ATMs) exhibit different phenotypes. In lean, non-obese individuals, ATMs have anti-inflammatory activity (M2 macrophages),

whereas in obese individuals, as a consequence of excessive triglyceride accumulation, they express pro-inflammatory genes (M1 “classically activated” macrophages) [30]. Pro-inflammatory cytokines produced by M1 ATMs (for example, TNFα or IL6) promote adipocyte hypertrophy, which further leads to the release of cytokines and chemokines that amplify and maintain adipose tissue inflammation, causing systemic inflammation through a positive feedback loop [31].

Adipose tissue is an endocrine organ that regulates a multitude of physiological processes through the mediation of chemokines, known as adipokines. Adipokines have emerged as key regulators of inflammation. Leptin and resistin are considered pro-inflammatory adipokines, while adiponectin is considered an anti-inflammatory adipokine. Mean serum adiponectin levels are significantly reduced in patients with HS, while serum resistin and leptin levels are significantly elevated compared to healthy individuals [32], [33].

Metabolic syndrome and HS share the same adipokine profile (HS-MetS adipokine profile) and significantly overlap in the activity of inflammatory pathways [34].

There are still not precisely defined clinical biomarkers for this low-grade systemic inflammation. Relevant indicators could be CRP, especially the high-sensitivity method, as well as cellular biomarkers such as leukocytes and platelets [35].

Metformin and hidradenitis suppurativa

Metformin is an oral biguanide approved for the treatment of type 2 diabetes [36]. By its mechanism of action, metformin is an activator of adenosine monophosphate-activated protein kinase (AMPK) and an mTORC1 inhibitor [37]. Hepatocytes are the main site of action of metformin, where it regulates hepatic glucose production. However, an increasing number of studies indicate that metformin may have additional sites of action, including the gastrointestinal tract, intestinal microflora, and tissue-resident immune cells. In addition, the use of metformin in various pathophysiological conditions is expanding [38].

One of the mechanisms by which metformin improves the clinical findings in HS is through its direct action on insulin resistance and meta inflammation. In a case-control study of 40 patients with HS (20 on metformin therapy for at least 6 months and 20 without metformin therapy in the last 6 months), there was a significant reduction in biomarkers of cardiovascular disease risk in the group that takes metformin (lymphocytes, monocyte-lymphocyte ratio, neutrophil-lymphocyte ratio, and platelet-lymphocyte ratio). Also, in the same study, a decrease in fasting insulin and a trend towards a decrease in insulin resistance (HOMA-IR) were observed in the group who took metformin over 6 months. CRP was also lower in the metformin group, but without statistical significance [39].

In order to detect the immunometabolic effects of metformin in patients with HS, a comparative analysis of peripheral blood mononuclear cells (PBMCs) from metformin-treated and untreated patients was performed, which showed an improvement in deregulated metabolic pathways and a decrease in inflammatory markers after a long-term metformin therapy. An ex vivo HS lesion model showed that metformin reduces inflammatory cytokines, chemokines, and glycolytic gene expression in lesions in patients with HS. In vitro analyses further suggest that these effects are mediated through the NLRP3 inflammasome and the AMPK-mTOR signalling pathway, which regulates glycolysis and protein synthesis [40].

To our knowledge, there are very few studies on the effects of metformin on keratinocytes. Under normal conditions, mTORC1 activity is suppressed when keratinocytes progress from proliferation to terminal differentiation. However, in inflammatory conditions, cytokines such as IL1β, IL17A, and TNFα excessively stimulate mTORC1 activity, leading to excessive keratinocyte proliferation and impaired differentiation. Metformin helps restore the balance by inhibiting mTORC1 activity, mainly through the activation of AMP-activated protein kinase (AMPK). This inhibition of mTORC1 restores normal keratinocyte differentiation and modulates key transcription factors such as the hypoxia-inducible factor HIF-1α and the signal transducer and activator of transcription STAT3. STAT3, together with HIF-1α, activates glycolysis and inflammatory responses, which are reduced when metformin blocks the mTORC1 signalling pathway [41].

Metformin treatment significantly reduces the severity of the disease, wherein 76% of patients show improvement in Sartorius score and almost half progressed from severe to mild/moderate HS. Additionally, the quality of life has improved in 64% of patients, with a reduction in DLQI score of more than 50%, and the number of lost work days decreased from 1.5 to 0.4 per month [42]. Another study showed improvement in the disease in 68% of patients after six months of metformin therapy, while 19% of them had complete remission with metformin as monotherapy [43].

Conclusions

The rate of obesity and overweight in children in the Republic of North Macedonia is on the rise, potentially contributing to an increase in the number of diagnosed cases of diabetes in adulthood. Although there is a lack of relevant epidemiological studies that would confirm an increase in the number of patients with HS, the close correlation between obesity and the development of this disease suggests that primary

prevention should focus on nutrition in childhood and the promotion of maintaining optimal body weight.

Obesity is a key factor in the development of metabolic disorders in patients with HS, which most often include insulin resistance (IR), hypertriglyceridemia, metabolic syndrome, metabolic-associated steatohepatitis (MASH) and type 2 diabetes (type 2DM). Although there is considerable heterogeneity of metabolic disorders in patients with HS, basically all of them are associated with dysregulation of mTOR signalling pathway, which plays a central role in cellular metabolic regulation.

Patients with HS exhibit serum proinflammatory biomarkers similar to those observed in meta inflammation. Chronic inflammation in HS can worsen metabolic disorders, while low-grade metabolic inflammation complicates the clinical findings of HS, creating a vicious circle (circulus vitiosus).

The promotion of a healthy lifestyle and maintaining optimal body weight from an early age are key preventive measures against the disease. Weight reduction can have a significant positive impact on the course of the disease.

The introduction of metformin therapy is recommended for obese patients with HS and metabolic disorders, which is applied in parallel with the standard therapeutic protocol.

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