

Management of Hidradenitis Suppurativa in Patients with Metabolic Comorbidities

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Hidradenitis suppurativa is a chronic inflammatory skin condition associated with an increased prevalence of individual metabolic conditions such as insulin resistance, obesity, hyperlipidemia, hypertension, and with the metabolic syndrome, as a constellation of these risk factors. This places affected patients at an increased risk of early cardiovascular morbidity and mortality. Moreover, many of the therapeutic options, including the newer biologics, used in the treatment of hidradenitis suppurativa have both beneficial and adverse metabolic effects. Therefore, it is critical for physicians to consider the complex interactions between the disease process and the treatment options in the holistic management of these patients with an intrinsically higher risk of metabolic consequences. Other chronic systemic inflammatory diseases such as psoriasis and rheumatoid arthritis have been studied more extensively with regard to their associations and share an underlying link with the metabolic syndrome; we can draw upon the existing knowledge in our understanding and management of hidradenitis suppurativa. (*Ann Dermatol* 28(2) 147~151, 2016)

-Keywords-

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INTRODUCTION

Hidradenitis suppurativa, or acne inversa, is a disorder of the follicular portion of the folliculo-pilo-sebaceous unit, with relapsing chronic skin inflammation characterized by subcutaneous abscesses and sinuses¹. It occurs predominantly in skin folds of the axilla, groins, and buttocks, and heals with substantial scarring, negatively impacting the quality of life². The onset is insidious, usually occurring after puberty in the second or third decades of life, with women more commonly affected². The greater female preponderance may imply greater end-organ sensitivity to androgens. Androgen receptors are regulated by the forkhead box transcription factor O1 (FoxO1), insulin and insulin-like growth factor-1 (IGF-1), which are also key factors involved in the metabolic syndrome³.

The pathogenesis of hidradenitis suppurativa is postulated to begin with hair follicle occlusion leading to lymphohistiocytic inflammation¹, with the involvement of pro-inflammatory cytokines interleukin (IL)-1 beta, IL-10, IL-12, IL-23, and tumor necrosis factor (TNF)-alpha^{4,5}, and over-activation of the mammalian target of rapamycin complex-1 (mTORC1) signalling³. Over-activated mTORC1 increases androgen hormonal secretion and contributes towards driving the proliferation of sebaceous follicles. Hence, the disease, at least as far as the initial plugging of the follicular epithelium is concerned, is driven by intracellular mechanisms that are in turn driven by, amongst other factors, diet. Indeed, the diet that is responsible for the metabolic syndrome contains the same metabolic drivers leading to the androgen-driven overproduction of sebum and overgrowth of the intra-ductal keratinocytes¹.

HIDRADENITIS SUPPURATIVA ASSOCIATED WITH THE METABOLIC SYNDROME

It is well established that chronic systemic inflammatory conditions such as rheumatoid arthritis and psoriasis are associated with the metabolic syndrome^{6,7} which comprises a combination of the following conditions: insulin resistance, abdominal obesity, atherogenic hyperlipidemia, hypertension, a pro-inflammatory state, and a pro-thrombotic state⁸. In contrast, hidradenitis suppurativa is a more localized inflammation of the skin. Nevertheless, in recent years, several studies have shown a clear association between hidradenitis suppurativa with the individual metabolic conditions, and with the metabolic syndrome as a constellation of risk factors⁹.

An Israeli cross-sectional study¹⁰ which included 3,207 patients with hidradenitis suppurativa and 6,412 controls, showed that hidradenitis suppurativa was significantly associated with the metabolic syndrome, with an odds ratio (OR) of 1.61, and with the individual risk factors of diabetes mellitus (OR 1.41), obesity (OR 1.71), hyperlipidemia (OR 1.14) and hypertension (OR 1.19). A Danish cross-sectional hospital-based population study¹¹ identified 32 patients with hidradenitis suppurativa from an outpatient dermatology clinic, 326 patients with hidradenitis suppurativa from the general population, and 14,851 controls from the general population and found an increased prevalence of metabolic syndrome amongst the hidradenitis suppurativa patients from the hospital and from the general population, with an OR of 5.74 and 2.44, respectively, compared to the control group. The OR was 6.38 and 2.56, respectively for diabetes mellitus, 3.62 and 2.24 for obesity, and 2.97 and 1.94 for lower levels of high-density lipoprotein (HDL) cholesterol. Overall, the ORs were higher for the hidradenitis suppurativa patients from the hospital group than from the population group. This is comparable to a German study¹² that examined 80 hidradenitis suppurativa patients hospitalized for surgical treatment and 100 controls, which showed an increased prevalence of metabolic syndrome, with an adjusted OR of 4.46. The trend was similar, in that the hidradenitis suppurativa group were 4.09 times more likely to have hyperglycemia, 5.88 times more likely to have central obesity, 2.24 times more likely to have hypertriglyceridemia, and 4.56 times more likely to have low HDL levels.

A possible reason obesity is strongly associated with the prevalence of chronic inflammatory conditions including psoriasis and possibly hidradenitis suppurativa may be because adipose tissue actively produces pro-inflammatory adipocytokines, including IL-6, and TNF-alpha¹³. The prevalence of metabolic syndrome in patients with hidradenitis

suppurativa may be even higher than in patients with psoriasis, with an OR of approximately 6.00 compared to 2.00¹². Surprisingly, there is a lack of association between disease duration and severity (by Sartorius score) and the development of metabolic syndrome in patients with hidradenitis suppurativa^{11,12} compared to psoriasis⁷. In addition, the metabolic syndrome affects much younger hidradenitis suppurativa patients¹². This is significant as the cardiovascular consequences of metabolic syndrome are likely to afflict these younger patients earlier, leading to decreased life expectancy.

While there is no clear genetic causality between hidradenitis suppurativa and metabolic syndrome, the association may be explained by the systemic effects of chronic inflammation, with common pro-inflammatory cytokines such as IL-1 and TNF-alpha upregulated in cardiovascular disease¹⁴, common lifestyle habits of poor dietary control, lack of exercise, and tobacco smoking¹⁵. In particular, a high glycemic and high dairy protein diet increases insulin and IGF-1 signaling at the cellular level. FoxO1 and mTORC1 are involved in the detection of nutritional status and subsequent androgen signaling to drive the regulation of protein and lipid synthesis, and cell differentiation including the proliferation of sebaceous glands and keratinocytes³. This may form the common basis for the metabolic syndrome, in particular, obesity and insulin resistance, and the initial triggers for the plugging of the follicular component of the folliculo-pilo-sebaceous unit in hidradenitis suppurativa.

MANAGEMENT OF HIDRADENITIS SUPPURATIVA IN PATIENTS WITH METABOLIC COMORBIDITIES

The treatment of hidradenitis suppurativa is challenging due to its chronic course and frequent relapses. There is no one overwhelmingly superior treatment over another, with the use of various treatment options directed by the severity of the disease. The first line of treatment for mild disease is often topical or oral antibiotics¹⁶, with the second line consisting of systemic retinoid acitretin¹⁷. Third-line options or adjunctive therapy include anti-androgens (cyproterone acetate-ethinylestradiol)¹⁸ and metformin¹⁹. In moderate disease, biologics such as infliximab²⁰, etanercept²¹, and adalimumab²² have been tried in addition to surgical and laser options. Anakinra²³ has been successfully used in the treatment of severe disease.

There are both beneficial and deleterious metabolic effects of the above treatment options with implications for the overall management of patients with hidradenitis suppurativa. Acitretin has a known side effect of worsening the

lipid profile¹⁷, which requires regular monitoring during therapy. The adjunct use of anti-androgens such as cyproterone acetate-ethinylestradiol may lead to thrombotic events and weight gain²⁴, which may further contribute towards the development of metabolic syndrome. Interestingly, but perhaps not surprisingly, the insulin sensitizer metformin, with its range of beneficial effects on the metabolic system beyond improving glycemic control, has been shown to control hidradenitis suppurativa with minimal side effects. Dysfunctional mTORC1 signaling, and, therefore, dysfunctional cell proliferation and metabolism, have been implicated in conditions such as obesity, diabetes mellitus, and cancer. Metformin has been found to inhibit mTORC1 through various mechanisms²⁵, resulting in the reduction of hyperandrogenism and lipid levels, which explains the improvement in the skin condition.

While there have been some studies examining the effect of other classes of oral hypoglycemic agents such as sulphonylureas and the newer dipeptidyl-peptidase-4 inhibitors on controlling autoimmune diseases including psoriasis^{26,27}, there is no published information on their effects in hidradenitis suppurativa. Infliximab, etanercept, and adalimumab are biologics targeted against the TNF-alpha receptors, and anakinra is an IL-1 receptor antagonist. The main adverse effect profile of biologics is not metabolic related but are instead serious infections, induction of lupus-like syndromes, and malignancies². In fact, some anti-TNF-alpha biologics have been demonstrated to lower C-reactive protein levels, decrease lipid peroxidation, and increase HDL levels in psoriasis patients²⁸, which are factors that contribute towards an improved metabolic profile. Epidemiological data has shown that patients with other chronic systemic inflammatory diseases like rheumatoid arthritis or psoriasis, who were treated with anti-TNF-alpha biologics, have a lower risk of developing diabetes mellitus, compared to other treatment options²⁹. On the other hand, there are small studies that suggest adverse metabolic effects of hyperlipidemia and weight gain in psoriasis patients who have received anti-TNF-alpha biologics. Lestre et al.³⁰ examined the impact of etanercept on the lipid profile of patients with psoriasis in a retrospective cohort study and found that levels of total cholesterol, low-density lipoprotein-cholesterol, and triglycerides increased after 24 weeks of treatment. However, none of the results were statistically significant to draw definite conclusions. Another retrospective cohort study by Gisondi et al.³¹ demonstrated that a quarter of the cohort of patients with psoriasis experienced on average, a four to ten kilogram weight gain after treatment with infliximab and etanercept. This weight gain was compared to patients treated with methotrexate alone and was found to

be statistically significant. There is no published data on any metabolic side effects of anakinra.

Lastly, lifestyle modifications in conjunction with medical therapy should be emphasized in the management of hidradenitis suppurativa. Many encouraging studies have demonstrated resolution of the skin condition after weight loss either through dietary measures alone³² or with the aid of bariatric surgery³³. In particular, weight loss of more than 15% results in a significant improvement in the severity of the skin condition³⁴. Latest insights into how the over-activity of diet-related mTORC1 signaling may form the trigger for the initial follicular plugging event in hidradenitis suppurativa provide a basis for dietary intervention, which should aim to reduce the intake of hyperglycemic carbohydrates and insulinotropic dairy proteins³. Tobacco smokers have been found to suffer from more severe hidradenitis suppurativa¹⁵, likely secondary to the effect of nicotine on promoting infundibular epithelial hyperplasia and thus follicular plugging. While there are no studies examining whether smoking cessation directly improves outcomes in hidradenitis suppurativa, it appears to reduce the development of the metabolic syndrome³⁵.

CONCLUSION

Hidradenitis suppurativa, with its significant psychosocial burden and metabolic implications, is not a disease that is just skin-deep. The appreciation of how the treatment options affect metabolic outcomes beyond the skin can lead to more holistic management, as the metabolic syndrome is a crucial predictor of cardiovascular mortality. In addition, it is worthwhile to focus on the modifiable lifestyle risk factors in the holistic management of these patients. Early intervention with systemic biologics for skin conditions may be beneficial in curbing the development of associated metabolic syndrome. However, further studies in these areas to examine the causal relationships between hidradenitis suppurativa and the individual components of the metabolic syndrome, the effect of therapy on reduction of cardiovascular morbidity and mortality, and the impact of lifestyle modifications on both the skin and metabolic disease will be necessary. Moreover, since more is known about the association of psoriasis, another chronic inflammatory skin condition, and the metabolic syndrome, we should leverage on the existing knowledge of their interactions to further research and treatment of hidradenitis suppurativa.

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