INSULIN RESISTANCE IN HIDRADENITIS SUPPURATIVA: A CASE-CONTROL STUDY

**Running head:** Insulin Resistance in Hidradenitis suppurativa


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ABSTRACT

Background: The association between chronic inflammatory diseases, such as rheumatoid arthritis and psoriasis, and insulin resistance (IR) has been well established. Hidradenitis suppurativa (HS) is a chronic inflammatory cutaneous disease that affects the apocrine gland-bearing areas of the body.

Objective: We aimed to determine the prevalence of IR in patients with HS.

Methods: This cross-sectional, case-control study enrolled 137 subjects, 76 patients with HS and 61 age- and gender-matched controls. Demographic data, clinical examination of HS patients, anthropometric measures, cardiovascular risk factors and laboratory studies were recorded. The homeostasis model assessment of IR (HOMA-IR) was calculated in all participants by measuring fasting plasma glucose and insulin levels.

Results: The median (IQR) HOMA-IR value in HS patients was significantly higher [2.0 (1.0-3.6)] than in controls [1.5(0.9-2.3)] (p=0.01). The prevalence of IR was significantly higher in cases (43.4%) compared with controls (16.4%) (p=0.001). In the linear regression multivariable analysis after adjusting for age, sex and body mass index (BMI), HS remained as a significant factor for a higher HOMA-IR [2.51(0.18) vs 1.92(0.21); p=0.04]. The HOMA-IR value and the prevalence of IR did not differ significantly among HS patients grouped by severity of the disease.

Conclusion: Our results show an increased frequency of IR in HS. Thus, we suggest HS patients to be evaluated for IR and managed accordingly.
Key words: Hidradenitis suppurativa; Insulin resistance; Metabolic syndrome; HOMA-IR; Cardiovascular disease.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease of the hair follicle characterized by relapsing painful inflammatory nodules, abscesses and fistula tracts in the apocrine gland-bearing areas of the body, most commonly in the axillae, inguinal and anogenital regions. HS incidence ranges between 4 and 10 cases per 100,000 population/year and prevalence between 0.2% and 4%. Although its pathogenesis is not completely understood, it is postulated to begin with disturbed keratinization of the follicular infundibulum which results in follicular occlusion. Current knowledge indicates that inflammation induced by abnormal immune response plays an important role in the pathogenesis of HS. To this respect, several investigations have shown an increased expression of proinflammatory cytokines, such as tumor necrosis factor alpha (TNF-α) and interleukin (IL) IL-1β in HS lesions. Moreover, the presence of elevated serum TNF-α and IL-6 levels in HS patients has been reported, suggesting a systemic inflammatory activation as a pathogenic mechanism for the disease.

HS is currently recognized as a systemic inflammatory condition extended beyond the skin, and there is an increasing evidence of an association between HS and other comorbidities, including cardiovascular (CV) risk factors, inflammatory joint disorders, inflammatory bowel disease, endocrinological disorders and psychological disorders. In a recently population-based cohort study, HS was associated with a significantly increased risk of major adverse CV events, including myocardial infarction, ischemic stroke and CV-associated death. In keeping with these findings, we and others have recently demonstrated an increased...
prevalence of subclinical atherosclerosis in HS patients. Furthermore, HS has also been associated with a greater prevalence of CV risk factors, such as diabetes mellitus (DM), dyslipidaemia, cigarette smoking, metabolic syndrome (MS) and obesity. However, it should be noted that the premature and accelerated development of atherosclerosis in patients with HS is independent of these CV risk factors. This fact suggest that HS itself may be an independent risk factor for atherosclerotic CV disease, and that other disease-related factors may be implicated in the premature development of the atherogenic process in HS patients.

Insulin resistance (IR) represents the best predictor of type 2 DM and plays a central role in the high CV risk of the MS. The metabolic changes induced by IR may contribute to the development of accelerated atherosclerosis and CV disease. This occurs by increasing serum glucose and insulin concentrations, but also through mechanisms that involve dyslipidaemia, hypertension, and systemic inflammations. In this sense, IR is closely related to the presence of a chronic systemic inflammation and has been linked to several chronic inflammatory conditions such as rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), and psoriasis. Thus, it has also been postulated that IR might to explain the increased CV comorbidity associated with these inflammatory diseases.

Taking all of these considerations into account, the aim of this study was to analyze, for the first time to our knowledge, the prevalence of IR in a relatively large, ethnically homogeneous cohort of HS patients. Furthermore, we sought to assess whether there is a correlation between IR and the severity of the HS.
METHODS

Study participants and protocol

This was a cross-sectional, case-control study that included 76 patients with HS and 61 age and gender-matched controls. The HS patients were recruited from our Dermatology outpatient clinic at the University Hospital Marques de Valdecilla (Santander, Northern Spain). The diagnosis of HS was always done by dermatologists based on clinical findings, including a history of recurrent inflamed and non-inflamed nodules, abscesses and sinus tracts involving of typical skin areas. The control group consisted of hospital medical staff and of subjects who attended the dermatology department due to skin disorders other than HS, such as melanocytic nevus, warts or epithelioma.

The exclusion criteria for both groups were as follows: (a) age<18 years; (b) documented history of major adverse cardiovascular events; (c) type 1 or type 2 DM; (d) chronic kidney or liver diseases; (e) diseases that might influence glucose metabolism (such as Cushing syndrome, thyroid disorders, polycystic ovary syndrome…); (f) treatment with drugs that might affect carbohydrate metabolism (i.e. systemic corticosteroids, retinoids, cyclosporine, hypoglycaemic drugs…) in the previous 6 months; and (g) concomitant inflammatory disorders, such as cutaneous diseases (psoriasis or atopic dermatitis among others), inflammatory bowel disease, inflammatory arthritis (RA or ankylosing spondylitis), or autoimmune or connective tissue diseases (scleroderma, SLE…).

The study protocol was approved by the local institutional ethics committee and all the participants provided informed written consent.

The severity of HS was assessed by the HS Physician Global Assessment (HS-PGA), which includes 6 stages (scale 0-5) (Table I). According to HS-PGA and as we have previously described in detail, HS was classified as moderate-severe-very severe (PGA>3)
and as minimal-mild HS (PGA<3). The Hurley grade of disease severity for each zone involved at the time of clinical examination was also evaluated. Moreover, information on previous treatment for HS was also assessed in all the patients.

All the participants provided information on their demographic features, past medical history, and data on current and prior systemic therapy. Traditional CV risk factors were defined as previously reported. Body height and weight, body mass index (BMI), waist circumference (WC), systolic blood pressure (BP) and diastolic BP were measured in all patients and controls. BMI was calculated as weight (kg)/ [height (m)]². Blood samples were drawn after an overnight fast in all participants, and serum total cholesterol (TC), HDL-c, low-density lipoprotein cholesterol (LDL-c), triglycerides, glucose, high-sensitivity C-reactive protein (hs-CRP) levels and erythrocyte sedimentation rate (ESR) were assessed.

MS was diagnosed by the presence of three or more criteria according to the National Cholesterol Education Program´s Adult Treatment Panel III (ATPIII): waist circumference >102 cm in men or >88 cm in women; hypertriglyceridaemia ≥150 mg/dl or lipid lowering treatment; HDL-c <40 mg/dl in males and <50 mg/dl in females; BP ≥130/85 mm Hg or current use of medication for hypertension; fasting plasma glucose ≥110 mg/dl or use of antidiabetic drugs.

The homeostatic model assessment for IR (HOMA-IR) was calculated using this formula: fasting insulin level (µIU/ml) x fasting glucose level (mg/dl)/405. IR was defined as an elevated HOMA-IR value of >2.5, based on the original HOMA research.
**Statistical analysis**

Results were expressed as number (percentage), mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Mann-Whitney U-test was performed to compare quantitative variables and Chi-square test or Fisher exact test, to compare qualitative variables. Multivariable general linear regression models, using HOMA-IR levels as dependent variable was performed to assess the relationship between HS and IR. A p value <0.05 was considered statistically significant. All the analyses were performed with the Stata V.12/SE package (Stata Corp, College Station, Texas, USA).

**RESULTS**

A total of 137 participants, 76 patients with HS and 61 control subjects were included in the study. Table 2 shows the main demographic, clinical and laboratory findings of patients and controls. Patients and controls were similar in age and sex (51% and 49% women, respectively, p=0.80). According to HS-PGA, 32 (42.1%) patients were classified as having minimal-mild HS (HS-PGA score<3) and the remaining 44 (57.9%) as having moderate-severe-very severe HS (HS-PGA score≥3). Nineteen HS patients (25%) were classified as Hurley stage I, 44 (57.8%) as stage II and 13 (17.1%) as stage III. Twenty-three HS patients (30.2%) were on anti-TNF-α agents.

There was no significant statistical difference between patients and controls in terms of height and triglyceride levels. The HS group had significantly higher weight, BMI, waist perimeter, systolic and diastolic BP than controls. Moreover, HS group showed lower serum HDL levels than the control group (p<0.05).
Noteworthy, fasting serum glucose and insulin levels, as well as HOMA-IR values were higher in HS patients than in controls (Figure 1). As seen in the table 2, IR, defined as a HOMA-IR value greater than 2.5, was observed in 43% of cases and 16 % of controls (p=0.001). Besides, the prevalence of MS was 3 times more common in HS patients than in control subjects.

In the general linear regression multivariable analysis after adjusting for age, sex and BMI, HS remained as a significant factor for HOMA-IR [mean (SE) 2.51(0.18) vs 1.92(0.21); p=0.04].

To determine if the severity of the HS had any impact on the association between HS with both IR and MS, we divided the HS patients into two subgroups, according to their HS-PGA score (>3 or <3). There was no a significant association between disease severity and the prevalence of the MS and/or the HOMA-IR value. Although IR was higher in patients with moderate-severe HS (52.3%) than in those with HS-PGA score <3 (31.3%), this difference did not reach statistical significance (p=0.06) (Table 3).

DISCUSSION

The current study shows that patients with HS have a significantly higher prevalence of IR compared to age- and sex-matched controls. Moreover, and in accordance with other previous reports,27-29 we found in our series of HS patients a significantly higher prevalence of MS than in the control group. Moreover, patients with HS were more obese and had higher prevalence of hyperglycemia, lower HDL-cholesterol levels and raised systolic and diastolic BP than control subjects. Nevertheless, no correlation was observed between the severity of HS and both IR and MS.
Our results suggest that HS may predispose to the development of IR. In this sense, we consider that the high prevalence of obesity found in our HS patients might have influenced the obtained results, since it is well-known that obesity can impair the effects of insulin. However, even after adjustment for BMI, age and sex, the HOMA-IR value remained significantly higher in HS patients than in controls. This fact suggest that HS itself may be an independent risk factor for the development of IR.

A possible explanation for the link between HS and IR could be the presence of chronic inflammation that occurs due to persistent secretion of several pro-inflammatory cytokines, such as TNF-α and IL-6. In this regard, TNF-α is considered nowadays one of the major pathogenic factors for HS as demonstrated by the efficacy of the anti-TNF-α agent adalimumab in the treatment of this disease. Furthermore, it is known that TNF-α plays a key role in the impairment in glucose tolerance and insulin sensitivity. Thus, TNF-α is able to induce insulin signalling defects by acting on adipocytes and muscle cells, impair insulin signalling through inhibition of tyrosine kinase activity of the insulin receptor, and suppress the secretion from adipocytes of adiponectin, an anti-inflammatory molecule that also regulates insulin sensitivity. To this respect, Malara et al. recently reported that patients with HS have significantly decreased the serum adiponectin levels.

On the other hand, it has been shown that IL-6 induces IR in hepatocytes. In this scenario, the increased inflammatory burden in HS could alter glucose metabolism and induce IR. IR may in turn contribute to endothelial dysfunction, leading subsequently to atherosclerosis and finally to long-term clinical events, like myocardial infarction or stroke.

Eddy et al observed that IR prevention may reduce myocardial infarction risk by 42% in young adults. Thus, it is worth emphasizing that several studies have demonstrated a beneficial effect of the TNF-α blockade on the mechanisms of accelerated atherogenesis in patients with chronic inflammatory diseases, such as RA or psoriasis, including specifically...
the effect of these agents on IR.\textsuperscript{20,36} In this regard, it should be noted that about 30% of our patients were on adalimumab therapy. Anti-TNF-\(\alpha\) therapy may therefore have improved the insulin sensitivity in these patients, underestimating the actual prevalence of IR in HS. On the other hand, it is also noteworthy that several studies have shown that metformin, an antihyperglycemic agent used for treating type 2 DM, could be beneficial in the treatment of HS.\textsuperscript{37-38} Metformin decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Although metformin in HS acts by a mechanism yet unknown, it has been suggested that the beneficial effects of this drug might be, at least in part, through lowering the IR that is present in some patients with HS.\textsuperscript{38}

Our study has the inherent limitations of its cross-sectional design. Despite these limitations, we think that it provided important insights into the association of HS and IR that may have clinical implications for the overall management of these patients.

In conclusion, our study provides evidence that patients with HS have a significant higher prevalence of IR than controls. There is growing evidence that HS is not only a cutaneous disease but a chronic systemic inflammatory disorder with increased CV risk. Thus, it is important to control known modifiable CV risk factors according to current guidelines, as well as monitoring serum glucose levels in patients with HS. Besides its clinical benefit, treatment with anti-TNF-\(\alpha\) agents can provide an effective treatment strategy for the prevention and control of the development of IR. Nevertheless, further investigations are needed to elucidate the beneficial effects of biological therapy on IR in patients with HS.
REFERENCES


| Clear (score=0) | No abscesses, no draining fistulae, no inflammatory nodules, and no noninflammatory nodules |
| Minimal (score=1) | No abscesses, no draining fistulae, no inflammatory nodules but presence of noninflammatory nodules |
| Mild (score=2) | No abscesses, no draining fistulae, and 1-4 inflammatory nodules, or 1 abscess or draining fistula and no inflammatory nodules |
| Moderate (score=3) | No abscesses, no draining fistulae and ≥5 inflammatory nodules and ≥1 inflammatory nodule, or 2-5 abscesses or draining fistula and < 10 inflammatory nodules |
| Severe (score=4) | 2-5 abscesses or draining fistula and > 10 inflammatory nodules |
| Very severe (score=5) | >5 abscesses or draining fistula |

Table 1. Hidradenitis suppurativa-Physician’s Global Assessment (HS-PGA)
Table 2. Demographic, clinical and laboratory findings of patients with HS and controls

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HS patients (n=76)</th>
<th>Controls (n=61)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>42.6 ± 11.8</td>
<td>45.6 ± 12.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.67 ± 0.1</td>
<td>1.69 ± 0.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td>82.5 ± 17.9</td>
<td>76.1 ± 16.9</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>29.3 ± 5.4</td>
<td>26.4 ± 4.5</td>
<td>0.004</td>
</tr>
<tr>
<td>Waist perimeter, cm</td>
<td>99.5 ± 14.1</td>
<td>91.2 ± 13.7</td>
<td>0.001</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>132.3 ± 16.5</td>
<td>124.0 ± 15.9</td>
<td>0.003</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>81.8 ± 13.9</td>
<td>77.0 ± 8.4</td>
<td>0.02</td>
</tr>
<tr>
<td>HDL-c, mg/dl</td>
<td>46.0 (41.0-56.8)</td>
<td>53.0 (46.5-70.0)</td>
<td>0.01</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>96.6 ± 45.2</td>
<td>96.9 ± 66.7</td>
<td>0.97</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dl</td>
<td>94.9 ± 13.7</td>
<td>89.1 ± 8.1</td>
<td>0.003</td>
</tr>
<tr>
<td>Fasting plasma insulin, µIU/ml</td>
<td>10.1 (5.4-16.7)</td>
<td>7.3 (4.9-10.7)</td>
<td>0.009</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.0 (1.0-3.6)</td>
<td>1.5 (0.9-2.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Insulin Resistance, %</td>
<td>43.4</td>
<td>16.4</td>
<td>0.001</td>
</tr>
<tr>
<td>Metabolic Syndrome, %</td>
<td>34.2</td>
<td>11.5</td>
<td>0.002</td>
</tr>
</tbody>
</table>

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, Homeostatic model assessment for insulin resistance. *Values are expressed as mean ± SD or median (interquartile range) as appropriate.
Table 3. Study parameters in the two HS severity groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PGA &lt; 3 (n=32)</th>
<th>PGA ≥ 3 (n=44)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>39.1 ± 11.6</td>
<td>45.2 ± 11.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.68 ± 0.1</td>
<td>1.67 ± 0.1</td>
<td>0.79</td>
</tr>
<tr>
<td>Weight, Kg</td>
<td>79.6 ± 20.2</td>
<td>84.7 ± 15.9</td>
<td>0.22</td>
</tr>
<tr>
<td>BMI, Kg/m²</td>
<td>28.0 ± 5.5</td>
<td>30.2 ± 5.2</td>
<td>0.08</td>
</tr>
<tr>
<td>Waist perimeter, cm</td>
<td>95.8 ± 15.3</td>
<td>102.1 ± 12.6</td>
<td>0.05</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>130.2 ± 17.4</td>
<td>133.9 ± 15.8</td>
<td>0.33</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>79.0 ± 10.1</td>
<td>83.9 ± 16.0</td>
<td>0.13</td>
</tr>
<tr>
<td>HDL-c, mg/dl</td>
<td>49.5 (42.0-62.0)</td>
<td>45.5 (41.0-55.8)</td>
<td>0.15</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>81.1 ± 37.4</td>
<td>107.8 ± 47.4</td>
<td>0.01</td>
</tr>
<tr>
<td>Fasting plasma glucose, mg/dl</td>
<td>93.8 ± 15.8</td>
<td>95.7 ± 12.2</td>
<td>0.56</td>
</tr>
<tr>
<td>Fasting plasma insulin, µIU/ml</td>
<td>7.1 (1.4-16.9)</td>
<td>11.4 (8.1-16.7)</td>
<td>0.08</td>
</tr>
<tr>
<td>HOMA</td>
<td>1.4 (0.9-3.6)</td>
<td>2.6 (1.2-3.7)</td>
<td>0.17</td>
</tr>
<tr>
<td>Insulin Resistance, %</td>
<td>31.3</td>
<td>52.3</td>
<td>0.06</td>
</tr>
<tr>
<td>Metabolic Syndrome, %</td>
<td>25.0</td>
<td>40.9</td>
<td>0.14</td>
</tr>
</tbody>
</table>

PGA, physician global assessment; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein; HOMA-IR, Homeostatic model assessment for insulin resistance. *Values are expressed as mean ± SD or median (interquartile range) as appropriate.
Figure 1. Box plot showing median HOMA-IR values in HS patients and controls.

\[ p = 0.01 \]