Association between hidradenitis suppurativa and metabolic syndrome: Systematic Review and Meta-analysis

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1. Introduction

   a. Problem Description

Metabolic Syndrome (MS) is a burden public health problem worldwide due to the increase prevalence of obesity. Furthermore, obesity is the result of inadequate lifestyles and diet, and lack of exercise routine since young ages, with a prevalence in Latin America around 17%, even higher in main cities, around 21% (1).

Several studies have shown that MS is a risk factor for developing cardiovascular disease (CVD). A meta-analysis that included 172,573 individuals showed that MS patients have increased almost twice risk of CVD and death (OR 1.78, 95% CI 1.58-2.00). It is also known that patient who meet the criteria for SM, have six-fold increase risk to develop Diabetes Mellitus (DM)(2).

Hidradenitis suppurativa (HS) is a chronic, inflammatory, debilitating skin disease, and recent studies have shown its association with MS. In a meta-analysis conducted by Tzellos et a (3), authors showed that patients with HS had twice of risk to develop MS (OR 2.22, 95% CI 1.62-3.06, P < 0.001) than controls. This association is even higher in hospital population, than in general population(3).

The first study that reported this association was carried out in Germany(4). They found that the prevalence of MS in the HS group was 40.0% versus 13.0% in the control group (OR 4.46, 95%CI 2.02-9.96; p<0.001). However, they did not adjusted they result for covariates. On the other hand, Shalom et al.(5) showed that after adjustment for several covariates (age, sex, diabetes, hypertension, hyperlipidaemia, obesity and smoking status) this association was not as higher as the first, but significant (OR 1.61, 95%CI 1.36-1.89).

Thus, to the extent that HS is associated with MS, these patients will have increased risk of developing CVD and DM. However, data is biased as adjusted and unadjusted studies were included in observational studies and meta-analyses. Therefore, we still lack of information of the real dimension of the association between HS and MS, after adjusting for several covariates.

   b. Problem formulation

Is there an association between Hidradenitis suppurativa and Metabolic Syndrome?

   c. Justification

There are studies reporting an association between HS and MS, with prevalence ranging from 35% to 50% in HS cohorts. However, we still lack of studies with adjusted ORs only, as the last meta-analysis included mix adjusted and unadjusted OR. Therefore, it justifies the conduct of this study.
Results are of great interest since they serve as basis for hypotheses and studies of greater complexity, which are needed to further investigate efficient treatments based on improving the MS.

d. Goals
   • Main goal
     • To evaluate the association between HS and MS in observational studies with adjusted results.
   • Secondary goals
     • To evaluate the association between HS and MS in observational studies with crude results.
     • To compare the results of adjusted ORs vs. results with crude ORs in order to see the differences of degree of association.
     • To conduct a regional analysis by subgroup, grouping studies have been conducted in Latin American, North American, European, Asian and African population, with both crude and adjusted ORs when possible.
     • To conduct a subgroup analysis, according to several characteristics as type of population (hospital vs. general), type of MS criteria (IDF vs. NCEP-III vs. AHA), etc., with both crude and adjusted ORs when possible.
     • To describe observational studies of HS and MS.

e. Hypothesis
   • Null Hypothesis (H0)
     HS is not associated with MS in observational studies.
   • Alternative Hypothesis (H1)
     HS is associated with MS in observational studies.

2. Theoretical framework

a. Background

A recent meta-analysis found a significant association between HS and MS. They included five studies with 3888 patients with HS and 21,585 controls. A significant association with MS was detected with a pooled OR of 2.22 (95% CI 1.62–3.06, P < 0.001). No evidence of publication bias was detected. Heterogeneity was significant ($I^2 = 77\%$). Sensitivity analysis for origin of patients with HS (general population or hospital-based) did not change the results and the associations continued to be significant for both populations. For patients with HS from the general population the pooled OR was 1.59 (95% CI 1.40–1.80). The association for patients with HS from
dermatology clinics was much higher at 3.20 (95% CI 2.07–4.96). However, authors used adjusted and unadjusted OR while pooling the results.

2.2. Definitions

2.2.1. Hidradenitis suppurativa

Hidradenitis suppurativa/acne inversa (HS) is a chronic, inflammatory, recurrent, debilitating skin disease of the hair follicle that usually presents after puberty with painful, deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly the axillae, inguinal and anogenital regions(6). Prevalences are reported as low as 0.00033% and as high as 4.1%(7).

The pathogenesis of HS is not completely understood. Recent research has led to greater insight into the mechanisms involved in the disease. The primary defect in HS pathophysiology rests with the hair follicle. Follicular occlusion, followed by follicular rupture, and a foreign body-type immune response are necessary conditions for the development of clinical HS. A specific genetic signature and environmental factors, such as cigarette smoking, microbial colonization, and adiposity, all contribute to the HS phenotype(8).

Oclusion of the follicular infundibulum in HS pathogenesis is a certainty. Regardless of disease duration, follicular occlusion is an early feature in the pathogenesis, as a result of hyperkeratosis and hyperplasia of the epithelial lining of terminal follicles(9).

Follicular occlusion leads to dilatation of the hair follicle followed by rupture and discharge of contents, including keratin and bacteria into the surrounding dermis. Therefore, vigorous inflammatory response that recruits neutrophils, lymphocytes, and histiocytes(10). It has been postulated that deficiencies in the follicular skin immune system may result in microbial overgrowth, while another theory suggests that an overactive immune system may result in an inflammatory response to normal, harmless flora(8).

HS is epidemiologically associated with smoking. Tobacco smoke is composed of thousands of chemicals that activate keratinocytes, fibroblasts, and immunocytes via at least 2 types of receptors: nicotinic acetylcholine receptors and aryl hydrocarbon receptors. In keratinocytes, this leads to acanthosis, infundibular epithelial hyperplasia, and excessive cornification. Tobacco smoke also induces proinflammatory cytokines like TNF-a, interleukins (ILs)-1a, -1b, and -8, leading to neutrophil chemotaxis and TH17 cell induction(8, 11).

Hormones may induce follicular occlusion via increased proliferation of follicular keratinocytes, leading to intrafollicular acanthosis, keratinosis, and plugging of the follicle. However, a normal androgen profile is found in most of HS patients.

Obesity may aggravate HS via increased skin friction. Mechanical stress is associated with worsening of HS by increasing follicular occlusion
and follicular rupture. Mechanical compression, friction, or shear forces are sensed by several mechanotransducers in human skin. These signals altogether result in the activation of transcription factors that translocate to the nucleus and activate mechanoresponsive genes. Activation of these genes may contribute to local skin irritation, sweat retention, intrafollicular acanthosis, and keratinization. In addition, the proinflammatory state, which is common in obese individuals, may synergize with proinflammatory cytokines found in lesional HS skin, contributing to overall inflammation.

The cytokines and immune pathways that drive inflammation in HS continue to be investigated. TNF-α, a proinflammatory cytokine produced by innate and adaptive immune cells, has a critical role in several autoinflammatory diseases. Some studies have noted the presence of TNF-α at the mRNA and protein levels in HS skin. This is consistent with the clinical improvement that is usually observed with infliximab and adalimumab therapy.

For the diagnosis of HS, 3 criteria must be present. First, typical lesions must be present (i.e., deep-seated painful nodules). These are often described as “blind boils” in the early lesions. Other lesions are abscesses, draining sinus (inflamed tunnels), bridged scars, and postinflammatory “tombstone” double-ended pseudocomedones. Most often, multiple elements are present simultaneously. It is, however, important to avoid confusion with nondiagnostic elements, such as simple folliculitis, when making the diagnosis. Second, these elements mainly occur in one of the areas for which HS has a predilection: the axillae, groin, perineal region, buttocks, and infra and intermammary folds. Lesions may appear ectopically, but they must involve the areas for which the disease has a predilection to meet the diagnosis. Third, there must be a clear history of chronicity and recurrence. Lesions initially recur in the areas for which HS has a predilection, only to turn chronic later on in the course of the disease. Arbitrarily, 2 recurrences over a period of 6 months have been used as a qualifier for a diagnosis. All 3 criteria must be present for the definitive diagnosis, and because of the diagnostic requirement for recurrence/chronicity, an observation period may be necessary before the definitive diagnosis is made. There has been described several clinical types:

- The regular type of HS fulfills all of the diagnostic criteria. This is probably the most common type, and all HS patients who lack other specific characteristics belong in this category.
- Frictional furuncle type. These patients are usually overweight; in addition to regular HS, they are characterized by the presentation of multiple deep nodules and abscesses on sites exposed to enhanced friction, such as the abdomen, thighs, and buttocks. The formation of tunnels and fistulas in these areas is unusual.
- Scarring folliculitis type. Patients with the scarring folliculitis type of HS have, in addition to regular HS, pustules, cysts, superficial nodules, depressed cribriform scarring, and double-ended comedones. These lesions are frequently seen on the buttocks, inguinal region, and pubic region. The formation of sinus tracts and fistulas in these sites may be unusual, and
although the inflammatory lesions are small and superficial (Hurley stage I),
scarring typically occurs. These patients are also frequently overweight and
often smoke.
• Conglobata type. These patients are character- ized by cyst formation and acne
conglobata lesions on the back especially, but also the face. HS usually runs in
the family in this type, and is moderate to severe, Hurley stages II to III.
Patients are usually men and are not overweight. The Chinese cases in whom
the initial finding of gamma-secretase mutations were found may belong to this
putative group.15
• Syndromic type. Patients with syndromic type HS are characterized by
concomitant manifestations, such as pyoderma gangrenosum and arthritis, in
the syndromic constellation recognized as pyoderma gangrenosum, acne, and
suppurative hidradenitis syndrome or pyogenic arthritis, pyoderma
gangrenosum, acne, and hidradenitis suppurativa syndrome.
• Ectopic type. The existence of an ectopic type involving the face has been
proposed.

On the other hand, Hurley et al. first described a severity classification for HS.
• Stage I—Abscess formation, single or multiple, without sinus tracts and
cicatrization.
• Stage II—Recurrent abscesses with tract formation and cicatrization, single or
multiple, and widely separated lesions
• Stage III—Diffuse or near-diffuse involvement or multiple interconnected
tracts and abscesses across the entire area
Stage I disease is most common, affecting 68% of patients, while stage II occurs in
28% of patients, and 4% of HS patients develop stage III.
The Hurley classification is useful for rapid classification of HS severity, but it has
serious limitations. First, it cannot be considered a surgical classification because it
does not incorporate inflammatory features, such as erythema and discharge. It is
based on static disease characteristics, such as scarring and fistulas, which are only
treatable with surgery. It is therefore static and not useful to monitor the efficacy
of medical therapy. Second, because scarring is a key feature of stage II and III patients
and irreversible, the score can never fall below II, even if the disease is in complete
remission. Third, the classification, with just 3 stages, is not a precise monitoring tool
in the clinical trial setting.

2.2.2. Metabolic syndrome

MS is a group of metabolic risk factors, which directly promote the development of
atherosclerotic cardiovascular disease(12). The most widely recognized metabolic
risk factors are atherogenic dyslipidemia, elevated blood pressure and elevated
plasma glucose baseline. Individuals with these characteristics commonly manifest
prothrombotic states and a proinflammatory state(13). This constellation of metabolic
risk factors is strongly associated with type 2 diabetes or elevated risk for this condition(14).

It is currently unclear whether the MS has a single cause or is precipitated by multiple underlying risk factors. The underlying risk factors are those that would be associated with MS and those seem to be the predominant are abdominal obesity and insulin resistance(15). Other conditions may be associated with physical inactivity, age, hormonal imbalance, genetic or ethnic predisposition. While an atherogenic diet can accentuate the risk for developing CVD in people with this syndrome, it is still considered a specific underlying risk factor for this condition(16).

It is further contemplated that non-obese people may have insulin resistance and have abnormal levels of metabolic risk factors. Although individuals with insulin resistance are not required to be obese, often have abnormal body fat distribution, being predominantly upper body. Adipose tissue exhibits increased production of inflammatory cytokines and adiponectin reduction, a protective adipokine(17).

On the other hand, the AHA/NHLBI indicates that MS is associated with a state of chronic low-grade inflammation, having reported that inflammatory cytokines can induce insulin resistance both in adipose tissue and muscle(18). These concepts, chronicity and low-grade inflammation, although they are reported in the studies are not yet strictly defined by the authors.

To evaluate the prevalence of MS in different populations is difficult despite attempts to reach an agreement on the definition of this syndrome. In Western Europe it is estimated that the prevalence of the syndrome would range between 15 and 35%(19). They found differences in the prevalence of MS in relation to sex, being higher in women. In those studies involving people aged 20-25 years, the prevalence in urban populations between 8% (India) and 24% (USA) in males; and 7% (France) and 43% (Iran) in women(20). Moller et al. reported that about 25% of US adults met criteria for MS(21).

The prevalence is lower in developing countries but with numbers increasing. Ford et al.(21) suggested that ethnicity has effects on the presence of MS. In the USA, MS is less prevalent in non-Hispanic whites than in Mexican Americans; and MS is even lower in African American males as compared with non-Hispanic white and Mexican-American males. Another important fact is that the prevalence of MS is highly dependent on age. USA reported MS of 7% in those aged 20-29 years, 44% of those between 60-69 years and 42% in 70 years or older.

According to historical reviews of MS(22, 23), it was first described 80 years ago by Kilyn, a Swedish doctor who defined the association between hypertension, hyperglycemia and gout. In 1947, Vague published an article describing the phenotype of android obesity and its association with metabolic alterations observed in patients with type 2 diabetes and coronary heart disease. Subsequently, Avogaro documented the simultaneous occurrence of obesity, hyperinsulinemia, hypertriglyceridemia and
hypertension. In 1988, the clinical significance of the association of metabolic disorders was highlighted again by Reaven that considers insulin resistance as a common pathophysiological feature, calling this picture "Syndrome X", but surprisingly did not include obesity.

Later in 1998, the World Health Organization (WHO)(24) published the first official definition of MS, and proposed insulin resistance as a factor of greater underlying risk and required his presence for the diagnosis of MS. Patients with diabetes mellitus 2 were included in this definition.

The following year, the European Group for the Study of Insulin Resistance (EGIR)(25), used the term "syndrome insulin resistance", requiring more than two diagnostic criteria besides elevated insulin levels. They performed a modified version from the WHO for the diagnosis of MS, introducing waist circumference as a measure of adiposity. It excluded patients with diabetes mellitus syndrome since insulin resistance was considered as a risk factor for diabetes mellitus.

Two years later, the National Cholesterol Education Program (NCEP) introduced the definition ATP III (Adult Treatment Panel III)(26), keeping as a parameter of obesity, waist circumference but with higher thresholds than those used in the EGIR definition. This definition achieved great popularity because of its simplicity, given equally to all MS components, without requiring specific quantification of insulin sensitivity as the two previous definitions. Abdominal obesity was not considered a prerequisite because certain ethnic groups appear to be susceptible to the development of MS with lower abdominal circumferences. The ATP III also noted that some individuals having other criteria of the syndrome seemed to have insulin resistance even when the abdominal circumference was below the threshold values. The syndrome also included patients with diabetes mellitus.

Then, in 2003, the American Association of Clinical Endocrinologists (AACE) made an amendment to the ATP III definition, considering again that resistance to insulin was the basic problem(12). The AACE collected four identifiable abnormalities syndrome: high blood pressure, high triglycerides, impaired tolerance to glucose and reduced HDL cholesterol. They excluded obesity as a basic component. Other factors were taken into account to assess the clinical criteria such as family history of cardiovascular disease or diabetes mellitus, polycystic ovary syndrome and hyperuricemia.

In 2005, the International Diabetes Federation (IDF) issued a new definition of the metabolic syndrome considering central obesity as a mandatory requirement(23).

The same year, the AHA/NHLBI, published an update of the definition of ATP-III(27) maintaining the same criteria of ATP III considering that are simple to use and have the advantage of not relying on a single criterion. The value for impaired fasting glucose decreased from 110 to 100 mg/dl, according to the amendment issued by the American Diabetes Association (ADA). As described in the version of ATP III, some
individuals of non-Asian origin (white, black, Hispanic), having only two criteria of metabolic syndrome, appear to be insulin resistant even with only marginal increases in abdominal circumference (94-101cm in men and 80-87cm in women). Therefore, the criteria currently include at least three of the following five conditions: glucose greater than or equal fasting 100mg/dl (or treatment for hyperglycemia present); blood pressure greater than or equal to 130/85 mmHg (or presence of treatment for hypertension (HBP), triglycerides (or presence of treatment for hypertriglyceridemia), greater than or equal to 150mg/dl; HDL (high density lipoprotein) under 40mg/dl in men or less than 50 mg/dl in women (or presence of low HDL cholesterol treatment), and finally an abdominal circumference greater or equal to 102cm in men or greater or equal to 88cm in women.

Among the characteristics that could predispose to insulin resistance and development of MS in such individuals, the authors consider: 1. Type 2 diabetes mellitus in first-degree relatives before 60 years. 2. Polycystic ovary disease. 3. Fatty liver. 4. CRP > 3 mg / dl, if quantifiable. 5. microalbuminuria, if detected. 6. impaired glucose tolerance. 7. Total apolipoprotein B high. According to this definition, these individuals should be handled as those who meet three criteria of MS. In addition, the authors describe some populations would be predisposed to the development of insulin resistance, metabolic syndrome and diabetes mellitus 2 with only moderate increases in abdominal circumference (populations of South Asia, China, Japan and other Asian countries) by what they consider appropriate to reduce the value of the abdominal circumference diagnostic criterion to consider in these populations.

These definitions have not only presented differences in the proposed components but also in the values used to define each of the components, all of which has generated considerable confusion. This confusion has not only reduced the usefulness of definitions in the clinical setting, but also difficult to compare the prevalence of MS in different population groups.

2.2.3. Metabolic syndrome and hidradenitis suppurativa

Increasing evidence furthermore proposes HS to be associated with the metabolic syndrome. Because the metabolic syndrome is a cluster of cardiovascular risk factors including diabetes/insulin resistance, hypertension, dyslipidemia, and obesity, there is a clear overlap between this comorbidity and the risk factors obesity and smoking.

Possible pathophysiologic mechanisms behind the supposed association of HS and the metabolic syndrome introduce a hypothesis concerning the long-term effects of the chronic inflammatory state of HS, the sedentary lifestyle (i.e., overeating, lack of physical exercise) that may accompany HS patients as a consequence of psychological stigmatization, inflammation-induced neuropsychological factors affecting appetite and cortisone levels, and concomitant pharmacotherapy with subsequent increased cardiovascular risk(7).
As systemic inflammation might be a factor related to MS, some authors suggested measuring neutrophil to lymphocyte ratio as a marker of systemic inflammation. Studies of psoriasis patients have found their neutrophil to lymphocyte ratio to be increased. Blood samples collected during control visits from 50 HS patients were examined, and compared to routine blood samples from 250 age- and sex-matched dermatological outpatients. The neutrophil to lymphocyte ratio was not significantly increased in HS patients as seen in psoriasis patients, but CRP was found to be higher in HS patients, indicating systemic inflammation. However, N/L ratio was positively correlated to Hurley stage (p < 0.006)(10).

The pathogenesis of HS is postulated to begin with hair follicle occlusion leading to lymphohistiocytic inflammation, with the involvement of pro-inflammatory cytokines IL-1 beta, IL-10, IL-12, IL-23, and TNF-alpha, and overactivation of the mammalian target of rapamycin complex-1 (mTORC1) signalling. 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 MS contains the same metabolic drivers leading to the androgen-driven overproduction of sebum and overgrowth of the intra-ductal keratinocytes(28).

Similar to other chronic systemic inflammatory conditions, such as rheumatoid arthritis and psoriasis that are associated with the MS, HS in contrast is a more localized inflammation of the skin.

A sizable body of literature demonstrates obesity as a paramount risk factor. Recently, a cross-sectional hospital- and population-based study comparing 32 hospital-based HS subjects, 326 population-based HS subjects, and 14,851 controls (non-HS subjects) found an OR for obesity (body mass index >30 kg/m2) of 6.38 (95% CI, 2.99–13.62) and 2.56 (95% CI, 2.00–3.28) for hospital- and population- based HS subjects, respectively, when compared with controls. Correspondingly, this study found an OR for abdominal obesity of 3.62 (95% CI, 1.73–7.60) and 2.24 (95% CI, 1.78–2.82) for the hospital- and population-based HS subjects, respectively. Overall, the ORs were higher for the HS patients from the hospital group than from the population group(29).

An Israeli cross-sectional study(5) which included 3,207 patients with HS and 6,412 controls, showed that HS was significantly associated with MS, with an 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).

Sabat et al.(4) and Gold et al.(30) performed hospital-based studies of 80 and 366 HS patients, respectively, and found the MS to be a comorbidity of HS. Sabat et al.(4) 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 HS 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. Gold et al. (30) found that 50.6% of HS patients compared with 30.2% of the controls suffered from the MS (P<.001).

A possible reason obesity is strongly associated with the prevalence of chronic inflammatory conditions including psoriasis and possibly HS may be because adipose tissue actively produces pro-inflammatory adipocytokines, including IL-6, and TNF-alpha (31). The prevalence of MS in patients with HS 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 MS in patients with HS compared to psoriasis. In addition, the MS affects much younger HS patients. This is significant as the cardiovascular consequences of MS are likely to afflict these younger patients earlier, leading to decreased life expectancy.

While there is no clear genetic causality between HS 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 disease (32), common lifestyle habits of poor dietary control, lack of exercise, and tobacco smoking (33). 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 keratinocytes (34). This may form the common basis for MS, in particular, obesity and insulin resistance, and the initial triggers for the plugging of the follicular component of the folliculo-pilo-sebaceous unit in HS.

The treatment of HS 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 antibiotics, with the second line consisting of systemic retinoid as acitretin. Third-line options or adjunctive therapy include anti-androgens (cyproterone acetate-ethinylestradiol) and metformin (35). In moderate disease, biologics such as infliximab, etanercept, and adalimumab have been tried in addition to surgical and laser options. Anakinra has been successfully used in the treatment of severe disease.

The insulin sensitizer metformin, with its range of beneficial effects on MS beyond improving glycemic control, has been shown to control HS 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 mechanisms,
resulting in the reduction of hyperandrogenism and lipid levels, which explains the improvement in the skin condition(36).

Metformin helps control HS with minimal side effects and good patient compliance. In a study of 25 patients with HS treated with Metformin over a period of 24 weeks, 18 patients clinically improved with a significant average reduction in their Sartorius score of 12.7 and number of monthly work days lost reduced from 1.5 to 0.4. Dermatology life quality index (DLQI) also showed a significant improvement in 16 cases, with a drop in DLQI score of 7.6(35).

Lastly, lifestyle modifications in conjunction with medical therapy should be emphasized in the management of HS. Many encouraging studies have demonstrated resolution of the skin condition after weight loss either through dietary measures alone(37) or with the aid of bariatric surgery(38). In particular, weight loss of more than 15% results in a significant improvement in the severity of the skin condition.

In a recent study, authors found using questionnaires that the number of patients reporting HS symptoms after weight loss decreased by 35% and the mean number of involved sites was reduced from 1.93 to 1.22 following weight loss (p = 0.003). The prevalence of HS appeared higher in the obese than in the background population, and a weight loss of more than 15% was associated with a significant reduction of disease severity(39).

Latest insights into how the over-activity of diet-related mTORC1 signaling may form the trigger for the initial follicular plugging event in HS provide a basis for dietary intervention, which should aim to reduce the intake of hyperglycemic carbohydrates and insulinotropic dairy proteins. Tobacco smokers have been found to suffer from more severe HS, 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 HS, it appears to reduce the development of the MS(40).

3. Methodology

Design
A systematic review and meta-analysis of observational studies that examine the relationship between HS and MS will be conducted. The observations studies will be cohort study, case-control or cross-sectional. Studies must have a group of psoriatic patients and a control group. We will analyze the number of patients with MS in each arm in order to obtain a pooled-OR. Studies that have adjusted their OR for various variables, such as age, sex, etc., will be analyzed separately from those with crude data. In addition, we will perform a subgroup analysis by region: Latin America, North America, Europe, Africa, Middle East and Asia; according to design, type of participants, and MS criteria used (ATP-III, IDF, AHA).
Type of studies
The studies are observational, cross-sectional, cohort, case-control, in adults older than 18 years old, who have 2 arms of the study: a group having HS and another control group. They must have been published from inception until March 2017(3). If there is duplication of publication, population or a nested population, the one that contains the most complete information or one that contains the largest population will be included. Finally, studies that have adjusted results by some variable such as sex, age, or condition associated with MS will be included as main outcome. Studies with crude ORs will be also included and will be analyzed separately. The study should be clear reporting the number of patients who have met the criteria for MS in each group, HS and Control. Similarly, studies should be clear to report the prevalence of each condition associated with MS in each group HS and Control.

Type of participants
Studies can included both children and adult population. HS patients included will be grouped according to severity and duration of disease, type of treatment, case definition, origin of control subjects (general population or dermatology patients).

Type of intervention
Studies should study the Odd Ratio of having MS in HS and control groups. MS diagnostic criteria have changed as the years have passed, and the criteria defined by the AHA/NHLBI and ATP-III(17, 26) are currently accepted. However, meta-analysis studies have defined the criteria SM available when published will be accepted in the present.

Type of measured results
Primary outcome: the pooled-OR of MS in HS group compared with the control group, using studies that have adjusted their OR in their analysis.

Secondary outcomes: we will measure and compare studies with crude OR; further analysis will be performed by grouping studies by region: Latin America, North America, Asia, Europe, Africa and Middle East; by data collection process (prospective or retrospective); by design (case-control, cross-sectional); case definition (ATP-III, AHA, IDF), type of population (hospital, general), HS severity (mild, severe), age group (only adult vs. adult and children); instrument (electronic database vs. hospital charts).

Search strategy
First, we will conduct a systematic review of observational studies published in MEDLINE, SCOPUS (Including Embase), SCIELO, GOOGLE SCHOLAR, SCIENCE DIRECT and LILACS from inception to March 2017. For unpublished studies we will review open gray literature and authors and experts on the topic opinion. In addition, we will scan bibliographies of published studies for unpublished studies by a manual search of the literature, searching in virtual libraries of universities and thesis work, and requesting authors for papers presented at conferences and congresses. We will look
for additional studies searching published reviews on hidradenitis suppurativa and metabolic syndrome. We will search for abstracts of studies in the field presented in international congresses of dermatology societies. Also we will follow references in the articles that we found in the main search. Languages restricted to Spanish and English for this review.

Search strategy will be according to the NCBI MESH terms:
The search strategy will be specific for each database according to the medical subject headings (MeSH) and free text terms for the key concepts. The search terms will be combined as follows: "hidradenitis suppurativa"[MeSH Terms] AND "metabolic syndrome"[MeSH Terms] AND "Observational Study [Publication Type]"[MeSH Terms].

1. Medline: ((hidradenitis suppurativa) OR (acne inversa)) and ((metabolic syndrome) OR (syndrome x) OR (metabolic syndrome X) OR (Syndrome X, Metabolic)) AND ((case-control) OR (cohort) OR (observational) OR (nested) OR (cross-sectional) OR (transversal)) . Publication dates: to 2017/03/31
   URL: https://www.ncbi.nlm.nih.gov/pubmed/?term=((hidradenitis+suppurativa)+OR+(acne+inversa))+and+((metabolic+syndrome)+OR+(syndrome+x)+OR+(metabolic+syndrome+X)+OR+(Syndrome+X%2C+Metabolic))+AND+((+observational+)OR+(+cross-sectional+))OR+((+case-control+))OR+((+cohort+))OR+((+transversal+))

2. SCOPUS (Including Embase): ((hidradenitis suppurativa) OR (acne inversa)) AND ((metabolic syndrome) OR (syndrome x) OR (metabolic syndrome x) OR (syndrome x, metabolic)) AND ((observational) OR (cross-sectional) OR (case-control) OR (cohort) OR (transversal) OR (observational) OR (nested)) AND (LIMIT-TO (DOCTYPE , "ar" ) ) AND ( LIMIT-TO ( SUBJAREA , "MEDI" ) )
   Date of search: April 1st 2017.

3. ScienceDirect: Search results: 254 results found for ((hidradenitis suppurativa) OR (acne inversa)) and (((metabolic syndrome) OR (syndrome x, metabolic)) and ((cross-sectional) OR (case-control) OR (nested) OR (observational))). Date of search: April 1st 2017.

   URL: https://scholar.google.com/scholar?start=103&q=((hidradenitis+suppurativa)+OR+(acne+inversa))+AND+((metabolic+syndrome)+OR+(syndrome+X+metabolic))+AND+((cross-sectional)+OR+(case-control)+OR+(nested)+OR+(observational)+OR+(transversal))+&hl=es&as_sdt=0,21

5. Scielo: ((hidradenitis suppurativa) OR (acne inversa)) AND ((metabolic syndrome) OR (syndrome x) OR (metabolic syndrome x) OR (syndrome x, metabolic)) Date of search: April 1st 2017.
6. Lilacs: (tw:((hidradenitis suppurativa) OR (acne inversa))) AND (tw:((metabolic syndrome) OR (syndrome x metabolic) OR (syndrome X))) AND (tw:((case control) OR (cross sectional) OR (observational) OR (nested) OR (cohort))) Date of search: April 1st 2017.
URL: http://pesquisa.bvsalud.org/portal/?lang=es&q=%28tw%3A%28%28tw%3A%28%28hidradenitis+suppurativa%29+OR+%28acne+inversa%29%29%29+AND+%28tw%3A%28%28metabolic+syndrome%29+OR+%28syndrome+x+metabolic%29+OR+%28syndrome+X%29%29%29+AND+%28%28case+control%29+OR+%28cross+sectional%29+OR+%28observational%29+OR+%28nested%29+OR+%28cohort%29%29%29%29%29

Some databases do not allow performing exact date searching; therefore, those were carried out on the date April 1st 2017.

Selection criteria

The selection criteria for this systematic review and meta-analysis are:

1. Inclusion
   • Studies should be observational cohort type, case-control, cross-sectional and nested case-control; they must study the association between HS and MS with two study arms: one group of cases and control; within the period from inception to March 31st, 2017.
   • Study population could be children or adult.
   • Studies should contain information on the OR of having MS in patients with HS and control group, using methods for diagnosis: physical examination, laboratory analysis and review of charts, or by international codes stories, retrospectively or prospectively.
   • Studies must have adjusted their results by some variable such as sex, age, or condition associated with MS.
   • Studies that report crude OR will be included in a separated analysis.
   • Studies will be included in English and Spanish.
   • Clinical diagnostic criteria for HS and MS defined by the authors themselves available for publication date will be used.

2. Exclusion
   • Studies that did not report the incidence or prevalence of MS in any of the study arms, neither in the case or control groups, will be excluded.
   • Studies that duplicate the study population are excluded, and be chosen above all those that meet the criteria for inclusion and present the largest population included.
   • Studies that report a similar condition or associated with MS (e.g. cardiovascular risk factors such as smoking, hyperhomocysteinemia, etc.), but not MS itself; or those that have not a clear distinction of cases of MS will be excluded.
Data collection and analysis

1. Selection of studies
Initially, after searching in mentioned databases, potential studies will be obtained. The authors independently will review all titles and abstracts obtained by applying the criteria of inclusion and exclusion. The name of the authors and their institutions, the name of the journal and its sponsors and funding will be blinded. If any disagreement on the choice of an article arises, authors will be discussed reasons. Finally, we will have to reach to an agreement and a final decision.

2. Data Extraction
Of all eligible studies, the relevant data is extracted in duplicate, using a standard datasheet on Microsoft Excel 2010. An author will review the complete filling of the datasheet for each selected study at least twice. The variables are as follows:

### Variables of Articles

<table>
<thead>
<tr>
<th>Coding</th>
<th>Variable</th>
<th>Decoding</th>
<th>Type of variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Author</td>
<td>Wells</td>
<td>Qualitative nominal</td>
<td>Family name of the study first author.</td>
</tr>
<tr>
<td>A2</td>
<td>País</td>
<td>Canada</td>
<td>Qualitative nominal</td>
<td>Country where the study was conducted.</td>
</tr>
<tr>
<td>A3</td>
<td>Language</td>
<td>Spanish</td>
<td>Qualitative nominal</td>
<td>Language in which the study was made.</td>
</tr>
<tr>
<td>A4</td>
<td>Year</td>
<td>2010</td>
<td>Numeral discrete</td>
<td>Year when the study was made.</td>
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</table>

### Variable of design

<table>
<thead>
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<th>Variable</th>
<th>Decoding</th>
<th>Type of variable</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>Size of groups</td>
<td>230</td>
<td>Numeral discrete</td>
<td>Number of subjects in the study.</td>
</tr>
<tr>
<td>T2</td>
<td>Patients in HS</td>
<td>115</td>
<td>Numeral discrete</td>
<td>Number of patients having HS.</td>
</tr>
<tr>
<td>T3</td>
<td>Patients in Control</td>
<td>115</td>
<td>Numeral discrete</td>
<td>Number of patients that do not have HS.</td>
</tr>
<tr>
<td>T4</td>
<td>Type of study by design</td>
<td></td>
<td>Nominal categorical</td>
<td>Type of study according to its design</td>
</tr>
<tr>
<td>T5</td>
<td>Type of study</td>
<td></td>
<td>Nominal</td>
<td>Type of study</td>
</tr>
</tbody>
</table>
by temporality 1= prospective  categorical according to temporality.

Variables of participants

<table>
<thead>
<tr>
<th>Name</th>
<th>Label</th>
<th>Decoding</th>
<th>Variable type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>P1</strong></td>
<td>Average age</td>
<td>14.3</td>
<td>Numeric continua</td>
<td>The average of age of the participants in the study.</td>
</tr>
<tr>
<td><strong>P2</strong></td>
<td>Sex</td>
<td>0= female.</td>
<td>Nominal categorical</td>
<td>Phenotypical sex of the participants in the study.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1= male.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>2= both.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>P3</strong></td>
<td>Number of female patient</td>
<td>110</td>
<td>Discrete numerical</td>
<td>Number of female participants in the study.</td>
</tr>
<tr>
<td><strong>P4</strong></td>
<td>Number of male patient</td>
<td>120</td>
<td>Discrete numerical</td>
<td>Number of male participants in the study.</td>
</tr>
<tr>
<td><strong>P5</strong></td>
<td>Patients with MS in HS group</td>
<td>1095</td>
<td>Discrete numerical</td>
<td>Number of patients with MS in patients with HS.</td>
</tr>
<tr>
<td><strong>P6</strong></td>
<td>Patients with MS in Control group</td>
<td>1095</td>
<td>Discrete numerical</td>
<td>Number of patients with MS in patients with out HS.</td>
</tr>
<tr>
<td><strong>P8</strong></td>
<td>Crude OR</td>
<td>2.5</td>
<td>Discrete numerical</td>
<td>Odd Ratio of MS between HS and control</td>
</tr>
<tr>
<td><strong>P9</strong></td>
<td>Adjusted OR</td>
<td>2.5</td>
<td>Discrete numerical</td>
<td>Odd Ratio of MS between HS and control that has been adjusted for covariates</td>
</tr>
<tr>
<td><strong>P10</strong></td>
<td>Adjusted covariates</td>
<td>Sex, age, smoking status</td>
<td>Nominal</td>
<td>List of covariates adjusted for OR.</td>
</tr>
</tbody>
</table>

Quality assessment of studies

After obtaining the studies to be included in the main analysis, we will perform quality assessment of each study based on a modified version of the Cochrane risk of bias table. Two groups of study quality will be defined: high, and low. Subgroup analysis will be performed accordingly.

Missing data
Only studies containing information on patients presenting with MS on both the HS and the control group will be included; or in any case, that show the Odd Ratio, whether adjusted or unadjusted for variables. If this study do not show such data will not be included in the analysis.

Heterogeneity
Heterogeneity between trials will be assessed by the I² statistic, which indicates the percentage of variation in the effect-size estimate attributable to heterogeneity rather than sampling error. It provides a measure of the degree heterogeneity in the studies' results. A value equal to zero of I² means no heterogeneity, and larger means that heterogeneity is increasing. I² would be described as low, moderate, and high according to its corresponding value (I² values of 25%, 50%, and 75%)(41). Finally if I² has a value greater than 50%, it will be considered as heterogeneous which means that we will use random-effects model for meta-analysis.

Evaluation of publication bias
The possibility of publication bias will be assessed by mean of a Funnel plot; it is a graph of treatment effect against a measure of study size: in this case, a symmetric inverted funnel means that publication bias is unlikely. On the other hand an asymmetric funnel means that the possibility of publication bias or a systematic difference between smaller and larger studies.

Data synthesis
Odd Ratio (OR) with patients having MS for both the HS group versus the control group with a confidence interval (CI) of 95% for each study will be obtained. The pooled-OR is obtained with a random effects model (Random-effect Model) if heterogeneity is high; otherwise, if heterogeneity is low, a Fixed-effect Model will be used(47). It will be presented by Forest Plot graphs showing the effect size of each study with its corresponding CI. RevMan 5 for data analysis and graphic production will be used.

Subgroup analysis
Subgroup analyses will be performed, with tests for heterogeneity and obtaining a pooled-OR in each subgroup. Each subgroup corresponds to the analysis of studies showing an adjusted-OR vs. those with crude OR. Also, studies grouped by region: Latin America, North America, Asia, Europe, Africa and Middle East; by data collection process (prospective or retrospective); by design (case-control, cohort); case definition (ATP-III, AHA, IDF), type of population (hospital, general), HS severity (mild, severe), age group (only adult vs. adult and children); instrument (electronic database vs. hospital charts); with both crude and adjusted ORs when possible.

Sensitivity analysis
Sensitivity analysis is an informal way to prove that the results have a high degree of certainty. The procedure involves the removal of a representative study and then compares the result of the new pooled-OR obtained with the original result. If they are similar, then the results have a high degree of certainty. If the results vary
considerably, then these should be interpreted cautiously. We will exhaust efforts to obtain additional information on these studies to try to explain this difference. Sensitivity analysis will be presented in a summary table with studies excluded in a column, and the new pooled-OR obtained in the next column.
References


