CO-MORBIDITIES OF HIDRADENITIS SUPPURATIVA

MD Thesis

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This thesis is submitted to Trinity College Dublin in fulfilment of the requirements for the degree of Doctor of Medicine

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Declaration of Authorship

This report represents the sole work of the author except where stated and has not been submitted in whole or in part to any other university or institution as part of a degree or other qualification.

The design and implementation of this body of work was conceived by myself and Professor Anne Marie Tobin, who was involved in all stages of the project including hypothesis formulation, design of studies, review of experiment progress, results, manuscripts and presentations.

I obtained ethical approval, recruited patients, conducted all clinical assessments, and drew blood from patients where necessary.

Blood samples for CRP, insulin, glucose, homocysteine levels and lipids were analysed in the hospital laboratory. Lipoprotein analysis was also performed in the Biochemistry Laboratory in Tallaght University Hospital under the supervision of Professor Gerard Boran.

I have performed all relevant statistical analysis on data collected.

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Shivashini Kirthi

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Summary

Hidradenitis suppurativa (HS), is a chronic inflammatory skin disorder which can have debilitating consequences if not managed appropriately from early on of its course of disease. Patients with this condition, also previously known as ‘acne inversa’ present with recurrent, inflamed nodules in intertriginous areas such as the axillary, inguinal, and perianal areas. In more severe stages, this condition can lead to the formation of fistulas, sinus tracts, and extensive scarring. Various pathogenic mechanisms have been proposed in HS, including immune dysregulation, smoking, obesity and genetics however, the precise etiology remains to be elucidated. There is some evidence in the literature demonstrating the association of HS with inflammatory bowel disease, cardiovascular disease risk factors, arthritis and psychiatric disorders, suggesting that HS is a systemic disease.

In our thesis we specifically investigated two comorbidities, Cardiovascular risk and psychological impact of this condition. Our prospective case-controlled study demonstrated that patients with HS have a significantly increased cardiovascular disease risk. We also showed for the first time to our knowledge that patients with HS have a significantly higher relative QRISK2 which is a tool used to evaluate absolute and relative cardiovascular risk in patients. We also found an increased prevalence of hyperhomocysteinemia within the HS cohort, as a non-classical cardiovascular risk factor that can further increase their risk of cardiovascular disease. Furthermore, we demonstrated in this thesis that our very young cohort of HS patients tend to have a pro-atherogenic lipid profile with significantly higher numbers of small dense LDL and a non-Type A lipoprotein profile.

In terms of HS and its level of impact on mental health within our patients, we found that HS imposes a significant impairment in quality of life on patients who have this condition, with different type of distress being exhibited by the HS group when compared to psoriasis patients. We also showed that patients with HS have significantly higher levels of depression and anxiety than patients with psoriasis. This condition understandably has been proven to have a severe, adverse impact on patient's physical, social and mental health wellbeing, therefore warranting a holistic management approach by treating physicians.

Publications

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Abstract

CO-MORBIDITIES OF HIDRADENITIS SUPPURATIVA

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Hidradenitis suppurativa (HS) is a distressing chronic, inflammatory condition characterized by recurrent nodules, abscesses, sinus tracts and fistula formation in the axillae, inframammary, groin and perianal regions. The prevalence of HS has been reported to range between 0.00033% and 4.1% and is more common in females than males at a rate of approximately 3:1[1]. The underlying precise pathophysiology of this condition is not fully understood. In a similar paradigm to psoriasis, it is becoming apparent that HS is a systemic inflammatory condition and is associated with metabolic abnormalities and cardiovascular disease. It is also increasingly evident that the condition confers significant psychological morbidity and impairment of quality of life. We quantified and measured metabolic and cardiovascular co-morbidity as well as psychological distress in our cohort of HS patients, as a research question but also to inform service provision and planning for our patients.

We have identified an increased prevalence of metabolic syndrome defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III and insulin resistance measured by the HOMA-IR model in our HS population. Using the Framingham Risk and QRISK2 cardiovascular risk calculators, we showed that patients with HS had a significantly higher risk of cardiovascular disease compared to controls. Additionally, we also quantified and compared lipoprotein subclasses in HS patients using the Lipoprint method and showed that our young cohort of HS patients have a pro-atherogenic lipid profile with a significantly higher numbers of small dense LDL and a non-Type A

lipoprotein profile, therefore increasing the risk of cardiovascular disease. To the best of our knowledge, this is the first study to analyse lipoprotein subclasses in HS patients.

Additionally, using the Dermatology Life Quality Index (DLQI) we demonstrated that HS has significant impairment on quality of life measured by the DLQI, with different types of distress being exhibited by this group when compared to psoriasis patients. We also showed that patients with HS have significantly higher levels of depression and anxiety than patients with psoriasis which was measured using the Hospital Anxiety and Depression Scale (HADS).

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Finally, I am forever grateful for my family who have constantly encouraged and motivated me from the very beginning of this journey.

Abbreviations

BMI: Body mass index

C: Celsius

CRP: C-Reactive protein

CVD: Cardiovascular disease

DLQI: Dermatology life quality index

EDTA: Ethylenediaminetetraacetic acid

HADS: The Hospital Anxiety and Depression Scale

HDL: High density lipoprotein

HOMA-IR: Homeostasis model of insulin resistance

HS: Hidradenitis suppurativa

HTN: Hypertension

IHD: Ischaemic heart disease

LDL: Low density lipoprotein

MACEs: Major adverse cardiac events

MI: Myocardial infarction

NICE: National Institute for Health and Care Excellence

TC: Total Cholesterol

TG: Triglycerides

T2DM: Type 2 Diabetes Mellitus

QoL: Quality of life

WHO: World Health Organization

Chapter 1: General Summary of Hidradenitis Suppurativa

Definition

Hidradenitis suppurativa (HS), frequently referred to as acne inversa has been defined as a chronic, inflammatory, recurrent, debilitating, skin follicular disease that usually presents after puberty with painful deep-seated, inflamed lesions in the apocrine gland-bearing areas of the body, most commonly, the axillary, inguinal and anogenital regions. (The First International Hidradenitis Suppurativa, Research Symposium. Dessau, Germany 2006)

Epidemiology

The prevalence of HS has been estimated at approximately 1–4% in the U.K population with the typical age of onset being in the second to fourth decades of life**Error! Bookmark not defined.**. There appears to be a strong female preponderance (3 : 1, F : M) and an association with smoking and obesity, with odds ratios of 3.3 and 3.6, respectively, compared with controls [108]. Nevertheless, non-smokers with normal body mass index (BMI) are still seen in clinical practice. A population-based study in the United States found that the prevalence of HS in African-American and mixed-race individuals was 3 times and 2 times higher than that of white individuals, respectively[2].

Clinical Presentation

Patients with HS may present with comedones (characteristically with two or more heads), papules, pustules, nodules, cysts, abscesses, sinus tracts and fistulae with a

predilection for the axillae and/or inguinal areas. Patients often experience severe pain and chronic malodorus discharge as well as pruritus. Fibrosis, dermal contractures, scarring and a consequent reduction in mobility can occur in patients who have long standing disease.

Although the prototypic patient with HS presents with recurrent, painful, inflamed nodules, abscesses and in more severe cases sinus tracts, most commonly in the axillae and/or inguinal areas, there is considerable heterogeneity in the clinical features of HS. Male patients tend to present with gluteal, perianal/perineal, and atypical areas (e.g., ears, chest, and legs) involvement whereas female patients have a higher preponderance to having frontal areas (inguinal and inframammary folds) involvement[11].

HS has also been reported in the literature to be part of several autoinflammatory syndromes such as PASH Syndromic (pyoderma gangrenosum, acne, and HS) and PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and HS) syndromes. Syndromic HS such PASH and PAPASH have been reported to be of a more severe phenotype and accompanied by other systemic symptoms such as a fever [107] .

Diagnostic Criteria

HS is a clinical diagnosis that can be a challenge. Three diagnostic criteria must be present for definitive diagnosis [108].

1. The presence of typical lesions (painful nodules, abscesses, sinus tracts, bridged scars or open comedones).

2. Lesions occurring in at least one typical body location such as the axillae, groin, perineal and perianal region, buttocks, and inframammary and intermammary folds.

3. Chronic nature of disease, relapses, and recurrences.

Measure of Disease Severity

Baseline disease severity in each skin region is often measured using the Hurley staging system which includes three disease severity categories as below [77] :

Stage 1 : Abscess formation, single or multiple, without sinus tracts and cicatrization

Stage 2 : Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions.

Stage 3 : Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area

Although this system is simple and quick to perform, the disease characteristics used are static, and not quantitative. Furthermore, this tool is not particularly useful in measuring treatment response. A more dynamic and quantitative disease severity assessment tool, the Sartorius Hidradenitis Suppurativa Score (HSS) is used mainly in a clinical trial setting as given its complexity and time-consuming calculation, it is impractical to be used in a clinical setting [47]. More recently, the Hidradenitis Suppurativa Clinical Response (HiSCR) has been developed as an endpoint for clinical trials which is defined as a 50% reduction from baseline in inflammatory nodules and abscesses, with no increase in abscesses or draining sinuses [108].

Disease Pathogenesis

The pathogenesis of HS is not entirely understood. Histopathological studies suggest that HS is primarily a disease of follicular occlusion. Several pathogenic mechanisms have been proposed, including; genetic, infectious, hormonal, and/or host defence factors.

Genetic background

Up to 42% of patients with HS report a family history of the condition and it can follow autosomal dominant inheritance in some kindreds [109] . Although several genetic loci have been detected in HS, a single causative gene has not been established yet. Numerous heterozygous mutations in subunits of the gamma-secretase genes; presenilin 1 (PSEN1), presenilin enhancer 2 (PSENEN), and nicastrin (NCSTN) have been identified in families with multiple family members who have HS [110, 111]. Many patients with the identified mutations have more severe and atypical disease, with involvement of the back, face and abdomen. The influence of genetics in HS remains unclear and perhaps genome wide sequencing studies are needed to further explore this element.

Dysregulated Immunity

More recent research suggests HS to be an inflammatory disease with dysregulated skin immunity around hair follicles in intertriginous regions as opposed to previous theories of this condition being primarily an infectious disease of apocrine sweat glands [112]. Perifollicular inflammation leading to hyperkeratosis and occlusion of hair follicles in the predilection areas, with subsequent rupture of the dilated follicle and extrusion of sebum and debri accumulated in the follicular duct into the adjacent dermis initiating an

inflammatory response which ultimately results in the formation of painful, inflamed nodules appear to be the key pathogenic features in this condition. Prolonged inflammation contributes to the formation of abscesses, fistulas, and sinus tracts which then create a favorable environment for bacterial colonization.

The inflammatory response seen in HS has led to the theory that HS may be a disease of aberrant immunity. Several studies have shown elevated levels of pro- and anti-inflammatory cytokines, notably interleukin (IL)-1beta, TNF, IL-17, and IL-10 in lesional skin of HS patients [113]. IL-23 is central to the development of Th17 cells and, the recently described IL-23/Th17 pathway is known to play a key role in many autoimmune diseases. Th17 cells have been found to infiltrate the dermis in chronic HS [113]. Further research on detailed cytokine profiles and exact pathogenic pathways in HS is required.

Bacteria

The role of bacteria in HS exacerbations is uncertain. Deep tissue samples or samples taken from ruptured or open HS lesions have generally demonstrated a wide range of flora, commonly including coagulase negative staphylococci (CNS), Streptococcus milleri, Streptococcus viridians, Coryneform bacteria and gram negative bacteria including Escherichia coli, Klebsiella and Proteus [114]. In contrast, cultures taken from early or intact HS lesions however interestingly have been often shown to be sterile [115]. Additionally, short courses of antibiotics do not seem to alter the natural history of a flare indicating that the use of antibiotics is possibly beneficial via their anti-inflammatory properties rather than any bactericidal or bacteriostatic effects [108].

Obesity

The link between obesity and HS have been explored in depth over the years and is now well established [6,7,8,9]. Increased mechanical friction and maceration of the overlying skin promoting follicular occlusion and triggering rupture of dilated follicles , a warm, humid and occlusive environment favouring microbial growth and colonization as well as adipose tissue being an active endocrine organ secreting a variety of proinflammatory cytokines driving the inflammatory process in the skin of patients with HS are some of the hypothesis surrounding this aspect of obesity and its link with HS [4,13] . Additionally, there is increasing evidence in the literature of improvements in HS occurring following weight-reduction in patients with obesity further supporting this pathogenic link [15].

Cigarette smoking

The exact mechanisms by which cigarette smoking contributes to disease pathogenesis in HS remain unclear; however, nicotine has been shown to induce epidermal hyperplasia and follicular plugging and inflammation [51] .The rate of active cigarette smoking among HS sufferers has been reported at an incidence of up to 98% [44] . Although a causal relationship between smoking and HS has not been established, smokers do appear to suffer from more severe disease than non-smokers [43,44]

Treatment

HS treatment choice is dependent on the disease severity and individual preferences. Treatment can be challenging particularly in more severe cases and complete response rates are generally low and relapses are common.

General Measures

Smoking and obesity are well known risk factors for developing HS which can also negatively impact HS severity and course [47]. Lifestyle changes including losing weight and smoking cessation have been proposed to favour longer remission periods and decrease frequency and severity of HS flare ups . Not only smoking is a comorbidity , it is also a well-established HS-aggravating factor [47]. The concern of obesity should also be addressed when managing patients with HS who are overweight since weight gain and related insulin resistance may drive the development of new HS lesions [12, 13, 14]. Weight loss can also help minimize friction in body folds, which is a proposed trigger factor for new HS lesion development. There is evidence in the literature proving that dramatic weight loss due to bariatric surgery has been noted to possibly be able to induce an improvement in long-standing treatment-refractory HS with a long remission period [12, 15].

Topical Clindamycin 0.1%

Clindamycin is the only antibiotic that has been studied as a topical agent for HS [116, 117]. It is most effective when used to treat more superficial lesion (folliculitis, pustules and papules) with poor outcomes for treating deeper lesions (nodules and abscesses), suggesting its indication in localized Hurley Stage I disease or a mild Hurley Stage 2 disease [114].

Oral Tetracyclines

There is a place for oral tetracyclines in managing HS in those with Hurley Stage 1 disease particularly if the lesions are too extensive and not practical for topical clindamycin [114.]

The mechanism by which antibiotic therapy improves HS is not definitively known considering that HS is not primarily driven by an infective process. Although antibiotics may however help to control skin bacterial load which is an exacerbating factor for HS, it is the anti-inflammatory effects associated with some antibiotics that may play a role in this condition.

Rifampicin and Clindamycin

Combined rifampicin and clindamycin for 10 weeks is considered as a second line systemic therapy for any stage of active HS [108, 114]. This was initially based on a case series evidence showing improvement in disease severity scores and quality of life scores after treatment with this combination therapy. [118, 119]

Anti-inflammatory therapy

Dapsone

Dapsone is a sulfone drug with immunomodulatory and antibacterial properties that is utilized for the treatment of multiple neutrophil-predominant skin diseases and may be effective in mild to moderate HS. The current BAD guidelines have given it importance

in its most recent guidelines published in 2018 [108]. It is recommended for a minimum of 3 months in patients with Hurley Stage 1 or 2 disease if standard first or second line therapy fails (ie failure to antibiotic therapy) [108]. Patients however need to be made aware of its side effect risk of agranulocytosis amongst others.

Ciclosporin

The current European guidelines suggest that despite the high risk of side effects including hypertension, malignancy and nephrotoxicity, ciclosporin can be used as a treatment option in HS [114]. Beneficial effects of ciclosporin A are reported in limited cases [120-122]. Use of ciclosporin A should therefore be reserved to cases where failure of response to standard first, second- and third-line therapies occurs until further evidence is available [114]

Steroids

Administration of intralesional steroid injection can be considered for carefully selected, individual HS lesions during the acute phase either as a monotherapy or in combination with another treatment [123].Systemic steroids in the form of oral prednisolone are more widely used though only case series evidence is available to support it[123] .The European society guidelines have recommended that using 0.5–7mg/ Kg of oral prednisolone is an option, reducing with a view to stopping over a few weeks [114].

Acitretin

Acitretin is mainly indicated in early HS stages (Hurley I or mild II) however can also be considered in the chronic stages of HS with recurrent abscesses with sinus tracts and/or scarring. Current guidelines suggest that Acitretin 0.3–0.5mg/kg/day can be considered in males and non-fertile females with HS who are unresponsive to antibiotic therapies[108]

Antiandrogens

Although there is paucity in high quality efficacy data, there are indications that antiandrogens, such as the combined oral contraceptive pill and spiranolactone improve HS [125, 126] . The European guidelines have highlighted female patients with menstrual abnormalities, signs of hyperandrogensim or upper normal or high serum levels of dehydroepiandrosterone, androstenedione and/or sexual hormone-binding protein as being potentially suitable for such therapy [114].

Metformin

Current recommendations advise for metformin to be considered in people with HS with concomitant diabetes mellitus, and females with HS and polycystic ovary syndrome or pregnancy [108]. The anti-androgenic properties of metformin have long been established, and androgens imbalance have been found to be a contributory factor to HS. Metofrmin can also treat comorbid conditions that HS patients are more prone to having, such as obesity, insulin resistance, and PCOS [124].

Monoclonal antibody

In HS, adalimumab and infliximab inhibit TNF-α to switch off the inflammatory cascade which is thought to be a pathogenic driver in this condition. It is recommended for the treatment of patients with Hurley stage 2 or 3 who are unresponsive or intolerant to oral antibiotics [114]. The BAD guidelines recommend that Adalimumab should be offered (licensed for children and young people aged 12–17 years, and adults) at a dose of 40 mg weekly to patients with moderate-to-severe HS that is unresponsive to conventional systemic therapy [108]. Infliximab at 5mg/kg every 8 weeks is suggested as a treatment option for moderate-severe HS that is unresponsive to Adalimumab therapy [108].

Treatment with Ustekinumab [127] and Etanercept [128- 132] have also been reported in case reports.

Surgical Therapy

Surgical therapy can be considered as a therapeutic option for a specific cohort of HS patients depending on severity of disease and body region affected. Several surgical treatment methods co-exist, with radical excision being the treatment of choice for HS [114]. Other available surgical treatment options include deroofing, a procedure in which the skin overlying an inflamed nodule or sinus tract is removed, and the resulting wound is allowed to heal via secondary intention. This surgical option is especially appropriate for recurrent HS lesions at fixed locations in Hurley 1 or 2 areas.

Other options include carbon dioxide laser therapy and Nd: Yag Laser therapy which still require further studies in order for it to be established treatment options.

In summary, hidradenitis suppurativa is a common but massively overlooked inflammatory skin disease. There has been no one treatment that has proven to have an overwhelming positive effect on this condition. HS is also associated with several comorbidities which have been reviewed in detail in the following chapter. The hope is that as our knowledge of this condition expands, the optimism for new therapeutic options remains.

Chapter 2 : Co-morbidities of Hidradenitis Suppurativa

Hidradenitis Suppurativa (HS), previously known as acne inversa, is a chronic relapsing inflammatory skin disease affecting younger, predominantly female patients. It is characterized by recurrent, painful abscesses, nodules and draining sinus tracts in the axillae and groin and can result in significant scarring. In Europe, several studies have estimated the prevalence as 1% in the general population and 4% in young adult women[3]. Approximately 30-40% of patients with HS have reported a family history of same, suggesting a genetic susceptibility[2]. The pathogenesis of HS is not entirely understood and is probably multifactorial.

It is apparent that HS carries a substantial burden of co-morbidity including obesity, metabolic and cardiovascular disease, inflammatory bowel disease and inflammatory joint disease. Unsurprisingly the condition also confers significant psychological morbidity and quality of life impairment. Identifying these comorbidities is important for the patient and dermatologist to ensure an optimal outcome.

2.1 Obesity

Obesity is considered a low-grade inflammatory condition[4]. A study by Welsh et al [5] exploring the causal direction of the relationship between adiposity and inflammation using a bidirectional Mendelian randomization method showed that greater adiposity conferred by fat mass and obesity linked gene (*FTO)* and melanocortin-4 receptor (*MC4R*) led to higher C-reactive protein (CRP) levels, with no evidence for any reverse pathway. Several studies have confirmed that patients with HS have a higher Body Mass Index (BMI) compared to the general population and this ranges from 12% to 88%, depending on the population (Table 1.1).

Sabat et al [6] conducted a hospital-based, case - control study in 2012, investigating the prevalence of metabolic syndrome and obesity as part of this syndrome in 80 HS patients and 100 control participants from Berlin. The quantification of metabolic syndrome parameters in HS patients found the prevalence of central obesity in HS vs controls of 87.6% vs 66.4%, p <0.001 (OR 5.88, 95% CI 2.93-11.91). Miller et al [7]also looked at the association of two subsets of obesity; general and abdominal obesity, with HS, adjusting for age, sex, and smoking status and found a significant association between general obesity by BMI and abdominal obesity as measured by waist circumference for the population and the hospital HS groups included. The OR in the hospital HS group for general obesity was 6.38 (95% CI, 2.99-13.62) and the OR in the population HS group was 2.56 (95% CI, 2.00-3.28). This study showed a relatively lower level of abdominal obesity overall, with the OR in the hospital HS 3.62 (95% CI, 1.73-7.60) and the OR population HS of 2.24 (95% CI, 1.78-2.82).

In a more recent study carried out by Vossen et al [8] in 2017, patients with HS had a significantly higher BMI compared to controls at 27.8kg/m^2 vs 25.6kg/m^2 respectively, p<0.0001. The subset analysis of this study found HS patients had more peripheral rather than central weight distribution, defined by the waist-hip ratio, confirming the findings of Miller et al[7]. A large retrospective, matched case-control study carried out by Shlyankevich et al.[9] found a prevalence rate of obesity in HS vs control of 11.6% vs 0.75% (p<0.0001). In this study, the association between obesity and HS remained high with 17.3-fold higher odds of being obese when also afflicted with HS.

Several studies have demonstrated a significant association between obesity and HS disease severity. In a case-controlled study by Revuz et al.[10] of 302 HS patients and 906 age and sex matched patients, it was found that the risk of developing HS increased by 1.12 for each increase of 1 BMI unit. Similarly, a French study by Canoui-Poitrine *et al* [11]

, found a significant association between BMI and the severity of HS as measured by the Sartorius score and concluded that for each unit increase in BMI, the HS score increased by 0.84 units. Several other studies also demonstrated an association between disease severity and obesity in HS patients as (Table 1.1).

Kromann et al [12] in 2014 conducted a retrospective questionnaire study on patients who had bariatric surgery 2 years prior to study inclusion and collected data on pre- and post-surgery symptoms and disease severity as determined by number of involved regions and HS flares. Within 249 patients included in this study, it was found 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). A weight loss of more than 15% was associated with a significant reduction of disease severity. Similar findings were also reported by Boer [13] and Thomas et al [14] demonstrating long standing treatment-refractory HS following significant weight loss post bariatric surgical intervention. Anecdotally, we have reported two patients in whom HS severity was ameliorated following bariatric surgery[15]. Kromann et al[16] in a retrospective questionnaire study showed that the rate of HS disease remission in non-obese (BMI <30kg/m2) vs obese HS patients were 45% vs 3%.

There have been several theories suggested to explain the link between obesity and HS. Overweight individuals tend to have larger and increased skin folds, leading to increased mechanical friction and maceration of the overlying skin. Mechanical friction plays a role as an exogenous factor in the pathogenesis of HS by promoting follicular occlusion and triggering rupture of dilated follicles in genetically susceptible individuals. Repetitive mechanical forces also contribute to microcomedo formation, considered an early step in the cascade of development of HS.

In addition, a warm, humid and occlusive environment in these areas favours microbial growth and colonization. Bacterial infection may serve a secondary role in the pathogenesis of HS by exacerbating local inflammation via a series of pathogen associated molecular pathways[17].

Adipose tissue which is found in abundance in overweight individuals is an active endocrine organ with many secretory products including a variety of proinflammatory cytokines such as TNF-Alpha and IL-6 as well as adipokines (adiponectin and leptin)[18]. A study by Malara et al in 2017 assessing the levels of adipokines in HS patients, found the adipokine balance in HS is shifted towards increased expression of pro -inflammatory resistin and leptin, which may be driving the inflammatory process in the skin of patients with HS[19].

Table 2.1 Summary of studies of obesity in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Revuz, 2008	Population HS: 67 Hospital HS: 302	Mean BMI in population HS vs controls (n=200) :25.6 vs 24.3 Mean BMI in hospital HS vs controls (n=906) :25.6 vs 23.2 P<0.0001	Population HS : ORa, 1.05 (95% CI , 0.99-1.10) Hospital HS: ORa, 1.12 (95% CI 1.08-1.15)

Kromann et al 2014	129	Rate of HS disease remission in non-obese (BMI <30 kg/m^2) vs obese: 45% vs 23%	OR, 3.9 (95% CI, 1.4-11.0)
Shlyankevich et al , 2014	HS patients: 1730 Controls: 1730	Prevalence of obesity in HS vs control: 11.6% vs 0.75% (P < .0001)	OR, 2.09 (95% CI, 1.03-4.22)
Schrarder et al 2014	846	Mean BMI in HS Hurley stage I vs Hurley stage II vs Hurley stage III: 27.6 ± 11.6 vs 28.5 ± 5.9 vs 28.9 ± 7.0	OR, 1.03 (95% CI, 1.01-1.05)
Vazquez et al 2013	255	Prevalence of Hurley stage II or III in obese vs non-obese: 42.1% vs 39.1% (P = .63)	OR, 1.1 (95% CI, 0.7-1.9)
Sartorius et al 2009	246	HS disease severity by median (IQR) Hidradenitis Suppurativa Score in obese BMI vs overweight BMI vs normal BMI: 50 (18-86) vs	NA

		44 (22-56) vs 32 (12-54) (*P* = .036)	
Canoui-Poitrine et al 2009	301	Median (IQR) Sartorius score in normal vs overweight vs obese: 15 (12), 20.5 (16.5), 25.5 (19) (*P* < .001)	OR, 0.85 (95% CI, 0.62-1.09)
Sabat et al 2012	HS patients: 80 Controls: 100	Prevalence of central obesity in HS vs control: 65.0% vs 24.0% (*P* < .001)	OR, 5.88 (95% CI, 2.93-11.91)
Miller et al 2014	HS population: 326 HS hospital: 32 Controls: 14 851	General obesity—prevalence of general obesity in population HS vs hospital HS vs control: 32.8% vs 50.0% vs 18.8% Abdominal obesity—prevalence of abdominal obesity in population HS vs hospital HS vs control: 51.5% vs 62.5% vs 37.2%	General obesity—population: ORa, 2.58 (95% CI, 2.00-3.23); hospital: ORa, 6.38 (95% CI, 2.99-13.62) Abdominal obesity—population: ORa, 2.24 (95% CI, 1.78-2.82); hospital: ORa, 3.62 (95% CI, 1.73-7.60)

Crowley et al. 2014	154	BMI >40 kg/m^2 in high disease burden HS vs medium disease burden HS: 22/60 (36.7%) vs 21/94 (22.3%)	OR, 2.01 (95% CI, 0.985-4.114)
Shalom et al 2015	HS patients: 3207 Controls: 6412	Prevalence of obesity In HS vs control 22% vs 14%	OR 1.7(CI, 1.5-1.9)
Gold et al 2014	HS patients: 233 Controls: 222	Prevalence of obesity in HS vs control: 87.6% vs 66.4% ($P < .001$)	OR, 3.6 (95% CI, 2.2-5.6)
Vossen et al 2017	106	Mean BMI in HS vs controls: 27.8 25.6 ($p<0.001$)	

2.2 Metabolic Syndrome

Metabolic syndrome is a cluster of risk factors for cardiovascular disease and according to the 2005 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, is defined by the presence of three or more of the following criteria:

a) Abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in).

b) Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides.

c) Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol.

d) Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure.

e) Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Increased prevalence of metabolic syndrome is a well-known phenomenon in patients with psoriasis[20, 21, 22]. Several studies have investigated the prevalence of metabolic syndrome in patients with Hidradenitis Suppurativa (Table 1.2). A large comparative cross-sectional study by Shalom G et al including 3,207 HS patients and 6,412 age- and sex-matched controls found that HS was significantly associated with metabolic syndrome [OR : 1·61, 95% confidence interval (CI) 1·36-1·89] [23]. This was replicated in a recently published study in 2017 by J.C Pascual[24] showing a prevalence of metabolic syndrome in HS vs controls of 38.7% vs. 8.1 (P<0.001).

Additionally, Sabat et al showed similar prevalence of metabolic syndrome in HS (HS vs. control: 40.0% vs. 13.0%)[6]. More interestingly, this study also demonstrated that there was no significant correlation between the patients' age and the number of fulfilled metabolic criteria or between the age and respective parameter levels. In this study, the author subdivided patients into three age groups <34 years, 35-44 years and >45 years, to determine the prevalence of metabolic syndrome in each group. Surprisingly, they

discovered that the odds ratios for the prevalence of metabolic syndrome calculated for each age group of HS patients were: >20 (≤34-year-olds), 6.18 (35 to 44-year-olds), and 1.97 (≥45-year-olds). These data provide evidence that metabolic syndrome disproportionately affects younger HS patients. In addition, this study also found no correlation between metabolic syndrome and disease severity or disease duration.

Furthermore, a retrospective chart review including 243 HS patients and 222 controls by Gold et al reported similar findings whereby the association between metabolic syndrome and HS remains high with 2.37 higher odds of having metabolic syndrome with a known diagnosis of HS. In this study there was no correlation with disease severity however[25].

These somewhat unanticipated findings raise questions about the mechanism underlying the increased frequency of metabolic syndrome in patients with HS. A reasonable hypothesis ise that chronic inflammation stimulates and modifies metabolic parameters; the lack of correlation between disease severity or disease duration and metabolic syndrome suggests that the degree of inflammation in HS is not linked to metabolic syndrome however, and that the metabolic alterations in these patients may be a primary rather than a secondary pathological phenomenon. A hypothesis suggested by Sabat et al[6] is that metabolic alterations can lead to hypoxia in respective skin areas, which in turn induces IL-10 production in CD4+ T cells. IL-10 subsequently inhibits the production of IL-22, an important inducer of keratinocyte IL-20 production. The lack of IL-22 and IL-20 being major inducers of antibacterial proteins in epithelia, could eventually lead to enhanced cutaneous bacterial persistence, sustained inflammation and the outbreak of HS. This hypothesis however needs to be investigated with further studies.

Table 2.2 Summary of studies of metabolic syndrome in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Sabat et al 2012	HS patients: 80	Prevalence of metabolic syndrome in HS vs. control: 40.0% vs. 13.0%	OR: 4.46 (CI: 2.02–9.96)
Miller et al 2014	15,209 (326 HS population; 32 HS hospital)	Prevalence of metabolic syndrome in population HS vs. hospital HS vs. control: 32.2% vs. 53.1% vs. 21.5%	Population: OR: 2.08 (CI: 1.61–2.69); hospital: OR: 3.89 (CI: 1.9 –7.98)
Gold et al 2014	Patients with HS: 243 Controls: 222	Prevalence of metabolic syndrome in HS vs. control: 50.6% vs. 30.2%	OR: 2.37 (CI: 1.62–3.47)
Shalom et al 2015	Patients with HS: 3207 Controls: 6412	Prevalence of metabolic syndrome in HS vs. control: 10.4% vs. 7.1%	OR: 1.53 (CI: 1.32–1.77)
J.C Pascual 2017	HS patients: 62 Controls: 62	Prevalence of metabolic syndrome in HS vs control: 38.7% vs. 8.1 (P<0.001)	

2.3 Diabetes Mellitus

The association of impaired glucose tolerance and HS was recognized as early as 1988[26], with more recent studies supporting this finding (Table 1.3). A systematic review and

meta-analysis of 7 observational studies of diabetes in 5,685 patients with HS and 23, 515 controls showed that a significant association with diabetes was present with a pooled OR of 2·85 (95% CI 1·34–6·08, $P = 0·007$)[27].

One of the largest studies by Shlyankevich et al, a retrospective case control study included 1,730 HS patients[9]. In this study, 20.4% of HS patients had a diagnosis of diabetes compared to 1.5% of the control group (P<0.0001). A similar trend was demonstrated in several other studies listed in Table 1.3 including an Israeli study by Shalom et al [28] which showed patients with HS had 1.6 higher odds of having diabetes.

Miller et al examined metabolic syndrome components individually in their study and found that there was a positive association between HS and diabetes mellitus, in particular Type 2 Diabetes Mellitus[7]. Via further quantification studies, they found that HBA_{1C} levels were 1% to 10% higher in the HS groups compared to controls. Macisaac et al[29] suggested that a decrease in HbA_{1c} levels by 0.9% resulted in a significant 15% relative reduction in coronary heart disease events, affirming that these abnormalities in glucose levels within HS patients have an important clinical significance.

In a separate prospective, clinical observational and analytical study published in 2017 by J.C Pascual investigating the presence of subclinical atherosclerosis in 62 HS patients and 62 age, sex and smoking habit matched controls, the prevalence of diabetes in HS vs. controls was 22.6% vs. 6.5% ($P = 0.02$)[24]. In total, 19 (30.6%) patients in the HS group had subclinical atherosclerosis, and a further univariate analysis showed that diabetes was one of the variables associated with subclinical atherosclerosis within HS patients in this study.

Interestingly, Schrader et al found no significant association between increased HS disease severity and diabetes[30]. Conflicting with this finding however are results from an Italian

cross- sectional study including 245 HS patients which showed that the presence of type II diabetes was correlated with HS severity in both their univariate and multivariate analyses [31] .

An underlying link between diabetes and HS is not fully understood. It has been proposed that increased insulin and insulin-like growth factor in high glycaemic diets and the sensitization of follicular androgen receptors in patients with HS may play a role[9]. Furthermore, indirect support for this association is reflected in some studies and case reports that found metformin treatment to be effective in HS[32]. There may be two possible explanations for this; first is through lowering of insulin resistance that is commonly present in patients with HS and the second being via its anti-androgenic property.

Table 2.3 Summary of studies of Diabetes Mellitus in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Revuz 2008	Patients with HS: 67 Controls: 200	Prevalence of diabetes in HS vs. control: 4.5% vs. 3.0 (P = 0.56)	OR: 1.53 (CI: 0.36–6.55)
Sabat, 2012	Patients with HS: 80 Controls: 100	Prevalence of hyperglycaemia in HS vs. control: 26.3% vs. 8.0% (P < 0.001)	OR: 4.09 (CI: 1.59–10.84)

Gold 2014	Patients with HS: 243 Controls: 222	Prevalence of glucose intolerance in HS vs. control: 38.7% vs. 24.3%	OR: 2.0 (CI: 1.3–2.9)
Schrader 2014	846	Prevalence of history of diabetes in HS Hurley stage I vs. Hurley stage II vs. Hurley stage III: 5.2 vs. 5.8 vs. 16.1	OR: 1.43 (CI: 0.77–2.68)
Miller 2014	HS population: 326 HS hospital: 32 Controls: 14 851	Prevalence of diabetes in population HS vs. hospital HS vs. control: 7.1% vs. 12.5% vs. 4.9%	Population: OR: 2.44 (CI: 1.55–3.83) Hospital: OR : 5.74 (CI: 1.91–17.24)
Shlyankevich, 2014	Patients with HS: 1730 Controls: 1730	Prevalence of diabetes in HS vs. control: 20.4% vs. 1.5% (P < 0.0001)	OR: 16.8 (CI: 11.2–25.3)
Shalom 2015	Patients with HS: 3207 Controls: 6412	Prevalence of diabetes in HS vs. control: 11% vs. 7%	OR: 1.6 (CI: 1.3–1.8)
J.C Pascual 2017	HS patients: 62 Controls: 62	Prevalence of diabetes in HS vs. Control: 22.6% vs. 6.5% (*P* = 0.020)	

A. Egeberg 2016	HS patients: 5964 Controls: 29404	Prevalence of diabetes in HS vs. control: 4.3% vs 1.4%	
C.R Juhl 2017	HS patients: 404 Controls: 19001	Prevalence of diabetes in HS vs. control: 10.6% vs 6.2%(P<0.01)	

2.4 Dyslipidaemia

Several studies have documented dyslipidemia in HS, the majority of these conducted in the context of identifying patients who have metabolic syndrome (Table1.4). Revuz et al carried out a questionnaire study and found that there was no association with dyslipidemia in HS [10]. Shlyankevich et al on the other hand found a significant association, with a prevalence of dyslipidaemia in HS vs. control: 35.8% vs. 1.6%, and an adjusted OR of 4.06 (CI: 2.54–6.48) in a retrospective case-control study[9].

Several other studies examined individual elements of lipid profile including HDL, LDL, triglycerides and total cholesterol levels. A hospital-based case-control study in 80 HS patients and 100 age- and sex-matched control subjects found the prevalence of hypertriglyceridemia in HS vs. control subjects was significantly higher at: 38.8% vs. 22.0% respectively, (P = 0.014). It also found that patients with HS had an OR 4.56 of having a low HDL level compared to controls. These findings were similarly reflected in

a further study by Gold et al demonstrating that patients with HS had a significantly higher triglycerides level and lower HDL levels compared to controls[25].

A meta-analyses of 4 studies with 15,148 controls and 641 HS patients exploring hypertriglyceridemia in HS found a significant association between HS and hypertriglyceridemia with a pooled OR of 1.67 (95% CI 1.14-2.47, p = 0.009[27]. Similar analyses were conducted to evaluate the association of HDL and HS. In this analysis, four studies with 639 HS patients and 15,151 controls were included and significant association with low HDL was detected with a pooled OR of 2.48 (95% CI 1.49–4.16, P < 0.001). For both these analyses, the subgroup of HS cohort ie general population or hospital-based population did not make a difference to the results.

Table 2.4 Summary of studies of Dyslipidemia in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Revuz 2008	Patients with HS: 67 Controls: 200	Prevalence of dyslipidaemia in HS vs. control: 10% vs. 13%	OR: 0.6 (CI: 0.2–1.7)
Shalom, 2015	Patients with HS: 3207 Controls: 6412	Prevalence of hyperlipidemia in HS vs. control:	ORa: 1.14 (CI: 1.0–1.2)

		30% vs. 27%	
Shlyankevich, 2014	Patients with HS: 1730 Controls: 1730	Prevalence of dyslipidaemia in HS vs. control: 35.8% vs. 1.6%	ORa: 4.06 (CI: 2.54–6.48)
Miller, 2014	HS population: 326 HS hospital: 32 Controls: 14 851	Prevalence of hypertriglyceridemia in population HS vs. hospital HS vs. control: 48.8% vs. 50.0% vs. 43.3% Prevalence of low HDL cholesterol in population HS vs. hospital HS vs. control: 33.1% vs. 46.9% vs.	Population: OR: 1.49 (CI: 1.18–1.87); hospital: OR: 1.67 (CI: 0.81–3.44) Population: OR: 1.94 (CI: 1.52–2.48); hospital: OR: 2.97 (CI: 1.45–6.08)

		18.1%	
Gold, 2014	Patients with HS: 243 Controls: 222	Prevalence of hypertriglyceridemia in HS vs. control: 48.3% vs. 28.4% Prevalence of low HDL cholesterol in HS vs. control: 53.7% vs. 48.5%	OR: 2.4 (CI: 1.6–3.6) OR: 1.2 (CI: 0.8–1.8)

2.5 Hypertension

The association between HS and hypertension has been analysed in a number of studies assessing for metabolic syndrome (Table 1.5). A retrospective study by Shlyankevich et al[9] in 1,730 HS and control patients respectively found a prevalence of hypertension as defined by the World Health Organization International Classification of Diseases in HS vs. control of 34.3% vs. 3.0%, $p<0.001$ respectively. These findings were mirrored in a study by Shalom et al[45] which also found a significant association between HS patients and the presence of hypertension, OR: 1.19 (CI: 1.0–1.4), p=0.01.

Other studies show conflicting evidence. Revuz et al found no significant difference in the prevalence of treated, self-reported hypertension in HS patients vs. controls 20.9% vs.

17% , P = 0.47 in their case-control study[10]. In fact, although not significant, Gold et al showed a higher prevalence of hypertension in the control group when compared to HS cohort (HS vs controls : 45.3% vs 50.5%)[25].

A recent meta analyses of HS and hypertension by Tzellos et al including seven studies with 5,685 patients with HS and 23,515 controls showed no significant association between HS and hypertension with a pooled OR of 1.5 (95% CI 063–358, P = 0.36) suggesting that hypertension is not associated with HS[27].

Table 2.5 Summary of studies of Hypertension in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Shlyankevich, 2014	Patients with HS: 1730 Controls: 1730	Prevalence of hypertension in HS vs. control: 34.3% vs. 3.0%, p<0.001	OR: 1.84 (CI: 1.22–2.79)
Shalom, 2015	Patients with HS: 3207 Controls: 6412	Prevalence of hypertension in HS vs. control: 14.2% vs. 12.8%	OR: 1.19 (CI: 1.0–1.4)

Miller, 2014	HS population: 326 HS hospital: 32 Controls: 14 851	Prevalence of hypertension in population HS vs. hospital HS vs. control: 48.2% vs. 56.3% vs. 60.6%	1.08 (CI: 0.85–1.38); hospital: ORa: 2.14 (CI: 1.01–4.53)
Gold 2014	Patients with HS:243 Controls: 222	Prevalence of hypertension in HS vs control: 45.3% vs 50.5%	0.8 (CI : 0.6-1.2)
Revuz 2008	Patients with HS: 67 Controls : 200	Prevalence of treated hypertension in HS patients vs. controls 20.9% vs. 17%, P =0.47	1.39 (CI: 0.61 – 3.19)
Gonzales 2017	Patients with HS: 50	Prevalence of hypertension: 25 (50%)	NA

2.6 Cardiovascular Disease

Given the observed increase in obesity and diabetes in HS, studies have documented that HS is associated with several other CVD risk factors such as dyslipidemia, and smoking. A more recent study has also found that HS patients carry a higher systemic inflammatory load, with higher CRP levels, compared to other dermatological patients[33]. Therefore unsurprisingly, there is emerging evidence that patients with HS have an increased risk of cardiovascular disease (Table 1.6).

One of the first studies to evaluate CVD risk in HS patients using a validated risk assessment tool, the Framingham Risk Score (FRS) was by Hughes et al[34]. In this study, of which we participated, patients with HS had similar risk profiles to psoriasis patients. We also documented increased cardiovascular risk in a case-controlled study using the QRISK2 Validation tool (manuscript in preparation).

Additionally, a population-based cohort study of 5,964 HS patients in Denmark showed a significantly increased risk of myocardial infarctions, ischaemic strokes, CV- associated death, MACEs and all- cause mortality in patients compared to controls after adjusting for confounding factors[35]. A comparison was also performed between HS and psoriasis patients and although the risk of MI, ischaemic stroke, MACEs and all-cause mortality in HS patients was similar in patients with severe psoriasis, this study found that there was a significantly higher risk of CV-associated death in HS patients.

Gonzales et al explored the association between HS and subclinical atherosclerosis by measuring carotid intima-media thickness (cIMT) and plaque formation in HS patients with no history of CVD, diabetes mellitus, chronic kidney disease (CKD) or concomitant inflammatory conditions and healthy control subjects[36]. In this study, HS patients had an increased cIMT compared to control subjects (0.615 ± 0.097 vs 0.578 ± 0.098 mm;

P = 0.012). Additionally, it was found that carotid plaques were more common in the moderate-severe/very severe HS group compared to controls (41% vs 22.1%, p=0.023). HS was also significantly related to the presence of carotid plaques, (OR 2.99, 95% CI 1.26-7.13; P = .013) after adjusting for age, sex and traditional CVD risk factors. Further analysis revealed a strong correlation between disease duration of HS and level of cIMT as well as longer disease duration and disease severity with presence of carotid plaques. Despite adjusting for potential confounding risk factors such as obesity and smoking, there was still a significant difference in cIMT between HS patients and controls, indicating that HS may be an independent risk factor for atherosclerosis, regardless of the presence of traditional CVD risk factors.

Although not statistically significant, a similar trend was reflected in a prospective, clinical observational study exploring the prevalence of subclinical atherosclerosis (defined by pathological cIMT of >0.9mm or the presence of carotid plaques) in HS. Nineteen of 62 HS patients had subclinical atherosclerosis compared to 10 of 62 controls (30.7% vs 16.1% , p=0.05 and OR 3.8 (CI 0.9-16.0, p=0.066)[24]. A subsequent study from Gonzalez and Pascual et al assessing CVD risk using SCORE and carotid ultrasound in 50 HS patients, showed that 11 of 50 patients (22%) were reclassified to very high risk (≥10%) having found plaques on carotid ultrasound compared to only 2 (4%) in the initial assessment using the SCORE tool only[37]. The presence of plaques on carotid ultrasound reclassifies SCORE to very high risk (>10%) regardless of any previous calculations, suggesting that the European Heart SCORE may underestimate the risk of CVD in HS patients.

Furthermore, Juhl et al investigated the hitherto unknown electrocardiographic changes associated with HS in a Danish cohort and found that HS patients had significantly higher heart rates compared to controls when adjusted for age and gender. Increased heart rate

has been associated with increased risk of all-cause and cardiovascular mortality and sudden death[38].

Atherosclerosis has been proven to be an inflammatory disease with an association with high CRP and TNF[39]. Increased circulating levels of inflammatory markers such as TNF and IL-17 have been previously reported in HS patients[40]. A more recent study has also found that HS patients carry a higher systemic inflammatory load, with higher CRP levels, compared to other dermatological patients[41]. This association of HS and a high inflammatory load therefore may also contribute to the increased risk of CVD within this cohort.

Moreover, a further potential explanation for the increase in CVD risk within HS patients stems from findings of a previous study showing decreased number of endothelial progenitor cells among HS sufferers suggesting endothelial malfunction might also increase cardiovascular risk[42].

Table 2.6 Summary of studies of Cardiovascular Disease risk in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Gonzales 2017	50	CV risk categories: Low risk (Score <1%) : 0 (0.0) Moderate	

		risk (Score ≥1% and <5%) : 41(82.0%) High risk (Score ≥ 5 and < 10%) : 7 (14.0%) Very high (Score ≥ 10%) : 2 (4.0%) Modified risk after carotid ultrasound : Low risk (Score <1%) : 0 (0.0) Moderate risk (Score ≥1% and <5%) : 35 (70.0%) High risk (Score ≥ 5 and < 10%) : 2 (4.0%) Very high (Score ≥ 10%) : 13 (26%)	

Gonzales 2016	Patients with HS: 68 Controls: 136	Carotid intima-media (cIMT) thickness HS vs controls 0.615 ± 0.097 vs 0.578 ± 0.098 mm, P =0.012 Frequency of presence of carotid plaques HS vs controls 30.9% vs 22.1%, P=0.17	Presence of carotid plaques ORa 2.99, 95% confidence interval 1.26-7.13, P = 0.013
Juhl 2017	Patients with HS: 404 Controls without HS: 19,001	Heart rate 64.7 (11.0) vs. 66.3(11.1) , p<0.01	
Egeberg 2016	Patients with HS: 5964	HS vs Controls:	HS vs Controls:

	Controls without HS : 29820 Patients with severe psoriasis : 13 093	62 (42 749.0 person-years) MIs, 74 (42 647.8 person-years) ischemic strokes, 63 (42 941.7 person-years) cardiovascular-associated deaths, 169 (42 463.5 person-years) MACEs, and 231 (42 941.7 person-years) all-cause deaths	Adjusted (age, sex,socioeconomic status, smoking, comorbidity, and medication) IRRs (95% CIs) : 1.57 (1.14-2.17) for MI p=0.005 1.33 (1.01-1.76) for ischemic stroke,p =0.04 1.95 (1.42-2.67) for CV-associated death, p<0.001 1.53 (1.27-1.86) for MACEs,p=0.01

			1.35 (1.15-1.59) for all-cause mortality, p=0.05 HS vs severe psoriasis : Adjusted (age, sex, socioeconomic status, smoking, comorbidity, and medication) IRRs (95% CIs) IRRs in patients with HS were 1.00 (0.74-1.35) for MI, 0.93 (0.71-1.22) for ischemic stroke, 1.58 (1.17-2.12) for CV-associated death, 1.08 (0.90-1.29) for MACEs, and 1.09

			(0.94-1.28) for all-cause mortality.
Pascual 2017	Patients with HS: 62 Controls: 62	Presence of subclinical atherosclerosis HS vs controls: 30.6% vs. 16.1%, P = 0.06	
Hughes 2017	Patients with HS: 263 Patients with psoriasis: 103	HS patients: Low FRS < 10% = 80% Moderate FRS 10%-20% = 15% High FRS >20% = 5% Psoriasis patients: Low FRS < 10% = 80% Moderate FRS 10%-20% = 10% High FRS >20% = 10%	

2.7 Smoking

In 2011, authors Happle and Konig proposed the more specific term “smoker’s boils” for HS lesions in patients who are smokers[43]. This stemmed from a previous randomized, matched-pair control group study by the authors showing that the percentage of active cigarette smokers among HS patients was 88.9% (56 out of 84 patients), with an odds ratio of 9.4 and the percentage of smokers in the matched-pair control group was 46%[44].

A multivariate analysis by Revuz et al showed showed a strong association with self-reported, current smoking (odds ratio=4.16) in a medically assessed (odds ratio=12.55) population[10]. Further studies similarly found significantly higher prevalence of smokers within the HS population[45,46] .

In addition, several studies investigated the association between smoking and HS disease severity. Sartorius et al used the modified Hidradenitis Suppurativa score (HSS) to evaluate the impact of tobacco smoking on HS severity in 2,46 HS patients[47]. They observed that patients who smoked had a higher median HSS compared to non-smokers, 41(22-75.5) vs. 22(10-57). A population-based study of Olmsted County, Minnesota by Vazquez et al also showed that smoking was associated with more severe disease[48]. These findings however were not consistent with the findings of Schrader et al that found a similar prevalence of current smokers in HS Hurleys Stage 1 vs Hurleys Stage 2 vs Hurleys Stage 3 of 67.9% vs 74.7% vs.68.2%[30].

More recently in 2017, Dessinioti et al[49] conducted a retrospective chart review study investigating the association of smoking with HS severity defined by Hurley Stage or number of body areas affected. This study included 133 patients, of which 77% (n=102) were current smokers. Following multiple logistic regression analysis adjusting for possible confounders, Hurley's Stage severity was not associated with smoking, however the number of affected body areas was increased in current or former compared to non-smokers however (OR 3.56, 95% CI 1.27-9.96, p= 0.016). Furthermore, a single-centre retrospective cohort study investigating the effect of smoking and age on response to first line therapy of HS, demonstrated that non-smokers (OR 2.63, 95% CI 1.30-5.33, p=0.007) were more likely to show improvement at follow up[50].

Kromann et al[16] in their postal follow up survey, studied 212 patients diagnosed with HS between 1981 and 2001 with a median follow-up period of 22 years (range 12–32). They noted that tobacco smoking was reported by 92.2% (119/129) of HS patients. Significantly, non-smokers, 40% (35/88) reported remission from disease and only 29% (17/59) of active smokers reported same.

The role of cigarette smoking in HS is however still unclear. Potential mechanisms of cigarette smoking in the pathogenesis of HS have been proposed by Kruzen et al[51]. Nicotine causes release of tumour necrosis factor alpha causing inflammation, promotion of follicular occlusion and epidermal hyperplasia. Nicotine in tobacco smoke also contains polyaromatic carbohydrates, arsenic and dioxin- like compounds that may activate keratinocytes and cells of the immune system via nicotinic acetylcholine receptors (AChR).

Table 2..7 Summary of studies of Cigarette Smoking in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Konig, 1999	Patients with HS: 63 Controls: 63	Prevalence of active smokers in HS vs. control: 88.9% vs. 46%	OR: 9.4 (CI: 3.7–23.7)
Revuz, 2008	1475 (67 HS population; 302 HS hospital)	Current smoker: prevalence of current smokers in population HS vs. control: 40.3% vs. 19.2%; prevalence of current smokers in hospital HS vs. control: 75.6% vs. 24.7%. Ex-smoker: prevalence of ex-smokers in population HS vs. control: 28.4% vs. 28.8%; prevalence of ex-smokers in hospital HS vs. control: 9.3% vs. 21.6%. Cigarettes per day: cigarettes per day in population HS vs.	Current smoker: population: ORa: 3.79 (CI: 1.86–7.74); hospital: ORa: 12.55 (CI: 8.58–18.38). Ex-smoker: population: ORa: 1.55 (CI: 0.74–3.32); hospital: ORa: 1.46 (CI: 0.86–2.46). Cigarettes per day: population: ORa: 1.04 (CI: 0.98–1.10); hospital: ORa: 1.05 (CI: 1.02– 1.08). Age of

		control: 13.9 vs. 11.2; cigarettes per day in hospital HS vs. control: 16.1 vs. 13.0. Age of smoking start: age of starting smoking in population HS vs. control: 18.9 vs. 19.6; age of starting smoking in hospital HS vs. control: 17.4 vs. 17.6.	smoking start: population: ORa: 0.98 (CI: 0.91–1.06); hospital: ORa: 0.98 (CI: 0.93– 1.03).
Sartorius, 2009	246	HS disease severity by median (IQR) Hidradenitis Suppurativa Score in smokers vs. non-smokers: 41 (22–75.5) vs. 22 (10–57) NA	NA
Vazquez, 2013	265	Prevalence of Hurley stage II or III in past/current smoker vs.	OR: 2.0 (CI: 1.1–3.5)

		never smoker: 45.2% vs. 29.1%	
Schrader, 2014	846	Current smoker: prevalence of current smoker in HS Hurley stage I vs. Hurley stage II vs. Hurley stage III: 67.9 vs. 74.7 vs. 68.2. Ex-smoker: prevalence of ex-smoker in HS Hurley stage I vs. Hurley stage II vs. Hurley stage III: 13.3 vs. 13.2 vs. 20.0. Smoking pack-years: mean smoking pack-years in HS Hurley stage I vs. Hurley stage II vs. Hurley stage III: 15.5 12.7 vs. 19.3 13.2 vs. 27.9 24.5	Current smoker: OR: 0.94 (CI: 0.60–1.47). Ex-smoker: OR: 1.14 (CI: 0.64–2.02). Pack-years: OR: 1.02 (CI: 1.01–1.03)

Shalom, 2015	Patients with HS: 3207 Controls: 6412	Active smokers in HS vs. control: 47% vs. 30%	OR: 2.1 (CI: 1.9–2.3)
Shlyankevich, 2014	Patients with HS: 1730 Controls: 1730	Prevalence of current OR, former smokers in HS vs. control: 29.5% vs. 0.92%	OR: 5.34 (CI: 2.09–9.83)
Miller, 2014	HS population: 326 HS hospital: 32 Controls: 14 851	Active smokers in population HS vs. hospital HS vs. control: 40% vs. 53% vs. 18%	Population: OR: 3.12 (CI: 2.49–3.91) Hospital: OR: 5.1 (CI: 2.56– 10.30
Oberleitner L, 2014	118	Prevalence of active smokers was 91.3%.	NA
Kromann, 2014	127	Rate of HS disease remission in non-smokers vs. active smokers: 40% vs. 29%	OR: 2.8 (CI: 1.3–6.3)2

Dessinioti, 2017	133	More than 2 body areas affected in HS patients who ever smoked (current or former smokers) vs never smoked OR 3.56 (CI : 1.27–9.96 , p=0.016)	

2.8 Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) which includes Crohn's Disease (CD) and Ulcerative Colitis (UC) has been associated with several dermatological manifestations. These include pyoderma gangrenosum, Sweet's syndrome, psoriasis and erythema nodosum. An association between IBD and HS has been reported as early as in 1991[52]. In 1993, Church et al[53] described a cohort of 24 patients with an overlapping disease of HS and CD. In this retrospective review, the diagnosis of CD preceded that of HS by 3.5 years and majority of the patients (19 of 24) had large bowel only CD. All patients had HS occurring in the perineal or perianal area but also involving other sites in 20 cases.

In a pilot study by Van Der Zee et al[54], 158 IBD patients were interviewed and were asked about the presence of recurrent painful boils in the groin and/or axillae suggestive of HS. Patients were also shown two prototypical clinical pictures of HS to allow for visual comparison of the condition. Of the 158 patients interviewed, 102 (65%) had CD and 56 (35%) UC. Twenty-five patients (16%) reported a history of painful boils in the axillae or groin, of whom 17 (17%) were CD patients and eight (14%) were UC patients. In 2014,

the same authors conducted a sequel study in a much larger population of 1,093 IBD patients and found that overall 255 patients with IBD reported having HS (23%), with 26% of those with CD and 18% of those with UC having HS[55]. They also showed a female preponderance in their study and a correlation between smoking and disease severity. Both studies, have several flaws. There are numerous causes of painful boils in the groin and axillary regions including furunculosis, lymphadenitis or cutaneous Crohn's disease and in this study, patients were not physically examined, neither did they have skin biopsies taken to confirm the diagnosis of HS histologically.

In 2016, Yadav et al followed 679 IBD patients over a median of 19.8 years, and identified 8 patients with HS (mean age, 44.4±8.3 years; 7 females), 5 with CD and 3 with UC[56]. All cases of HS were confirmed by biopsy and/or dermatologic evaluation. The prevalence of HS in this cohort of IBD patients was 1.18% and the 10- and 30-year cumulative incidence of HS was 0.85% and 1.55%, respectively. This population-based study concluded that patients with IBD were 9 times more likely to develop HS than the general population and there was a significant association with obesity, female sex and perianal CD disease.

Janse et al[57] sent a questionnaire validated for HS to 1,969 patients suffering from IBD. Of 1,260 patients who responded to these questionnaires it was found that the prevalence of HS was 10.6% (134 out of 1,260) with a higher association with CD (15.1%) than with UC. In this study, IBD patients with earlier onset of disease were more like to have HS. Female gender, smoking, higher body mass index, and younger age were independent, associated parameters for HS.

Principi et al[58] performed a pooled-data analysis of the four cited studies mentioned above and found that the pooled prevalence of HS in IBD patients was 12.8%, (95%CI of 11.7%-13.9%). A stronger association was noted with CD, HS was present in 17.3% of subjects

with CD (95%CI: 15.5%-19.1%) and 8.5% of patients with UC (95%CI: 7.0%-9.9%). It was acknowledged that as 3 of the 4 studies were questionnaire studies, this prevalence rate could be an overestimate in comparison to the physician direct clinical assessment.

A multicentre, cross - sectional study published in 2017 by Deckers et al [59] , found that of 1,076 patients with HS, 36 (3.3%) had IBD, with a prevalence of 2.5% for CD and 0.8% for CD. Using the estimated prevalence of IBD in the general population in northern Europe which ranges between 0.41% and 0.74%, with a prevalence of CD between 0.14% and 0.32% and a prevalence of UC between 0.24% and 0.41%, it was indicated that the prevalence of IBD is 4-8 times higher in the included HS cohort than in the general population.

Shalom et al[60] in a cross-sectional study included 3,207 HS patients and 6,412 age and sex matched controls without HS. The authors in this study concluded that HS was significantly associated with CD (odds ratio = 2.03, 95% confidence interval: 1.14-3.62, P =0.01) but not with UC (odds ratio=1.82, 95% confidence interval: 0.81-4.05, P =0.15), compared with control subjects.

Finally, the largest study exploring the association between HS and IBD is a Danish population study by Egeberg[61] consisting of 7,732 patients with a diagnosis of HS, and 4,354,137 general population control subjects. This study showed that HS was associated with a significantly increased risk of concurrent and new-onset IBD, with a prevalence ranging from 0.7% to 1.3%, and an incidence of 0.13 to 0.97 per 1,000 patients with HS per year.

HS and CD share several similar clinical and pathogenic features. Both conditions are chronic diseases of epithelia which are inhabited by commensal flora and both have demonstrated a clinical response to anti-TNF α therapy. They share several predisposing

factors including genetic predisposition and smoking association. There is some evidence to suggest that CD is associated with shifts in the common gut flora secondary to disrupted immune tolerance and that chronic gut inflammation is the result of abnormal immune responses in genetically predisposed individuals to microorganisms that reside in the gut[62]. This pathogenic theory could resemble the immune response to skin commensal bacteria that may be altered, with the triggering threshold lowered in patients with HS. Additionally, smoking being a common factor between CD and HS may result in the activation of aryl hydrocarbons which may represent a common molecular trigger in CD and HS indirectly leading to changes in the microbiota.

Table 2.8 Summary of studies of Inflammatory Bowel Disease in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Church 1993	Patients with HS: 61 Patients with CD and HS: 24	Prevalence of CD: 39.3%	N/A
Van Der Zee 2010	Patients with IBD: 158 Patients with IBD and HS: 25	Prevalence of HS: 15.8%	N/A

Van Der Zee 2010	Patients with CD: 102 Patients with CD and HS: 17	Prevalence of HS in CD patients 16.7%	N/A
Van Der Zee 2010	Patients with UC: 56 Patients with UC and HS: 8	Prevalence of HS in UC patients: 14.3%	N/A
Van Der Zee 2014	Patients with IBD: 1093 Patients with IBD and HS: 255	Prevalence of HS: 23.3%	N/A
Van Der Zee 2014	Patients with CD: 688 Patients with CD and HS: 181	Prevalence of HS in CD patients: 26.3%	N/A
Van Der Zee 2014	Patients with UC: 405 Patients with UC and HS: 74	Prevalence of HS in UC patients: 18.3%	N/A

Yadav 2016	Patients with IBD: 679 Patients with IBD and HS: 8	Prevalence of HS in IBD patients followed up over a median of 19.8 years: 1.18%.	N/A
Yadav 2016	Patients with CD: 313 Patients with CD and HS: 5	Prevalence of HS in CD patients followed up over a median of 19.8 years: 1.60%.	N/A
Yadav 2016	Patients with UC: 366 Patients with UC and HS: 3	Prevalence of HS in UC patients followed up over a median of 19.8 years: 0.82%.	N/A
Yadav 2016	Patients with IBD: 679 Patients with IBD and HS: 8	The incidence of HS after IBD diagnosis was 0.55 cases per 1000 person-years, with no significant difference in patients with CD (0.71) or UC (0.42).	The incidence of HS in patients with IBD compared with the incidence in the general population (IRR) was 8.9 (CI: 3.6 –17.5) with no significant

			difference in patients with CD (11.5) or UC (6.8).
Yadav 2016	Patients with IBD: 679 Patients with IBD and HS: 8	Cumulative incidence in 10 years: 0.85% (CI: 0.1%–1.6%). 20 years: 1.2% (CI: 0.2%–2.2%). 30 years: 1.5% (CI: 0.3%–3.5%)	N/A
Janse et al 16	Patients with IBD: 1260 Patients with IBD and HS: 134	Prevalence of HS 10.6%	N/A
Shalom 2016	Patients with HS: 3207 Controls: 6412	Prevalence of CD: 0.8% in HS vs 0.4% in general population Prevalence of UC: 0.4% in HS vs 0.2% in general population	CD: OR 2.03 (95% CI:1.14-3.62, P =0.01) UC: OR 1.82 (95% CI :0.81-4.05, P =0.15)

Deckers 2017	Patients with HS: 1076	Prevalence of CD: 2.5% (CI: 1.6–3.4). Prevalence of UC: 0.8% (CI: 0.3–1.4)	
Egeberg 2017	Patients with HS: 7732 General population: 4,354,137	Prevalence of CD: 0.8% in HS vs. 0.3% in general population. Prevalence of UC: 1.3% in HS vs. 0.7% in general population.	CD: OR 2.04 (CI: 1.59–2.62) UC: OR 1.75 (CI: 1.44–2.13

2.9 Inflammatory joint disorders (Spondyloarthritis (SpA))

Rosner et al were the first to describe arthropathy associated with acne conglobata and HS in 1982 in 10 patients[63]. A follow up study by the same authors reported 44 HS patients this time, having an association with peripheral inflammatory arthropathy (29%), axial arthropathy (14%), or a combination of both in 57%. In this study, the only difference detected was the lack of association with HLA-B27, whereas clinical and laboratory findings were characteristic of those seen in other seronegative spondyloarthropathies[64].

Richette et al conducted the first prospective study involving a systematic screening of 640 patients with HS for presence of inflammatory rheumatologic disease[65]. In this cohort, the estimated prevalence of spondyloarthropathy was 3.7% which far exceeded that estimated

for the French population, 0.3%. In a retrospective, case-control study of 1,730 HS patients in Massachusetts General Hospital, it was found that 908 patients had spondylarthritis compared to only 52 in those who did not have HS (52.5% vs. 3.0% p< 0.0001)[9].

More recently, Sylke Schneider-Burrus conducted a prospective questionnaire survey in 100 HS patients and a retrospective evaluation of pelvic magnetic resonance imaging (MRI) scans in 46 HS patients[66]. They demonstrated that back pain was a common phenomenon in HS with 71% of their cohort suffering with back pain. In this cohort, 56.5% revealed typical radiological changes of spondyloarthropathy-related, sacroiliitis in their MRI analyses.

Interestingly, there were no significant differences between patients with/without SpA found in view of age at time of MRI, age at onset of HS, disease duration, smoking habits, and BMI.

The pathogenesis underlying the development of SpA in HS patients is unclear. The shared pathophysiologic features of dysregulated innate immune response and the role of microbial factors may be contributing factors. Although studies on this element of SpA in HS patients are limited, it has undoubtedly shown that physicians should always keep in mind its association with HS and screen patients for same as part of their routine standard of care.

Table 2.9 Summary of studies of Inflammatory joint disorders (Spondylarthritis (SpA)) in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association

Shlyankevich, 2014	Patients with HS: 1730 Patients with HS and SpA: 908 Patients without HS (controls): 1730 Patients without HS with SpA: 52	Prevalence of arthropathies in HS vs. control: 52.5% vs. 3.0% (P < 0.0001)	OR: 35.6 (CI: 26.6–47.7) ORa: 9.41 (CI: 6.81–12.9)
Richette, 2014	Patients with HS: 640 Patients with SpA† and HS: 24	Prevalence of SpA† in HS vs. French population estimate: 3.7% vs. 0.3%	NA

Rosner, 1993	Patients with HS: 44, 21 had inflammatory arthropathy (18 peripheral arthritis, 15 axial arthropathy and 12 both)	Prevalence of inflammatory arthropathy: 47.7% Prevalence of peripheral arthritis: 40.9%. Prevalence of axial arthropathy: 34.1%. Prevalence of both (peripheral and axial) arthropathy: 27.3%.	NA
Schneider-Burrus, 2016	146	32.6% of HS patients showed signs of chronic SpA and 39.1% signs of active SpA.	NA

2.10 Depression/Anxiety

There has been an established link between HS and psychiatric disease, anxiety and depression. One of the largest studies exploring the psychosocial effect of HS was a cross-sectional study conducted by Shavit et al and included 3,207 HS patients and 6,412 age and gender-matched controls[67]. In this study, depression was diagnosed in 5.9% of HS patients vs. 3.5% controls ($P < 0.001$) whereas anxiety was diagnosed in 3.9% of HS patients vs. 2.4% of patients without HS ($P < 0.001$). These associations were significant

after controlling for the confounders age and gender (Depression: OR = 1.7, 95% CI: 1.4–2.1; Anxiety: OR = 1.7, 95% CI: 1.3–2.1).

Onderdjik et al explored patient-reported degree of depression as determined by the Major Depression Inventory (MDI) questionnaire[68]. It was found that although clinically defined depression rates according to the International Classification of Diseases, 10th edition (ICD-10) criteria were not significantly higher in HS patients compared to controls (9% vs. 6%), mean MDI scores were significantly higher for HS patients, 11.0 vs. 7.2 ($P < 0.0001$). The DLQI in HS patients was also significantly higher than controls 8.4 ± 7.5 vs. 4.3 ± 5.6 ($P < 0.0001$) and correlated with Hurley stage severity scores.

A further study by Crowley et al[69] and a population-based study of Olmsted County, Minnesota by Vazquez et al[48] found a high prevalence of depression in their population of 41.6% and of 42.9% respectively. More recently, Kouris *et al*. highlighted a significant association between HS and depression, anxiety, and social isolation, as well as lower levels of self-esteem, compared to controls[70]. In this study, patients with HS had statistically significantly higher anxiety (6.41 ± 3.31 vs. 5.00 ± 1.59, $p < 0.001$), depression (5.45 ± 2.79 vs. 4.16 ± 1.54, $p < 0.001$), and loneliness and social isolation scores (42.86 ± 8.63 vs. 35.57 ± 6.17, $p < 0.001$) and lower self-esteem scores (18.91 ± 1.79 vs. 19.77 ± 2.53, $p = 0.008$) than healthy controls.

A study evaluating the pyschosocial effects of HS compared to age, gender and BMI matched controls using the Hospital Anxiety and Depression Scale (HADS), showed that 38.6% of HS patients suffered from depression compared to 2.4 % of the control subjects[71]. Interestingly, in this study, although there was a significant correlation between disease severity and degree of depression, neither the duration of the disease nor the age correlated with the degree of depression. These findings support several other studies in the literature

suggesting a possible link between chronic inflammation and depression. Pro-inflammatory cytokines are elevated in both major depressive disorder and anxiety disorders as well as schizophrenia and other psychiatric disorders suggesting that elevated pro-inflammatory cytokines in both skin and the brain may explain the association between HS and psychiatric disorders[72],[73],[74]. In addition, HS patients suffer significant pain and foul-smelling suppuration from abscesses or sinuses in affected areas during flares which leads to disruption of activities of daily living as well as work and embarrassment contributing to psychological distress.

Table 2.10 Summary of studies of Depression and Anxiety in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Shavit, 2015	Patients with HS: 3207 Controls: 6412	Prevalence of depression in HS vs. control: 5.9% vs. 3.5%. Prevalence of anxiety in HS vs. control: 3.9% vs. 2.4%.	Depression: OR: 1.7 (CI: 1.4–2.1) Anxiety: OR: 1.7 (CI: 1.3–2.1)
Crowley, 2014	154	Prevalence of depression (PHQ-9 scores ≥10): 41.6%	NA

Onderdijk, 2013	Patients with HS: 211 Controls: 230	Prevalence of depression (MDI score ≥20): 20.8% vs. 11.3% (P = 0.006)	OR: 2.07 (CI: 1.22–3.50)
Vazquez, 2013	268	Prevalence of depression: 42.9%	NA
Kurek, 2013	Patients with HS : 44 Controls : 41	Prevalence of depression in HS vs. controls : 38.6 % vs. 2.4 % (P<0.001)	NA
Kouris 2017	94 HS patients	Anxiety (6.41 ± 3.31 vs. 5.00 ± 1.59, $p < 0.001$), Depression (5.45 ± 2.79 vs. 4.16 ± 1.54, $p < 0.001$	NA

2.11 Alcohol Consumption

Studies in the literature exploring the level of alcohol consumption among HS patients are limited. Revuz et al in a self-reported case control study did not show a statistically higher level of alcohol consumption in HS patients compared to controls[10]. A larger study including 1,730 patients showed conflicting results with much higher prevalence of alcohol dependence in the HS cohort compared to controls; 4.2% vs. 0.52% ($P < 0.0001$)[9]. Although alcohol dependence had 8.43 greater odds in the HS population in compared to controls in the univariate analysis (OR: 8.43), the odds ratio was significantly lower in the multivariate analysis OR 0.25 after adjusting for other comorbidities.

Table 2.11 Summary of studies of Alcohol Consumption in Hidradenitis Suppurativa

Study	Sample size	Outcome Measure	Measures of association
Shlyankevich, 2014	Patients with HS: 1730 Controls: 1730	Prevalence of alcohol dependence in HS vs. control: 4.2% vs. 0.52% (P < 0.0001)	ORa: 0.25 (CI: 0.087–0.73)
Revuz, 2008	Patients with HS: 67 Controls: 200	Prevalence of >1 alcoholic drink per day in HS vs. control: 16.7% vs. 15.1%	OR: 1.09 (CI: 0.59–2.01)

2.12 Conclusion

Hidradenitis suppurativa carries a systemic burden and substantial comorbidities, therefore it is crucial for treating physicians to consider these comorbidities and endeavour to identify them as early as possible to facilitate early intervention in this young cohort of patients. Dermatologists should take a comprehensive history including presence of symptoms such as joint pains, or abnormal bowel habits as well as assessing mood and psychological status of patients. In addition, HS patients should have routine lipid profile and diabetes screening tests performed, along with their blood pressure checked for early risk stratification of cardiovascular disease. Appropriate referrals should be initiated for those who require expert input from other specialities including rheumatologists, psychiatrists and cardiologists. Patients who smoke should be offered smoking cessation advice in the clinic and referral to smoking cessation services. Dauden et al recommend that HS patients should be screened for these comorbidities every 12 months, or more frequently if the clinical situation suggests[75]

2.13 Aims:

In this thesis, we aimed:

- To assess if patients with HS had elevated cardiovascular risk compared to healthy age and sex matched controls using Framingham Risk and QRISK2

- To ascertain if certain ‘non-classical’ cardiovascular risk factor such as Homocysteine, C-reactive protein and insulin resistance were elevated in HS
- To specifically quantify and compare LDL subclasses in women aged >18 years with HS and age, sex, BMI and HOMA-IR (insulin resistance) matched healthy controls that may still increase their risk of CVD despite having a normal total LDL level
- To evaluate the Quality of Life (QoL) in the two cohorts of patients (HS and psoriasis) using the Dermatology Quality of Life Index (DLQI)
- To evaluate the level of disease-related pain within the HS cohort using the Visual Analogue Pain Score (VAPS).
- To investigate the impact of HS on depression and anxiety and compared it to psoriasis patients.

Chapter 3: Materials and Methods

3.1 Patients

Ethical approval was obtained from the Tallaght Hospital Research Committee for all parts of this study. Sequential patients attending the Dermatology Outpatients Department in Tallaght Hospital, with a known diagnosis of Hidradenitis Suppurativa (HS) and over 18 years of age were recruited.

Diagnostic criteria for HS which were employed for the purpose of this study are based on the British Association of Dermatologists (BAD) guideline and are as follows :

1. The presence of typical lesions (painful nodules, abscesses, sinus tracts, bridged scars or open comedones.
2. Lesions occurring in at least one typical body location such as the axillae, groin, perineal and perianal region, buttocks, and inframammary and intermammary folds.
3. Chronic nature of disease, relapses, and recurrences.

The inclusion criteria for enrolment of the HS patients were:

I. 18 years and older
II. No history of CVD including ischaemic heart disease, peripheral vascular disease, strokes or transient ischemic attacks.
III. A known diagnosis of HS.

The inclusion criteria for control patients were:

I. 18 years or older and were age (+/- 5 years) and sex matched with the HS patients

II. No history of CVD including ischaemic heart disease, peripheral vascular disease, strokes or transient ischemic attacks and
III. No known diagnosis of HS or any other inflammatory skin conditions

The inclusion criteria for psoriasis patients were:

I. 18 years and older
II. A known diagnosis of psoriasis

Additional healthy controls were recruited and included in the lipoprotein analysis study.

For this study the exclusion criteria were:

I. <18 years
II. Personal or family history of familial hyperlipidemia

All patients were given patient information leaflets (Appendix A) and written informed consent (Appendix B) was obtained.

3.2 Demographic data and questionnaires

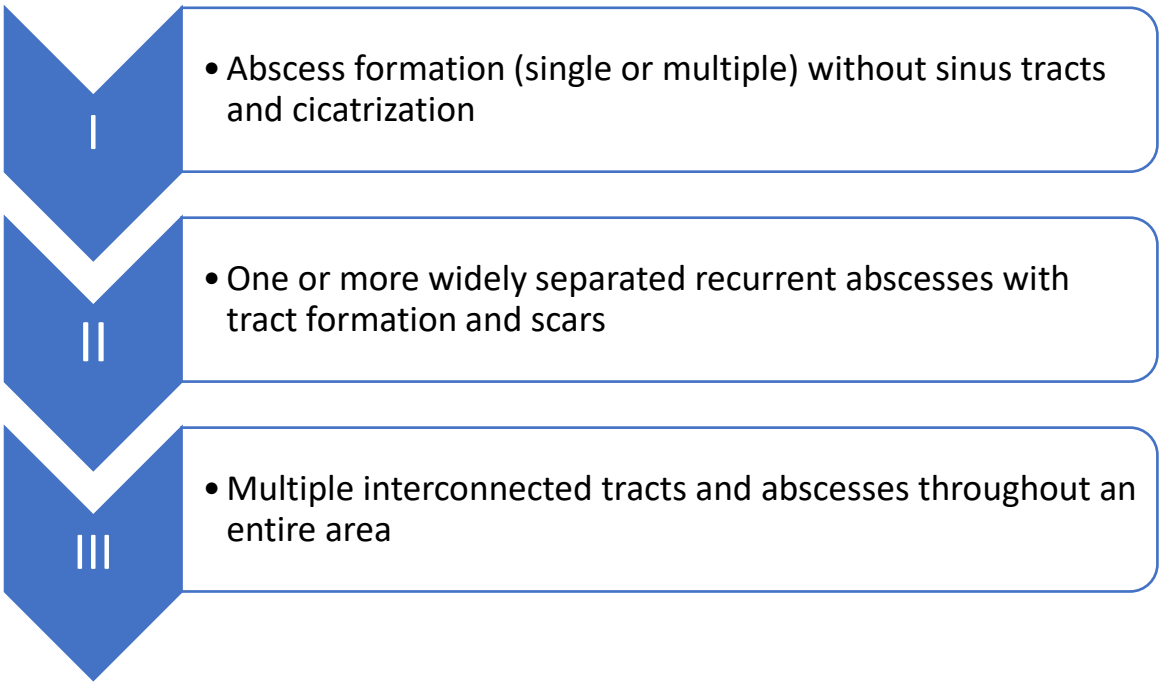
A proforma was devised to record demographic and other relevant data of patients included (Appendix C). Patients attending the Dermatology Department at Tallaght Hospital who met the criteria for Hidradenitis Suppurativa were recruited. They were met with by the investigator either at the start or end of the consultation and given information on studies being conducted. Patient information leaflet was also provided and participants were given time to read the PIL and ask questions. Once agreeable to partake, a consent form was signed.

Basic demographic data, smoking status and alcohol intake were documented in the proforma. Duration of HS disease, treatments for HS to date including medical and/or surgical, a family history of HS, all other past medical history and list of medications were recorded.

All patients completed the Dermatology Life Quality Index (DLQI)[76] (Appendix D), the Hospital Anxiety and Depression Scale (HADS) (Appendix E) and a Visual Analogue Score (VAS) for pain (Appendix F) at their outpatient visit.

3.3 Clinical Examination

Patients were examined in the clinic and disease severity was recorded using the Hurley's Staging[77]



3.4 Physical measurements

All patients had the measurements below recorded:

I. Height (cm)

II. Weight (kg)

III. Waist circumference (cm)

IV. Blood pressure (mmHg)

A body mass index was calculated for all patients recruited using the formula:

BMI = Weight (kg) /Height (m2)

Body mass indices were classified using the World Health Organization (WHO) definition as below:

Classification	BMI (kg/m2)
Underweight	≤18.49
Healthy	18.5-24.9
Overweight	25-29.9
Obese	≥ 30
Morbid obesity	≥ 40

Blood pressure was taken using a sphygmomanometer in the sitting position on the left forearm in all patients.

3.5 Blood samples

Fasting blood samples were taken to test all following parameters from participants by the study investigator. In total, blood was drawn into three EDTA and two biochemistry test tubes from each participant and sent to the hospital lab to measure the following:

Test	**Method**	**Normal Range**
Glucose	Measured using the enzymatic reference method with hexokinase	2.8-6.0 mmol/L
Insulin	Measured using the Elecsys insulin assay	2-25 mU/L
Homocysteine	Measured using the homocysteine Enzymatic Assay based on a novel enzyme cycling assay principle that assesses the co-substrate conversion product instead of assessing co-substrate or Hcy conversion products of Hcy.	0-15 umol/L
C- Reactive Protein	Measured using the article enhanced immunoturbidimetric assay.	0-5mg/L
Total Cholestrol	Measured using the Roche cholesterol assay	<5.0mmol/L

LDL	Calculated using the Friedwald equation; (Trig x 0.458) + (Cholesterol-HDL).	<3.0 mmol/L
HDL	Measured using the homogeneous enzymatic colorimetric test	>1.2 mmol/L
Triglycerides	Measured using a lipoprotein lipase from microorganisms for the rapid and complete hydrolysis of triglycerides to glycerol followed by oxidation to dihydroxyacetone phosphate and hydrogen peroxide with subsequent photometric measurement.	<1.7 mmol/L

3.6 Insulin resistance:

Fasting blood samples were taken for the measurement of insulin and glucose. Serum insulin concentrations were determined in the hospital laboratory by automated chemiluminescence immunoassay on a Tosoh platform (Tosoh, Tokyo, Japan). Plasma glucose concentrations were quantified with a hexokinase method (Roche Diagnostics).

Insulin resistance was measured using the homeostasis model with the formula:

Insulin x glucose/ 22.5 (Matthews, 1985)

A value greater than 2.5 indicates a state of insulin resistance.

3.7 Cardiovascular Risk Calculation

3.7.1 Framingham Risk Score

Cardiovascular risk was determined using the Framingham Risk score[78] which was calculated using the established gender specific MedCalc online calculator to generate the 10-year CVD risk in our patients (Appendix G). This generates a patient's 10-year risk of having a myocardial infarction or a cerebrovascular event in patients > 30 years of age.

To assess patients cardiovascular risk, fasting lipids (total cholesterol, triglycerides and high density lipoprotein) analysed using a colorimetric method Roche Diagnostics and low density lipoprotein (Calculation: LDL Cholesterol = T.Chol – (HDL Cholesterol + (Triglycerides/2.2)) were measured in the hospital laboratory.

Patients' age, sex, smoking status (ex-smokers were considered non-smokers five years after quitting smoking), total cholesterol, high density lipoprotein, history of diabetes, systolic blood pressure and history of blood pressure treatment were entered into the MedCalc® Framingham Risk Calculator to generate each patients individual 10 year risk of having a cardiovascular event. A family history of myocardial infarction or stroke recorded. Patients with less than 10% CVD risk at 10 years were deemed to be at low risk, with intermediate risk 10-19%, and with high risk of 20% or more.

Systemic Coronary Risk Evaluation tables were used by the Framingham Risk calculator to calculate individual patients 10-year risk of having a fatal coronary or cerebrovascular event. Ireland is defined as a high-risk area and hence the appropriate high-risk area table was used.

Non-classical cardiovascular risk factors such as homocysteine were also measured using the Colorimetric Method (Roche Diagnostics). Samples for homocysteine were taken in a chilled EDTA tube and transported to the hospital laboratory on ice. Fibrinogen (High

Performance Liquid Chromatography) and C-reactive protein (particle-enhanced turbidimetric assay, Roche Diagnostics) were also measured.

3.7.2 QRISK2

In the UK, current National Institute for Health and Care Excellence (NICE) guidelines recommends using QRISK (as opposed to the Framingham Risk Score). QRISK2 is also a prediction algorithm for cardiovascular disease (CVD) that uses traditional risk factors (age, systolic blood pressure, diabetes mellitus, smoking status and ratio of total serum cholesterol to high-density lipoprotein cholesterol) together with body mass index, ethnicity, family history, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, and antihypertensive treatment. It includes patients in the range between 25- 84 years. A QRISK2 of over 10 (10% risk of CVD event over the next ten years) indicates that primary prevention with lipid lowering therapy (such as statins) should be considered. In addition to an individual's absolute risk, the QRISK2 generates a relative risk, which is the excess risk a patient has compared to a healthy person without any risk factors.

3.8 Lipoprotein Subclasses Analysis

Two EDTA blood samples were obtained from patients included in the lipoprotein analysis study. Blood samples obtained were centrifuged at 1000 x g for 15 minutes. The serum component was aliquoted and stored at -80°C for batch analysis.

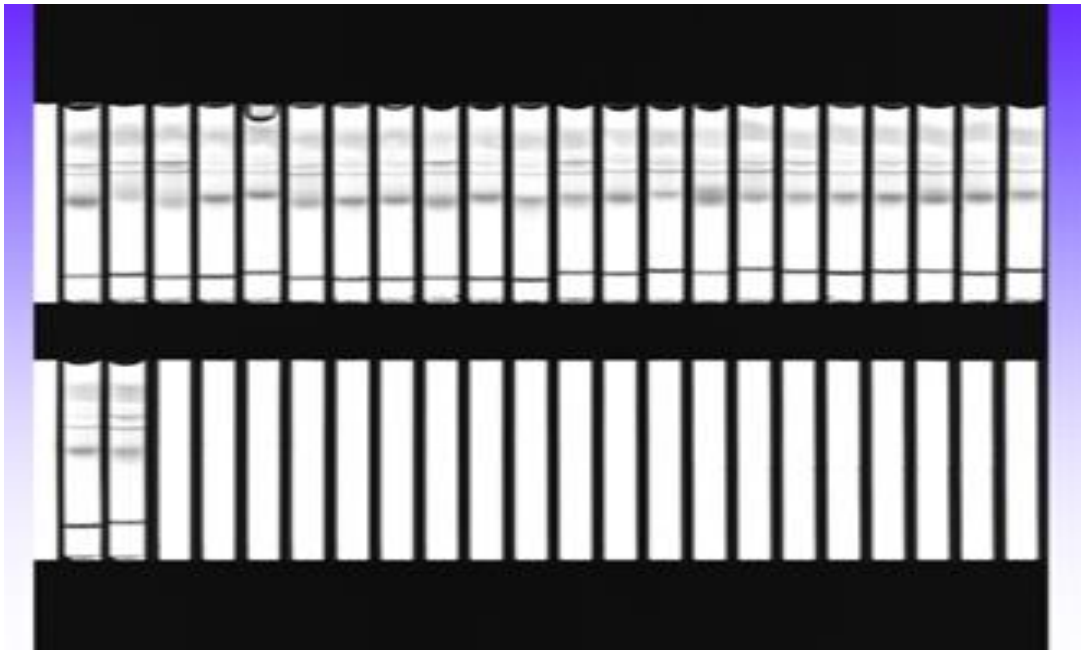
Lipoprotein subclasses were measured using the Quantimetrix Lipoprint System. Lipoprint® is an FDA-approved test for measuring LDL subfraction cholesterol levels. It uses high resolution polyacrilamide gel electrophoresis to separate and measure the amount of cholesterol in each LDL and HDL subfraction on the basis of size ;Very Low Density Lipoprotein (VLDL),VLDL remnants, Intermediate Density Lipoprotein (IDL) , Low Density Lipoprotein (LDL) 1 through LDL 7, and High Density Lipoprotein (HDL)

in serum or plasma. Lipoprint also measures cholesterol and area percent for each fraction and subfraction as well as mean LDL particle size.

I. Serum samples are electrophoresed using high resolution polyacrylamide gel electrophoresis

II. The electrophoresed gel tubes are loaded on to the Lipoware scanner

III. A digitized image of the electrophoresed gel tubes are generated

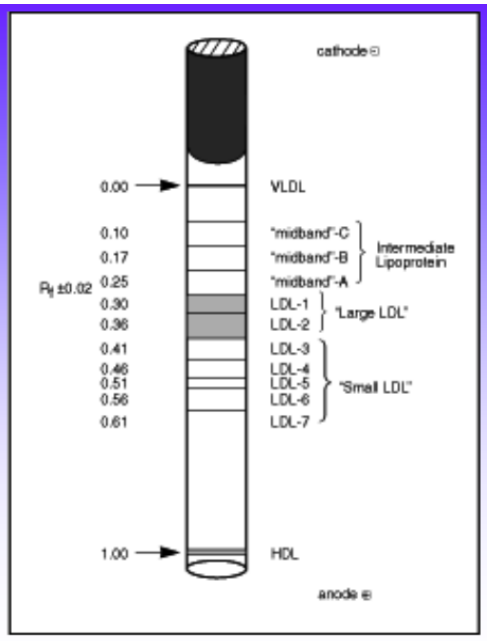


IV. Up to 12 lipoproteins bands are resolved according to size

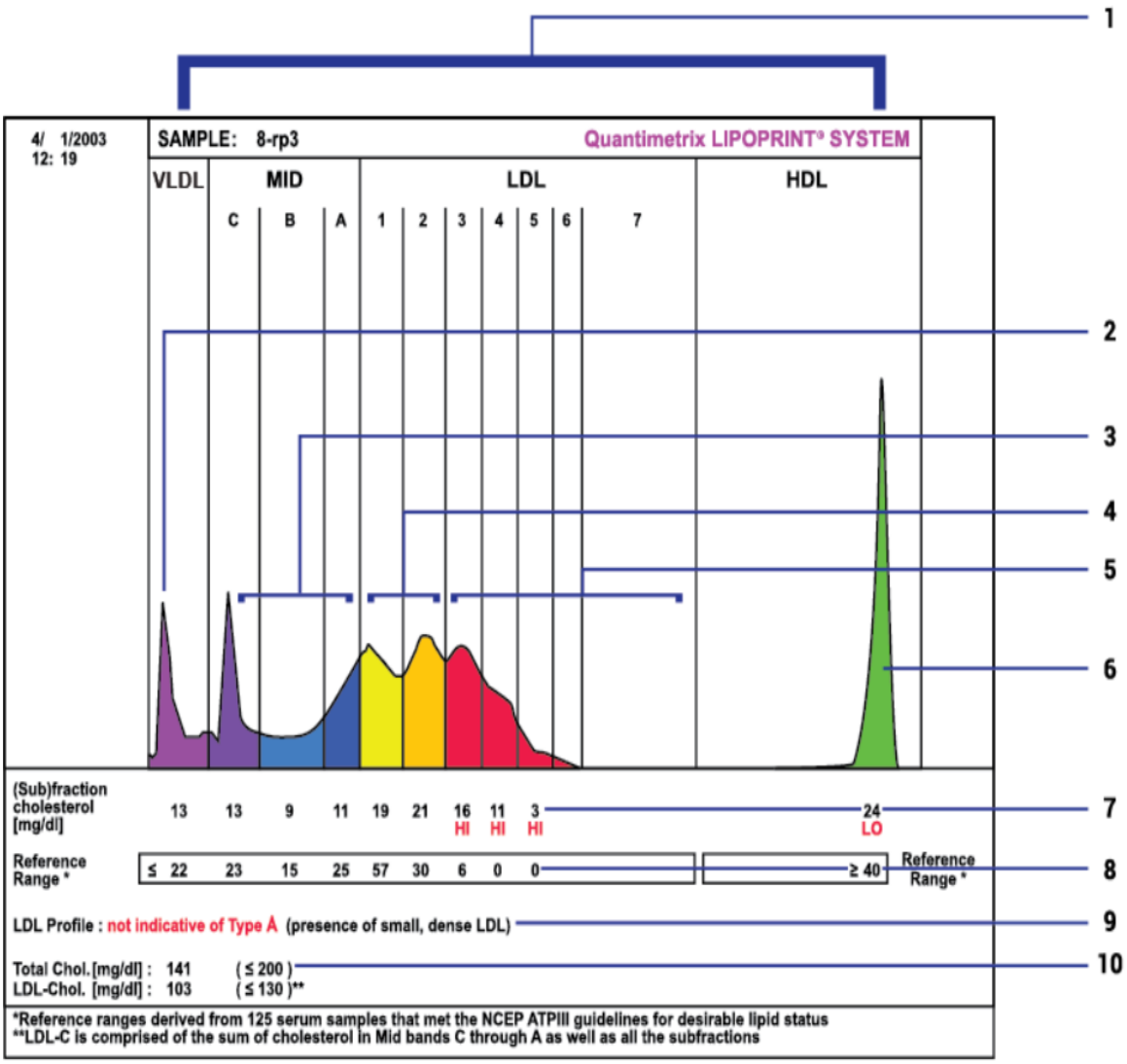
Up to 12 lipoproteins bands are resolved according to size (1 VLDL, 3 Mid Bands, 7 LDLs and 1 HDL)

VLDL migrates at the top of the separating gel Rf = 0 and HDL migrates at the front Rf = 1

Mid Bands and LDL subfractions migrate at specific rates between VLDL and HDL



Ultimately, a colour coded easy-to-interpret patient profile is generated, featuring lipoprotein subfraction distribution, cholesterol levels in each fraction, and a comparison to the normal reference range. Cholesterol values outside the normal reference range and the presence of atherogenic small dense LDL are flagged in red for ease of interpretation. Lipoprotein Profile Classification is also generated with a predominance of large LDL being classified as Type A and predominance of small dense LDL classified as Not Indicative of Type A.



1. Measurement of up to twelve lipoprotein fractions and subfractions are generated. Results for every lipoprotein subfraction are reported as mg/dL cholesterol which inform patient treatment.

2. VLDL increased levels – associated with hypertriglyceridemia, one of the components of the lipid triad of atherogenic dyslipidemia.

3. Midbands A, B and C (include VLDL remnants and IDL) – associated with atherogenic Type III dyslipidemia and combined hyperlipoproteinemia.

4. LDL 1 and 2 (large buoyant LDL) – not associated with CVD risk.
5. LDL 3 through 7 (small dense LDL) – component of the lipid triad associated with 3-fold increase of CVD, metabolic syndrome and diabetes.
6. HDL cholesterol (good cholesterol) – Low HDL is a component of the lipid triad associated with increased CHD risk.
7. Cholesterol values outside the normal reference range are flagged in red for ease of interpretation. Elevated Mid B, Mid C (IDL and VLDL remnants) and small-dense LDL 3 through LDL 7 pose the highest risk for CVD.
8. Normal Reference Range for each subfraction based on NCEP ATP III guidelines for desirable lipid levels.
9. Lipoprotein Profile Classification – predominance of large LDL is classified as Type A and predominance of small dense LDL is classified as Not Indicative of Type A.

3.9 Statistical Analysis

The computer-based statistics software GraphPad Prism was used to analyse standard descriptive statistics such as mean, standard deviation (SD) and odds ratio (OR). Mann-Whitney Tests for non-parametric data was used to analyse numerical differences between numerical variables and Chi square test for categorical variables. Spearman's correlation co-efficient for non-parametric data was used to assess associations. Relative risks were measured using the Kruskall Wallis Test. Wilcoxon matched pairs signed rank test, assuming non-parametric distribution. P-value of <0.05 was considered statistically significant.

Chapter 4: Cardiovascular Risk in Hidradenitis Suppurativa

4.1 Introduction: Cardiovascular disease in Hidradenitis Suppurativa

A large study performing an unadjusted analysis of 1,776 HS patients from Massachusetts General Hospital reported significantly higher comorbidities including dyslipidemia, polycystic ovarian syndrome, obesity, hypertension, diabetes, thyroid disease, alcohol dependence, and lymphoma compared with controls[9]. Several recent studies have also suggested that HS is associated with metabolic syndrome[6,7]. Metabolic syndrome is an important risk factor for subsequent development of Type 2 diabetes and/or cardiovascular disease (CVD). A similar paradigm is observed in psoriasis patients whom are also known to have increased rates of metabolic syndrome[79]. Psoriasis has also been shown to carry excess risk of cardiovascular disease and this risk this appears to be accentuated in younger patients with more severe disease[80].

4.2 Aims:

Based on these studies documenting increased cardiovascular risk factors in HS we wished to quantify the cardiovascular risk in our patient cohort, the aim of our study was three-fold:

- To assess if patients with HS had elevated cardiovascular risk compared to healthy, age and sex matched controls using Framingham Risk and QRISK2
- To ascertain if certain 'non-classical' cardiovascular risk factor such as Homocysteine, C-reactive protein and insulin resistance were elevated in HS
- To explore the influence of disease severity and duration of HS on cardiovascular risk

4.3 Methods

4.3.1 Patients

This was a prospective, case-controlled study, of cardiovascular risk (CVD) in HS patients with age (+/- 5 years) and sex-matched controls. Patients were recruited from the Dermatology Outpatients at Tallaght Hospital Dublin, Ireland. The inclusion criteria for enrolment of the HS patients were a) 18 years and older, b) no history of CVD including ischaemic heart disease, peripheral vascular disease, strokes or transient ischemic attacks and c) a known diagnosis of HS. Control patients were a) 18 years or older and were age (+/- 5 years) and sex-matched with the HS patients, b) no history of CVD including ischaemic heart disease, peripheral vascular disease, strokes or transient ischemic attacks and c) no known diagnosis of HS or any other inflammatory skin conditions. Demographic details including age, gender and ethnicity were documented and weight, height, waist circumference and blood pressure were measured. Co-existing medical conditions, current medications and smoking history were also recorded.

4.3.2 Serum samples:

Venous blood samples were drawn for measurement of fasting glucose, HBA1c, fasting lipid profile, insulin, C-peptide, homocysteine and C-reactive protein (CRP) levels. Body Mass Index (BMI) was calculated using the formula Weight (kg)/Height(m^2) and a BMI greater than or equal to 25 was classified as overweight and greater than 30 as obese. Insulin Resistance was calculated using the Homeostasis Model (fasting insulin x fasting glucose/ 22.5) with a value of > 2.5 indicating insulin resistance.

4.3.3 Metabolic syndrome

Metabolic syndrome was defined by the presence of three or more of the following criteria, according to the 2005 National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines[81] :

a) Abdominal obesity, defined as a waist circumference in men ≥102 cm (40 in) and in women ≥88 cm (35 in)

b) Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides

c) Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol

d) Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure

e) Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose

4.3.4 Framingham Risk:

Cardiovascular risk was determined using the Framingham Risk which was calculated using the established gender-specific online calculator to generate the 10 year CVD risk in our patients (Appendix G). This generates a patients' 10-year risk of having a myocardial infarction or a cerebrovascular event in patients > 30 years of age. Parameters included in this Framingham Risk calculator include age, gender, history of diabetes, use of antihypertensive medications, smoking history, systolic blood pressure(mmHg), fasting total cholesterol(mg/dL) and high density lipoprotein (HDL, mg/dL) levels. Patients with less than 10% CVD risk at 10 years were deemed low risk, with intermediate risk 10-20%, and high risk of 20% or more.

4.3.5 QRISK 2:

QRISK2 is also a prediction algorithm for cardiovascular disease (CVD) that uses traditional risk factors (age, systolic blood pressure, diabetes mellitus, smoking status and ratio of total serum cholesterol to high-density lipoprotein cholesterol) together with body mass index, ethnicity, family history, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, and antihypertensive treatment. It includes patients in the range between 25-84 years. A QRISK2 over 10 (10% risk of CVD event over the next ten years) indicates that primary prevention with lipidlowering therapy (such as statins) should be considered. In the UK, current National Institute for Health and Care Excellence (NICE) guidelines recommends using QRISK2 (as opposed to the Framingham Risk Score). In addition to an individual's absolute risk, the QRISK2 can be used to generate a relative risk, which is the excess risk a patient has compared to a healthy person without any risk factors.

4.4 Statistical Analysis

GraphPad Prism was used to analyse standard descriptive statistics such as mean, standard deviation (SD) and odds ratio (OR). Mann-Whitney Tests for non-parametric data was used to analyse numerical differences between numerical variables and Chi square test for categorical variables. P-values of <0.05 were considered statistically significant. Spearman's correlation co-efficient for non-parametric data was used to assess associations. Relative risks were measured using the Kruskall-Wallis Test.

4.5 Results

4.5.1 Framingham Risk and QRISK2:

In all, 102 patients with HS and 42 age (+/-5 years) and sex-matched controls were recruited. Baseline characteristics of the study population are presented in Table 3.1. The

mean age for our HS group was 38 years (range 21- 67 years) and the mean age in the control group was 43 years (range 22 to 72 years). There was a significantly higher proportion of females in both groups, 73.5 % (n=75) and 67 % (n=28) females in the HS and control groups respectively. The mean duration of disease was 9.75 years.

Table 4.1 Baseline characteristics of the study population

	HS	**Controls**
Total Recruited	102	42
Female	73 (71.6%)	28(66.7%)
Male	29 (28.4%)	14 (33.3%)
Mean age (years)	38	43
Mean duration of disease (years)	9.75 years	N/A
Ethnicity	86 (84%) Caucasian	22 (52.3%) Caucasian
Smoking (including ex-smokers)	81(82.3%)	10 (23.8%)
Family History of CVD	16 (15.7%)	1(2.38%)

Although not statistically significant, metabolic syndrome was more prevalent in HS patients compared to the control patients (29.4% vs 16.7%, p=0.11), OR 2.4 (CI : 0.963-6.078 , p=0.06) (Table 4.2).

Table 4.2 Cardiovascular risk factors and its association with HS and the control groups

	HS mean (n=102) %	Controls mean (n=42) %	P value	Odds Ratio
Waist circumference (cm) (men ≥102 cm and in women ≥88 cm)	102cm (75) 73.5%	89cm (15) 35.7%	< 0.0001	N/A
Metabolic syndrome	30 29.4%	7 16.7%	0.11	2.0 (CI 0.8 – 5.2)

No. of Known Diabetes	5 4.9%	1 2.4%	0.50	1.98 (CI 0.22 – 17.5) p = 0.5
Family hx of premature CAD	16 15.7%	1 2.4%	0.02	6.3 (CI 0.8 – 49.3) p = 0.07
High Systolic BP (>130mm/Hg)	129 (22) 21.6%	124 (6) 14.3%	0.32	
High BMI (>25kg/m2)	33 (94) 92.2%	26 (18) 42.3%	<0.0001	2.1 (CI 1.1 – 3.8) p = 0.02
High Total Chol (>5mmol/l)	4.65 (28) 27.5%	4.8 (18) 42.9%	0.07	0.6 (CI 0.3 – 1.2) p = 0.2
Low HDL (>1.0 in male and > 1.3mmoL in female)	1.25 (42) 41.2%	1.6 (6) 14.3%	0.002	2.7 (1.1 – 7) p = 0.03
High TG (>1.7)	1.3 (15) 14.7%	1.0 (2) 4.76%	0.09	3 (0.05 – 13.6) p = 0.16

High Glucose >5.6mmol/L	5.43 (11) 10.8%	4.85 (2) 4.8%	0.26	2.2 (0.5 – 10.2) p = 0.3
High HOMA IR (<2.5)	3.9 (58) 56.9%	2.09 (7) 16.7%	<0.0001	3.2 (1.4 – 7.7) p = 0.007
High CRP (>5)	7.3 (49) 48.0%	2.5 (3) 7.1%	<0.0001	6.5(1.9 – 21.9) P = 0.003
High Homocysteine (0-15)	13.2 (27) 26.4%	10.8 (3) 7.14%	0.009	3.5 (1 – 12.3) P = 0.048

Overall, 78 HS patients and 40 controls met the age criteria for calculation of their cardiovascular risk with the Framingham risk assessment tool (>30 years). We found that HS patients had significantly higher Framingham risk than controls, with a mean of 6.9% 10 year risk vs 2.98% , p<0.0001. Within the HS cohort, 23.0% (n=18) had a Framingham risk of >10% vs 5.0 % (n= 2) in the control group (OR = 4.5 CI 1- 20.6, p < 0.05) (Table 3.3). When broken down, 6.4% (n=5) of HS patients had a high Framingham Risk > 20% vs none in the control group, and 16.7% (n=13) had intermediate Framingham Risk of 10-20% in the HS group vs only 2 in the control group (Table 4.3 and Fig 1, Fig 2).

Table 4.3 No. of patients in each Framingham cardiovascular risk category

Framingham Risk	HS (n=78)	Controls (n=40)
Low (<10%)	60 (76.9%)	38 (95%)
Intermediate (10-19%)	13 (16.7%)	2 (5%)
High (≥20%)	5 (6.4%)	0

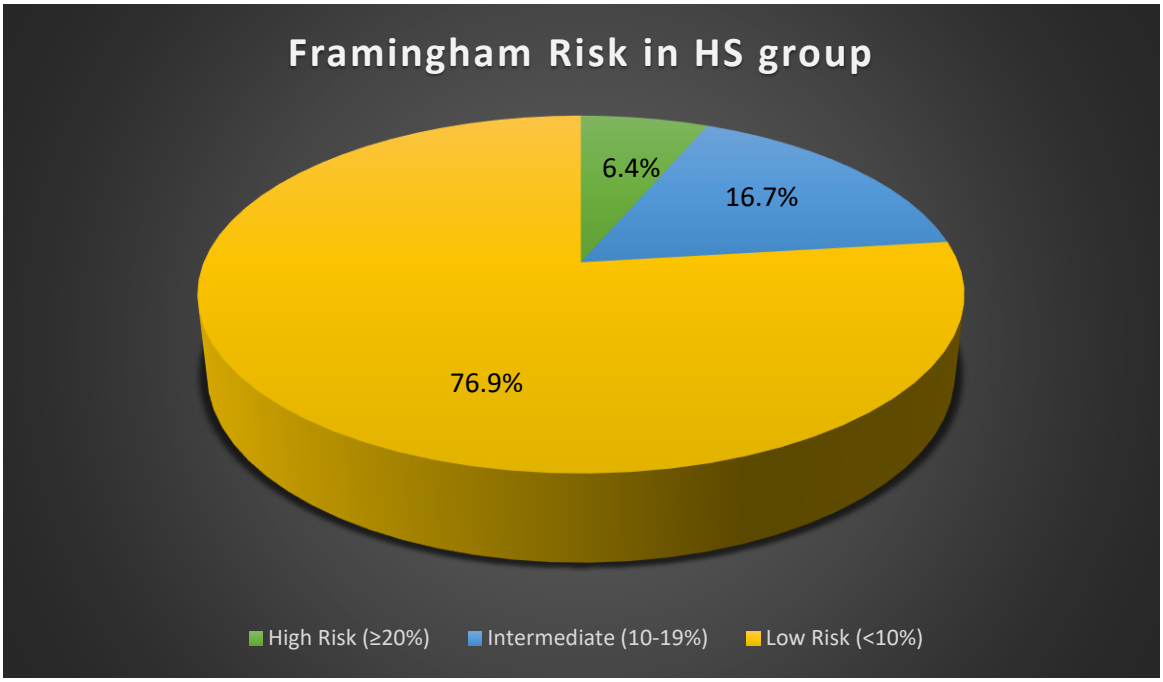


Figure 1 Proportions of HS patients in each Framingham Risk category

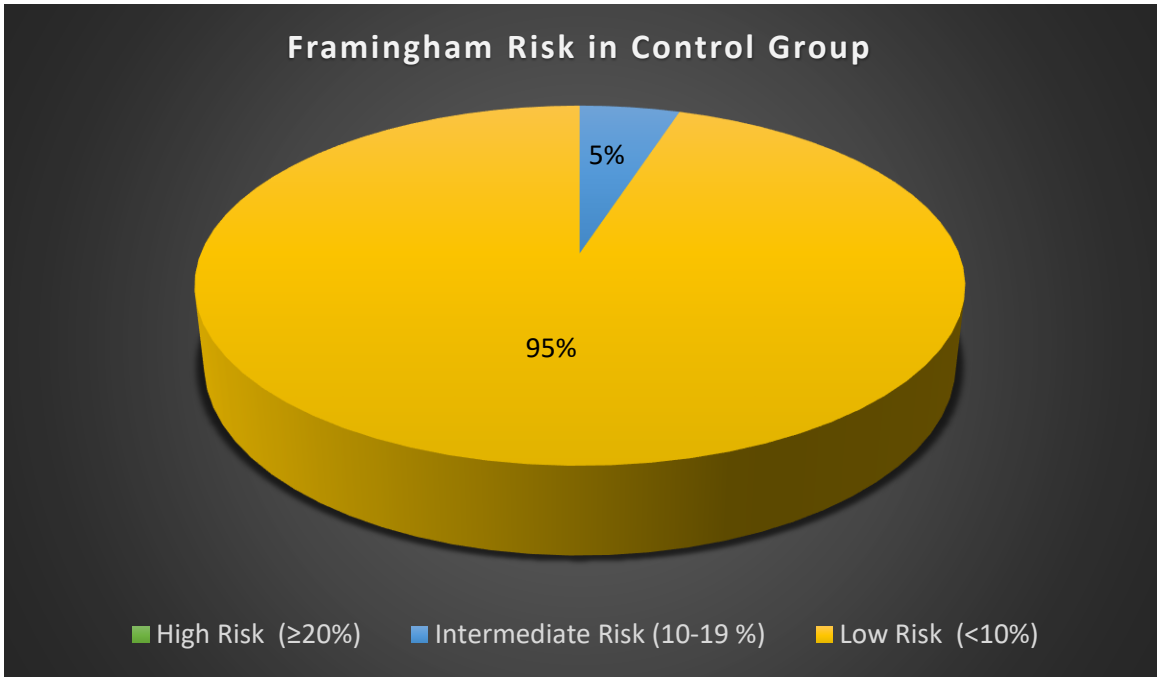


Figure 2 Proportions of control patients in each Framingham Risk category

When evaluating the QRISK2 within the HS cohort, 10 patients were excluded as they were younger than 25 years of age. However, in the remaining 92 patients, 4.4% (n=4) of HS patients had QRISK2 > 20% and 10.9 % (n=10) had intermediate Risk of 10-20% (Table 3.4 and Fig 1b) and the mean relative QRISK2 was 3.15. Although HS patients did not have significantly higher absolute QRISK2, (15.2% vs 5.1% p=0.1), they did have a significantly higher relative risk compared to controls, with a mean of 3.1 vs 1.1 10 year risk , p<0.001 (Table 4.4, Figure 3 ,Fig 4).

Table 4.4 No. of patients in each QRISK 2 cardiovascular absolute and relative risk category

QRISK2	HS (n=92)	Controls (n=39)
Low (<10%)	78 (84.7%)	37 (94.9%)

Intermediate (10-19 %)	10 (10.9%)	2 (5.1%)
High (≥ 20%)	4 (4.4%)	0
Relative Risk	3.1	1.1

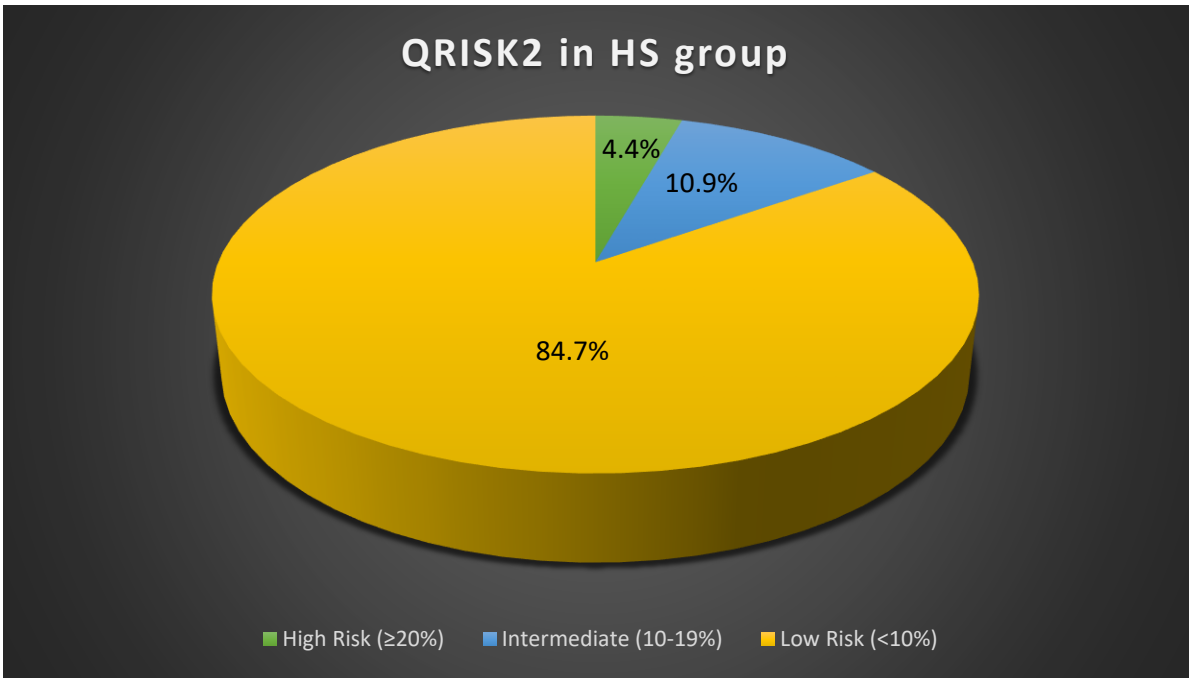


Figure 3 Proportions of HS patients in each QRISK2 category

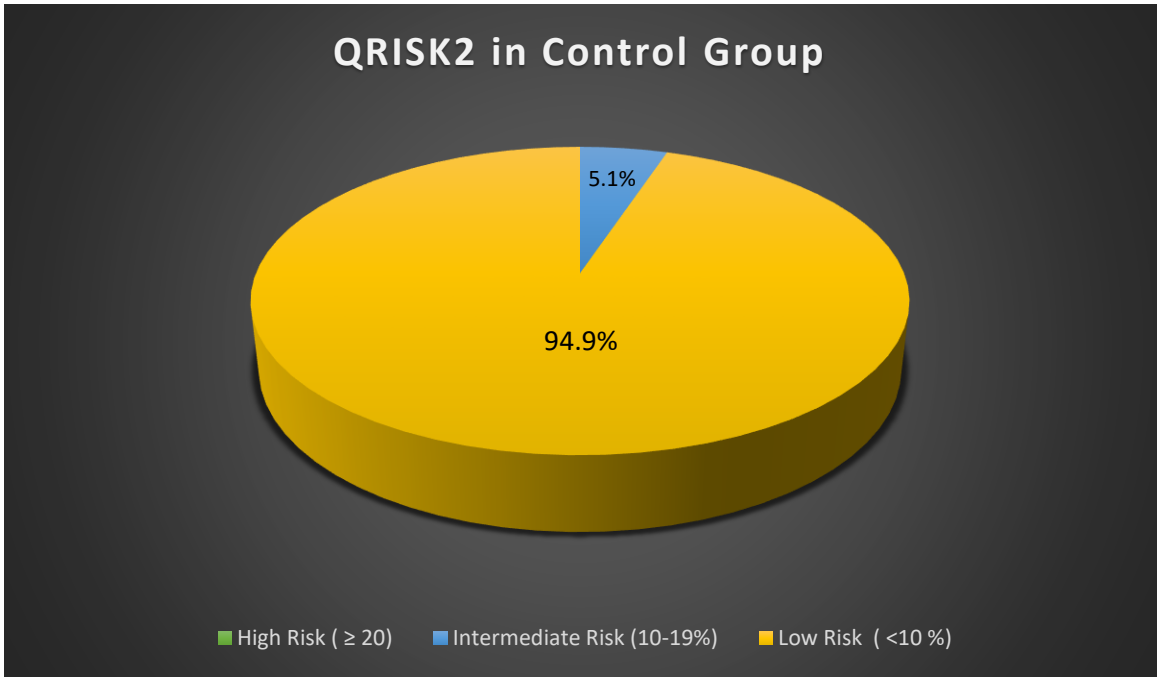


Figure 4 Proportions of control patients in each QRISK2 category

When divided according to Hurley Stage 1, 2 and 3, there was no difference in Framingham Risk, Q Absolute Risk or Q Relative Risks between the stages (p = 0.9, 0.6 and 0.6 respectively). We did not observe a correlation between Framingham Risk, Q Absolute Risk and Q Relative Risk and duration of HS, r = 0.16, p = 0.16; r = 0.2, p = 0.08; r= 0.08, p = 0.4 respectively (Table 4.5).

Table 4.5 Correlation between CRP and disease duration with Framingham Risk, QRISK2 and Homocysteine

	CRP		Disease Duration	
	r	(p value)	r	(p value)
Framingham (n=73)	-0.002	(0.1)	0.16	(0.2)

QRISK 2 (n=92)	0.08	(0.4)	0.16	(0.1)
Homocysteine (n=97	0.04	(0.6)	0.01	(0.1)

4.5.2 Individual Cardiovascular Risk Factors

When individual risk factors comprising the Framingham Score were compared (Table 4.2), we found that 41.2 % (42 of 102) vs. 14.3 % (6 of 42) of HS vs. controls respectively had a low HDL level, p = 0.002 but no statistical difference in the total cholesterol in both groups 27.5% vs 42.9%, p = 0.07 in the HS and control groups respectively. The prevalence of patients with Type 2 Diabetes in both groups were not statistically different, 4.9% in HS vs. 2.5% in controls, p = 0.5. There was no significant association between HS and increased blood pressure (OR 1.4, CI 0.55 – 3.8, p = 0.45), neither was there a significant association between HS and increased triglyceride level (OR: 3, CI 0.05 –13.6, p=0.16). Unsurprisingly, a significantly higher rate of smoking was identified in HS patient's vs controls; 82.3% (n=84), mean 9.8 pack years and 23.8% (n=10), mean 1.1 pack years of the patients in the HS and control group respectively ever smoked, p<0.0001.

Analysis of the additional individual risk factors used to generate QRISK2, showed no HS patients or controls with a history of atrial fibrillation, rheumatoid arthritis or chronic kidney disease. In all, 15.7% of HS patients had a family history of CVD vs. 2.4% in controls, p = 0.02. Hidradenitis patients had significantly higher Cholesterol: HDL ratios (3.6 vs 2.8, p 0.02) and as expected, patients with HS had significantly higher BMI than their counterparts (33 kg/m^2 vs 26 kg/m^2, p < 0.0001).

4.5.3 Non-classical Cardiovascular Risk Factors

Circulating homocyesteine levels > 12μ/L have been shown to elevate cardiovascular risk independently of other risk factors[82]. In our study, there was a significantly higher prevalence of hyperhomocysteniemia in HS patients compared to controls 26.4% vs 7.1% p=0.009.

Additionally, our cohort of HS patients had a higher circulating CRP than in the control group, 7.3mg/L vs 2.5mg/L p <0.0001.

We also found that 56.9% of our HS patients were insulin resistant (defined as HOMA-IR > 2.5) versus 16.7% in the control's cohort p< 0.0001.

4.6 Discussion:

When calculating risk of cardiovascular disease, the 2008 Framingham Risk Score was traditionally widely used. However, as Framingham Risk did not include all relevant risk factors and was found to overestimate risk in UK populations, the National Institute for Health and Care Excellence (NICE) recommended that the QRISK2 Risk Assessment tool to be used instead. The QRISK2 calculator is a prediction algorithm for cardiovascular disease that uses traditional risk factors (age, systolic blood pressure, smoking status and ratio of total serum cholesterol to high-density lipoprotein cholesterol) together with body mass index, ethnicity, measures of deprivation, family history, chronic kidney disease, rheumatoid arthritis, atrial fibrillation, diabetes mellitus, and antihypertensive treatment. The QRISK2 not only generates an absolute risk of cardiovascular disease, it also calculates relative risk.

Although there was a higher prevalence of HS patients having an increased Framingham risk (≥10%), the overall mean Framingham Risk was considered low in our cohort (6.9%), this masked a small minority of patients with significantly raised cardiovascular risk. Framingham Risk is based on a population of US patients and only applies to patients > 30 years of age. In other disease settings, Framingham has been found to overestimate cardiovascular risk[83], [84]. QRISK2 has been developed in the European setting and is more comprehensive including co-morbidities such as rheumatoid arthritis and chronic kidney disease, it also integrates BMI and family history of CVD. As it calculates risk in patients over 25 years of age it is probably more applicable in HS. Consistent with several other studies investigating CVD in HS[35], our study did demonstrate an increased prevalence of high CVD risk within our HS cohort compared to controls, potentially driven by a high BMI, low HDL levels and increased smoking.

It has been long established that obesity is a pro-inflammatory state and adipose tissue is a rich source of adipokines which are thought to be an important link between obesity, insulin resistance and inflammatory disorders [85, 86.] In our case-controlled study, patients with HS showed significantly higher levels of insulin resistance. High circulating levels of insulin are associated with excess sweating, particularly post-prandially, which may promote occlusion and maceration of axillae and inguinal creases. Manipulation of insulin resistance using the insulin-sensitizer metformin has shown some effect in HS[87]. These findings suggest that the metabolic alterations seen in the HS cohort could be the primary triggering and driving factor of HS rather than metabolic syndrome being a secondary pathological event of HS contributed by chronic inflammation.

Homocysteine (HCY) is a non-classical risk factor that has been shown to be an independent predictor for cardiovascular disease[88]. There has been limited reported

association in the literature between homocysteine levels and HS patients. It has been proposed that HCY causes endothelial cell injury by inducing oxidative stress, followed by platelet aggregation and thrombus formation, promoting atherosclerosis[89]. Our study showed a significantly higher prevalence of hyperhomocystenaemia in our HS cohort. According to a study by Vaya A et al, obesity is associated with insulin resistance; lack of insulin may increase homocysteine production in patients with obesity [90]. Furthermore, it has been suggested in the literature that there is a significant inverse association between BMI and plasma folate concentration, possibly reflected by the poor nutritional status in our HS cohort who are overweight, inhibiting methionine synthetase and therefore enhancing homocysteine levels [91].

Our prospective case-controlled study demonstrates that patients with HS have a significantly increased cardiovascular disease risk. We also showed for the first time to our knowledge that patients with HS have a significantly higher relative QRISK2. The increased prevalence of hyperhomocysteinaemia within the HS cohort additionally increase this calculated risk of CVD. Current NICE guidelines recommend that patients with severe psoriasis be offered a cardiovascular risk assessment at presentation using a validated risk estimation tool, followed by further assessment every 5 years or more frequently if indicated[92]. We suggest this practice be adopted in patients with HS and to approach the disease as a potential systemic condition to enable early risk stratification and prevention of cardiovascular complications.

Chapter 5: Lipoprotein Subclasses in Hidradenitis Suppurativa

5.1 Introduction:

We previously demonstrated that patients with HS have a higher cardiovascular disease (CVD) risk determined by Framingham risk[93]. One of the main risk factors for cardiovascular disease is dyslipidaemia, defined as hypertriglyceridemia, reduced high density lipoprotein (HDL) and increased low density lipoprotein (LDL). There are several studies documenting higher prevalence of dyslipidaemia in patients with HS[8, 25]. In a meta-analysis by Tzellos et al, patients with HS was significantly associated with hypertriglyceridemia and a low HDL with an OR of 1.67 (95% CI 1.14-2.47, p = 0.009) and OR of 2.48 (95% CI 1.49–4.16, P < 0.001) respectively[27]. Most studies so far have not shown significantly higher levels of LDL in patients with HS, however.

Lipoproteins are biochemical structures that enable transport of lipids throughout the body. Lipoproteins have been classified into five major classes based on their density; Chylomicrons ,VLDL (very low density lipoprotein),IDL (intermediate density lipoprotein), LDL (low density lipoprotein) which is the primary carrier of cholesterol throughout the body , and HDL (high density lipoprotein) which is responsible for the removal of excess cholesterol from the body. These lipoprotein classes consist of multiple subclasses within each class, with 7 subclasses in the LDL. Within subclasses 1 and 2 are the large LDL that are the “good cholesterol” and confers the Type A pattern. Subclasses 3 – 7 consist of small dense LDL that are easily oxidized and promotes CVD with predominance of the latter conferring atherogenic non-Type-A pattern. Small dense LDL is associated with a three to seven-fold increase in risk of coronary artery disease and ischemic strokes independent of total LDL cholesterol concentration[94], probably because

smaller LDL particles penetrate the endothelium more easily resulting in atherosclerosis. This essentially means that high concentration of small dense LDL particles, even though potentially carrying the same total cholesterol content as a low concentration of large particles, correlates with progression of atherosclerosis and earlier and or more severe cardiovascular disease.

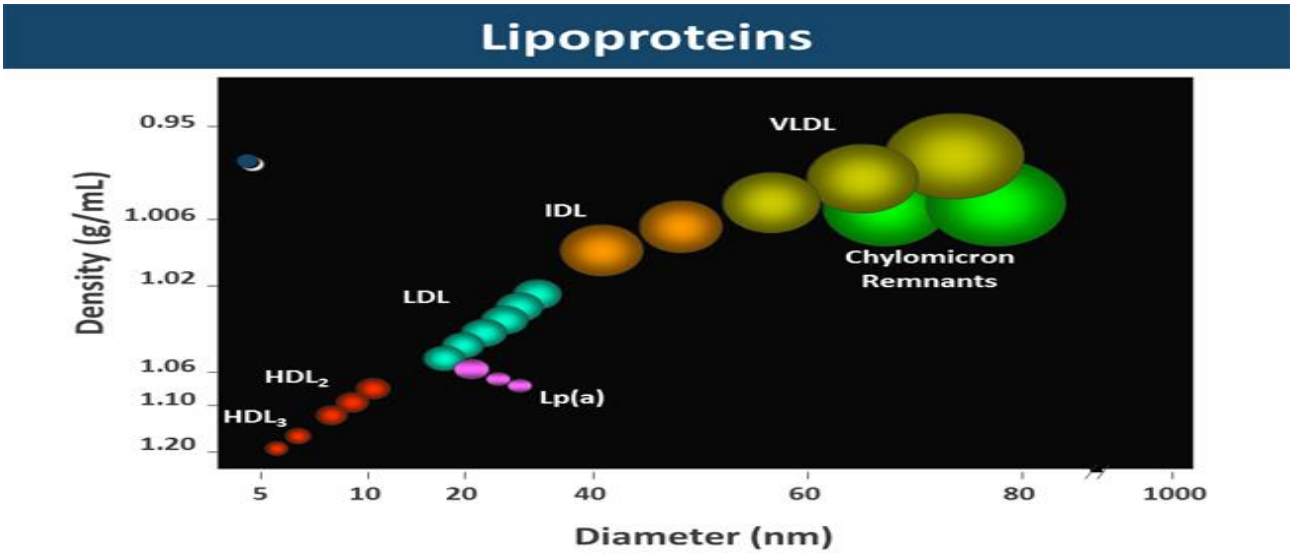


Figure 5 Lipoprotein subclasses based on size and density

5.2 Aim

As most studies did not find a significantly higher prevalence of an increased LDL in HS patients , we wished to specifically quantify and compare LDL subclasses in female HS patients aged >18 years with HS and age, sex, BMI and HOMA-IR matched healthy controls that may still increase their risk of CVD despite having a normal total LDL level.

5.3 Methods

Successive female patients attending the HS Clinic in Tallaght Hospital were recruited. Demographic data were recorded, and fasting blood samples to measure lipid profile, insulin levels, glucose levels and lipoprotein subclasses were obtained. Age (+/- 5 years), sex, BMI (+/- 3kg/m^2) and HOMA-IR (+/-1) matched healthy controls were also recruited. Patients with known family history of hyperlipidaemia were excluded from this study. The NCEP lll guidelines were used to determine normal and abnormal levels of lipid profile. Lipoprotein subclasses were measured using the Quantimetrix Lipoprint System. This is an FDA-approved test for measuring LDL subfraction cholesterol levels using high resolution polyacrylamide gel electrophoresis to separate and measure the amount of cholesterol in each LDL subfraction based on particle size. Data were analyzed using GraphPad Prism and Wilcoxon matched pairs signed rank test, assuming non-parametric distribution and a p value < 0.05 was considered significant.

5.4 Results:

In total, 30 HS patients and 28 age, sex, HOMA-IR and BMI matched patients were included in this study (Table 4.1). The mean age for both groups were 33 years (range 18-45 in HS group and range 22-41 in control group). The mean BMI was 30.2kg/m2 and 30.8kg/m2 in the HS and controls group respectively. Sixteen patients had Hurley Stage II disease and the remaining had Hurley Stage I. The HOMA-IR was 2.5 and 2.4 in the HS and controls group respectively.

Table 5.1 Basic demographic data of patients included in study

	HS (n=30)	Controls (n=30)	P value
Age	33 (range 18-45)	33 (range 22-41)	ns

BMI (kg/m2)	30.2 (range 21.0-42.0)	30.8 (range 23.2-41.0)	ns
Mean Hurley Score	2	Na	na
HOMA-IR	2.5(0.37-8.8)	2.4(0.5-8.1)	ns

Although there was a higher prevalence of high total cholesterol, triglycerides and LDL levels and a lower HDL level compared to controls, there was no significant differences in these categories (Table 4.2).

Table 5.2 Prevalence of HS and control patients with abnormal lipid profile parameters

	HS (n=30)	Controls (n=28)	P value
High total cholesterol	5 (16.7%)	5 (17.9%)	1.0
Low HDL	15 (50%)	9 (32.1%)	0.2
High Triglycerides	10 (33%)	3 (10%)	0.06
High LDL	2 (6.7%)	3 (10.7%)	0.7

When subclasses of LDL were analysed, the percentage fraction of large LDL particles which are the “good” particles were significantly lower in the HS cohort (22% vs 26%, p=0.03). More importantly, we found that the percentage fraction of small dense LDL subclasses which promote cardiovascular disease, was significantly higher in the HS

cohort compared to controls, (4.8% vs 1.03%, p =0.03) despite the prevalence of high LDL in the HS and control cohorts not differing significantly.

On analysing the mean LDL particle size in patients with normal LDL levels (28 of 30 HS patients and 25 of 28 controls), the mean LDL particle size was also significantly lower in the HS group compared to controls , 266.6 vs 271.1, p =0.03 despite having a normal total mean LDL (overall mean LDL 2.57mmol/L in HS vs 2.40 mmol/L in control group). We also identified that a significantly higher number of HS patients had the more pro-atherogenic non-Type A lipoprotein profile pattern compared to controls (33.3% vs 7.1%) OR 6, p = 0.03 (Table 5.3).

Table 5.3 LDL subclasses analysis in HS and control cohorts

	HS (n=30)	Controls (n=28)	P value
Large LDL particles	22%	26%	0.03
Small LDL particles	4.8%	1.03%	0.03
Non-Type A Profile	10 (33.3%)	2 (7.1%)	OR = 6, p=0.03
Mean LDL particle size	266.6	271.4	0.03

This study identified a pro-atherogenic lipoprotein profile in young women compared to their age and BMI counterparts, this was despite normal lipid profile on routine laboratory

testing. This may be contributing to the excess cardiovascular risk we have observed in HS patients.

The unfavourable lipoprotein profile may be driven by increased central adiposity in HS and excess androgens. It has been noted in previous studies that androgens may prime adipocytes in early life predisposing to dyslipidemia with inflammation in HS. A study by A.Malara et al in 2017 assessing levels of adipokines in HS patients showed that the adipokine balance in HS is shifted towards increased expression of pro - inflammatory resistin and leptin, which may be driving the inflammatory process in the skin of patients with HS[20]. Abnormal lipoprotein profile may therefore be linked with inflammation in HS. Further studies exploring the correlation between LDL particle size with central adiposity and androgen levels in this cohort is warranted.

In conclusion we showed that our very young cohort of HS patients tend to have a pro-atherogenic lipid profile with significantly higher numbers of small dense LDL and a non-Type A lipoprotein profile.

Chapter 6: Psychological Distress in Hidradenitis Suppurativa

6.1 Introduction

Depression is known to be a common mental health illness in the Western world. Studies in the literature have shown that there is a possible link between chronic inflammation and degree of depression[95, 96]. As HS is a chronic, recurrent and debilitating skin condition producing a malodorous and recurrent discharge and significant pain during a flare up, it may have a severe impact on patient's quality of life. The areas affected, the chronicity of the condition and the relative paucity of effective treatments compounds this distress.

The impact of chronic skin disease on psychological well-being has been intensively characterised in psoriasis. Patients with psoriasis are known to have higher rates of depression and anxiety than the normal population with studies suggesting a psychological link between psoriasis and depression[97, 98]. This may be due to social stigmatisation and the impact of having a disfiguring skin condition. The practice of evaluation of psychological well-being and Quality of Life is well-established, and we carry this out routinely in our psoriasis clinic.

Onderdijk, A.J explored the psychosocial effects of HS and found this disease has a profound negative effect, often exceeding the negative quality of life reported in other dermatological conditions such as atopic dermatitis and psoriasis[68]. Despite the significant psychosocial impact of HS being observed in a clinical setting, information of this element of the disease is limited in the literature.

HS patients like psoriasis patients are more likely to be smokers. Smoking appears to be implicated in the pathogenesis of HS. One of the suggested mechanism cigarette smoking in the pathogenesis of HS is the release of tumour necrosis factor alpha by the nicotine in

cigarettes causing inflammation, promotion of follicular occlusion and epidermal hyperplasia[51].

Similarly, excess alcohol consumption has been documented in psoriasis[99]. Although limited, several studies have evaluated the level of alcohol consumption in HS patients [9, 10]. One of the largest studies which was conducted by Shlyankevich et al showed a significantly higher prevalence of alcohol dependence in the HS cohort compared to controls; 4.2% vs. 0.52% ($P < 0.0001$), with a 8.43 greater odds of the HS population being alcohol dependent than controls[9].

6.2 Aims

In this study we:

- Evaluated the Quality of Life (QoL) in the two cohorts of patients (HS and psoriasis) using the Dermatology Quality of Life Index (DLQI). We also evaluated the level of disease-related pain within the HS cohort using the Visual Analogue Pain Score (VAPS).
- Investigated the impact of HS and depression and anxiety and compared it to psoriasis patients.
- Assessed smoking history and alcohol consumption in both HS and psoriasis patient populations.

6.3 Methods

Following ethical approval from the local ethics committee, consecutive patients with an established diagnosis of HS and psoriasis attending the Dermatology Outpatients Department were recruited. Pertinent clinical data including gender, age, smoking history, duration of disease, height, weight, PASI and Hurley's Score were recorded. After clinical review, patients were asked to complete two questionnaires; the Dermatology Life Quality

Index to assess Quality of Life impairment and the Hospital Anxiety and Depression Scale (HADS) to assess depressive and anxiety levels.

The DLQI was analysed under six domains: ‘symptoms and feelings, ‘daily activities’, ‘leisure’, ‘work and school’, ‘personal relationships’ and ‘treatment’ (Table 5.1). HS patients were also requested to complete the Visual Analogue pain score (VAPS), reflecting the level of pain in the last week in relation to their HS as pain is a prominent symptom in HS.

Table 6.1 Individual Domains of the DLQI

Domain	Questions
Symptoms and feelings	1 & 2
Daily Activities	3 & 4
Leisure	5 & 6
Work and School	7
Personal relationships	8 & 9
Treatment	10

The HADS, scores for each subscale (anxiety and depression) ranged from 0 to 21 with scores categorized as follows:

- normal 0–7
- mild 8–10
- moderate 11–14

- severe 15–21

Scores for the entire scale (emotional distress) range from 0 to 42, with higher scores indicating more distress. Both questionnaires require the individual to respond to the question in relation to how they felt in the past week.

All data were analysed by Graphpad prism using the Mann Whitney test and Spearmans Rank correlation for non-parametric data and a p value of <0.05 was considered significant. Fisher's exact test was used to analyse categorical variables.

6.4 Results

6.4.1 Patient Demographics

Eighty-six HS patients and 103 psoriasis patients were included in this study (Table 5.2). In the HS group, 72% (n = 62) were female whereas 49 % (n = 50) were female in the psoriasis group (p = <0.001). Psoriasis patients were older with a mean age of 40 years (SD = 12.01; range 19-69 years) compared to 37 years (SD = 10; range 22-59) in the HS group, p > 0.05.

Table 6.2 Basic demographic characteristics of hidradenitis suppurativa and psoriasis cohorts

	HS	Psoriasis
Total recruited	86	103
Female	62 (71%)	51 (49.5%)
Male	24 (29%)	52 (50.5%)
Mean age (years)	37 (22-59)	40 (19 – 69)
Mean duration (years)	10	23

Disease Severity	33(38%)-Hurley's Stage 1 45(53%)-Hurley's Stage 2 8(9%) -Hurley's Stage 3	Mean PASI : 10

6.4.2 Disease characteristics

On average, psoriasis patients had significantly longer disease duration of 23 (SD = 11.6) years compared to 10 (SD = 7.6) years in the HS group ($p < 0.001$). In relation to disease severity in the HS cohort, 33 patients (38%) were Hurley's Stage 1, the majority, 45 (53%) had Hurley's Stage 2 disease, and only 8 (9%) had Hurley's Stage 3 disease (Figure 6.3). The mean PASI score in the psoriasis group was 10.0 , range 1.8-20.6 (SD = 4). There were significantly higher numbers of obese patients in the HS group (n= 41, 51%) in comparison to the psoriasis group (n = 31, 30%), $p < 0.01$ (Table 6.3). The mean BMI was also higher in patients with HS 32.2 kg/m^2 versus 27.9 kg/m^2, $p < 0.001$.

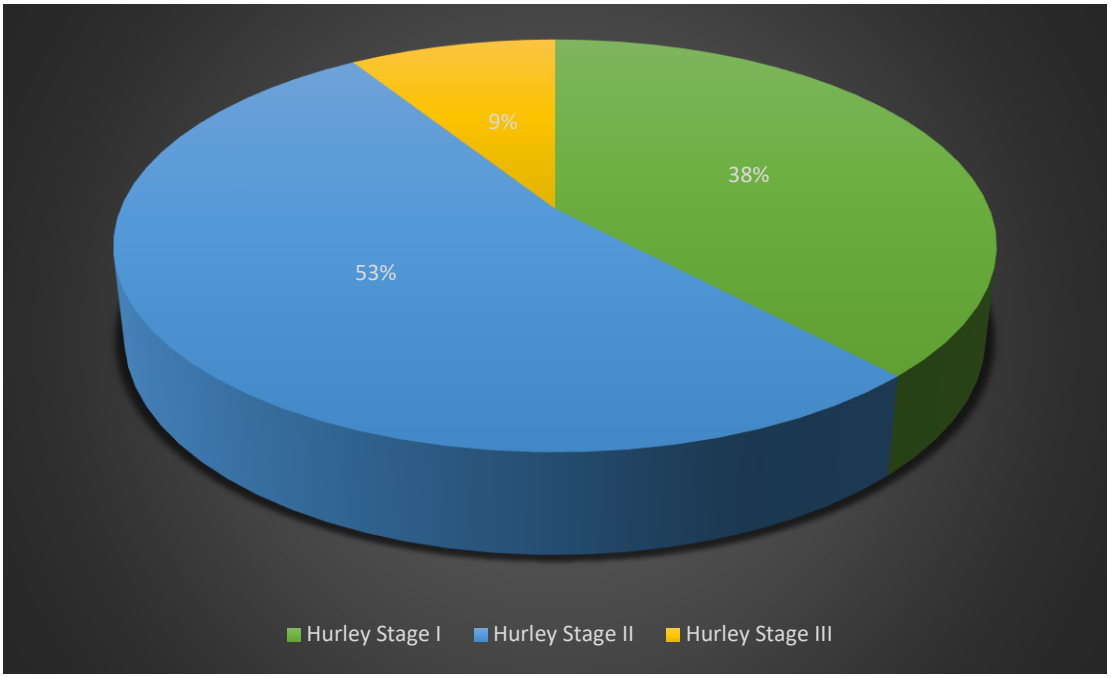


Figure 6.3 Distribution of Hurley Stage in patients with HS

Table 6.3 Classification of HS and psoriasis groups based on BMI

Body Mass Index (BMI)	HS(n = 86)	Psoriasis (n= 103)
Normal 18.5-24.99	18	28
Overweight 25-29.9	19	43
Obese 30-39.9	31	28
Extreme 40 +	18	2

Table 6.4 Comparison of Dermatology Life Quality Index and individual domains

DLQI-Mean Values (range 0-30)	HS patients(n=86)	Psoriasis patients (n=103)	P Value
Total scores	12.2	9.1	<0.001
Symptoms and feelings(Q1+Q2)	2.9	2.6	>0.05
Daily Activities(Q3+Q4)	2.77	2.05	<0.005
Leisure(Q5+Q6)	2.3	1.56	<0.005
Work and School (Q7)	0.9	0.2	<0.001
Personal relationships (Q8+Q9)	2.7	1.25	<0.01
Treatment (Q10)	0.6	1.3	<0.001

6.4.3 Quality of Life in HS and Psoriasis

The overall mean DLQI scores were significantly higher in HS (12.2; SD = 7.72) than in the psoriasis (9.1; SD = 6.49) group, $p < 0.001$.

When the individual domains of the DLQI were explored, HS patients had significantly higher impairment in the majority of DLQI domains than patients with psoriasis; DLQI daily activities- 2.77 vs. 2.05, $p < 0.005$, DLQI leisure- 2.3 vs. 1.56, $p < 0.005$, DLQI work and school- 0.9 vs. 0.2,$p < 0.001$, DLQ personal relationships -2.7 vs. 1.25,$p < 0.01$(Table 5.5). Psoriasis patients however showed a higher level of impairment in the DLQI treatment category, 1.3 vs. 0.6, $p < 0.001$. There was no difference between both groups in the domain of symptoms. Controlling for age, duration, smoking (pack years), alcohol and BMI, differences between both patient groups in DLQ remain significant, except for in the DLQI daily activities domain (Table 6.5).

Table 6.5

	Patients	N	Mean	Std. Deviation
Age	Psoriasis	102	39.98	12.013
	HS	86	37.36	10.744
Duration	Psoriasis	102	23.28	11.635
	HS	86	9.90	7.604
Pk years	Psoriasis	94	11.55	16.125
	HS	86	6.85	10.131
Etoh	Psoriasis	102	14.89	16.877
	HS	86	2.80	4.178
BMI	Psoriasis	102	27.968	6.0387

	HS	86	32.237	7.3330
HADS Anx	Psoriasis	102	7.76	3.407
	HS	86	9.64	5.174
HADS Dep	Psoriasis	102	4.27	3.322
	HS	86	7.34	3.818
Symp	Psoriasis	102	2.63	1.377
	HS	86	2.90	1.708
Daily act	Psoriasis	102	2.05	1.424
	HS	86	2.77	2.062
Leisure	Psoriasis	102	1.56	1.453
	HS	86	2.31	1.849
Work	Psoriasis	102	.23	.595
	HS	86	.86	.960
Personal	Psoriasis	102	1.25	1.389
	HS	86	2.74	2.059
Treatment	Psoriasis	102	1.32	.834
	HS	86	.66	.876
Total	Psoriasis	102	9.12	5.414

	HS	86	12.24	6.596

We found a significant correlation between the Hurley Staging and total DLQI score (r = 0.31 , p = 0.02) as well as between PASI and total DLQI r=0.22 for PASI, p=0.02).

6.4.4 Anxiety and Depression in HS and psoriasis

In total, 52 HS patients and 71 psoriasis had completed the HADS questionnaire. HS patients had an overall mean HADS of 17, with a mean of 7.7 in the HADS depression domain and 6.6 in the anxiety domain. Fifty-six percent of HS patients were in the possible clinical range for anxiety, whereas 42% of the psoriasis patient were in this category(Table 6.7). Approximately one third (38%) of the HS patients were in possible clinical range for depression whereas only 18% of psoriasis patients were in this category, p<0.05 (Table 6.6). When age, duration, smoking (pack years), alcohol and BMI were controlled, differences between both patient groups in overall mean HADS remain significant. There was no correlation with Hurley Stage and HADS depression (r = 0.2, p = 0.1) or anxiety (r = 0.1, p = 0.2 in psoriasis or HS patients**.**

Table 6.6 Depression scores in HS and Psoriasis groups

	HS n=52 (%)	Psoriasis n=71 (%)	P value
Normal (0-7)	32 (62%)	58 (82%)	P = 0.01*
Mild (8-10)	8 (15%)	6 (8.5%)	P = 0.03*
Moderate (11-14)	11 (21%)	6 (8.5%)	P = 0.06

Severe (15-21)	1 (2%)	1 (1.4%)	P = 0.01*
Mean Depression score	6.6	4.0	0.002

Table 6.7 Anxiety scores in HS and Psoriasis groups

	HS n=52 (%)	Psoriasis n=71 (%)	P value
Normal (0-7)	23 (44%)	41 (58%)	P = 0.1
Mild (8-10)	10 (19%)	13 (18%)	P < 0.001
Moderate (11-14)	13 (25%)	13 (18%)	P = 0.4
Severe (15-21)	6 (12%)	4 (6%)	P = 0.32
Mean anxiety score	7.7	7.3	0.5

6.4.5 Smoking and alcohol consumption in HS and psoriasis

Fifty-three percent of HS patients were currents smokers versus 37% of patients with psoriasis, p= 0.09. There was a significant difference in mean pack years between the HS (mean = 6.9 pack years) and psoriasis (mean= 11.5 pack years) p < 0.05 groups (Figure 7), which may reflect the longer disease duration and older age in the psoriasis cohort. There was also significantly less alcohol consumption within the HS group (mean = 2.8 units per week) than the psoriasis group (mean = 14.9 units per week), p <0.001 (Figure

8). Only 1% of HS patients self-reported drinking a weekly excess of 14 units for women and 21 units for men versus 19% of patients with psoriasis, p = 0.002.

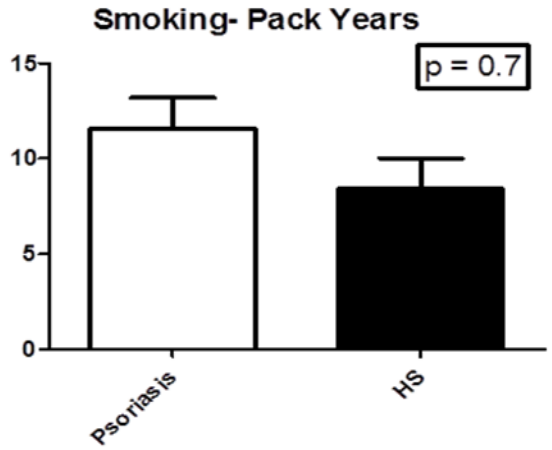


Figure 6 Mean smoking pack years between both groups

Figure 7 Mean alcohol consumption levels between both groups

6.4.6 Pain in patients with HS

The mean VAPS within the HS cohort was 5, with a significant correlation between the VAPS and DLQI, $r = 0.6$, $p < 0.0001$. No significant correlation was found between VAPS and the mean HADS Depression ($r = 0.2$ $p = 0.1$), however a positive correlation between the VAPS and HADS Anxiety ($r = 0.2$, $p = 0.04$) was demonstrated.

6.5 Discussion

Hidradenitis suppurativa is a chronic inflammatory condition that may inflict considerable psychological distress which has been confirmed in our study. Patients suffer significant pain and foul-smelling suppuration from abscesses or sinuses in affected areas during a flare. This commonly leads to disruption of activities of daily living as well as work due to pain, embarrassment from the odour and the risk of soiling. Unsurprisingly patients with HS have impaired quality of life and may also be psychologically affected with depression and anxiety. From our study, the impact of HS appears more disabling than psoriasis in our patients.

Thirty seven percent of patients with HS reported moderate to severe anxiety and 23% had moderate to severe depression based on the HADS. None of the patients we recruited were being treated pharmacologically for depression or anxiety. Our results are lower than that reported by Kurek et al who also used the HADS, reporting that 38.6% patients with HS were depressed[71]. In a hospital-based, case – controlled study of 211 Dutch patients, 9% of patients fulfilled the International Classification of Disease 10th Edition classification of depression[68]. In a cross-sectional case-controlled study of an Israeli healthcare database, Shavit et al found that 3.9% of patients with HS also had a diagnosis of anxiety and 5.9% had a diagnosis of depression[67]. In addition, a population-based study from Minnesota revealed 268 cases (42.9%) of patients had a concurrent diagnosis of depression[48].

When we compared the level of depression and anxiety between HS and psoriasis, we found that HS patients reported higher levels of depression and anxiety than their psoriatic counterparts. Our two groups of patients were not age or sex-matched and this could explain the difference we observed. This may not be clinically relevant, as our results and the published literature indicate that psychological distress is a significant co-morbidity in many of our young patients and may be under-recognised and under-treated.

Patients with HS reported a mean DLQI of 12.2 versus 9.1 in patients with psoriasis. In a study of 114 Danish patients, Von der Werth et al reported a mean DLQI of 8.9 +/- 8.3 in a cohort of older patients 40.9 +/- 11.7 years[96]. The average age of our patients was 37 years and they also had shorter disease duration 10 years versus 18.8 years +/- 11.4 years. Although impossible to extrapolate, it is possible the onset of the disease and younger age might incur greater life impairment. In another study of 246 HS patients by Sartorius et al, the mean DLQI was 10.9 +/- 7.5[47]. In Matusiak's study of 54 Polish patients the mean DLQI was 12.7 +/- 7.7, but in 211 Dutch patients Onderdijk et al found a mean DLQI of 8.4 +/- 7.5[100, 68]. The average DLQI for patients recruited to randomized control trials of biological agents for the treatment of psoriasis trials was 8 which is not dissimilar to our finding of 9[101].

The DLQI was developed in 1994 in patients with atopic eczema, psoriasis, basal cell carcinomas and viral warts[76]. It quantifies the impact of disease on work, study and personal relationships and quantifies itch and the burden of treatment over the preceding week. It is widely used in clinical trials. We found intriguing differences within individual domains of the DLQI between HS and psoriasis. Patients with hidradenitis have more impairment of work, leisure and study related activities, this concurs with reports in the literature of 2.7 workdays lost per patient year[102]. Matusiak et al reported that 58% of 30

patients missed work from 3-96 days per year[103]. There was also a significantly higher impact in patients' personal relationships, whereby Kurek et al reported profound impairment of HS patient's sexual health which is unsurprising given the predilection of the disease for the perineal area[71].

We also found a significant correlation between Hurley Score and DLQI but not HADS score, bearing in mind that 52% of our HS patients included were at Hurley Stage 2 and only 9% were at Hurley Stage 3. There is a significant correlation between the VAP score and DLQI, p value < 0.001, indicating that pain may be a major determinant of life quality impairment.

Patients with HS consumed significantly less alcohol than patients with psoriasis. Shlykanevich et al reported from their chart-review case control study an association between HS and alcohol dependence[9]. There is a paucity of other studies which have addressed alcohol consumption in HS.

From this study of our patients, our findings are concurrent with studies in the literature. Our psoriasis patients were older and were not sex-matched, but this reflects the real-life preponderance of females with HS

6.6 Conclusion

We have demonstrated that HS has significant impairment on quality of life, with different type of distress being exhibited by this group when compared to psoriasis patients. We also showed that patients with HS have significantly higher levels of depression and anxiety than patients with psoriasis. We also confirmed high rates of smoking but not alcohol consumption in our HS patients. It is therefore imperative for treating physicians to screen for psychological distress within this group/ This study also highlights the need

for HS patients to have prompt access to psychological services in the hospital or community.

Chapter 7 : Conclusion and Recommendations

7.1 Hidradenitis Suppurativa is a systemic condition associated with multiple comorbidities

Hidradenitis suppurativa is an inflammatory skin condition which causes recurrent abscesses, sinuses and scarring in the axillae, groin and inframammary areas. The exact incidence is unknown but has been suggested to range between 0.00033% and 4.1%[1]

In a similar paradigm to psoriasis, it has become more apparent that HS is a systemic inflammatory condition and is associated with a range of comorbidities which has been presented in the review section of this thesis. Patients with HS carry a large comorbidity burden of increased risk of metabolic syndrome and cardiovascular disease. It is also increasingly evident that the condition confers significant psychological morbidity and impairment of quality of life.

We quantified and measured metabolic and cardiovascular risk as well as evaluated the level of psychological distress in our cohort of HS patients. In addition, we performed lipoprotein subfraction analysis to quantify and compare lipoprotein subclasses between HS and control patients using the Lipoprint method.

7.1.1 Cardiovascular Risk

In our study, we identified an increased prevalence of metabolic syndrome defined by the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III and insulin resistance measured by the HOMA-IR model in our HS population. We present evidence demonstrating that our patients with HS carry a significantly increased cardiovascular risk, a higher Framingham and relative QRISK2 compared to age and sex matched controls. Our study also revealed a significantly higher prevalence of hyperhomocysteniemia in the HS cohort which is a known non-classical cardiovascular

risk factor that can further increase the calculated risk of cardiovascular disease within this cohort. These findings highlight the need for routine screening and management of HS patients for modifiable cardiovascular risk factors.

Additionally, we showed that our very young cohort of HS patients tend to have a pro-atherogenic lipid profile with significantly higher numbers of small dense LDL and a non-Type A lipoprotein profile compared to their age, sex and BMI counterparts. To the best of our knowledge, this is the first study to analyze lipoprotein subclasses in HS patients.

7.1.2 Psychological Distress

Understandably, hidradenitis suppurativa has been shown to have significant effects on self-esteem and can be associated with psychiatric conditions such as depression and anxiety. It was found that HS is in the top five skin diseases with the most negatively impacted quality of life and that predictive factors were having a young age of onset and more lesions per month. This was demonstrated using EuroQoL-5D and DLQI scores[104].

We demonstrated that our cohort of HS patients had significant impairment on quality of life, with different type of distress being exhibited by this group when compared to psoriasis patients whom we are also aware have negative psychological effects as a consequence of their disease. In our study we however demonstrated that HS patients had significantly higher impairment in DLQI daily activities, leisure, work and school as well as personal relationship domains compared to psoriasis patients. We also found a significant correlation between HS disease severity and DLQI. Furthermore, we demonstrated a significant correlation between the VAP score and DLQI, indicating that pain may be a major determinant of life quality impairment.

In addition, in this thesis we showed that patients with HS have significantly higher levels of depression and anxiety than patients with psoriasis. It is logical to deduce that this

association is likely due to the nature of the disease itself. However interestingly, Kohler et al identified some evidence that pro-inflammoarty cytokines such as IL10 and TNF alpha may be linked to some mental health conditions such as depression, and these cytokines have been demonstrated in the pathogenesis of HS[105]. Further studies focusing on the immunopathomechanisms of HS and psychiatric conditions will shed some light if these diseases share a similar inflammatory process [106].

7.2 Recommendations

Current NICE guidelines recommend that patients with severe psoriasis be offered a cardiovascular risk assessment at presentation using a validated risk estimation tool, followed by further assessment every 5 years or more frequently if indicated[92]. We suggest this practice be adopted in patients with HS and to approach the disease as a potential systemic condition to enable early risk stratification and prevention of cardiovascular complications.

Based on our results looking the psychological effects of HS on patients, we also suggest that the development of strategies to identify and treat those with psychiatric comorbidities is warranted. This can be achieved using simple screening tools such as the HADS and DLQI during routine clinical assessments.

Lastly, we suggest that a multidisciplinary approach with involvement of a number of specialists as necessary including gastroenterologists, rheumatologists, endocrinologists , the smoking cessation team, psychologist/psychiatry and plastics surgeons be applied in the management of this complex cohort of patients on the background of its frequent association with other systemic comorbidities.

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Appendix A: Patient Information Leaflet

PATIENT INFORMATION LEAFLET

1. **Title of Study** :Measuring Cardiovascular Risk and Metabolic Parameters in Patients with Hidradenitis Suppurativa

2. **Introduction** :

   Thank you for reading this information leaflet, you have been chosen to take part in this study because you have a skin condition called hidradenitis suppurativa. It is known from recent studies that some chronic skin conditions such as psoriasis can increase risk of heart disease. On that basis, this study is being carried out to measure cardiovascular risk in patients with Hidradenitis Suppurativa. Hidradenitis can also be associated with hormone abnormalities and this study is also going to measure certain hormones such as insulin and some sex hormones.

3. **Procedures** :

   If you wish to take part in this study, we will arrange a date and time for you to come into the Dermatology Department in Tallaght Hospital fasting. During this

time we will take your blood pressure and ask you a few questions including your age, if you are on any blood pressure treatment, if you have diabetes and if you smoke. We will also take your height, weight and waist circumference. We will then take blood samples from you to check your cholesterol level, glucose , HBA1C levels and a hormone profile. If we find any abnormal results we will inform your GP.

4. **Benefits of taking part in this study** :

   You will find out your cholesterol, blood pressure, glucose and hormone levels.

5. **Risks of taking part in this study** :

   Blood samples are slightly painful and can leave a bruise.

6. **Alternative Treatment**:

   If you take part your current management of Hidradenitis Suppurativa will not be changed. You will be followed up as planned by your doctor.

7. **Confidentiality**:

   Your identity will remain confidential. Your name will not be included in any publications. Information about your hidradenitis will be accessed from your medical records but all your information will be anonymous, it will not be possible to identify you.

8. **Compensation** :

Participation in this study is covered by an approved policy of insurance in Tallaght Hospital. In addition, the medical practitioners involved in this current study have medical malpractice insurance cover. Nothing in this document restricts or curtails your rights.

9. **Voluntary Participation** :

   You may quit from this study at any time. If you decide not to take part, or if you quit, this will not affect your treatment or care.

10. **Stopping the study** :

    Your doctor may stop your participation in the study at any time without your consent.

11. **Permission** : This study has been approved by the Research Ethics Committee of Tallaght Hospital/St James's Hospital ,Dublin.

12. **Further Information** : You can obtain more information or answers to your questions about the study, taking part in the study, and your rights from Dr.Anne Marie Tobin and Dr.Shivashini Kirthi. If your doctor learns of important new information that might affect your desire to remain in the study, she will inform you.

Appendix B: Consent form

CONSENT FORM

Title of Study : Measuring Cardiovascular Risk and Metabolic Parameters

in patients with Hideradenitis Suppuritiva

I confirm that this study and this consent form have been explained to me.

I have had the opportunity to ask questions and all my questions have been answered to my satisfaction.

I freely and voluntarily agree to be part of this research study, though without prejudice to my legal and ethical rights.

I have received a copy of this agreement and I understand that, if there is a sponsoring company, a signed copy will be sent to that sponsor.

Name of sponsor: AMNCH , Tallaght

Having been assured of total anonymity, I consent to the collected data being used for analysis, presentation and publication.

PARTICIPANT'S NAME:
PARTICIPANT'S SIGNATURE: **DATE:**

NAME OF CONSENTOR, PARENT or GUARDIAN:
SIGNATURE:

RELATION TO PARTICIPANT: **DATE:**

I have explained the nature, purpose, procedures, benefits, risks of, or alternatives to, this research study to the above patient. I have offered to answer any questions and fully answered such questions. I believe that the participant understands my explanation and has freely given informed consent.

Physician's signature:
Date :

Appendix C: Patient Proforma

Measuring Cardiovascular Risk and Metabolic Parameters in Patients with Hidradenitis Suppurativ

Section 1: Patient Demographics

Name:

Age:

Date of Birth:

Gender:

Ethnicity:

Address:

Section 2 : Medical History

HS disease duration:

Current HS treatment :

Previous treatment for HS :

Surgical intervention for HS :

Premenstrual HS flares:

History of Cardiovascular Disease:

Angina or heart attack in a 1st degree relative < 60 years (Y/N) :

Smoker (Y/N):

Alcohol (units/week):

Diabetes Melitus (Y/N) :

Hypertension (Y/N) :

On antihypertensive treatment (Y/N) :

Chronic kidney disease (Y/N) :

Atrial Fibrillation (Y/N) :

Rheumatoid Arthritis (Y/N) :

PCOS (disease duration) :

Ammenorrhea/oligomenorrhea :

Average length of menstrual cycle/shortest – longest cycle :

Hirusitism/Acne/Male pattern balding (specify):

On Oral contraceptive pill? (specify) :

Section 3 : Physical Measurements

Blood Pressure :

Height :

Weight :

BMI :

Waist Circumference :

Hurley’s Stage :

Sartorius Score :

DLQI :

HADS :

Appendix D: Dermatology Life Quality Index (DLQI)

DERMATOLOGY LIFE QUALITY INDEX (DLQI)

Hospital No: □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ . **Date:** □ □ □ □ □ □ □ □ .

Name: □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ . **Score:** □ □ □ □ □ □ □ □ .

Address: □ □ □ □ □ □ □ □ □ □ □ □ □ □ □ . **Diagnosis:** □ □ □ □ □ □ □ □ .

□ □ □ □ □ □ □ □ □ □ □ □ □ □ □ .

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick (✓) one box for each question.

1.	Over the last week, how **itchy**, **sore**, **painful** or **stinging** has your skin been?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
2.	Over the last week, how **embarrassed** or **self conscious** have you been because of your skin?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	
3.	Over the last week, how much has your skin interfered with you going **shopping** or looking after your **home** or **garden**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
4.	Over the last week, how much has your skin influenced the **clothes** you wear?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
5.	Over the last week, how much has your skin affected any **social** or **leisure** activities?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
6.	Over the last week, how much has your skin made it difficult for you to do any **sport**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
7.	Over the last week, has your skin prevented you from **working** or **studying**?	Yes No	❒ ❒	Not relevant ❒
	If "No", over the last week how much has your skin been a problem at **work** or **studying**?	A lot A little Not at all	❒ ❒ ❒	
8.	Over the last week, how much has your skin created problems with your **partner** or any of your **close friends** or **relatives**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
9.	Over the last week, how much has your skin caused any **sexual difficulties**?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒
10.	Over the last week, how much of a problem has the **treatment** for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all	❒ ❒ ❒ ❒	Not relevant ❒

Please check you have answered EVERY question. Thank you.

Appendix E: Hospital Anxiety and Depression Scale (HADS)

Hospital Anxiety and Depression Scale (HADS)

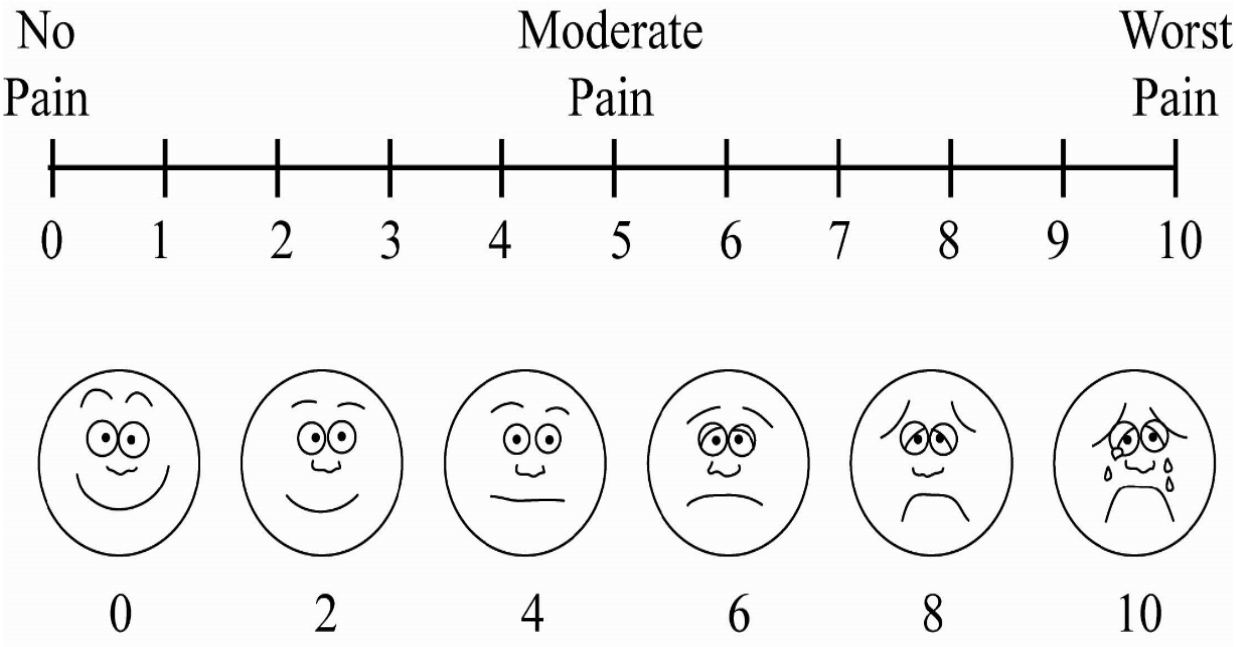
Tick the box beside the reply that is closest to how you have been feeling in the past week.
Don't take too long over you replies: your immediate is best.

D	A		D	A	
		I feel tense or 'wound up':			**I feel as if I am slowed down:**
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time, occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy the things I used to enjoy:			**I get a sort of frightened feeling like 'butterflies' in the stomach:**
0		Definitely as much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite Often
3		Hardly at all		3	Very Often
		I get a sort of frightened feeling as if something awful is about to happen:			**I have lost interest in my appearance:**
	3	Very definitely and quite badly	3		Definitely
	2	Yes, but not too badly	2		I don't take as much care as I should
	1	A little, but it doesn't worry me	1		I may not take quite as much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see the funny side of things:			**I feel restless as I have to be on the move:**
0		As much as I always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind:			**I look forward with enjoyment to things:**
	3	A great deal of the time	0		As much as I ever did
	2	A lot of the time	1		Rather less than I used to
	1	From time to time, but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful:			**I get sudden feelings of panic:**
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed:			**I can enjoy a good book or radio or TV program:**
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not Often	2		Not often
	3	Not at all	3		Very seldom

Please check you have answered all the questions

Scoring:
Total score: Depression (D) _____ Anxiety (A) _____
0-7 = Normal
8-10 = Borderline abnormal (borderline case)
11-21 = Abnormal (case)

Appendix F: Visual Analogue Score for Pain (VAS)



Verbal scale:

No pain	Mild	Moderate	Severe pain

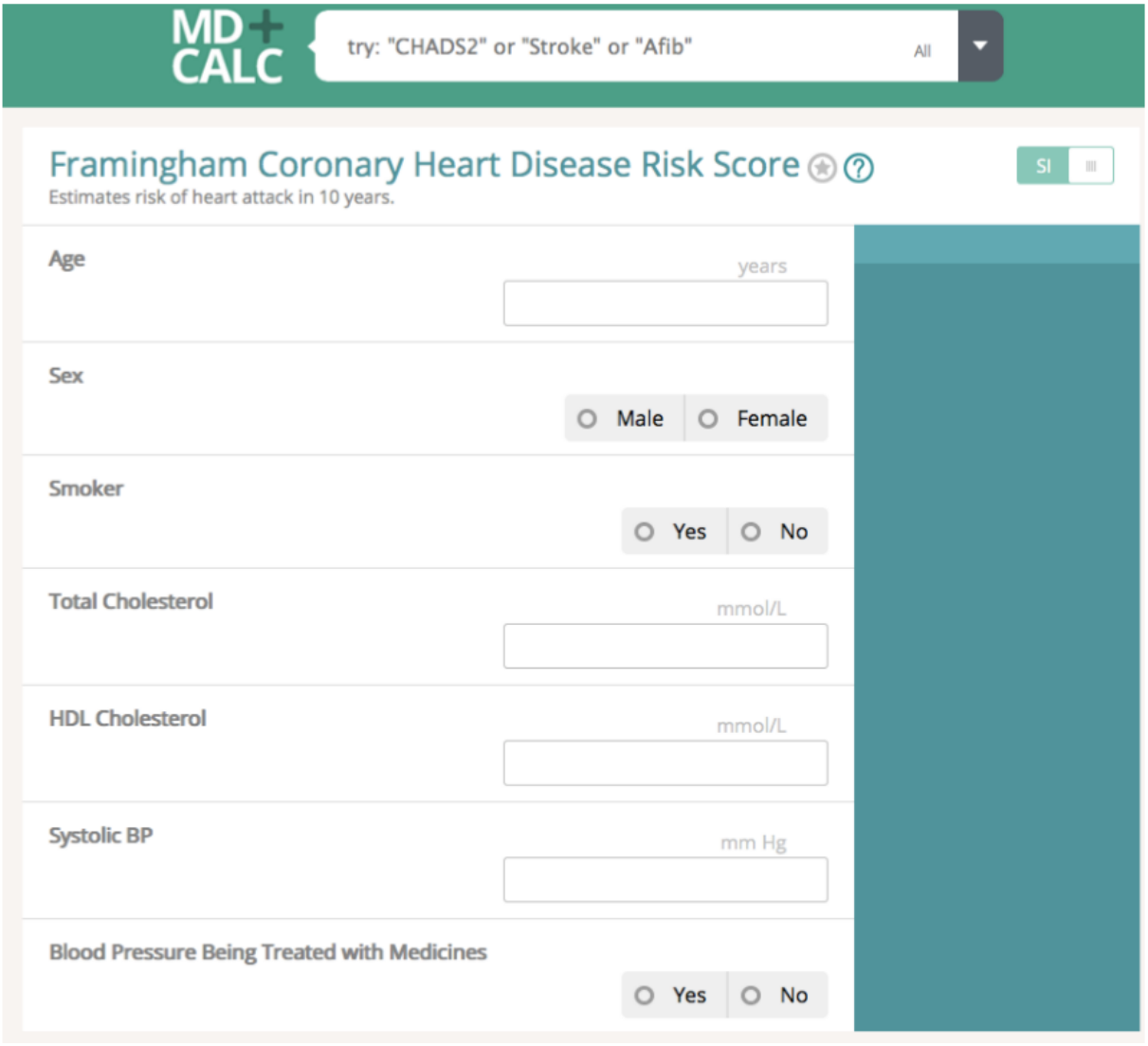
Correlation between Visual and verbal scale:

1-3 = mild pain; minimal impact on ADL's

4-6 = moderate pain; moderate impact on ADL's

7-10 = severe pain; major impact on ADL's

Appendix G: MedCalc Framingham Risk Calculator



Appendix H: QRISK2 Calculator