Facultad de Medicina

GRADO EN MEDICINA

TRABAJO FIN DE GRADO

Riesgo cardiovascular en las enfermedades inflamatorias cutáneas crónicas

Cardiovascular risk in chronic inflammatory cutaneous diseases

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Abstract

Psoriasis and hidradenitis suppurativa (HS) are both chronic inflammatory diseases with common immunopathogenic pathways in which TNF-α, IL-17 and IL-23 play a key role. Therefore, despite these conditions being normally classified as skin diseases they are actually systemic pathologies.

In recent years the spotlight has focussed on the cardiovascular health of these patients given the augmented prevalence of cardiovascular (CV) risk factors among these subjects.

Moreover, both diseases have been associated with accelerated subclinical atherosclerosis. In addition, there seems to exist a correlation between disease severity and the degree of subclinical atherosclerosis. Thus, psoriasis and HS should be considered as independent risk factors for the development of accelerated atherosclerosis.

These findings are consistent with the increased incidence of major cardiovascular events and cardiovascular associated death that has been observed in these conditions and which is apparently directly proportional to disease severity.

Nonetheless, CV risk assessment tools do not include any parameter regarding insulin resistance or inflammation and therefore they underestimate CV risk in this population.

Finally, TNF-α and IL-17 inhibitors have proved to diminish the inflammatory burden of these diseases and therefore, to reduce subclinical atherosclerosis progression, endothelial dysfunction and myocardial infarction risk while improving the microvascularization and insulin resistance.

Keywords: psoriasis; hidradenitis suppurativa; cardiovascular risk; TNF-α inhibitors; IL-17 inhibitors

Resumen

La psoriasis y la hidradenitis supurativa (HS) son enfermedades inflamatorias crónicas en cuya fisiopatología desempeñan un papel central el TNF-α, la IL-17 y la IL-23 de manera que a pesar de que suelen clasificarse como enfermedades cutáneas son en realidad patologías sistémicas.

Tanto es así que estos pacientes presentan una prevalencia aumentada de factores de riesgo cardiovasculares (CV).

De forma similar, se ha visto que la psoriasis y la HS constituyen factores de riesgo para el desarrollo de aterosclerosis subclínica acelerada siendo esta relación más fuerte cuanto mayor es la gravedad de la enfermedad.

También se ha observado un aumento de la incidencia de eventos cardiovasculares mayores y de muerte de causa cardiovascular en estos pacientes, especialmente en aquéllos con una enfermedad más grave.

A pesar de esto, las herramientas de evaluación de riesgo CV no incluyen ningún parámetro que evalúe la resistencia a la insulina o la inflamación y, por tanto, subestiman el riesgo CV de esta población.

Finalmente, los inhibidores de TNF-α e IL-17 han demostrado disminuir la carga inflamatoria de estas enfermedades y, con ello, la progresión de la aterosclerosis subclínica y del riesgo de infarto de miocardio, al tiempo que mejoran la resistencia a la insulina.

Palabras clave: psoriasis; hidradenitis supurativa; riesgo cardiovascular; inhibidores de TNF-α; inhibidores de IL-17

1. Psoriasis and hidradenitis suppurativa

1.1. Psoriasis

- *Introduction*

Psoriasis is a common, chronic, papulosquamous skin disease occurring worldwide, presenting at any age and leading to a substantial burden for individuals and society.

It was first accurately described by Robert Willan, a British dermatologist in his treatise *On Cutaneous Diseases*, published in 1808. Since then, our understanding of the pathogenesis of psoriasis has greatly advanced. However, relatively little is known about the natural history of the disease; despite being considered a chronic disease, some studies suggest that spontaneous remission (for as long as 54 years) might occur in about a third of patients. (1)

- *Epidemiology*

The prevalence of psoriasis is difficult to assess giving the absence of validated diagnostic criteria(1). Furthermore, the prevalence of psoriasis is known in only 19% of countries worldwide and is unequally distributed. Overall prevalence ranges from 0·1% in east Asia to 1·5% in western Europe and is highest in high-income countries (2).

Some evidence suggests a differential effect of latitude on psoriasis prevalence (2) probably because of the beneficial effect of sunlight on the disease. For instance, there is an increased prevalence and incidence in Scotland compared with that of the southwest of England. However, this differential effect has not been observed uniformly across disparate geographical regions (2).

Psoriasis occurs equally in men and women, it can appear at any time of life and its prevalence and incidence is greater in adults than in children. The age of onset seems to be slightly earlier in women than in men. The mean age of onset for psoriasis vulgaris has been estimated at 33 years, with 75% of cases occurring before 46 years of age.

Some studies suggest that the onset is bimodal, with peaks between 16 years and 22 years and later at 57–60 years(1).

- *Histological features*

Psoriasis has three principal histological features: epidermal hyperplasia, dilated, prominent blood vessels in the dermis and an inflammatory infiltrate of leucocytes, predominantly into the dermis(1).

Hyperplasia is associated with loss of the granular cell layer, parakeratosis (retention of nuclei in cells of the stratum corneum) and elongation of rete ridges(1). When present, neutrophil clustering in pustules (Kogoj spongiform micropustules) or surrounded by parakeratosis (microabscesses of Munro), can be pathognomonic of psoriasis (2).

The third main histological feature is the increased vascularity in the dermis which is drived by angiogenic factors produced by keratinocytes. In fact, levels of VEGF are significantly raised in plaques of psoriasis and its serum concentration correlates with the clinical severity of the disease (1).

- *Clinical presentation*

Psoriasis has different clinical phenotypes, but the most frequent and the most easily recognised is chronic plaque or psoriasis vulgaris accounting for 90% of all cases (1). The classic morphology is that of well demarcated, salmon-pink plaques covered in silvery scales in white skin and of grey plaques in black skin. Removal of the adherent scales can result in small bleeding points (known as the Auspitz sign). An individual plaque is dynamic: its edge moves outwards and is the most active area, which can lead to a central clearing, showing as lesions with annular appearance. The disease typically shows a symmetric distribution affecting the extensor aspects of the knees and elbows, the lumbosacral region, and the scalp, rarely encroaching much beyond the hairline, although any skin surface can be involved. If the disease is very active, lesions can occur at sites of trauma or pressure on the skin, known as the Koebner phenomenon (2).

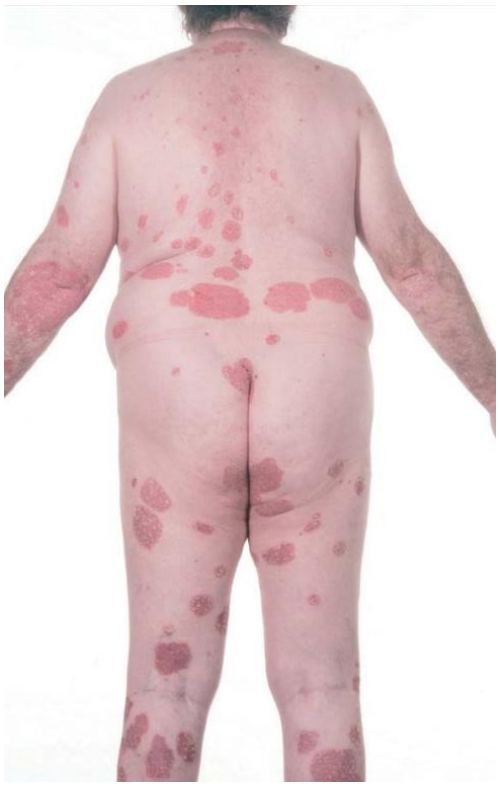

Figure 1. Chronic plaque psoriasis (1)

Less common forms of psoriasis include guttate, erythrodermic, and pustular psoriasis(2).

Children and adolescents can develop an acute form of psoriasis known as guttate psoriasis (1) which is characterised by the apparition of numerous, small, and scaly papules distributed in a centripetal pattern about 2 weeks after a β-haemolytic streptococcal infection such as tonsillitis, pharyngitis or a viral infection (1). Whereas most children and young adults with guttate psoriasis have spontaneous resolution after several weeks or months, approximately 40% of cases progress to chronic plaque disease. The role of antibiotics in managing guttate psoriasis is unclear but tonsillectomy has shown some benefit in recurrent cases associated with tonsillitis (2).

In erythroderma more than 75% of the total body surface area is affected by confluent erythema, scales, or exfoliation (2). It can lead to hypothermia, hypoalbuminemia, and high output cardiac failure (1). Erythroderma can be a life-threatening condition affecting approximately 2–3% of adults with psoriasis (2) and can be caused by other

diseases, including atopic dermatitis, drug eruptions and cutaneous T-cell lymphoma (1).

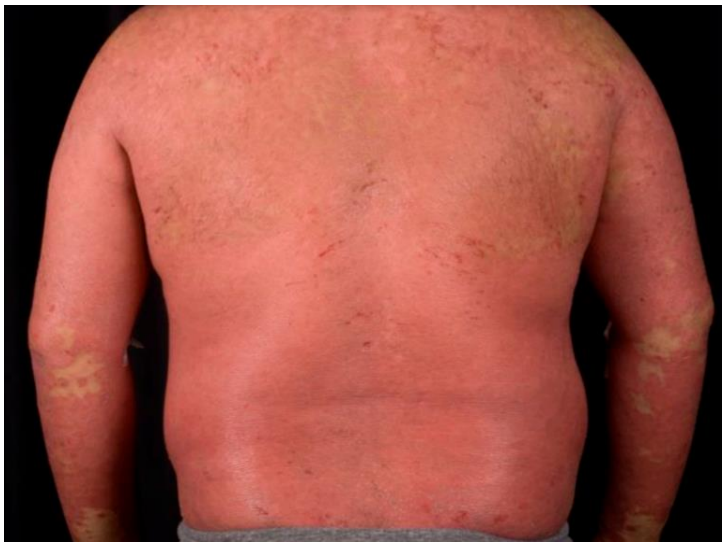

Figure 2. Erythrodermic psoriasis (3)

Pustular forms of psoriasis are uncommon and morphologically distinct, characterised by sterile pustules and erythema. They are divided into three subgroups based on the involved anatomical location: generalised pustular psoriasis (also known as von Zumbusch disease), palmoplantar pustulosis, and acrodermatitis continua of Hallopeau (2).

Generalised pustular psoriasis (von Zumbusch psoriasis) has the hallmarks of an autoinflammatory disease associated with periodic flares (2) in which small, monomorphic sterile pustules develop on painful inflamed skin. The patient has fever, is systemically unwell and their life can be at risk (1). It is epidemiologically distinct from chronic plaque psoriasis and more common in women than in men (2). Precipitants of generalised pustular psoriasis include intercurrent infection, abrupt withdrawal of systemic treatment and, on occasions, ultrapotent topical corticosteroids (1).

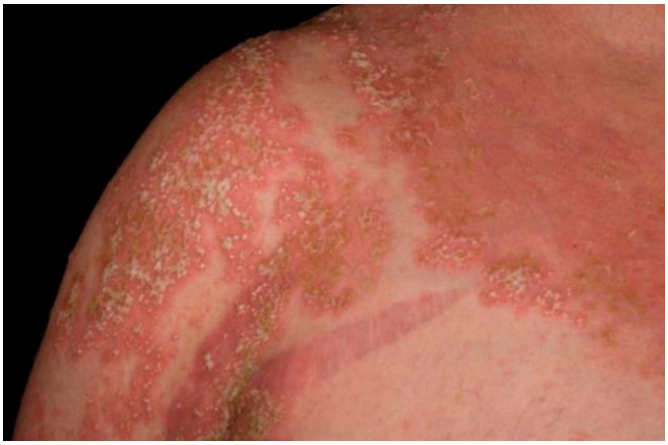

Figure 3. Generalized pustular psoriasis (3)

The second subgroup, palmoplantar pustulosis, classically presents as sterile yellow-brown pustules on the palms and soles, resolving over several weeks to red or brown macules. Palmoplantar pustulosis occurs predominantly in middle-aged female smokers; approximately 20% of patients have concomitant chronic plaque psoriasis (2). Moreover, genetic analysis has implied that palmoplantar pustulosis and psoriasis vulgaris have different causes (1).

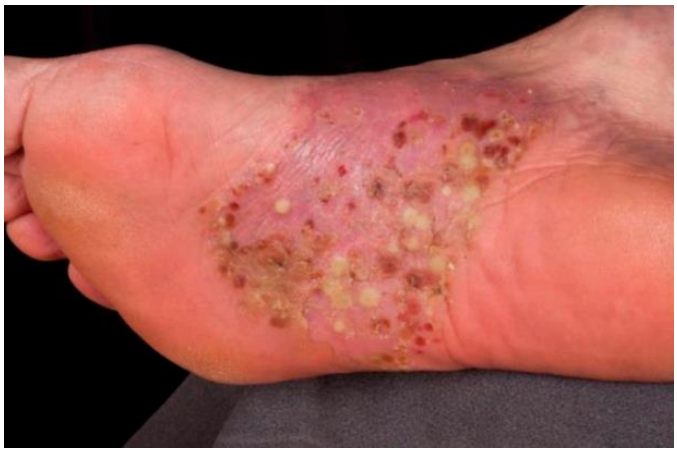

Figure 4. Palmoplantar pustulosis (3)

Acrodermatitis continua of Hallopeau is a rare disease, characterised by pustules on the distal portions of the fingers and sometimes toes, which can lead to shedding of the nail plate; approximately 40% of affected individuals have concomitant chronic plaque psoriasis (2).

Other psoriasis variants are characterised by location. These include inverse or flexural psoriasis, palmoplantar psoriasis, and nail psoriasis (2).

Inverse psoriasis involves the skin folds, such as the axillary, inframammary, inguinal, and intergluteal areas. Due to its occluded location, this form is shiny, red, and does not present the characteristic scaling seen in plaque disease. It can be mistaken for candidiasis or another fungal infection (2).

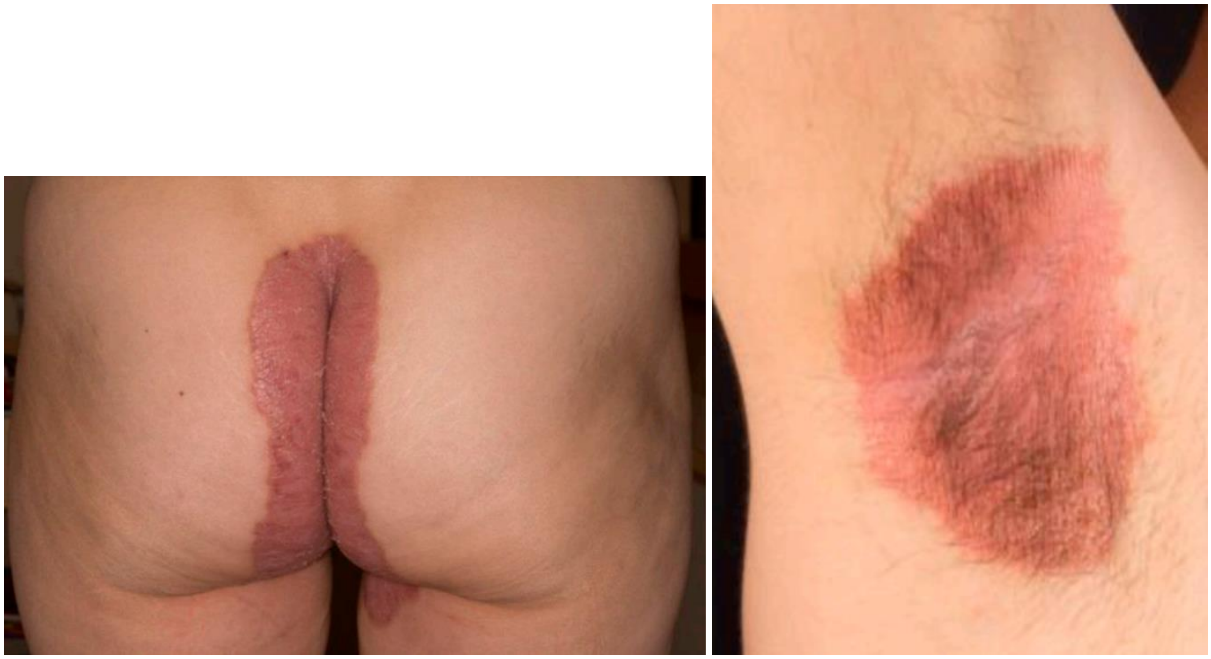

Figure 5. Inverse psoriasis (3)

Palmoplantar psoriasis presents as hyperkeratotic, fissured plaques on the palms and soles, greatly impairing manual dexterity and walking (2).

Nail psoriasis is reported to affect more than half of psoriasis patients and can present as the only psoriasis manifestation in 5–10% of patients.

The clinical presentation of nail psoriasis depends on the structure affected by the inflammatory process. Nail matrix involvement presents as pitting, leukonychia, and onychodystrophy(3). Pitting is the commonest manifestation and it is best seen under oblique lighting conditions (1). On the other hand, inflammation of the nail bed presents as oil-drop discoloration(3), (orange-yellow subungual discolouration) splinter hemorrhages, and dystrophy similar to that observed in onychomycosis (1).

The presence of nail disease, particularly onycholysis, is associated with a doubled risk of psoriatic arthritis and with longer disease duration than in patients with psoriasis without nail involvement (2).

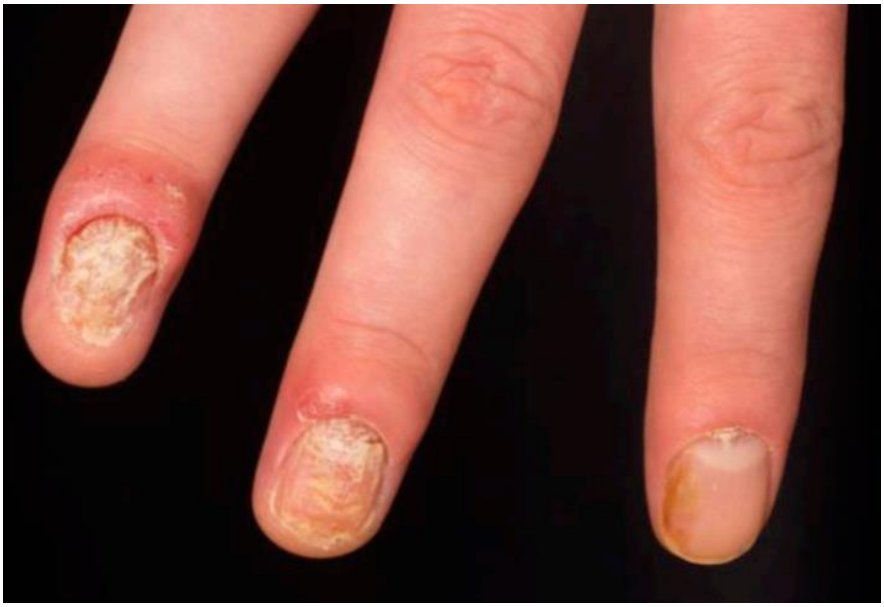

Figure 6. Onycholysis and oil drop changes on psoriatic nail involvement (3)

- *Pathogenesis*

Progression of non-lesional skin into a fully developed psoriasis plaque is dependent on gene–environment interaction; the disease does not manifest unless there is an environmental trigger such as stress, infection (particularly streptococcal), alcohol consumption, smoking, exposure to drugs such as lithium, antimalarials, non-steroidal inflammatory agents and, in some cases, sunlight. Weight gain and obesity are both risk factors and triggers, as well as a possible consequence of living with psoriasis (2).

Psoriasis is classified as a Th1 disease, which is consistent with the relative under-representation of Th2 diseases, such as atopic dermatitis in patients with psoriasis. This explains why T-cell-targeted immunosuppressants such as cyclosporin are effective in psoriasis. Moreover, bone marrow transplantation can appear to transmit or clear psoriasis (1).

In recent years, it has been shown that innate as well as adaptive immunity are crucial in the initiation and maintenance of psoriasis plaques (1).

Its pathogenesis has been related to T cells, dendritic cells, neutrophils and non-classic immune cells such as keratinocytes. Communication between these cells

happens mainly through cytokines such as TNF-α, IFN-γ, IL-17 and IL-22, and through activation of keratinocytes, driving epidermal hyperproliferation and production of antimicrobial proteins, growth factors and chemokines. These factors promote the characteristic changes in psoriasis including angiogenesis, neutrophil infiltration and increased numbers of T helper cells type 1 and Th17 cells, creating a self-sustained inflammation cycle (2).

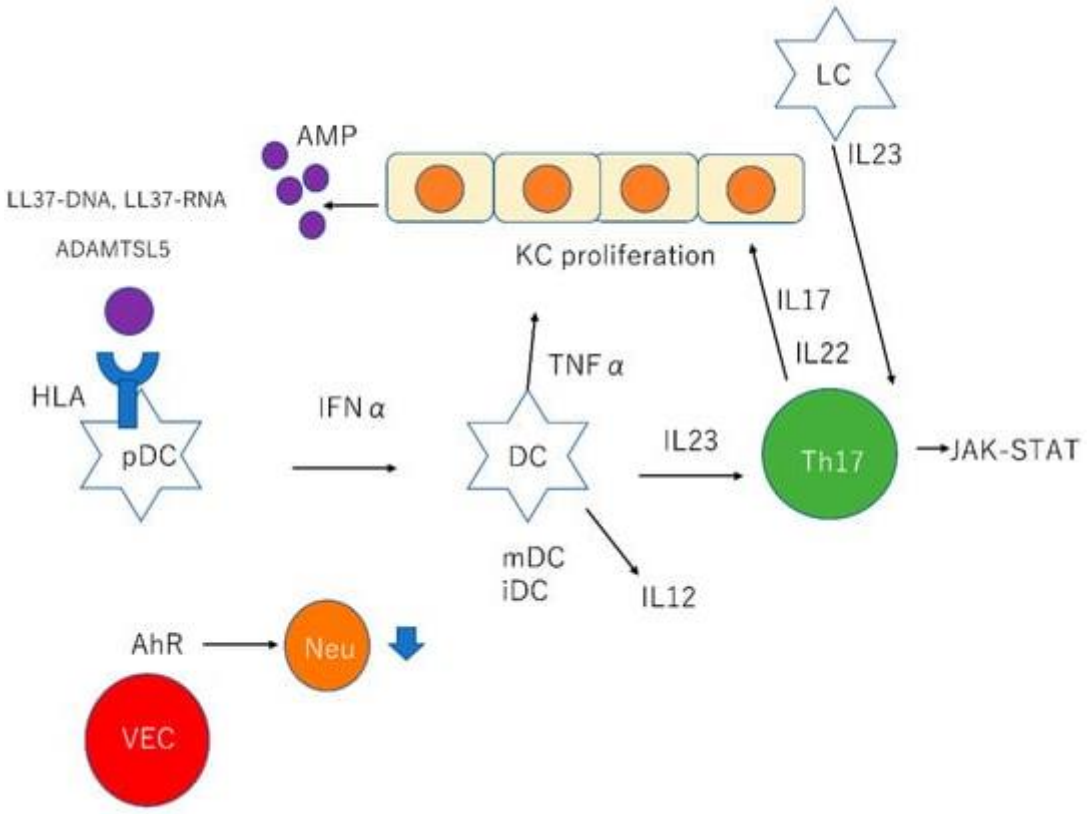

Figure 7. Summary of psoriasis pathogenesis. (4) KC: keratinocyte; AMP: antimicrobial peptides; ADAMTSL5: A disintegrin and metalloprotease domain containing thrombospondin type 1 motif-like; pDC: plasmacytoid dendritic cell; IFN-γ: interferon; mDC: myeloid dendritic cell; iDC: inflammatory dendritic cell; TNF-α: tumour necrosis factor; IL: interleukin; JAK: Janus kinase; STAT: signal transducer and activator of transcription; LC, Langerhans cell; AhR: aryl hydrocarbon receptor; VEC: vascular endothelial cell; Neu: neutrophil; HLA: human leukocyte antigen.

Antimicrobial peptides play important roles in host protection by killing pathogenic microorganisms. They also affect host inflammatory responses by acting as chemotactic agents, angiogenic factors and regulators of cell proliferation. In psoriasis, certain antimicrobial peptides including β-defensins, S100 proteins and cathelicidin, are highly expressed and secreted by keratinocytes, neutrophils, and macrophages in response to injury and cytokine stimulation (4).

This overexpression of antimicrobial peptides contrasts with atopic dermatitis, in which such peptides are underexpressed. This is congruent with the clinical observation that psoriatic skin is rarely secondarily infected, whereas in atopic dermatitis secondary infection is a substantial problem (1).

These antimicrobial peptides as well as the melanocyte antigen ADAMTSL5 act as autoantigens activating tissue-resident memory T cells via HLA-C*06:02. The persistence of these memory T cells in the skin can explain several features of psoriasis, including the sharp demarcation of involved skin from clinically healthy skin and the characteristic recurrence of psoriasis at previous sites of involvement (2).

Activated T cells synthesise IL-17 and IL22 through the JAK-STAT (4) pathway leading to upregulation of CCL20, a Th17 chemoattractant, which thereby sets up a positive IL-17 response feedback loop (2).

On the other hand, IL-23 also plays a major role in psoriasis through maintenance and expansion of IL-17-producing immune cells (2).

The balance between the key cytokine circuits in psoriasis might help to explain some of the clinical manifestations of the disease, with IL-23 and IL-17 dominating in plaque psoriasis. These inflammatory circuits amplify each other, with IFN-γ promoting IL-23 and Th17 responses creating complex, interacting, and self-sustaining inflammatory circuits in psoriasis (2).

As a prominent cellular source of IFN-α, TNF-α, IL12, and IL23, *dendritic cells also* play an important role in psoriasis (4).

Plasmacytoid dendritic cells recognize autoantigens such as antimicrobial peptides and LL37–DNA complexes through Toll-like receptors (TLRs) 7, 8, and 9 leading to the production of large amounts of type I IFN which contributes to psoriatic inflammation (4).

Under healthy conditions, conventional dendritic cells are also associated with maintaining immune tolerance through depletion of autoimmune T cells, expressing anti-inflammatory cytokines including IL10, transforming growth factor β, and IL27 and promoting regulatory T cells homeostasis (4).

1.2. Hidradenitis suppurativa

- *Introduction*

Hidradenitis suppurativa (HS) was first described by a French surgeon in 1839. Nowadays it is known to be a debilitating condition that stems from follicular hyperkeratosis and apocrine gland inflammation. Patients are frequently smokers,

obese, and report pain and a significantly decreased quality of life. HS pathogenesis involves immune dysregulation with inflammatory cytokines, specifically TNF-α and IL-17, playing important roles, likely with an underlying genetic predisposition and altered microbiome(5).

- *Epidemiology*

Hidradenitis suppurativa occurs most frequently in young adults, between 18 and 44 years of age(5). Its prevalence is unknown but estimations in Western population range from 0.3% to 1.7% (6). On the other hand, Asian estimations fall on the lower end of this range: 0.2% in Taiwan and around 0.1% in Korea(6). It is also known to be more common in African Americans and biracial individuals than whites(5). These differences may be explained by variations in the genetic background and distribution of environmental factors(6).

Regarding the sex predominance, in the Western world HS tends to affect mainly women (5) with a female-to-male ratio of 3:1. In contrast, recent studies from East and Southeast Asia show a clear male predominance. This difference may be related to sex differences in obesity and smoking rates, which are known risk factors for HS. The clinical presentation also seems to vary between Western and Asian populations (6).

- *Disease presentation, course and clinical classification*

Hidradenitis suppurativa is diagnosed clinically and there are 3 criteria for diagnosis: characteristic lesions, predilection for flexural sites and lesion recurrence(5).

- The classic clinical presentation of HS is characterised by inflamed nodules and abscesses. Only a subgroup of patients develops epithelialized tunnels, also known as sinus tracts, that are frequently accompanied by hypertrophic scarring. In addition to these characteristic lesions, a multitude of other less typical lesions can be seen. These include papules, pustules, ulcers, plaques, comedones, epidermal cysts and excessive granulation tissue at the opening of tunnels or ruptured abscesses (6).
- HS lesions characteristically develop in the axillae and in the inframammary, inguinal or gluteal regions. However, atypical sites are not uncommon and include the abdomen, the flanks, the nape of the neck and the popliteal fossa. In Asian populations, axillary lesions seem to be less common whereas gluteal involvement is frequent with men showing a higher frequency of acne conglobata, preauricular, postauricular and neck lesions (6).
- Acute exacerbations alternating with periods of quiescence are typical(5).

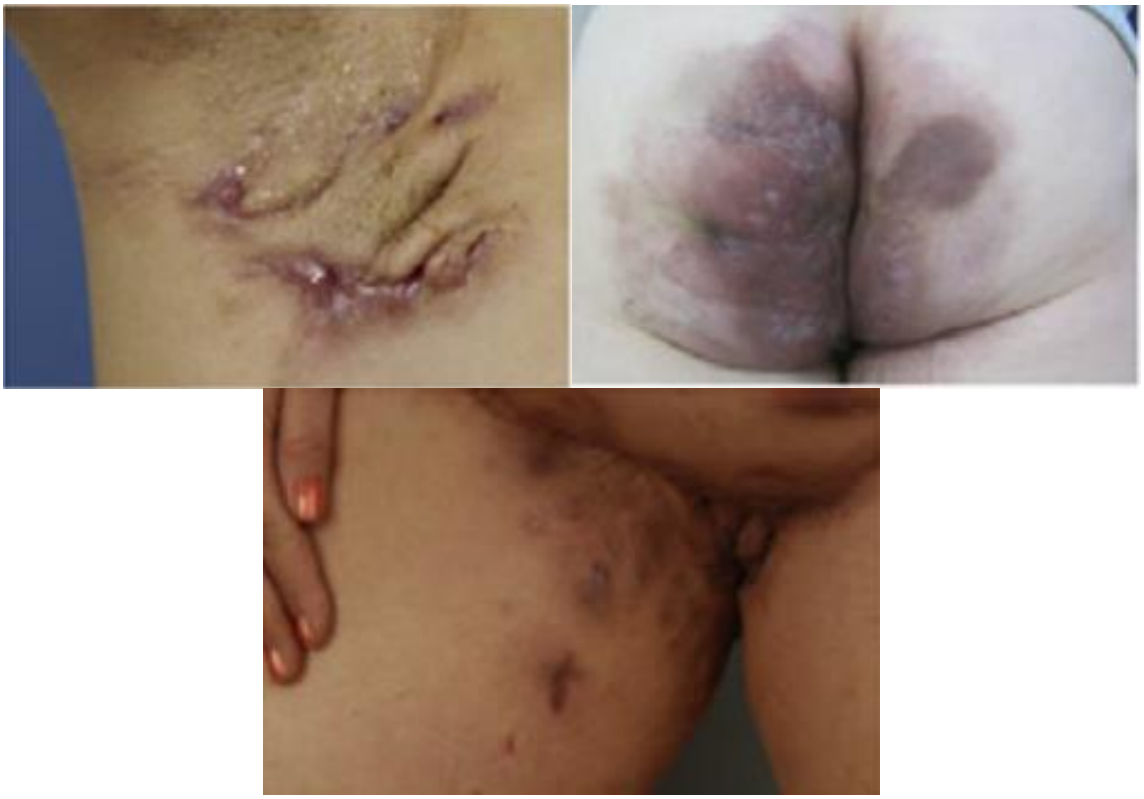

Figure 8. Hidradenitis suppurativa affecting axilla, buttocks and groin (6)

Triggers for flares have been identified; they include stress, diet, exercise, weight gain (6), heat, sweating, shaving (5) and friction (6). Moreover, the majority of patients report local (ie, erythema, pain, paraesthesia, and pruritus) or systemic prodromal symptoms (ie, fatigue, malaise, and headache) within 24 hours before development of a lesion (6). On average, patients experience a median of 2 lesions per month, with each exacerbation lasting 7 days on average. Perimenstrual flares have been reported by up to 77% of women with HS. Nearly a quarter of women report disease improvement during pregnancy, and 60% experience a postpartum flare (6).

Nonobese participants and patients who quit smoking or never smoked have significantly greater rates of self-reported remission (odds ratio [OR] = 3.9 and OR = 2.8, respectively).

Disease course and progression also differ between different Hurley stages with lower stages being less prompt to develop tunnels (6).

This Hurley staging system is the most common HS classification (5) that classifies disease severity into three stages depending on the type and extent of the lesions present (6). It was designed to help select treatment although it fails to assess disease activity or treatment response(5).

There are multiple HS phenotypes. The regular type is the one described above which is the most common and consists of patients who fulfil the diagnostic criteria for HS. However, some patients have specific characteristics which makes their disease been categorised into three varieties which are: frictional furuncle type, conglobata type or as ectopic type. The frictional furuncle type features lesions in frictional sites in patients who are overweight. The conglobata type consists of cysts and acne conglobata primarily on the face and trunk in men who are not overweight. Lastly, the ectopic type involves the face(5).

Finally, HS has been described as part of several autoinflammatory syndromes such as SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis), PASH (pyoderma gangrenosum, acne, and suppurative hidradenitis), PAPASH (pyogenic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis), PsAPASH (psoriatic arthritis, pyoderma gangrenosum, acne, and suppurative hidradenitis), PASS (pyoderma gangrenosum, acne, suppurative hidradenitis, and ankylosing spondylitis), and familial Mediterranean fever (6).

Despite the different sorts of HS described, treatment does not vary from one type to another(5).

- *Pathogenesis*

Early skin alterations in hidradenitis suppurativa are likely the result of a complex interplay between environmental risk factors (smoking, obesity and hormones) and genetic predisposition (6).

The role of female hormones in HS is unclear. Up to 43% of female patients with HS experience worsening symptoms around menses. Contraceptives containing progesterone appear to induce flares, potentially because of their androgen-like effects. Alternatively, spironolactone, which is antiandrogenic, has been shown to decrease HS lesion count, severity and pain. Nonetheless, hyperandrogenism is usually absent in patients with HS and testosterone and dihydrotestosterone levels in patients with HS do not differ compared with control subjects, suggesting that (5) the influence of hormones is mediated through peripheral receptor sensitivity, increased local conversion of androgens or local production of androgens and oestrogens in the skin (6).

HS is thought to be a complex polygenic disease in which multiple genetic variants interact with specific environmental factors to ultimately result in different HS phenotypes. Moreover, environmental exposures such as smoking and obesity both in utero and in adult life have been shown to induce persistent and sometimes heritable alterations in the epigenome, potentially contributing to the development of HS (6).

It has been demonstrated a heritability of HS in the general population of around 80% (6) and 30 to 40% of patients with HS have 1 family member with the disease, supporting a genetic predisposition(5).

Furthermore, some variants affecting the g-secretase complex genes have been described to predispose to HS development. These rare variants are present in less than 5% of patients with HS in the general population and affected individuals typically present with an atypical clinical phenotype with lesions extending to the trunk, nape of the neck, and the face, resembling acne conglobata (6).

The relationship between smoking and HS is thought to involve TNF-α. Nicotine increases eccrine gland secretion, and nicotine excretion in sweat induces TNF-α release by keratinocytes and TH17 cells (5). Nicotine has been shown to induce epidermal hyperplasia through non-neuronal acetylcholine receptors present in the follicular infundibulum, facilitating immune cell infiltration (6), follicular occlusion and rupture(5).

Other toxins such as polycyclic aromatic hydrocarbons may affect TH17 cell–Treg cell balance. Moreover, the peripheral blood of smokers shows a significantly higher percentage memory B cells than in nonsmokers. Tobacco may also affect skin microbiome, the changes in which are less pronounced in ex-smokers, thus suggesting some level of reversibility.

The association between smoking and HS is well established in Western populations, with up to 90% of patients being current or ex-smokers. Smoking rates among patients with HS in Asian and Southeast Asian populations are generally lower (29%-73%) (6).

Obesity is another well-established risk factor for HS in Western populations, with up to 50% of patients being obese. Obesity is thought to induce follicular plugging through increased friction in skin folds and ectopic sites, such as in abdominal skin folds in overweight patients (6).

Moreover, obesity promotes systemic, subclinical inflammation through increased levels of circulating proinflammatory cytokines and adipokines such as leptin, resistin, and omentin-1 (6).

TNF-α, whose levels are increased in HS patients, acts on adipocytes and muscle cells to induce insulin-signalling defects and suppresses the secretion of adiponectin from adipocytes. Adiponectin is an antiinflammatory hormone that regulates glucose metabolism and insulin sensitivity. Thus, decreased circulating levels are associated with diabetes, high BMI and metabolic syndrome (5).

Since adiponectin levels are significantly decreased in patients with HS, these subjects have higher fasting serum glucose, insulin levels and insulin resistance (5).

- *Skin alterations in hidradenitis suppurativa*

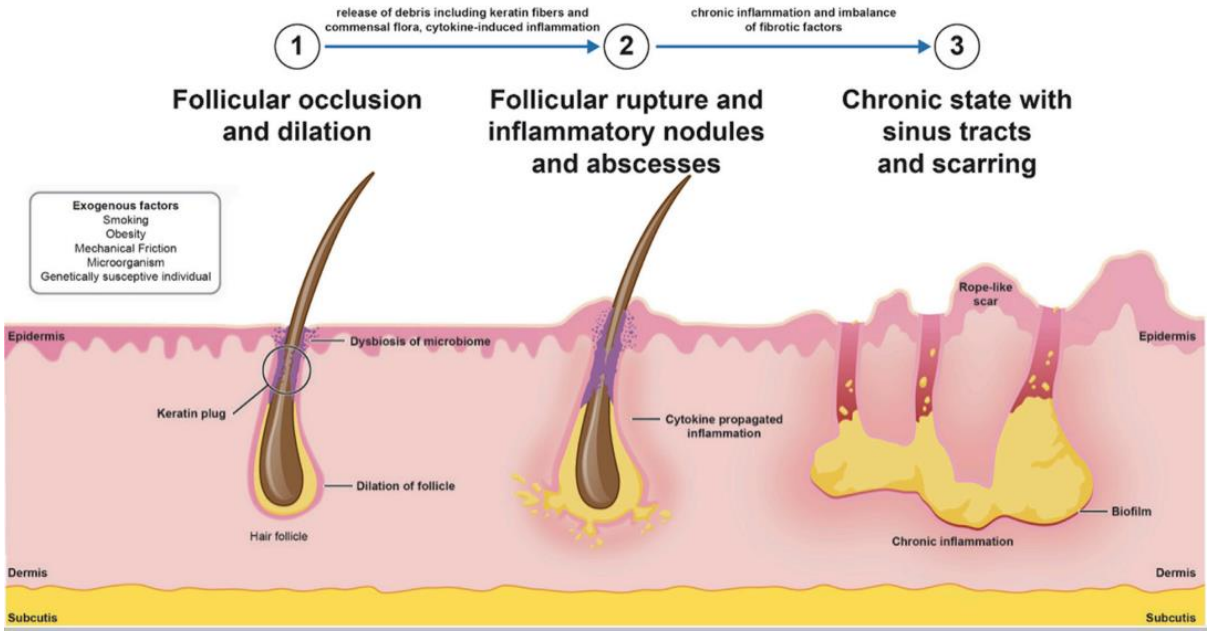

Figure 9. postulated sequence of events underlying the pathophysiology of hidradenitis suppurativa (5)

In unaffected skin from predilection sites of patients with hidradenitis suppurativa, the infundibular outer root sheath shows hyperplasia and hyperkeratosis that are likely driven by an intrinsic dysregulation of the hair follicle stem cell compartment. The outer root sheath cells exhibit type I interferon responses, altered microRNA expression, upregulated production of antimicrobial peptides (human b-defensin 2, S100A7-9), and increased secretion of chemokines (IP-10 [CXCL10], RANTES [CCL5]) (6).

These subclinical alterations are accompanied by a shift in the affected skin microbiome (6) towards increased abundance of *Propionibacterium*, *Porphyromonas*, and *Peptoniphilus* species while nonlesional skin has predominantly *Acinetobacter* and *Moraxella* (5).

Propionibacterium acnes is a skin commensal with bactericidal properties against other pathogens that, along with *Staphylococcus epidermidis*, constitutes the microbiome of healthy adults. Both of them are decreased in HS lesional sites potentially allowing pathogenic bacteria to flourish (5).

In addition to the dysbiosis inherent to HS, colonisation with biofilm-forming bacteria is common in HS, likely because of inflammation and rupture of the innate skin barrier.

Biofilm forms in 67% to 75% of sinus tracts and infundibula and are decreased in lesional than perilesional skin (5) contributing to a proinflammatory environment (6).

Infundibular hyperplasia can lead to follicle occlusion and stasis of keratin and bacteria within the dilating hair follicle. This cyst formation is accompanied by subclinical inflammation in the form of a mixed mononuclear infiltrate located primarily around the follicle, with small scattered interfollicular subepidermal infiltrates (Fig 2). In combination with mechanical stress and possibly nicotine exposure, this infiltrate, through secretion of proinflammatory cytokines such as TNF-α, IL-17A and GMCSF, promotes interfollicular hyperplasia and further influx of immune cells. Among these cytokines, TNF-α and IL-17 appear to play a prominent role in HS pathogenesis (6); they are secreted by innate and adaptive immune cells and is significantly increased in patients with HS compared with both healthy and psoriatic subjects. In addition, their levels correlate with disease severity (5).

There are several theories which explain the formation of epithelial tracts within the dermis; one of them proposes that these structures may arise from the infundibulum of dilated follicles growing as tendrils into the adjacent dermis. Other ones include the seeding of follicular stem cells and strands of proliferating keratinocytes in the dermis after cyst rupture. Whatever their origin is, this infiltrative epithelium subsequently forms keratin-filled cysts away from the original infundibulum originating biofilm-paved lumens with or without communication to the original hair follicle. These tunnels, extending deep into the dermis, provide excellent conditions for colonisation of anaerobic bacteria such as *Prevotella* or *Actinomyces spp* (6).

Eventual cyst or tunnel rupture is likely caused by mechanical stress and/or tissue damage from the immune cell infiltration and activation in response to damage-associated molecular patterns secreted by keratinocytes (6).

Furthermore, a cyst or tunnel breakdown exposes highly immunogenic keratin fragments and bacteria to the dermis. This provokes an acute immune response that is characterised by a mixed immune infiltrate of myeloid cells (neutrophils, macrophages and dendritic cells), followed by influx and activation of T and B cells (Fig 3). This response is clinically seen as acutely inflamed nodules, abscesses and inflamed, draining tunnels (6).

After encountering the contents of the cysts or sinus tracts, macrophages are activated and produce various proinflammatory mediators (including IL-1b, TNF-α, IL-6, and CXCL8 [IL-8]) inducing further expression of chemokines by keratinocytes (IL-8, CXCL11, CCL2, and CCL20) and fibroblasts (CXCL1 and CXCL6) attracting neutrophils, T cells, and monocytes into the dermis (6).

Moreover, it is believed that TNF-α, IL-1b, and IL-6 are responsible for the systemic effects such as fatigue or fever (6).

Fibroblasts respond to IL-1b by producing both additional chemokines and matrix metalloproteinases (MMP) promoting cysts or tracts disintegration, resulting in non–epithelial-lined or minimally epithelial-lined tunnels which makes them more vulnerable to rupture (6).

In regards to infiltrating monocytes, they develop into macrophages and dendritic cells, which through production of TNF-α and IL-23 induce TH17 cell development.

TH17 cells produce IL-17A, IL-22 and TNF-α and amplify the inflammatory cascade through release of chemokines and antimicrobial peptides (6). TH17 cells and IL-17A are increased in lesional and perilesional HS skin and correlate with disease severity. IL-17 induces the expression of IL-1b, IL-6, and TNF-α. IL-1b further increases TH17 cell levels and IL-17 in turn increases macrophage production of IL-1b and TNF-α, enhancing the immune response (5).

The upregulation of Toll-like receptors (TLRs) and matrix metalloproteases observed in HS activate gene expression of proinflammatory cytokines including TNF-α, IL-1b and IL-6 (5).

B cells and plasma cells have been identified as key players in HS lesions and have been found in increasing numbers from early to chronic lesions. The latter tend to have the greatest number of plasma cells as well as an increased production of immunoglobulins, which form immune complexes in HS lesions (6).

Single cyst ruptures and associated flares last about 7 days on average. After several of these episodes, inflammation might become chronic by forming lymphoid follicles with multinucleated giant cells that frequently contain keratin fragments. Increased expression of B-cell survival factors gives rise to the persistence of these cells as well as B cells, T cells, follicular dendritic cells, and follicular TH cells. The number of B cells increases as lesions evolve, with progressive differentiation of B cells towards memory B cells, plasma cells, and plasmablasts, which are mainly found in end-stage lesions. Plasma cells and plasmablasts are the source of increased expression of IgG in HS skin lesions, which contributes to local immune complex formation (6).

Further architectural changes, including fibrosis, are driven by activated fibroblasts and can be so severe that lymphedema may appear particularly in the pubic area. Remnants of cyst wall epithelium or the single collection of keratinocytes that remain in the dermis after tunnel or cyst destruction may potentially allow for formation of additional tunnels, further propagating the disease process (6).

2. Psoriasis and hidradenitis suppurativa as systemic diseases: associated comorbidities

Psoriasis and hidradenitis suppurativa are currently considered two systemic diseases “that extend beyond the skin, and that share various pathogenic aspects, as well as the association with several comorbidities. It should be noted that both diseases are characterized by unbalanced interactions between the innate and adaptive immune systems. To this respect, dendritic cells, activated by a variety of cell types (keratinocytes, natural killers, T cells, macrophages, etc.), secrete IL-23 and IL-12, which in turn induce differentiation of native T-cells to Th17 and Th1, respectively. IL-

23 plays a major role in the survival and proliferation of Th17 and Th22 cells. Th17 cells produce IL-17 while Th1 and Th22 cells secrete TNF-α and IL-22, respectively(7).

Furthermore, these common pathogenic pathways could also justify the effectiveness of various treatments in both diseases; among them, anti-TNF-α monoclonal antibodies (adalimumab and infliximab). Similarly, the IL-17 inhibitor secukinumab, which has shown broad efficacy in the treatment of psoriasis, has recently been approved for moderate to severe HS.

2.1. Comorbidities

- *Inflammatory bowel disease*

Up to 10% of patients suffering from inflammatory bowel disease (IBD) can have psoriasis. Inflammatory bowel disease, particularly Crohn disease (CD), has also possible epidemiologic and pathogenic connections with hidradenitis suppurativa (5). Analyses from 4 studies found HS prevalence in IBD and CD patients to be 12.8-23% and 17.3-26%, respectively. On the other hand, the prevalence of Crohn disease among patients with HS is in the range of 0.8% to 2.5% versus 0.3% in the general population. On average, Crohn disease presents 5.3 years before the diagnosis of HS (6).

Further complicating the matter is the fact that differentiating perianal CD from HS may prove difficult. Lesions in CD tend to be more ulcerative, the scars more retractile and largely confined to the anorectal skin and initial rectal mucosa. However, these lesions commonly extend to create fistulas, strictures, and even incontinence when the anal sphincter is involved. HS lesions, on the other hand, do not form endoanal lesions or primary ulcerations. Comedones, nodules, skin bridging and sinuses are present instead(5).

- *Arthritis*

Inflammatory arthritis also has a higher prevalence in hidradenitis suppurativa population compared to the general population (5). In a prospective study of 640 patients, 3.7% had comorbid spondyloarthritis and in more than 90% of those patients HS preceded articular symptoms (8).

Similarly, psoriasis is most notably associated with psoriatic arthritis (PsA), a seronegative inflammatory arthritis observed in 10–40% of patients with psoriasis and typically lagging in onset behind the skin disease by 10 years. Psoriatic arthritis shares the inflammatory chronicity of psoriasis and requires systemic therapies due to a potential destructive progression (3).

Psoriatic arthritis develops in up to 40% of psoriatic patients and around 15% of psoriatic patients are thought to have undiagnosed arthritis (3).

- *Neoplasias*

One well-established and grave complication of hidradenitis suppurativa is the development of squamous cell carcinoma (SSC) (6) which has a prevalence of approximately 4.6% among these patients (5). SSCs are mainly found in chronic, perianal, gluteal and genital lesions and they are likely a consequence of long-standing active inflammation. Prognosis is often poor, as these tumours are associated with a high metastatic and mortality rate (6).

In regard to psoriasis, it is unclear whether cancers, particularly lymphoma and skin cancer, are related to psoriasis or to its treatment. For example, the risk of developing non-melanoma skin cancer is increased by the excessive use of photochemotherapy which can be aggravated by the subsequent use of ciclosporin (1).

- *Psychiatric disorders*

The adjusted odds of depression among patients with hidradenitis suppurativa ranges from 1.3 to 4.8 times that of the control population and it tends to arise 4.7 years after the onset of HS.

A meta-analysis of 4 studies found a prevalence of anxiety among patients with HS of 4.9% and it has been observed to develop 1.6 years lagging the onset of HS.

Patients with HS have also been shown to have a higher risk of schizophrenia than age- and sex-matched controls (OR 1.4) which on average develops 6 years before the onset of HS.

Patients with HS also have a higher risk of suicide and substance abuse (4% vs 1% in controls), with alcohol, anxiolytics and opioid use being the most frequent. Nonetheless, once the comorbidities (psychiatric disorders, smoking status, arthropathies, diabetes mellitus, obesity, etc.) are controlled this risk is markedly reduced (6).

Concerning psoriasis, it also associates an increased prevalence of depression (3) and stress. Further to this, it has been stated that its impairment to psychological

quality of life is comparable to cancer, myocardial infarction (3), diabetes, ischaemic heart disease, chronic obstructive pulmonary disease (1) and depression (3).

- *Hidradenitis suppurativa and psoriasis*

It has been described that hidradenitis suppurativa prevalence is increased in patients with psoriasis compared to control subjects after adjusting for smoking, obesity and additional comorbidities. Further to this, it has been observed that psoriatic patients with coexistent HS are younger and have a higher prevalence of obesity and smoking (5).

- *Other comorbidities*

In a minority of patients, hidradenitis suppurativa presents within the setting of other autoinflammatory syndromes, resulting from defects or dysregulation of the innate immune system as well as an upregulation of IL-1b, TNF-α, and other cytokines (6). Such is the case of pyoderma gangrenosum, acne, and HS whose association is an established disorder known as PASH. If a patient has PASH with the addition of pyogenic arthritis, it is designated as PAPASH (PG, acne, HS, and pyogenic arthritis) (5) and PASS when the subject suffers from PG, acne conglobata, HS, and axial spondyloarthopathy(5).

Recently, patients with HS have been found to be twice as likely to develop atopic dermatitis than controls. Paradoxically, another study demonstrated that patients with HS have a lower risk of allergic rhinitis, allergic conjunctivitis and allergic contact dermatitis than controls do.

In addition, patients with HS have been found to have increased risk of both hepatitis B and C infections (OR of 1.9 and 1.7, respectively).

Lastly, common autoimmune diseases such as thyroid disease, type 1 diabetes, alopecia areata, and vitiligo have also been reported in higher frequency among patients with HS than among controls (6).

3. Cardiovascular risk in psoriasis and hidradenitis suppurativa

3.1. Cardiovascular risk factors in psoriasis and hidradenitis suppurativa

- *Metabolic syndrome*

The association of psoriasis and cardiovascular (CV) comorbidities has been recently described in many epidemiological studies (9).

A Slovak study showed that 44.9% of their patients had metabolic syndrome compared to 20.1% prevalence in the Slovak general population ($p<0.001$) (9). This data is supported by four systematic reviews which reported that patients with psoriasis are at a higher risk of developing complicated metabolic syndrome (10).

On the other hand, there is an active discussion whether there exists a correlation between psoriasis severity and metabolic syndrome prevalence (9); in this regard, a meta-analysis carried out by L. Liu and X.-c. Cai found that patients with severe psoriasis were more prone to develop metabolic syndrome (37%) than those with mild-to-moderate psoriasis (31%) (10), probably because of common inflammatory mechanisms (9). On the contrary, Tomáš Kampe et al. did not find any correlation between metabolic syndrome and psoriasis severity (9).

In addition, the prevalence of metabolic syndrome in patients with psoriasis is similar between men and women. Differences have also been found between regions, with the highest prevalence of metabolic syndrome in Latin America (47%) and the lowest in North America (26%). Furthermore, metabolic syndrome prevalence also seems to depend on the different psoriasis type, being higher among patients with psoriasis vulgaris (28%) and lower in patients with pustular psoriasis (15%) (10).

hidradenitis suppurativa is also associated with CV risk factors such as obesity, smoking, hypertriglyceridemia, diabetes mellitus (11) and with over twice the risk of metabolic syndrome, after adjustment for confounding factors (12). Just hypertension has not been found at a significantly higher rate. The association between HS and metabolic syndrome has been reported to be stronger in hospitalised patients (OR 3.89) than in population ones (OR 2.08) (5). Some authors suggest that this finding could be due to a correlation between HS severity and metabolic syndrome, assuming that hospitalised patients will suffer from a more severe form of HS (5). However, this finding could be due to a detection bias.

Having said this, the correlation of HS severity with metabolic syndrome remains to be elucidated since there are still contradictory studies regarding this point. However, it is logical to think that a higher inflammatory load in more severe HS cases would likely have more metabolic pathologies compared to mild HS cases (12).

Some hypotheses have arisen to explain the relation between HS and metabolic syndrome; firstly, adipose cells are considered an independent endocrine tissue capable of secreting proinflammatory cytokines, which may add to the chronic inflammatory state of HS. The sedentary lifestyle that may accompany these patients as a consequence of psychological stigmatisation would also play its part as well as inflammation-induced neuropsychological factors affecting appetite and cortisone secretion(13). Furthermore, obesity may lead to large skin folds enhancing the warm, humid milieu and skin-to-skin contact which favours exacerbations or maintenance of HS lesions(13). Hyperglycaemic states have also been linked to increased keratinocyte proliferation and lipogenesis, increasing risk of follicular occlusion and scarring in HS (12).

- *Obesity*

Of the conditions comprising the metabolic syndrome, obesity has been demonstrated to be a paramount risk factor and it is the most commonly associated with hidradenitis suppurativa: 50% to 75% of patients are overweight or obese(5). In the study by Tomáš Kampe et al. on psoriasis, the main cardiometabolic comorbidity was also obesity; 64.3% of patients had an increased BMI while 78.4% of patients showed waist circumferences equal or greater than 102 cm or 88 cm, which is a criterion used to diagnose metabolic syndrome in men and women respectively (9).

There possibly exists a dose-response relationship between BMI and HS severity (5) given that high-BMI patients tend to have higher Hurley scores, more affected areas and greater self-reported severity compared to low-BMI patients (5). Nonetheless, it is worth saying that some studies have failed to assess a correlation between HS severity or duration and obesity(5).

What is more, one study has demonstrated that weight reduction in patients with BMI greater than 30 kg/m2 ameliorates HS supporting this dose– response relationship (14). According to recent studies, weight reduction would not only affect HS severity but also its prevalence and prognosis, being the resolution of the disease more frequent in patients who lose weight. In addition, obesity has been shown to influence the effect of treatments; for instance, recurrence rates after CO2 laser surgery are better in patients with lower BMI (15).

Likewise, a randomised controlled trial revealed that a 20-week dietetic intervention associated with increased physical exercise reduced psoriasis severity in systemically treated overweight or obese patients with active psoriasis. Several studies have also found that exercise reduces the risk of psoriasis (16)

Additionally, obesity has also been identified as a poor response predictor to biological therapies and bariatric surgery has been shown to have a beneficial effect on psoriasis.

- *Diabetes mellitus*

Type 2 diabetes has been reported to be twice as common in psoriatic patients as it is in the general population, probably because of common inflammatory pathways. Moreover, it is the comorbidity with the highest number of reports evaluating the association of its prevalence in relation to the severity of psoriasis (9).

On the other hand, patients with HS have a higher frequency of diabetes mellitus and increased serum insulin and serum insulin growth factor. These metabolic alterations are thought to lead to over-sensitization of follicular androgen receptors in patients with HS, which has been speculated to influence the disease course. This association is further supported by observations that metformin may positively influence HS. Therefore, a low glycaemic load diet may be important not only for glucose control but also to promote weight loss in patients with HS (15).

- *Other cardiovascular risk factors*

Smoking, another classical CV risk factor, is also closely associated with hidradenitis suppurativa in both population-identified cases as well as hospital-based ones. The exact mechanism is unknown but an altered chemotaxis of polymorphic neutrophils possibly plays a role.

The association to disease severity and the effect of smoking cessation on long-term prognosis is less pronounced than in the case of obesity. Smoking cessation should nevertheless be encouraged in patients with HS (15).

Similarly, several studies confirm the association between psoriasis and other classical CV risk factors such as tobacco, HDL reduction and TG increase (9).

3.2. Cardiovascular events in psoriasis and hidradenitis suppurativa

A significantly increased risk of major adverse cardiovascular events -MACES- (myocardial infarction, ischemic stroke), and death associated with CV diseases has been found in patients with hidradenitis suppurativa and psoriasis after adjustment for confounding factors (23) such as smoking, obesity, hypertension and type 2 diabetes (24). Psoriasis has further been associated with an increased incidence of thromboembolism and arrhythmias (16). Meta-analyses conducted by Kevin Phan et al. or Bailey et al. discovered an increased odds of stroke between 1.22 and 1.74 in HS whereas in psoriasis the risk of major adverse cardiac events was estimated to range from 8% to 71% (11,17). In part, this association is due to the over-

representation of classical risk factors, but evidence indicates that psoriasis and HS themselves act as independent predisposing factors. In addition, the strength of association between HS and psoriasis with MACEs is greater in younger patients and it seems to decline with increasing age groups (17).

It has been identified a 58% (18) increased risk of cardiovascular-associated death in patients with HS compared with the risk in individuals with severe psoriasis in the absence of significant differences in the risk of first-time myocardial infarction or stroke between the two diseases. This may suggest that patients with HS have increased mortality after these adverse CV events. Consequently, the risk of CV disease in HS has been positioned alongside that of severe psoriasis, which is clinically well established and likely to be of the same magnitude as in people with diabetes mellitus (18).

In cohort studies, the largest increase in CV risk in HS has been observed in groups with the longest average follow-up time. Consequently, it has been hypothesized that the association between HS and CV risk may take several years, or even decades to manifest. Thus, duration of inflammation in patients who develop HS at an earlier age may also influence the risk of myocardial infarction and cerebrovascular accident (17).

In psoriasis, the risk of suffering from a MACE is greater in severely affected patients, as Samarasekera et al. observed in a meta-analysis which indicated that the hazard ratio of CV disease in these subjects was 1.57 (95% CI, 1.26–1.96) (16). A. Svedbom and M. Ståhle showed that psoriasis disease activity measured using the PASI is associated with CV events after controlling for shared risk factors. Each one-point increase in the PASI was independently associated with an increased risk of hospitalization for CV events of approximately 4% (6).

Additionally, Lu Liu et al. also found that CV morbidity was significantly increased in patients with mild psoriasis compared with non-psoriatic subjects, having adjusted for traditional CV disease risk factors (16).

The reason for the magnified CV risk in HS is that these patients have a greater systemic inflammatory load, with higher circulating leukocyte counts, C-reactive protein levels, TNF-α, C-reactive protein and IL-6 and diminished numbers of circulating endothelial progenitor cells (17,18). These laboratory findings have been associated with an independent risk of CV disease (18) by contributing to endothelial dysfunction and promoting oxidative stress which thus predisposes to atherosclerosis (17).

Additionally, increased expression of proinflammatory cytokines, such as interleukin 1b, IL-12, IL-17 and TNF-α have been identified in the skin of patients with HS. These cytokines are also known to be associated with atherosclerosis (11).

Vascular inflammation assessed via 18F-FDG PET/CT in patients with psoriasis suggests that the cumulative effects of low-grade chronic inflammation might accelerate vascular disease development (19). This supports that the potential mechanisms of this elevated CV risk could include the presence of circulating proinflammatory factors and endothelial activation, analogous to the situation noted in

HS (1) and other inflammatory diseases including rheumatoid arthritis, inflammatory bowel disease and periodontal disease which share inflammatory profiles and higher incidence of myocardial infarction and cerebrovascular accident (17).

3.3. Subclinical atherosclerosis in psoriasis and hidradenitis suppurativa

The inflammatory cells and proinflammatory cytokines implicated in the chronic inflammation observed in hidradenitis suppurativa and psoriasis may also promote the development of endothelial cell dysfunction and the subsequent development of accelerated atherogenesis which in its early stages will be asymptomatic (20). Atherosclerosis in asymptomatic individuals, also known as subclinical atherosclerosis (21), is suggested by indirect markers such as endothelial function and carotid intima-media thickness (CIMT). Endothelial function is assessed by evaluating flow-mediated dilation (FMD) with ultrasound in the brachial artery whereas CIMT is usually determined by using B-mode ultrasound technique in the common carotid artery (22). Having said this, a study found that a difference of 100 μm in CIMT increased the risk of a significant CV event by 13–18% and the presence of non-stenosing carotid plaques by 10–61% (23).

In a study, psoriatic patients had 2.79% reduction in brachial artery FMD and 0.11 mm thicker CIMT compared to controls. Interestingly, psoriatic arthritis had less impaired brachial artery FMD and thinner CIMT than total psoriatic patients(22). A cross-sectional study demonstrated that 30.2% of patients had atherosclerosis compared to 9.4% of controls ($p = 0.007$), judging by ultrasound study (23). Similarly, a systematic review concluded that patients with psoriasis and psoriatic arthritis had impaired endothelial function compared to the general population, as measured by pulse wave velocity and aortic stiffness parameters (22).

Moreover, two different studies have found an increased risk of carotid plaques in psoriatic arthritis (PsA) patients with the magnitude of this risk being OR 3.8 (95% CI 1.2– 12.5) and OR 3.12 (95% CI 1.03–9.39) (23). These data are consistent with a study carried out by Rosario Ibáñez-Bosch et al. who reported a higher frequency of carotid plaques and greater CIMT in patients with PsA adjusted for smoking and age which supports PsA as an independent CV risk factor. In this same study the prevalence of past CV events was the same compared to controls despite the increased frequency of carotid atheroma in patients with PsA. This may be because 45% of subjects were on biological treatment which is known to reduce CV risk probably by decreasing the inflammatory burden (23).

The presence of carotid plaques has also been observed to be 3-fold more frequent in subjects with moderate to very severe HS compared to matched control subjects (20).

The mean difference of impaired FMD or increased CIMT remains statistically significant for psoriatic subjects without other atherosclerotic risk factors such as BMI,

concomitant CV risk factors and age. Similarly, subgroup analysis in a study by Na Fang et al. demonstrated a CIMT increase in psoriatic patients after adjusting for BMI (22). Other study found a CIMT increase of 53.1 μm (0.4–105.6) having adjusted for age and smoking (23). These findings implied that the clustering of CV risk factors in psoriatic patients may amplify the effect of psoriasis on subclinical atherosclerosis (22).

On the other hand, the difference in CIMT between patients with HS and control subjects also remains significant after adjusting for smoking, obesity, age and sex. This suggests that HS itself may be an independent risk factor for atherosclerosis, regardless of the presence of classic CV disease risk factors (20).

Carotid plaques have been more commonly observed in patients with HS who had longer disease duration and more severe forms of the disease (20). Likewise, psoriatic patients with mean age >45 years appear to have greater CIMT than those younger than 45 years (22), being this association stronger in patients with PsA (23). On the contrary, the impaired brachial artery FMD is more pronounced in patients with mean age <45 years. Thus, impaired endothelial function might precede CIMT alterations. These findings reveal that determination of FMD may be recommended for psoriatic patients with mean age <45 years, whereas measurement of CIMT might be suitable for older patients (22).

3.4. Pathophysiology of atherosclerosis in psoriasis and hidradenitis suppurativa

The proposed concept of how severe psoriasis and hidradenitis suppurativa may be related to CV comorbidity is that the increased inflammatory burden of these conditions results in endothelial dysfunction and insulin resistance via TNF-α, IFN-γ, IL-23 and IL-17 which, in turn, increases the endothelial dysfunction which subsequently leads to atherosclerosis and major adverse CV events (MACEs)(24,25).

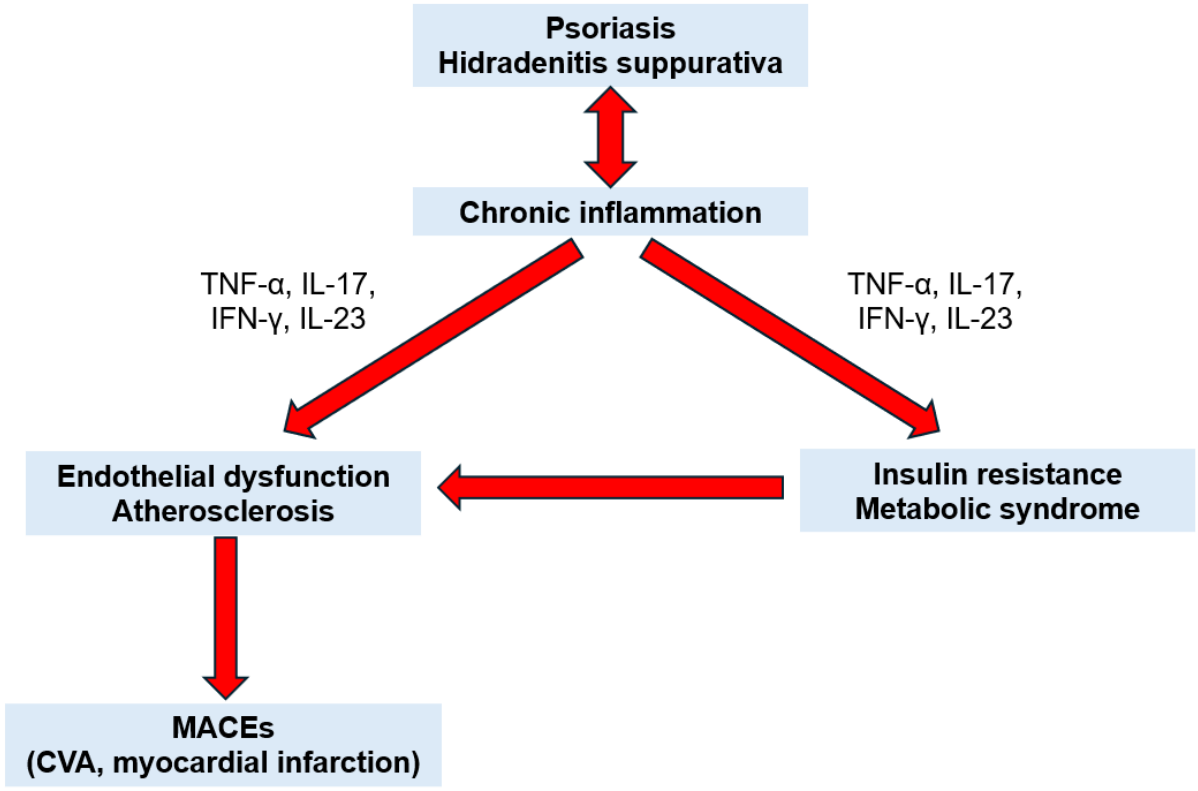

Figure 10. Pathophysiology of atherosclerosis in psoriasis and hidradenitis suppurativa

The increased inflammatory state of these patients is reflected on the elevated biomarkers of inflammation in peripheral blood, such as C-reactive protein (CRP) and vascular endothelial growth factor (VEGF), as well as adipokines, such as the insulin antagonists resistin and leptin, and indicators of platelet activation, such as P-selectin. In addition, visceral adipocytes represent a source of proinflammatory mediators, underlining the role of obesity as an aggravating factor for systemic inflammation(24).

Angiogenesis constitutes an important inflammatory response in psoriasis, while pro-angiogenic cytokines, including TNF-α, IL-8 and IL-17, seem to be involved in the pathogenesis of both psoriasis and atherosclerosis. VEGF, a major angiogenic growth factor, is overexpressed in psoriatic lesions, while this cytokine as well as its receptors have also been found to be expressed in atherosclerotic lesions of coronary arteries(24).

Moreover, the pathophysiology of psoriasis involves platelet activation which can be assessed by the expression of the surface antigen, p-selectin (CD62). P-selectin serves multiple proinflammatory roles and it has been found to be overexpressed in patients with psoriasis, exhibiting a significant correlation with the Psoriasis Area and

Severity Index (PASI) score, and to be further implicated in the shared immunological mechanisms between psoriasis and atherosclerosis(24).

Psoriasis and HS are characterised by Th1 and Th17 polarisation of the adaptive immune response. Th1 cells produce IFN-γ and TNF-α (24), which induce production of other proinflammatory cytokines and adhesion molecules as well as the activation of macrophages and vascular endothelial cells, leading to the development of atherosclerotic lesions (25), whereas Th17 cells secrete IL-17 and IL-22, promoting keratinocyte proliferation and angiogenesis(24).

The IL-17 receptor is known to be also expressed on vascular endothelial cells, where it is believed to promote the production of inflammatory cytokines such as granulocyte colony stimulating factor (GCSF) and IL-6 (25), that promotes neoangiogenesis, intensification of inflammation, degradation of the collagen fibrous cap and finally, destabilisation and rupture of the atherosclerotic plaque. This proatherogenic effect of IL-17 is supported by the reduction of CV risk reported in patients with psoriasis treated with IL-17 inhibitors(24).

However, IL-17 has been implicated to have anti-atherogenic effects too (25). For instance, this cytokine apparently stabilises the atherosclerotic plaque (25) since low serum IL-17A has been associated with recurrent major CV events and increased mortality in patients with acute myocardial infarction, suggesting a protective role of IL-17A (24).

- *Insulin resistance*

According to what has already been discussed, hidradenitis suppurativa and psoriatic patients are specially prone to develop CV risk factors such as metabolic syndrome, obesity, hyperglycaemia, low HDL-cholesterol levels and raised systolic and diastolic blood pressure (26). Normal glucose-tolerant patients with moderate to severe psoriasis have significantly reduced insulin sensitivity compared with age-, gender- and body mass index matched control subjects judging by the hyperinsulinemic euglycemic clamp (a technique considered to be the gold standard for quantifying whole-body insulin sensitivity in vivo) (27). Similarly, after adjustment for BMI, age and sex, the HOMA-IR value (the most widespread technique to assess insulin resistance) remains significantly higher in HS patients than in controls. This suggests that psoriasis and HS themselves may be independent risk factors for the development of insulin resistance (26).

Having said this, one explanation for the association of HS and psoriasis with insulin resistance and metabolic syndrome are thought to involve certain common genetic background (27). Moreover, the augmented incidence of insulin resistance among these patients could be due to chronic inflammation (26) which is reflected on the elevated levels of C-reactive protein, which has been linked to increased risk of type 2 diabetes in a recent meta-analysis (27).

In this regard, insulin resistance is thought to occur due to the persistent secretion of several proinflammatory cytokines, such as TNF-α and IL-6 which has been shown to induce insulin resistance in hepatocytes. TNF-α is considered nowadays one of the major pathogenic factors for HS as demonstrated by the efficacy of the anti- TNF-α agent adalimumab in the treatment of this disease. Furthermore, it is known that TNF-α plays a key role in the impairment of glucose tolerance and insulin sensitivity. Thus, TNF-α is able to induce insulin signalling defects by acting on adipocytes and muscle cells, impair insulin signalling through inhibition of tyrosine kinase activity of the insulin receptor and suppress adiponectin secretion from adipocytes, an anti-inflammatory molecule that also regulates insulin sensitivity and that is known to be diminished in HS patients (26).

The aforementioned cytokines are also implicated in the pathogenesis of cardiometabolic comorbidities(24). Some of these factors, such as hypertension (25), obesity (24), hypercholesterolemia (25) and insulin resistance will in turn contribute to endothelial dysfunction (26). In the case of insulin resistance, it has been proven to induce endothelial dysfunction by activating the pro-atherogenic mitogen-activated protein kinase (MAPK) pathway in endothelial cells and by inducing nitric oxide dependent vasodilatation. As a result, the imbalance between vasodilating and vasoconstricting substances could lead to an abnormal response to physical and chemical stimuli, which characterises endothelial dysfunction and constitutes an early feature of the atherosclerotic process (24) which will subsequently lead to long-term clinical events, such as myocardial infarction or stroke (26).

Finally, other conditions normally accompanying psoriasis and HS such as hypertriglyceridemia or smoking have been demonstrated to constitute independent risk factors for insulin resistance development. In fact, a report from the US Department of Health and Human Services concluded that the risk of developing type 2 diabetes is up to 40% higher among smokers than non-smokers (27).

On the other hand, it is also noteworthy that several studies have shown that metformin, an antihyperglycemic agent used for treating type 2 DM, could be beneficial in the treatment of HS. Metformin decreases hepatic glucose production and improves insulin sensitivity by increasing peripheral glucose uptake and utilisation. Although metformin in HS acts by a mechanism yet unknown, it has been suggested that the beneficial effects of this drug might be, at least in part, through lowering the insulin resistance that is present in some patients with inflammatory diseases (26).

3.5. Underestimation of cardiovascular risk in psoriatic and hidradenitis suppurativa patients

The four mostly used CV risk assessment tools, including Framingham Risk Score (FRS), QRISK2, SCORE and ASCVD were developed for the CV risk stratification of the general population. Thereby, they just take into account traditional CV risk factors and fail to include inflammatory biomarkers despite atherosclerosis being an

inflammatory disease. Among all four CV risk assessment tools, only rheumatoid arthritis is included as one of the CV risk factors in QRISK2 (28).

This is why the preset cutoff values of all scores underestimate the risk of subclinical atherosclerosis present in subjects suffering from either hidradenitis suppurativa or severe psoriatic patients (28), not accounting for the excess risk attributable to such conditions(29).

The correlation of subclinical atherosclerosis and high CV risk is well recognized. In studies based on the general population, the 10-year risk of coronary heart disease ranged from 11% to 25% in patients with carotid plaque or increased intima-media thickness, while in patients without subclinical atherosclerosis, it ranged only from 1% to 8% (28).

When using CV risk assessment tools and applying the standard cutoff values (FRS > 10%, QRISK2 > 20%, SCORE > 5%, ASCVD > 7.5%), 55.9%, 98.2%, 89.1 and 56.4% of the patients with subclinical atherosclerosis were classified as “low risk” according to FRS, QRISK2, SCORE and ASCVD, respectively. This demonstrates the poor discriminating ability of the 4 scores in classifying psoriatic and HS patients and reflects the need for lower cutoff values (28).

Methta et al. found that severe psoriasis confers an attributable risk of major adverse cardiac events of 6.2% on 10-year follow up. Considering this attributable risk, in a cohort of severe psoriatic patients without psoriatic arthritis, it was observed that a considerable proportion of patients was reclassified to a higher risk category and that 28% and 42% of the patients considered well treated for hypertension and hypercholesterolemia, respectively, were undertreated if considering their new CV risk category. Moreover, and of more importance, it had implications in the correct primary prevention of CV disease, as a significant proportion of severely psoriatic patients may be at coronary heart disease equivalent risk and not being managed as such (29).

In summary, due to this higher risk attributable to HS and psoriasis, probably owing to systemic inflammation, these patients should be more aggressively treated and controlled for their CV risk factors. Current treatment goals for CV risk factors, such as hypertension and hypercholesterolemia, may be inappropriate for patients with severe psoriasis and should be reevaluated for such patients, similarly to what has been done for rheumatoid arthritis patients with the recent European League Against Rheumatism evidence-based recommendations on managing CV risk in patients with rheumatoid arthritis and psoriatic arthritis (29).

3.6. Impact of biologics on cardiovascular risk

Inflammation is part of atherosclerosis pathogenesis as it can be deduced from the fact that inflammatory diseases such as hidradenitis suppurativa and psoriasis have a

disproportional rate of CV events compared to age and gender matched counterparts (30).

Thus, by controlling inflammation in psoriasis or HS it could also be tackled the excessive CV risk of these patients. Following this principle, a study followed a sample of psoriasis patients for one year after any treatment, and a 6% decrease in aortic vascular inflammation was observed (30). Similarly, oral agents and phototherapy are also associated with a statistically significant reduction of 46% in myocardial infarction risk compared to the use of topical agents for psoriasis (31). In regards to conventional systemic antipsoriatic treatment, the greatest reduction in CV risk has been attributed to methotrexate, followed by retinoid and cyclosporine (32). Moreover, Prodanovich and Ahlehoff both concluded that the use of methotrexate had beneficial effects on the CV outcome of patients with severe psoriasis. Methotrexate has also proved to improve inflammatory markers (33–35)

However, the most promising treatment for reducing CV comorbidities in psoriatic and HS patients are the so called biologics which have been shown to reduce coronary inflammation assessed as perivascular fat attenuation index. Furthermore, biologics can also decrease the intima–media thickness, an indicator of subclinical atherosclerotic plaque development (25). In fact, Hong et al. reported a lower CV risk in patients who received biologics as compared to those who were treated with other antipsoriatic therapies (36). Moreover, Bo Ri Kim et al. revealed, in a case–control study, an inversely proportional association between systemic antipsoriatic therapy duration and cardio-cerebrovascular disease risk in psoriatic patients after adjusting for age, sex, diabetes, hypertension and dyslipidaemia. These results implied that long-term control of psoriasis can decrease cardio-cerebrovascular disease development in psoriatic patients. In this regard, long-term sustained control of psoriasis could reduce the cumulative effect of systemic inflammation observed in psoriasis patients (32). Youssef A. Elnabawi et al. demonstrated in an observational study a favourable modulation in coronary artery plaque disease indices by coronary computed tomography angiography in a sample of severe psoriasis patients treated with anti- TNF-α, anti-IL12/23 or anti-IL-17, compared with those not treated with biologic therapy. In those treated with biological therapy, they found that lipid-rich plaque and necrotic cores decreased following therapy (30). Therefore, anti-inflammatory therapy targeting TNF-α, IL-23 and IL-17, the main pathological factors in psoriasis and HS, can potentially contribute to the reduction of CV disease risk (25).

The following paragraphs will address the different effects of TNF-α and IL-17 inhibitors:

3.6.1. TNF-α inhibitors

- *Inflammatory markers modifications*

Recently, Wu et al. showed that the use of TNF-α inhibitors concomitantly with methotrexate in patients with psoriasis and psoriatic arthritis was associated with a clinical and significant reduction in C-reactive protein compared with those treated with methotrexate alone (37). These findings were corroborated by Strober et al. who found that C-reactive protein levels were significantly reduced after 12 weeks of etanercept therapy. This finding is of paramount importance given that an elevated level of C-reactive protein is associated with an increased risk of myocardial infarction (38). On the other hand, in another study by Wu et al., no significant difference in cholesterol level was found between psoriatic patients treated with TNF-α inhibitors and methotrexate compared to those treated with methotrexate only (39).

Other beneficial effects of TNF-α inhibitors are the reduction of other inflammatory parameters such as erythrocyte sedimentation rate (40), IL-6, TNF-α (41) and glycoprotein acetylation (30).

In addition, by inhibiting proinflammatory cytokines involved in insulin regulation, lipid metabolism and body weight homeostasis, TNF-α blockers reduce the prevalence of metabolic syndrome (40).

- *Insulin resistance*

TNF-α production is known to be increased under chronic hyperglycaemia. Moreover, it has ominous effects on insulin sensitivity as it has been observed in obesity and diabetes through its ability to decrease the tyrosine kinase activity of the insulin receptor. It also directly prevents insulin-mediated glucose uptake in the skeletal muscle (42).

Thus, it is not surprising that TNF-α inhibitors have been reported to be effective in treating insulin resistance in psoriasis patients (25). This was confirmed by a study which proved that non-diabetic patients with moderate to severe psoriasis on treatment with adalimumab experienced an improvement of insulin sensitivity(42). Marra et al. (43) and Dalia Shaaban and Nawaf Al-Mutairi (44) also had similar findings regarding increase of insulin sensitivity in case of treatment with etanercept and the combination of MTX and TNF-α inhibitors, respectively. Furthermore, Martínez López et al. showed how patients under anti- TNF-α treatment improved their insulin levels (45).

Additionally, the risk of incident diabetes mellitus is also apparently diminished in TNF-α inhibitor psoriasis patients compared to those treated with non-biological drugs, as Solomon et al. recently reported (31).

Since it is widely accepted that TNF-α inhibition therapy improves insulin metabolism, this class of therapy may affect atherosclerotic risk via this mechanism as well (31).

- *Cardiovascular risk*

Introduction of the TNF-α inhibitors therapy with infliximab, etanercept and adalimumab has intensely enhanced the outcome of severe psoriasis further than that achieved with traditional systemic drugs (44). While most meta-analyses agree with this, one large study from the US failed to demonstrate a significant difference in the rate of clinical CV events among psoriatic patients receiving TNF-α inhibitors (46).

Ahlehoff et al found that among a psoriasis cohort with severe psoriasis, TNF-α inhibitors were associated with significantly lower risk of death, myocardial infarction and stroke compared with those treated with non-biologic, non-methotrexate, anti-inflammatory medications (35). This reduction in CV events, mainly myocardial infarction, has been reported to vary between 50 and 86% compared with psoriasis patients treated with topical agents (31,44,47).

Interestingly, this risk reduction will depend on the clinical response to TNF-α inhibitors therapy. This was noticed in a study in which patients treated with TNF-α inhibitors were categorised into two categories, “responders” and “non-responders”, according to the change in PASI score from baseline. In psoriasis patients who responded to TNF-α inhibitor therapy, the risk of myocardial infarction was reduced by more than half compared to non-responders (44).

However, the longer duration of TNF-α inhibitors therapy has not been associated with significantly lower risk of myocardial infarction compared with shorter treatment duration (44).

It seems that treatment with TNF-α inhibitors and oral agents/ phototherapy has stronger protective effects in the group older than 60 years compared with the group 60 years and younger. One reason for this is that older patients are more likely to have type 2 diabetes mellitus and the benefits of TNF-α inhibitors may be mediated through improving the risk of type 2 diabetes mellitus (31).

- *Endothelial dysfunction and subclinical atherosclerosis*

TNF-α contributes to microvascular dysfunction through various mechanisms. It blocks the activation of endothelial nitric oxide synthase (eNOS), degrades eNOS mRNA, alters vasomotor function acting on vascular smooth muscle cells and induces oxidative stress by increasing the production of reactive oxygen species. The inhibition of these detrimental effects of TNF-α, together with a lower systemic inflammation, as evidenced by a significant decline in the inflammatory biomarkers may be the reasons for the improved microvascular function that has been observed after treatment with TNF-α inhibitors (48).

It has also been emphasised the importance of comorbidities and proinflammatory state in the development of heart failure with preserved ejection fraction. TNF-α effects may explain the diastolic dysfunction observed by Stefano Piaserico et al. and specially, its recovery with TNF-α inhibitors treatment. In line with this hypothesis, psoriasis could be counted among the comorbidities contributing to systemic inflammation and oxidative stress in the coronary microvascular endothelium and, finally, to myocardial fibrosis and diastolic dysfunction (48).

As it has previously been mentioned, subclinical atherosclerosis can be assessed by flow mediated dilation (FMD), pulse wave velocity and intima-media thickness, among other techniques. The three parameters have been confirmed to improve with TNF-α inhibitors. For instance, patients with moderate to severe psoriasis experienced an increase in FMD after 6 months of therapy and a decrease in arterial wall stiffness characterised using pulse wave velocity (42). Nonetheless, in an observational study, some patients under TNF-α inhibitors did not experience a coronary microvascular function improvement and others remained with a reduced coronary flow reserve. The fact that in these patients the duration of a severe grade of psoriasis was longer, suggests that the pathologic process may be at least partially irreversible due to microvascular structural remodelling, as demonstrated in other diseases such as hypertension. Consequently, the effect of TNF-α inhibitors treatment to restore coronary microvascular function observed in many patients clearly indicates that, at least in the earlier stages of the disease, coronary microvascular dysfunction may still be a reversible phenomenon (48).

In parallel with this, TNF-α antagonist therapy accounted for a significant reduction of carotid intima-media thickness (CIMT) in a series of 16 patients with severe psoriasis (42). This is consistent with other studies that also documented the efficacy of TNF-α blockers to be lightly related to treatment duration which is consistent with a progressive effect of inflammation on the CIMT (40). According to Sánchez-Díaz et al., those patients with less severe disease, those with classical CV risk factors (such as glycaemic disorders, diabetes mellitus, high blood pressure, higher BMI or tobacco consumption) and those with higher burden of subclinical atherosclerosis would be more likely to improve their intima–media thickness under adalimumab treatment. On the contrary, those patients with higher inflammatory load after treatment could be more prone to have a lack of improvement of intima–media thickness (49).

In addition, TNF-α inhibitor therapy has been associated with improvement in aortic vascular inflammation and reduced progression of carotid plaques independently of

traditional CV risk factors. Lastly, it is worth saying that the association between TNF-α inhibitors and carotid plaque progression was stronger in men than in women (50).

- *Inconvenients*

Anti- TNF-α therapy is commonly accepted as the first line biologic agent for the management of psoriasis; however, some of the patients on this treatment do not have adequate response and do not experience a reduction in vascular inflammation. In psoriasis, TNF-α inhibitors have also been linked to worsening of cardiometabolic risk factors, including weight gain and a shift in apolipoprotein B (30).

3.6.2. IL-17 inhibitors

Apart from TNF-α, the other main driver of psoriasis and hidradenitis suppurativa systemic inflammation is IL-17 which is why therapeutic prospects now focus as well on IL-17 blockade.

In 2019, the CARIMA (Evaluation of Cardiovascular Risk Markers in Psoriasis Patients Treated with Secukinumab) study found a significant increase in absolute flow mediated dilation of 2.1% in patients treated with secukinumab for 52 weeks, which was comparable to those in volunteers without psoriasis. Improvements in skin lesions become evident with secukinumab at 12 weeks of treatment, which suggests that changes in the vessel wall and endothelial function occur later than those observed in the skin. This study also showed a great impact on the perivascular fat attenuation index and pulse wave velocity between psoriasis patients and control individuals while no proatherogenic vessel wall changes or alterations in CV biomarkers were reported (25,41,51).

Another prospective study found significant improvements in carotid-brachial-femoral intima media thickness following secukinumab or ixekizumab therapy. In half of the studied population, non-calcified plaques had also reduced to below-measurable sizes (51) which is a similar result to that of Hitoshi Terui and Yoshihide Asano in 2023 (25) or Youssef A. Elnabawi in 2018 (30). Nevertheless, the treatment had no effect on calcified plaques which is consistent with the results of other similar studies that could just assess improvements in non-calcified plaques (51).

Moreover, IL-17A blockade has been shown to reduce peripheral oxidative stress levels, proinflammatory cytokines (25) and the vascular inflammation (30) that impairs endothelial vasodilatory capacity (41).

Murine model studies have also suggested that IL-17 increases monocyte adhesion to the vascular walls, promoting inflammatory cytokine production and endothelial dysfunction, with this phenomenon being normalised by IL-17A blockade (30).

4. Conclusions

The increased inflammatory burden of psoriasis and HS results in endothelial dysfunction and insulin resistance via TNF-α, IFN-γ, IL-23 and IL-17 which, in turn, increases endothelial dysfunction and subsequently leads to an accelerated and premature development of subclinical atherosclerosis. This makes these patients suffer from an increased risk of major adverse cardiovascular events (MACEs).

In addition, traditional CV risk assessment tools fail to assess inflammatory conditions as independent CV risk factors and therefore, they underestimate this risk in psoriatic and hidradenitis suppurativa patients.

Lastly, in the last years there is an increasing bibliography supporting the beneficial effect of TNF-α and IL-17 inhibitors in reducing systemic inflammation and with it, subclinical atherosclerosis progression, endothelial dysfunction and myocardial infarction risk while improving the microvascularization.

5. References

1. Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet. 2007 Jul 21;370(9583):263-271. doi: 10.1016/S0140-6736(07)61128-3. PMID: 17658397.
2. Griffiths CEM, Armstrong AW, Gudjonsson JE, Barker JNWN. Psoriasis. Lancet. 2021 Apr 3;397(10281):1301-1315. doi: 10.1016/S0140-6736(20)32549-6. PMID: 33812489.
3. Rendon A, Schäkel K. Psoriasis pathogenesis and treatment. Int J Mol Sci. 2019;20.
4. Tokuyama M, Mabuchi T. New treatment addressing the pathogenesis of psoriasis. Int J Mol Sci. 2020;21:1–16.
5. Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis. J Am Acad Dermatol. 2020;82:1045–58.
6. van Straalen KR, Prens EP, Gudjonsson JE. Insights into hidradenitis suppurativa. J Allergy Clin Immunol. 2022 Apr;149(4):1150–61.
7. Macca L, Li Pomi F, Ingrasciotta Y, Morrone P, Trifirò G, Guarneri C. Hidradenitis suppurativa and psoriasis: the odd couple. Front Med. 2023;10.
8. Richette P, Molto A, Viguier M, Dawidowicz K, Hayem G, Nassif A, et al. Hidradenitis suppurativa associated with spondyloarthritis - Results from a multicenter national prospective study. J Rheumatol. 2014;41(3):490–4.
9. Kampe T, Dorko E, Rimárová K, Houžvičková A, Baloghová J, Baranová Z, et al. Prevalence of cardiovascular risk factors in patients with psoriasis. Cent Eur J Public Health. 2022;30:S5–10.
10. Liu L, Cai XC, Sun XY, Zhou YQ, Jin MZ, Wang J, et al. Global prevalence of metabolic syndrome in patients with psoriasis in the past two decades: current evidence. J Eur Acad Dermatol Venereol. 2022;36:1969–79.
11. Phan K, Ng WHS, Lai B, Garg A, Smith SD. Hidradenitis suppurativa and association with stroke: systematic review and meta-analysis. J Dermatolog Treat. 2022;33(4):2309–16.
12. Phan K, Charlton O, Smith SD. Hidradenitis suppurativa and metabolic syndrome – systematic review and adjusted meta-analysis. Int J Dermatol. 2019;58:1112–7.
13. Miller IM, McAndrew RJ, Hamzavi I. Prevalence, Risk Factors, and Comorbidities of Hidradenitis Suppurativa. Dermatol Clin. 2016;34:7–16.
14. Kromann CB, Ibler KS, Kristiansen VB, Jemec GBE. The influence of body weight on the prevalence and severity of hidradenitis suppurativa. Acta Derm Venereol. 2014;94(5):553–7.
15. Tzellos T, Zouboulis CC, Gulliver W, Cohen AD, Wolkenstein P, Jemec GBE. Cardiovascular disease risk factors in patients with hidradenitis suppurativa: A systematic review and meta-analysis of observational studies. Br J Dermatol. 2015;173:1142–55.
16. Liu L, Cui S, Liu M, Huo X, Zhang G, Wang N. Psoriasis Increased the Risk of Adverse Cardiovascular Outcomes: A New Systematic Review and Meta-Analysis of Cohort Study. Front Cardiovasc Med. 2022;9.
17. Reddy S, Strunk A, Jemec GBE, Garg A. Incidence of Myocardial Infarction and Cerebrovascular Accident in Patients with Hidradenitis Suppurativa. JAMA Dermatol. 2020;156(1):65–71.

18. Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. JAMA Dermatol. 2016;152(4):429–34.
19. Egeberg A, Skov L, Joshi AA, Mallbris L, Gislason GH, Wu JJ, et al. The relationship between duration of psoriasis, vascular inflammation, and cardiovascular events. J Am Acad Dermatol. 2017;77(4):650-656.e3.
20. González-López MA, Hernández JL, Lacalle M, Mata C, López-Escobar M, López-Mejías R, et al. Increased prevalence of subclinical atherosclerosis in patients with hidradenitis suppurativa (HS). J Am Acad Dermatol. 2016;75(2):329–35.
21. Mendieta G, Pocock S, Mass V, Moreno A, Owen R, García-Lunar I, et al. Determinants of Progression and Regression of Subclinical Atherosclerosis Over 6 Years. J Am Coll Cardiol. 2023 Nov 28;82(22):2069–83.
22. Fang N, Jiang M, Fan Y. Association between Psoriasis and Subclinical Atherosclerosis. Medicine (United States). 2016;95.
23. Ibáñez-Bosch R, Restrepo-Velez J, Medina-Malone M, Garrido-Courel L, Paniagua-Zudaire I, Loza-Cortina E. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients: a study based on carotid ultrasound. Rheumatol Int. 2017;37(1):107–12.
24. Tsiogka A, Gregoriou S, Stratigos A, Soulaidopoulos S, Rompoti N, Panagakis P, et al. The Impact of Treatment with IL-17/IL-23 Inhibitors on Subclinical Atherosclerosis in Patients with Plaque Psoriasis and/or Psoriatic Arthritis: A Systematic Review. Biomedicines. 2023;11.
25. Terui H, Asano Y. Biologics for Reducing Cardiovascular Risk in Psoriasis Patients. J Clin Med. 2023;12.
26. Vilanova I, Hernández JL, Mata C, Durán C, García-Unzueta MT, Portilla V, et al. Insulin resistance in hidradenitis suppurativa: a case–control study. J Eur Acad Dermatol Venereol. 2018 May 1;32(5):820–4.
27. Gyldenløve M, Storgaard H, Holst JJ, Vilsbøll T, Knop FK, Skov L. Patients with psoriasis are insulin resistant. J Am Acad Dermatol. 2015 Apr 1;72(4):599–605.
28. Shen J, Lam SH, Shang Q, Wong CK, Li EK, Wong P, et al. Underestimation of risk of carotid subclinical atherosclerosis by cardiovascular risk scores in patients with psoriatic arthritis. J Rheumatol. 2018 Feb 1;45(2):218–26.
29. Torres T, Sales R, Vasconcelos C, Martins Da Silva B, Selores M. Framingham Risk Score underestimates cardiovascular disease risk in severe psoriatic patients: Implications in cardiovascular risk factors management and primary prevention of cardiovascular disease. J Dermatol. 2013 Nov;40(11):923–6.
30. Elnabawi YA, Dey AK, Goyal A, Groenendyk JW, Chung JH, Belur AD, et al. Coronary artery plaque characteristics and treatment with biologic therapy in severe psoriasis: Results from a prospective observational study. Cardiovasc Res. 2019 Mar 15;115(4):721–8.
31. Wu JJ, Poon KYT, Channual JC, Shen AYJ. Association between tumor necrosis factor inhibitor therapy and myocardial infarction risk in patients with psoriasis. Arch Dermatol. 2012 Nov;148(11):1244–50.
32. Kim BR, Lee KH, Kim J, Kim JW, Paik K, Myung W, et al. Association between cardio-cerebrovascular disease and systemic antipsoriatic therapy in psoriasis patients using population-based data: A nested case–control study. J Dermatol. 2023 Nov 1;50(11):1442–9.
33. Prodanovich S, Ma F, Taylor JR, Pezon C, Fasihi T, Kirsner RS. Methotrexate reduces incidence of vascular diseases in veterans with psoriasis or rheumatoid

arthritis. J Am Acad Dermatol. 2005 Feb;52(2):262-7. doi: 10.1016/j.jaad.2004.06.017. Erratum in: J Am Acad Dermatol. 2005 Apr;52(4):670. Prodanowich, Srdjan [corrected to Prodanovich, Srdjan]. PMID: 15692471.
34. Ahlehoff O, Skov L, Gislason G, Gniadecki R, Iversen L, Bryld LE, et al. Cardiovascular outcomes and systemic anti-inflammatory drugs in patients with severe psoriasis: 5-year follow-up of a Danish nationwide cohort. J Eur Acad Dermatol Venereol. 2015 Jun 10;29(6):1128–34.
35. Ahlehoff O, Skov L, Gislason G, Lindhardsen J, Kristensen SL, Iversen L, et al. Cardiovascular disease event rates in patients with severe psoriasis treated with systemic anti-inflammatory drugs: a Danish real-world cohort study. J Intern Med. 2013 Feb 11;273(2):197–204.
36. Hong JR, Jeong H, Kim H, Yang HS, Hong JY, Kim SM, et al. The potential impact of systemic anti-inflammatory therapies in psoriasis on major adverse cardiovascular events: a Korean nationwide cohort study. Sci Rep. 2021 Apr 21;11(1):8588.
37. Wu JJ, Rowan CG, Bebchuk JD, Anthony MS. Association between tumor necrosis factor inhibitor (TNFi) therapy and changes in C-reactive protein (CRP), blood pressure, and alanine aminotransferase (ALT) among patients with psoriasis, psoriatic arthritis, or rheumatoid arthritis. J Am Acad Dermatol. 2015 May;72(5):917–9.
38. Strober B, Teller C, Yamauchi P, Miller JL, Hooper M, Yang YC, et al. Effects of etanercept on C-reactive protein levels in psoriasis and psoriatic arthritis. Br J Dermatol. 2008 Aug;159(2):322–30.
39. Wu JJ, Rowan CG, Bebchuk JD, Anthony MS. Total cholesterol, lipoprotein, and triglyceride levels in tumor necrosis factor inhibitor-treated patients with psoriasis, psoriatic arthritis, or rheumatoid arthritis. Int J Dermatol. 2015 Oct 31;54(10).
40. Di Minno MND, Iervolino S, Peluso R, Scarpa R, Di Minno G. Carotid intima-media thickness in psoriatic arthritis: Differences between tumor necrosis factor-α blockers and traditional disease-modifying antirheumatic drugs. Arterioscler Thromb Vasc Biol. 2011 Mar;31(3):705–12.
41. von Stebut E, Reich K, Thaçi D, Koenig W, Pinter A, Körber A, et al. Impact of Secukinumab on Endothelial Dysfunction and Other Cardiovascular Disease Parameters in Psoriasis Patients over 52 Weeks. J Invest Dermatol. 2019 May 1;139(5):1054–62.
42. Pina T, Corrales A, Lopez-Mejias R, Armesto S, Gonzalez-Lopez MA, Gómez-Acebo I, et al. Anti-tumor necrosis factor-alpha therapy improves endothelial function and arterial stiffness in patients with moderate to severe psoriasis: A 6-month prospective study. J Dermatol. 2016 Nov 1;43(11):1267–72.
43. Marra M, Campanati A, Testa R, Sirolla C, Bonfigli AR, Franceschi C, et al. Effect of Etanercept on Insulin Sensitivity in Nine Patients with Psoriasis. Int J Immunopathol Pharmacol. 2007 Oct 23;20(4):731–6.
44. Shaaban D, Al-Mutairi N. The effect of tumor necrosis factor inhibitor therapy on the incidence of myocardial infarction in patients with psoriasis: a retrospective study. J Dermatolog Treat. 2018 Jan 2;29(1):3–7.
45. Martinez-Lopez A, Blasco-Morente G, Perez-Lopez I, Tercedor-Sanchez J, Arias-Santiago S. Studying the effect of systemic and biological drugs on intima-media thickness in patients suffering from moderate and severe psoriasis. J Eur Acad Dermatol Venereol. 2018 Sep 30;32(9):1492–8.

46. Abuabara K, Lee H, Kimball AB. The effect of systemic psoriasis therapies on the incidence of myocardial infarction: a cohort study. Br J Dermatol. 2011 Nov 1;165(5):1066–73.
47. Sherer Y, Shoenfeld Y. Mechanisms of Disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol. 2006 Feb;2(2):99–106.
48. Piaserico S, Osto E, Famoso G, Zanetti I, Gregori D, Poretto A, et al. Treatment with tumor necrosis factor inhibitors restores coronary microvascular function in young patients with severe psoriasis. Atherosclerosis. 2016 Aug 1;251:25–30.
49. Sánchez-Díaz M, Salvador-Rodríguez L, Cuenca-Barrales C, Arias-Santiago S, Molina-Leyva A. Potential Predictors of Cardiovascular Risk Improvement in Patients with Hidradenitis Suppurativa Treated with Adalimumab: A Pivotal Study of Factors Associated with Carotid Intima–Media Thickness Reduction. Dermatol Ther (Heidelb). 2023 Mar 1;13(3):817–26.
50. Eder L, Joshi AA, Dey AK, Cook R, Siegel EL, Gladman DD, et al. Association of Tumor Necrosis Factor Inhibitor Treatment With Reduced Indices of Subclinical Atherosclerosis in Patients With Psoriatic Disease. Arthritis Rheumatol. 2018 Mar 1;70(3):408–16.
51. Piros ÉA, Szabó Á, Rencz F, Brodszky V, Szalai K, Galajda N, et al. Impact of interleukin-17 inhibitor therapy on arterial intima-media thickness among severe psoriatic patients. Life. 2021 Sep 1;11(9).

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