INTRODUCTION

Hidradenitis suppurativa (HS) has traditionally been considered as a disorder of the apocrine glands where the suppurative process was associated with the apocrine sweat glands, and this conclusion was based purely on the characteristic distribution of the condition ***(Verneuil, 1854).*** Also, HS was identified as a deep-seated inflammatory suppurative disease of the apocrine sweat glands ***(Brunsting, 1939)***.

Hidradenitis suppurativa is a chronic, recurrent, debilitating disease that presents with painful, inflammed lesions in the apocrine-gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital areas ***(Shah, 2005).***

Although skin diseases are often immediately visible to both patients and society and the morbidity they cause is only poorly defined, hidradenitis suppurativa (HS) leads to painful eruptions and malodorous discharge and cause a high degree of morbidity, with the highest scores obtained for the level of pain caused by the disease ***(von der Werth and Jemec, 2001).***

Hidradenitis suppurativa predominantly affects women more than men and its aetiology is unclear but there are many suggested causes such as occlusion of the

pilosebaceous apparatus, bacterial infections, obesity, excessive sweating, and cigarette smoking as predisposing factors ***(Parks and Parks, 1997).***

Fitzsimmons et al. (1985) speculated that there may be an autosomal dominance inheritance pattern of hidradenitis suppurativa. Over one quarter of patients related a family history of the disease. ***(Von Der Werth and Williams, 2000).*** Although ***Mortimer et al. (1986)*** found higher plasma concentrations of androgens in women with HS; others have been unable to verify those findings ***(Barth et al., 1996).*** In addition, a link between Crohn's disease and HS has been suggested ***(Churc et al., 1993; Roy et al., 1997; Martínez et al., 2001).***

The association of HS with Crohn's disease has been postulated that these two conditions may share the same pathogenesis with the possible involvement of similar immune mechanisms, such as the proliferation of tumor necrosis factor-α (TNF-α) with resultant neutrophilic chemotaxis ***(Katsanos et al., 2002 and Tsianos et al., 1995).***

Tumor necrosis factor-alpha (TNF-α) is a multifunctional cytokine that mediates inflammation, immune response and apoptosis. It is produced by monocytes and macrophages and exerts host-damaging effects in different autoimmune and inflammatory diseases. Inappropriate production or persistent activation

of TNF-α participates in a wide spectrum of diseases, including septic shock, diabetes, cancer, graft rejection, rheumatoid arthritis, Crohn's disease, psoriasis, pyoderma gangrenosum, and Behcet's syndrome. In skin, TNF-α is the master cytokine regulator in inflammatory diseases ***(Banno et al., 2004).***

In hidradenitis suppurativa, TNF-α induces proinflammtory cytokines and activates neutrophils and lymphocytes, also recruits inflammatory cells to the site of inflammation, thus, it contributes to granuloma formation. It may there for play an important role in HS pathogenesis ***(Fardet et al., 2007).***

AIM OF THE WORK

The aim of this work is to estimate the serum levels of tumor necrosis factor alpha (TNF-α) in patients with hidradenitis suppurativa, to assess its possible role in HS pathogenesis and to correlate such levels with the disease severity.

Chapter 1

1.1. MICRO ANATOMY AND PHYSIOLOGY OF APOCRINE GLANDS

Sweat glands are small glands that secrete sweat, situated in the dermis of the skin (Fig 1). There are two types of sweat glands, eccrine sweat glands and apocrine sweat glands. They are developed in the fourth and fifth month of intrauterine life. In the embryo, they are present over the entire skin surface, but most glands subsequently disappear ***(Coulson, 2008).***

Eccrine and apocrine sweat glands are controlled by the sympathetic nervous system. These glands differ from each other in many aspects such as; the size, the age that they become active and the composition of the sweat that they make. In Comparison between eccrine and apocrine glands, the eccrine glands are smaller, active from birth and produce a sweat that is free of proteins and fatty acids ***(Foltynski et al., 2004).***

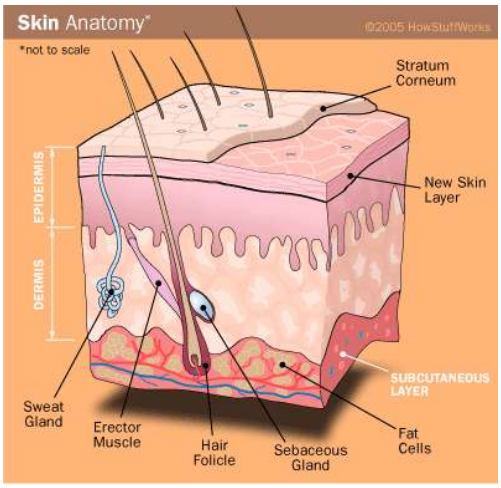

Figure (1): Sweat glands have a simple coiled tubular structur and discharge sweat by tiny openings in the surface of the skin ***(Folk and Semken, 1991)***

Eccrine sweat glands are distributed over the entire body surface except the lips, external ear canal, and labia minora and they are particularly abundant on the palms of hands, soles of feet, and on the forehead. They produce sweat that is composed chiefly of water with various salts. These glands are used for body temperature regulation ***(Foltynski et al., 2004)***. Each gland consists of a coiled secretory intradermal portion that connects to the epidermis via a relatively straight distal duct (Fig 2) ***(Kreyden et al., 2002).***

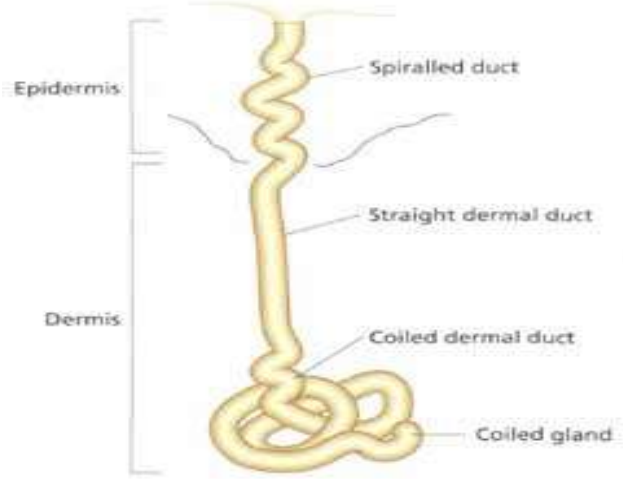

Figure (2): An eccrine sweat gland: most of the body's sweat production is the result of eccrine gland activit ***(Gray, 1997).***

Apocrine glands are poorly developed in childhood, and begin to enlarge with the approach of puberty. They develop their secretory portion and become functional only at puberty. The activity of the glands is androgen dependant, and the glands show marked testosterone 5α reductase activity ***(Coulson, 2008).***

Apocrine glands are composed of three segments: intraepithelial duct, intradermal duct, and secertory portion (Fig 3). Because apocrine glands originate from the hair germ, or primary epithelial germ, the duct of the apocrine gland usually leads to a pilosebaceous follicle entering it in the infundibulum above the entrance of the sebaceous duct. In contrast to eccrine glands, the basal coil of apocrine glands which are located in the subcutaneous fat is composed entirely of secretory cells and contains no ductal cells ***(Schaller and Plewig, 2008).***

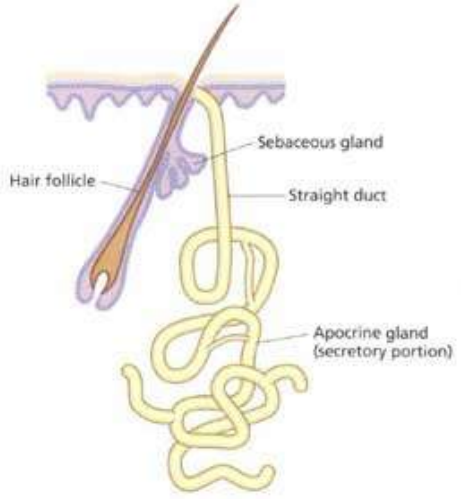

Figure (3): An apocrine gland, which produces little sweat but is responsible for the body's natural 'scent ***(Gray, 1997).***

Apocrine glands are encountered in only a few areas: in the axillae, in the anogenital region, and as modified glands in the external ear canal (ceruminous glands), in the eye lid (Moll's glands), and in the breast (mammary glands). Occasionally, a few apocrine glands are found in the face, in the scalp, and on the abdomen; these glands are usually small and non functional ***(Schaller and Plewig, 2008).***

1.1.1. Composition of the Sweat:

The eccrine sweat is a watery clear, hypotonic (neutral) solution where it consists of water and salts such as sodium, chloride, potassium, urea, bicarbonate, calcium as well as other excretions from the body such as amino acids. Apocrine secretion is a thick, milky fluid and includes protein, ammonia, lipids, chromogranins (family of proteins) and bacterial decomposition leads to odor. Excretion or the propulsion of the apocrine secretion through the duct is episodic, although the actual secretion of the gland is continues ***(Odom et al., 2000).***

1.1.2. Functions of the Sweat:

The normal function of the sweat glands is to produce sweat, which cools the body by evaporation. The thermoregulatory center in the hypothalamus controls sweat gland activity through sympathetic nerve fibers that innervate the sweat glands. Sweat excretion is triggered

when core body temperature reaches or exceeds a set point**.** So the main functions of the sweat are: thermoregulation and emotional response; provide a response to psychological stimulus ***(Sato et al., 1989)*****.**

1.1.3. Regulating factors of sweat glands:

Eccrine Sweat glands are under sympathetic nervous control and they are stimulated by acetylcholine (a neurotransmitter).They are activated to prepare the body for physical activity or emergency. Apocrine sweat glands activated by same sympathetic nerves as eccrine glands in the same region, but different nerve fibers and different nerve transmitters control the glands and they respond to catecholamine, not acetylcholine (unlike ecrine glands). Other regulating factors include: hormones, pyrogens (bacterial toxins), physical activities, emotional stimuli and temperature ***(Sato et al., 1989)*****.**

1.2. DEFINITION, EPIDEMIOLOGY AND ETIOPATHOGENESIS OF HIDRADENITIS SUPPURATIVA

1.2.1. Definition:

Hidradenitis suppurativa, also known as acne inversa, is a chronic, recurrent, debilitating disease that presents with painful, inflammed lesions and tender subcutaneous nodules in the apocrine-gland-bearing areas of the body, most commonly the axillary, inguinal, and anogenital areas. These lesions may spontaneously rupture or coalesce to form deep dermal, painful abscesses ***(Alikhan et al., 2009).***

Hidradenitis suppurativa was identified as a disorder of follicular occlusion rather than an apocrine occlusion where the inflammatory changes which involve the apocrine glands present only in one third of cases of HS and occur only when the inflammation is extensively involving the hair follicles and eccrine glands. Also, the inflammation of apocrine glands did not occur in the absence of adjacent folliculitis, so involvement of apocrine glands occurs incidentally or secondary. Therefore, HS is better to be identified as a disorder of the terminal follicular epithelium in the apocrine gland-bearing skin ***(Cook and Yu, 1990)***. The draining sinus is a late complication of acne inversa ***(Prasad et al., 2008).***

1.2.2. Epidemiology:

The prevalence of hidradenitis suppurativa appears to be 1% of the general population; it was 4% in a group of young adults who were treated at a clinic for sexually transmitted diseases ***(Jemec, 2000).*** A study done by ***Revuz et al. (2008)*** showed that the prevalence among persons aged 55 years and older was significantly lower than in younger age groups (0.5% vs 1.4%).

The onset of hidradenitis suppurativa is predominant after puberty although it has been described in neonates ***(Attanoos et al., 1995),*** with an average patient age of 23 years ***(von der Werth and Williams, 2000).*** Children are never affected unless they have precocious puberty ***(Mortimer and Lunniss, 2000).*** In less than 2% of patients, the disease appears before age 11 years ***(Palmer and Keefe, 2001).*** In extremely rare cases, hidradenitis suppurativa occurs before puberty or after menopause ***(Weber-LaShore and Huppert, 2009)***.

The incidence of hidradenitis suppurativa is greater in females than in males, thought to be in the range of 4:1 or 5:1***(Shah, 2005).*** Active genitofemoral lesions occur significantly more often in females, whereas perianal involvement tends to be more common in males. No sex difference is seen in the axillary lesions. Comedones have been suggested as precursor lesions for hidradenitis suppurativa, and they appear to be equally distributed in both sexes and sites ***(Jemec, 2003).***

Hidradenitis suppurativa is one of the most

distressing conditions observed in dermatology ***(Wolkenstein et al., 2007).*** A study done by ***von der Werth and Jemec (2001)*** showed that HS causes a high degree of morbidity, with the highest scores obtained for the level of pain caused by the disease. The mean dermatology life quality index (DLQI) score for HS was higher than for previously studied skin diseases, and correlated with disease intensity as expressed by lesions per month. This suggests that the DLQI may be a relevant outcome measure in future therapeutic trials in HS.

1.2.3. Etiopathogenesis:

Hidradenitis suppurativa is a disorder of follicular occlusion with secondary involvement of the apocrine glands and surrounding structures with superinfection. Its pathogenesis is believed to start with occlusion and dilation of the pilosebaceous unit, with subsequent rupture and extrusion of follicular contents into dermis; this stimulates chemotactic inflammatory response with influx of neutrophils, lymphocytes and histiocytes leading to abscess formation. Chronic and recurrent process is affecting the apocrine gland-bearing areas (axillary, inguinal, perianal, perineal, areolar and inframammary areas), and leads to scarring, contractures and increase size of affected region with number of episodes ***(Kurzen et al., 2008).*** Contributing factors include friction from axillary adiposity, sweat, heat, stress, tight clothing, smoking and

genetic and hormonal components ***(Shah, 2005).***

The course of hidradenitis is usually a chronic one. However, there is some evidence that in women the disease eases or may even subside following the menopause, which supports the view that hormonal influences are important in its pathogenesis. The precise role of hormones in the aetiology of HS remains unclear, and this also applies to the role of microbes ***(Von Der Werth et al., 2000).***

The possible predisposing and precipitating factors include**:**

1.2.3.1. Genetic factors:

A study was done by ***Fitzsimmons et al. (1985)*** showed that hidradenitis suppurativa may have an autosomal dominant mode of transmission. They found that 34% of first-degree relatives of probands also had HS. Both males and females were affected via vertical transmission through several generations, consistent with AD inheritance. Many of the first-degree relatives were under 20 years of age during the study. It was hypothesized that if the study subjects were followed up for longer periods of time, more of them might develop the disease, bringing the percentage of those affected closer to 50%. In support of this supposition, ***Von der Worth et al. (2000)*** restudied these same families 15 years later and noted that additional

cases of HS had developed. However, the transmission rate was still less than the 50% rate associated with AD inheritance. They suggested that this might be because of their rigid disease definition, incomplete penetrance, and hormonal influences.

Genetics studies in a large four-generation Chinese family with HS indicated a locus for the disease on chromosome 1p21.1-1q25.3. However, because of the considerable size of this region, a specific gene was not identified ***(Gao et al., 2006).***

1.2.3.2 Follicular occlusion tetrad:

Hidradenitis suppurativa may also be seen in association with other conditions where occlusion of follicular structures plays a more obvious role, namely acne conglobata and dissecting folliculitis of the scalp. These three conditions have been referred to collectively as the "follicular occlusion triad". Another component, pilonidal sinus, has been added to form a "tetrad" ***(Carmen and Cook, 1990).***

1.2.3.3 Relation to acne:

Hidradenitis suppupurativa resembles acne in several ways, and it has been suggested that the name hidradenitis should be changed to acne inversa. Histologically, the two diseases are similar and experimental evidence suggests that follicular occlusion is a shared pathogenic factor. The patients also appear to share other characteristics as both diseases have been described as clinical markers of androgenicity and anti androgen treatment has been shown to be effective in both conditions ***(Sellheyer and Krahl, 2005).***

Clinical important differences between hidradenitis and acne exist and oral isotretinoin is not effective in the treatment of HS as do in acne ***(Soria et al., 2009).*** The characteristic lesions in HS are deep-seated subcutaneous nodules or abscesses ***(Poli et al., 2006).*** In acne vulgaris, the primary lesions are either open or closed comedones. In HS, closed comedones are never present, and open comedones can be found as secondary lesions, but they are absent in early lesions of HS. They may appear in long-standing HS. Thus, the clinical appearance of HS and acne vulgaris is quite distinct, and it adds little to our