INTRODUCTION

Striae distensae are well defined, linear atrophic skin lesions and secondary to connective tissue abnormalities ***(Cambazard and Michel, 2006)***. In the early stages, striae may appear pink to red (striae rubra), which over time become atrophic and attain white color (striae alba) ***(Burrow and Lovell, 2004)***.They can also be distinguished into four distinct types; namely, striae alba, striae rubra, striae caerulae, and striae nigra, melanin pigmentary system may have a role in various colors of striae distensae ***(Hermanns and Piérard, 2006).***

Several observations within the disease express gender influence. The highest incidence of striae is between 10 and 16 years of age among girls, and between 14 and 20 years of age among boys ***(Burrow and Lovell, 2004)***. The commonest sites are the outer aspect of the thighs and lumbosacral region in males, while in females; the disease affects thighs, upper arms, buttocks, and breasts ***(Nigam, 1989)***.Transverse atrophic striae of the back are more common in men than in women and are often associated with striae elsewhere, acne, hidradenitis suppurativa, obesity, corticosteroid therapy, and prolonged heavy lifting ***(Carr and Hamilton, 1969)***.

Striae are seen in 90% of pregnant women due to a combination of hormonal factors along with increased lateral stress

on connective tissue ***(Lawley and Yancey, 2003)***. The action of estrogens in the skin is well-known to increase the thickness and elastic fibers in the papillary layer ***(Punnonen et al, 2003)***, increase in dermal collagen ***(Sauerbronn et al, 2000)***, interfere in the mechanism of wound repair and extracellular matrix reorganization ***(Zecchin et al., 2005)***, and participate with androgens in skin homeostasis ***(Mills et al., 2005; Gilliver et al., 2003)***. In males, striae typically occur as a result of a rapid growth spurt or weight gain at puberty, from endocrine disorders or as a consequence of participation in certain sports, especially weight lifting. Excessive or chronic use of potent topical or systemic corticosteroids also promotes the formation of striae ***(Lebwohl and Ali, 2001)***.

Multiple treatment modalities are available including tretinoin, glycolic acid, pulsed dye laser, CO_2 laser, Intensed pulsed laser, excimer laser, and others ***(Elsaie et al., 2009)***. No specific treatment exists as the exact pathogenesis is still unknown.

The pathology may originate due to changes in the structures that provide skin with its tensile strength and elasticity. Such structures include components of the extracellular matrix, including fibrillin, elastin, and collagen ***(Watson et al., 1998; Thomas and Liston, 2004)***. They may be caused through loss of fibroblast synthesis capability and abnormalities to connective tissue, in addition to significantly decreased collagen, elastin, and fibrilin fibers. They may develop as an end result of various physiologic

states, including pregnancy, adrenocortical excess, and changes in body habitus, as seen in rapid weight change. A genetic predisposition is also presumed ***(Viennet et al., 2005; Cambazard and Michel, 2006)***.

It is postulated that some hormones, like estrogen, relaxin, and glucocorticoid hormones, decrease the adhesiveness between collagen fibers and increase ground substance through different mechanisms, which results in the formation of striae in areas of stretching ***(Schäcke et al., 2002; Thomas and Liston, 2004)***.

AIM OF THE WORK

The aim of this thesis is to study the influence of gender on expression of estrogen, androgen, and glucocorticoid receptors in striae distensae.

STRIAE DISTENSAE: OVERVIEW

Definition:

Striae distensae, commonly known as stretch marks, is a skin condition that is often asymptomatic, but creates considerable cosmetic concerns for patients ***(Nigam, 1989)***. Striae are visible linear scars which form in areas of dermal damage produced by stretching of the skin ***(Burrows and Lovell, 2004)***.

Causes:

Women develop striae more commonly than men (reportedly 90% of pregnant women, 70% of adolescent females, and 40% of adolescent males) ***(Arnold et al., 2000)***.

The occurrence of striae correlates closely with obesity. They are highly prevalent in obese adults and children. Striae also occur frequently in patients with hypercortisolism as in Cushing's syndrome and in those using topical steroids ***(Burrows and Lovell, 2004)***.

It has been noted that striae are prevalent in cachetic states, such as tuberculosis, typhoid, and after intense slimming diets ***(Sparker et al., 1996)***.Men and women with chronic liver disease may also have striae ***(Johnston and Brown, 2003)***.

The exact cause of striae in pregnancy is unknown, although a combination of hormonal factors (e.g. adrenocortical hormones, oestrogen, relaxin) associated with increased lateral stress on the connective tissue due to increased size of the various portions of the body is thought to be important ***(Lawley and Yancey, 2003)***.

In men, striae typically occur as a result of a rapid growth spurt or weight gain at puberty, from endocrine disorders or as a consequence of participation in certain sports, especially weightlifting. Excessive or chronic use of potent topical or systemic corticosteroids also promotes the formation of striae ***(Lebwohl and Ali, 2001)***.

Table (1): Different causes for the development of stretch marks ***(Elsaie et al., 2009)***:

1- Infection leading to the release of striatoxin that damages the tissues in a microbial toxic way.
2- Mechanical effect of stretching, which is proposed to lead to rupture of the connective tissue framework (e.g., pregnancy, obesity, weight lifting).
3- Normal growth as seen in adolescence and the pubertal spurt that leads to increase in sizes of particular body regions.
4- Increase in the levels of body steroid hormones; Cushing's syndrome, local, or systemic steroid therapy that has a catabolic effect on fibroblasts.
5- Genetic factors (absence of striae in pregnancy in people with Ehlers-Danlos syndrome ,and their presence as one of the minor diagnostic criteria for Marfan syndrome suggest an important genetic element).
6- Immunosuppression states associated with pregnancy-induced hypertension medications, human immunodeficiency virus, or diseases such as tuberculosis and typhoid.
7- Associated with chronic liver disease.

Clinical Picture:

The natural evolution of striae is for the red to purple, raised wavy lesions (striae rubra) to fade and leave white atrophic lesions with a wrinkly surface (striae alba) ***(Hidalgo, 2002)***.

Table (2): Classification of striae based on clinical appearance ***(Adatto and Deprez, 2004)***:

Stage I	Fresh, inflammatory usually livid striae.
Stage II a	White, superficial striae without laddering, and without palpable depression at the surface of the skin.
Stage II b	White, superficial striae without laddering, but with palpable depression at the surface of the skin.
Stage III a	White, atrophic striae with laddering measuring less than 1 cm width, without deep pearliness.
Stage III b	White, atrophic striae with laddering measuring less than 1 cm width, with deep pearliness.
Stage IV	White, atrophic striae with laddering measuring more than 1cm width, with or without deep pearliness.

Figure (1): Striae distensae in a morbidly obese woman ***(Gil et al., 2007).***

The commonest sites of striae are the outer aspects of the thighs and the lumbosacral region in boys, and the thighs, upper arms, buttocks, and breasts in girls ***(Burrows and Lovell, 2004)***. Striae may develop on shoulders in young male weight lifters when their muscle mass rapidly increases ***(Carr and Hamilton, 1969)***.

Striae are very common over the abdomen and breast in pregnancy ***(Osman et al., 2007)***.

Pathogenesis:

The pathogenesis of striae is unknown but probably relates to changes in the components of extracellular matrix, including fibrillin, elastin, and collagen ***(Watson et al., 1998)***.

In a study on early striae distensae***, Sheu et al.,*** found that sequential changes of elastolysis accompanied by mast cell degeneration occur in the very early stage of striae distensae ***(Sheu et al., 1991)***.

The striae origin is multifactorial and, despite several studies, their physiopathogenic mechanisms are not entirely understood. In a study on straie four etiologic mechanisms have been postulated:(i) insufficient development of the tegument, including a deficiency in its elastic properties; (ii)rapid stretching of the skin; (iii)endocrine imbalance; and(iv)other causes, possibly toxic ***(Rosenthal, 1937)***.

Histopathology:

Histologic and biochemical analyses have revealed that stretch marks are characterized by a thin epidermis, loss of dermal papillae, and loss of rete ridges ***(Zheng et al., 1985)***. There is also decrease in net content of the extracellular matrix (ECM) components collagen, fibronectin, and fibrillin ***(Lee et al., 1994)***.

In the early stages, inflammatory changes may be conspicuous, but later the epidermis is thin and flattened. Recent striae distensae (SD) shows a deep and superficial perivascular lymphocytic infiltrate around the venules ***(Arem and Kischer, 1980)***.Collagen bands on the upper third of the reticular dermis are stretched and aligned parallel to the surface of the skin. In the latter stages, there is thinning of the epidermis due to flattening of the rete ridges and loss of collagen and elastin ***(Pierard et al., 1999)***.

Treatment:

Several treatments have been proposed, yet no consistent modality is available. Some authors have suggested that time is the only treatment for SD and that it returns to normal over years, which is not true ***(Alaiti and Obagi, 2006)***.It has always been suggested that effective treatment of SD be instituted during the active stage, well before the scarring process is complete ***(Garcia, 2002)***. The first reliable method of treatment involved using tretinoin cream ***(Elson, 1990)***. Subsequent modalities were reported afterward, with variable results.

1- Diet and Exercise:

There is lack of data concerning the effect of diet and diet restrictions on stretch marks. Eighty women aged 24 to 53 participated in a 3-month weight-loss program; 29 were on a diet, 31 were on a diet plus aerobic exercise program, and 20 obese women were on a diet plus a resistance exercise program. It was inferred that a weight loss program using diet alone or a combination of diet and exercise did not change the degree of SD. Further studies are required to establish a clear effect of diet and exercise on SD ***(Schwingel et al., 2003)***.

2- Topical Therapies:

Table (3): Different Topical Products and Their Speculated Modalities of Action ***(ELSaie et al., 2009)***:

Product	Indication	Suggested Mode of Action
Tretinoin	Therapeutic	Exact mechanism unclear, but recent studies suggest fibroblastic stimulation.
Trofolastin	Therapeutic	Active ingredient (centella asiatica) stimulates fibroblasts and inhibits glucocorticoids.
Verum	Preventive	Active ingredient hyaluronic acid is speculated to increase tensile resistance to mechanical forces.
Alphastria	Preventive	Hyaluronic acid, the main ingredient, acts by increasing volume to oppose mechanical atrophy.
Massage with oils	Preventive	Dual action of massage and hydrant action of oils.
Glycolic acid and	Therapeutic	Glycolic acid is reported to stimulate collagen production by fibroblasts and to

trichloroacetic acid peels		increase their proliferation in vivo and in vitro.

3- Lasers:

Many modalities used to ameliorate and improve stretch marks, lasers have recently become a popular therapeutic alternative. The 585-nm flash lamp- pumped pulsed-dye laser (PDL) is the most commonly reported laser used in treatment of SD. The use of ablative technologies such as the short pulse carbon dioxide and erbium-substituted yttrium aluminium garnet (YAG) enjoyed a brief popularity because of prolonged healing and pigmentary alterations, especially in darker skin tones ***(McDaniel, 2002)***. Newer applications of other laser modalities such as neodymiumdoped YAG (Nd:YAG), diode, and Fraxel are finding a way into treatment of stretch marks.

4- Radiofrequency Devices:

The uses of radiofrequency (RF) devices have been reported to be an effective and safe noninvasive technique to tighten the face and neck skin. Unlike lasers, which convert light to heat and target a specific chromophore through the selective photothermolysis, RF devices transfer higher-energy fluences to the skin through a coupling method. The electrical energy transmitted is converted to heat upon reacting with the skin's resistance ***(Hsu and Kaminer, 2003)***.

STRIAE DISTENSAE: HORMONAL FACTOR

Steroid Hormones:

Many physiological processes in organisms are regulated by a relatively small number of steroid hormones, all synthesized from cholesterol. Being small hydrophobic molecules, they are thought to be able to cross the plasma membrane of the cell by simple diffusion. In the cell, steroid hormones bind to specific intracellular receptor proteins, converting these proteins to functional transcription factors, which are then able to regulate in the nucleus the expression of specific genes ***(Jensen and DeSombre, 1973)***. The steroid hormones include gonadal hormones (estrogens, progestins, and androgens) and adrenal cortical hormones (glucocorticoids and mineralocorticoids).

The sex steroid receptors are not only expressed in sex accessory tissues, but in many other types of cells including liver, bone, pituitary, and cardiovascular cells. Androgen receptors are encoded by a single gene whereas there are two genes for estrogens (ERs), ERa and ERb ***(Kuiper et al., 1996)*.**

In the skin, oestrogens and androgens are involved in the proliferation and differentiation of epithelial cells, and the activity of fibroblasts and skin immune cells, and they play important roles in wound healing ***(Strudwick et al., 2006)***. In the skin, marked structural and functional changes, including a decrease in

dermal collagen and reduced skin thickness, occur after menopause ***(Ashcroft et al., 2003)***. Oestrogen can reverse age-related impaired healing in females when applied topically or given systemically, and is associated with reduced local inflammation and enhanced matrix deposition ***(Jorgensen and Schmidt, 1962)***. In this regard, recent reports have shown that hormone replacement therapy prevents the development of chronic wounds in postmenopausal women ***(Margolis et al., 2002)***.

Androgen:

Androgens affect several functions of the human skin, such as sebaceous gland growth and differentiation, hair growth, epidermal barrier homeostasis, and wound healing. Their effects are mediated by binding to nuclear androgen receptors ***(Zouboulis and Degitz, 2004)***.

Androgens act through a single nuclear receptor, the AR. AR is a ligand-activated, intracellular transcription factor that belongs to the steroid ⁄ nuclear receptor superfamily. Like all nuclear receptors, AR is a soluble molecule with a proclivity for employing transcriptional regulation as a mean of promoting its biological effects. In common with other steroid receptors, AR is compartmentalized in the cytoplasm, existing in polymeric complexes that include the heat shock proteins hsp 90, hsp 70, and hsp 56. The association of androgens with AR results in dissociation of the heat shock proteins. This in turn exposes a

nuclear translocation signal previously buried in the receptor structure and initiates transport of the ligand- receptor complex to the nucleus. There, AR occupies androgen response elements in the promoter regions of androgen-regulated genes to initiate the signaling cascade. AR is present in epidermal and follicular keratinocytes, sebocytes, sweat gland cells, dermal papilla cells, dermal fibroblasts, endothelial cells, and genital melanocytes. It is stabilized by ligand binding and is up-regulated in fibroblasts and sebocytes ***(Zouboulis and Degitz, 2004)***.

Ashcroft and Mills reported an AR-mediated inhibition of cutaneous wound healing in adult individuals ***(Ashcroft and Mills, 2002)***. Endogenous testosterone inhibited cutaneous wound healing in males and was associated with an enhanced inflammatory response. Blockade of androgen action via AR antagonism accelerated wound healing significantly ***(Zouboulis and Degitz, 2004)***.

In the epidermis, AR immunoreactivity was detected in nuclei of interfollicular keratinocytes and pilosebaceous duct keratinocytes. The stained nuclei were uniformly distributed throughout the different layers of the epidermis. In the dermis, about 10% of the fibroblasts exhibited AR immunostaining. In sebaceous glands, AR was expressed in nuclei of both basal cells and differentiated sebocytes. In the hair follicle, no AR immunoreactivity could be detected in the epithelial cells of the outer root sheath including the bulge region and the inner root