Study of the Cutaneous Expression of Estrogen, Androgen, and Glucocorticoid Receptors In Recent and Mature Striae Distensae

Thesis

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*in **Dermatology, Venereology and Andrology***

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INTRODUCTION

Striae distensae are well defined, linear atrophic skin lesions and secondary to connective tissue abnormalities ***(Cambazard and Michel, ٢٠٠٦).*** The commonest sites are the outer aspect of the thighs and lumbosacral region in males, and thighs, upper arms, buttocks and breasts in females. 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, [illegible]).*** 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, ٢٠٠٦).***

Multiple treatment modalities are available including tretinoin, glycolic acid, pulsed dye laser, CO٢ laser, Intensed pulsed laser, excimer laser, and others ***(Elsaie et al., ٢٠٠٩).***

The pathogenesis is still unknown, but probably relates to changes in the structures that provide skin with its tensile strength and elasticity. Such structures include components of the extracellular matrix (ECM), including fibrillin, elastin, and collagen ***(Watson et al., [illegible]; Thomas and Liston, [illegible]).***

They may be caused through loss of fibroblast synthesis capability and abnormalities to connective tissue, in addition to significantly decreased collagen, elastin, and fibrillin 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., ; Cambazard and Michel., ٢٠٠٦).***

Striae are seen in ٩٠٪ of pregnant women due to a combination of hormonal factors along with increased lateral stress on connective tissue ***(Lawley and Yancey,).*** The action of estrogens in the skin is well-known to increase the thickness and elastic fibers in the papillary layer ***(Punnonen et al.,),*** increase in dermal collagen ***(Sauerbronn et al.,),*** interfere in the mechanism of wound repair and extracellular matrix reorganization ***(Zecchin et al.,),*** and participate with androgens in skin homeostasis ***(Mills et al., ; Gilliver et al.,).***

Under the physiologic conditions, glucocorticoids may regulate the synthesis of glycosaminoglycans ***(Smith, ١٩٨٨)***, while most relevant adverse effect of glucocorticoid therapy is skin atrophy through suppression of cutaneous cell proliferation and protein synthesis, which concerns keratinocytes as well as dermal fibroblasts resulting in depressed collagen turn over. They may also intervene in regulation of proinflammatory cytokines, growth factors, matrix proteins, and matrix proteases which have impact on wound healing ***(Schäcke et al.,*** ٢٠٠٢***).***

It is postulated that some hormones, like estrogen, relaxin, and adrenocortical hormones, decrease the adhesiveness between collagen fibers and increase ground substance, which results in the formation of striae in areas of stretching ***(Thomas and Liston,*** [illegible] ***).***

AIM OF THE WORK

The aim of this thesis is to study the expression of estrogen, androgen and glucocorticoid receptors in recent and mature striae distensae to explore the proposed role of hormonal factor throughout the clinical course of the disease.

STRIAE DISTENSAE: OVERVIEW

Definition

Striae distensae are well-recognized common disfiguring skin condition that rarely cause a significant medical problem but is often a significant source of distress for those affected ***(Bleve et al.,* [illegible]*).*** The first morphologically correct description of these lesions, calling them striae atrophicae was by Nardelli in ١٩٣٦ ***(Tsuji and Sawabe,* [illegible]*).*** They are atrophic linear dermal scars with overlying epidermal atrophy ***(Cho et al.,* ٢٠٠٦*).*** They arise from progressive or rapid stretching of the dermis ***(De Angelis et al.,* [illegible]*)***, and appear along cleavage lines perpendicular to the direction of greatest tension in areas with the most adipose tissue ***(Scheinfeld,* [illegible]*; Elsaie et al.,* [illegible]*).***

Pathogenesis

The pathogenesis of striae is unknown but in the light of morphological and molecular data, striae suggests correlation between loss of fibroblast synthesis and abnormalities in connective tissue, in addition to decreased collagen, elastin and fibrillin fibers when compared with normal skin ***(Vinnet et al.,* [illegible]*)***. It was found that sequential changes of elastolysis accompanied by mast cell degeneration occur in the very early stage of striae distensae. Elastic fibers are the primary target of the pathological process and the abnormalities extend as far as ٣ cm beyond the lesion into the normal skin ***(Sheu et al.,)***. Striae are a form of dermal scarring in which the dermal collagen ruptures ***(Garcia,)***. It has been suggested that they develop more easily in skin which has a critical proportion of rigid cross linked collagen as occurs in early adult life ***(Burrows and Lovell,)***. Recently, it has been suggested that regions undergo greater mechanical stretching of skin may express greater hormonal receptor activity. This activity may influence metabolism of extracellular matrix including fibrillin, elastin and collagen ***(Cordeiro et al.,)***.

Changes in the extracellular matrix (ECM); collagenous or elastic components, play a key role ***(Lee et al.,)***. Functional analysis of fibroblasts explanted from active lesional skin have determined that these cells possess a contractile phenotype more akin to myofibroblasts than to cells from mature lesions or cells explanted from healthy volunteers ***(Viennet et al.,)***. Expression of fibronectin and both type I and III procollagen were found to be significantly reduced in fibroblasts from striae suggesting that there exist fundamental aberrations of fibroblast metabolism in striae distensae ***(Lee et al.,)***. It is suggested that the elastic fiber network is more prone to reorganization and destruction in active striae ***(Sheu et al.,)***. There are also alterations in both elastic fibers and the fibrillin-rich microfibrillar apparatus proximal to the dermal-epidermal junction ***(Watson et al.,).***

The controversial etiology of SD have been explored through multiple factors such as genetic predisposition, normal growth, mechanical stretch, hormonal changes, and others ***(Elsaie et al.,).***

SD have been reported in monozygotic twins ***(Dilernia et al.,).*** There is decreased expression of collagen and fibronectin genes in affected tissue ***(Lee et al.,).*** The role of genetic factors is further emphasized by the fact that they are common in inherited defects of connective tissue as in Marfan's syndrome ***(Viennet et al., ; Burrows and Lovell.,).***

Mechanical stretching may lead to rupture of the connective tissue framework (e.g., pregnancy, obesity) ***(Atwal et al., ٢٠٠٦).*** SD are highly prevalent in obese children and adults. They occur in ٩٠٪ of pregnant women and ٤٠-٧٠٪ of the adolescent population ***(Elsaie et al.,).*** Young male weight lifters develop striae on their shoulders ***(Burrows and Lovell,).***

Normal growth (in adolescence and pubertal spurt) leads to increase in sizes of particular body regions ***(Cho et al., ٢٠٠٦).*** The development of striae in adolescence is not related to obesity but rather coincides with the markers of adolescence such as breast development, pubic hair growth and menarche ***(Novak,).*** In a study on skin diseases in children with organ transplants, steroid-induced striae distensae were found only in adolescents and not among younger children ***(Euvrard et al,).*** Idiopathic SD also occur in healthy non-obese individuals around time of puberty ***(Cho et al., ٢٠٠٦).***

Elevated body steroid hormones; as in Cushing's syndrome and steroid therapy, have a catabolic effect on fibroblasts and decrease the deposition of collagen in the substance of the dermal matrix ***(Nieman and Ilias, ; Das et al., d).*** Striae gravidarum occur in up to ٩٠ % of pregnant women by the third trimester ***(Kroumpouzos and Cohen,).*** They are more common in younger and obese women, and those with larger babies ***(Thomas and Liston,).*** Females with a personal or family history of striae are at higher risk ***(Chang et al.,).*** The cause of striae gravidarum is multifactorial and includes physical factors (e.g., actual stretching of the skin) and hormonal factors (e.g., effects of adrenocortical steroids, estrogen, and relaxin on the skin's elastic fibers) ***(Lawley and Yancey,).*** No relationship was found between growth in abdominal girth in pregnant women and formation of SD. There was also no significant correlation existed between SD and the number of births, the age at the first birth, weight immediately before pregnancy, weight immediately after pregnancy ***(Osman et al., ٢٠٠٧).*** These findings may point to the role of hormonal changes that associate pregnancy.

It has been also noted that striae may associate cachectic states ***(Sparker et al., ١٩٩٦),*** anorexia nervosa ***(Strumia et al.,),*** patients receiving protease inhibitor indinavir for human immunodeficiency virus ***(Burrows et al.,),*** and chronic liver disease ***(Johnston and Graham, ٢٠٠٧).***

Clinical Picture

Lesions generally follow cleavage lines transverse to the direction of greatest tension, occurring most commonly on the abdomen, buttocks and thighs. The buttock, upper thigh and calf, all of which are areas with generous amounts of fat and muscle, that are prone to get wider and thicker during weight gain and muscle development, with greatest tension applied horizontally, and the striae in these areas run vertically. The striae of the thigh and calf in the male subjects and those of the calf in female subjects showed correlations with body weight and BMI ***(Agache et al., ١٩٧٦).*** In contrast, the striae on the knees and lower back, which are areas of articulation that are subjected to constant flexion/extension plus axial elongation rather than widening, run horizontally. Indeed, there was a correlation between occurrence of striae on the knee and height in the male subjects. Most of the subjects with striae on the upper arms had them running in various directions around the axillae ***(Cho et al., ٢٠٠٦)*** (Figure ١).

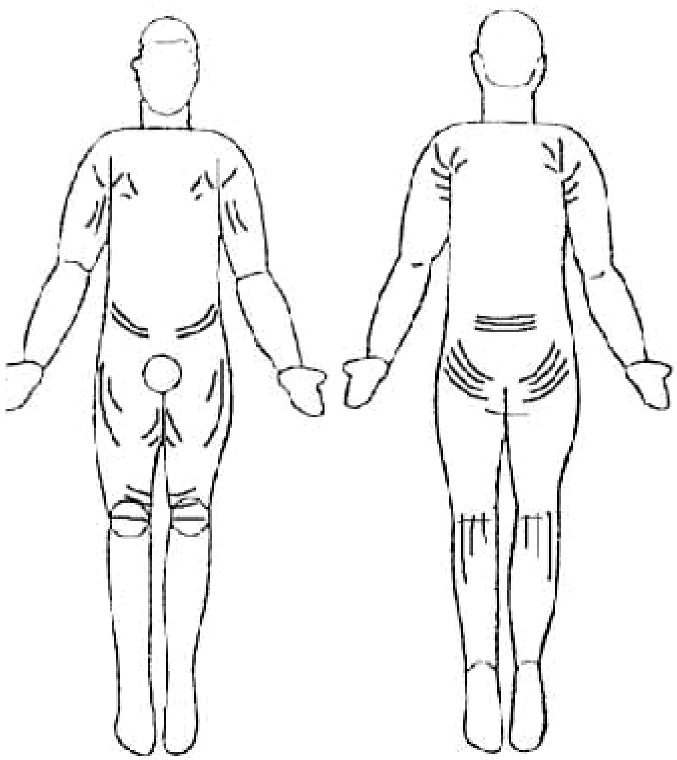

Figure (١): Potential distribution and direction of SD ***(Cho et al., ٢٠٠٦).***

Striae progress through three different stages of maturation: the acute stage is characterized by red and slightly raised striae (rubra), the subacute stage characterized by purpuric striae, and the chronic stage is characterized by hypopigmented and atrophic striae (alba) ***(Kim et al.,).***

Recent or immature SD are flattened areas of skin with a pink-red hue that may be itchy and slightly raised. Such striae maintain their characteristics for a short period, usually approximately ٦ to ١٠ months ***(Sheu et al., [illegible]).*** Striae distensae then tend to increase in length and acquire a darker purple color. Over time, they become white, flat, and depressed ***(McDaniel., [illegible]).*** The direct and indirect influences of melanocytes mechanobiology appear to have a prominent effect on the various colors of SD ***(Hermans and Pierard, ٢٠٠٦).*** High-resolution epiluminescence colorimetric assessment of SD identified four distinct types: striae alba (whitish and iridescent), striae rubra (erythematous), striae caerulea (bluish striae), and striae nigra (blackish striae) ***(Hermans and Pierard, ٢٠٠٦).*** Striae cerulae were encountered in subjects under prolonged corticticosteroid therapy, while striae nigra were identified in subjects of dark complexion ***(Hermans and Pierard., ٢٠٠٦).*** A classification of striae, based on clinical signs and used to assess treatment response, is proposed in Table (١) ***(Adatto and Deprez, [illegible]).***

Table (١): Clinical classification of SD ***(Adatto and Deprez,).***

Stage	Clinical appearance
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
Stage III a	White, atrophic striae with laddering measuring less than ١ cm width, without deep pearliness.
Stage III b	White, atrophic striae with laddering measuring less than ١ cm width, with deep pearliness.
Stage IV	White, atrophic striae with laddering measuring more than ١ cm width, with or without deep pearliness.

Striae may involve face and flexures in case of striae induced by Cushing's syndrome or steroid therapy ***(Burrows and Lovell, ; Cho et al., ٢٠٠٦).*** Striae gravidarum appear as pink-purple, atrophic lines or bands on the abdomen, buttocks, breasts, thighs, or arms. They are more common in younger women, with larger babies, and women with higher body mass indices ***(Thomas and Liston,).*** In obese patients striae are lighter, with less atrophy, and narrower than those with Cushing's syndrome ***(Garcia,)*** (Figures ٢-٥).

Figure (٢): Systemic steroids-induced widespread symmetric linear and reticulated violaceous atrophic striae ***(Nhan D Nguyen., ٢٠٠٧)***

Figure (٣): Transverse linear atrophic purple striae on back ***(Bernard Cohen., ٢٠٠٦).***

Figure (٤): Linear atrophic hypopigmented striae on thighs ***(Jayakar Thomas,).***