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Expression of Estrogen Receptor Beta in Striae Distensae of Different Sites of the Body

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Abstract

Background: Striae distensae (Stretch marks) are common cutaneous lesions that are characterised terminally by linear bands of atrophic skin. They run perpendicular to the direction of skin tension. The pathogenesis of striae remains unclear. The etiological mechanisms involved in striae are usually classified under the headings of genetic predisposition and the mechanical rupture of dermal components as an important initiating event. The estrogen and its receptors can play an important role in the pathogenesis of stretch marks despite their presence in the epidermis.

Patients and Methods: This study was carried out on 44 female patients complaining of stretch marks on different body parts. Punch skin biopsies were taken from striae distensae of the abdomen, thighs, breasts and buttocks. Immunohistochemical staining of these samples was done using estrogen receptor beta (ER-β).

Results: The intensity of ER-β expression was significantly related with the site of the stretch marks (P=0.0124). The abdominal striae showed stronger staining and the buttocks showed the least expression of ER-β. Conclusion: Using hormonal replacement therapy on the skin showing early stretch marks can be helpful as prophylactic and therapeutic modality for stretch marks.

Keywords: Striae distensae; Estrogen receptor beta

Introduction

Striae distensae (Stretch marks) are common cutaneous lesions that are characterised terminally by linear bands of atrophic skin [1]. They run perpendicular to the direction of skin tension. They have initial inflammatory phase known as (striae rubra) which appear as elevated red to violaceous streaks. Over time, the colour fades and they become white and atrophic and called (striae alba). Bluish striae encountered in subjects under prolonged steroid therapy are called (Striae caeruleae) and blackish striae identified in subjects of dark complexion are calles (Striae nigrae). The microanatomy support of stretch marks colours appears to be a combination of variations in microvasculture size and melanocyte activity [2].

The onset of striae is generally associated with two independent predisposing factors; (a) rapid skin distension due to underlying tissue expansion and (b) compromised dermis affected by normal loads. Striae are often found on the abdomen, thighs, buttocks, and breasts [3]. It is associated with rapid gain and rapid loss of weight, pregnancy, use of drugs like topical [4] and systemic corticosteroids [5], androgenic and anabolic substances [6], as well as the prolonged use of skin lightening creams [7].

The pathogenesis of striae remains unclear. The etiological mechanisms involved in striae are usually classified under the headings of genetic predisposition and the mechanical rupture of dermal components as an important initiating event [8]. Other investigators have suggested that, beside skin stretching, the endocrinal factor plays a role where it was noticed that the number of the hormone receptors are increased in the epidermis of skin of the striae, suggesting that the regions of the skin that undergo greater mechanical stretching display hormonal receptor activity [3].

The importance of estrogens in the maintenance of human skin is highlighted. A number of studies have shown that estrogens have many important beneficial and protective roles in skin physiology. They have been shown to accelerate cutaneous wound healing [9], while a significant number of women notice an improvement in inflammatory skin disorders such as psoriasis during pregnancy [10]. Estrogens also offer some degree of protection against skin photoaging [11].

Estrogen receptors are a group of proteins found inside the cells. They are receptors activated by the estrogen hormone. Since the isolation and cloning of the estrogen receptor (ER), it was thought that only a single nuclear ER existed until a second gene coding for another ER was cloned. This second receptor was termed ER-β, whereas the the classical ER is now referred to as ER-α, ER-α and ER-β are expressed in most cell types in the body: epithelium, endothelium, stroma, smooth and skeletal muscle, bone, cartilage, hematopoietic cells, neurons and glia. In some organs, both receptor subtypes are expressed at similar levels, sometimes, in different cell types within the same organ, whereas in others, one of them predominate. ER-α is primarily expressed in uterus, prostate, ovary, testes, epididymis, bone, liver, kidney, white adipose tissue and various regions of the brain. ER-β is predominantly expressed in skin, colon, bone marrow, salivary gland, vascular endothelium, lung, bladder and hypothalamus [12]. A third ER, called ER-γ is found to be expressed in the brain, kidney, pancreas and placenta [13]. The binding of estrogens to ERs produces genomic

effects that regulate gene transcription and non-genomic effects that regulate ion channels and signal transduction pathways. The genomic pathway is better characterised [14]. There is sufficient evidence according to receptor distribution and related actions to show that estrogens exert major direct influences on all elements of skin. The number of estrogen receptors has been reported to vary in different parts of the body [15]. While ER-α is localised in neonatal keratinocytes, ER-β is predominantly expressed in the epidermis, dermal fibroblasts, blood vessels and hair follicles of human scalp skin [16].

Collagen production is regulated by a variety of factors including growth factors, cytokines and hormones as estrogen hormone. Decreased level of estrogens lead to a number of cutaneous changes, including loss of elasticity, thinning, and wrinkling of the skin [17]. Estrogen receptors, despite their presence in the epidermis, they are important in the process of collagen biosynthesis in the dermal compartment of skin. They have distinct roles in the regulatory pathways involved in the synthesis and degradation of extracellular matrix. Their activation was found to inhibit photodamage and skin wrinkling in a mouse model [18]. On the other hand, their inhibition may be useful in treating fibrotic skin conditions by promoting collagen degradation [19]. At the same time, the effect of estrogens on the thickness of the skin epithelial layer is well understood. They act by reducing metalloprotease activity in the skin. Therefore, this should result in less degradation of skin collagen fibres during estrogen treatment. They also elevate skin water content consequently increasing skin turgor [20].

In this study, we intend to evaluate the differences of expression of ER-B in stretch marks of skin in different parts of the body as skin of the breast, abdomen buttocks and thighs, to spot light on its possible role in the etiology, pathogenesis and new models of therapy for these marks.

Patients and Methods

This study was carried out on forty four female patients complaining of stretch marks. All patients showed stretch marks on the abdomen. Fourteen patients had them on the thighs, 10 patients on the buttocks and 6 on the breast. All patients were subjected to complete history taking and thorough general and dermatological examinations. Punch biopsy (3.5-5 mm) was taken from the nearby normal skin beside the lesion to serve as control. The punch biopsies taken were for experimental purpose and informed consents were signed by the patients of the study. All specimens were preserved immediately in 10% neutral buffered formalin solution for 24-48 hours, processed and embedded in paraffin blocks. Immunohistochemical staining for estrogen receptor-β (ER-β) to evaluate its expression in different body parts (Abdomen, thighs, knee and breast). Immunohistochemistry was performed using the immunoperxoidase method on 4-m-thick sections from formalin-fixed, paraffin-embedded blocks. The antigen retrieval (PBS buffer; pH 7.4) was done for all sections and were incubated with the primary antibody for 2 hours at room temperature. The sections were incubated with secondary antibody (rabbit monoclonal antihuman antibody for ER (1:200, Thermo Scientific, Egypt) for 15 min at room temperature. Nuclear staining was considered positive for ER-β expression. Tissue was scored according to Deroo and Korach scoring system [21] based on the total percentage of positive nuclei (0%) = negative (0), weak (+1) (<10% of nuclei stained), moderate (+2) (10-50% of the nuclei stained) and strong (+3) (>50% of nuclei stained). Immunohistochemical staining was evaluated independently by two pathologists.

Statistical analysis was performed by using the Kruskal Wallis test, 2-tailed Fisher exact test or the χ^2 test with Yates continuity correction. A P value of less than 0.05 was considered statistically significant.

Results

This study included 44 patients diagnosed clinically and histopathologically confirmed as stretch marks, which were divided into 14 patients had them on the abdomen, 12 cases on the thighs, 10 cases on the buttocks and 8 cases on the breast.

The age of patients ranged from 20 to 65 with a mean of 38.59. Age groups were 18 patients < 40 years and 26 patients > 40 years old. Twenty eight patients had striae rubra and 16 patients had striae alba. According to body weight, 8 (18.2%) patients were normal weight, 14 patients (31.9%) were overweight, 12 patients (27.3%) were obese and 10 patients (22.8%) were morbid obesity. According to the etiology of stretch marks, pregnancy was in 28 patients (86.4%), obesity in 30 patients (68.2%), puberty in 6 patients (13.6%) and 4 patients (9.1) were due to oral corticosteroid therapy (Table 1).

	Number	%
Site of stretch marks		
Abdomen	14	31.80%
Thighs	12	27.30%
Buttocks	10	22.70%
Breast	8	18.20%
Age		
<40 years	18	40.90%
>40 years	26	59.10%
Type of stretch marks		
Striae rubra	28	63.60%
Striae alba	16	36.40%
Body weight		
Normal	6	13.60%
Overweight	12	27.30%
Obese	16	36.40%
Morbid obesity	10	22.70%
Aetiology		
Pregnancy	28	86.40%
Obesity	30	68.20%
Puberty	6	13.60%
Steroids	4	9.10%

Table 1: Clinical characteristics of the studied cases

Immunohistochemical results of ER-β

Positive expressions of ER-β were seen in 24 patients (54.6%), 14 cases showed weak expression, 6 cases were moderately positive and 4 cases were strongly positive for ER-β. Eight cases of abdominal stretch marks showed positive expression for ER-β, 8 cases of the thigh marks were positive, 8 cases of the marks on the breasts showed positivity and all 10 cases of the buttocks were negative for ER-β. The intensity of ER-β expression was stronger in cases of abdominal stretch marks and the weakest in the stretch marks on the buttocks (Figure 1 and 2). In comparison, the normal nearby perilesional skin showed weak or even negative expression for ER-β (Figure 3).

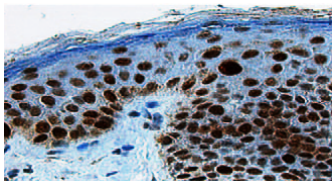

Figure 1: Strong positive ER- β expression in the nuclei of keratinocytes (arrows) in the skin of the abdominal stretch marks (X400).

Detailed immunohistochemical results of ER-β are shown in (Table 2).

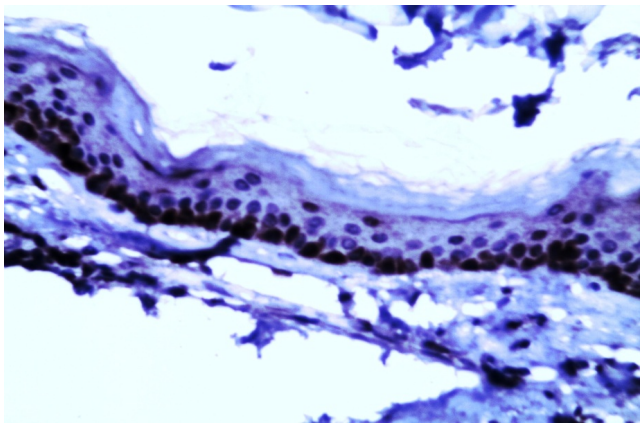

Figure 2: Moderate positive expression of ER-β in nuclei of keratinocytes of skin (arrows) in area of stretch marks of the thigh (X400).

Statistical analysis revealed a significant association between the intensity of ER-β expression and the site of stretch marks (p=0.0124) (Table 2).

Discussion

Striae distensae or stretch marks are common condition associated with considerable cosmetic morbidity that are characterised by linear bundles of collagen lying parallel to the surface of the skin, as well as eventual loss of collagen and elastin. The causes of stretch marks are not well understood. Excessive skin distension (such as that which occurs during pregnancy, growth spurts in puberty, or rapid weight gain), prolonged exposure to cortisol (such as in individuals with Cushing syndrome), and genetics may all have a role [22]. Stretch marks pass through three stages of maturation: the acute phase (striae rubra) which is red and slightly raised, the subacute stage which is purpuric striae and the chronic stage (striae alba) which is hypopigmented and atrophic [23].

In spite of the frequency of stretch marks, its etiology and pathogenesis are not very well understood. In this study, we intended to evaluate the relation between estrogen hormone receptors and the development of stretch marks as well as the effect of ER-β tissue distribution on the site of occurence of these marks. Many studies revealed that stretch marks result from the initial inflammatory reaction that destroys collagen and elastic fibres followed by the regeneration of collagen and elastic fibres in the direction of mechanical forces thus permitting a limited degree of stretch and intradermal rupture [24].

Estrogen hormone was suggested to decrease the adhesiveness between collagen fibres and increase ground substance, resulting in the formation of stretch marks in areas of stretching [25]. ER-β is expressed in epidermis, outer root sheath keratinocytes, melanocytes, dermal fibroblasts, dermal papilla cells, sebocytes, endothelial cells and adipocytes [16]. Hormonal receptor expression is increased under certain conditions suggesting that regions undergoing greater mechanical stretching of the skin may express greater hormonal receptor activity. This may influence the metabolism of extracellular matrix causing stretch mark formation [26].

In our study, 44 patients were diagnosed clinically and histopathologically confirmed as stretch marks, which were divided into 14 patients had them on the abdomen, 12 cases on the thighs, 10 cases on the buttocks and 8 cases on the breast. The age range was from 20 to 65 with a mean of 38.59. Twenty eight patients had striae rubra and 16 patients had striae alba. According to body weight, 18.2% of patients were normal weight, 31.9% were overweight, 27.3% were obese and 22.8% were morbid obesity. Pregnancy was the cause in 86.4% of cases, obesity in 68.2%, puberty in 13.6% and 9.1% of patients were having oral corticosteroid therapy.

In approval with our results, Osman et al. 2007, found that stretch marks have a predilection to the abdomen (47%), 24% had stretch marks on the thighs and/or breasts [27]. At the same time, our results were also in agreement with McGrath et al. 2010, as they found that the common sites were the outer aspect of the thighs, the lumbosacral region in boys and the thighs, buttocks and breasts in girls with some, despite their finding of stretch marks in other sites as on the outer aspect of the arm [28].

Similarly, another study done by Moustafa et al. 2014, found that stretch marks were overwhelmingly on the abdomen and buttocks followed by the thighs, knees and breasts [29].

In contrast to these results, Tedeschi et al. 2013, reported that stretch marks occur initially and predominantly on the breasts and some areas affected by cellulite, like hips and abdomen [30].

Concerning the immunohistochemical results of ER- β, this study showed significant differences in the intensity of ER- β expression among the various sites of stretch marks with the highest intensity found in the abdomen and the lowest in the buttocks. These results were supported by Cordeiro et al. 2010, who stated that estrogen receptor expression and activity is increased in regions undergoing

great mechanical stretching as in abdomen with pregnancy or abdomen and thighs with obesity [3].

Intensity of ER-β expression	Site of stretch marks								X2	P- value
	Abdomen		Thighs		Breast		Buttocks			
	No	%	No	%	No	%	No	%		
-ve	6	42.9	4	33.3	-	-	10	100	21.06	0.0124 *
Weak	-	-	8	66.7	6	75	-	-		
Moderate	4	28.6	-	-	2	25	-	-		
Strong	4	28.6	-	-	-	-	-	-		
Total	14	100	12	100	8	100	10	100		

Table 2: The relation between ER-β expression and the site of stretch marks.*P-value showed significant relation between the intensity of ER-β expression and site of striae distensae.

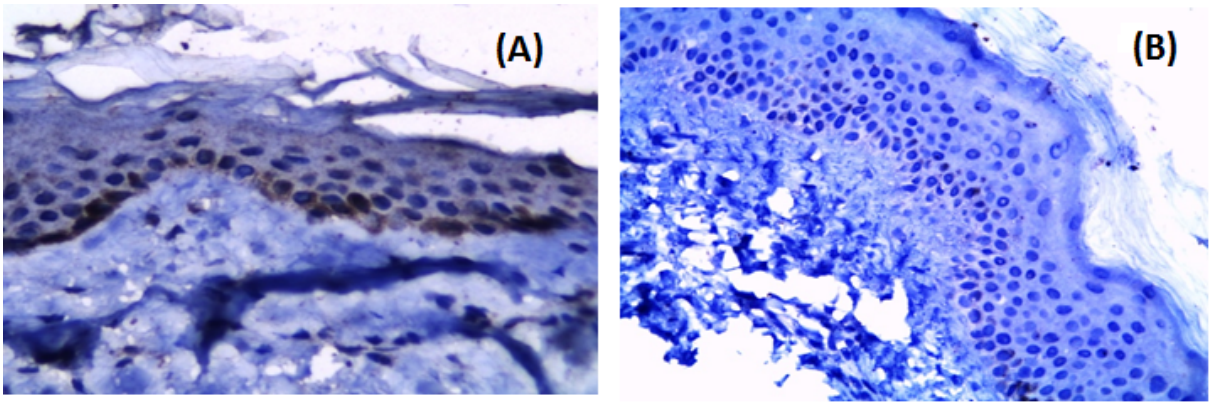

Figure 3: A. Normal perilesional skin showing weak expression of ER-β (X400); B. Normal perilesional skin showing negative expression of ER-β (X200).

Interestingly, another study done by Stevenson & Thornton, 2007, showed that the number of estrogen receptors differ with the anatomical site, as the face has greater number of receptors than breast or thighs [31]. Thornton et al. in 2003, demonstrated that only ER-β were expressed in dermal fibroblasts of skin in the papillary dermis of human scalp skin in both sexes, but not ER-α 16. In the same year, Fuchs et al. stated that the increase in the number of skin elastic and collagen fibres would presumably be mediated by the activation of estrogen receptors [32].

Conclusion

Estrogen receptor beta was found to be more expressed in the stretch marks of the abdomen, thighs and breast. Therefore, using hormonal replacement therapy on the skin showing early stretch marks in these areas can be helpful as prophylactic and therapeutic modality especially for the areas with greater estrogen receptor expression. Further studies are needed on larger numbers of patients to evaluate the expression of estrogen receptors in normal and pathological skin conditions. Such knowledge may open a new avenue in using receptor-specific ligends as therapeutic agents.

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