INTRODUCTION

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Definition

Stretch marks (also known as striae distensae) are a common skin condition that appear initially as red (stria rubra), and later on as white (stria alba) lines on the skin. These lines represent scars of the dermis, they are linear atrophic depressions of the skin that form in areas of dermal damage produced by stretching of the skin, and are characterized by linear bundles of collagen lying parallel to the surface of the skin, as well as eventual loss of collagen and elastin accompanied by epidermal atrophy. Though, striae do not cause any significant medical problem, they can be of significant disfigurement to those affected [1,2,4].

They are associated with various physiologic states, including puberty, pregnancy, growth spurts, rapid weight gain or loss, obesity, and states that induce high steroid hormone levels, such as prolonged use of systemic or topical corticosteroids and Cushing's syndrome [3].

Histology of the skin [5]

Human skin is considered the largest organ of the body and form about 16% of the body weight with a surface area somewhat less than 1.5 m^2. The skin form the external surface of the human body. At the orifices of the mouth, nose and the anal canal, the skin join the mucous membrane at the muco-cutaneous junction.

Types of human skin:

1. *Thick skin (Non-Hairy)* which has thick epidermis and found only in the palms and soles as they are the most sites subjected to abrasions and trauma and thick skin shows characteristic parallel ridges and grooves which are called "Finger prints".
2. *Thin skin (Hairy)* which has thin epidermis and covers the rest of the body.

Histological structure of the skin:

Skin is composed of 3 layers epidermis, dermis and hypodermis (subcutaneous fatty layer) (figure 1).

1- Epidermis:

It is the outer superficial epithelial layer of skin. It is composed of Stratified squamous keratinized epithelium. The thickness of the epidermis varies in different types of skin. It is the thinnest on the eyelids and the thickest on the palms(0.8mm) and soles(1.4mm). It is ectodermal in origin, devoid of blood vessels and gets its nutrition through diffusion.

It consists of:

- ***Keratinocytes*** (85% of cells) which are responsible for formation of keratin,
- ***Dendertic cells*** which are (melanocyte and the Langerhans cell)

- ***Merkel cells*** which until recently, were not consistently identified as the third dendritic cell in human epidermis, because light microscopy and low power electron microscopy did not readily allow the differentiation of merkel cells from the other two dendritic cells of the epidermis.

Keratinocytes are arranged in 5 layers from below upwards:-

- ***Stratum basale (basal cell layer)(The stratum germinatum):*** which is single layer of columnar cells with basal oval nuclei, cells of this layer are resting on basement membrane and attached to each other and with the overlying cells by inter-cellular bridges called "desmosomes" these basal cells continue to divide throughout the life so they are called mother cells of epidermis.
- ***Stratum spinosum (prickle cell layer):*** formed of 5-7 layers of nucleated poly-gonal cells attached to each other by desmosomes which are like spines hence its name.
- ***Stratum granulosum (Granular cell layer):*** formed of 2-3 layers of nucleated spindle shaped cells which accumulate dense basophilic keratohyalin granules, these granules contain lipids, which along with the desmosomal connections, help to form a waterproof barrier that functions to prevent fluid loss from the body.
- ***Stratum lucidum (Clear layer):*** only well seen in thick epidermis and represents a transition from the stratum granulosum to the stratum corneum and formed of dead clear non nucleated containing eleidin granules.
- ***Stratum corneum (horny layer):*** formed of flattened non nucleated cells called "squames" condensed in linear manner and containing Keratin which derived from eleidin granules. These squames are continuously shed from the surface and replaced from the deeper layer by new ones.

Melanocytes: They form melanin from tyrosine under the effect of tyrosinase enzyme and lie just under and in between basal cells and in hair matrix.

The Langerhans' cells: Present in Stratum spinosum, they act as macrophages. **The Merkel's cell's:** Present in Stratum basale and they act as receptors for touch sensation.

2- Dermis:

The dermis is mesodermal in origin and typically subdivided into two zones, a papillary layer and a reticular layer. It is 15-40 times thicker than epidermis.

Function: acts as a frame work and supports for nerves, lymphatics, hair follicles, sweat glands, Sebaceous glands and blood vessels to supply the avascular epidermis with nutrients.

The dermis contains mostly fibroblasts which are responsible for secreting collagen, elastin and ground substance that give the support and elasticity of the skin. Also present are immune cells that are involved in defense against foreign invaders passing through the epidermis.

The papillary layer lies below and interdigitates with the epidermal rete ridges, papillary layer is formed of loose connective tissue with fine collagenous fibers type II,

reticular and elastic fibers. It contains the free sensory nerve endings and structures called Meissner's corpuscles in highly sensitive areas.

The reticular layer lies below papillary layer and is formed of dense connective tissue with coarse collagenous fibers type I and some elastic fibers the fibers are irregularly arranged, this layer contain Pacinian corpuscles.

3- Hypodermis:

Contains adipose tissue and this layer is rich in adipose tissue except in scrotum and eyelids.

Skin has 4 appendages:

- Hair.
- Nails.
- Sweat Glands.
- Sebaceous glands.

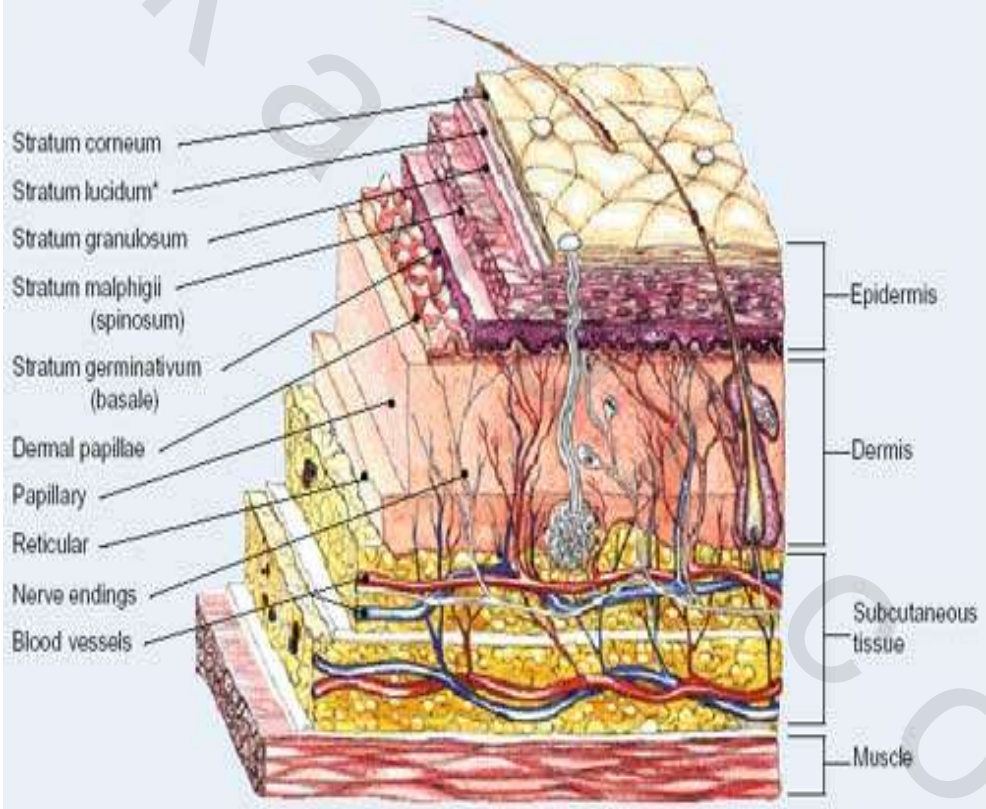

Figure (1): layers and structure of the skin.

Dermal connective tissue composition

The dermis is mainly acellular and consists primarily of the extracellular matrix of connective tissues, components of which are synthesized and regulated by fibroblasts cells in the dermis, and are classified into four main classes [: (6,7)]

A. **Collagen fibers**: which provide tensile strength allowing the protective function of the skin.

B. **Elastic fibers:** which provide elasticity and resilience to normal human skin.

C. **Non-collagenous glycoproteins:** such as fibrillins, fibulins and integrins, which often serve as organizers of the matrix and facilitate cell-matrix interaction.

D. Proteoglycan/glycosaminoglycan macromolecules: which provide hydration to the skin. Maintenance of proper quantities and appropriate interactions between the extracellular matrix components is a prerequisite for the physiological homeostasis of the dermis.

Collagen fibers

Collagen occurs in many places throughout the body. Over 90% of the collagen in the body, however, is of type I. So far, 28 types of collagen have been identified and described. The five most common types are:

1. Collagen I: skin, tendon, vascular ligature, organs, bone (main component of the organic part of bone)
2. Collagen II: cartilage (main component of cartilage)
3. Collagen III: reticulate (main component of reticular fibers), commonly found alongside type I.
4. Collagen IV: forms bases of cell basement membrane
5. Collagen V: cell surfaces, hair and placenta

Collagen is the major component of the dermal connective tissue. It consists of fibers represented as either a finely woven network or as thick bundles. The diameter of collagen fibers is ranging from 2µm to 15µm (figure 2). It provide tensile strength to the skin to serve as a protective organ against external trauma. [6,7]

Collagen in the papillary dermis

Collagen as a finely woven meshwork of fibers is found in the papillary layer of the dermis, which not only includes the subepidermal papillae situated between the rete ridges but also the subpapillary layer forming a narrow ribbon between the rete ridges and the subpapillary blood vessels. This is referred to as the papillary dermis. In addition, the pilosebaceous units and the eccrine and apocrine glands are encircled by a thin meshwork of collagen fibers similar to that present in the papillary dermis.

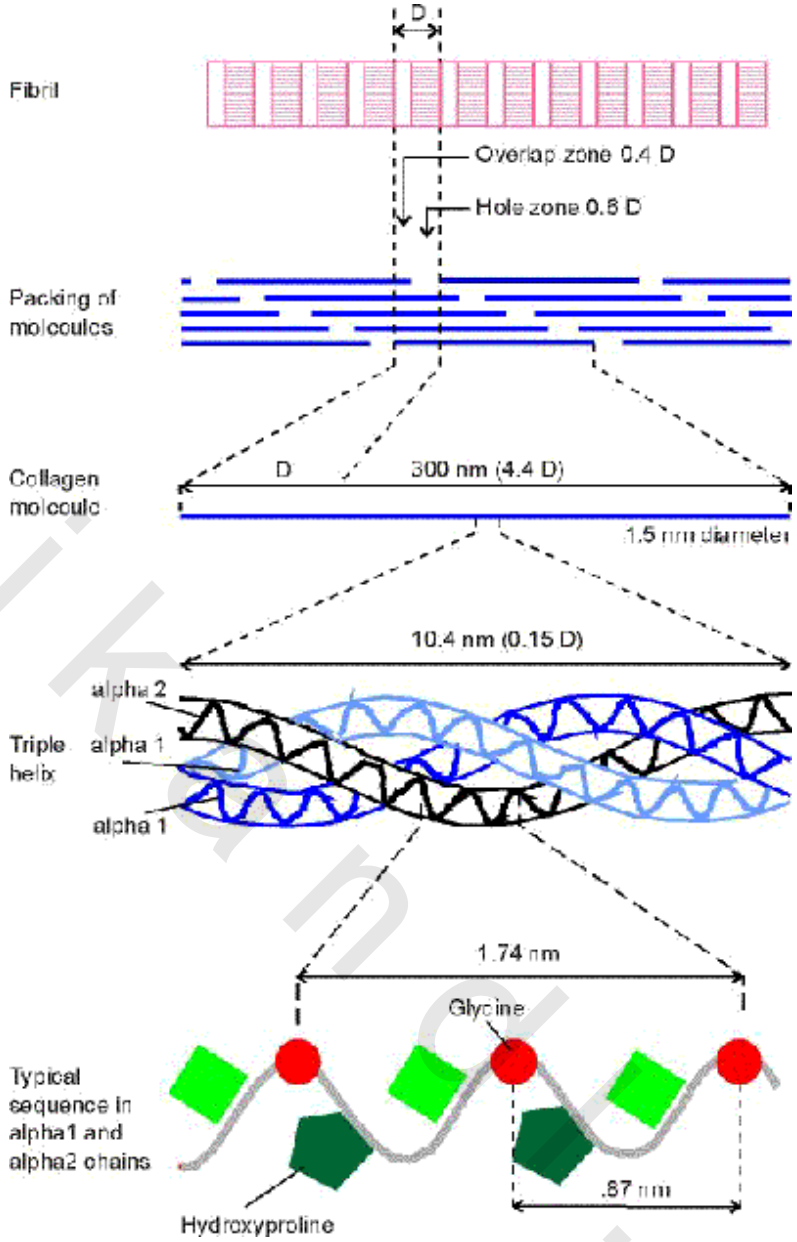

Figure (2): Diagram showing the molecular character of a collagen fibril in increasing order of structure (redrawn from Ross, 1995).

Therefore, the papillary and the periadnexal dermis are regarded as an anatomical unit, the adventitial dermis. The blood vessels of the dermis are also surrounded by a thin layer of fine collagen fibers. Biochemically, the papillary dermis is composed primarily of type III collagen.[8]

Collagen in the reticular dermis

The rest of the dermis, constituting by far the largest portion of the dermis and referred to as the reticular dermis, shows the collagen fibers united into thick bundles. These collagen bundles extend in various directions horizontally, and thus some are cut lengthwise and others across in histologic sections. As a rule, collagen bundles that are cut

lengthwise appear slightly wavy. Biochemically, reticular dermal collagen is composed primarily of type I collagen.[8]

Cross-striation of collagen fibers

Collagen fibrils possess characteristic cross-striations with a periodicity of 68 nm. The periodicity of the cross-striations in the collagen fibrils can be explained as follows; each collagen molecule possesses along its length of 300 nm five charged regions 68 nm apart, and although neighboring collagen molecules overlap with each other, they always have their charged regions lying side by side. This parallel alignment of the charged regions produces the cross-striations. Reticulum fibrils possess the same 68-nm periodicity of their cross-striations as collagen fibrils but have a smaller diameter than collagen fibrils, varying between 40 nm and 65 nm rather than between 70 nm and 140 nm. Furthermore, reticulum and collagen differ in the number of fibrils present in the cross-section of each fiber and in the amount of ground substance present within and around each fiber.[6,7,9] (Figure 3).

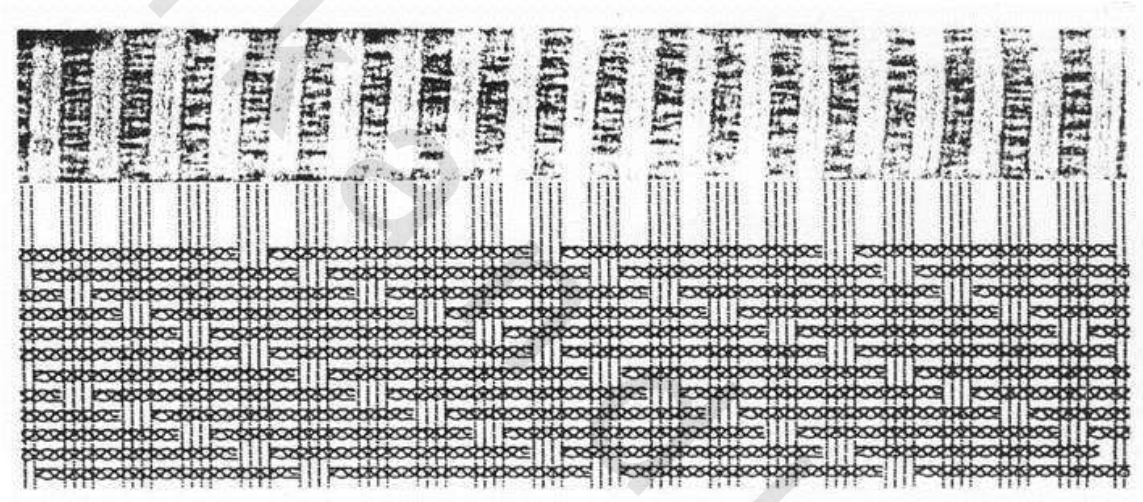

Figure (3): Collagen fibril and cross-striation.[10]

Elastic fibers

Elastic fibers are the concurrent fibrillar network in the dermis besides collagen which provide elasticity and resilience to the tissues. This network of fibers consists of elastin and microfibrils composed by several proteins, such as fibrillins, latent transforming growth factor (TGF)-β–binding proteins (LTBPs), fibulins and microfibril-associated glycoproteins (MAGPs).[6,9]

Development of the elastic fibers

Elastic fibers appear in the dermis at 22 weeks, much later than the collagenous fibers. At this time, acid orcein stains show elastic tissue in the reticular dermis either as granular material interspersed with occasional short fibers or as a delicate network of branching fibers. As gestation progresses, elastic fibers increase in quantity. At 32 weeks, a well-developed network of elastic fibers indistinguishable from that seen in term infants is present in both the papillary and the reticular dermis. Young elastic fibers, as seen in a 22-

week-old fetal dermis, show masses of peripheral microfibrils surrounding a small amorphous electron-lucent core representing elastin, with only a few internal microfibrils. As the embryo matures, the amount of elastin and the number of microfibrils within the elastin increase while the number of peripheral microfibrils decreases.[12]

Components of the elastic fibers

The elastic fiber of the dermis consists of two components: the microfibrils and the matrix elastin. The microfibrils are electron-dense and measure 10 nm to 12 nm in diameter. They are aggregated at the periphery of the elastic fiber, giving the fiber its characteristic frayed appearance by ultrastructure. In addition, microfibrils are present within the elastin as strands 15 nm to 80 nm in diameter, extending in a longitudinal direction. The microfibril component constitutes only 15% of the elastic fiber, on the other hand, the amorphous electron-lucid elastin makes up 85% of the fiber. It is the elastin that stains with elastic tissue stains, is removable by elastase, and is markedly extensible, whereas the microfibrils are the elastic resilient component of the elastic fiber.[13] (Figure4).

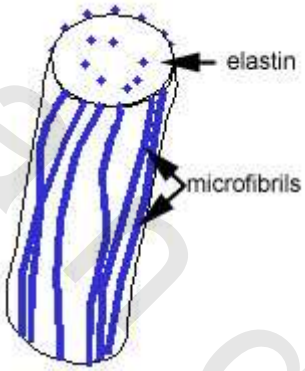

Figure (4): Schematic representation of the components of elastic fibers.[10]

Relationship between elastic fibers and TGF-β

Transforming growth factor (TGF-β) is the most powerful growth factor that is responsible for controlling expression, deposition and degradation of collagens and other extracellular matrix proteins in the skin. It initiates paracrine and autocrine signaling pathways acting on the transcriptional and/or translational levels, and it also induces the expression of other growth factors, in particular connective tissue growth factor.[9,11]

The primary sequence of fibrillins, latent transforming growth factor (TGF)-β–binding proteins (LTBPs) and fibulins are dominated by multiple calcium-binding, epidermal growth factor (EGF)-like motifs. These proteins are of considerable interest because they modulate TGF-β bioavailability. Cells secrete TGF-β as a small latent complex, in which the latency-associated propeptide prevents binding of the growth factor to its receptors, or as a large latent complex with LTBP, which mediates interactions with fibrillin-1 and probably fibulin 4⁄5 and thus anchorage to microfibrils for storage. Binding of MAGPs to microfibrils is thought to displace the small latent complex and release free TGF-β. [9,11]

Changes of elastic fibers and collagen during life

Elastic fibers undergo significant changes during life. One change, representing aging, is best studied in non-exposed skin. The other change, elastotic degeneration, is the result of chronic sun exposure.[14]

In young children up to the age of 10 years, the elastic fibers may not be fully matured, so that microfibrils predominate. Physiologic aging is a gradual process and usually becomes quite apparent by ages 30 to 50. There is a gradual decrease in the number of peripheral microfibrils, so that ultimately there may be none and, instead, the surface of the elastic fiber appears irregular and granular. The microfibrils within the elastin matrix become thicker and show electron-lucent holes of varying sizes. In very old persons, fragmentation and disintegration of some of the elastic fibers may be observed. Oxytalan fibers that consist of microfibrils diminish and ultimately disappear in aging skin.[14]

The deleterious age-related changes in collagen are primarily due to the intermolecular cross-linking of the collagen molecules within the tissues. Cross-linking involves two different mechanisms, one a precise enzymatically controlled cross-linking during development and maturation and the other an adventitious non-enzymatic mechanism following maturation of the tissue. It is this additional non-enzymic cross-linking, known as glycation, involving reaction with glucose and subsequent oxidation products of the complex, that is the major cause of dysfunction of collagenous tissues in old age. The process is accelerated in diabetic subjects due to the higher levels of glucose. The effect of glycation on cell-matrix interactions is now being studied and may be shown to be an equally important aspect of ageing of collagen. An understanding of these mechanisms is Dnow leading to the development of inhibitors of glycation and compounds capable of cleaving the cross-links, thus alleviating the devastating effects of ageing.[15,16]

Pathogenesis

Striae distensae affect skin that is subjected to continuous and progressive stretching; increased stress is placed on the connective tissue due to increased size of the various parts of the body. It occurs on the abdomen and the breasts of pregnant women, on the shoulders of body builders, in adolescents undergoing their growth spurt, and in individuals who are overweight. Factors leading to the development of striae have not been fully elucidated. Striae distensae are a reflection of "breaks" in the connective tissue. Skin distension may lead to excessive mast cell degranulation with subsequent damage of collagen and elastin. Prolonged use of oral or topical corticosteroids or Cushing syndrome (increased adrenal cortical activity) leads to the development of striae. Genetic factors could certainly play a role, although this is not fully understood [17].

Histology of stretch marks

The histology of stretch marks is that of a scar, and the development of SD has been likened to that of wound healing or scar formation. In the early stages, inflammatory changes may be conspicuous, but later the epidermis is thin and flattened. Recent SD show a deep and superficial perivascular lymph-ocytic infiltrate around the venules. 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.The histology of stretch marks is that of a

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Etiology

1. Pregnancy:

Stretch marks in pregnancy, also referred to as striae gravidarum or striae distensae gravidarum, is considered a physiologic occurrence during pregnancy due to the high frequency of cases among pregnant women. They are a common finding on the abdomen, breasts and thighs, of pregnant women, especially during the last trimester. They are more common in younger primigravidas than in older pregnant women. Striae gravidarum can be associated with a higher risk of lacerations during vaginal delivery. [19]

2. Sports:

Striae distensae have been associated with weightlifters and other sports involving weights and/or stretching of the skin. The areas of the skin most frequently involved are the anterior shoulders, lower back and thighs. [20]

3. Glucocorticosteroid-induced striae:

Both systemic and topical steroid therapy can produce cutaneous atrophy by a dose-related pharmacological effect. The effect is more severe with the more potent steroids , but both fluorinated and non-fluorinated topical steroids can cause atrophy. The effect is most marked when potent steroids are applied topically under an occlusive dressing. The skin becomes thin, fragile and transparent, and striae may develop. [21]

4. Obesity:

Striae distensae is associated with obesity due to overstretching of the skin. [22]

5. Cushing's disease:

Cushing's syndrome is the abnormal excessive production of endogenous cortisol. Similar clinical picture can be seen from chronic exogenous administration of glucocorticoids. [22]

Common skin findings in Cushing's syndrome include easy bruising and skin atrophy. Mild hypertrichosis, most commonly of the lanugo type, and acne may occur. Hirsutism and severe acne raises the possibility of a concurrent androgen-secreting tumor.[23]

The development of multiple violacious striae wider than 1 cm on the abdomen or proximal extremities is highly suggestive of Cushing's syndrome. The width and color of these striae differentiate them from striae gravidarum or other types of striae distensae. [23]

6. 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. [24]

7. Infection:

Leading to the release of striatoxin that damages the tissues in a microbial toxic way. [25]

8. Mechanical effect of stretching:

Which is proposed to lead to rupture of the connective tissue framework (e.g., pregnancy, obesity, weight lifting). [26]

9. Immunosuppression states:

Associated with pregnancy-induced hypertension medications, human immunodeficiency virus or diseases such as tuberculosis and typhoid. [27]

10. Associated with chronic liver disease. [28]

Other rarely reported causes of SD include cachectic states, such as tuberculosis and typhoid and after intense slimming diets. They may also be seen in anorexia nervosa. SD has been reported to occur rarely in patients positive for the human immuno-deficiency virus receiving the protease inhibitor indinavir. A case of idiopathic SD was also reported. Men and women with chronic liver disease may also have SD. [27,29]

Clinical picture and distribution [4,5,30-35]

Striae distensae affect skin that is subjected to continuous and progressive stretching. They occur on the abdomen and the breasts of pregnant women, on the shoulders of body builders, in adolescents undergoing their growth spurt, and in individuals who are overweight. [4,34]

Earlier or immature stages of striae distensae, appears clinically as flattened areas of skin with a pink-red hue that may be itchy and slightly raised (striae rubra). Then and due to atrophic changes stretch marks tend to increase in length and acquire a darker purple color. Over time, they become white, flat, and depressed [17]. High-resolution epiluminescence colorimetric assessment of striae distensae, identified four distinct types: striae alba, striae rubra, striae caerulea, and striae nigra. The direct and indirect influences of melanocyte mechanobiology appear to have a prominent effect on the various colors of striae distensae. [4]

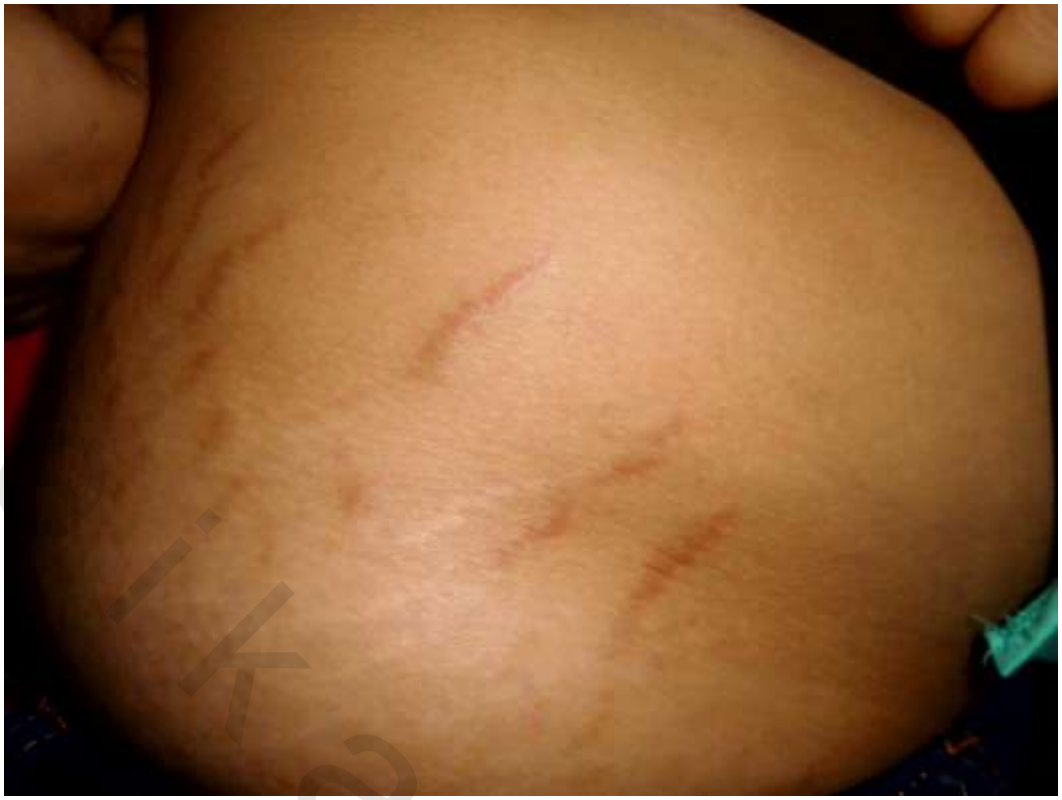

Figure (5): Stretch marks that develop during pregnancy are known as striae gravidarum

Treatments

In current practice, even with the significant dermatologic advances in topical medicaments and light-based devices, total resolution of these lesions remains an unattainable goal. Avoidance of rapid weight loss or gain may help prevent the emergence of stretch marks, especially in high-risk groups such as teenagers and expecting mothers. Adolescents with striae can expect some improvement in their striae over time. [30]

Striae distensae are most likely to respond to pharmacologic products and clinical interventions at their early stage (striae rubra). Once they become white (striae alba), only few treatment modalities exist and they are become quite difficult to treat. Intensive moisturization of the lesions and the use of vitamin C, fruit acids, retinols, and other pharmaceuticals have been advocated for the early treatment of striae distensae rubra. [5]

Various treatments are available for the purpose of improving the appearance of existing stretch marks, including topical preparations such as tretinoin, glycolic acid and trichloracetic acid peels, laser treatments; UVB/UVA1 combined therapy, microdermabrasion, radiofrequency devices and micro-needling therapy alone or combined with platelet rich plasma. [30,31]

The following treatments are among those available to help improve the appearance of stretch marks. None has been proved to be more consistently successful than the others.

Topical Tretinoin application

Topical application of tretinoin has been shown to significantly improve the clinical appearance of early striae distensae (striae rubra). Some research has shown that Topical application of tretinoin may improve the appearance of recent stretch marks those that are less than a few months old and still pink or red in color. Tretinoin, when it works, helps to rebuild collagen, making the stretch mark look more like the normal skin. It should not, however, be used in pregnant or breastfeeding females owing to a theoretical concern about its teratogenic effects. The use of other retinoids such as adapalene and tazarotene may also hold promise in the treatment of striae distensae. Tretinoin can be irritant to skin. This treatment isn't effective on older stretch marks (striae alba). [30,31]

Hydrant Creams

Anecdotal treatments are numerous and unproven. Despite the general understanding that proper hydration is necessary to maintain the integrity and barrier function of skin, little in the literature is available on the use of such creams in stretch mark prevention. Three studies involving 130 men in total were found. The active creams in the studies described are not widely available, and it was not clear whether any particular ingredient was helpful. The lack of clarity on the studies and the scientific data available makes it difficult to conclude such creams are effective, and larger studies are needed to determine the efficacy and safety of such products in combating stretch marks. [32]

Alphastria is a cream that is composed of hyaluronic acid, allantoin, vitamin A, vitamin E, and dexpanthenol. The name is composed of the Greek word ‘‘alpha’’ prefix meaning ‘‘without,’’ and the Latin word ‘‘stria,’’ which means ‘‘lines.’’ Hyaluronic acid is an organic substance found in human skin and is the main constituent of the cream. The hyaluronic content stimulates fibroblast activity and collagen production to restore any inhibition and collagen loss induced by hormonal fluctuations or mechanical stretch. Only one study was conducted to demonstrate the efficacy and safety of the cream. Thirty pregnant women were recruited to receive the cream, and 30 others received a placebo as a control group. Three subjects in the exposed group and 21 in the control group developed SD. The study concluded that the product markedly lowered the incidence of stretch mark development after pregnancy. [33-35]

Topical Oil Massage and Herbal Topical Remedies

Some unconventional therapies and anecdotal reports recommend applying unproven oils and natural remedies to stretch marks. The underlying principle for this use would probably be keeping the skin well hydrated. Sweet almond oil, wheat germ oil, olive oil, avocado oil, and castor oil and applying seaweed wraps have these properties. Other remedies such as comfrey, hypericum, maritime pine, equisetum, slippery elm, and wheat grass and eucalyptus tree oil are all used in creams or oils, but no efficacy studies have been performed to support these practices. [36]

Chemical peeling

Glycolic acid (GA) is an alpha hydroxyl acid. Although there are several reports on the clinical effects of Glycolic acid in rejuvenation, peeling, and photoaging, no data on the effectiveness of Glycolic acid to prevent stretch marks could be found in the scientific

literature. The mechanism of action of Glycolic acid is still unknown because the biological effects of Glycolic acid on cells has not been fully studied, although Glycolic acid is reported to stimulate collagen production by fibroblasts and to increase their proliferation in vivo and in vitro. This mechanism can be useful for stretch mark treatments. [37,38]

Anecdotal reports have indicated the use of TCA in stretch marks, although there is a lack of clarity and absence of data for assessment of this subject. Some authors have had good success using low concentrations (15–20%) of TCA and performing repetitive papillary dermis-level chemexfoliation repeated at monthly intervals with reported improvement in texture and color of marks. [39,40]

Microdermabrasion

Aluminum oxide resurfacing has become a popular method of resurfacing. Microdermabrasion is effective in many skin conditions such as acne scars, mottled pigmentation, and fine wrinkles. It has been established too that microdermabrasion induces epidermal signal transduction pathways that are associated with remodeling of the dermal matrix. Microdermabrasion appears to set in motion a cascade of molecular events capable of causing dermal remodeling and repair. There is a paucity of literature about the efficacy of microdermabrasion in stretch mark therapy, but Mahuzier in his text book on microdermabrasion stated that 10 to 20 sessions of microdermabrasion at an interval of not less than 1 month, each session resulting in bleeding points, provide satisfactory improvement in SD. [41,42]

Radiofrequency Devices

The use of radiofrequency (RF) devices have been reported to be an effective and safe noninvasive technique to tighten the face and neck skin. 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. It is reported that collagen fibril contraction occurs immediately after RF treatments, which induces new collagen formation. [43]

Laiser therapy

Laser therapies use intense wavelengths of light to stimulate the growth of collagen, elastin or melanin production in the skin. Treatment with the 585-nm flashlamp pulsed dye laser at low energy densities was shown to improve the appearance of striae. [30,44,45] Multiple treatments at 4- to 6-week intervals are usually required. At a lower fluence (2-4 J/cm^2), the 585-nm flashlamp pulse dye laser (FLPDL) has been purported to increase the amount of collagen in the extracellular matrix. The 585-nm FLPDL has a moderate beneficial effect in reducing the degree of erythema in striae rubra but has no apparent benefit in striae alba. Because of the potential for adverse effects, FLPDL treatments should be performed with extreme caution or even not at all in darker-skinned patients (phototypes V and VI). [30,46,47]

A study from Korea evaluated the effectiveness of using 585-nm pulsed dye laser with radiofrequency (Thermage; Hayward, Calif) for striae distensae. Thirty-seven patients with abdominal striae distensae were treated with the Thermage and 585-nm pulsed dye

laser in the first session at baseline. An additional 2 sessions of pulsed dye laser therapy were performed at weeks 4 and 8. Thermage was used at a fluence of 53-97 J/cm^2, and pulsed dye laser-therapy was used at a fluence of 3 J/cm^2 with a 10-mm spot. Skin biopsy specimens were taken from 9 patients. [30,61]

In the subjective assessment, 89.2% of the patients showed "good" and "very good" overall improvement, and 59.4% were graded as "good" and "very good" in elasticity. All of the 9 specimens showed an increase in the amount of collagen fibers, and increased elastic fibers were found in 6 specimens. The authors reported that Thermage and pulsed dye laser appear to be an effective treatment for striae distensae. [30,45,46,61]

In another study involving the use of a 1064-nm long-pulsed Nd:YAG laser, the authors reported subjective data (55% of patients reported excellent improvement), and objective photographic findings (40% of evaluating physicians reported excellent improvement). Minimal adverse effects were reported. [30,31,44-47,62]

Intense pulsed light

A noncoherent, nonlaser, filtered flashlamp that emits a broadband visible light, has been reported to yield clinical and microscopic improvement in striae distensae. It seems to be a promising treatment modality with minimal adverse effects and little-to-no down time. Its efficacy in the treatment of photodamaged facial skin has been widely reported; it promotes the production of neocollagen and elastic fibers. [30,31,44-47]

Most of the enhancements in the treatment of striae pertain to striae rubra; only very limited modalities have shown promise in improving the appearance of striae alba. Lasers and light sources emitting UV-B irradiation (eg, the 308-nm excimer laser) have been shown to repigment striae distensae (striae alba). The improvement is due to an increase in melanin pigment, hypertrophy of melanocytes, and an increase in the number of melanocytes. Histologic examination revealed a substantial increase in epidermal thickness as well as collagen and elastic fiber deposition. Minimal pain and post treatment hyperpigmentation were the main adverse events reported. Fractional photothermolysis laser treatments appear to improve the appearance of striae distensae alba, particularly through repetitive treatments. [30]

Pertaining to the use of carbon dioxide ablative fractionated lasers in the treatment of striae distensae, Alexiades-Armenaka et al found that the treatment gives rise to unpredictable results. "The data were inconclusive regarding the treatment of striae distensae following a series of treatments, with some patients demonstrating significant improvement while others showed no change from baseline." On the other hand, other authors found benefit of using fractional photothermolysis via fractional carbon dioxide laser for treatment of striae alba. [30]

Micro-needling therapy

The earliest form of micro needling, acupuncture, can trace its roots to the Chinese centuries ago. Nappage, a French skin rejuvenation technique used the past fifty years, is another form of micro needling where micro incisions are made into the skin placing a drop of vitamins, minerals and anti-oxidants to replace depleted cellular levels. (63,64)

In the 1990's (Orentreich, 1995) advocated the "subcision" with a needle to treat wrinkles near the lip lines. In 1997, (Comrade, et al.) reported that hypochromic facial scars were tattooed with a skin color pigment and 1 to 2 years later, even after the pigment was gone, it was replaced by actual melanin and the scars were improved in texture, appearance and color. After observing this, scars were tattooed without pigment with the idea that breaking down the scar collagen in this manner would cause realignment and stimulate melanogenesis. (63,64)

Dermal Integrity offers the Microneedle Therapy System (MTS) patented MTS Roller™ – a unique 'Type I' FDA-approved supplemental tool is ideal for non-surgical and non-ablative treatment of various skin concerns in conjunction with a skin care product. Clinical studies have shown MTS to be more effective than ablative treatments like laser resurfacing, dermabrasion, and chemical peels and just as effective as non-ablative treatments like IPL, CO2 laser, and Fraxel. (65)

Absolute Absorbency:

Dermal Integrity MTS Roller™ uses 200 very fine needles to injure the skin and then you add your skin care product. (65)

Two major advantages for using MTS Roller™: (65)

1. MTS Skin Rollers are affordable for the patient and practitioner. Compared to the cost of the "high-tech equipment"
2. MTS DermaRollers are safe. "Non-surgical and non-ablative" means more 'forgiving' and skin-friendly. Patients experience little or no pain, downtime, and risk for complications.

Ablative treatments like dermabrasion, chemical peels and laser resurfacing (C02 / Fraxel Repair) do one thing: remove the protective epidermis to force the body to produce a new tissue layer. However, once the epidermis is removed, the lower levels of skin are completely exposed--vulnerable to environmental contamination from dirt, dust, and bacteria. Certain risks must be accepted with these procedures: pain, long-term discomfort, long prevailing inflammation and redness, long healing period, extreme light-sensitivity for a month or more, possible irreversible pigment changes and even additional scarring. (65)

Ablative treatments have their limits. Due to different skin structures on the neck for instance, laser re-surfacing may not be possible. Moreover, because these treatments leave the skin thinner, in some cases these procedures may actually age the skin. microneedling is far more 'skin friendly'. (65)

Downtime

The downtime required of various skin therapies depends on the depth of the injury caused to the skin. Microdermabrasion produces very little downtime – a few hours of tingling and redness. But a deep chemical peel can keep you at home on painkillers for as long as 2-weeks. [65]

Dermabrasion and laser resurfacing will leave your skin red and swollen for around 10-days, total recuperation can be up to 3-weeks. Because they are non-ablative, CO2 and Fraxel lasers, Thermage, and IPL treatments do not produce significant downtime, but the claim of 'no downtime' is somewhat exaggerated. For instance, some Thermage and CO2 patients develop redness and swelling that may last 2-3 days; residual pain may linger for several days. [65]

Microneedling is non-ablative and produces little downtime – skin may be pink after rolling, but will disappear by morning. [65]

Advantages & Indications of microneedling:

Indications for rolling [65]

- Scarring less noticeable
- Reduces the signs of aging

Advantages [65]

- It's safe for all skin types.
- There is no damage to the skin.
- It can be used on thin skin.
- The process is not painful.
- It can be used on any area (face, neck and body).
- It can be used for domestic use without medical supervision safely.

Side effects [65]

- Possible pinkness of the skin which should subside by morning.
- Possible slight skin swelling initially.
- A possible retinoid reaction (redness, flaking, burning or stinging), due to the increase in Vitamin A penetration. This is not harmful, just unpleasant. It does not indicate an allergy to your product and subsides quickly once the Vitamin A is reduced.
- If irritation of the skin results, delay use of the dermaroller for a day or two or until the skin feels comfortable. Or consult with your skin care professional.

Also known as collagen induction therapy (figure 6). It has been shown that rolling with a dermaroller (192 needles, 200 micrometer length and 70um diameter), over an area for 15 times will result in approximately 250 holes per cm^2.during the treatment the needles pierce the stratum corneum and create microconduits (holes) without damaging the

epidermis. Microneedling leads to the release of growth factors which stimulates the formation of new collagen (natural collagen) and elastin in the papillary dermis. In addition, new capillaries are formed. This neovascularization and neocollagenesis following treatment leads to reduction of scars. Microneedling has many uses such as restoring skin tightness in the early stages of facial aging, fine wrinkles, acne scarring, tightening skin after liposuction, stretch marks, lax skin on the arms and abdomen and scars [48].

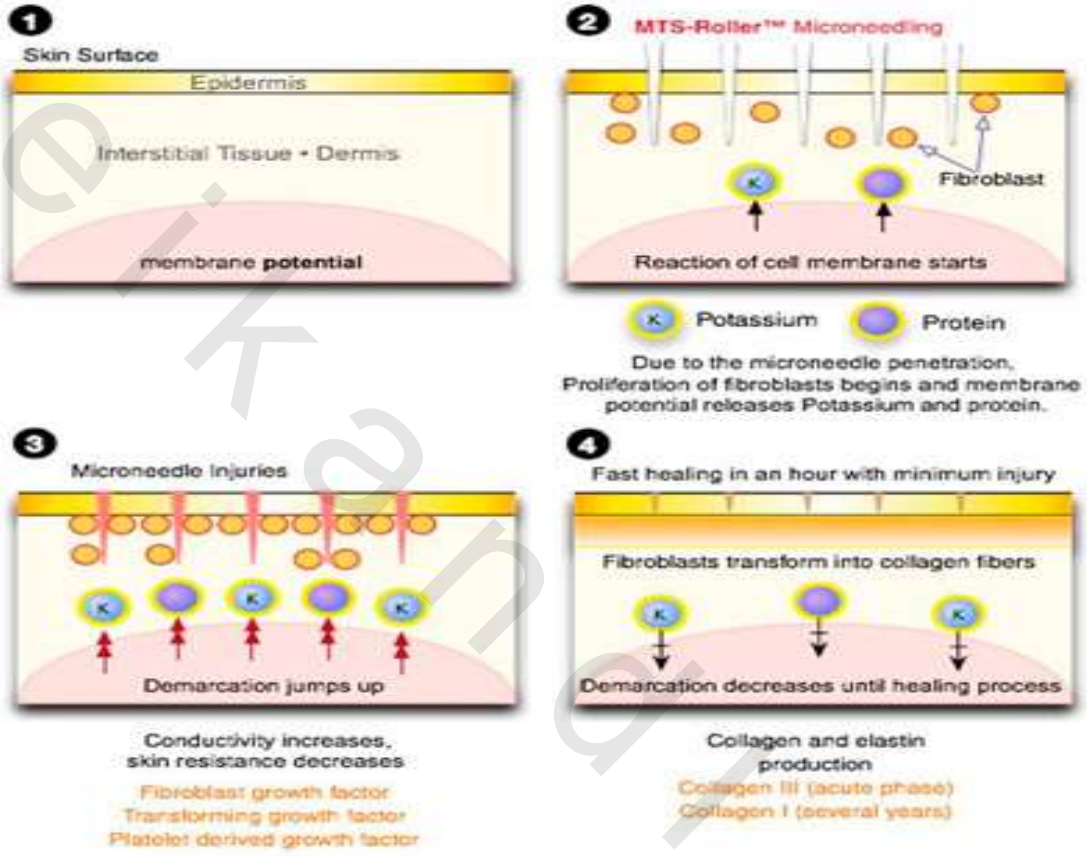

Figure (6): Collagen induction therapy

Microneedling may be used alone or combined with the use of other products which contain multiple growth factors that enhance healing such as platelet-rich plasma (PRP) [49].

Platelet rich plasma (PRP)

PRP describes any autologous blood product that has been processed to increase the concentration of platelets within a small volume of plasma, and therefore the concentration of growth factors. Both the plasma and the concentrated platelets contain fundamental growth factors that may be valuable in PRP preparations. PRP has been used over the last several years as an effective treatment in various surgical and medical fields. It is used in oral surgery for bone grafts and continues to be used in maxillofacial and plastic surgery to augment the healing of a wide range of tissues. [50,51]

Platelet derived growth factors' main functions are to stimulate cell replication (mitogenesis) of healing capable stem cells (table I). It also stimulates cell replication of endothelial cells. This will cause budding of new capillaries into the wound (angiogenesis), a fundamental part of all wound healing. In addition, PDGF seems to promote the migration of perivascular healing capable cells into a wound and to modulate the effects of other growth factors [58, 59]. Fibroblasts are among the cells that are activated by TGF-beta. When a fibroblast is activated it will undergo cell division and produce collagen. Collagen deposition is responsible for plumping the skin. [60]

Table (I): Contents of PRP: Growth factors and their actions [66]

Growth factor	Function
PDGF- αα, αβ, β β	Chemotactic for fibroblasts and macrophages
	Mitogenic for fibroblasts, smooth muscle cells and endothelial cells
TGF*- β1, β2	Mediates angiogenesis
	Chemotactic for fibroblasts, keratinocytes and macrophages
	Mitogenic for fibroblasts and smooth muscle cells
	Inhibits endothelial cells, keratinocytes and lymphocytes
	Regulates matrix proteins, including collagen, proteoglycans, fibronectin and matrix-degrading proteins
VEGF†	Chemotactic and mitogenic for endothelial cells
	Mediates angiogenesis
EGF‡	Mediates angiogenesis
	Mitogenic for fibroblasts, endothelial cells and keratinocytes
HGF§	Mediates regeneration
FGF‖	Mediates tissue organization and regeneration
FGF-9	Aids generation of new follicles

*TGF: Transforming growth factor,
†VEGF: Vascular endothelial growth factor,
‡EGF: Epidermal growth factor,
§HGF: Hepatocyte growth factor,
‖FGF: Fibroblast growth factor

Degranulation of the pre-packaged GFs in platelets occurs upon "activation" i.e., on coming in contact with coagulation triggers. The secreted GFs in turn bind to their respective trans-membrane receptors expressed over adult mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells. This further induces an internal signal-transduction pathway, unlocking the expression of a normal gene sequence of a cell like cellular proliferation, matrix formation, osteoid production, collagen synthesis, etc., thereby augmenting the natural wound-healing process. [52,53]

In 2003, PRP was first reported to be used for musculoskeletal-related injuries. Many musculoskeletal injuries involve anatomic areas with minimal blood flow and a low cell turnover rate. Therefore, the number of growth factors available to enhance healing is not optimized. Platelet-rich plasma may offset this imbalance of growth factor supply and demand that typically hinders the regenerative process, thus enhancing recovery in patients who desire a rapid return to pre-injury level of function. Platelet rich plasma (PRP) contains several growth factors, including platelet-derived growth factors (PDGF), transforming growth factor-beta 1 (TGF-beta 1) at high levels and vascular endothelial growth factor (VEGF). When platelets are activated growth factors are released which emit chemical signals to surrounding areas multiplying the growth factors thus causing a heighten "immune response". [49-51]

Dermatologic indication: [66]

In the field of dermatology, PRP has proven successful for accelerating wound healing. The use of PRP has recently been applied to aesthetic medicine, but there are few studies on the rejuvenation effects of PRP. PRP contains significant amounts of platelet-derived growth factor, transforming growth factor, vascular endothelial growth factor, epidermal growth factor, and fibroblast growth factor and has been shown to enhance early healing through the release of growth factors. [54-57] Data analysed from peer-reviewed journals demonstrates a wide range of dermatological indications ranging from hair restoration to acne scarring: [66]

- Androgenetic alopecia.
- Alopecia areata.
- Skin rejuvenation.
- Acne scars and contour defects.
- Wound ulcers, Connective tissue disease associated ulcers.
- Striae distensae.
- Lipodermatoslerosus.
- Lichen sclerosus.

1. Androgenetic alopecia (AGA) [66,67]

AGA is associated with a significant amount of psychosocial distress both in men and women. Much research has been done to expand the available therapeutic armamentarium. Hair transplantation has proven to be a boon for patients consenting for surgical procedures. Minoxidil and finasteride have an established efficacy in AGA, also as

an adjuvant to hair transplantation. The angiogenic role of PRP has recently caught the attention of dermatologists and plastic surgeons, to explore its usefulness as a hair growth modality.

Various modes of PRP therapy for AGA are as follows:

1. Inter-follicular injection of PRP at the amount of 0.05-0.1 ml/cm2, in a retrograde fashion from deep to superficial, at every centimetre, throughout the treated site.
2. PRP mesotherapy: Scalp is punctured with microneedle roller of 1-mm fine needles followed by interfollicular injections of PRP (or by using mesogun) over the treated area and later, PRP is also sprayed on top of the scalp and left on overnight. It is usually done in 3 monthly sessions.
3. PRP can be used as an adjunct to hair transplantation

Mechanism of action of PRP in AGA

- Upregulation of transcriptional activity of β-catenin→Differentiation of stem cells into hair follicle cells
- Increased bcl-2 levels→Anti-apoptotic→Prolongs survival of dermal papilla cells
- Activation of Akt and ERK signalling pathways→Prolongs survival of dermal papilla cells
- Expression of FGF-7 in dermal papilla cells→Prolongs anagen phase of hair cycle
- Increased VEGF and PDGF→Proangiogenic→Increases peri-follicular vascular plexus

Other alopecias: Alopecia areata, telogen effl uvium

There is a clear paucity of published data in support of this application in alopecia areata and telogen effluvium. Greco et al., tried it in a single patient of alopecia areata as mesotherapy, with good subjective results at 10-months follow-up. Recently a randomized double bind, placebo and active controlled, half-head study evaluated PRP in 45 patients of alopecia areata. Monthly regimen for three sessions resulted in significant increase in hair regrowth and decrease in hair dystrophy and burning/ itching sensation at 1-year follow-up, when compared with intralesional triamcinolone acetate or placebo. However, patients with alopecia areata and telogen effluvium, usually tend to have spontaneous remissions and respond well to commonly used medications, so it is difficult to attribute the regrowth of hair to PRP.

2. Skin rejuvenation [66,68]

Afresh PRP has been an emerging area of interest in aesthetic medicine. PRP has been reported to augment dermal elasticity by stimulating the removal of photodamaged extracellular matrix (ECM) components and inducing the synthesis of new collagen by dermal fibroblasts via various molecular mechanisms.

Mechanism of action of PRP in skin rejuvenation

- Increased proliferation of human dermal fi broblasts
- Increased expression of MMP*-1 and MMP-3→removal of photodamaged ECM

- Increased production of procollagen type I peptide and expression of collagen type I, alpha-I→Synthesis of new collagen
- Increases expression of G1 cell cycle regulators→accelerates wound healing

* MMP: Matrix metalloproteinase

3. Scars and contour defects [66,69]

PRP has become a promising modality among soft tissue augmentation techniques. PRFM has been used as a filler to correct deep nasolabial folds without any adverse effects. As an adjuvant, it has been studied with autologous fat transfer procedures. An *in vitro* pilot study, revealed that fat grafts when mixed with PRP resulted in greater vascularity, fewer cysts and vacuoles, less fibrosis and overall improved survival and quality of fat grafts as compared to saline.

This novel regimen was found to maintain fat graft survival in a patient with facial contour defect for upto 2 years. Data suggests that fat grafts can be admixed with PRP in treating traumatic scars, and further can be followed by fractional laser resurfacing to give best results. PRP injections in combination with fractional carbon dioxide resurfacing have shown good results in acne scar resurfacing also, apart from skin rejuvenation.

4. Acute and chronic ulcers [66,70]

The success of recombinant PDGF-ββ (becaplermin) gel in the treatment of diabetic neuropathic and other chronic wound ulcers, has been translated into the potential use of PRP in the same. It can either be used as topical spray or as perilesional injections. PRFM, a viscous fibrin meshwork rich in GFs, has shown promising results when applied topically to the non-healing ulcers, to augment re-epithelialization. Kim *et al*., treated 16 patients affected by various acute and chronic ulcers including stasis ulcers, diabetic ulcers, livedoid vasculitis, claw foot and traumatic ulcers with PRP. Topical application of PRP significantly accelerated the re-epithelialisation process, shown to be through the upregulation of cell cycle regulatory proteins like cyclin A and CDK4. Even dermatomyositis associated elbow ulcers have been successfully treated with PRP.

However, in view of a small number of randomized controlled trials, most of which being either at high or unclear risk of bias, a recent review concluded that there is no current evidence to recommend the role of PRP for treating chronic wounds.

5. Striae distensae [66,71]

The wound healing properties of PRP has also been applied in treating striae distensae Kim *et al*., treated 19 patients of striae, by employing an intradermal radiofrequency (RF) device, capable of delivering higher energy fluencies directly to the dermis, along with injecting PRP as a filler through its needle electrode. The thermal energy generated by bipolar RF, denatures the elastic fibres and collagen bundles and PRP stimulates wound healing, thereby providing synergistic benefits and good results. Transepidermal delivery of PRP using ultrasound has also been combined with fractional RF for treating striae with post inflammatory pigmentation as the only reported side effect.

6. Lipodermatosclerosis [66,72]

In an isolated case report, refractory lipodermatosclerosis was treated with intralesional subcutaneous injections of PRP in five sessions (fortnightly) that led to complete re-epithelialization of venous ulcer and marked improvement in hyperpigmentation and induration at the treated site.

7. Lichen sclerosus [66,73]

Although the evidence is anecdotal, multilayer PRP injections used along with autologous fat transfer, deserves a special mention as a novel technique in the management of lichen sclerosus of vulva.

Safety of PRP [66,74]

True PRP is definitely autologous. Homologous platelets such as lyophilised donor platelets have no place in this field as they are antigenic by virtue of the abundance of cell membranes. The mitogenic effects of PRP are only limited to augmentation of the normal healing process and is theoretically not mutagenic, as the GFs released do not enter the cell or its nucleus, but only bind to the membrane receptors and induce signal transduction mechanisms.

Being an autologous preparation, PRP is devoid of any serious adverse effects, apart from local injection site reactions like pain or secondary infection, which can be avoided with proper precautions. PRP has no issues regarding transmission of infections such as hepatitis-B, C or HIV. However, safety concerns with bovine thrombin have been raised about the potential transmission of Cruetzfeld-Jacob disease (mad-cow disease). These have been refuted by some stating that the prion vector has been found only in the neural tissues of cattle, whereas thrombin is solely isolated from the blood and is also further processed by heating. Furthermore, reports of post-operative bleeding due to bovine thrombin-induced factor-V deficiency, have made it an unpopular choice.

Table (II): Other Different therapeutic applications using platelet rich plasma therapies. [66]

Emerging field	*Target*	*Results*
Neural regeneration	Peripheral nerve regeneration	Promote regeneration of injured peripheral nerve.
	Central nervous system diseases	Cytokines in PRGFs could be involved in the protecting neurons and glia from apoptosis. Promote axonal outgrowth and remyelination. PRP facilitate angiogenesis and collagen synthesis.
Ophthalmology	Corneal persistent epithelial defects and ocular burns	An effective therapeutic agent for the treatment of a broad etiopathological spectrum of corneal persistent epithelial defects as well as ocular burn.

Cardiovascular therapy	Refractory angina	Intramyocardial injection of autologous PRP combined with Transmyocardial revascularization may be more efficacious at relieving angina and (TMR) improving myocardial function than TMR alone.
	Bypass graft surgery and/or aortic surgery	Enhanced hemostatic success rate, effects on wound healing and increased resistance to infection.
	Post-myocardial infarction remodeling	Improvement of ventricular remodeling and accelerated healing.
Dermatology	Burns	PRGF have the potential to accelerate the wound healing.
	Ulcers	Platelet rich plasma favors the healing process of chronic ulcers.
Cosmetic and plastic surgery	Facial rejuvenation	Non-surgical reduction of wrinkles.
	Surgical intervention	Stop capillary bleeding.
	Dermal augmentation	Platelet rich preparations provide significant long-term and potential for stimulated dermal augmentation.
	Enhancement the regeneration of substance loss	Platelet rich plasma and autologous adipose graft are able to regenerate substance loss and epithelialization with wound closure with a significant healing-time reduction.
	Free fat graft survival	The infiltration of free fat graft with PRGF reduces the inflammatory reaction and increases the maintenance of the transplanted fat cells.
Endodontics	Periapical tissue regeneration	Platelet rich plasma could provide an ideal scaffold for the regeneration of vital tissues in a tooth with necrotic pulp and a periapical lesion.
Cell delivery and regenerative medicine	Enhance cellular proliferation and differentiation	Neural differentiation of human bone marrow stem cells is enhanced over platelet-rich plasma scaffolds.
		Human endothelial progenitor cells interact in vitro with activated platelets under static and flow conditions.
	Increase the efficacy of in vivo tissue regeneration induced by the delivered cells	Platelet rich plasma can potentially accomplish convenient and effective cell delivery into porous scaffolds, for bone tissue engineering as well as soft tissue regeneration.

In conclusion, the potential role of PRP in dermatology and aesthetic medicine is an exciting frontier that may eventually lead to superior therapies in the near future, however according to the evidence based medicine, the level of evidence from the available published data is low. There are no double blind, randomized, placebo controlled trials conducted on a large sample size to constitute a good quality of evidence. Hence, a healthy amount of caution should be exercised by the treating physician in its preparation and use during procedures. Further research is awaited to unfold its long term efficacy and safety.[66]