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Review Article

Skin Ageing-Childhood to Adult

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Abstract

Skin ageing is becoming a growing concern to a wider population as the people in developed countries live longer than ever before. This report aims to review the symptoms of skin ageing, how these changes come about and how the skin heals.

Studies have shown that as age increases, the skin gets drier, more wrinkled, less supple and takes longer to heal from injury. The main reason these changes occur in the skin is the change in hormone levels. There is a big drop in the sex hormones, estrogen and testosterone in both men and women. However, it is estrogen that has the biggest positive effect on the appearance of the skin.

Estrogen therapy increases the thickness of the skin layers, especially the epidermis and dermis, and increases its elasticity by increasing the number of elastic fibres in the skin. The number of collagen fibres and the water content of the skin also increases due to estrogen. The healing time of wounds is increased when estrogen is administered.

Estrogen has many positive effects on the skin and hormone therapy helps the skin to retain its normal functioning into greater ages.

As the life expectancy rises around the world and an increasing proportion of women's lives are spent post-menopause, skin ageing has become a growing concern. This report will be looking at how hormones, particularly estrogen, affect healthy skin ageing. It is important to distinguish intrinsic ageing from extrinsic, which is due to the environment and UV exposure so is often considered 'unhealthy'. Intrinsic ageing is part of an unavoidable chronological process.

Cutaneous aging is the lower keratinocyte turnover rate decreasing skin thickness. Estrogen combats this by stimulating secretion of transforming growth factor beta 1 by fibroblasts leading to synthesis of collagen. Transforming growth factor beta 1 also speeds up the process of wound healing due to lowered elastase levels allowing collagen deposition.

Matrix metalloproteinases and oxidative stress breaks down elastic fibre as you age. Estrogen therapy increases elasticity of the skin by increasing tropoelastin and fibrillin mRNA. It increases the water content of skin by producing more hyaluronic acid. It also prevents the decrease in glandular secretions lowering sebum levels.

The effects of estrogen on wrinkles is quite controversial but most studies agree that hormone therapy has many positive effects on not only the skin but also other systems in the body.

Keywords: *Skin Ageing; Childhood; Adult*

Introduction

The skin is the largest organ of the body, accounting for 15% of the total body weight. This makes it a clinically significant organ as it is a major part of us and often is the first to display signs of malaise of the body, regardless of the system being affected. As the average life expectancy continues to increase, from 200,000 people over the age of 85 in 1948 to 1.4 million in 2012 [1], there is more interest in the skin and the effects of ageing on it. This interest is not only for aesthetic and cosmetic reasons but also has clinical relevance. This literature review will look at the (i) the skin structure and function (ii) estrogen and other hormones involved in ageing (iii) the effect of these hormones and finally (iv) how ageing affects wound healing.

Skin structure

The skin has varying thickness at different anatomical sites of the body. Skin around the eyes is the thinnest in the body at 0.5mm and the soles of the feet are 4mm, the thickest [2]. Multiple studies have found that men have thicker skin than women [3,4]. Firooz., *et al.* [4] conducted a study that found that males have statistically significant thicker skin in the neck and dorsum of the foot compared to women. The skin consists of 3 layers; the dermis, epidermis and hypodermis.

The surface layer, epidermis, has a keratinized stratified squamous epithelium with 4 or 5 layers of keratinocytes depending on the skin thickness. The stratum corneum is the most superficial and then the stratum lucidum (only present in thick skin), stratum granulosum, stratum spinosum and the strum basale [5]. The stratum corneum's main function is to protect the skin and maintain hydration. The epidermis has the important task of creating a functioning stratum corneum. The primary cells are keratinocytes which produce keratin but there are also other cell types dispersed in the epithelium [6]. These cells are the melanin producing melanocytes, antigen presenting Langerhans cells and Merkel cells which synapse with dermal sensory axons and epithelial to detect mechanical stimuli and pressure.

The dermis is between the hypodermis and dermal-epidermal junction (shown in figure 1 as the basement membrane).

It consists of elastic fibres, blood and lymph vessels and some muscle fibres, as seen in figure 1. The dermis delivers nutrients and provides circulatory support to the epidermis so is highly vascularised. It also has pilosebaceous and sweat glands.

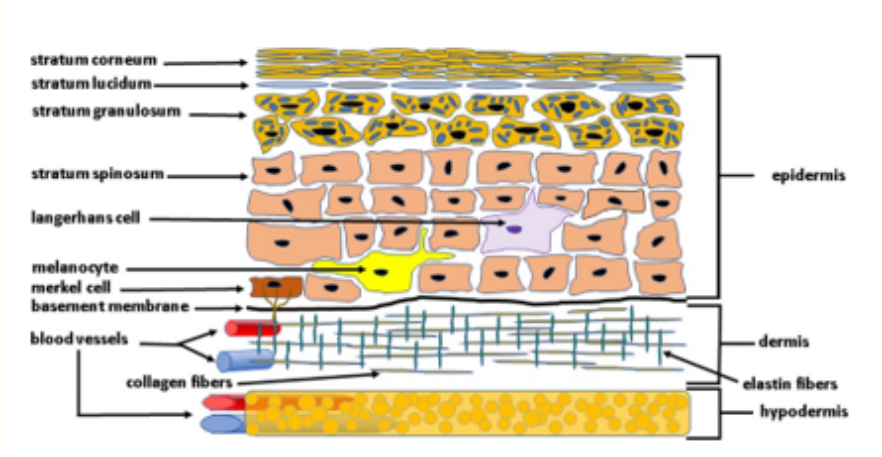

Figure 1: *Sourced from [7] showing the structure of the skin. The three layers of the skin can be seen labelled to the right of the figure. On the left the five layers if the epidermis and the content of the three layers can be seen.*

Often it is called a connective tissue matrix as 90% of the dermis is collagen and the vast majority of that (80%) is type I collagen [6] Type 1 collagen determines the strength of the skin while type iii is more involved with elasticity [8]. There are 2 layers, the papillary dermis and the reticular dermis. The papillary dermis interacts with rete ridges from the epidermis and hair follicles. It has small diameter collagen fibres, Type iii, interspersed with elastic fibres. Type i collagen fibres have a larger diameter and are densely packed in the reticular dermis [9].

The hypodermis is the deepest layer of the skin and consist mainly of loose connective tissue organised into adipose tissue to insulate the skin. This tissue has lots of proteoglycans and glycosaminoglycans which attract fluids. Adipose homeostasis is regulated by macrophages, adipose cells and fibroblasts found in this third layer [10].

Extracellular matrix (ECM) molecules are between the cells in the skin to provide a constructive framework. The ECM helps cells bind together and regulate their adhesion, proliferation and differentiation. These molecules include glycosaminoglycans bound to proteoglycans, structural fibrous proteins (collagen and elastin) and adhesive fibrous proteins (fibronectin and laminin) [11]. Their receptors are called integrins and can be found on the majority of cell surface membranes in the body. When it binds to its ligand, there is an immediate signal transduction induced causing changes in cellular function.

The three layers of the skin consist of many different molecules and cells such as keratinocytes, Langerhans and Merkel cells, collagen and elastin. These constituents and the ECM molecules have a variety of jobs and roles that they have to carry out for the proper functioning of the skin.

Skin function

The structure of the skin allows it to perform the essential functions of the body.

The skin has seven major functions: protection, sensation, homeostatic regulation, excretion, immune surveillance, growth and endocrine [12].

Protection is the skins most evident function. Strong and elastic protein fibres such as keratin, collagen and elastin protect the body form physical and mechanical forces. As well as preventing internal organ damage the skin protects from UV exposure, microorganisms, dehydration and dangerous chemicals. Melanin from melanocytes is produced to absorb some of the UV radiation and protect the body from it.

Somatic sensory receptors can be found in the skin to aid in sensation. These receptors range from pressure receptors to pain and temperature. Merkel cells in the epidermis are also involved in this.

The adipose cells in the hypodermis create a layer of insulation for the body. Exothermic processes in the body produce excessive energy that must be dissipated to prevent overheating. Blood vessels in the dermis expel heat via radiation and evaporation. Heat loss can be prevented by vasoconstriction and vasodilation directing blood away from the skin.

The skin is an excretion organ. It excretes water to the skins surface by diffusion and other waste products i.e. urea, salts and sodium are removed by sweating.

Langerhans cells from the epidermis interact with T cells to help protect the body from bacterial agents [13]. Phagocytic cells in the hypodermis engulf the bacteria.

The skin can expand due to the elastin fibre therefore as the organism grows so does the skin.

Cells in the epidermis use energy stored in the UV radiation to produce vitamin D3 (cholecalciferol). This goes to the liver and then the kidneys where it is activated to the hormone calcitriol. Calcitriol regulates levels of calcium and phosphate ions found in the skin and in blood.

The skin's barrier function is it's most obvious function. It helps keep the body hydrated and prevents the loss of excess water or heat energy. It also keeps out pathogens. The sensory receptors on the skin are essential to be able to feel pain and know when in danger. The elastin fibre in our bodies help us grow and not stretch skin in the process. All of these functions of the skin are affected by ageing in various ways.

Healthy skin ageing

Ageing is defined as the loss of structural integrity and function and in regard to the skin involves the degradation of the cutaneous barrier. It affects structural and functional properties of the skin, mostly by changing collagen content and elasticity.

Skin ageing can be intrinsic and extrinsic and both of these have different characteristic. Extrinsic factors include lifestyle influence i.e. smoking and drink as well as UV exposure, photoageing [14]. Intrinsic ageing is the deterioration of regenerative abilities of the skin. Its factors include ethnicity, anatomical variations and hormonal changes, which is the focus of this review.

Telangiectasia, hyperpigmentation due to melanocytic hyperplasia, diminished elasticity causing wrinkles and xerosis are the basic biomarkers of aged skin. Intrinsically aged skin tends to be smooth and pale, with fine wrinkles and dryness [9]. Extrinsically aged skin, on the other hand, is characterised by darker, more pigmented skin which is rough.

Histologically there are many changes in aged skin. Rete ridges (epithelial extensions projecting into mucous underneath) flatten out and retract so the epidermis gets less blood supply due to decreased surface area. This thins the epidermal layer and the epidermal turnover rate decreases 30 - 50% by the age of 80 years old [14]. The lowered mitotic activity in the basal layer increases time for the keratinocytes to move to the stratum corneum. The epidermis' main role is make a fully functioning stratum corneum and ageing causes a decline in the skin's ability to form a protective barrier. The slow replacement of lipids in the stratum corneum increases transdermal water loss in the lipid barrier is compromised. The vertical height of keratinocytes and their adherence decreases. Corneocyte surface area increases causing the keratinocytes to become resistant to apoptosis and accumulate DNA and protein damage over time.

The stratum spinosum also sees a decrease in thickness with the number of melanocytes, Langerhans and Merkel cells dropping. Melanocytes decrease in number with age causing greying hair and decreased UV protection. This decrease in UV protection presents clinically as darker age spots in sun exposed areas. A layer of amyloid P deposit can be found on the elastic fibres in the papillary dermis due to light damage after decrease in UV protection from the melanocytes [14].

The stratum germinativum sees a big change with the cells increasing in size and volume due to decreased mitotic activity with age [15]. The skin has less dendrite formation and less antigen trapping capabilities with age as the number of Langerhans cells decrease 50% by 80.

The dermis loses thickness due to extracellular matrix atrophy. Collagen and elastin synthesis slow down as matrix metalloproteinase enzymes such as MMP1 break down the elastin and collagen fibres. Mitochondrial oxidative stress is also involved in the process. This causes in the skin of mitochondrial DNA in dermal fibroblasts. Loss of collagen and elastin increases distensibility of the skin and loses tonicity, increasing appearance of wrinkles [16].

The decreased blood supply to the epidermis, loss in thickness of the layers of skin and increased appearance of the hallmarks of ageing are mostly accounted for by endocrine changes in the body as age increases.

Hormonal changes in ageing

In healthy skin ageing, there are changes in endocrine systems like oestrogen (menopause), testosterone (andropause), somatopause which involves the GH/IGF-1 axis and adrenopause.

There is a net decline in sex hormones with ageing due to a loss of function of the gonads. This has many implications on various systems of the body [17]. This decline is shown in figure 2. The estradiol (E2) levels in women have a sudden, steep decline at menopause, around 55 years of age, from approximately 200 pg/mL to near 0. In males, the initial levels of E2 are lower than in females, peaking at 60 pg/mL around 40 years and gradually decreasing to 10 pg/mL. Testosterone follows a similar shape as E2 in both sexes. In women, it peaks at 100 ng/dL and in men at 600 ng/dL.

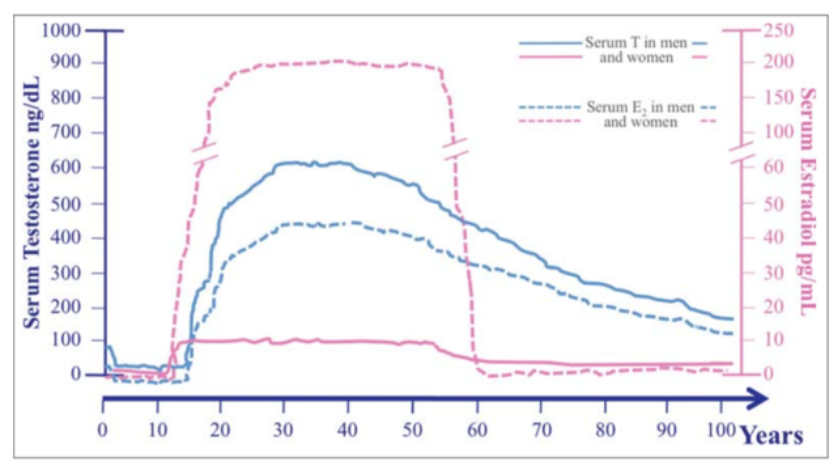

Figure 2: *Sourced from [18] showing the serum levels of testosterone and estradiol in men (in blue) and women (in pink). Testosterone is T and Estradiol is E2.*

To summarise, in men, the sex hormone levels steadily decrease alongside testicular function but in women the decline is more sporadic during menopause. After 50, however, there is a steady decline in serum E2 in both sexes.

In women, menopause happens in 3 stages: perimenopause, menopause and post menopause. Andropause is a decrease in testosterone levels at mid-age in men. This drop is more gradual compared to women but can be drastic in some. Symptoms of andropause include an increase in growth of facial and body hair.

As people age, their pituitary hormone levels, i.e. growth hormone (GH), also decrease. The decrease in GH with age (somatopause) presents as an increase in visceral body fat, a decrease in lean body mass and in aerobic capability [19]. The increased abdominal fat further inhibits GH secretions in the body, exacerbating the decline in levels.

Changes in serum prolactin levels with age is a controversial topic. Some studies suggest that the levels decrease alongside other pituitary hormones [18]. A study by Sawin, Carlson, Geller, Castelli and Bacharach [20], however, suggests that serum prolactin rises slightly with age in men but in women it falls until approximately 80.

Thyrotropin hormone (TSH) is an exception as it increases over time. Insulin like growth factor 1 (IGF-1) also decreases with age [18].

The decrease in GH, IGF-1 and the sex hormones have major effects throughout the body and cause many of the changes seen in senescence. In particular, menopause, and the lowered levels of estrogen in the body that accompany it, determine the cutaneous changes seen with ageing.

Types of estrogen

This review's main focus will be the effect of estrogens on healthy skin ageing. Estrogen is a complex of three hormones that work together in different ratios. There are 3 major types of estrogen: estrone (E1), estradiol (E2) and estriol (E3) [21]. E1 is mainly found in postmenopausal women when it is synthesised from adipose tissue. It has medium potency and is needed for bone health. E2 is the most potent estrogen produced by estrogen biosynthesis from the ovaries. It is highest in concentration in women pre-menopause. The third estrogen, estriol is only found in significant levels during pregnancy when its produced by the placenta. It is a waste product made after the metabolism of E2. It is important in maintain the ratio of the other two types of estrogens and protects against breast and uterine cancers. The three types of estrogen all share the two receptors that are expressed on human cells.

Estrogen receptors

There are two molecular mechanisms of estrogen effect. The classical mechanism involves estrogen directly interacting with estrogen receptors (ER) on the nuclear membrane to regulate gene transcription. This is done by the receptor ligand binding to the DNA in the regulatory region of the target gene. The intracellular steroid receptors have two isomers ER-α and ER-β. They are coded by genes on chromosomes 6 and 14 respectively [22]. They often coexist as homodimers and E2 has similar affinity to both receptors so is the most potent sex steroid hormone in the body.

Estrogen in non-reproductive tissue activates the non-classical pathway. The non-genomic mechanism uses membrane estrogen receptors i.e. GPR30 coupled to the cytosolic signal transduction pathway.

The membrane ERs have a similar structure to ER-α and they activate G proteins and therefore the signal transduction stimulates a mitogen activated protein kinase (MAPK) called extracellular regulated kinase (ERK). ERK promotes osteoblast proliferation and stimulates nitric oxide production in endothelial cells, stimulating angiogenesis [8]. This pathway works within seconds to minutes but the classical pathway has a more delayed onset.

Both ER-α and ER-β are expressed mid gestation. A study by Ohata., *et al.* [23] shows that ER-α is expressed in 70% of sebaceous glands and 17% of hair follicles and is equal in both sexes. ER-β is expressed in every normal constituent of the skin including sebaceous glands, hair follicles, adipocytes, epidermis, eccrine glands, blood vessels, nerves and fibroblasts. Dermal papilla cells stained for ER-β but not for ER-α [23].

The two estrogen receptors have a similar structure but are expressed differently. Membrane ERs work via the non-classical pathway while ER-α and ER-β mostly use the nuclear membrane receptor mechanism which is called the classical pathway, The location of expression of the estrogen receptors is related to the effect estrogen will have there.

Estrogen effects on skin structure and function

Estrogens have a major role is skin ageing homeostasis. They increase collagen content, skin thickness and improve skin moisture by inhibiting matrix metalloproteinases that break down collagen thus increasing fibroblast viability.

Studies show that estrogen has an effect on the skin's collagen content, which provides support for skin resistance. There is an average linear decline of 2.1% of skin collagen and 1.13% of skin thickness per postmenopausal year [8]. Ritté L, Kang S and Voorhees JJ [24]

showed that topical E2 application increases procollagen 1 and 3 mRNA and collagen 1 protein levels in women after menopause. Thus, they proved that the menopause associated decline in estrogens is involved in lowered collagen production. A study furtherer supports this by indicating that the proportion of type iii collagen is higher in women receiving hormone therapy [25]. E2 promotes collagen production by increasing transforming-growth-factor-beta-1 (TGF-β1) production by dermal fibroblasts. TGF-β1 also is involved in accelerated wound healing [8].

When estrogens 20-hydroxyecdysone (Ecd) and E2 were administered to ovariectomised rats, they showed an increase in epidermal and dermal thickness [26]. The skin's thickness increases due to greater collagen synthesis and turnover as shown in a study with rats [27]. The increase in skin thickness possibly is the cause of the unchanged pigmentation and telangiectasia, dilated capillaries that appear in small red clusters on the skin, post hormone therapy [28]. Table 1 shows the results of more studies involved with estrogen's effects on skin thickness.

Study	Type of measurement	Hormones used	Results
1	Skin biopsy	Conjugated equine estrogens or transdermal 17β-estradiol	Increase in skin collagen of 1.8-5.1% after HRT for 12 months
2	Skin thickness	17β-estradiol gel or estradiol patches	Increase in skin thickness of 7-15%
3	Skin thickness	Conjugates estrogen 0.625 mg	Increase in skin thickness by 11.5% after HRT for 1 year
4	Skin biopsy	Topical 17β-estradiol	Increase in hydroxyproline by 38% after 3 months of treatment

Table 1: *Sourced from [8] showing the effects of estrogen on skin thickness.*

Skin elasticity decreases with ageing. This loss may cause delayed wound healing, wrinkles and ulcers. A cutometer reading of 339 women showed that breast skin elasticity decreases with age [29]. 7 months of estradiol/dyhydrogesterone therapy showed an increase in gross and net elasticity of the skin from the baseline [28]. There is an increase in tropoelastin and fibrillin mRNA due to estrogen which increases elastic fibres.

The skin retains moisture more when being treated with estrogen. Hyaluronic acid is a glycosaminoglycan with the capacity to retain water molecules. Studies [30,31] show that estradiol treatment induces an increase in hyaluronic acid and therefore dermal water content in mice. A study also suggested that the increase in hyaluronic acid synthesis is directly proportional to the age of the mouse [30]. The stratum corneum lipids hold water and maintain skin barrier function. Estrogen prevents the decrease in glandular secretions with age, increasing sebum levels and therefore increasing skin moisture [7]. There is a decrease in sebum secretion with ages as sweat glands shrink and relocate closer to the skin surface due to increased expression of matrix metalloproteinases [32]. These mechanisms increase the water content of the skin.

Wrinkling in the skin histologically refers to the atrophy of dermal collagen, alteration of elastic fibres and decrease in glycosaminoglycans. Estrogen's effect on the appearance of wrinkles is controversial. Some studies suggest it increases collagen and glycosaminoglycans content in the dermis. The elastic fibres have also been proven to thicken in the papillary dermis, be in better orientation and higher in number due to estrogen [8]. Owen., *et al*. [33] showed in a randomised, double blind placebo controlled trial that hormone therapy doesn't significantly affect wrinkles and skin rigidity at most facial locations. The study shows that lowered estrogen levels decrease capillary blood flow. Similarly, a trial by Yoon HS, Lee SR and Chung JH [34] shows that topical oestrone application doesn't increase type 1 procollagen staining but does increase MMP1 mRNA. Wolff EF, Narayan D and Taylor HS [35] on the other hand, indicated that the average wrinkle

scores are higher in women who didn't use hormone therapy. The scores were measured by dermatologist, with a higher wrinkle score signifying deeper and more visible wrinkles, and a durometer was used for the skin rigidity measure.

Estrogens also have an effect of keratinocyte function. E2 *in vitro* supresses apoptosis in keratinocytes by promoting Bcl-2, cyclin D2 and D1 expression. This simulates proliferation and DNA synthesis of keratinocytes by binding to GPR30 and activating the cAMP/PKA signalling pathway. These go on to produce more collagen which improves skin structure and wound healing times.

Estrogen and wound healing

One of the skin's most important functions is protection and so it is imperative for it to form a barrier against the rest of the environment. When there is a lesion in the skin this allows for microorganisms to enter the body and in serious cases this could possibly lead to death due to sepsis or infection. This makes wound healing essential for the wellbeing of the body.

The three overlapping steps of cutaneous wound healing are inflammation, proliferation and maturation and remodelling. The inflammatory phase prevents bleeding, combats infectious agents that may be present and attracts cells vital for repair to the zone of injury. Macrophages are essential for this phase. The blood around the lesion coagulates via and aggregation of thrombocytes and platelets in fibrin temporarily restoring the skin barrier function. Leukocytes and other cells migrate to the area and secrete chemokines and cytokines i.e. IL-1, tumour necrosis factor alpha and interferon gamma, causing inflammation. They activate neutrophils and macrophages. The macrophages phagocytose muscular debris and make prostaglandins.

The proliferation phase involves angiogenesis, granulation tissue formation, wound contraction and epithelialisation. Granulation of the tissue involves increased proliferation of fibroblasts and more synthesis of collagen an elastin fibres. The fibroblasts release interferon beta, IFN- β. The rest of the repair process is regulated by keratinocytes. Myofibroblasts contract the wound to close the lesion. Angiogenesis is the final stage and occurs in the extracellular matrix.

The maturation and remodelling phase increases the strength of the scar tissue up to 2 years post wound closure [36]. As age increases wound healing slows down due to fibronectin being broken down by elastase. At this stage, the extracellular matrix matures and the inflammation goes down. When the wound closes there is increased degradation of Type iii collagen and instead Type I collagen is synthesised.

Topical estrogen application in mice reduces neutrophils, macrophages and the expression of tumour necrosis factor alpha (TNF-α). It also increases Ym1-positive cells which are macrophages involved in tissue repair by releasing anti-inflammatory cytokines and the expressing TGF-β1 [37]. TGF-β1 is a cytokine for cell proliferation, differentiation and matrix production. In wounds, TGF-β1 and mRNA levels are higher in those that are younger. Estrogen shows an increase in collagen and strength. It does this by reducing neutrophil chemotaxis and inhibiting L-selectin expression. This reduces elastase levels so fibronectin is preserved and accelerates wound healing. The decreased wound elastase and fibronectin degradation allow for increased fibronectin levels.

Estrogens have been shown to accelerate wound healing and androgens make it slower. It decreases reepithelialisation time and wound breadth [7]. A study by Mirnezami, Rahimi, Fakhar and Rezaei [38], however, showed that although conjugated estrogen decreased healing time from 11.87 ± 2.01 days to 11 ± 1.81, it is not as effective as other studies suggest.

Conclusion

Cutaneous ageing has hallmark structural changes, both macroscopic and microscopic, that define it. These include decreased thickness in the skin due to a lower keratinocyte turnover rate. MMPs and oxidative stress break down the collagen and elastic fibres. This

increases distensibility of the skin, making it look more wrinkled. The decrease in melanocyte number causing greying hair and less UV protection. Ageing increases the time taken for cutaneous wounds to heal due to the decrease in estrogen levels and general senescence.

Chronological skin ageing is heavily reliant on the endocrine changes of the body. In particular, the serum estrogen levels have an effect on the structure and function of the skin.

Hormone therapy in postmenopausal women shows an increase in epidermal and dermal thickness due to increased synthesis and deposition of collagen. Elasticity increases after estrogen therapy because there are more and better orientated elastic fibres. The increase in number of elastic fibres in due to more tropoelastin and fibrillin mRNA. The effectiveness of hormone treatment on the appearance of wrinkles is controversial. Some studies claim that skin rigidity and depth of wrinkles increases post hormone treatment. Other trials show that although estrogen increases MMP1 mRNA, there isn't any change in procollagen type 1, which is essential in skin elasticity. Estrogen increases the water content of skin by increasing hyaluronic acid levels and stopping the decrease of glandular secretion with age. It also stimulates the secretion of TGF-β1 by fibroblasts which increases the synthesis of Type iii collagen in particular.

TGF-β1 is also involved in wound healing. Increased collagen deposition speeds up the process of wound healing. It inhibits L-selectin expression to lower elastase level. The degradation of fibronectin slows down allowing wound healing time to decrease. Although there are contradictions in some studies, in general most agree that estrogen administration decreases healing time to a certain extent. It is not agreed to what degree that is applicable yet.

Estrogen has proven itself to be essential for the wellbeing of the skin. Lowered serum estrogen levels have shown to cause many skin problems in women and men as they age. Studies about hormone therapies have shown the structural improvements in skin regarding wound healing ability, barrier function and thickness.

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