1. INTRODUCTION

Wound healing is a natural restorative response to a tissue injury. It is the interaction of a complex cascade of cellular events that generates resurfacing, reconstitution, and restoration of the tensile strength of injured skin **(Simon et al., 2016)**.

Hypertrophic scars and keloids can be described as variations of typical wound healing. As the scar matures, it becomes hyperemic and it may be thickened; however, it tends to subside gradually until a flat, white, pliable, possibly stretched and mature scar develops. When an imbalance during the healing process occurs, more collagen is produced than is degraded, and the scar grows in all directions **(Berman et al., 2016)**.

A keloid is an abnormal proliferation of the scar tissue that forms at the site of cutaneous injury. It does not regress and grows beyond the original margins of the scar **(Wilhelmi, 2015)**. On the other hand, the hypertrophic scar is a widened or unsightly scar that does not extend beyond the original boundaries of the wound. Unlike keloids, the hypertrophic scar reaches a certain size and subsequently stabilizes or regresses **(Kokoska et al., 2016)**.

Dermoscopy is a widely used non-invasive diagnostic technique which provides up to a ten times greater magnification than the unaided eye and can show the structure of the upper layer of the dermis, and therefore yielding many

diagnostically relevant findings **(Yoo and Kim, 2014)**. It improves the diagnostic accuracy for pigmented lesions in comparison with the examination with the unaided eye. Although initially it was mainly used for diagnosis of neoplastic lesions, its indications have recently been expanded to include inflammatory skin diseases, hair and nail diseases **(Kittler et al., 2016)**.

Because of the difficult distinction between keloids and hypertrophic scars clinically and the unpractical application of histopathological differentiation due to the high cost and lengthy preparation time; **Yoo and Kim** in **2014** studied the dermoscopic features of keloids and hypertrophic scars to differentiate them based on their characteristic dermoscopic features and they could demonstrate distinctive dermoscopic features especially in keloids where vascular structures including arborizing, linear irregular and comma shaped vessels were frequently seen.

2. AIM OF THE WORK

The aim of this work was to find out the dermoscopic differentiating features between keloids and hypertrophic scars in their recent phases of development in Egyptian population.

3.1. DERMATOSCOPY

Dermatoscopy is a non-invasive method which allows the in vivo evaluation of colors and microstructures which are invisible to the naked eye. It can identify the microstructures located in the epidermis, dermoepidermal junction, and papillary dermis, which are correlated to histologic features **(Stanganelli and Pizzichetta et al., 2016)**. Thus, dermatoscopy acts as a link between macroscopic clinical dermatology and microscopic dermatopathology **(Zivkovic et al., 2006)**.

3.1.1. Models of Dermatoscopes:

The models of dermatoscopes have been classified into:

3.1.1.1. Dermatoscopes without Image Capturing Facility:

It is the simplest and best-recognized piece of equipment used to perform a dermoscopic examination ***(Fig.3.1.1)*** **(Campos-do-Carmo and Ramos-e-Silva, 2008)**. It is similar to an otoscope, user friendly, and inexpensive. The optical features include monocular observation, magnification X10, and the use of an illumination system (3.5-V halogen lamp) **(Stanganelli and Pizzichetta et al., 2016)**.

Fig. (3.1.1): A handheld dermatoscope ***(Campos-do-Carmo and Ramos-e-Silva, 2008).***

3.1.1.2. Dermatoscopes with Image Capturing Facility:

These instruments are capable of image capture either through an inbuilt system or through an attached camera **(Marghoob et al., 2003)**.

3.1.1.3. Dermatoscopes with Image Capture Facility and Analytical Capability:

In these models, advanced computer based systems are used to capture the image, and then analyse it by checking its morphological and color characteristics and extracting measurable features **(Maglogiannis and Delibasis, 2014)**.

3.1.2. Physics and Essential Components of a Dermatoscope:

3.1.2.1. Principles of Dermatoscopy:

Normally much of the light is reflected off the surface of the skin because the refractive index of the stratum corneum is higher than that of air. Dermatoscopy works principally through modifying the cutaneous air–tissue optical interface **(Wang et al., 2012)**.

The non-polarized dermatoscopy (NPD) changes the air–tissue optical interface through the use of a liquid interface that optically matches the refractive index of the glass plate of the dermatoscope with the stratum corneum. Elimination of the air interface reduces the amount of light reflected off the stratum corneum, and thus allowing for increased light penetration into the skin **(Pan et al., 2008)**. NPD requires a contact interface, and thus the pressure on the skin surface might lead to blanching and obscuration of cutaneous blood vessels. The polarized dermatoscopy captures a superior image with more details of deeper structures in the skin rather than the surface details and superficial skin structures **(Marchetti et al., 2015)**.

3.1.2.2. Components of a Dermatoscope:

- ***Achromatic Lens:*** usually provides 10x magnifications, **(Marghoob et al., 2013)**.

- ***Inbuilt Illuminating System:*** Halogen lamps are placed within the handheld piece. The color contrasts of lesions are altered by the yellow light of halogen lamps. Light emitting diodes (LED) provide a high intensity white light and consume 70% less power than halogen lamps. Illumination can be altered by turning off a set of LEDs **(Nischal and Khopkar et al., 2005)**.
- ***Power Supply:*** Handheld instruments are usually powered by batteries.

3.1.3. The dermoscopic colors:

Dermatoscopes are modified magnifying devices that permit the visualization of pigmented structures or vessels in the epidermis and superficial dermis **(Micali et al., 2011)**.

Colors of skin lesions can provide important morphologic information ***(Fig.3.1.2)*** **(Weismann and Lorentzen et al., 2006)**. Melanin is the main chromophore in the pigmented skin lesions. Depending on the anatomic location and concentration of melanin in the skin, the colors perceived on dermatoscopy range from black to blue **(Reisfeld, 2000)**. If melanin is located in the stratum corneum or immediately beneath it, the lesion would appear black on dermatoscopy. Melanin at the dermoepidermal junction would be perceived as light brown to dark brown, depending on its density. Melanin in the dermis results in shades of blue to grey. Other important determinants of lesion color include hemoglobin in red blood

cells which is perceived as pink to red colors, collagen fibers in the dermis reflected as white colors and keratin which gives orange to yellowish discoloration on dermoscopy **(Wang et al., 2012)**.

Fig. (3.1.2): The interpretation of colors seen with a dermatoscope ***(Weismann and Lorentzen et al., 2006)*.**

3.1.4. Vascular Structures in Dermoscopic examination:

Different vascular patterns are identified through dermatoscopy ***(Fig.3.1.3)*** **(Malvehy et al., 2006)**. The most important ones are comma-shaped vessels, dotted vessels, linear irregular vessels, hairpin vessels, glomerular vessels, arborizing vessels, crown vessels, the strawberry pattern, milky-red areas or globules, and lacunae **(Martin et al., 2012)**. Erythema, which presents as diffuse areas of pink-reddish

color, is a non-specific feature frequently seen in melanoma as well as in any irritated lesion. Telangiectasia presents as ramified dilated vessels and they are frequently detected on the face and, if presents as branch-like, it is highly suggestive of basal cell carcinoma. The presence of red lines and red spots in irregular pattern along with small parallel and vertical vessels is a frequent feature of invasive melanoma. Red-milky globules occur in melanoma. Vessels in uniform hairpin form seen in seborrheic keratosis, whereas vessels in irregular hairpin form with bizarre patterns of vases on the surface are suggestive of melanoma. **(Campos-do-Carmo and Ramos-e-Silva, 2008)**.

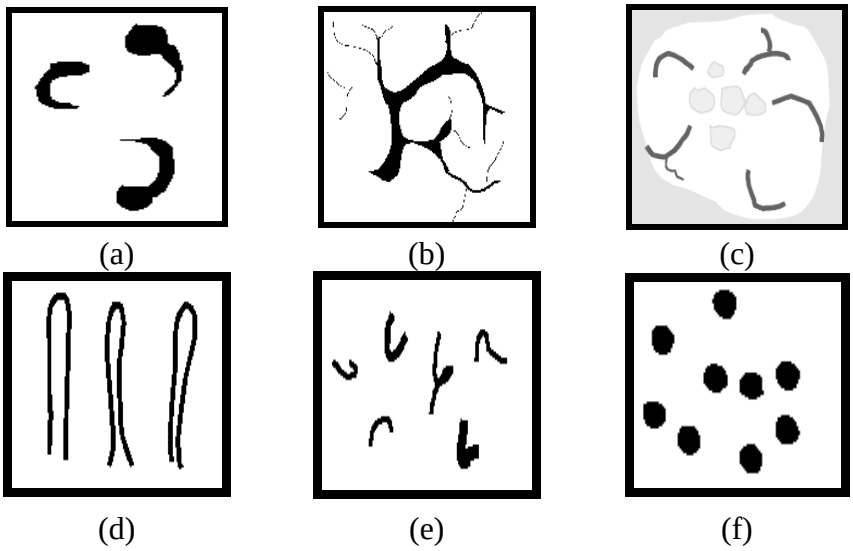

Fig. (3.1.3): Examples of vascular patterns in tumoral lesions: (a) comma vessels; (b) wreath vessels; (c) arborizing vessels; (d) hairpin vessels; (e) linear irregular vessels. ;(f) dotted vessels ***(Malvehy et al., 2006).***

3.1.5. The uses of dermatoscopy:

Initially dermatoscopy was largely used for diagnosis of melanocytic lesions and melanoma; however, it can be also used in evaluation of amelanotic lesions; this is feasible because of the ability to evaluate the morphology, distribution, arrangement of blood vessels, white shiny structures and the superficial dermal microstructure; thus, it improved the diagnosis of many diseases and was used as a diagnostic tool for basal cell carcinoma, dermatofibroma, seborrheic keratosis, hemangioma, melanoma, Spitz nevi, and clear cell acanthoma. It also helps in monitoring the adverse effects of topically applied drugs like topical corticosteroids and for the perfect determination of sites of biopsy (**Marghoob et al., 2013)**.

3.2. KELOID AND HYPERTROPHIC SCARS

The keloid is an abnormal scar that grows beyond the boundaries of the original site of skin injury. Keloids have the clinical appearance of a raised amorphous growth and are frequently associated with pruritus and pain. Electron microscopy reveals a number of distinguishing features, including randomly organized collagen fibers in a dense connective tissue matrix. In normal scars, the collagen bundles are arranged parallel to the skin surface **(Kokoska et al., 2016)**.

On the other hand, the hypertrophic scars are erythematous, raised, firm areas of fibrotic skin that are limited to the original wound site. They tend to form within the first month after the injury but can become flatter and more pliable over time and often resolve within a year (**Ud-Din and Bayat, 2013)**.

3.2.1. Epidemiology:

- **3.2.1.1. Incidence:**

The excessive wound healing in both keloids and hypertrophic scars is found only in humans and occurs in 5-15% of wounds. Moreover, hypertrophic scars are more common than keloids. They could be seen in approximately 50% of post-surgical wounds and more than 50% of healed deep burns **(Newsome et al., 2006)**.

- **3.2.1.2. Age:**

Keloids are more prevalent in persons aged 10-30 years, while hypertrophic scars occur in persons of any age. In general, the risk for either type of abnormal scar diminishes with age **(Wilhelmi, 2015)**.

- **3.2.1.3. Sex:**

The prevalence has been reported to be higher in young females than in young males, probably reflecting the greater frequency of earlobe piercing among females. Keloids and hypertrophic scars affect both sexes equally in other age groups. Both keloids and hypertrophic scars tend to be familial **(Berman et al., 2016)**.

- **3.2.1.4. Race:**

A higher risk of hypertrophic scars and keloids exists in dark-skinned individuals **(Simon et al., 2016)**.

3.2.2. Predisposing factors:

Several genetic and environmental causes have been implicated in the aetiology of keloid and hypertrophic scars. In both keloid and hypertrophic scar formation, an excessive accumulation of collagen from increased collagen synthesis or decreased collagen degradation occurs **(Wilhelmi, 2015)**.

The exact mechanism by which keloids and hypertrophic scars develop is not well known. However, predisposing factors including trauma, skin tension, foreign body, infection are more associated with

keloids and hypertrophic scars, although some individuals report spontaneous keloids formation **(Kokoska et al., 2016)**.

3.2.3. Aetiopathogenesis:

Wound healing is classically divided into four stages: hemostasis, inflammation, proliferation and tissue remodelling. In these four stages, there are complicated interactions within a complex network of profibrotic and antifibrotic molecules, such as growth factors, proteolytic enzymes and extracellular matrix (ECM) proteins **(Tredget, 1999)**. Fibrosis occurs when the repair process becomes deregulated and/or accentuated, leading to excessive ECM accumulation, which can result in the formation of hypertrophic scars or keloids **(Andrews et al., 2016)**.

The imbalance of the deposition and degradation of ECM proteins occurs when there is excessive production of collagen, proteoglycans and fibronectin by fibroblasts or deficient degradation and remodelling of the ECM occurs **(Wang et al., 2011)**. Collagen over-synthesis is found in hypertrophic scars and it is even higher in keloids. Moreover, the ratio of type I to type III collagen is also high in both keloids and hypertrophic scars. The collagen overproduction can be attributed to the increased fibroblastic activity together with their higher rate of fibronectin biosynthesis **(Wilhelmi, 2015)**.

The inflammatory response immediately after injury may play a pivotal role in determining the outcome. Although not entirely clear, regulation of the inflammatory response through the proinflammatory cytokines IL-6 and IL-8, and anti-

inflammatory cytokine IL-10 may contribute to scarring **(Breman et al., 2016)**.

Growth factors like transforming growth factor β (TGFβ), platelet-derived growth factor (PDGF), and epidermal growth factor (EGF) may also contribute in the pathogenesis of keloids and hypertrophic scars. It has been shown that TGF-β 3 prevents, whereas TGF-β 1 & 2 enhance the scarring process **(Breman et al., 2016)**. PDGF acts through increasing the fibroblastic proliferation and collagen production. Fibroblast growth factor receptors have been shown to up-regulated in the scarring tissue **(Simon et al., 2016)**. EGF mediates its effects by binding with its receptor on the keratinocytes and fibroblasts **(Nanney, 1990)**; the stimulatory effect of EGF on keratinocyte proliferation and fibroblast activity results in reduction of the healing time and improvement of the tensile strength **(Browen et al., 1986).**

3.2.4. Clinical Picture:

Keloid formation can occur within a year after injury **(Jansen et al., 2016)**. Keloid scars can be differentiated from hypertrophic scars by their spread beyond the original wound. Keloid scars tend to remain red, pruritic, and painful for many months to years **(Wilhelmi, 2015)**.

On the other hand, hypertrophic scars remain within the confines of the wound. Initially, they can be raised, red, pruritic and even painful **(Berman et al., 2014)**. Hypertrophic scars usually develop 6 to 8 weeks after injury and a period of at least 6 to 18 months is required for their maturation. They may then

undergo partial regression within 1 to 2 years without any intervention **(Karagoz et al., 2012)**.

3.2.5. Histopathology:

Keloids are characterized by haphazard deposition of thick, hyalinized eosinophilic collagen bundles within the dermis forming nodules that contain an abundance of eosinophils, mast cells, plasma cells and lymphocytes ***(Fig.3.2.1).*** Moreover, keloids also exhibit abundant mucinous mucopolysaccharide ground substance **(Jumper et al., 2015)**.

Hypertrophic scars ***(Fig.3.2.2)*** also demonstrate increased collagen bundles histologically which lie parallel to the epithelial surface; however, the collagen lacks the hyalinized appearance noted in keloids **(Jumper et al., 2015)**. Flattening of the epidermis and replacement of the papillary and reticular dermis by scar tissue with prominent vertically oriented blood vessels are characteristics for hypertrophic scars **(Rabello et al., 2014)**. **Lee et al (2004)** pointed out that keloidal collagen which was diagnostic for keloid, was only found in 55% of keloidal specimens. Alpha -smooth muscle actin (α-SMA) expression was found in both hypertrophic scar (70%) and keloid (45%), thus it would not be a differentiating marker and the authors suggested that in scars with no detectable keloidal collagen, the presence of the following feature(s) favours the diagnosis of keloid: non-flattened epidermis, non-fibrotic papillary dermis, a tongue-like advancing edge, horizontal cellular fibrous band in the upper reticular dermis, and prominent fascia-like band.