Comparison between Dermoscopic and Histopathological Features of Keloids and Hypertrophic Scars Before and After Different Treatment Modalities.

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Abstract

Background: Keloids and hypertrophic scars (HTS) are abnormal wound responses. Lack of knowledge about their basic biology had prevented development of a targeted approach to the treatment of keloids and hypertrophic scars.

Aim of the work: The study aimed to evaluate the dermoscopic and histopathological features of keloids and hypertrophic scars before and after different treatment modalities.

Methods: Thirty-two patients with keloids and hypertrophic scars were included in the study for clinical, dermoscopic and histopathological examination.patients receieved tratment in form of Fractional Co_2 laser or 5FU or verapamil . Examination of slides stained by H&E and the special stain (Masson trichrome) was performed, also CD31 immunohistochemistry was performed in all cases. The histopathological examination of slides both HTS and keloid before and after treatment was done. The pattern of collagen fibers was determined by hematoxylin and eosin stained sections and Masson Trichrome stained sections. The pattern and extent of vascularity demonstrated by CD31 immunostaining was evaluated.

Results: Vancouver scar scale showed significant improvement in all patients. histopathological improvement (the collagen fibers detected by Masson trichrome in the upper dermis of HTS cases become thinner and the MVD detected by CD31 IHC staining showed increased vascularity after treatment). Hypertrophic scars showed better improvement than keloids in all groups. Arborizing and linear vessels showed significant improvement in group 1&2. Linear vessels showed significant improvement in group 3.

Conclusion: Fractional Co_2 laser combined with 5FU is an excellent choice of treatment in keloids and hypertrophic scars.

Keywords: HTS, keloid, Masson trichrom, CD31.

Introduction:

keloids and hypertrophic scars are macroscopic cutaneous scarring resulted from disturbance of wound healing, that occurs on predisposed individuals **(1)**. It shows a kind of over-healing, producing over abundant wound matrix responsible for raised, inflexible red scar tissue, that causes pain and itching**(2-3)**. Also, it can lead to serious functional and cosmetic concerns. Excessive scarring following trauma that causes tissue loss is identified into two types; keloid and hypertrophic scars **(4)**.

Keloids and hypertrophic scars are resulted from skin injury and irritation, including trauma, insect bite, surgery, burn, vaccination, skin piercing, acne,

folliculitis, herpes zoster and chicken pox infection. The injuries that don not affect the reticular dermis not cause keloid or hypertrophic scars **(5)**. This may denots that the pathological scars are caused by cutaneous injury and subsequent excessive wound healing. Such excessive wound healing is characterized by progressive and localized inflammation, leading to presence of proliferated inflammatory cells, fibroblasts, excessive collagen deposition and newly formed blood vessels in the dermis **(6)**.

Inflammation of the reticular dermis is stimulated by many intrinsic and extrinsic factors. The features, amount, and course of keloids and HTS are affected by these stimuli (**7)**. It is suggested that the intensity, duration and frequency of these stimuli determine the rate of scar formation, the direction and speed of growth, symptoms intensity. The stimuli are variable, including local, systemic and genetic factors. It is concluded that the difference between keloids and HTS clinically may be due to difference in the intensity, frequency and duration of inflammation of the reticular dermis **(8)**.

Hypertrophic scars remain confined to the boundaries of the original lesion, regressing spontaneously after the initial injury. They may produce scar contractures when located over joints **(9).** Most hypertrophic scars do not recur after surgical excision. Keloids develops from either a deep or a superficial injury. They are also red and itchy, exceed the boundaries of the initial injury as they do not regress with time,or with high recurrent rate after surgical excision, and usually do not provoke contractures **(10)**.

There are many histopathological differences between keloid and hypertrophic scar. Among these differences, keloid scar is characterized by the presence of thick, hyalinized collagen bundles or 'keloid collagen' with mucinous ground substance and few fibroblasts, but in hypertrophic scar, little or no keloidal collagen is found **(11)**. Hypertrophic scar ischarecterized by the presence of nodules containing a high density of cells and collagen. The collagen fibers are cigar-shaped and run parallel to the surface of the skin, located in the middle or deeper layer of the scar, and oriented along the tension lines of the scar. Such nodules are absent in keloid scars. Also, hypertrophic scars are characterized by the presence of numerous fibroblasts but few glassy collagen bundles and scanty mucinous ground substance, their collagen fibers are oriented parallel to the long axis of the scar, but in keloid, collagen is arranged in a haphazard pattern **(12)**.

Aim of the work:

This study aimed to identify the morphological features in depth; the possible diagnostically relevant differences between keloid and hypertrophic scar before and after treatment through using histopathological, special stains, and immunohistochemical studies. Such distinctive features may help in understanding the pathogenesis of these lesions; their differentiation and interpretation of the clinical behavior.

Material and methods:

This was a follow up prospective study approved by the Research Ethics Committee of Benha Faculty of Medicine, Benha University. All patients provided a written informed consent before initiating the study procedures. A total of 32 egyptian patients with hypertrophic scar or keloids (Fitzpatrick skin type III to IV), who attended out-patient clinic of Dermatology Department, Benha University hospitals in the period between November 2015 to January 2017 were enrolled in this study. Exclusion criteria for study participation were pregnancy or breastfeeding, patients using oral retinoids six months prior to this study or active infection at site of lesion. Lesions suspicious for malignancy and patients suffering from cardiac diseases were also excluded.

A complete history was taken from the patients (including personal history, history of scars, history of other skin diseases or drug intake) and general clinical and cutaneous examination for size and location of the scars and digital photography was performed before and after treatment. Baseline scar assessment was made using Modified Vancouver Scar Scale. Cases were randomly classified into three treatment protocols groups. Group 1 (Co_2 laser + 5-Fluorouracil), Group 2 (Co_2 laser + topical verapamil hydrochloride), Group 3 (CO2-Laser).

Skin specimens from all cases with keloids and hypertrophic scars were taken before and 6 months after Co_2 laser sessions. The samples were fixed in 10% formalin for 24 hours at room temperature, embedded in paraffin, and sectioned at 5 μm for conventional histological examination. Histological analysis and photographs were carried out using Leica Research microscope (Model no DM 1000 LED, Germany). Sections were stained with hematoxylin-eosin (H&E), Masson's trichrome to highlight the orientation and thickness of collagen fibers. Sections were stained with anti-CD31 antibody to determine the pattern and extent of vascularity.

Immunohistochemical staining for CD31:

Sections of three micron were cut and carried to aminopropyl triethoxy silane (Sigma-Aldrich Chemical Co., USA) coated slides and incubated overnight at room temperature. The slides were warmed in a slide warmer for 15 minutes. Deparaffinization were carried out through three changes of fresh xylene. Each change was for 5 minutes, then dehydration was carried through absolute alcohol seies,each for 5 minutes. Peroxide block (Biogenex life science Pvt.Ltd.,CA,USA) was used to block the endogenous peroxidase for 15 minuteat room teperature. Washing with distilled water, followed by citrate buffer (PH 6.0) wash for 10 min. Biogenex antigen retrieval system was used for antigen retrieval. Dipping of the sections in citrate buffer solution, the were put in Biogenex antigen retrieval system and warmed for 15 minutes. The system was put under tap running water for cooling, then the slides were washed with distilled water for 5 minutes. Sections were incubated with a blocking agent for blocking the endogenous biotin for 15 minutes. Then incubation of the section with the primary monoclonal antibody of CD31 (dilution 1: 50, Biogenex life Science Pvt Ltd., CA, USA) for 1 hour was done. The slides were washed thoroughly with citrate buffer. DAB chromagen was prepared just before the use, and then it was added for 5 minutes on the sections. Then the sections were washed in buffer followed by water. The last step was counterstaining the slides with Harris hematoxylin, air dried, cleared and mounted with Canada balsam. Pyogenic granuloma tissue was used as positive control.

Interpretation of CD31immuno staining:

According to **Connolly et al., 2014** blood vessels were counted using a Leica Research microscope with provision for photomicrograph (Model no DM 1000 LED, Germany). The stained sections were first screened at low power (×10) to determine the areas of most intense staining for CD31. Blood vessel counting was then performed under × 40 magnification. The area of each field was almost 0.2 mm^2. The blood vessel density was recorded as a mean ± standard deviation (SD). Those endothelial cells colored with brown CD31 and formed a cluster of endothelial cells with a lumen were considered as blood vessels. Single CD31-positive endothelial cells were also included in the count. Blood vessels with muscle wall were excluded. Three high-power fields (HPF) with the highest number of blood vessels (hot spots) were chosen. The representative areas were carefully scanned from left to right of every slide to avoid recounting of same areas. The endothelial cells for each case were the average number of blood vessels in these three chosen HPFs and expressed as the number of endothelial cells per HPF (endothelial cells/HPF). The mean of three values was calculated and expressed as cut off point to classify cases as hypovascular and hypervascular. Cut off point for cases before treatment was 16 and after treatment was 21. Positive and negative controls were performed for the stain.

Results

Demographic and clinical data of the studied patients

Fifteen patients had hypertrophic scars (46.9%), and 17 had keloids (53.1%). Mean scars duration (from exposure to the cause to the time of first evaluation at the outpatient clinic) was 9.1± 2.3 months, ranged from 2 to 180 months. The size of the scar ranged from 2 cm^2 to 160 cm^2 (mean =25.6 ± 16 cm^2). The age of the studied groups ranged from 3 to 52 years (mean=24.5 ± 15.3 years). Both genders were equally represented (16 males and 16 females). Skin type IV was the most common type (71.9%) according to Fitzpatrick classification.

Seven cases had personal history of keloids and hypertrophic scars, 3 had family history. The most prevalent symptom was itching (62.5%) followed by pain (43.8%). Scald was the predominant cause of scars (40.6%), followed by burn (31.3%), idiopathic (18.8%), trauma (6.3%) and plastic surgery (3.1%). The most common site of lesions was the upper limb (40.6%), followed by chest (25%), abdomen (15.6%), back (9.4%), face (6.3%) and lower limb (3.1%). Most of patients (40.6%) were subjected to intralesional injections of steroids (ILI), followed by cryotherapy (21.9%), topical creams (9.4%) and lastly surgical removal (6.3%). Half of patients have not received any therapy

Dermoscopic results:

No statistically significant differences were found in dermoscopic improvement between different treatment modalities. Arborizing and linear vessels showed significant improvement in group 1&2. Linear vessels showed significant improvement in group 3.

Histopathological results:

- **Hematoxylin and eosin**: HTS was significantly associated with higher proportion of normal epidermal thickness with flattening, disorientation of basal cell organization, absent basal cell vascular changes; while keloid was significantly associated with higher proportion of normal epidermal thickness of rete ridges, regular palisading of basal cell organization, presence of basal cell vascular changes. In cases of HTS, the BVs in 100% of cases were vertically oriented around nodules, however in cases of keloids , 100% of cases showed BVs aggregating below the epidermis with in or out growth and that difference in the BVs distribution was statistically highly significant (P value < 0.01) as showen in the figures 2, 8. Also regarding the degree of inflammation, it was found marked increase in the degree of inflammation in the cases of HTS, and keloid after treatment, and that increase was statistically significant (P value < 0.05) as shown in Fig 1(A,B,C).

Table 1 : Histopathological features of HTS and keloid before treatment.

Histopathological features	Hypertrophic scar (N: 15)	Keloid (N:17)
Histopathological features in the Epidermis:		
Normal thichness of rete redges.	0	15
Normal thickness with flattening	15	0
Hyperkeratosis	13	15
Hypergranulosis	13	15
Spongiosis	3	3
Basal cell palsiding	2	15
Basal cell disorientation	13	2
Histopathological features in the Dermis		
Collagen site	100% papillary dermis, upper 1/3 of reticular dermis.	100% papillary dermis, full thickness of reticular dermis.
Collagen arrangement and quality • **Haphazard** • **Nodules** • **Parallel to the skin**	 0 15 cases with fibrillar collagen of fairly regular thickness. 15	 17 with large broad, glassy esinophilic collagen. 0 0
Collagen cellularity: • **Acellular:** • **Numerous**	 1 14	 5 12
Orientation of blood vessels *Vertically oriented around nodules *Aggregate below epidermis	 15 0	 0 17
Chronic inflammation • **Mild**	 13	 15

• **Moderate**	2	2

Table 2: Histopathological features of HTS and keloid after treatment.

Histopathological features	Hypertrophic scar (N: 15)	Keloid (N:17)
Collagen:	Decrease size of nodules with decrease space between fibrils of collagen.	Decrease thickness of collagen bundles, bundles become more compacted, less space between fibers.
Blood vessels density:		
• **Hypovascular:**	2	9
• **Hypervascular:**	13	8
Chronic inflammation		
• **Mild**	5	9
• **Moderate**	10	8

Results of Masson Trichrome stain:

HTS showed thinner blue stained collagen fibers in the papillary dermis and upper one third of reticular dermis. Keloids showed thinner better organized collagen bundles and that difference in the thickness of collagen in cases of HTS and keloid before and after treatment was statistically significant (P value< 0.05) Fig 1(D,E).

Table (3). Histopathological features of lesions stained with Masson Trichrome before and after treatment.

	Histopathological features	
	Before treatment	**After treatment**
Keloid	Large broad blue stained focally fragmented collagen in papillary dermis and full thickness of reticular dermis.	Thinner better organized collagen bundles.

Hypertrophic scar	Fibrillar, of fairly regular thickness blue stained collagen fibers in the papillary dermis and upper one third of reticular dermis.	Thinner blue stained collagen fibers in the papillary dermis and upper one third of reticular dermis.

- **Results of CD31 immunostaining**:

HTS was significantly more vascular before (p=0.047) and after (p=0.019) treatment than Keloid cases which were significantly less vascular. MVD in cases of HTS increased after treatment and the difference in MVD in cases of HTS was statistically significant before and after treatment (P value< 0.05), unlike cases of keloid (p=0.607) Fig 1(F,G,H).

Table (4) Comparison between results of CD31 immuno-staining:

	Before treatment N=32				**After treatment N=32**			
	Hypovascular		**Hypervascular**		**Hypovascular**		**Hypervascular**	
	No	%	No	%	No	%	No	%
HTS	5	33.3%	10	66.7%	2	13.3%	13	86.7%
Keloid	11	64.7%	6	35.3%	9	52.9%	8	47.1%
P value	0.077				0.019			

N: B. P1, comparison between hypo and hyper in HTS and keloid, compared by Fisher exact and Chi square tests; p2, comparison between hypo and hyper before and after treatment, compared by Mc Nemar test. Categorical data are expressed as number and percentage.

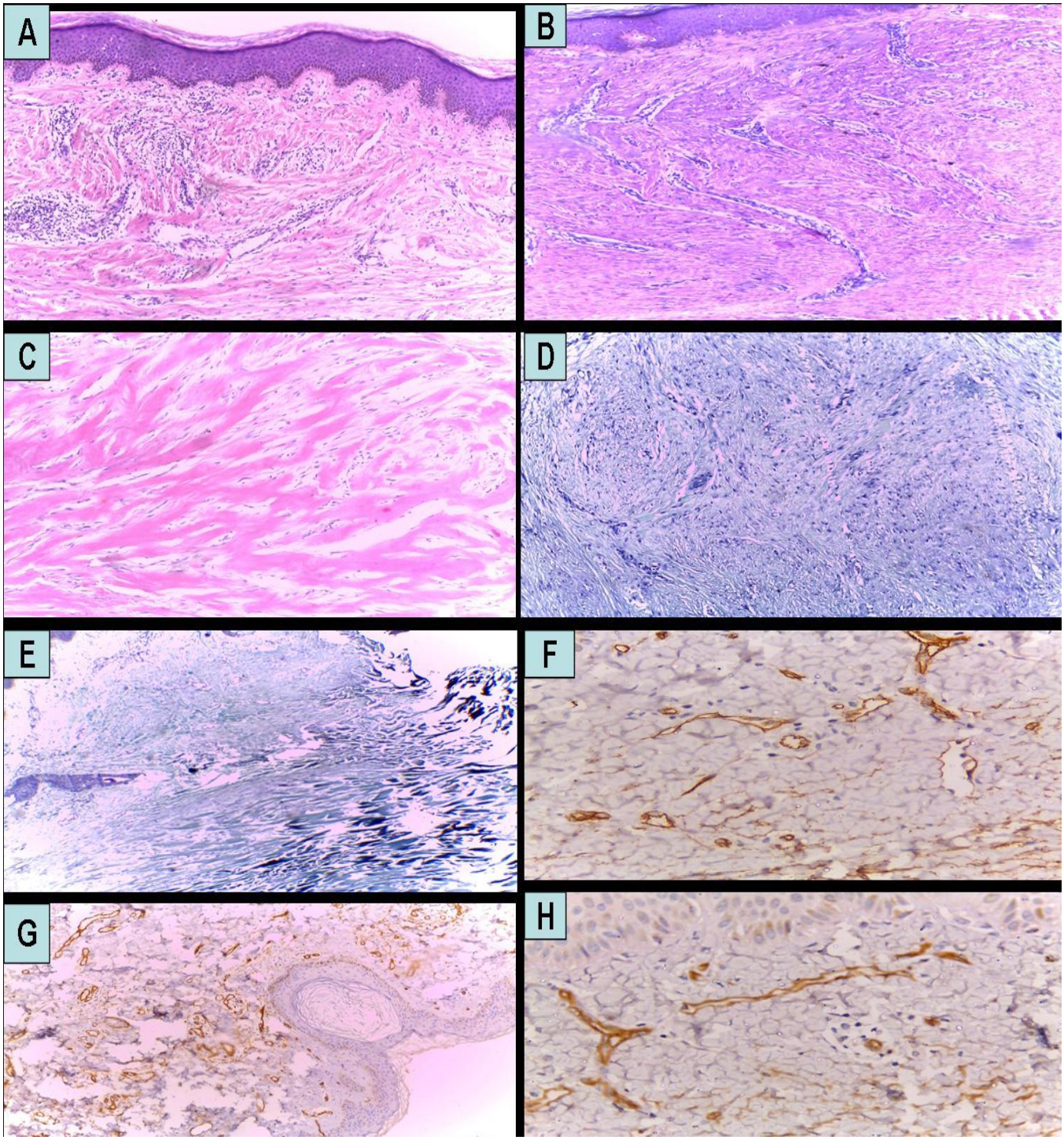

Fig (1). A: HTS showed moderate inflammation after treatment with reduced collagrn thickness (H&E X200), **B:** HTS showed vertically oriented blood vessels within or out the collagen nodules (H&E X200).**C:** Keloid scar before treatment showing abnormally large dense, broad, glassy, eosinophilic, arranged haphazardly (H&E X200).**D:** 4. HTS showed nodules of fibrillary collagen of fairly regular thickness (Masson Trichrome X200).**E:** A case of Keloid with decreased thickness of collagen after treatment (Masson trichrome X200).**F:** CD31 expression in a hypervascular case of HTS before treatment (IHC, DAB x 400). **G:** CD31 expression in a hypervascular case of HTS after treatment (IHC, DAB x 200). **H:** CD31 expression in a hypovascular case of keloid before treatment with BVs accumulation beneath epidermis (IHC, DAB x 400).

Discussion:

Keloids and HTS are different variants of scaring process, so each type needs a different way of treatment. It is essential to differentiate between them, both clinically and histopathologically **(3).** In the current study histopathological differences including epidermal and dermal changes specifically collagen orientation and thickness were examined in 15 hypertrophic scar, and 17 keloid biopsies, before and after treatment which were selected on clinical diagnosis. Histopathological differences between them are often considered to be significant. There are conflicting reports in literature as to whether there are histopathological distinctions between these two scars. The results of current study confirm and extend the reports of histopathological differences.

Before treatment, histopathological features of HTS includes normal epidermal thichness with flattening, hyperkeratosis, hypergranulosis, spongiosis and basal cell disorientation. The collagen was in papillary dermis, upper 1/3 of reticular dermis in all cases. The collagen nodules showed fibrillar collagen of fairly regular thickness, collagen cellularity was moderate. The blood vessels were vertically oriented around nodules, and the inflammation was mild. The main histopathological features of keloid were normal epidermal thichness of rete ridges, hyperkeratosis, hypergranulosis, and basal cell palasiding. The collagen in all the cases was in the papillary dermis, full thickness of reticular dermis, large broad, glassy esinophilic , hypercellular collagen. The blood vessels were below epidermis, and the inflammation was mild. Such differnce in collagen pattern and orientation and site of blood vessels in HTS and keloid was statistically significant (P value < 0.01).

These results parallel to results reported by other study **(12)** who found that the orientation of BVs and the epidermal features are clues for differentiation between keloid and hypertrophic scar. Also, it was found that in keloid samples the presence of hyalinized collagen is the most important feature for differentiation, however in cases of HTS the presence of collagen nodules are pathognomonic feature. Also noticed that pathological criteria of inflammatory reactions as microvessels proliferation, fibroblastic proliferation, and inflammatory cells infiltrate diminished gradually from periphery to keloid centre **(8)**.

After treatment with different modalities, in all cases of HTS, collagen nodules showed decrease in size of nodules with decrease space between fibrils of collagen, 13/15 was hypervascular and 66.7% of cases showed moderate inflammation, however in all cases of keloid, there was decrease in thickness of collagen bundles, bundles become more compacted, less space between fibers. Increased number of cases showed moderate inflammation. Such changes in collagen pattern, vascularity intensity and degree of inflammation between cases of HTS and Keloid was statistically significant (P value < 0.05). Similarly, it was found that there was a marked increase (82.6%) in blood vessels in the papillary dermis in cases with mature HTS after being treated with fractional CO2 laser **(13)**. That was associated with a paradoxical decline of the degree of erythema measured by Vancouver Scar Scale. Also, other study reported that verapamil had the ability to inhibit the proliferation of scars via preventing the proliferation of fibroblasts and inhibit fibroblast TGF-β1 expression, also it induces apoptosis **(14)**.

In this study, using CD31 immunostaining, MVD in cases of HTS increased after treatment and the difference in MVD in cases of HTS was statistically significant before and after treatment (P value< 0.05), unlike cases of keloid (p=0.607). This comes in agreement with other study that found that the number of capilleries were less in cases of keloids than in cases of HTS and the lumen of blood vessels were flat **(15)**.

In the current study, vascularity, pliability, height and total Vancouver score showed significant improvement in cases treated with Co_2 laser followed by topical 5FU and this comes in agreement with other result that noticed 50% improvement in 85% of their cases **(16)**. To our knowledge, this is the first study to observe vascular patterns in keloids and hypertrophic scars using dermoscopy before and after 5FU topical application and we found that arborizing and linear vessels showed significant improvement in cases treated with 5FU. Histopathological improvement showing decrease in inflammation, decrease space between collage fibers that were consistent with the improvement seen clinically and this comes in agreement with other studies **(16, 17)** who found that there were declining of hyalinized collagen fibers, declining of nodular concentric arrangement of collagen fibers, declining of the vascularity and flattening of dermal papillae. The last group was treated with Co_2 laser only and there was significant improvement in vascularity, pliability, height and total score and this comes in agreement with the results reported by other study who found that fractional Co_2 laser decreased the mean Vancouver scar scale in hypertrophic scars patients **(18).**

The present study evaluated vascular patterns in keloids and hypertrophic scars using dermoscopy before and after Co_2 laser treatment and found that linear vessels showed significant improvement in cases treated with CO_2 laser. In cases treated with CO_2 laser, HTS showed decrease size of nodules with decreased space between fibrils of collagen with moderate chronic inflammation. With Masson Trichrome stain, thinner blue stained collagen fibers in the papillary dermis and upper one third of reticular dermis were found and this comes in agreement with other results **(19)** who found that collagen bundles within the ablative zone appeared significantly less dense and displayed a more regular horizontal and parallel arrangement as well as minimal chronic inflammatory infiltrate.

In cases treated with CO2 laser, keloids showed lose swirl structure, decreased thickness of collagen layer; bundles become more compacted, less space between fibers. Clear distinct transition zone between treated from unaffected area. With Masson Trichrome stain, thinner better organized collagen bundles as seen with **El-Zawahry et al., 2015** who founds that there was dense bundles of collagen in papillary dermis and superfiscial third of reticular dermis, and the collagen bundles were arranged in haphazard pattern before treatment, then after treatment with laser sessions, there was marked decline in the collagen bundles density, and become more horizontal arrangement.

Regarding dermoscopy, in our study, HTS showed significantly higher improvement in arborizing vessels when compared to keloids in all treatment groups except for Co_2 laser group. Linear vessels and comma shaped vessels improvement did not differ significantly between HTS and keloids in all treatment groups. In this study 5 FU group showed significantly better improvement than other groups, while, Co2 group showed least improvement.

Both of in vivo and in vitro experiments revealed that 5-flourouracil can prevent the fibroblastic proliferation **(20).** Also, through prevention the transforming growth factor–beta, It stimulated the expression of type I collagen gene **(21).** Concurrently to such results, many researches had examined the possibility of clinical application of intralesional 5-flourouracil,seperately or in association with convenential theraputic modalities aiming to inhibit keloid formation or to stimulate resolution of the formed keloid **(10,22).**

Some studies reported that the scars with age less than one year had a better response to therapy than the old ones; but other studies did not find such relation. Such response of the younger scars may be attributed to the presence of cytokines and growth factors that are released at early stages of wound maturation, and respond well to laser leading to decrease in fibroblastic proliferation and collagen deposition **(23).**

Conclusion:

Collagen arrangement, quality, cellularity and site are distinctive features between HTS and keloid in cases before and after treatment. Also vascular pattern and extent may help to differentiate between HTS and keloid before and after treatment.

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الملخص العربى

الخلفية: الجُدريات والندبات الضخامية (HTS) هي استجابات غير طبيعية للجروح. وقد منع الافتقار إلى المعرفة حول بيولوجيتهم الأساسية تطوير نهج موجه لعلاج الجدرة والندوب الضخمة.
هدف العمل: هدفت الدراسة إلى تقييم السمات التنظيرية والهيستوباثولوجية للجدرة والندوب الضخمة قبل وبعد طرق العلاج المختلفة.
الطريقة: تم تضمين اثنين وثلاثين مريضا يعانون من الجدرة وندوب تضخم في الدراسة للفحص السريري ، والجلدي والتنظير المرضي. المرضى الذين يتلقون العلاج في شكل ليزر CO2 الجزئي أو FU٥ أو فيراباميل. تم فحص الشرائح الملطخة بواسطة H & الطريقة: تم تضمين اثنين وثلاثين مريضا يعانون من الجدرة وندوب تضخم في الدراسة للفحص السريري ، والجلدي والتنظير المرضي. المرضى الذين يتلقون العلاج في شكل ليزر CO2 الجزئي أو FU٥ أو فيراباميل. تم فحص الشرائح الملطخة بواسطة E & H والبقع الخاصة (Masson trichrome) ، كما تم تنفيذ CD31 المناعية في جميع الحالات. فحص الأنسجة من الشرائح HTS و الجدرة قبل وبعد العلاج. تم تحديد نمط ألياف الكولاجين من خلال الأقسام الملطخة بالهيماتوكسيلين والأيوزين والأقسام الملطخة ماسون ترايكروم. تم تقييم نمط ومدى الأوعية الدموية الموضحة بواسطة CD31 المناعي.
النتائج: أظهر مقياس ندبة فانكوفر تحسنا كبيرا في جميع المرضى. التحسن النسيجي المرضي (ألياف الكولاجين المكتشفة بواسطة ترايكروم ماسون في الأدمة العلوية لحالات HTS تصبح أرق وأظهرت MVD المكتشفة بواسطة كيمياء المناعة النسيجية للدلالة CD31زيادة الأوعية الدموية بعد العلاج). أظهرت الندوب الضخامية تحسنًا أفضل من الجدرة في جميع المجموعات. أظهرت الأوعية الشجرية والخطية تحسنًا ملحوظًا في المجموعة ١ و ٢. أظهرت الأوعية الخطية تحسنا كبيرا في المجموعة ٣.
الخلاصة: ليزر ثاني أكسيد الكربون الجزئي مع FU٥ هو اختيار ممتاز للعلاج في الجدرة والندوب الضخمة.