Am J Transl Res 2023;15(3):1889-1896
www.ajtr.org /ISSN:1943-8141/AJTR0145241

Original Article

Histopathologic study of keloid vascular structures shows the vascular origin pattern of keloid subepidermal vascular network flaps

Zheng-Yun Liang[1,2], Ya-Wen Wang[2], Yan Hao[1,2], Meng-Jie Shan[1,2], Hao Liu[1], Yi-Jun Xia[1,2], Qiao Chen[1], Guo-Jing Chang[1], You-Bin Wang[1]

[1]Department of Plastic Surgery, Peking Union Medical College Hospital, No. 41 Damucang Hutong, Xicheng District, Beijing 100005, China; [2]Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100005, China

Received July 9, 2022; Accepted January 11, 2023; Epub March 15, 2023; Published March 30, 2023

Abstract: Background: Keloid subepidermal vascular network flaps (KSVNFs) have achieved satisfactory results in clinical practice. Through this retrospective study, we further examined keloid vascular structure to better understand vascular origin pattern in KSVNFs. Methods: Paraffin-embedded keloid tissues were stained for CD31. Distances from keloid subepidermal capillaries to the skin surface were measured. The included angle between the pedicle vessels and skin surface (angle PV), as well as the included angle between the keloid margin and skin surface (angle KM), were also measured. The major and minor axes of the capillary in the central areas of keloid (KDC), adjacent skin (AS) and marginal areas of keloid (KDM) were analyzed, and the major:minor axis ratios (M/m) were calculated. Vessels in KSVNF pedicle sites (KDP) were compared with vessels in adjacent skin as a subgroup analysis. Results: Twenty-nine keloid specimens in total were collected. Based on 1630 measured data points, the capillary distance to the skin surface was 387.2±96.7 μm. The angle PV was 70.1±36.6°, and the angle KM was 67.0±18.1°. The major axis of the KDM capillaries was significantly longer than that of KDC and AS (both $P < 0.001$). The major and minor axes were longer in KDP than in AS (both $P < 0.001$). Conclusion: Suprakeloidal blood vessels are mainly distributed at a depth of 387.2±96.7 μm from the skin. The subepidermal plexus in KSVNF pedicle sites enters the skin at an acute angle and runs parallel to the keloid margin layer. Vessels in keloid marginal areas had crushed vascular lumen, but vessels in KSVNF pedicles did not.

Keywords: Keloid, vascular network, flap, blood supply

Introduction

Keloids are pathological cutaneous scars arising from aberrant dermal fibrosis and excessive collagen fiber deposition. The incidence of keloid ranges from 0.15% to 16% [1, 2]. Pain, pruritus and cosmetic disfigurement are common complaints by keloid patients, all of which lead to poor quality of life [3]. Considered benign lesions histologically, keloids can exhibit some malignant characteristics, such as invasion and a high recurrence rate. There is no standard treatment modality for keloids due to their unclear pathophysiology. Current therapeutic methods include pressure therapy, local drug injection, cryotherapy, laser therapy, radiotherapy, surgical excision and combined therapy [4, 5].

The concept of "core excision" was first described in Salasche's study [6] and later improved by Lee in 2001 [7]. This surgical technique involves complete removal of the keloid mass while preserving some keloid skin to cover the defect. The work of Ogawa showed that this core excision technique did not increase the recurrence rate compared to total resection [8]. A similar surgical technique called the "keloid fillet flap" for earlobe keloids was mentioned by Kim in 2004 [9]. Liu proposed a whole keloid skin retention method and designed a two-pedicle flap to manage facial keloids. Good aesthetic results were achieved, with a satisfaction rate of 84.4% [10]. Based on Liu's work, the term "keloid subepidermal vascular network flaps" (KSVNFs) was later introduced by Teng [11] and Hao [12]. Unlike fillet

flaps, KSVNFs involve less trimming of the keloid skin; thus, disruption of the skin flap blood supply is minimized. Hao's research indicated that the partial necrosis rate of KSVNFs was only 5.714% [12].

Understanding the anatomic structures of KSVNFs, especially epidermal thickness and vessel networks, is essential for preventing necrosis and ensuring flap survival. KSVNFs can consist of total keloid epidermis, partial subepidermal tissue and its vascular plexus. Teng's research already demonstrated the layer thickness of keloid skin, as well as the subepidermal vascular density and blood vessels traveling in KSVNFs [11], but the vascular characteristics in the pedicle site and vascular origin pattern have not been deeply studied.

On the basis of these studies, we further examined keloid vascular structures, such as capillary distances to the skin surface and the origination pattern of these capillaries in the pedicle site, to better understand their blood supply. This study might shed some light on KSVNF design and future clinical applications.

Material and methods

The study was conducted retrospectively. From December 2019 to January 2020, keloid patients in the plastic surgery department of Peking Union Medical College Hospital were enrolled in the study. The inclusion criteria were as follows: 1. patients presenting with clinically diagnosed and pathologically confirmed keloids; 2. patients indicated for surgical excision and postoperative radiotherapy; and 3. no previous keloid-related therapy or current systemic drug use. The exclusion criteria included: 1. less than 18 years old or more than 65 years old; 2. diagnosed with mental illness; 3. with surgical contraindications, such as severe brain, heart, liver, kidney diseases and coagulation disorder; 4. with radiotherapy contraindications; 5. patients who refused surgery or radiotherapy; 6. pregnancy or lactation; 7. with malignant tumors or severe infections; and 8. with comorbidities that might affect vascular structure, such as autoimmune diseases and vasculitis. Written informed consent from patients was obtained prior to our study. The study was approved by the Ethics Committee of Peking Union Medical College Hospital, China (No. I-22PJ648). Keloid samples, along with adjacent skin as controls that had to be removed during surgery, were obtained and used in this study. All keloid tissues were 2 cm in width and 5 cm in length, with the average width of adjacent skin ranging from 2 to 3 mm.

Histological and immunohistochemical staining

All keloid tissues along with adjacent skin were paraffin-embedded. Tissue slices (4 μm thick) were stained with hematoxylin and eosin. Primary CD31 antibodies (AF6191, Affinity Biosciences, Changzhou, China) diluted 200-fold were used for immunohistochemical staining. The Dako REAL EnVision kit (K5007, DAKO, Denmark) was applied in later steps of immunohistological staining.

Measurement of capillary distances to the skin surface

To identify keloid subepidermal tissue (KDS), CD31 immunostained sections were first observed at low magnification (40×). Then, at 200× magnification, at least 3 fields of view were randomly selected, and at least 50 measured data points were obtained for each specimen. Only blood vessels with a minor axis diameter no more than 50 mm [13] were included in the measurement. Capillary distance to the skin surface was defined as the perpendicular distance from the capillary center to the tangent line of the suprakeloid skin surface, as shown in **Figure 1**. The fit ellipse function of ImageJ software (NIH, USA) was utilized to find the centroid of capillary blood vessels.

Measurement of two included angles

To better understand the origination of the KSVNF pedicle vessels, we measured the included angle between the subepidermal plexuses and the adjacent normal skin surface, along with the included angle between the keloid margin and the skin surface. By comparing these two angles, we could explore the relationship between the keloid mass and the subepidermal plexuses.

Subepidermal plexuses in the marginal regions between the keloid and the adjacent skin (KSVNF pedicle sites) were first identified at 40× magnification. Views were then switched to 200× magnification, and we used the fit

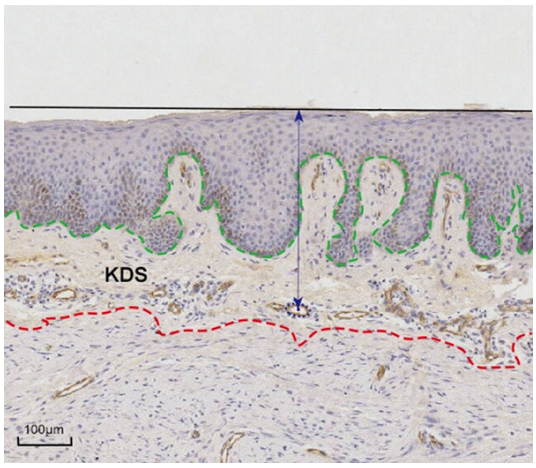

Figure 1. Diagram displaying the measurement of capillary distances to the skin surface (original magnification ×200). The area between the red and green dotted line shows keloid subepidermal layer (KDS). The black line indicates the tangent line of the suprakeloid skin surface and the blue dotted line indicates ellipse model of blood vessel approximated by ImageJ. The blue arrow shows the perpendicular distance from the ellipse center to the black line.

ellipse function in ImageJ to approximate these marginal blood vessels to ellipse models. The included angle between the subepidermal plexuses and skin surface was defined as the angle between the line skin surface (line SS) and line subepidermal plexus, as shown in **Figure 2A**. The line skin surface was the tangent line of the adjacent normal skin surface, and the line subepidermal plexus was the major axis line of blood vessels.

For the included angle between the keloid margin and the skin surface, the most prominent part of the keloid mass close to KSVNF pedicle sites was selected and outlined along the margin, which would later be approximated into an ellipse by the fit ellipse function in ImageJ. The major axis line of the ellipse was defined as line KD. The angle between line SS and line KD was our target angle, as shown in **Figure 2B**.

Measurement of the major and minor axes of a capillary

To study the morphology of keloid blood vessels and KSVNF pedicle vessels, we measured the major and minor axes of the capillary, along with the ratio of these two indices. Central areas of the keloid (KDC), adjacent skin (AS) and marginal areas of keloid (KDM) were our target areas. At least 3 fields of view of these target areas were randomly selected, and at least 55 measured data points were obtained for each specimen. The major and minor axes of the capillary blood vessels were automatically measured by the fit ellipse function in ImageJ. The length of the major axis divided by that of the minor axis equaled the major: minor axis ratio (M/m). For subgroup analysis, we compared the aforementioned indices of pedicle vessels in keloid marginal areas (KDP) with those of blood vessels in AS to better understand the morphological changes in KSVNF pedicle vessels and their blood supply.

Statistical analysis

IBM SPSS Statistics software, version 25.0, was utilized to perform statistical analysis. Descriptive indices, such as minimum (min), maximum (max) and mean values, were obtained. The Kolmogorov-Smirnov test (K-S test) was used to test normality when n>50; otherwise, the Shapiro-Wilk test (S-W test) was used [14]. Normally distributed data were presented as the mean ± standard deviation, while non-normally distributed data were expressed as the median (1^{st} quartile, 3^{rd} quartile). Tests for homogeneity of variance were performed before comparing the significance of differences between groups. If both conditions of homogeneity of variance and normal distribution were satisfied, analysis of variance (ANOVA) was used; otherwise, a nonparametric test was applied. A P value <0.05 was considered significant.

Results

Six male and four female patients aged 18 to 46 years old were recruited for our study. In total, 29 keloid samples were collected. Eleven specimens were from the chest, 8 from the shoulders, 6 from the back and 4 from the arm.

Capillary distances to the skin surface

A total of 1630 measured data points were obtained, and the data conformed to a normal distribution (P = 0.14 by the K-S test). As shown in **Table 1**, the capillary distance to the skin surface was 387.2±96.7 μm (min: 111.1 μm; max: 680.1 μm), with a median of 390.2 μm. The 1^{st} and 3^{rd} quartiles were 324.3 μm and 453.7 μm, respectively. The distribution of the values of

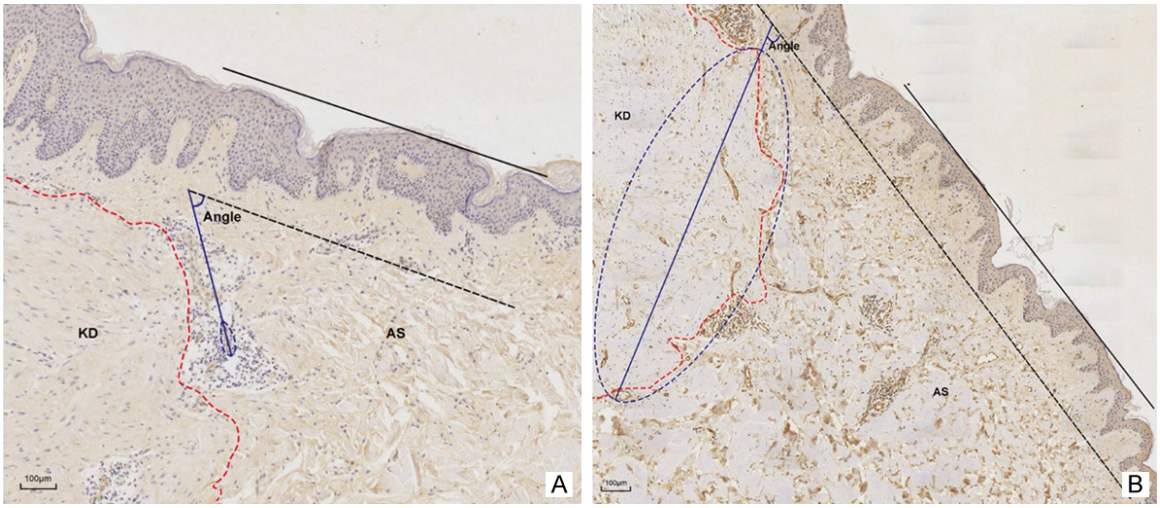

Figure 2. Diagram displaying the measurement of two included angles (original magnification ×200). AS stands for adjacent normal skin and KD for keloid tissue. The black line indicates the tangent line of the adjacent normal skin surface, in parallel with the black dotted line. The Angle stands for our target included angle, respectively. A. The measurement of included angle between subepidermal plexuses and skin surface. The red dotted line area shows keloid tissue (KD). The blue dotted line indicates ellipse model of subepidermal blood vessel approximated by ImageJ, with the blue line being the major axis line of this ellipse. B. The measurement of the included angle between keloid margin and skin surface. The red dotted line represents keloid margin close to subepidermal plexuses. The blue dotted line indicates ellipse model of keloid margin approximated by ImageJ, with the blue line being the major axis line of this ellipse.

Table 1. Statistic data of capillary distances to the skin surface

	No. of capillaries	Mean (μm)	SD	1st Quart (μm)	Median (μm)	3rd Quart (μm)	Min (μm)	Max (μm)
Capillary distances to the skin surface	1630	387.2	96.7	324.3	390.2	453.7	111.1	680.1

SD: Standard Deviation; Quart: Quartile; Max: Maximum; Min: Minimum.

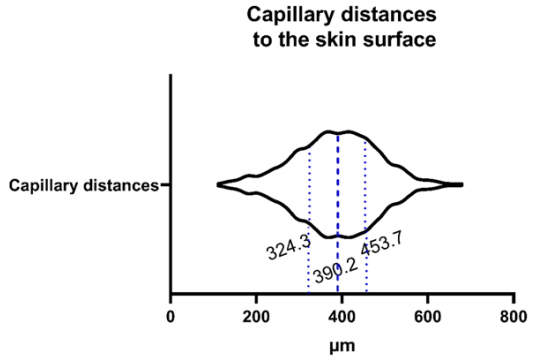

Figure 3. Distribution of the values of the capillary distance to the skin surface. The 1st and 3rd quartile were 324.3 μm and 453.7 μm, with the median being 390.2 μm.

capillary distance to the skin surface is shown as violin plots in **Figure 3**.

Two included angles

For the included angle between the pedicle vessels and skin surface (angle PV), 147 measured data points were obtained, and a test confirmed normality. As shown in **Table 2**, the included angle PV was 70.1±36.6°, ranging from 5.9° to 168°. This result suggested that the subepidermal plexus in the pedicle of KSVNFs might approach the skin surface at an acute angle (70.1°).

For the included angle between the keloid margin and the skin surface (angle KM), 33 measured data points in total were collected, and the dataset obeyed a normal distribution. The included angle KM (67.0±18.1°) was found to be slightly smaller than the angle PV, but with no significant difference (P = 0.67), as shown in **Table 2**. This result indicated that blood vessels

Table 2. Data of two included angles: pedicle vessels vs. keloid margin

	No.p	Mean (°)	SD	Min (°)	Max (°)
Pedicle vessels	147	70.1	36.6	5.9	168
Keloid margin	33	67.0	18.1	29.7	107.5
p value		0.67 n.s			

SD: Standard Deviation; Max: Maximum; Min: Minimum; n.s: no significance.

Table 3. Data of capillary axes, presented as median (1st quartile, 3rd quartile)

	No. of capillaries	Major axis (μm)		Minor axis (μm)		M/m	
KDC	1669	25.5 (17.1, 39.3)	n.s	13.6 (10.5, 17.8)	**	1.7 (1.3, 2.8)	**
AS	1648	23.6 (16.0, 39.6)	**	14.9 (10.9, 20.1)	**	1.5 (1.2, 2.2)	**
KDM	1657	34.6 (20.9, 59.5)		11.8 (8.6, 15.7)		2.9 (1.8, 5.2)	

KDC: Central areas of keloid; AS: Adjacent Skin; KDM: Marginal areas of keloid; *P* values = **0.00; n.s: no significance.

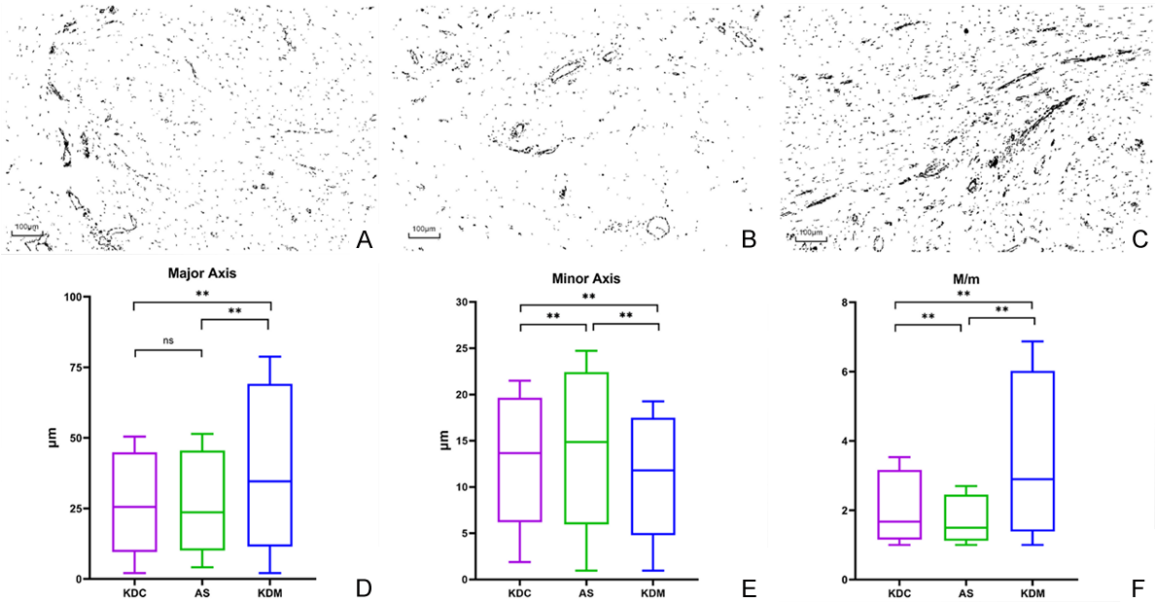

Figure 4. The major and minor axes of capillary in central areas of keloid (KDC), adjacent skin (AS) and marginal areas of keloid (KDM). A-C. Binary images of CD31 immunostained blood vessels processed by Image J in KDC, AS and KDM respectively (original magnification ×200). D-F. The difference of capillaries among KDC, AS and KDM with regard to the major axis, the minor axis and the major:minor axis ratio (M/m), respectively. *P* values < **0.001; ns: no significance.

in the KSVNF pedicle might be parallel to the keloid margin layer nearby.

The major and minor axes of a capillary

The major and minor axis data of the capillary cross-sections are shown in **Table 3**. The major axis of KDM capillaries was significantly longer than that of KDC and AS capillaries (P < 0.001 vs. KDC or AS). KDM<KDC<AS was significantly true for the minor axis of capillaries, and KDM>KDC>AS for the major:minor axis ratio. **Figure 4** shows the difference in capillary axes among KDC, KDM and AS. All of these results indicated that blood vessels in the marginal areas of keloids were longer and that their lumens were compressed compared to normal skin and the central areas of keloids.

In the subgroup analysis, we collected 274 data points from pedicle vessels in keloid marginal areas (KDP). Compared to the AS, both the

Table 4. Comparison between pedicle vessels and adjacent skin vessels, presented as median (1st quartile, 3rd quartile)

	No. of capillaries	Major axis (μm)	Minor axis (μm)	M/m
KDP	274	34.5 (26.1, 52.4)	20.0 (15.8, 24.8)	1.6 (1.3, 2.6)
AS	1648	23.6 (16.0, 39.6)	14.9 (10.9, 20.1)	1.5 (1.2, 2.2)
p value		0.00	0.00	0.01

KDP: Pedicle vessels in keloid marginal areas; AS: Adjacent Skin.

major axis and the minor axis of KDP were significantly longer, implying that blood vessels in the KSVNF pedicle might be longer and more dilated. The major:minor axis ratio of KDP was slightly larger than that of AS (1.6 vs. 1.5, P = 0.01), as shown in **Table 4**.

Discussion

Many previous studies have focused on the blood vessel density of keloids compared to that of hypertrophic scars (HTS) and/or normal skin [15-19]. Although Kurokawa suggested that the capillary density is significantly lower in keloid tissue [15], most studies have indicated the opposite [11, 16, 17]. It has been shown that keloids are rich in microblood vessels, especially in the subepidermal layer, and scholars have supposed that these capillaries might be located at a depth of 0.15 mm to 0.4 mm [11], partially consistent with our results. In our study, the mean capillary distance to the epidermal surface was approximately 387.2±96.7 μm. This distance might suggest that suprakeloidal blood vessels are mainly distributed at a depth of 387.2±96.7 μm from the skin. The total thickness of the keloid epidermis and subepidermal layer is approximately 0.4 mm [11], indicating that the subepidermal vascular network is in close proximity to the borders between the keloid epidermis and subepidermal layer. Since these blood vessels should be included in KSVNFs, extreme caution should be taken when separating the surface of keloid masses from the above subepidermal layer. If necessary, a small amount of keloid tissue might be left attached to KSVNFs to avoid damaging the subepidermal vascular network. Conversely, as long as the KSVNF is thicker than 387.2±96.7 μm, there should be a reliable vessel network to support its survival.

With regard to blood supply, KSVNFs are similar to local flaps, which are supplied by a vascular network from the pedicles of the flaps [12, 20]. In our study, we found that blood vessels in the pedicles of KSVNFs might approach the skin surface at an acute angle (70.1°). After entering the keloid subepidermal layer, branches of these vascular plexuses run mostly parallel to the flap surface and travel far along KSVNFs [11]. Moreover, arterial insufficiency [21], especially disruption of pedicles, could lead to flap failure. Thus, a certain thickness of tissue should be preserved when dissecting near the KSVNF pedicle. At the same time, we found that the angle between the keloid margin and the skin surface was also an acute angle (67°), so blood vessels might be parallel to the nearby keloid mass margin layer before entering the flap. In clinical practice, it would be safe to dissect closely along the keloid borders without damaging the pedicle vascular network when harvesting the KSVNF pedicle.

The major axis of capillaries was significantly longer, and the minor axis was shorter in keloid marginal areas (KDM) than in adjacent normal skin (AS). There was a significantly higher major/minor ratio (M/m) in KDM than in AS. These findings suggest that blood vessels in keloid marginal areas have a more flattened appearance. The results were similar when comparing keloids with HTS [15]. Amadeu reported that keloid vascular plexuses were longer but more dilated than normal skin vessels, with no significant differences [16]. It was found that areas of angiogenesis are more commonly seen in the margins between keloids and normal tissue [22], which might explain the changed vessel morphology of keloid margin areas. Flattened and compressed blood vessel lumens might impair blood perfusion. However, we discovered that blood vessels in the KSVNF pedicle were longer and more dilated than those in normal skin in the subgroup analysis. The morphology of pedicle blood vessels might bear a closer resemblance to normal skin blood vessels rather than KDM blood vessels. This result indicated unimpaired blood perfusion of KSVNFs, as confirmed by Hao's clinical research [12]. Therefore, it seems that the subepidermal

vascular network in the pedicle site is sufficient to supply KSVNFs.

It is generally accepted that the blood vessel density of keloid central regions (KDC) is lower than that of marginal areas or normal skin. Additionally, we found that the vessel major axis of KDCs is significantly shorter than that of KDMs, in contrast to the vessel minor axis. For M/m, KDC is greater than AS but less than KDM. These results may indicate that KDC vessels experience morphologic changes but not as much as KDM vessels. As keloids progress, tissue stiffness and tension increase with excessive extracellular matrix [23], which compresses the blood lumen into a flattened shape. This phenomenon should be most prominent in the keloid central areas, if not for the heterogeneity inside keloid mass. A large mass of keloid tissue may consist of many inner small keloids, the margin areas of which are rich in vessels. Additionally, severely ischemic central regions of keloids [18] might induce compensatory neovascularization, which also affects the blood lumen shape. Even with less crushed vascular lumens, KDC is significantly lower in blood perfusion than KDM due to severe extracellular matrix overproduction [24].

Lastly, keloid subepidermal vascular network flaps have a theoretically reliable blood supply, which with proper design could support flap survival in clinical practice. Regarding the problem of keloid residue, postoperative radiotherapy is highly recommended because the recurrence rate can be up to 100% with only surgery, regardless of the surgical technique [25, 26]. KSVNFs tend to be thinner than normal skin flaps because of keloid tissue compression. We recommend hyperbaric oxygen therapy (HBOT) to prevent potential radiation injury and improve the blood supply [27]. KSVNFs combined with postoperative radiotherapy and HBOT have been utilized in managing keloids in various body sites, and satisfactory results have been achieved [10, 12]. Additionally, KSVNFs are versatile, with one or two pedicles and different incision shapes [28].

One of the limitations of this study was that all keloid patients in the study were Han Chinese. Since there might be differences regarding keloid characteristics among different ethnicities, future studies with ethnic diversity are needed to improve our understanding of KSVNFs. Additionally, keloids from other parts of the body, such as the earlobe and head, were not fully studied in this research, and different body locations could have differences in blood supply. Although the basic principles of KSVNF design remain the same, future KSVNF research could focus on keloids from the aforementioned body parts for a more individualized surgery design. Finally, this study was conducted retrospectively, and other imaging tools were not available. Diverse imaging methods, such as laser speckle contrast imaging systems, could be used to observe the blood supply of KSVNFs from different angles.

Conclusion

Our study was the first to measure the subepidermal blood vessel distances to the skin surface in keloids, and clinicians should include these blood vessels in KSVNF design. We also found that the subepidermal plexus in the KSVNF pedicle site entered the skin at an acute angle and ran parallel to the nearby keloid margin layer. Dissection along the keloid borders to preserve the pedicle vascular network is recommended when harvesting KSVNFs. Vessels in keloid marginal areas had crushed vascular lumens but not vessels in KSVNF pedicles, indicating a reliable blood supply of KSVNFs. These findings could help better explain the vascular origin of KSVNFs and facilitate their clinical application.

Acknowledgements

This project was supported by The National Natural Science Foundation of China (Grant No. 81871538) and the 2019 Grant of Research and Application of Clinical Diagnosis and Treatment Technology in Beijing from Beijing Municipal Science and Technology Commission (Z191100006619009).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. You-Bin Wang, Department of Plastic Surgery, Peking Union Medical College Hospital, No. 41 Damucang Hutong, Xicheng District, Beijing 100005, China. E-mail: wybenz@sina.com

References

[1] Sun LM, Wang KH and Lee YC. Keloid incidence in Asian people and its comorbidity with

other fibrosis-related diseases: a nationwide population-based study. Arch Dermatol Res 2014; 306: 803-808.
[2] Alster TS and Tanzi EL. Hypertrophic scars and keloids: etiology and management. Am J Clin Dermatol 2003; 4: 235-243.
[3] Huang C and Ogawa R. Keloidal pathophysiology: current notions. Scars Burn Heal 2021; 7: 2059513120980320.
[4] Barone N, Safran T, Vorstenbosch J, Davison PG, Cugno S and Murphy AM. Current advances in hypertrophic scar and keloid management. Semin Plast Surg 2021; 35: 145-152.
[5] Ekstein SF, Wyles SP, Moran SL and Meves A. Keloids: a review of therapeutic management. Int J Dermatol 2021; 60: 661-671.
[6] Salasche SJ and Grabski WJ. Keloids of the earlobes: a surgical technique. J Dermatol Surg Oncol 1983; 9: 552-556.
[7] Lee Y, Minn KW, Baek RM and Hong JJ. A new surgical treatment of keloid: keloid core excision. Ann Plast Surg 2001; 46: 135-140.
[8] Ogawa R, Akaishi S, Dohi T, Kuribayashi S, Miyashita T and Hyakusoku H. Analysis of the surgical treatments of 63 keloids on the cartilaginous part of the auricle: effectiveness of the core excision method. Plast Reconstr Surg 2015; 135: 868-875.
[9] Kim DY, Kim ES, Eo SR, Kim KS, Lee SY and Cho BH. A surgical approach for earlobe keloid: keloid fillet flap. Plast Reconstr Surg 2004; 113: 1668-1674.
[10] Liu S, Liang W, Song K and Wang Y. Keloid skin flap retention and resurfacing in facial keloid treatment. Aesthetic Plast Surg 2018; 42: 304-309.
[11] Teng Y, Hao Y, Liu H, Shan M, Chen Q, Song K and Wang Y. Histology and vascular architecture study of keloid tissue to outline the possible terminology of keloid skin flaps. Aesthetic Plast Surg 2022; 46: 985-994.
[12] Hao Y, Shan M, Liu H, Song K, Chen Q, Meng T, Feng C, Wang Z, Qi Z, Xia Y and Wang Y. Clinical observation of subepidermal vascular network flaps in keloid patients. Aesthetic Plast Surg 2022; 46: 2015-2022.
[13] Weidner N, Semple JP, Welch WR and Folkman J. Tumor angiogenesis and metastasis-correlation in invasive breast carcinoma. N Engl J Med 1991; 324: 1-8.
[14] Rosenthal R. An application of the Kolmogorov-Smirnov test for normality with estimated mean and variance. Psychol Rep 1968; 22: 570.
[15] Kurokawa N, Ueda K and Tsuji M. Study of microvascular structure in keloid and hypertrophic scars: density of microvessels and the efficacy of three-dimensional vascular imaging. J Plast Surg Hand Surg 2010; 44: 272-277.
[16] Amadeu T, Braune A, Mandarim-de-Lacerda C, Porto LC, Desmoulière A and Costa A. Vascularization pattern in hypertrophic scars and keloids: a stereological analysis. Pathol Res Pract 2003; 199: 469-473.
[17] Zhang Z, Nie F, Chen X, Qin Z, Kang C, Chen B, Ma J, Pan B and Ma Y. Upregulated periostin promotes angiogenesis in keloids through activation of the ERK 1/2 and focal adhesion kinase pathways, as well as the upregulated expression of VEGF and angiopoietin-1. Mol Med Rep 2015; 11: 857-864.
[18] Touchi R, Ueda K, Kurokawa N and Tsuji M. Central regions of keloids are severely ischaemic. J Plast Reconstr Aesthet Surg 2016; 69: e35-41.
[19] Ueda K, Yasuda Y, Furuya E and Oba S. Inadequate blood supply persists in keloids. Scand J Plast Reconstr Surg Hand Surg 2004; 38: 267-271.
[20] Bednarek RS, Sequeira Campos M, Hohman MH and Ramsey ML. Transposition flaps. StatPearls. Treasure Island (FL): StatPearls Publishing LLC.; 2022.
[21] Kerrigan CL. Skin flap failure: pathophysiology. Plast Reconstr Surg 1983; 72: 766-777.
[22] Bux S and Madaree A. Keloids show regional distribution of proliferative and degenerate connective tissue elements. Cells Tissues Organs 2010; 191: 213-234.
[23] Zhou B, Gao Z, Liu W, Wu X and Wang W. Important role of mechanical microenvironment on macrophage dysfunction during keloid pathogenesis. Exp Dermatol 2022; 31: 375-380.
[24] Yang Y, Liu L, Yang R, Ding X, Li Y, Liu H and Yan H. Blood perfusion in hypertrophic scars and keloids studied by laser speckle contrast imaging. Skin Res Technol 2021; 27: 789-796.
[25] Niessen FB, Spauwen PH, Schalkwijk J and Kon M. On the nature of hypertrophic scars and keloids: a review. Plast Reconstr Surg 1999; 104: 1435-1458.
[26] Al-Attar A, Mess S, Thomassen JM, Kauffman CL and Davison SP. Keloid pathogenesis and treatment. Plast Reconstr Surg 2006; 117: 286-300.
[27] Wang CH, Shan MJ, Liu H, Hao Y, Song KX, Wu HW, Meng T, Feng C, Qi Z, Wang Z and Wang YB. Hyperbaric oxygen treatment on keloid tumor immune gene expression. Chin Med J (Engl) 2021; 134: 2205-2213.
[28] Qi Z, Liang W, Wang Y, Long X, Sun X, Wang X, Zhao Z, Zhou Z and Qiao Q. "X"-shaped incision and keloid skin-flap resurfacing: a new surgical method for auricle keloid excision and reconstruction. Dermatol Surg 2012; 38: 1378-1382.