IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 23, Issue 8 Ser. 4 (August. 2024), PP 06-09
www.iosrjournals.org

Higher Interleukin-17 Expression In High-Tension Site Of Keloid

Rieska Widyaswari*, Nugrohoaji Dharmawan, Muhammad Eko Irawanto,
Departement Of Dermatovenereology, Faculty Of Medicine, Sebelas Maret University, Dr. Moewardi General Regional Hospital, Surakarta, Indonesia

Abstract
Introduction*: Keloid is a benign fibroproliferative disorder caused by various factors, including the elongated inflammatory phase. High mechanical tension due to repeated stretching in certain body sites such as the anterior chest, shoulders, scapula, and suprapubic causes an increase in the inflammatory process. Interleukin (IL)-17 is an inflammatory cytokine found to be increased in keloids. This study aims to compare the expression of IL-17 at the high-tension site of keloid versus another site.*
Methods*: This is an observational analytic study with a cross-sectional design on keloid patients visiting the Dermatovenereology Outpatient Clinic of Dr. Moewardi Hospital Surakarta, Indonesia from December 2023 to March 2024. Keloid sites are divided into high-tension site (anterior chest, shoulder, scapula, and suprapubic) and other sites. Samples were taken with a 5 mm punch biopsy on the intralesional keloid. An immunohistochemical examination to assess IL-17 expression was carried out and assessed with SPSS software version 22.0. and ImageJ software.*
Results: *A total of 22 keloid patients were divided into 2 groups. Eleven samples on the high-tension site group and 11 samples at another site group. A comparative test using an independent t-test compared IL-17 expression in the high-tension site of keloid versus another site showed that keloids at high-tension sites had higher IL-17 expression. Interleukin-17 expression was significantly higher in high-tension keloid sites than in other sites with a p-value of <0.001 (p <0.05)*
Conclusion: *Interleukin -17 expression is higher in keloid areas with high tension compared to other areas.*
Keywords: *Interleukin-17, keloid, skin tension*

Date of Submission: 03-08-2024 Date of Acceptance: 13-08-2024

I. Introduction

Keloids are benign fibrous tissue growths that affect individuals with a genetic predisposition, cross the border of the wound, and have a high recurrence rate.[1] Keloid incidence varies and is reportedly influenced by racial and ethnic differences ranging from 0.09% of cases in the United Kingdom to 16% in Zaire.[2,3] Factors that play a role in the formation of keloids such as genetic predisposition, signaling disorders such as prolongation of the inflammatory response, and anatomical location.[4]

Keloids generally occur in areas that have high tension and mechanical stretch such as the anterior chest, shoulders, scapula, and suprapubic.[1,5] Mechanical stress due to strain will cause inflammation of the skin and accelerate the inflammatory process due to other factors such as infection. Vasodilation in inflammation will increase growth factors such as TGF-B found in higher amounts in keloid fibroblasts.[6]

Abnormal scar tissues such as keloids and hypertrophic scars arise due to disturbances in the wound healing process that cause excessive accumulation of extracellular matrix.[7] Clinical, histopathological, and molecular studies have shown the role of chronic inflammation in addition to fibroblast hyperproliferation in the process of keloid formation.[8] The elongated inflammatory phase leads to an increase in inflammatory cells and mediators that affect the proliferation and differentiation of fibroblasts and collagen deposition.[9]

Interleukin-7 is a cytokine produced by T helper (Th) 17 cells that develop from an activated cluster of differentiation (CD) 4^+ cells.[10] Interleukin-17 signaling plays a role in IL-6-mediated keloid pathogenesis.[11] Interleukin-17 was found to be significantly higher in perilesional areas of keloid that have higher levels of inflammation than intralesional areas.[12] Here, we conducted a study that aimed to compare IL-17 expression in a higher tension site of keloid with another site.

II. Materials And Methods

We conducted an analytic observational study with a cross-sectional design on keloid patients visiting the Dermatovenereology Outpatient Clinic of Dr. Moewardi Hospital Surakarta, Indonesia from December 2023

to February 2024. The consecutive sampling technique was applied for the sample collection. The inclusion criteria in this study were patients aged> 18 years old with keloid lesions based on physical examination, keloid duration for more than 6 months, and no history of previous keloid treatment. The presence of keloids with secondary infections, chronic inflammatory diseases, autoimmune diseases, pregnancy, hypertension, and diabetes mellitus were excluded. Keloid sites are divided into high-tension site groups (anterior chest, shoulder, scapula, and suprapubic) and other sites groups. Samples were taken with a 5 mm punch biopsy on the intralesional keloid. Immunohistochemical examination to assess IL-17 expression was carried out at the Laboratory of Pathology Anatomy, Faculty of Medicine Sebelas Maret University, Indonesia, and will be assessed using SPSS software version 22.0. and ImageJ software.

III. Result

The total subjects of this study were 22 patients aged 18-60 years with a mean age of 31.95±31.95 years. Keloids were more common in females (63.6%) than in males (36.4%). The most common predilection site of keloid in this study was the anterior chest (31.8%), followed by scapular and wrist areas. A total of 22 keloid patients were divided into 2 groups. Eleven samples on the high-tension site group and 11 samples at another site group. The cause of keloids was mostly due to traumatic injury (68.2%), followed by inflammation and unknown cause (**Table 1**).

Table 1. Demographic characteristics of study subjects.

Characteristics	**Number (n=22)**	**Percentage (%)**
Gender		
Male	8	36.4
Female	14	63.6
Age		
18-25 y.o	8	36.4
26-35 y.o	7	31.8
36-45 y.o	4	18.1
>45 y.o	3	13.6
Causes of keloid		
Inflammation	5	22.7
Traumatic injury	15	68.1
Unknown	2	9.1
Sites of keloid		
Ear	2	9.1
Upper arm	2	9.1
Lower arm	1	4.54
Wrist	3	13.6
Anterior chest	7	31.8
Scapular	3	13.6
Abdominal	1	4.54
Suprapubic	1	4.54
Lower leg	2	9.1

The data normality test with a sample number of <50 was carried out using *the Saphiro-Wilk test.* The expression of IL-17 based on *the Saphiro-Wilk* test obtained a value of p>0.05 which indicates normal of the distributed data, the data analysis then was continued using the unpaired independent T-test (**Table 2**).

Table 2. Normality test of IL-17 expression

Keloid	**Interleukin-17 expression**			**Information**
	Statistic	**df**	**p-value**	
High tension site	0.951	11	0.662	Normal
Other sites	0.909	11	0.235	Normal

A comparative test using an independent t-test compared IL-17 expression in the high-tension site of keloid versus other sites showed that keloids at high-tension sites group had higher IL-17 expression (mean = 48.56) compared to another site group (mean = 19.09). Interleukin-17 expression was significantly higher in high-tension site keloid than in other sites with a p-value <0.001 (p <0.05) (**Table 3; Figure 1**).

Table 3. Comparative test of IL-17 expression between high-tension site and other sites of keloid

Keloid		Interleukin-17 expression		Mean Diff	95%CI		p-value
	N	Mean	SD		Lower	Upper	

High tension site	11	48.56	13.68	29.47	19.39	39.55	<0.001*
Other sites	11	19.09	8.36				

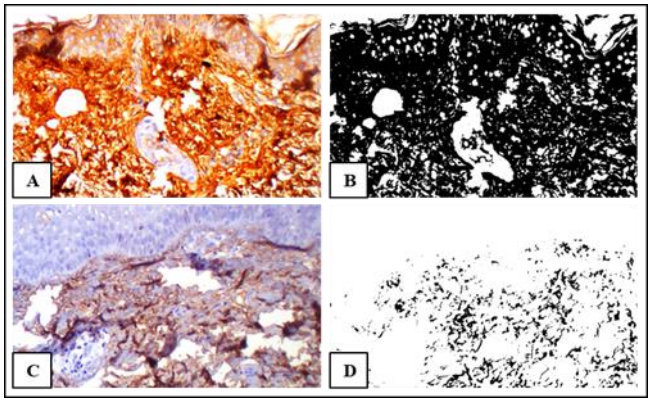

Figure 1. Immunohistochemistry and *ImageJ* pictures of IL-17 expression (200x magnification). (**A-B**) Highest IL-17 expression on the anterior chest area. (**C-D**) Lowest IL-17 expression on the wrist area.

IV. Discussion

Keloid is a fibroproliferative disorder that can affect all ages but is most commonly found in the 2nd and 3rd decades.[1] This may be because young adults have higher levels of sexual hormones, more frequent trauma, and higher skin tension than older individuals. Keloid incidence is found more in women related to estrogen hormone activity.[1,13] The results in this study are similar to the previous study where keloids are more common in women than in men and mostly in the age range of 20-30 years old.

The formation of keloids is due to a prolonged inflammatory phase. The elongated inflammatory phase leads to an increase in inflammatory cells and mediators that affect the proliferation and differentiation of fibroblasts and collagen deposition. This is supported by evidence of many inflammatory cells and serum inflammatory cytokines such as IL-6 and IL-17 in keloids.[9,13]

Various factors are reported to play a role in keloid formation, one of which is the anatomical location. The high tension on human skin varies in different areas of the body which is related to body movement, age, and other factors.[14] The neurogenic inflammation theory of keloids explains the expansion of keloids in the direction of skin tension and the high tension at the perilesional site. Mechanosensitive receptors will be stimulated when the skin is stretched continuously and neuropeptide activity on skin inflammation can be observed in the form of erythema, edema, hyperthermia, and pruritus. Vasodilation in inflammation will increase growth factors such as transforming growth factor (TGF)-β which are found in higher amounts in keloid fibroblasts.[6]

Interleukin 17 is a cytokine that plays an important role in the chronic inflammatory process.[15] Interleukin-17 levels increase in keloid tissue due to chronic inflammation that promotes fibrosis. Interleukin-17 signaling has been reported to inhibit the autophagy process in fibroblasts via the signal transducer and activator of transcription (STAT)-*3* pathway. Disruption to the autophagy process can decrease collagen degradation resulting in increased collagen deposition in the extracellular matrix.[16]

The results of this study showed that keloids in areas with higher mechanical strain had higher IL-17 expression than in other areas. The results of this study are supported by research by Lee *et al* (2020) that stated that IL-17 expression is higher in perilesional keloid lesions which have a higher level of inflammation than in intralesional areas. Continuous local inflammation can increase the expression of stomal-derived factor (SDF)-1 and stimulate the recruitment of Th-17 cells resulting in a local increase in IL-17 levels.[12]

This study is limited by the small number of study subjects. Further studies with larger sample sizes are required to generalize the study outcome.

V. Conclusion

IL-17 expression is higher in high-tension keloid areas than in other areas

References

[1] Shaheen A. Comprehensive Review Of Keloid Formation. J Clin Res Dermatology. 2017; 4(5): 1–18.
[2] Limandjaja GC, Niessen FB, Scheper RJ, Gibbs S. The Keloid Disorder: Heterogeneity, Histopathology, Mechanisms And Models. Front Cell Dev Biol. 2020; 8(5).
[3] Huang C, Wu Z, Du Y, Ogawa R. Textbook On Scar Management. Textb Scar Manag. 2020; 29–35.
[4] Ogawa R. Keloid And Hypertrophic Scars Are The Result Of Chronic Inflammation In The Reticular Dermis. Int J Mol Sci. 2017; 18(3).
[5] Harn HIC, Ogawa R, Hsu CK, Hughes MW, Tang MJ, Chuong CM. The Tension Biology Of Wound Healing. Exp Dermatol.

2019; 28(4): 464–71.
[6] Akaishi S, Akimoto M, Ogawa R, Hyakusoku H. The Relationship Between Keloid Growth Pattern And Stretching Tension: Visual Analysis Using The Finite Element Method. Ann Plast Surg. 2008; 60(4): 445–51.
[7] Ţuţuianu R, Roşca AM, Florea G, Prună V, Iacomi DM, Rădulescu LA, Et Al. Heterogeneity Of Human Fibroblasts Isolated From Hypertrophic Scar. Rom J Morphol Embryol. 2019; 60(3): 793–802.
[8] Dong X, Mao S, Wen H. Upregulation Of Proinflammatory Genes In Skin Lesions May Be The Cause Of Keloid Formation (Review). Biomed Reports. 2013; 1(6): 833–6.
[9] Wang ZC, Zhao WY, Cao Y, Liu YQ, Sun Q, Shi P, Et Al. The Roles Of Inflammation In Keloid And Hypertrophic Scars. Front Immunol. 2020; 11(12):1–10.
[10] Yang B, Kang H, Fung A, Zhao H, Wang T, Ma D. The Role Of Interleukin 17 In Tumour Proliferation, Angiogenesis, And Metastasis. Mediators Inflamm. 2014.
[11] Ghazizadeh M, Tosa M, Shimizu H, Hyakusoku H, Kawanami O. Functional Implications Of The IL-6 Signaling Pathway In Keloid Pathogenesis. J Invest Dermatol. 2007; 127(1): 98–105.
[12] Lee SY, Kim EK, Seo HB, Choi JW, Yoo JH, Jung KA, Et Al. IL-17 Induced Stromal Cell–Derived Factor-1 And Profibrotic Factor In Keloid-Derived Skin Fibroblasts Via The STAT3 Pathway. Inflammation. 2020; 43(2): 664–72.
[13] Nangole FW, Agak GW. Keloid Pathophysiology: Fibroblast Or Inflammatory Disorders?: Pathophysiology Of Keloids. JPRAS Open. 2019; 22: 44–54.
[14] Ogawa R. Mechanobiology Of Scarring. Wound Repair Regen. 2011; 19(1): 2–9.
[15] Beringer A, Noack M, Miossec P. IL-17 In Chronic Inflammation: From Discovery To Targeting. Trends Mol Med. 2016; 22(3): 230–41.
[16] Lee SY, Lee AR, Choi JW, Lee CR, Cho KH, Lee JH, Et Al. IL-17 Induces Autophagy Dysfunction To Promote Inflammatory Cell Death And Fibrosis In Keloid Fibroblasts Via The STAT3 And HIF-1α Dependent Signaling Pathways. Front Immunol. 2022; 13(6): 1–9.