Relationship between transforming growth factor beta 1 (TGF-ß1) level and skin tag

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ABSTRACT

Background: Skin tag, also known as acrochordons, are benign neoplasms that look like a protrusion skin growth. Multifactorial causes of skin tags such as aging, obesity, metabolic and hormonal disorders. One of the mechanisms for the occurrence of skin tags by repeated scratching or friction trauma and continuously triggers an inflammatory response. During inflammation, TGF-ß1 has been activating to prevent the adhesion of neutrophils and T cells to endothelial cells, then limiting the recruitment of inflammatory cells. In addition, TGF-ß1 expression is the main promoter in fibroblast proliferation and collagen synthesis as a response to cell repair function. This study aims to determine the relationship between TGF-ß1 level and skin tags.

Methods: This observational study has a cross-sectional design of 39 skin tag patients and 40 non-skin tags. Each patient underwent history taking, dermatological examination, then took the blood sampling to analyze the TGF-ß1 level using the ELISA test. These data were statistically analyzed with the Mann-Whitney analytic test.

Results: The average TGF-ß1 level on skin tags group was 549.05±173.52 ng/ml. Most subjects with skin tags had 1–5 lesions, were 24 people (61.5%). The most common type of skin tag was pedunculated in 9 people (23.1%), followed by the flat type in 6 people (15.3%) and the spherical in 6 people (15.3%). The majority shows that 16 people (41%) have more than one type of skin tag in one region. The results of this study reveal that there is a relationship between TGF-ß1 low level and skin tags.

Conclusion: There is a significant relationship between TGF-ß1 and skin tags.

Keywords: Skin tag, TGF-ß1, Type of skin tag.

INTRODUCTION

Skin tag, also known as acrochordon, is a common benign skin tumor. It appears as small protrusions measuring 2–5 mm but can be larger, up to 5 cm, soft, and colored similar to the skin or slightly hyperpigmented. Skin tags typically pedunculated, and their shape has other clinical variations. They are commonly found in the neck, armpits, groin folds, or other fold areas. Skin tags usually do not cause symptoms but can be problems when irritated or with secondary infection.¹,²

The risk factors of skin tags increase in aging population and numerously found in the fourth decade of life. The incidence and prevalence of this condition might vary.³,⁴ Recent study by Ridlo et al. at the Universitas Sumatera Utara Hospital in Medan from 2019 to 2020, most skin tag patients were females (75%) compared to males (25%). The risk of developing skin tags increases by the age, the high incidence observed in 50–59 years old subjects, approximately 14 patients (35%) from total of 40 patients.⁵

The etiology of skin tags is not clearly understood, but several factors can influence the development of skin tag lesions.³,⁴,⁶ Currently, there are many theories explaining the pathogenesis of skin tags, such as persistent and repetitive pressure, scratching, or friction, especially in obese persons, which can lead to disruption the elastic skin tissue.⁴,⁷ One case reports of multiple skin tags along the waistband of an obese woman, caused by repeated skin friction with the clothes.⁸

Skin tags are often associated with several diseases such as diabetes mellitus, obesity, dyslipidemia, atherosclerosis, and human papillomavirus (HPV).⁹,¹⁰ Variations estrogen levels and tropic hormones such as insulin-like growth factor-1 (IGF-1) and insulin, transforming growth factor (TGF), and epidermal growth factor (EGF) are also considered as triggering factors in the formation of skin tags.¹¹–¹⁷

The hypothesis that mast cells, tumor necrosis factor alpha (TNF-α) and TNF-related apoptosis-inducing ligands (TRAIL) play a role in the pathogenesis of skin tags as response to injury. It has been proven that mast cells progressively recruited to the injury area as an initial response to trauma and increase the production of tumor necrosing factor alpha (TNF-α) for regulates cell repairs.¹² A study by Litchman et al. (2015) mentioned that the TGF-ß isoform plays a role in the wound healing and fibrosis processes. Natural wound healing involves the deposition of extracellular matrix, followed by collagen synthesis from fibroblasts, influenced by various growth factors and cytokines such as platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), TGF-ß, interleukin 1 (IL-1), IL-4, TNF α produced by leukocytes.
and lymphocytes. Subsequently, this stimulates and modulates the synthesis of other connective tissues and activates metalloproteinase, which is enzymes that degrades the extracellular matrix (ECM). Microscopic examination of fibroblastic scar reveals excessive deposition of dysfunctional extracellular matrix (ECM), which inhibited tissue regeneration (complete restoration of structure and function) during the wound healing process. Transforming growth factor beta (TGF-ß) was involved in this process, indicating that targeting the TGF-ß pathway as therapeutic agents can enhance wound healing, in reverse, overexpression can lead to scar tissue formation. Another observation from histological examination of skin tags in the dermis composed of loose collagen, a reduction in elastin fibers, and sometimes, fat tissue.

TGF-ß has been extensively explored, including its various connections to wound healing, fibrosis, and carcinogenesis. TGF-ß1 is the largest isomer and its expression serves as a major promoter in fibroblast proliferation. Based on the pathomechanism suggests a potential role of TGF-ß1 in the occurrence of skin tags. This study aims to evaluate the average number of TGF-ß1 levels from the skin tag group compared to the control group and then analyze the relationship between TGF-ß1 levels and skin tags.

**METHODS**

**Participants**

This research was held from December 2022 to May 2023 with 79 participants which are 39 skin tag patients and 40 patients without skin tags. Each participant underwent history taking, physical, dermatological examination and took the blood sample to measure of TGF-ß1 plasma level.

**Study procedure**

Blood sample examination was conducted at the Integrated Laboratory of the Faculty of Medicine, Universitas Sumatera Utara. Blood sampling (approximately 3 cc) was centrifuged to take the plasma and measured TGF-ß1 levels by using Human TGF-ß1 ELISA KIT Cat No. E0134 Hu.

The inclusion criteria for this study were skin tags patients aged ≥ 25 – 45 years old, be able to participate in this study by signing the informed consent. The exclusion criteria were: pregnancy or breastfeeding, obesity, recent consumption of antioxidant supplements within the last month, and diagnoses of cancer, lung infection, coronary heart disease, diabetes mellitus, psoriasis, or keloids as determined through history taking and physical examination.

**Statistical analysis**

This is an observational study with cross-sectional design. The data were collected and analyzed statistically. Data was processed using univariate analysis to analyze the characteristics of a single variable, and then the data was presented descriptively in the form of a frequency distribution table. This was followed by bivariate analysis to analyze the relationship between the research variables. In this study, to determine the relationship between TGF-ß1 levels and skin tags. The data was not normally distributed, it was used the Mann-Whitney test with a significance level less than 5%.

**RESULT**

**Demographic and Clinical Characteristics**

The demographic characteristics of the research subjects, which include age and gender, are shown in tables 1.

**DISCUSSION**

Based on the demographic characteristics of the subjects, similar conditions were found in the research by Sinaga et al. at H. Adam Malik Hospital in Medan (2014), the occurrence of skin tags was found in the age group of 29-39 years, about 34.4% (11 patients) out of a total of 32 skin tags.
The majority of skin tags patients had 1-5 lesions, with 27 subjects (69.2%). These findings are similar with the results of Banik et al. study, which found that 71.3% of skin tags patients had 1-3 lesions, with the most common location in the neck region (48%), followed by the axillary region (35%).

Different results were reported in Platsidaki et al. study, which categorized the number of skin tags as < 10, 10 - 30, and > 30. They found the largest number of skin tags patients had 10 - 30 skin tags. Interestingly, there was also a similarity to this research, which is the common location for the appearance of skin tags in the neck region, with a total of 87 subjects (98.86%).

The most type of skin tag is pedunculated, found in 9 subjects (23.1%), followed by the drop form in 6 subjects (15.3%) and the spherical type in 6 subjects (15.3%). The data from Table 2, reveals that totaling 16 subjects (41%) had more than one type of skin tag in one region, referred to as a mixed type.

The analysis outcome of the study, evidence a significant relationship between TGF-β1 levels and skin tags occurrence. The TGF-β1 levels in the skin tag group tend to be lower compared to the control group. This is consistent with the literature, which suggests that the expression of TGF-β1 is triggered by ongoing internal processes in the body. The activation and regulation of TGF-β1 are controlled through specific pathways in various tissues, involving various micro-molecular components.

A literature review mentions the existence of specific mechanisms in the early inflammatory phase, TNF-α is part of the initial cytokine cascade when skin injury occurs. TGF-β is stored in wounds by platelets trapped in fibrin clots during hemostasis. Proposes that the regulation of TGF-β1 is controlled by various activation pathways to cell response. The production of TGF-β1 is limited before binding occurs between latent TGF-beta and its receptors to transform into an active form as physiological functions.

During inflammation, TGF-β1 blocks the production of superoxide and nitrate oxide inside macrophages. Other suppressive mechanisms are clearly relevant to the systemic response of TGF-β1, including its ability to inhibit the adhesion of neutrophils and T cells to endothelial cells, thereby limiting the recruitment of inflammatory cells into the lesion. Furthermore, platelets and macrophages produce TGF-β1 as a major growth promoter in fibroblast proliferation and collagen synthesis, but other mechanisms suppress inflammation. However, mast cells increase at the site of the lesion and release TNF-α, an inflammatory mediator, as an immunological response. This checkpoint is one of the mechanisms of skin tag formation, which is preceded by trauma related to the activation of TGF-β1 as an anti-inflammatory response and cell repair regulation, thus contributing to the pathophysiology of skin tag formation.

**CONCLUSION**

There is a significant relationship between TGF-β1 levels and skin tags. The average TGF-β1 level in the skin tag group is 549.05 ng/ml.

**DISCLOSURE**

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