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CORRELATION BETWEEN TGF-B LEVELS AND DEGREE OF WOUND HEALING IN LEPROSY ULCER PATIENTS: AN OBSERVATIONAL STUDY AT DR. REHATTA REGIONAL HOSPITAL JEPARA

Rizki Alfarizi[1*], Renni Yuniati[2], Farmaditya Eka Putra Mundhofir[3], Noor Wijayahadi[4], Yora Nindita[4]
[1]Department of Biomedicine, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[2]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[3]Department of Histology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
[4]Department of Pharmacology, Faculty of Medicine, Universitas Diponegoro, Semarang, Indonesia
* Corresponding Author: E-mail: rizkialfarizi33@gmail.com

ABSTRACT

Background: Ulcers are one form of chronic wounds as one form of complication experienced by leprosy sufferers. In the process of healing wounds such as ulcers, TGF-β has a broad role. Several studies have stated that in chronic wound conditions there is a decrease in TGF-β levels so that the wound is increasingly difficult to heal. This study aims to determine the relationship between TGF-β serum levels and the degree of ulcer wound healing. **Methods:** This study is an observational analysis study with a cross-sectional design and involved 33 leprosy ulcer patients undergoing treatment at the dr. Rehatta Jepara Hospital in the period March-April 2024. Serum TGF-β levels were measured using the Enzyme-linked immunosorbent assay (ELISA) method while the degree of wound healing was assessed by scoring the Pressure Ulcer Scale for Healing (PUSH). Bivariate analysis using the Spearman Correlation Rank Test. **Results:** The correlation test between serum TGF-β levels and the degree of wound healing ($p = 0.807$) and duration of leprosy as covariate ($p = 0.96$) showed insignificant results. **Conclusion:** There is no relationship between serum TGF-β levels and the degree of wound healing and duration of leprosy.

Keywords: *Leprosy ulcer, Pressure Ulcer Score Healing, Transforming Growth Factor-β, wound healing.*

INTRODUCTION

Leprosy is a disease caused by *Mycobacterium leprae* infection which is a global problem. In 2022, there were about 174,087 new cases reported globally. According to the WHO report, Indonesia had 12,441 new cases annually in 2022.[1] Because there are few comprehensive services available, leprosy frequently has an impact on a variety of professions in addition to the health sector.[2] Leprosy frequently results in several other problems, including leprosy ulcers. One of the chronic symptoms of leprosy, this illness can result in major abnormalities such deformities or amputations if treatment is not received.[3] Like other chronic diseases, leprosy ulcers require a fairly long healing process and involve various immunological responses to drive the process.[4-6] A number of roles of growth factors and cytokines that influence the wound healing process have been studied in various studies, one of which is Transforming Growth Factor-β (TGF-β).

Ulcers are one form of chronic wounds as one form of complication experienced by leprosy patients. In this case, TGF-β has a broad role and pleiotropic effect on the wound healing process through its role in cell proliferation and differentiation, extracellular matrix production, endothelial cell migration and angiogenesis and modulating the immune system.[7-8] Numerous research investigations have demonstrated a reduction in TGF-β levels in chronic wounds, making it increasingly difficult for the wound to heal. Many factors, including dysregulation of TGF-β target genes and reduced TGF-β receptor expression, are associated with this condition. A study also mentioned a decrease in TGF-β signaling which is marked by decreased expression of the TGF-β Type II receptor (TGF-βRII).[9] Although the specific cause of this condition is still unidentified, research has suggested that microRNA may be involved in blocking the signaling from several growth factors that influence TGF-β release.[7]

Researchers of this study are interested in examining the association between serum TGF-β levels and wound healing in leprosy ulcer patients because of the critical function that TGF-β plays in the healing process of wounds, including ulcers. Researchers have not found similar studies before, so the results of this study are expected to be one of the scientific references for the development of future studies.

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METHODS

This study is an observational analysis study with a cross-sectional design and involved 33 leprosy ulcer patients undergoing treatment at the dr. Rehatta Jepara Regional Hospital in the period March-April 2024. Research ethics permit was obtained from the Health Research Ethics Commission of the Diponegoro Faculty of Medicine.

Each participant has signed an informed consent form after receiving a thorough explanation of the technical components of the study. The inclusion criteria for this study were leprosy ulcer patients aged 20-60 years, receiving Multi Drug Therapy for leprosy and NaCl dressing for ulcers, and agreeing and signing an informed consent. The exclusion criteria for this study were patients receiving therapy other than standard therapy. Serum TGF-β levels were measured using the Enzyme-linked immunosorbent assay (ELISA) method with the Human TGF-β ELISA Kit E3051hu at the GAKI Laboratory, Faculty of Medicine, Diponegoro University. Wound healing was assessed using the Pressure Ulcer Scale for Healing (PUSH) scoring which involved 3 aspects, namely wound area, amount of exudate, and type of wound. Wound area was calculated using the formula length x width of the wound. The amount of exudate was assessed visually after the wound bandage was removed. Tissue type was assessed based on the tissue in the wound area. Necrotic tissue can appear firmer or softer than the surrounding skin and is identified by black, brown, or tan tissue that adheres firmly to the edges of the wound or ulcer. Slough is characterized by mucinous or yellow-or white tissue that sticks to the ulcer in clumps or strings. Pink or beefy red tissue that appears shiny, moist, and granular is known as granulation tissue. New pink tissue that forms the borders or islands on the ulcer surface is what defines epithelial tissue. While resurfaced is when the wound completely covered with epithelium. The three aspects were assessed based on the existing sub-scoring and then added up to produce a PUSH score with a maximum value of 17 and a minimum value of 0. The lower the PUSH score, the better the wound healing.

LENGTH X WIDTH	**0** 0	**1** <0.3	**2** 0.3-0.6	**3** 0.7-1.0	**4** 1.1-2.0	**5** 2.1-3.0	**Sub-score**
		6 3.1-4.0	**7** 4.1-8.0	**8** 8.1-12.0	**9** 12.1-24.0	**10** >24.0	
EXUDATE AMOUNT	**0** None	**1** Light	**2** Moderate	**3** Heavy			**Sub-score**
TISSUE TYPE	**0** Closed	**1** Epithelial Tissue	**2** Granulation Tissue	**3** Slough	**4** Necrotic Tissue		**Sub-score**
							TOTAL SCORE

Figure 1. Pressure Ulcer Scale for Healing Tool 3.0

Bivariate analysis used the Spearman's Correlation Rank Test if the data distribution was not normal. Research data was considered significant if a p value <0.05 was obtained. Statistical analysis was performed using a data analysis application.

RESULTS

The characteristics of the subjects involved in this study are as shown in Table 1.

Table 1. Characteristics of Subjects

Characteristics	n=33
Type Gender, n (%)	
- Man	21(63.6)
- Woman	12(36.4)
Age, n (%)	
- 21-30 years old	2(6.1)
- 31-40 years old	7(21.2)
- 41-50 years old	11(33.3)
- 51-60 years old	13(39.4)
Duration of illness (months), median (min-max)	84(2-300)

The total number of subjects involved in this study was 33 people. Male subjects, 21 people, in this study were more numerous than female subjects, which numbered 12 people. The characteristics of the study subjects were reviewed from age, the most in the range of 51-60 years as many as 13 people then in the range of 41-50 years as many as 11 people. The age range of 31-40 years as many as 7 people and the least in the age of 21-30 years as many as only 2 people. The duration of leprosy from all patients had a median of 84 months with a minimum duration of 2 months and a maximum of 300 months.

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Table 2. Correlation test results between variables

Variable		PUSH Score	Duration of illness
TGF-β	*p*	0.807	0.96

Significant: p<0.05

The results of the correlation test with Spearman's correlation rank of serum TGF-β levels and PUSH scores in all study subjects showed a p value = 0.807 as in table 2. The same test was also conducted to see the correlation of serum TGF-β levels with the duration of leprosy and showed a p value = 0.96. The results are considered significant if the p value <0.05. Thus, both correlation test results showed insignificant results.

DISCUSSION

Leprosy is a disease that can cause various symptoms and complications as the disease progresses. Ulcers are among the complications that people with leprosy undergo. As previously mentioned, transforming growth factor-β is involved in practically every stage of wound healing and has a road involvement in this condition.[7,8]

When a wound forms, the body reacts by creating fibrin threads through the actions of thrombospondin, fibrinogen, fibronectin, and platelet aggregation. This allows the body to secrete different vasoconstrictors to maintain hemostasis.[10] The growth factor transforming growth factor-β (TGF-β) will be stimulated by the presence of fibrin threads.[10-12] Macrophages and TGF-β trigger fibroblasts to produce collagen which plays a role in angiogenesis, wound epithelialization, and extracellular matrix deposition.[12] Function from matrix extracellular is provide substrate in migration cells and structures important To use repair integrity damaged network. This series of processes aim for healing wound through formation vessels blood new one which also improves perfusion network so that supply oxygen and nutrition to the wound area fulfilled.[13]

According to a study, TGF-β levels are lower in chronic wounds, which delays the healing process. Deregulation of TGF-β target genes, as well as decreased expression of TGF-β receptors, are associated with the decline in TGF-β signaling. It has yet to determine the exact process by which it occurs.[7,9]

Figure 2. Ulcers in the plantar area were common among the participants.

In an infected state, an experimental study shows that TGF-β levels start to rise at the beginning of the infection and gradually rise as the condition progresses.[14] For example, in active infections caused by *Mycobacterium tuberculosis*, TGF-β is expressed.[15] Increased levels of TGF-β are also related to the severity of tuberculosis infection.[16] Higher levels of TGF-β are also found in patients with active pulmonary tuberculosis compared to patients who have successfully undergone tuberculosis therapy.[17] Studies conducted on a number of leprosy subjects with different clinical phases showed the highest levels of TGF-β in lepromatous leprosy patients with the most severe clinical and untreated conditions.(18) In this case, it is possible that TGF-β plays a variety of different roles and might act oppose each other during *Mycobacterium* infections, including *M. leprae* and *M. tuberculosis*, by inhibiting exaggeration from infection responses and, in certain conditions, promoting pro-inflammatory responses.[18,19]

A difference was also observed in another study between TGF-β levels obtained from local lesions and systemic TGF-β levels. These findings suggest that the systemic immune response does not always mirror what occurs locally in lesions and vice versa.[18] Every participant in this study had a different immunological status because they had varied lengths of leprosy, had begun treatment at different times, and, in the case of the majority, had been cured of their disease for years. Several points above can possibly be an explanation related to the results of this study.

CONCLUSION

TGF-β serum levels did not have a significant correlation with the degree of wound healing in leprosy ulcer patients at dr Rehatta regional hospital Jepara. Likewise, TGF-β serum levels with the

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duration of leprosy suffered by patients also did not have a significant correlation**.**

ETHICAL APPROVAL

This research has obtained permission from the Medical Research Ethics Commission of the Faculty of Medicine, Diponegoro University. (No. 598/EC/KEPK/FK-UNDIP/XII/2023)

CONFLICT OF INTEREST

There is no conflict of interest in this study.

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