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DEBRIDEMENT WITH FASCIOTOMY ON DIABETIC FOOT REDUCES TUMOR NECROSIS FACTOR ALPHA AND INCREASES VASCULAR ENDOTHELIAL GROWTH FACTOR PLASMA WITH CLINICAL IMPROVEMENT

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Background: Clinical and animal studies find out any increase of TNF-α and decrease of VEGF level in tissues of diabetic foot ulcers. Levels and abnormal activity of VEGF related to hypoxia and increase of TNF-α in diabetic tissue lead to impaired healing of ulcers. This study aims to determine debridement with fasciotomy simultaneously reduce TNF-α and increases VEGF plasma level and clinical improvement of diabetic foot ulcers. **Methods:** A clinical study by a randomized pretest - posttest control group design was carried out. Patients were divided into two groups of debridement without fasciotomy as a control group and group of debridement with fasciotomy as the treatment group. Sixty patients of diabetic foot ulcer Wagner II, III, and IV classification met inclusion and exclusion criteria, 28 patients were selected as control group and 32 as treatment group. Clinical improvement of ulcers was observed every week for 4 weeks using the instrument of Leg Ulcer Measurement Tool (LUMT) score. **Result:** Plasma TNF-α pretest was 422.30±17.05 (pg/ml) on control group and 424.47±12.02 (pg/ml) on treatment group. Plasma TNF-α posttest was 390.91±12.85 (pg/ml) on control group and 290.26±16.42 (pg/ml) on treatment group (p<0.05), with Δ TNF-α (pg/ml) was 31,40±17,98 on control group and 134.21±14.50 on treatment group (p<0.05). Plasma VEGF level (pg/ml) pretest was 282.50±11.58 on control group and 286.74±10.19 on treatment group. Plasma VEGF level (pg/ml) posttest was 289.19±21.91 on control group, 338.70±20.11 on treatment group (p<0.05), with Δ VEGF (pg/ml) was 15.23±10.73 on control group and 51.96±13.54 on treatment group (p<0.05). There was significant clinical improvement of ulcer on treatment group on 2nd , 3rd, and 4th week of treatment (p<0.05) There was average increase pressure (13-21 mmHg) on all foot compartments of the two groups. **Conclusion:** debridement with fasciotomy simultaneously decreases TNF-α and increases VEGF plasma level accompanied clinical improvement of diabetic foot ulcer. Increase of foot compartment pressure may support phenomenon of microvascular permeability on diabetic patients, therefore fasciotomy on diabetic foot to become rational as adjunct of treatment.

Key words: diabetic foot, debridement, fasciotomy, TNF-α, VEGF, clinical improvement

INTRODUCTION

Diabetic foot ulcers until now has become a major health problem throughout the world, due to the increasing number of cases, chronic ulcers which are difficult to heal , infected ulcers and limb ischemia with risk of amputation and even life-threatening , needs of great health resources that give a socio-economic burden to the patients, community, and nation. Various treatment methods have been developed, but to date have not provided satisfactory results.

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Indonesia is the fourth rank of highest number of people with diabetes mellitus (DM) after India, China, and United States.[1] As many as 15-25 % of people with diabetes will experience diabetic foot ulcer in their lifetime.[2] The risk of infection and amputation is still quite high, i.e. 40-80% of diabetic foot ulcers get infected, 14-20% requires amputation, 66% experiences a recurrence and 12 % has a risk of amputation in 5 years after recovery.[3,4] Amputation of the foot more often done on the basis of extensive soft tissue infection or osteomyelitis combination , in addition to other factors such as ischemia due to peripheral artery disease (PAD), and neuropathy.[5,6]

The structured health care program, in which all related disciplines work in coordination has achieved a significant reduction in major amputation

rate of more than 75 % compared to standard care.[7] Impaired healing of diabetic foot ulcers occurs due to four factors: the presence of continuous hyperglycemia, a pro-inflammatory environment, peripheral artery disease, and peripheral neuropathy.[8] The four states above cause malfunctioning of the immune cells, ineffective inflammatory response, endothelial cell dysfunction, and impaired neo-vascularization. Guideline for the treatment of diabetic foot ulcers so far includes off - loading, debridement, and restoration of skin perfusion as a standard treatment.[8] However, until now the result remains unsatisfactory.

All chronic ulcers show tissue hypoxia, and local oxygen pressure on chronic ulcers half of the normal range resulting in impaired replication of fibroblasts, collagen deposition,and angiogenesis.[9] Form of vascular disorder that suspected as the cause of tissue hypoxia is a pressure increase in the foot compartment of diabetic foot ulcers. Strong evidence that supports the relation of foot compartment pressure increase to the DM is study report that the medial foot compartment, interosseous compartment and central compartment of diabetic neuropathy patients is higher than that of the normal patients.[10] Several case reports mention the existence of compartment syndrome in patients with DM that triggers tissue ischemia and ends with tissue necrosis, so presumably there is an indication of the relationship between diabetes, increased inter-compartment pressure, tissue ischemia, and tissue necrosis.[11-14] Seeing this evidence, fasciotomy is a response action to prevent further process of tissue hypoxia. However there have been no reports of foot compartment pressure measurement and fasciotomy as routine assessment and treatment of diabetic foot ulcers. Debridement until now is considered as the only standard in the treatment of diabetic foot ulcers.

There are relationship among impaired cell function, imbalance of inflammation, proteases, cytokines, and growth factor.[15] In diabetic foot ulcer occurs increased fibroblasts apoptosis, decreased cell proliferation of fibroblasts, and extended inflammatory reactions, evidenced by the large number of neutrophil granulocytes in the wound. Neutrophil granulocytes secrete pro-inflammatory cytokines, especially TNF - α and interleukin - 1 β (IL-1β). Both of these cytokines stimulate the synthesis of matrix metalloproteinases (MMP), causing degradation of matrix protein and growth factor so that the wound healing becomes disconnected and uncoordinated.[15] VEGF is one of growth factors that has an important role in wound healing neovascularization.[16] Some literatures report increased levels of TNF-α in the tissues of diabetic ulcer patients and experimental animals, an increase in local and systemic TNF-α in patients with type-2 DM, decreased levels of VEGF in the tissues of diabetic ulcers and in diabetic neuropathy.[15,17,18,] Debridement is a surgery to remove bacterial contamination, bacterial endotoxins, extracellular matrix fragments, detritus cells, and to discard the callus. Removing the factors that sustain inflammation at the base of the ulcer which triggers the secretion of TNF-α generates a local environmental changes (changes in cytokine milieu at the base of the ulcer) such as a decrease in TNF-α followed by an increase in VEGF, so that the progenitor cells or stem cells of bone marrow can effectively increase vasculogenesis that resulting in clinical improvement of diabetic foot ulcers.[9] Whereas fasciotomy has a role in reducing pressure on the foot intra-compartment that tissue hypoxia can be avoided, besides opening the infection pockets inside the compartments so that infection control is getting improved. Fasciotomy in molecular action is to restore a state of hypoxia into normoksia even to hyperoxia, increasing cellular activity to release VEGF.

The important aspect in the treatment of ulcers is ulcer development. Some researchers propose a method for assessing improvement, predicting healing, and evaluating ulcer treatment using ulcer area measurements, but the identification of the edge of the wound and measurement of ulcer area is difficult to do.[24-26] An instrument namely Leg Ulcer Measurement Tool (LUMT) with several advantages that LUMT can be applied by one or more assessors, the assessment of ulcer appearance can be multiplied, and ulcer changes can be recorded over time. The smaller the value of LUMT means the greater the ulcer improvement.[27]

Although debridement alone is very rational in lowering TNF-α followed by degradation of VEGF, still it is not able to fix the tissue oxygenation. If debridement with fasciotomy was performed together, then decreased TNF-α and increased VEGF as well as clinical improvement of diabetic foot ulcers will more effective. On that basis we conduct a study on debridement with fasciotomy carried out simultaneously on the ulcers of both mild and severe degree, to see the effect of the decreased TNF-α and increased VEGF as well as clinical improvement of diabetic foot ulcers that observed using the LUMT instrument.

MATERIALS AND METHODS

This is an experimental study (clinical trial) applying randomized pretest and posttest control group design. In this research, difference of TNF-α and VEGF plasma levels before and 1 week after debridement with or without fasciotomy were investigated. Furthermore, monitoring of clinical improvement was carried out by applying instruments of Leg Ulcer Measurement Tool (LUMT) score on a weekly basis up to 4 weeks posttest. The target population is all type-2 DM patients who undergo surgery for diabetic foot ulcer. The affordable population is all of type-2 DM

patient who underwent surgery for diabetic foot ulcer with Wagner II, III, and IV classification. Samples were selected consecutively from population, after meet the criteria of inclusion and exclusion.

The actual study subject is DM patient whom participate in the study by completing the informed consent. The samples are qualified research (eligible sample), random allocation is performed to determine the type of treatment by permuted block randomization. Then patient is selected in a sequence (consecutive sampling) up to the amount of sample required which are 64 patients.

Differences of TNF-α and VEGF plasma levels, as well as the clinical improvement (LUMT score) due to treatment of debridement with or without fasciotomy were analyzed statistically. Data collected were analyzed descriptively, followed by normality test with Shapiro Wilk, and homogeneous of variance was determined by Levene's Test.

Comparability analysis was carried out for pre test data of debridement with fasciotomy and debridement without fasciotomy group by applying t-test, analysis of average difference for both homogeneous groups, the average difference of measurement results of TNF-α and VEGF plasma levels of debridement with fasciotomy and debridement without fasciotomy group which are determined base on post test value of the two groups, then analyzed by independent sample t-test.

The difference of ulcer clinical improvement using LUMT score measured on 1st week, 2nd week, 3rd week, and 4th week after treatment. Pair t-test was applied at the level of significance $p < 0.05$. Linear regression analysis is constructed of increases levels of VEGF to the levels of TNF-α. The statistical analysis uses p value that less or similar to 0.05 as the limit of significance using SPSS for window program.

RESULTS

The number of subjects in this study as many as 60 patients affected diabetic foot ulcer meets the criteria of inclusion and exclusion. Patients are then randomly allocated into two groups: Group-1 consisted of 28 patients get treatment debridement and Group-2 as much as 32 patients get treatment debridement with fasciotomy. There was one patient in Group-1 dropped out because of death. Characteristics of patients are presented in Table 1.

This study was conducted on the examination pretest and posttest of tissue and plasma of TNF-α level, plasma VEGF level for Group-1 (debridement) and Group-2 (debridement with fasciotomy).

Data obtained subsequently tested normality and homogeneity. All data were homogeneous and in normal distribution. Pretest data overall of TNF-α and VEGF levels are presented in Table 2.

Table 1
Subject Characteristics

Variable	Group-1 (Debridement)	Group-2 (Debridement + Fasciotomy)	p*
N	27	32	
Sex			
Male (%)	18 (66.70)	22 (68.80)	
Female (%)	9 (33.30)	10 (31.20)	
Age (year)	54.59±8.23	54.72±11.67	0.963
Range of age (year)	42 – 70	28 – 77	
Education			
Elementary school (%)	8 (29.70)	11 (34.30)	
Junior High School (%)	3 (11.10)	4 (12.50)	
High School (%)	13 (48.10)	13 (40.60)	
University (%)	3 (11.10)	4 (12.50)	
Occupation			
Housewife (%)	3 (11.10)	2 (6.30)	
Private (%)	17 (63.00)	20 (62.50)	
Government (%)	7 (25.90)	10 (31.30)	
Body Mass Index	24.02±3.73	24.52±4.26	0.639
HbA1c (%)	10.19±2.14	10.75±2.80	0.404
Duration of DM (year)	8.52±8.57	9.81±7.65	
Duration of ulcer (week)	7.15±12.61	8.38±17.13	
Foot Compartment Pressure.(mmHg)			
Medial	15.19±7.34	18.59 ±11.74	
Lateral	13.63±7.70	15.06 ±8.19	
Central	14.04±9.60	21.75±12.89	
Interoseous	13.70±11.38	21.53±13.24	
Ulcer grading			
Wagner-II (%)	13 (48.10)	5 (15.60)	
Wagner-III (%)	11 (40.80)	16 (50.00)	
Wagner-IV (%)	3 (11.10)	11 (34.40)	
Ulcer type			
Neuroischemic (%)	8 (29.60)	9 (28.10)	
Neuropathic (%)	19 (70.40)	23 (71.90)	
PAD			
Yes (%)	7 (25.90)	13 (40.60)	
No (%)	20 (74.10)	19 (59.40)	

*No different (comparable) p>0.05

Table 2
Pretest Data of plasma TNF-α level, tissue TNF-α, and plasma VEGF

Variable	Group-1	Group-2	p**
	Pretest	*pretest*	
PlasmaTNF-α level (pg/ml)	422.30±17,05	424,47±12,02	0,093
Minimum	381,47	387,17	
Maximum	450,37	450,50	
p*	0,264	0,113	
Tissue TNF-α (pg/ml)	383,46±14,59	385,91±9,58	0,094
Minimum	348,39	363,09	
Maximum	407,47	410,79	
p*	0,270	0,66	
Plasma VEGF (pg/ml)	282,50±11,58	286,74±10,19	0,510
Minimum	264,36	269,20	
Maximum	304,13	308,24	
p*	0,218	0,590	

p* normal distribution on $p > 0.05$; p** variance homogeneous on $p > 0.05$, Group-1 (debridement), Group-2 (debridement with fasciotomy).

This study determines decrease of plasma TNF-α level and increased of plasma VEGF levels 7 days after treatment (posttest) of the two groups. Whereas, tissue TNF-α level (posttest) was not carried out for reasons of ethics. Data of plasma TNF-α and VEGF levels, and change of both markers after treatment were presented in Table 3.

Table 3
Level of TNF-α and VEGF plasma 7 days after treatment, and changes of both marker of Group-1 and Group-2

Variable	Group-1		Group-2		*p***
	Posttet	Changes (Δ)	*Posttest*	Changes (Δ)	
TNF-α plasma (pg/ml)	390.91 ± 12.85	31.40 ± 17.98	290.26 ± 16.42	134.21 ± 14.50	0.179
Minimum	368.69	9.51	259.54	90.03	
Maximum	412.10	70.08	332.86	158.33	
*p**	0,407	0.952	0.168	0.091	
VEGF plasma (pg/ml)	289.19 ± 21.91	15.03 ± 11.02	338.69 ± 20.11	51.96 ± 13.54	0.330
Minimum	248.53	2.67	303.46	29.38	
Maximum	327.48	35.89	395.80	92.44	
*p**	0.293	0.242	0.064	0.064	

*p** normal distribution $p > 0.05$
*p*** homogenous $p > 0.05$
Group-1 debridement
Group-2 debridement with fasciotomy

Changes (Δ) between levels of TNF-α and VEGF plasma of Group-1 and Group-2 due to the influence of the treatment was assessed by conducting independent t-test. T-test results were presented in Table 4.

To further clarify the differences of TNF-α and VEGF levels can be seen in Figure 1, Figure 2, Figure 3, and Figure 4.

Data of plasma TNF-α level on the Group-1 and Group-2 posttest presented on Figure 1. On Figure 1 shown that the level of TNF-α on Group-1 was significantly different compared with a group-2 shown with $p < 0.05$.

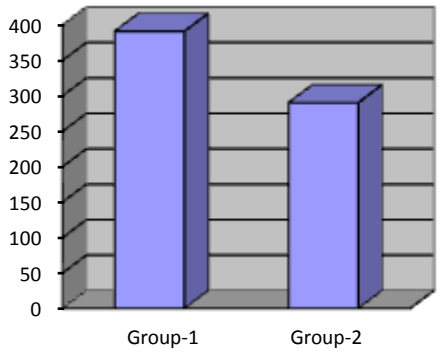

Figure 1
The difference of plasma TNF-α level of Group-1 (debridement) and Group-2 (debridement + fasciotomy) posttest.

Data of plasma VEGF level in the Group 1 and group 2-posttest were presented on Figure 2. Figure 2 shows that level of VEGF in the Group-1 was significantly different compared to the Group-2 ($p < 0.05$).

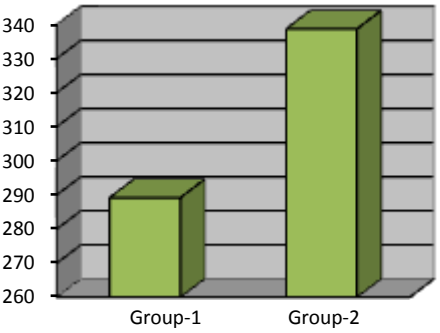

Figure 2
The differences of VEGF level on Group-1 (debridement) and Group-2 (debridement + fasciotomy) posttest.

Data of decrease plasma TNF-α level on the Group-1 and group 2 are presented in Figure 3. On Figure 3 shown that decrease plasma TNF-α levels on the Group-1 significantly difference from Group-2, $p < 0.05$

Table 4
Resume of t-test results of plasma TNF-α and VEGF levels changes 7 days posttest Group-1 and Group-2

Variable	Group-1	Group-2	Mean diff	*t*	*p**	Confidence Interval (95%)	
						lower	*Upper*
TNF-α (pg/ml) pre	422.20±17.05	424.47±12.02	2.17	0.571	0.570	-9.77	5.44
VEGF (pg/ml) pre	282.50±11.58	286.74±10.19	4.23	1.494	0.141	-9.91	5.70
TNF-α (pg/ml) post	390.91±12.85	290.26±16.42	100.64	25.85	0.001	92.84	108.44
VEGF (pg/ml) post	289.19±21.91	338.70±20.11	49.50	9.04	0.001	-60.47	-38.54
Δ TNF-α (pg/ml)	31.40±17.98	134.21±14.50	102.81	24.32	0.001	-111.27	-94.34
Δ VEGF (pg/ml)	15.23±10.73	51.96±13.54	36.73	11.39	0.001	-43.19	-30.27

*Significant on $p < 0.05$, Group-1 debridement, Group-2 debridement with fasciotomy

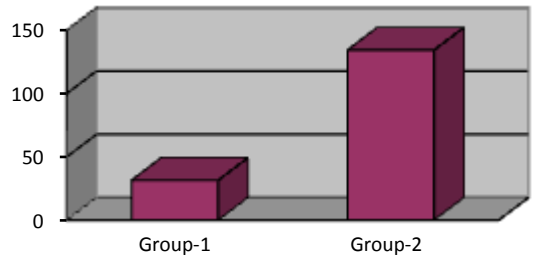

Figure 3
Decrease plasma TNF-α level on the Group-1 (debridement) and Group-2 (debridement + fasciotomy) posttest

Data of increase plasma VEGF levels in Group-1 and Group-2 are presented in Figure 4. Figure 4 shows increased of plasma VEGF levels on the Group-1 significantly different from Groups-2, $p < 0.05$.

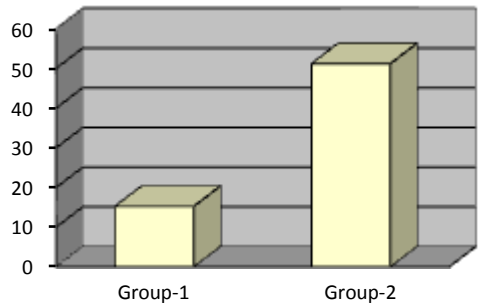

Figure 4
Increases of plasma VEGF levels on Group-1 (debridement) and Group-2 (debridement + fasciotomy) posttest.

Clinical improvement of debridement group and debridement with fasciotomi group were determined based on leg ulcer measurement tool (LUMT) scoore. LUMT data for four weeks observation were normally distributed and their variance were also homogene, therefore, independent t-test was performed (Table 5).

Table 5
Resume of the different clinical improvement data between debridement group (Group-1) and debridemen with Fasciotomi group (Group-2), First, Second, Third and Fourth weeks Posttest

LUMT Observation	Mean diff.	T	*p**	Confidence Interval 95%	
				Lower bound	*Upper bound*
First week	4.34	1.83	0.073	- 0.409	9.083
Second week	6.17	3.24	0.002	2.362	9.982
Third week	6.44	3.42	0.001	2.672	10.217
Fourth week	7.47	3.69	0.001	3.418	11.526

LUMT = Leg Ulcer Measurement Tool
*Significant if $p < 0.05$

In this study, linear regression was constructed for increase plasma VEGF level to the decrease of plasma TNF-α level. It is important to get linearity between two variables. Previously, both variables tested in advance with Pearson correlation (Product Moment). The results of correlation analysis revealed strong correlation (r = 0.753) and significant ($p < 0.05$) between increased levels of VEGF with decreased levels of TNF-α. Furthermore a linear regression analysis of the two variables was conducted using a simple linear regression. Resume linear regression analysis results is presented on Table 6

Table 6
Resume of Linier Regression Analysis Results Between Increased VEGF Level to the Decreased TNF-α Level

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	*p.*
		B	Std. Error	Beta		
1	Constant of	8.301	3.654		2.272	0.027
	Decreased TNF-α	0.308	0.036	0.753	8.627	0.001

a. Dependent Variable: Increased VEGF

DISCUSSION

Cytokine and growth factor works as a molecular signal that controls proliferation, differentiation, migration and cell metabolism, regulates and replace the various components of the extracellular matrix in wound healing. Some pro-inflammation cytokines (TNF-α, IL-4, IL-5, IL-6, IL-8, Interferon *γ)*, anti-inflammatory cytokines (IL-4, IL-10), and growth factor (PDGF, TGF, FGF, VEGF, EGF) involved in the process of wound healing. Impaired of wound healing in diabetic foot ulcer is caused by dysfunction of cells as well as an imbalance between growth factor and Cytokines, proteases, where an increase in cytokines pro-inflammation especially TNF-α and interleukins (IL-1β) that are directly capable stimulating of MMP synthesis. The high levels of MMP, causing the ulcers healing process become disconnected and uncoordinated because degradation of matrix proteins and growth factor which is very important in wound healing.[15-20]

In this research based on correlation analysis results obtained strong correlation (r = 0.753) and significant ($p < 0.05$) between increased levels of VEGF with decreased levels of TNF-α after debridement with fasciotomy. The strength of the correlation between increased levels of VEGF with decreased levels of TNF-α as shown in the following regression equation: VEGF = 0.308 + 8.301 TNF-α. This means that any decrease of 1 pg/mL levels of TNF-α will increase levels of VEGF as much as 8.301 + 0.308 = 8.609 pg/mL.

Decreased levels of plasma TNF-α occurs through the action of debridement. With a decrease

in the levels of TNF-α, then the process of degradation of the VEGF would be prevented, so that the levels of VEGF to be increased. In addition to its own debridement able to increase the levels of plasma VEGF, increase of VEGF plasma levels also occurred through the improvement of oxygenation of the tissues due to the fasciotomy.[21-27]

CONCLUSION

Based on the results of this study it can be concluded that:

a. There was an increase of plasma TNF-α level and decrease of plasma VEGF levels it appears contribute to impair healing of diabetic foot ulcers.
b. There was average increased pressure on all foot compartment of diabetic foot ulcer. Increased pressure of foot compartment was suspected contribute decrease plasma VEGF levels as the sign of hypoxic tissue.
c. The decreases of plasma TNF-α level on diabetic foot ulcer after debridement with fasciotomy greater than debridement without fasciotomy.
d. The increases of plasma VEGF level on diabetic foot ulcers after debridement with fasciotomy greater than debridement without fasciotomy;
e. There was a strong and significant correlation between increased levels of plasma VEGF with decreased level of plasma TNF-α on diabetic foot ulcer after debridement with fasciotomy.
f. Clinical improvement of diabetic foot ulcer after debridement with fasciotomy greater than debridement without fasciotomy.
g. Debridement and fasciotomy on diabetic foot ulcer were not only improve the inflammation environment of ulcer, but to restore the tissue hypoxia as well.
h. Increase of compartment pressure on foot compartments may support phenomenon of microvascular permeability on diabetic patients, therefore fasciotomy on diabetic foot to become rational as adjunct of treatment.
i. We proposed regulatory mechanism model of TNF-α and VEGF as a new pathogenesis of clinical improvement of diabetic foot ulcer caused effect of debridement with fasciotomy treatment.

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