

# Comparison of antithrombin III levels in type 2 diabetes mellitus patients with and without ulcers at Haji Adam Malik Hospital Medan Indonesia from may to july 2017



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## ABSTRACT

**Introduction:** People with diabetes mellitus (DM) have an increased risk for thrombosis compared with non-diabetic patients. Several studies showed contradicting in data on levels of antithrombin III (AT-III) in people with type 2 DM and diabetic ulcers.

**Methods:** This is a descriptive and analytical cross-sectional study on AT-III concentration of patients with type 2 DM with and without foot ulcers. A total of 40 subjects are divided equally into the control group, which consist of type 2 DM patients without foot ulcers, and the case group of type 2 DM patients with a diabetic foot ulcer based on the Wagner criteria. Blood samples are then taken after 8 to 10 hours of fasting to check for AT-III concentration and hemostasis examination including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen levels, and D-dimers.

**Results:** The mean AT-III level of diabetic foot ulcers group was  $216.02 \pm 71.23$  pg/mL, which was lower than the mean AT-III level of the group without diabetic foot ulcers, i.e.  $243.05 \pm 48.05$  pg/mL. The mean AT-III concentration in the diabetic foot ulcers group with hypercoagulation state was  $221.52 \pm 64.25$  pg/mL, which was slightly higher than the mean AT-III concentration of the diabetic foot ulcers group with hypocoagulation state of  $203.18 \pm 90.92$  pg/mL.

**Conclusion:** No statistically significant difference was found in the levels of AT-III between the diabetic foot ulcers group and the non-diabetic foot ulcers group ( $p > 0.05$ ). There was no statistically significant difference in AT-III levels of diabetic foot ulcers with hypercoagulation compared with no diabetic foot ulcers with hypocoagulation and no statistically significant relationship between grade diabetic foot ulcers and AT-III concentration.

**Keywords:** Antithrombin III, AT-III, type-2 diabetes mellitus, diabetic foot, diabetic ulcer

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## INTRODUCTION

The blood physiological condition can be obtained by a balanced hemostasis between coagulation and fibrinolysis activity involving vascular endothelial, platelets, clotting proteins, anticoagulant proteins, and fibrinolytic enzymes. Any defects in one or more of these components will cause disturbance of hemostasis balance and cause complications of bleeding or thrombosis.<sup>1,2</sup>

Evidence from various studies revealed that people with diabetes mellitus (DM) are in a state of hypercoagulation. The condition of hyperglycemia, hyperinsulinemia, and insulin resistance can trigger changes in the components of hemostasis that cause increased tendency to experience thrombosis compared with the non-DM patient.<sup>3,4,5</sup>

In a chronic diabetic foot ulcers with peripheral arterial disease (PAD) study in Sweden, it was found that elevated levels of several hemostasis parameters

suggesting hypercoagulation and a correlation between the density of fibrin gel structures formed by hemostatin.<sup>6,7</sup> According to a study, people with type 2 DM and ulcers in the lower extremities have a lower total plasma protein C level when compared with type 2 DM patients without ulcers in the extremities.<sup>8</sup> A study obtained decreased protein C, protein S, and antithrombin III (AT-III) and increased fibrinogen concentration in patients with type 2 DM in Turkey.<sup>9</sup>

The condition of hyperglycemia, hyperinsulinaemia, and insulin resistance in patients with type 2 DM may trigger a change in the components of hemostasis that may lead to increased coagulation activity and decreased fibrinolysis activity. This explains why diabetics patients have hypercoagulatory states.<sup>10,11,12</sup> A study found 33% patients in hypocoagulation state and 67% patients in normocoagulation or hypercoagulation state.<sup>13</sup>

Antithrombin (AT) is a serine protease inhibitor (serpin), a specific type of enzyme inhibitor that acts as a natural anticoagulant that inhibits thrombin (IIa), factor Xa, factor IXa, factor XIa, factor XIIa, kallikrein, and plasmin. Deficiency of AT will increase the risk of thromboembolism. AT deficiency can occur as a hereditary or acquired disorder. Decreased synthesis and excretion, drugs, or increased coagulation activity due to endothelial damage may be the causes of acquired AT deficiency.<sup>14,15</sup> In contrast to the above results, other studies showed increased levels of AT-III in patients with type 2 DM.<sup>16,17</sup>

The contradicting results of the previous studies on the levels of AT-III and the limitation of the available data about AT-III disorders are the reasons that intrigue the authors to conduct this study. This study assessed the changes in levels of AT-III in people with type 2 DM with diabetic foot ulcers and without.

## METHODS

This is a descriptive and analytical cross-sectional study conducted between May and July 2017 at RSUP Haji Adam Malik, Medan, Indonesia. The inclusion criteria were patients with type 2 DM who underwent treatment at RSUP Haji Adam Malik, Medan, and were willing to participate in the study. The diabetic foot ulcers were graded based on Wagner's criteria. The control group was type 2 DM patients without foot ulcers. The minimum sample size obtained from the sample size estimation formula was calculated to be 17 for each group. A total of 40 subjects were included in this study, 20 subjects in each group. Type 2 DM patients with other hematologic disorders such as heart failure, kidney failure, liver failure, pregnancy, malignancy, and ulcers due to major surgery or immobilization, are excluded. All basic information about age, gender, and comorbid diseases are collected. Blood samples were tested after 8 to 10 hours of fasting for AT-III concentration and hemostasis examination including platelet count, prothrombin time (PT), activated partial thromboplastin time (aPTT), thrombin time (TT), fibrinogen, and D-dimers. Quantitative data is shown in mean  $\pm$  SD. Categorical data is displayed in terms of numbers and percentages. Data processing is done by using Statistical Package for the Social Sciences (SPSS) program. Chi-Square test is used for comparison of categorical data. Unpaired t-test is used for comparison of parametric data. Pearson test is used for correlation. The result of any statistical analysis is considered to have significance if the value of  $p$  is less than 0.05.

## RESULTS

### Characteristics of Research Subjects

In the diabetic foot ulcers group, 13 patients (65%) were male and 7 patients (35%) were female. In the non-diabetic foot ulcers group, the samples consisted of 10 male and 10 female participants. There was no statistically significant difference in gender between the two study groups ( $p > 0.05$ ). The majority of the diabetic foot ulcers subjects were 50 - 59 year-old (11 patients (55%)) and the least frequent age group was 60 - 69 year-old with only 4 patients (20%) in this category. While in the non-diabetic foot ulcers subjects, 50 percent of the subjects were in the 50 - 59 year-old age group. Only 3 patients (15%) fell into the 40 - 49 year-old group. With Fisher exact test, no statistically significant difference in the age between the two study groups ( $p > 0.05$ ) was found. The most commonly found grade of diabetic foot ulcers was grade 4, which were constituted from 10 patients (50%), 3 patients (15%) were grade 5, and only 7% patients with a grade 3 ulcer.

The results of this study showed that the mean hemoglobin (Hb) level of diabetic foot ulcers was  $10.70 \pm 1.66$  g/dL, which was lower than the mean Hb of the non-ulcer group level of  $13.05 \pm 1.74$  g/dL. A significant difference was found between the concentration of Hb in the diabetic ulcer groups and the non-ulcer group using t-test ( $p < 0.05$ ).

The mean platelet level of the diabetic foot ulcers group was  $381 \pm 122$  mm<sup>3</sup>, which was higher than the mean platelet level of the non-ulcer group of  $303 \pm 110$  mm<sup>3</sup>. Statistically, there was a significant difference in the platelet value between the diabetic foot ulcers group and the non-diabetic foot ulcers group using t-test ( $p < 0.05$ ).

The mean fibrinogen level of the diabetic foot ulcers group was  $445 \pm 214$  mg/dL, which was higher than the mean Fibrinogen level of the group without diabetic foot ulcers of  $290 \pm 90$  mg/dL. There was a statistically significant difference between the fibrinogen level of diabetic foot ulcers group and the group without diabetic foot ulcer using Mann-Whitney test ( $p < 0.05$ ).

The mean D-dimer concentration of the diabetic foot ulcer group was  $647 \pm 313$  (ng / mL), which was higher than that of the non-diabetic foot diabetic ulcer group, i.e.  $404 \pm 301$  (ng/mL). Using t-test, there was a statistically significant difference between the diabetic foot ulcers group and the group without diabetic foot ulcers ( $p < 0.05$ ).

The coagulation status in patients with diabetic foot ulcer revealed that there were six people with hypocoagulation (30%) and fourteen people with hypercoagulation (70%).

### Differences of AT-III Levels between Diabetic Foot Ulcers and Non-Diabetic Foot Ulcers

Based on Table 2 below, the mean AT-III level of diabetic foot ulcers group was  $216.02 \pm 71.23$  pg/mL, which was lower than the mean AT-III level of the group without diabetic foot ulcers, i.e.  $243.05 \pm 48.05$  pg/mL. Using Mann-Whitney test, no statistically significant difference were found in the levels of AT-III between the diabetic foot

ulcers group and the non-diabetic foot ulcers group ( $p > 0.05$ ). The mean AT-III concentration in the diabetic foot ulcers group with hypercoagulation state was  $221.52 \pm 64.25$  pg/mL, which was slightly higher than the mean AT-III concentration of the diabetic foot ulcers group with hypocoagulation state of  $203.18 \pm 90.92$  pg/mL. However, statistical test with Mann-Whitney test showed no significant difference in AT-III levels in diabetic foot ulcers between the hypercoagulation and hypocoagulation state group ( $p > 0.05$ ).

**Table 1** Characteristics of research samples

Characteristics	Subjects		P
	Diabetic foot ulcers (n=20) Mean $\pm$ SD	Non-diabetic foot ulcers (n=20) Mean $\pm$ SD	
<b>Age (year-old)</b>			
40-49	5 (25)	3 (15)	
50-59	11(55)	10 (50)	0.493 <sup>a</sup>
60-69	4 (20)	7 (35)	
<b>Gender</b>			
Male	13 (65)	10 (50)	0.337 <sup>b</sup>
Female	7 (35)	10 (50)	
<b>Ulcer grade</b>			
0	0	20 (100)	
3	7 (35)	0	
4	10 (50)	0	
5	3 (15)	0	
<b>Complete Blood Count</b>			
Hb (g/dl)	10.7 $\pm$ 1.6	13 $\pm$ 1.7	0.001 <sup>d</sup>
Pletelet (mm <sup>3</sup> )	381 $\pm$ 122	303 $\pm$ 110	0.041 <sup>d</sup>
<b>Hemostasis test</b>			
Fibrinogen(mg/dL)	445 $\pm$ 214	290 $\pm$ 90	0.009 <sup>c</sup>
D-Dimer(ng/mL)	647 $\pm$ 313	404 $\pm$ 301	0.017 <sup>d</sup>
<b>Coagulation state</b>			
Hypercoagulate	14 (70)		
Hypocoagulate	6 (30)		

<sup>a</sup>Fisher exact test    <sup>b</sup> Chi-square test    <sup>c</sup>Mann-Whitney test    <sup>d</sup> t-test

**Table 2.** Differences in the Levels of AT-III in patients with and without Diabetic Foot Ulcers and its Relationship with the Coagulation Status

	With ulcers n=20	Without ulcers n=20	p-value	With hyper-coagulation and ulcers n=14	With hypocoagulation and ulcers n=6	p-value
AT-III (pg/mL)	216.02 $\pm$ 71.23	243.05 $\pm$ 48.05	0.093	221.52 $\pm$ 64.25	203.15 $\pm$ 90.92	0.509

### The Relationship between AT-III Concentration and Gender in Patients With and Without Diabetic Foot Ulcers

Based on Table 3 below, the AT-III concentration of male participants was lower than that of female, with  $215 \pm 76.9$  pg/ml and  $217.4 \pm 65$  pg/ml, respectively. However, this result was not statistically significant using t-test. This similar result also appears in the non-ulcer group where the levels of AT-III were found to be lower in male ( $231.8 \pm 58.1$  pg/ml) than in the female ( $254.8 \pm 34.4$  pg/ml). Nonetheless, this result was also not statistically significant.

### The Correlation between AT-III Concentration and Diabetic Foot Ulcers Grade

Pearson test was used to assess the correlation between diabetic foot ulcer grade and AT-III level. No significant correlation between the diabetic foot ulcer grade and AT-III level was found ( $r = 0.16$ ;  $p = 0.509$ , ( $p > 0.05$ )).

## DISCUSSION

The results which showed no significant differences between the lifespan of patients with type 2 DM with diabetic foot ulcers and patients without diabetic foot ulcers, is in accordance with a previous research where no significant differences were found between the lifespan of patients with type 2 DM and diabetic foot ulcers or patients without diabetic foot ulcers.<sup>8</sup> However, another study found a significant difference between the lifespan of patients with type 2 DM and diabetic foot ulcers with those without diabetic foot ulcers.<sup>18</sup> Based on another previous study, the prevalence of diabetic foot ulcer complications increases with age and duration of DM.<sup>19</sup> The duration of DM can be used to explain for the difference in these results. Based on a study, the longer the patient has DM, the higher the risk for chronic complications.<sup>20</sup>

The results where no statistically significant differences regarding the gender of the two study groups is consistent with the result of another study.<sup>8</sup> However, another study concluded that diabetic foot ulcers are significantly more likely to

**Table 3 Relationship between AT-III Concentration and Gender in Patients With and Without Diabetic Foot Ulcers and Without Diabetic Foot Ulcers**

	With ulcers		<i>p</i>	Without ulcers Male (=10)	Female (n=10)	<i>P</i>
	Male (n=13)	Female (n= 7)				
AT-III (pg/mL)	215.2 ± 76.9	217.4 ± 65	0.95	231.2 ± 58.1	254.8 ± 34.4	0.29

**Table 4 The Correlation between AT-III levels with Diabetic Foot Ulcers Grade**

	Grade 3	Grade 4	Grade 5	<i>P</i>	<i>R</i>
AT-III (pg/mL)	214.5 ± 65.2	227.1 ± 54.5	182.3±140.3	0.509	0.16

be suffered by men than in women because men tend to have limited joint mobility and higher foot pressure than women.<sup>20</sup>

The statistically significant lower mean Hb level of diabetic foot ulcers group than the non-ulcer group is consistent with previous studies in which 14 patients out of 27 diabetic foot ulcers patients had anemia, with 2 patients suffering severe anemia.<sup>21</sup> Another study also showed similar results with as much as 63% of 30 diabetic ulcers patients had anemia. Vascular complications in DM neuropathy, nepropathy, and retinopathy are associated with anemia that can affect wound healing and macrovascular disease. Low oxygen level in the blood followed by low levels of hemoglobin could cause ischemic worsening in the lower limbs. Various studies found that anemia was more common in people with DM than in those without. The association between anemia and diabetic foot ulcers remains unexplained, but the role of inflammatory and chronic disease in diabetic foot ulcers has an important role for the occurrence of anemia.<sup>21,22</sup>

A statistically significant higher mean platelet value of the diabetic foot ulcers group compared to the non-ulcers group is supported with a previous research, in which a higher platelet count was obtained in 152 diabetic foot ulcers patients (255 ± 79.5 mm<sup>3</sup>) compared to 52 control patients (233 ± 62.1 mm<sup>3</sup>).<sup>23</sup> This higher platelet value, however, could not serve as a reference to the severity of diabetic foot ulcers because platelet values may change with the degree of inflammation.

The statistically significant higher mean fibrinogen concentration in the diabetic foot ulcer group than the non-ulcer group is consistent with a research, in which fibrinogen levels in patients with DM with microvascular complications is increased.<sup>24</sup> Another research also found elevated fibrinogen levels in 152 patients with diabetic foot ulcers where fibrinogen were associated with severity of diabetic foot ulcers and amputation.<sup>23</sup>

The lower yet not statistically significant mean level of AT-III of the diabetic foot ulcer group obtained in this study might due to the thrombosis of DM patients with diabetic foot ulcers which triggered the use of AT-III that acts as a natural anticoagulant. The not-statistically significant difference between the two groups may be because the AT-III examination was not immediately done when the patient is admitted to the hospital. The initial DM treatment has been given prior to the examination because RSUP Haji Adam Malik is a regional referral hospital.

A previous study obtained a significantly lower plasma AT-III (26.6 + 0.4 mg/100 ml) in 116 type 2 DM patients with vascular complications, compared with the plasma AT-III of 64 control patients (31.0 + 0.3 mg/100 ml, *p*<0.01).<sup>25</sup> Another research examined the association of hyperglycaemia with AT-III, in 20 DM patients (76.5 ± 2.2 unit?) and 20 controls (96.3 ± 1.8 unit?), a significant reduction in AT-III levels was found in patients with hyperglycaemia.<sup>26</sup>

A research in Brazil revealed AT-III deficiency in 48 patients with chronic ulcers.<sup>27</sup> Similar results are reported by another study where natural anticoagulant activity (AT-III, protein C, and protein S) were lower in as many as 132 patients with type 2 DM compared with healthy individuals.<sup>28</sup>

A study found a decrease in levels of AT-III in patients with type 2 DM with angiopathy complications compared with no angiopathy complications.<sup>29</sup> This study was in contrast with another study where elevated AT-III levels were detected in type 2 DM patients, but the AT-III levels were not related to the duration of DM and diabetes complications.<sup>16</sup> (This comparison should not be drawn because the two studies had a very different design.) Another study found Increased AT-III levels in 92 patients with type 2 DM compared with control patients. However, no statistically significant decrease of AT-III levels between DM patients with or without complications.<sup>30</sup>

The lower AT-III concentration in male subjects as compared with the female in this study could be explained with a type of compensation reaction toward coagulation status.<sup>31</sup> This results were consistent with a study where There was no

significant difference in thrombin-antithrombin levels between the two genders in patients with type 2 DM.<sup>32</sup> (Consider to relocate the above paragraph to the discussion about the characteristics of the subjects which discuss whether gender affect AT-III or not)

In this study, no significant correlation between the grade of ulcers with levels of AT-III,  $r = 0.16$ ,  $p = 0.509$  ( $p > 0.05$ ). Currently, there is no previous research that studied the relationship between the grades of diabetic foot ulcers with AT III concentration to compare with. (Consider removing this as this paragraph is irrelevant)

### Limitations

The limitations of this study were the fact that all subjects were coming from only one hospital, the absence of data on how long the patient had suffered type-2 DM, and lack of examination of other factors that could affect coagulation such as hypoalbumin. (This confounder variable should be identified early in the methods section)

### CONCLUSION

There was no statistically significant difference in levels of AT-III between the diabetic foot ulcers patients with the non-diabetic foot ulcers group. Besides, there was also no statistically significant difference between the AT-III concentration and grade of diabetic foot ulcers. Further research with a broader population from several health care centers can be done. Additionally, other researches that look into finding a relationship between the degrees of diabetic foot ulcers and other factors that may affect coagulation could be pursued in the future.

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