Association of fibrinogen with HbA1C in diabetic foot ulcer

M A Pase\textsuperscript{1*}, D Gatot\textsuperscript{2} and D Lindarto\textsuperscript{1}

\textsuperscript{1}Division of Endocrinology, Metabolism and Diabetes, Internal Medicine Department, Medical Faculty, Universitas Sumatera Utara, Indonesia
\textsuperscript{2}Division of Hematology and Medical Oncologic, Internal Medicine Department, Medical Faculty, Universitas Sumatera Utara, Indonesia

\textsuperscript{*}Corresponding author: aron@usu.ac.id

Abstract. Fibrinogen is one of the inflammatory markers of vascular changes and endothelial dysfunction in diabetic patients. The aim of this study to associate serum fibrinogen levels with HbA1C in diabetic foot ulcer (DFU). This study was cross-sectional and retrospective in DFU patients from January to July 2017 in Haji Adam Malik Central General Hospital. The patients enrolled in the study were T2DM with DFU as a complication. The grading of DFU was evaluated according to the Wagner’s Classification. Serum fibrinogen level, HbA1C and ankle-brachial index (ABI) were carried out directly in the patients. Fibrinogen serum levels were found significantly with HbA1C (P=0.001, r=0.387) and ABI (P=0.008, r= -0.454). Fibrinogen serum levels in DFU patients were positively correlated with HbA1C and significantly higher in patients with poor glycemic control.

1. Introduction
Diabetes mellitus is the most common metabolic disorder characterized by abnormality of the metabolic system and long-term complications.[1] The vascular complications of type-2-diabetes-mellitus (T2DM) can be caused by either microangiopathy or macroangiopathy.[1] The macroangiopathy in T2DM is a form of accelerated atherosclerosis affecting carotid, coronary and peripheral arteries. This phenomenon inside the big vessels increases the incidence and prevalence of diabetic foot ulcer (DFU) in diabetic patients.[2,3] To this day, DFU is the leading cause of lower extremity amputation in diabetic patients, and known to give a poor prognosis to the patients.[3]

Serum fibrinogen is an inflammatory marker that has important role in the pathogenesis of inflammation, atherosclerosis, thrombogenesis, and development of vascular complications in T2DM patients. The complications include myocardial infarction, stroke, and peripheral arterial disease.[4,5] Fibrinogen has been estimated to increase in patients with DFU.[6] It has been demonstrated that patients with DFU have higher fibrinogen levels than those without any ulcers.[6] An increase in the synthesis of plasma fibrinogen levels in diabetic patients has been reported.[7] Another finding in diabetic patients is an increased rate of fibrinogen clearance, with shorter fibrinogen circulating half-life.[7] The aim of this study to associate serum fibrinogen levels with HbA1C in DFU patients.

2. Methods
This study was conducted as a cross-sectional, retrospective study carried out in Haji Adam Malik Central General Hospital. The study population included DFU patients. We use total sampling based on the criteria needed to determine the study population. The patients enrolled were those admitted as inpatients in the internal medicine ward starting from January to July 2017, also diagnosed with DFU
as a complication of the disease. There were a total of 33 patients who fulfilled the criteria and enrolled in the study. The data collected included the patients’ demographic information, history of illness, clinical examination and routine laboratory assays. All data were obtained from the patients’ medical records. The serum fibrinogen was measured by Clauss method. HbA1C, measured by HPLA assay. Measurement of the D-dimer done by immunoturbidimetry assay. The grading of DFU was evaluated according to the Wagner’s Classification.

Data were analyzed as univariate and bivariate using SPSS with 95% confidence interval. The analysis was carried out using Pearson Correlation and ANOVA with significance level p<0.05.

3. Results
We found 33 of DFU patients were hospitalized and have been considered as qualified as study participants. We found that DFU affected male (57.5%) and females (42.4%). The mean age was 52.58 ± 7.75 years. The grading of DFU was grade 4 (48.5%), grade 3 (39.4%) and grade 5 (9.1%) and most of the study population showed poor glycemic control (HbA1C ≥ 9% = 69.7%). The mean value of serum fibrinogen was 436.55 ± 222.28mg/dl as shown in Table 1.

| Characteristic                          | N=33 (%) | mean ±SD |
|----------------------------------------|----------|----------|
| Male                                   | 19 (57.6)|          |
| Female                                 | 14 (42.4)|          |
| Age (years)                            | 52.58 ± 7.75|        |
| Diabetes duration (years)              | 6.45 ± 2.4|          |
| Wagner Classification                   |          |          |
| Grade 1                                | 0 (0%)   |          |
| Grade 2                                | 1 (3%)   |          |
| Grade 3                                | 13 (39%) |          |
| Grade 4                                | 16(49%)  |          |
| Grade 5                                | 3 (9%)   |          |
| Hemoglobin, (Hb, g/dl)                 | 9.29 ± 2.27|        |
| White Blood Count, (WBC, /mm3)         | 19147.76 ± 7990.98| |
| Poor glycemic control (HbA1C ≥ 8%)    | 23 (69.7%)|          |
| HbA1C (%)                              | 9.72 ± 2.63|        |
| Fibrinogen,(mg/dl)                     | 436.55 ± 222.28|  |
| D-dimer,(ng/ml)                        | 443 (56-3110)|       |
| Ankle Brachial Index (ABI)             | 0.86 ± 0.18|        |

There was a significant correlation (positive) between serum fibrinogen with HbA1C levels, D-dimer, age, ABI and duration of diabetes (P = 0.026, r = 0.387; P = 0.797, r = -0.046; P = 0.811, r = 0.043; P = 0.008, r = -0.454; P = 0.370, r = -0.161, respectively) in patients with DFU (Table 2).

| Variables       | r   | p     |
|-----------------|-----|-------|
| HbA1C           | 0.387 | 0.026* |
| D-dimer         | -0.046 | 0.797 |
| Age             | 0.043 | 0.811 |
| ABI             | -0.454 | 0.008* |
| Duration of diabetes | -0.161 | 0.370 |

*p<0.05
There was significant difference of fibrinogen levels among Wagner classification in patients with diabetic foot ulcer. Fibrinogen levels were significantly higher in Wagner grade 5 than grade 3 and 4 (Table 3).

**Table 3.** Comparison of fibrinogen levels among Wagner classifications in DFU patients.

| Wagner Classification | Fibrinogen Levels | p  |
|-----------------------|-------------------|----|
| Grade 3               | 244.08 ± 63.4     |    |
| Grade 4               | 536.88 ± 129      | <0.001<sup>a</sup> |
| Grade 5               | 850.67 ± 57.85    |    |

<sup>a</sup>p<0.05

4. Discussion

Serum fibrinogen is an inflammatory marker that has an important role in the pathogenesis of inflammation, atherosclerosis, thrombogenesis, and development of vascular complications in T2DM patients.[8,9,10] Hyperfibrinogenemia in diabetes has been reported to as a cause of an increase in the synthesis of fibrinogen, which is not compensated by a proportionate increase in its clearance. This is associated with insulin deficiency, which have been corrected with insulin [11], suggesting that hyperfibrinogenemia is an expression of a poor glycemic control.[12] Fibrinogen is reported to be found in a higher level in patients with diabetes than those without it.[13,14] It is said that most of DFU patients had poor diabetic control (HbA1C > 8%).[13] Our study showed serum fibrinogen to be significantly associated with the glycosylated hemoglobin (HbA1c) (r = 0.387 and P-value =< 0.026). Similarly, in a study of plasma fibrinogen level and cardiovascular risk factor conducted in Japanese by Fujii et al (2006), it was found that there was a significant association between plasma fibrinogen and HbA1C level.[15] Another similarity found in a study by Kalfe et al [13] and Sanjay et al [4], in which the data suggested that patients with the diabetic foot disease have higher fibrinogen levels than those without ulcers.[7] Another study was done by Kuzhuppilly et al, who also found that there was a significant correlation between plasma fibrinogen level and fasting glucose but no correlation with post-prandial blood glucose.[16]

Similar results are found in a study conducted by Naga RV in which serum fibrinogen level was significantly higher in all DFU grade 2 patients compared to DFU grade 1 (p value < 0.05).[8] Other data also revealed a significant association between fibrinogen and DFU disease severity as reflected by amputation.[17]

5. Conclusion

In conclusion, this study has demonstrated that fibrinogen levels are significantly associated with HbA1C and ABI in patients with DFU, and fibrinogen was significantly difference according to Wagner classification. Fibrinogen may also be useful to predict glycemic control in the diabetic patient with DFU.

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