

Correlation of Glycated Hemoglobin and D-dimer in Diabetic Patient

Sry Suryani Widjaja¹ and Muhammad Syahputra¹

¹ Biochemistry Department, Medical Faculty Universitas Sumatera Utara, Medan, Indonesia

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Abstract: Diabetes Mellitus a chronic metabolic disease presented with chronic hyperglycemia, which will cause abnormalities in the endothelial cells, proinflammatory state, alter platelet function and plasma coagulation factors that lead to hypercoagulable state and thrombosis. D-dimer an indirect marker of thrombotic activity, is the final fragment of the plasmin mediated degradation of cross-linked fibrin. The elevated d-dimer level was detected at the onset of thrombosis, it was used to exclude the venous thromboembolism when it was negative. D-dimer was increased in diabetic patients under most studies, and when there is a hypercoagulable state, hyperfibrinolysis will occur, subsequently elevation of D-dimer. This study was aimed to study the correlation between glycated hemoglobin and d-dimer in diabetic patients. This is a case control study to evaluate the correlation of glycated hemoglobin (HbA1c) and d-dimer in diabetic patients. Total 60 patients were recruited, the blood glucose level, HbA1c, d-dimer were measured. There was statistical significant correlation between HbA1C and d-dimer ($p=0.019$, $r= 0.27$), HbA1c and age ($p=0.002$, $r=0.36$), d-dimer and age ($p=0.04$), blood glucose and HbA1C ($p=0.00$, $r=0.5$), blood glucose and age ($p=0.037$, $r=0.23$).

1 INTRODUCTION

Diabetes mellitus (DM), with an increasing prevalence worldwide, is a chronic metabolic disturbance disease with micro and macro vascular complications such as acute myocardial infarction, stroke, and peripheral arterial disease (Fulvio, 2015). In diabetic patients abnormalities in the endothelial cells (Kinlay S, 2001), proinflammatory state (Devaraj, 2010), altered platelet function and plasma coagulation factors leading to a hypercoagulable state with the propensity for thrombosis. (Mark AC, 2003) Either acute or chronic hyperglycemia plays an important role in hemostatic disturbances, prothrombotic condition (Lemkes, 2010), hypercoagulable state (Di Minno, 2011) and poor clinical outcome of thrombotic events. (Lemkes, 2010) From several studies, the risk of cardioembolic stroke was increased. Per year it was ranged between 3.6 and 8.6% (Stroke Risk in Atrial Fibrillation Working Group, 2007). The prothrombotic state in diabetes was contribute by the increasing levels of clotting factors, primary hemostasis changes and impaired of fibrinolysis and low grade inflammation (Nomura, 2009).

One of the most important pathway that associated with thromboembolism is platelet reactivity, (Vinik AI, 2001) this will accelerated platelet aggregation, hypercoagulable state, (Winocour PD, 1990) impaired fibrinolysis (Lu tjens A, 1985) and it was also reported to be correlated with the concentration of glycated hemoglobin (HbA1c) (Iwase E, 1998) a standard measure of chronic glycemia that is used to identifying high risk persons who will develop diabetes, control of diabetes and as a predictor of diabetes (William, 2015). Hyperglycemia was an important factor to induce endothelial dysfunction, (Jansson, 2007) increased the prothrombin fragment 1+2 and D-dimer (Nieuwdorp M, 2006).

An indirect marker of thrombotic activity, d-dimer (Antovic P, 2013) is the final fragment of degradation of cross-linked fibrin that was mediated by fibrin. (Righini M, 2008) The elevated d-dimer level was detected at the onset of thrombosis, (Ana Pilar NR, 2009) and the negative level was used to exclude the venous thromboembolism. (Nwose EU, 2007) D-dimer was increased in diabetic patients under most studies, (Nwose EU, 2007, Yamada T, 2000) and when there is a hypercoagulable state, hyperfibrinolysis will occur, subsequently elevation

of D-dimer. (Nwose EU, 2007) Due to hypercoagulable and hypofibrinolytic states, diabetes was considered important risk factor for thrombosis. (Yamada T, 2000) One of the marker is D-dimer, when elevated showed hyperactivation of hemostatic system (Meigs JB, 2000).

2 METHOD

This is a case control study to evaluate the correlation of glycated hemoglobin (HbA1c) and D-dimer in diabetic patients. The study received ethical approval from Health Research Ethical Committee Medical Faculty Universitas Sumatera Utara/H.Adam Malik General Hospital Medan Indonesia. Total 60 diabetic patients from hospital and private clinics, who signed the informed consent were admitted to the study.

2.1 Blood Collection

Blood sampling was performed from a clean venepuncture using the Vacutainer system (Beckton Dickenson, New Jersey, USA). About 6 mL of blood was collected into EDTA and heparin tubes. Both tubes spun for 15 min at 2000g within an hour of blood collection. Plasma EDTA and heparin samples were aliquoted and kept at -70 °C until assayed.

2.2 Laboratory Assays

Blood glucose, HbA1c, d-dimer were performed at the Integrated Laboratory Medical faculty University Sumatera Utara, Medan Indonesia. Blood glucose was measured with spectrophotometry, HbA1c with HPLC method, d-dimer with ELISA method.

Body Mass Index (BMI) was determined by using the BMI calculator (body weight and height).

2.3 Data Analysis

Non-parametric Mann Whitney U test was used to evaluate normality distribution of the blood glucose, HbA1c, D-dimer in diabetes. Spearman's Rho correlation analysis was used to determine the correlation between HbA1c against d-dimer seen in diabetic patients. A *P* value of less than 0.05 was considered statistically significant.

3 RESULTS AND DISCUSSIONS

3.1 Results

Total 60 samples were including in this study. The samples descriptive statistics and Laboratory assays are shown in table 1.

Table 1: Descriptive Statistics of the samples and Laboratory Assays.

| Parameter | Mean (range) |
|-----------------------|----------------|
| Age | 60 (27-80) |
| Body mass index (BMI) | 25 (19.5-35.2) |
| Blood Glucose | 240 (28-654) |
| HbA1c | 9.3 (5.4-14.3) |
| D-dimer | 1.7(0.15-5) |

From the study we got the mean age was 60 years (27-80 years), range of HbA1c was 5.4-14.3% with the mean 9.3, Blood glucose level ranged from 28-654 mg/dl with the mean 240, the blood glucose level was not well controlled, there were 78.3% samples with bad glucose control and 21.7% with good control. D-dimer ranged from 0,15-5 with the mean 1,7. The BMI range from 19.5-35.2, with the mean 25. Most of the samples were normal weight (55%), over weight (35%) and 10% obesity.

We use the Kolmogorov-Smirnov to test the normality of the datas and found that the datas were not distributed normally. The Spearman's Rho was used to study the correlation between datas, $p < 0.05$ is considered statistical significant.

Table 2. Correlation between control of blood glucose and hypercoagulable state

| | d-dimer | BMI | HbA1c |
|---------------|---------|---------|---------|
| Blood glucose | p=0.085 | p=0.27 | p=0.00 |
| HbA1c | p=0.019 | p=0.324 | 1 |
| d-dimer | 1 | p=0.117 | p=0.019 |

sig (1 tailed)
correlation is significant at the 0.05 level

There is statistical correlation between HbA1c and d-dimer ($p=0.019$, $r=0.27$).

4 DISCUSSION

This study showed that the blood glucose control is still an important issue to be warning in this region, this was showed from the mean level of blood glucose was 240 mg/dl, the mean of glycated

hemoglobin was 9.3 and most of the samples were not well controlled (78.3%). This condition will caused chronic hyperglycemia that will finally cause hypercoagulable state, hyperactivation of hemostatic system as shown in several studies that can be risk factor of thrombosis in diabetic patients. This study also showed significant correlation between HbA1c that reflects the control of blood glucose within three months with the d-dimer, marker that is use widely to exclude deep vein thrombosis and also a marker for hyperactivation of hemostatic system. One of the most common complications of diabetes that correlate with the hyperactivation of hemostatic system are involving macrovascular likes coronary heart disease, stroke and venous thromboembolism.

Another issue that has to be warning is the body mass index, in this study there was 35% of samples with overweight and 10% with obesity, though the BMI did not showed statistical correlation with the d-dimer, overweight and obesity were one of the criterias of metabolic syndrome that was risk factor of hemostatic disturbance and thrombosis.

5 CONCLUSION

Glycated hemoglobin (HbA1c) has statistical significant correlation with d-dimer, a marker used to exlude venous thromboembolism and marker for hyperactivation of hemostatic system.

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