# Correlation between Uncontrolled Blood Glucose and Oxidative Stress with Urinary Nephrin Level in Type 2 Diabetes Mellitus

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**Abstract.** Diabetes mellitus (DM) is one of the world's health problem with increasing prevalence and important medical and social impacts. Diabetes mellitus causes micro and macrovascular complications depending on the presence of blood glucose level disorder. Impaired glucose levels have two components, chronic hyperglycemia and acute fluctuations of blood glucose levels from peak to nadir. These two components cause DM with two main mechanisms, protein glycation, and oxidative stress. Glycated albumin describes uncontrolled medium range glucose level while malondialdehyde reflects oxidative stress. Nephrin is one of the damage markers of podocyte that represents diabetic kidney disease. To find out the correlation between uncontrolled blood glucose with urinary nephrin level in a patient with type 2 diabetes mellitus. This is an observational study with the cross-sectional method. Subjects are 30 types 2 DM patients. Patients serum glycated albumin (GA) are measured, along with serum malondialdehyde (MDA) and urinary nephrin. Among 30 types 2 DM patients, there is a significant increase in GA and MDA level. Mean serum GA level is 20,87% (5,91) %, serum MDA level is 9,24 (5,59 – 13,59) and urinary nephrin is 369,25 (6 – 3952) ng/ml. There is a moderate correlation between serum GA with urinary nephrin (p=0,027) and moderate correlation between serum MDA and urinary nephrin (p=0,003). There is a correlation between uncontrolled blood glucose with urinary nephrin level in type 2 diabetes mellitus.

**Keywords:** Glycated Albumin, Serum Malondialdehyde, Type 2 DM, Uncontrolled Blood Glucose, Urinary Nephrin.

## 1 Introduction

Diabetes mellitus (DM) is one of the world's health problem with increasing prevalence and important medical and social impact. According to the International Diabetes Federation (2013), 382 million people across the world had DM in 2013. The global prevalence of diabetes in 2035 is predicted to increase to 592 million people. In 2013, Southeast Asia held 72 million adults with diabetes and is estimated to increase to 123 million people in 2035. A significant increase in the DM prevalence occurs in Southeast Asia including Indonesia. In 2030 DM sufferers is estimated to be 21,3 million people [1],[2].

Diabetes mellitus can cause microvascular complication, including diabetic kidney disease (PGD) [3],[4]. Based on the American Diabetes Association (ADA), PGD occurs in 20-40% DM patient and becomes the main cause of end-stage renal disease [5],[6].

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Protein in the human body can be glycated. Glycation of various proteins increases in diabetic patients, as of these glycated proteins can be utilized to evaluate diabetes controlling. Of all glycated proteins, HbA1c is the gold standard for glycaemic control. In the last few years, glycated albumin (GA) becomes an index of glycation for medium range uncontrolled blood glucose because of the short albumin half-life compared to erythrocyte [7],[8].

Oxidative stress is caused by unbalanced production of oxidant or ROS and detoxification capacity to repair cell damage. There is a direct relationship between kidney damage severity with oxidative stress level in diabetic kidney disease. Several markers have been used to measure oxidative stress in diabetic patients. One of the markers is malondialdehyde (MDA) [9],[10]

In DM patient, a further pathologic kidney change occurs. Three components become the glomerular filtration barrier, which is the podocyte, capillary endothelial cell, and glomerular basal membrane. Certain proteins can reflect the condition of podocyte and nephrin. In diabetic condition, a downregulation of nephrin take place and acts as an antiapoptotic agent. Released nephrin escapes through the urine and can be detected in patients urine. The loss of nephrin cause flattening foot process of the podocyte and cause the increasing of proteinuria [11],[12].

Many studies show that hyperglycemia plays a role in the pathogenesis of diabetic kidney disease so that a glycaemic control to prevent complication is needed. The protein glycation process causes complication in diabetic patients and the oxidative stress occurred in the patient. Based on those backgrounds, we decided to study the correlation between uncontrolled blood glucose with urinary nephrin level in a patient with diabetes mellitus type 2 [11],[12].

## 2 Materials and Methods

This study is a cross-sectional observational study. Study is conducted in the inpatient room and polyclinic of the Internal Medicine Department RSUP M. Djamil Padang for 6 months. The population of this study is patients with type 2 DM, hospitalized in RSUP M. Djamil Padang or routine polyclinic patients within the age of 18-59 years. Samples are the population that matches the inclusion and exclusion criteria.

A correlation analysis made between serum glycated albumin with urinary nephrin level and the correlation between serum malondialdehyde level and urinary nephrin level. Data is processed with SPSS 21.0, the value of significance is calculated, and is significant if $p<0,05$.

## 3 Results

Table 1 shows the characteristics of 30 types 2 DM patients. This study consists 11 male patients (36,67%) and 19 females (63,3%). The mean age of type 2 DM patients is 52,03 years old, the youngest is 37 years old, and the oldest is 59 years old. The most amount of age obtained are 51-59 years old. Patients distribution based on the age groups are, 30-39 years old is 1 patient (3,33%), the groups of 40-49 years old has 8 patients (26,67%) and the age 50-59 years old as much as 21 patients (70%). The mean duration of disease suffering is 7,3 (5,4) years. The mean body mass index is 21,67 (3,9) kg/m$^2$. In this study, the average fasting blood glucose is 178,8 (71,4) mg/dl and postprandial blood glucose is 219,1 (89,7) mg/dl. Mean serum level is 34,7 (29,4) mg/dl and creatinine is 1,1 (0,5) mg/dl.

**Table 1.** Baseline Characteristics

| Characteristics | n (%) | Mean (SD) |
|---|---|---|
| Gender | | |
| Male | 11 (36,67) | |
| Female | 19 (63,33) | |
| Age (year) | | 52,03 (5,60) |
| 30 - 39 | 1 (3,33) | |
| 40 – 49 | 8 (26,67) | |
| 50 – 59 | 21 (70) | |
| Duration of disease suffering (year) | | 7,30 (5,40) |
| Body Mass Index (kg/m$^2$) | | 21,67 (3,90) |
| Fasting Blood Glucose (mg/dl) | | 178,80 (71,40) |
| Post Prandial Blood Glucose (mg/dl) | | 219,10 (89,70) |
| Ureum (mg/dl) | | 34,70 (29,40) |
| Creatinine (mg/dl) | | 1,10 (0,50) |

In this study, we obtained the mean level of serum glycated albumin at 20,87 (5,91) % (normal value 11-16 %). The result of the Kolmogorov Smirnov normality test shows the serum glycated albumin in this study is normally distributed. After performing one sample t-test, we found the GA level increases significantly with p<0,001.

**Table 2.** Serum Glycated Albumin in Type 2 DM patients

| Variable | n | Mean (SD) |
|---|---|---|
| *Glycated Albumin* (%) | 30 | 20,87 (5,91) |

glycated albumin normal value: 11- 16%

In this study, we obtained the level of serum malondialdehyde as much as 9,24 nmol/ml, with the lowest level 5,59 nmol/ml and the highest is 13,56 nmol/ml. Kolmogorov Smirnov normality test shows the data of serum malondialdehyde level in the study is not normally distributed. Table 3 shows the median level of serum malondialdehyde.

**Table 3.** Serum Malondialdehyde Level in Type 2 DM patients

| Variable | n | Median | Minimum – Maximum |
|---|---|---|---|
| Serum Malondialdehyde (nmol/ml) | 30 | 9,24 | 5,59 – 13,56 |

Serum MDA normal value : 0,9 - 1,59 nmol/ml

In this study, the median level of urinary nephrin is 369,25 ng/ml, with the lowest level is 6 ng/ml and the highest is 3952 ng/ml. Kolmogorov Smirnov normality test shows the data of urinary nephrin in the study is not normally distributed. Table 4 provides the median urinary nephrin level.

**Tabel 4.** Urinary Nephrin Level in Type 2 DM Patients

| Variable | n | Median | Minimum – Maximum |
|---|---|---|---|
| Urinary Nephrin (ng/ml) | 30 | 369,25 | 6 – 3952 |

Urinary nephrin normal value : not detected

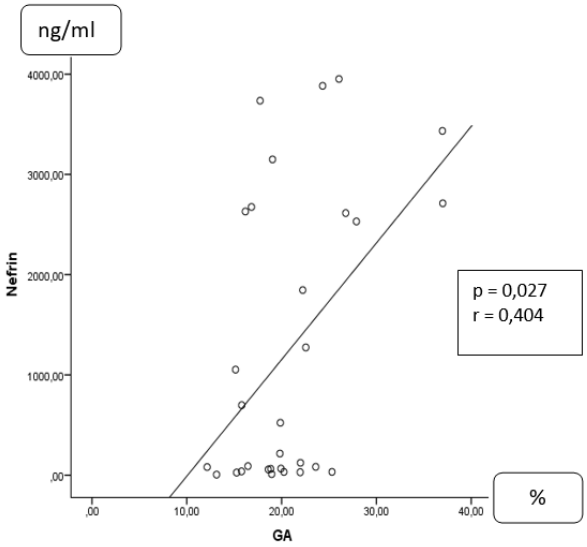


**Fig. 1.** Graphic of correlation between serum glycated albumin level with urinary nephrin level in the Type 2 DM patients

In figure 1 above, can be seen the correlation between serum glycated albumin level with urinary nephrin level in the Type 2 DM patients. The correlation analysis used is the Spearman correlation test and confidence level obtained is $p<0,05$. The analysis result shows a significant correlation between serum glycated albumin with urinary nephrin level ($p=0,027$), with positive correlation and the correlation strength is moderate. (Correlation coefficient $r=0,404$)

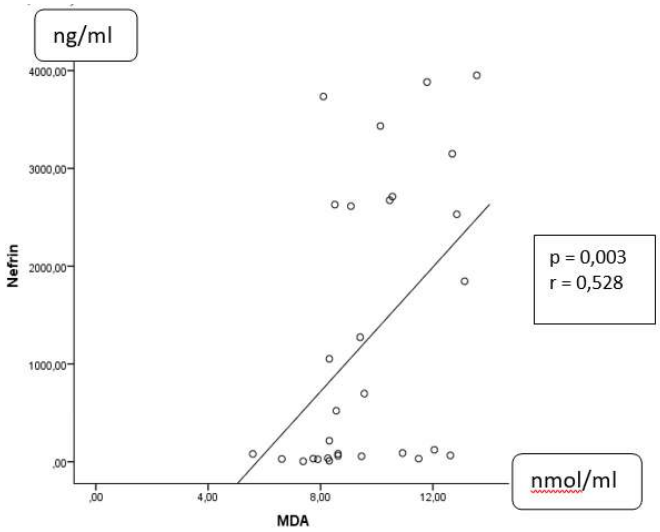


**Fig. 2.** Correlation graphic between serum malondialdehyde level with urinary nephrin level in type 2 DM patients.

In the figure above can be seen the correlation between serum malondialdehyde level with urinary nephrin level in type 2 DM patients. Correlation analysis used is the Spearman correlation test and confidence level obtained is $p<0,05$. The analysis result shows a significant correlation between serum malondialdehyde level with urinary nephrin level ($p=0,003$) with positive direction and moderate strength of correlation (correlation coefficient $r=0,528$).

# 4 Discussion

## 4.1 Baseline Characteristics

From 30 type 2 DM samples, 19 patients (63,33%) were female and 11 are male (36,67%). The study by Furusyo *et al.* (2011) on DM population in Japan found that there are more female patients than the male with a ratio of 70:30. Hilawe *et al.* (2013) published a meta-analysis of 36 studies and stated that the prevalence of type 2 DM in South Africa is much higher in women compared to men [13],[14].

In this study we found the mean age of type 2 DM patients treated in RSUP Dr. M. Djamil Padang is 52,03 (5,6) years old with the most amount of age groups are 50-59 years old, which is 21 patients (70%). Lopez *et al.* (2014) performed a study in New Jersey with 7,239 types 2 DM patients and found the mean age is 59,9 years old. Whereas Solini *et al.* (2013) reported a multicenter study of type 2 DM in Italia and found an older age range compared to the study, which is 59-73 years old [15],[16].

In this study, the mean disease suffering of the type 2 DM patients is 7,3 (5,4) years. There is 1 patient who just noticed that he already suffered type 2 DM after 1 month. The study by Petrica *et al.* (2014) in Greece found that the mean duration of disease suffering in type 2 DM patients is 9 years. Wang *et al.* (2016) in his study of DM population in China found the mean duration of disease suffering is 9 (3) years. While Solini *et al.* (2013) found the mean duration of disease suffering in Italia is longer, which is 11 years [16]-[18].

Mean body mass index (BMI) in this study is 21,67 (3,9) $kg/m^2$. A similar result is shown by Furusyo *et al.* (2011) in Japan DM population, who found a mean BMI of 21,6 $kg/m^2$. Xu Y *et al.* (2013) studied the type 2 DM population in China and obtained a mean BMI 23,7 $kg/m^2$, while Flegal KM *et al.* (2010) found a mean BMI he surveyed as 28,7 $kg/m^2$ in the population of America [13],[19],[20].

## 4.2 Serum Glycated Albumin Level in Type 2 DM Patients

According to *The Committee on Diabetes Mellitus Indices and Japan Society of Clinical Chemistry (JSCC)*, glycated albumin (GA) is an albumin-containing lysin that bounds to glucose. Diabetes mellitus patients will generate much glycated proteins. These glycated proteins are used to evaluate diabetes controlling, and these protein are also involved in the development and progressivity of long-term diabetic complications. Of all proteins that are glycated, glycated hemoglobin (HbA1c) is used as a gold standard in clinical blood glucose control. In the last few years, GA appear as a possible glycation index that can evaluate a mid-term control of diabetes [7],[21].

Average glycated albumin level in this study is 20,87 (5,9) % (normal value 11-16 %). Hsu P *et al.* (2015) obtained a lower mean GA level in the type 2 DM population in Taiwan, which is 18,1 %. This study was performed to 2.192 type 2 DM patients who received treatment

previously. Mean age in this study is 60,1 years old. Wang *et al.* (2016) studied 206 types 2 DM patients in China and found a similar serum GA level with the Taiwan study, which is 17,9 (5,9) %. Characteristic of the patient in both studies are identical [18],[22].

Glycated albumin describes uncontrolled glucose in type 2 DM patients. This marker has a double role in type 2 DM complications. Besides acting as a glycation marker, GA also acts directly as an agent that cause various complications of diabetes, for instance, nephropathy, atherosclerosis, and diabetic retinopathy [22].

### 4.3 Serum Malondialdehyde (MDA) Level in type 2 DM Patient

Malondialdehyde is one of the markers that represent the condition of oxidative stress. In Type 2 DM patients, hyperglycemia may increase oxidative stress through numerous mechanism, including the induction of ROS. In this study we obtain a median level of malondialdehyde as 9,24 nmol/ml, with the lowest measure of 5,59 nmol/ml and the highest measure was 13,56 nmol/ml. MDA level in this study is higher than normal, due to the presence of factors producing oxidative stress to patients in this study, such as fasting blood glucose level, postprandial glucose level, age and duration of disease. Kumawat *et al.* (2013) reported a significant increase in the malondialdehyde level in type 2 DM patients compared to the control group, with the mean MDA level 7,09 (1,15) nmol/ml. In this study, we found obesity, uncontrolled blood glucose, and dyslipidemia. BMI increase, uncontrolled blood glucose, and dyslipidemia will increase oxidative stress to patients [23].

Nakhjavani M *et al.* (2010) compared DM patients and healthy control subjects. It shows a significant increase of MDA level in the DM patients compared to control subjects and the duration of suffering DM is related to lipid peroxidase level. Mean level of MDA is 3,82 (0,93) nmol/ml. In the study, the mean age of patients is 58,38 years old with duration of disease suffering for more than 10 years. Patient with coronary heart disease and dyslipidemia is included in the study. Investigation of Morsi *et al.* (2016) also shows an increase in average malondialdehyde measure of 4,5 (1,5) nmol/l [24]-[26].

Recent studies demonstrated that glomerular podocyte is a key player in the pathogenesis of diabetic kidney disease. In the past, podocyte injury was thought to be the last process caused by proteinuria in diabetic kidney disease. But biopsy study in human demonstrated that podocyte injury whether functional or structural happens in the earlier phase of diabetic kidney disease. Nephrin is a specific protein in podocytes found in the urine that correlates with podocytes lesion in diabetic nephropathy. The presence of nephrin in the urine happens at the same time with an early injury of the podocyte, even before microalbuminuria exists [27].

Urinary nephrin median is 369,25 ng/ml, with the lowest level of 6 ng/ml and the highest is 3952 ng/ml. Lioudaki *et al.* (2015) compared 71 normoalbuminuria patients with type 2 DM and 39 healthy control. The study measures nephrin mRNA level and found a result that nephrin mRNA increased significantly in the normoalbuminuria patients [28].

The study by Jim *et al.* (2012) to 66 types 2 DM patients and 10 control patients. In this study, nephrinuria is defined as urine-creatinine (UNCR) $\geq$ 0,1 mg/g. In the control group no nephrinuria is present, and in the normoalbuminuria group, nephrinuria occur in 54% of all patients with type 2 DM, and of all patients with micro and macroalbuminuria, nephrinuria occurs 100% [29].

Shchukina *et al* (2015) studied 74 DM samples in Russia and found that nephrinuria is presented in 63% of normoalbuminuria patients. In a microalbuminuria condition, nephrinuria is found as much as 77% and 80% in macroalbuminuria [30].

### 4.4 Correlation between Serum Glycated Albumin with Urinary Nephrin Level in Type 2 DM patients.

Spearman test result between serum GA and urinary nephrin in this study reveals a statistically significant result (p=0,027) with a positive direction and moderate strength correlation (correlation coefficient r=0,404). Correlation between serum GA and urinary nephrin shows a positive correlation, means that the higher the serum GA level, the higher the level of urinary nephrin. In this study, we identify that uncontrolled blood glucose shown by GA level will aggravate the diabetic kidney disease, which is reflected by the urinary nephrin [30].

Study of Doublier in 2003 was the first study that correlates glycated albumin and nephrin expression. This study investigates the nephrin distribution in kidney biopsies of 17 patients with DM and nephrotic syndrome, DM microalbuminuria, and 10 control subjects. To the samples, GA was also examined. To determine whether GA influences the nephrin expression, the podocyte was incubated with GA for 48 hours. The study demonstrated a result that GA induced a reduction of nephrin expression on the podocyte surface [31].

A study by Cohen *et al.* (2013) measured the level of glycated albumin, creatinine, albumin, and nephrin in diabetic murine compared to nondiabetic marines. This study demonstrated a positive linear correlation between GA and urinary nephrin (p<0,05 and r=0,58). An increase in serum GA concentration is followed by nephrin level increase in diabetic murine. Conversely, if serum GA level is reduced by controlling hyperglycemia, the urinary nephrin also decreased [32].

The correlation strength between serum GA level and urinary nephrin level in this study shows a moderate correlation (r=0,404). We presume that the presence of a genetic factor affects diabetic kidney disease. Chen G *et al.* (2013) performed a study in Japan to identify genetic factors predisposing type 2 DM and the gene related to diabetic complications, such as cardiovascular risks and diabetic kidney disease. This study identifies a presence of 17 genes related to diabetes and 4 genes related to diabetic kidney disease. Patients with those genes will promote diabetic kidney disease faster than DM patients without these genes [33].

Bandeira *et al.* (2013) stated that DM complications could occur as a result of excess oxidative stress and protein glycation. Protein glycation, including albumin, will produce AGEs. Complications will happen if AGEs bounds to its receptor (RAGE). If AGEs doesn't bind to RAGE, then there will be no induction towards cytokines production and oxidative stress. Therefore complications will not appear. Aside from the binding between AGEs and RAGE, DM complications can also happen due to increased intracellular glucose that activates the oxidative stress pathway. In this study, it is not certain whether AGEs and RAGE binding or oxidative stress directly to the cell caused diabetic nephropathy [4].

### 4.5 Correlation between Serum Malondialdehyde with Urinary Nephrin Level in Type 2 DM Patients.

A Spearman test between serum MDA level and urinary nephrin shows a statistically significant result (p=0,003) with a positive correlation and moderate strength (correlation coefficient r=0,528). Correlation between serum MDA and urinary nephrin shows a positive correlation, that means the higher the level of serum MDA, the higher urinary nephrin. This study presented that oxidative stress described by MDA level will aggravate the diabetic kidney disease, which is defined by urinary nephrin [30].

We have not found any former research associated with the relation between serum MDA and urinary nephrin in type 2 DM patients. Li *et al.* (2010) investigated the relation between oxidative stress and nephrin using protein oxidative stress marker, the *advanced oxidation protein products* (AOPPs). This study reveals an exposure of AOPPs towards podocyte will induce a decrease in nephrin expression [34].

The correlation strength of serum MDA level with urinary nephrin level in this study demonstrated a moderate correlation (r=0,528). Genetic factor influences the incident of diabetic kidney disease. Gu *et al.* (2013) proposed relation between genetic polymorphism of ICAM1 (*Intercellular Adhesion Molecule 1*) with diabetes and diabetic kidney disease. The limitation of this study is the research did not reach those genetic aspects [35].

## 5 Conclusion

Glycated albumin level increased in type 2 diabetes mellitus patients. Serum malondialdehyde increased in patients with type 2 diabetes mellitus. All of the type 2 diabetes mellitus patients had a positive urinary nephrin. There is a positive correlation with a moderate strength between serum glycated albumin level and urinary nephrin level in type 2 diabetes mellitus patients. There is a positive correlation with a moderate strength between serum malondialdehyde level and urinary nephrin level in type 2 diabetes mellitus patients.

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