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α-Klotho as A Novel Biomarkers in Chronic Diabetic Nephropathy

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Abstract

Background: Type 2 diabetes mellitus (DM) is the most common cause of end- stage renal disease. Albuminuria is the foremost commonly utilized marker to anticipate onset of diabetic nephropathy (DN) without sufficient affectability and specificity to identify early DN.

Aim: This study aimed to evaluate plasma α-Klotho as a new biomarker for early DN.

Methods: This cross sectional study included 125 Egyptian subjects attending the out Patients Clinic of the Department of Internal Medicine, 10Th of Ramadan city Health Insurance Hospital and divided into:-control group, patient with diabetic mellitus, patients with Diabetic nephropathy and patient with diabetic nephropathy and other complications. Patients were subjected to measurement of plasma α- Klotho, FBS, HbAIC, serum Creatinine, serum urea, serum uric acid, k, Na, serum phosphorus, Albumin: Creatinine Ratio, GFR, Chol, TG, LDL HDL, AST, ALT, T.BIL, D.BIL ALB, TP, GLB and A/G ratio.

Results: Results showed that plasma a-klotho was significantly correlated with haemoglobin A1C, potassium, GFR, Albumin, TP and GLB. Meanwhile, plasma α - klotho was negatively correlated with duration of DM, CR, Urea, UR.A, Na, phosphorus, ACR, Chol, TG, LDL, AST, ALT, T.BIL, and D.BIL. However, there were no significant correlations between plasma a-klotho and FBS, HDL and A/G ratio. At cut-off level ≥2.6, plasma a-klotho had 95% sensitivity and 81% specificity for diagnosing diabetic nephropathy.

Conclusion: α-klotho may be the early markers for predict in renal injury in patients with type 2 diabetes.

Keywords: α-klotho; Diabetes Mellitus; Nephropathy

Introduction

Type 2 diabetes mellitus (DM) is the most common single cause of End -Stage Renal Disease (ESRD) [1]. ESRD in nearly half of patients is due to diabetic nephropathy (DN), and these cases have the most exceedingly bad result compared to patients with other causes of ESRD. In spite of the fact that there are numerous novel drugs for DM, there are no particular healing medicines however for DN.

Reasons for destitute result incorporate insufficient markers and the complicated components of DN [2]. Now, severity of this disease is decided agreeing to the levels of albuminuria. Albuminuria is the foremost commonly utilized marker to foresee onset and movement of DN clinically. In any case, this conventional marker for DN needs both affectability and specificity to identify early organizes of DN [3].

However, some DN patients with ESRD do not present with significant albuminuria [4-6]. There is lack of association between Glomerular Filtration Rate (GFR) and albuminuria suggests that an alternative to this albuminuria-based staging system is needed. Some studies have noted the existence of pathological change before micro albuminuria. Therefore, even if micro albuminuria can be regarded as the earliest manifestation of DN, it is possible that a new biomarker for DN exists. Recently, different markers of DN were reviewed including fibroblast growth factor 23, tubular markers inflammatory markers (Interleukin 6 [IL-6], IL-8, monocyte chemo attractant protein 1, and interferon γ–inducible protein) urinary 8-hydroxy-20- deoxyguanosine, serum cystatin C, and so on. Among these, genetic susceptibility almost always leads to irreversible DN, and detection of the clinical markers mostly occurs too late to diagnose and monitor the progression of DN. As such, it is crucial to find an earlier and reliable marker for DN. Earlier diagnosis and intervention may provide an opportunity to stop the permanent damage caused by DN. Although a-klotho was first described as an anti-aging factor, recent experimental and clinical studies suggest a-klotho also has important pleotroic effects on the kidneys. Soluble a-klotho is derived from the proteolytic cleavage of the extracellular portion of the membrane-bound a-klotho; alternatively, it can be generated directly by the alterative splicing of the a-klotho transcript. It can be measured in blood, urine, and cerebrospinal.

Animals with chronic kidney disease have very low renal, plasma, and urinary a-klotho levels. Furthermore, humans with chronic kidney disease exhibit markedly reduced a-klotho in serum and urine in the early stages of kidney disease, progressively decreasing in more advanced stages. However, with regard to diabetic nephropathy, the role of aklotho in the pathogenesis of kidney injury has not been fully studied. Renal a-klotho expression is markedly decreased in diabetic nephropathy in humans and mice. A similar decline is observed in kidney cells treated with methylglyoxal-modified albumin. These findings collectively suggest renal a- klotho deficiency is part of an underlying mechanism involved in diabetic kidney injury. However, the actual role of soluble a-klotho in diabetic

kidney disease has not been evaluated. So this study aimed to evaluate Plasma a-klotho as biomarkers in chronic diabetic nephropathy.

Aim of the work

The study aimed to evaluate Plasma a-klotho as biomarkers in chronic diabetic nephropathy.

Patients and Methods

Study design

Cross sectional study, aiming to evaluate plasma a-klotho as biomarkers in chronic diabetic nephropathy.

Study setting

The study was carried out at Clinic of the Department of Internal Medicine, 10Th of Ramadan city Health Insurance Hospital.

Target population

Diabetic patients attending the Out Patients Clinic of the Department of Internal Medicine, 10Th of Ramadan city Health Insurance Hospital. This study included 125 Participants who were divided into:-

1-Control group:- 20 healthy subjects whose age ranged between 30-50 years old were taken as control group.

2-Study group:- including 105 patients divided into.

Group 1 :- 20 patient with diabetic mellitus whose age ranged between 30-50 years old

Group 2 :- 65 patients Diabetic nephropathy whose age ranged between 30-50 years old

Group 3:- Diabetic nephropathy and other complications whose age ranged between 30-50 years old.

Inclusion criteria

Patients were free from infectious disease.

Patients were free from inflammatory disease.

Patients were free from liver disease.

Patients were free from malignancy.

All were non-smokers.

Exclusion criteria

Patients with active urinary tract infection.

Patients with renal disease other than diabetic nephropathy; neoplastic disorders; severe liver dysfunction; active or chronic infection or inflammatory disorders.

Pregnancy.

Patients with a recent (i.e., within 6 months) history of acute myocardial infarction, stroke, or occlusive peripheral vascular disease.

All patients were subjected to the following:

Collection of demographic data as required in the attached sheet including age, occupation, anthropometric measurements of height, weight, waist circumference, and history of disease.

Collection of morning urine samples in vacutaniner cup and also collection of 10 venous blood samples from the overnight fasted 5 ml blood were collected on plane tubes and other 5 ml blood were collected on EDTA tubes by vacutaniner system under complete aseptic conditions and HbAIC first done and the samples centrifuged for 10 min at 2,500 g within 30 min separated serum and plasma were stored at 20°C for the measurement of measurement of plasma a-klotho concentration, serum fasting glucose concentration, serum Creatinine, serum urea n, serum uric acid, serum potassium k, serum sodium Na serum phosphorus, Albumin: Creatinine Ratio, GFR concentration, serum cholesterol and serum triglyceride. AST, ALT, T.BIL, D.BIL ALB, TP, GLB and A/G ratio.

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package for Social Science (SPSS 23). Data was presented and suitable analysis was done according to the type of data obtained for each parameter. The following tests were used:

Descriptive statistics

Mean, Standard deviation (± SD) and range for parametric numerical data, while Median and Interquartile range (IQR) for non-parametric numerical data. Frequency and percentage of non- numerical data.

Analytical statistics

ANOVA test of significance was used when comparing between means of more than two groups.

Post-hoc test after ANOVA for significance between each two groups.

Chi-Square test was used to examine the relationship between two qualitative variables.

Fisher's exact test was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells.

Correlation analysis (using Pearson's method) to assess the strength of association between two quantitative variables. The correlation coefficient denoted symbolically "r" defines the strength (magnitude) and direction (positive or negative) of the linear relationship between two variables.

Results

A total of 125 subjects were enrolled in this study; their mean age was 55.8610.4 years (range, 24–82 years), and there were 71 men and 54 women. Age, BMI, Duration of D.M, F.B.G, C.P.A,

HBAIC, S. Creatinine, S. urea, UR.A, Na, ACR, GFR, Cholesterol, Triglycerides, HDL, LDL, AST, ALT, ALB, T.BIL, and D.BIL were significantly higher in diabetic patients than non-diabetic control. Meanwhile, K, Ph, T.P, AG ratio and KL were significantly lower in diabetic patients than in non-diabetic controls. Other parameters did not differ significantly between the diabetes group and non-diabetic controls.

Age, BMI, Duration of D.M, F.B.G, C.P.A, HBAIC, S. Creatinine, S. urea, UR.A, Na, ACR, GFR, Cholesterol, Triglycerides, HDL, LDL, AST, ALT, ALB, T.BIL, D.BIL, K, Ph, T.P, AG ratio and KL were significantly different between four groups. Plasma a-klotho was significantly correlated with haemoglobin A1C, potassium, GFR, Albumin, TP and GLB. Meanwhile, plasma a-klotho was negatively correlated with duration of DM, CR, Urea, UR.A, Na, phosphorus, ACR, Chol, TG, LDL, AST, ALT, T.BIL, and D.BIL. However, there were no significant correlations between plasma a-klotho and FBS, HDL and A/G ratio.

Figure 1 show that at cut- off level ≥ 2.6, plasma a-klotho had 95% sensitivity and 81% specificity for diagnosing diabetic nephropathy.

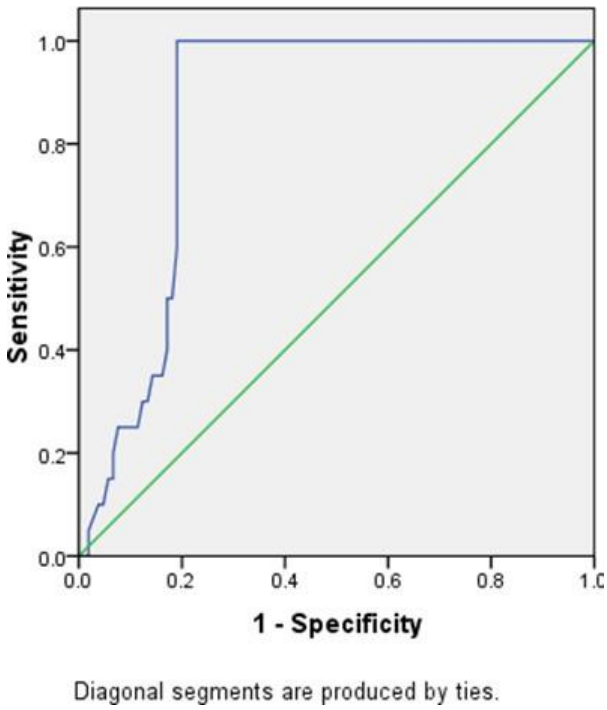

Figure 1: ROC curve of plasma a-klotho for diabetic nephropathy.

Discussion

α-Klotho is a single-pass transmembrane protein that is highly expressed in the kidneys and is known to act as a co-receptor for fibroblast growth factor-23. 19Circulating soluble α-klotho can be generated directly by the alterative splicing of the α-klotho transcript or the extracellular domain of membrane α-klotho can be released from membrane-anchored α-klotho on the cell surface .

Unlike membrane α- klotho, which functions as a co- receptor for fibroblast growth factor- 23, soluble α-klotho acts as a hormonal factor and plays important roles in anti-aging, anti-oxidation, ion transport modulation, and Wnt signalling? Previous studies aiming to clarify the role of α-klotho as a potential biomarker of kidney injury show the blood and urinary concentrations of α- klotho decrease early in the course of chronic kidney disease in mice with experimentally induced chronic kidney disease as well as humans.20 As blood α-klotho concentration was found to be linearly associated with eGFR in previous studies , plasma α-klotho was associated with the eGFR in the present study ($r=0.888$, $p<0.001$).

Meanwhile, little is known about circulating α-klotho levels in diabetes- related nephropathy. Recent studies in patients with diabetes report conflicting data. One study found serum α-klotho level was not significantly different between patients with diabetes without nephropathy and non-diabetic controls.

The findings that both exogenous soluble α-klotho administration and overexpression of membranous α-klotho in kidney cell culture suppress NF-κB activation and subsequent inflammatory cytokine production in the response to TNF-α stimulation suggest α-klotho serves as an anti- inflammatory modulator. Therefore, preventing deceases in α-klotho and α-klotho supplementation are potential novel therapeutic strategies for early diabetic nephropathy. In multiple experimental models of chronic kidney disease, the replacement or endogenous up regulation of α-klotho protects the kidneys from renal insults, preserves kidney function, and suppresses renal fibrosis. Thus, α-klotho is a highly promising candidate early biomarker as well as a novel therapeutic agent for chronic kidney disease. Blood α-klotho concentrations can easily be checked and used to assess the development of diabetic nephropathy prior to the onset of micro albuminuria, which is the earliest sign of diabetic nephropathy in clinical settings. To best of our knowledge, this study is the first study to assess validity of α-klotho for diagnosing diabetic nephropathy.

Conclusion

In conclusion, the results of the present study suggest plasma and urinary a-klotho may be the early markers for predicting renal injury in patients with type 2 diabetes and we need to do long-term prospective study in order to elucidate the role of a-klotho in the pathophysiological mechanisms of the development and progression of albuminuria in type 2 diabetes.

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