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Role of Plasma and Urinary YKL 40 in Early Diagnosis of Nephropathy in Type 2 Diabetic Patients

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Abstract

Background:*Diabetic Nephropathy is a microvascular complication of Type 2 diabetes mellitus (T2DM) and is an important cause of end stage renal disease (ESRD). The importance of YKL 40 in early diagnosis of diabetic nephropathy is undertaken in this study.*

Aim*:The aim of our Study is to assess usefulness of YKL 40 in early diagnosis of nephropathyintype2 diabetic patients*

Materials and Methods:*20 Type2 T2DM patients in the age group of 35 to 60 were selected for this study and the same were compared with age matched 20 healthy controls. Plasma and urine YKL-40 with complete Haemogram andHbA_1C were done by standardised methods.*

Results:*In this study we found that both plasma and urine YKL 40 levels were significantly higher in type 2 diabetes mellitus patients. Besides, YKL-40positively and significantly correlated with important measured renal parameters.*

Conclusion:*YKL-40 is a useful marker in the early diagnosis of nephropathy in T2DM patients.*

Keywords: *YKL-40, T2DM, Diabetic Nephropathy, Microalbuminuria, ACR (Albumin Creatinine Ratio)*

I. Introduction

Diabetes mellitus (DM) is a metabolic syndrome, affecting about 382 million people worldwide [1].DM is characterized by defective insulin secretion orinsulin action or both [2]. The chronic hyperglycemia in diabetes affects various organs like eye, kidney, heart, nerves and blood vessels [3].Diabetic nephropathy is an important complication of T2DM. It accounts for about 40% of end stage renal disease (ESRD) patients [4]. It is a microvascular complication of T2DM and usually occurs 10-12 years after the diagnosis of DM [5].

YKL-40 (chitinase 3-protein) is a reliable proinflammatory marker of endothelial dysfunction. YKL-40 induces maturation of monocytesto macrophages. It is secreted by activated macrophages [6].Several studies have demonstrated that plasma YKL-40 was elevated in T2DM and independently correlated with insulin resistance and various parameters of lipid profile [7].

Few investigators found out an association between YKL-40 levels with albuminuria in diabetic patients [8]. In view of this, we aim to assess the usefulness of YKL-40 as an early diagnostic marker of diabetic nephropathy.

II. Materials and Methods

The study group comprised of 20 T2DM patients with more than 5 years duration of diabetes and aged between 35-60 years, on oral hypoglycemic drugs, attending diabetic OPD of Rajah Muthiah Medical College Hospital, Annamalainagar, Tamil Nadu, India were selected for the present study. We excluded the patients based on the following criteria.

Exclusion criteria: Patients on insulin, primary hypertension, smokers, alcoholics, tobacco chewers, abnormal urinary sediment, active urinary tract infection, history of other renal diseases and active or chronic persistent infection or inflammatory disorders, neoplastic disorders, thyroid disorders, liver dysfunction, history of acute myocardial infarction, stroke, and occlusive peripheral vascular disease.

Inclusion criteria: T2DM of 5 years or above duration. Twenty healthy age matched subjects were selected as a controls. The informed written consent was obtained from all the study subjects and the study was approved by our Institutional Human Ethics Committee (IHEC). Experiments were done in accordance with Helsinki declaration of 1975.

Biochemical analysis:

A random spot urine and fasting blood samples were obtained from the subjects immediately after enrollment. Blood samples were centrifuged at 2000×g for 10 min. Samples were analyzed for fasting plasma glucose, lipid profile. HbA1C estimated by Ion exchange resin method and YKL-40 assessed by ELISA [9]. Urine samples were analyzed for YKL 40, microalbumin and creatinine.

Statistical analysis:

Statistical analysis were carried out with SPSS 20.0. Values were expressed as mean ± standard deviation, p value < 0.05 was considered statistically significant. Normally distributed data were analyzed by using one-way ANOVA. The Pearson correlation test was used for correlation analysis.

III. Results

Table 1: Comparison of baseline characteristics between control and study subjects.

Parameters	Control (n=20)	Study group(n=20)	p- value
Age	46.9±4.1	48.1±4.2	0.369
Body mass index	24.1±2.1	25.6±3.1	0.081
Waist/Hip ratio	0.88±0.04	0.92±0.06	0.017
Systolic BP (mm Hg)	114.4±6.9	126.5±9.8	0.001
Diastolic (mm Hg)	73.5±3.2	78.2±7.2	0.001

Data are expressed as mean ±SD, p value <0.05 was considered statistically significant.

Table 2: Comparison of biochemical parameters between control and study subjects.

Parameters	Control (n=20)	Study group(n=20)	p- value
ACR	18.8±2.6	129±14.1	0.001
FBS(mg/dl)	81.6±6.1	129.1±23.7	0.001
PPBS(mg/dl)	107.4±10.3	198.1±24.6	0.001
HbA1C	5.4±0.5	8.0±0.9	0.001
Serum cholesterol (mg/dl)	168.4±8.6	194.4±19.7	0.001
Serum Triglycerides (mg/dl)	96.7±7.6	144.3±42	0.001
HDL cholesterol (mg/dl)	43.1±2.2	37.8±1.7	0.001
LDL cholesterol (mg/dl)	105.9±8.7	127.7±21.9	0.001
Urea (mg/dl)	24.2±4.7	31.6±5.3	0.001
Creatinine(mg/dl)	0.69±0.2	0.9±0.2	0.007
Plasma YKL-40 (ng/ml)	20.2±3.6	108.2±19.5	0.001
U.YKL-40 (ng/mg of Creat)	0.07±0.01	0.50±0.29	0.001

Data are expressed as mean ±SD, p value <0.05 was considered statistically significant.

Table 3: **Correlation between plasma YKL-40 &measured parameters**

Parameters	Correlation Coefficient(r)
ACR	0.971**
FBS	0.624**
PPBS	0.762**
HbA1C	0.797**
Cholesterol	0.567**
TGL	0.651**
HDL	-0.769**
LDL	0.492**
Urine YKL-40	0.863**

**Correlation is significant at the 0.01 level (2-tailed).

Table 4: **Correlation between Urinary YKL-40 &measured parameters**

Parameters	Correlation Coefficient(r)
ACR	0.905**
FBS	0.380*
PPBS	0.458**
HbA1C	0.568**
Cholesterol	0.316*
TGL	0.521**
HDL	-0.605**
LDL	0.242

**Correlation is significant at the 0.01 level (2-tailed).

*Correlation is significant at the 0.05 level (2-tailed).

Table 1 shows base line parameters in control and study subjects. The systolic and diastolic B.P are significantly elevated in patients when compared to healthy controls.

Table 2 shows all the measured parameters are significantly elevated in the study group except HDL which was found to be decreased. Our study also exhibits disturbances in lipid profile as in the earlier studies. The renal parameters urea and creatinine were significantly higher in study group even though they were within physiological range. Another important and more reliable parameter is albumin creatinine ratio (ACR) was significantly elevated ($P<0.001$). It reveals the onset of renal disease. Both plasma and urine YKL-40 that reflects the endothelial dysfunction was found to be elevated manifolds ($P< 0.001$) thereby reveals underlying active inflammatory process. YKL-40 also positively correlates ($P<0.001$) with important parameters

Table 3 shows positive and significant correlation of plasma YKL 40 with parameters like ACR, Lipid profile, urinary YKL-40, fasting and postprandial plasma glucose and HbA_1C. It has negative correlation with HDL.

Table 4 shows statistically significant correlation of urinary YKL40 with plasma YKL, lipid profile, ACR, fasting and post prandial plasma glucose.

IV. Discussion and Conclusion

Diabetic nephropathy is an important microvascular complication of T2DM [10]. It remains the most common cause of ESRD. It usually occurs in about 10 to 12 years from the onset of T2DM. Even though microalbuminuria is a common predictor of diabetic nephropathy, there have been several instances where nephropathy has progressed to late stages without micro / macro albuminuria [10, 11, 12]. In contrast albumin creatinine ratio (ACR) is a more reliable indicator of early renal damage [13].

YKL-40, a chitin like glycoprotein is a well-known proinflammatory marker [14, 15]. It is commonly secreted in large amounts whenever there is endothelial dysfunction. In kidneys it yet unclear whether the high levels of YKL40 is due to enhanced secretion in response to inflammation or defective reabsorption in PCT or both. The fact that both plasma and urine YKL 40 are many times increased in study group signifies the extent of renal parenchymal damage [15]. Our study shows statistically significant increase in both systolic and diastolic B.P between the control and study groups an important risk factor for nephropathy [16, 17] .There was highly significant elevation in ACR level in T2DM patients.

Albumin creatinine (ACR) ratio is a well-known independent biomarker for diabetic nephropathy[18].The other biochemical parameters like fasting plasma glucose, 2hour plasma glucose, lipid profile, HbA_1C, also show appreciable increase in the study groups when compared to the healthy controls. The renal parameters like urea and creatinine were also elevated in T2DM patients even though they were within the normal physiological range. This may be due to the fact that our study groups of T2DM patients were in the very early stage of diabetic nephropathy.

The well-known proinflammatory marker YKL-40, a 40 KDa protein shows highly significant increase in both plasma and urine level in T2DM patients. YKL-40 is secreted by activated macrophages and it reflects the underlying endothelialdysfunction.Various studieshave established the fact that YKL-40 acts as an inflammatory marker for both acute and chronic inflammation and also participates in the early stages of atherosclerosis [19]. The above study suggest that YKL-40 might possibly be an early marker of microvascular complications like diabetic nephropathy.It is still unclear whether the increase in plasmaand urinary YKL-40 levels are due to increased inflammation or due to defective reabsorption in PCT of kidney or both. It may be possible that there is increased biosynthesis in the acute phase followed by defective reabsorption in the chronic phase.

YKL-40 positively and significantly correlates with all the measured biochemical parameters. This is particularly true in relation to the renal parameters like ACR, urea, creatinine and urinary YKL. This proves the fact that YKL-40 be can assumed as a reliable marker of early stage of diabetic nephropathy. The limitations of our study is that it was done using a single blood and urine sample in T2DM patients.A more elaborate and comprehensive study may prove the above fact that YKL-40 as a reliable and potential marker for early diagnosis of diabetic nephropathy.

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