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Value of Serum Cystatin C in Predicting Early Renal Impairment in Type 2 Diabetes Iraqi Patients

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Abstract
Background: Diabetes mellitus comprises a heterogenous group of metabolic disorders that share the common feature of hyperglycemia due to defects in insulin secretion, insulin action or both. Diabetes mellitus represents the most common metabolic disease worldwide. DM is the most frequent contributor to end stage renal disease. Microalbuminurea is currently the earliest easily detectable laboratory marker of diabetic nephropathy. Cystatin C is a protease inhibitor secreted at a constant rate by cells and released into bloodstream and detected in almost all body fluids. The aim of the present study was to see whether cystain C is elevated before the appearance of microalbuminurea in type 2 diabetic patients.**Subjects Materials and Methods:** The study was designed to be an observational case control study and was conducted in Al karama teaching hospital in Wassit governorate from January 2015 through November 2015. A random sample of type 2 DM patients was selected with an age range of 43-73 years. A comparable number of 79, 40 males and 39 females, apparently healthy control subjects was randomly selected with an age range of 44-86 years. Serum cystatin was measured for all patients. **Results:** Mean blood urea and serum creatinine were not significantly different between patient and control group ($P>0.05$), while mean serum cystatin c was significantly higher in patients than in control group, 0.80 ± 0.18 versus 0.56 ± 0.24 µg/ml, ($P<0.001$), Serum cystatin c was not significantly affected by, age, gender, weight, serum creatinine, blood urea and HbA1c in both groups.**Conclusion:** serum cystatin c is a useful marker for early detection of renal function detorioration deterioration in type 2DM patients before the development of microalbuminurea.
Keywords: Cystatin C, type 2 DM

Introduction

Diabetes mellitus comprises a heterogenous group of metabolic disorders that share the common feature of hyperglycemia due to defects in insulin secretion, insulin action or both [1-3]. Diabetes mellitus represents the most common metabolic disease worldwide. The number of individuals diagnosed with DM was estimated to be around 135 million in 1995 [4]. In 2011 the number increased substantially to reach a figure of 336 million, and the recent statistical estimation anticipated a gloomy future; by the year 2030 the number of diabetics is expected to be 552 million [5,6].

Generally speaking DM is a lifelong incurable disease which leads to significant morbidity and mortality due to macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular (diabetic nephropathy, neuropathy, and retinopathy) complications [7-10]. Till now there is no curative treatment for diabetes but early detection and control of blood sugar and other associated risk factors may prevent or at least delay the progression of microvascular and macrovascular complications [11].

DM is the most frequent contributor to end stage renal disease [12]. A substantial number of epidemiologic studies documented the progression of a significant proportion of diabetics (20-40%) into proteinuria and renal failure within 15-20 years following diabetic onset [13-15]. Diabetic nephropathy is a slowly progressive detorioration of renal function and extensive research was focused on early detection and starting treatment with angiotensin converting enzyme inhibitors to delay the progression into end stage renal disease with its consequences on morbidity and mortality [11]. Microalbuminurea is currently the earliest easily detectable laboratory marker of diabetic nephropathy before the the most commonly used parameters of renal function (blood urea and serum creatinine) become elevated above the reference range [16]. Serum creatinine is usually not increased until about 50 % of renal function have been lost and is affected by age , sex and muscle mass , so the need for a new more sensitive marker for renal function emerged [16]. Once microalbuminuria is present, the rate of progression to end stage renal disease and of cardiovascular disease can be delayed by aggressive management of blood pressure, glucose, and lipids and inhibition of the renin-angiotensin system [12].

Cystatin c is a protease inhibitor secreted at a constant rate by all investigated nucleated cells and released into bloodstream with a half-life of 2 hours and detected in almost all body fluids. It has a molecular mass of 13 kDa that make it almost freely filtered through the normal glomerular basement membrane and almost completely reabsorbed and degraded by the normal proximal tubular cells .It is not secreted in the tubules and also not reabsorbed back into the serum and therefore cystatin c was extensivly investigated as a marker of renal function to assess the glomerular filteration rate [17]. Age, sex and body weight had a lesser influence on serum cystatin than on serum creatinine but serum cystatin is significantly affected by thyroid function and smoking [18-21]. Studies show that serum cystatin is better than serum creatinine in assessment of renal function

and creatinine clearance can be calculated by cystatin based formula that is well correlated with the gold standard test (inulin clearance) that needs more time and taking exogenous substance [17].

The aim of the present study was to see whether cystain c is elivated before the appearnce of microalbuminurea in type 2 diabetic patients.

Patients Materials and Methods

The study was designed to be an observational case control study and was conducted in Al karama teaching hospital in Wasit province from January 2015 through November 2015. A random sample of type 2 DM patients was selected with an age range of 43-73 years. The sample was composed of 74 patients, 37 male and 37 female patients. After taking history and performing full physical examination , investigations were done ,random sample for blood sugar , blood urea , serum creatinine ,thyroid function test (for those without signs and symptoms of thyroid disease and don't have thyroid function test over the last 6 months), hemoglobin A1c serum creatinine and urine albumin. Exclusion criteria included the following: renal impairment (elivation of blood urea and serum creatinine above the reference range), thyroid function abnormalities and presence of microalbuminurea or frank protienurea. Serum cystatin was measured for all patients. A comparable number of 79, 40 males and 39 females, apparently healthy control subjects was randomly selected with an age range of 44-86 years.

Ten milliliters (mls) disposable plastic syringes were used to draw six mls of venous blood from each patient and control (healthy individuals). Serum was obtained and kept into small epindroof tubes capacity 1.5 ml at -20C° until time of analysis. The cystatin-C assay employs the quantitative sandwich enzyme immunoassay technique suppliers by cusabio companies [22]. The serum creatinine was done by Beckman Synchron method [23]. The HbA1c estimated by Tosoh A1c 2.2 Plus Glycohemoglobin Analyzer [24]. The estimation of urea was made by colorimetric method [22].

Statistical analysis was done using SPSS version 16 and Microsoft Office Excel 2007. Student t-test was used to study difference in mean between patients and control groups. Spearman's and Pearson's Correlation coefficients were used to study correlation of serum Cystatin C with other parameters in both groups. P-value was considered significant when it was less than 0.05.

Results

Table 1 showed comparison of clinical and biochemical parameters between patients group and control group. Mean age and sex ratio were not significantly different between patients and control groups (P>0.05), but patients had significantly greater weight than control group, 70.88±10.73 kg versus 66.29±9.45 kg, (P<0.05).

Table 1: General and biochemical characteristic of the study groups

Characteristic	Control (N = 79)		Patients (N = 74)		P-value
Age (years)	57.01	10.33	55.72	7.70	0.378
Gender (M:F)	1.03/1		1:1		0.938
Weight (Kg)	66.29	9.45	70.88	10.73	0.006*
Blood Urea (mg/dl)	29.72	4.49	30.39	3.62	0.313
Serum Creatinine (mg/dl)	0.69	0.15	0.67	0.14	0.389
Serum Cystatin C (µg/ml)	0.56	0.24	0.64	0.18	0.014*
HbA1c %	4.78	0.41	7.81	1.59	<0.001**

*Significant difference; ** Highly significant difference

Mean blood urea and serum creatinine were not significantly different between patient and control group (P>0.05), while mean serum cystatin c was significantly higher in patients than in control group, 0.64±0.18 versus 0.56±0.24 µg/ml, (P<0.05), as shown in table 1 and figures 1 and 2.

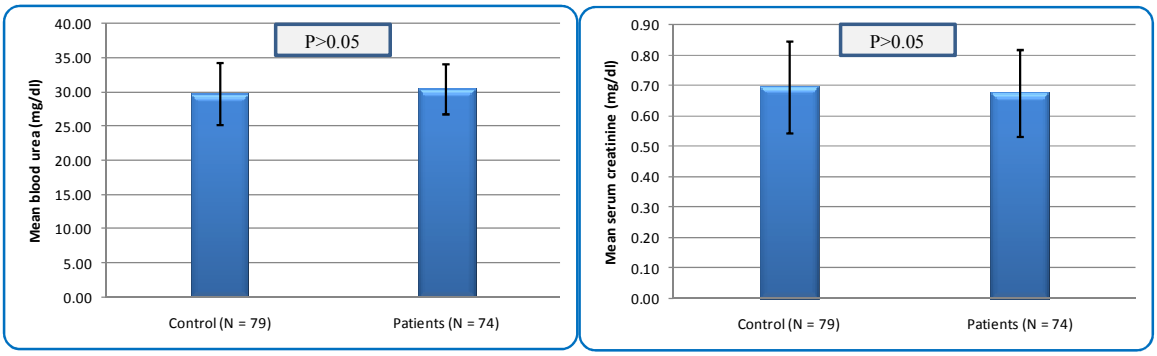

Figure 1: Mean blood urea and serum creatinine in patients and control subjects

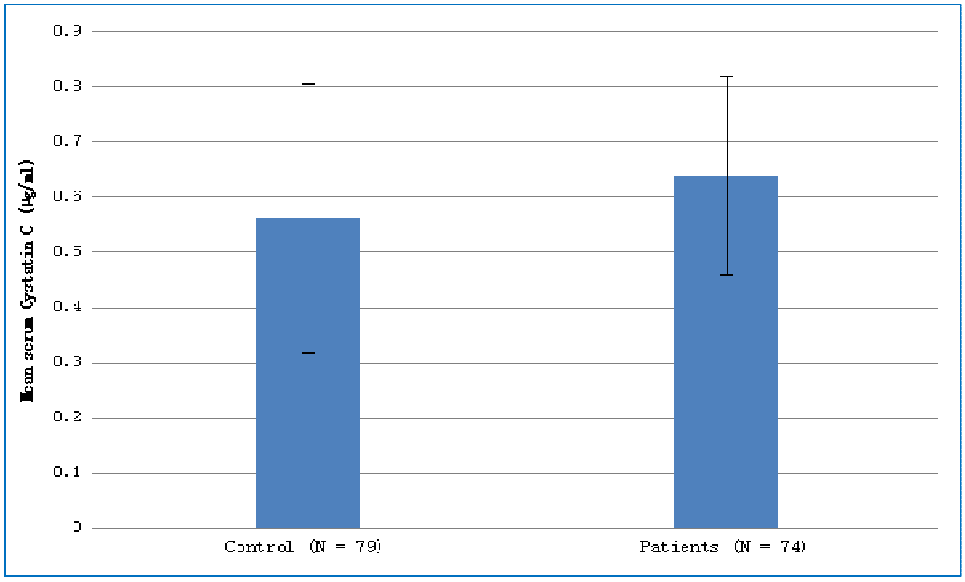

Figure 2: Mean serum cystatin c in patients and control group

Mean HbA1c was significantly higher in patients group than in control group, 7.81±1.59% versus 4.78±0.41%, (P<0.001), as shown in table 1. Serum cystatin c was not significantly affected by, age, gender, weight, serum creatinine, blood urea and HbA1c in both groups, as shown in table 2.

Table 2: Correlation between cystatin c and other parameters in patients and control subjects

Group	Parameter	Gender†	Age*	Weight*	Blood Urea*	Serum Creatinine*	HbA1c*
Control	r	0.133	0.201	0.105	0.223	0.145	0.089
	P	0.122	0.401	0.367	0.398	0.333	0.789
Patients	r	0.104	0.139	0.248	0.123	0.188	0.107
	P	0.322	0.388	0.401	0.399	0.505	0.301

†Spearman correlation coefficient
*Pearson's correlation coefficient

Discussion

The present study showed that mean age of patients with type 2 diabetes was 55.72 years and that all patients were above the age 40 years which is in accordance with most of literatures published so far [31]. The mean body weight of type 2 DM patients, enrolled in the current study, was significantly higher than that of control subjects thereby solidifying the already clear association between type 2 DM and obesity [32].

The current study came up with a result implying a poor control of DM by patients as the mean HbA1c was 7.81%. This may be due to lack of drug adherence. Lack of drug adherence is an important factor of poor DM control worldwide [33, 34].

The results of the present study showed that mean serum cystatin c was significantly higher in type 2 DM patients than in control group. Taking into consideration the fact that all patients participating in the present study had no albuminuria, this result pointed to the value of serum cystatin c in predicting early renal impairment in type 2 DM patients, before the onset of albuminuria. Several studies have shown the positive value of serum Cystatin C in predicting patients with early renal impairment and microalbuminuria in patients with type 2 DM

[27-30]. On the other hand both serum creatinine and blood urea showed no significant difference in both groups, which are both regarded as the classic biochemical indicator of renal functions.

Also the result of the present study showed that serum cystatin c was not affected by age, gender and weight neither of control subjects nor of patients, so one can conclude that serum cystatin c is a useful substitute to creatinine in early detection of renal deterioration in type 2DM patients. Age, weight, sex, and race influence creatinine production and thus need to be taken into account when evaluating a serum creatinine value. For example, an elderly woman with a serum creatinine in the "normal" range can have severely reduced renal function [24]. Two meta-analyses have concluded that serum cystatin C is superior to serum creatinine as a marker of kidney function [25, 26].

Cost might be the only drawback for the use of serum cystatin c in evaluation of renal function; the higher cost of cystatin C and the lack of ready availability have prevented its wide acceptance as the replacement for creatinine to estimate renal function [24].

Several studies proved a gradual increase in mean serum Cystatin C level in correlation with urine albumin. In other word these literatures proved that serum Cystatin C level is higher in patients with microalbuminuria than in those without and is further higher in those with macroalbumnuria [35, 36]. Unfortunately such relation was not evaluated in the present study because the aim was to study serum Cystatin C before the onset of proteinuria. Nevertheless the result of the present study brought an insight on the validity of serum Cystatin C in detectin early renal deterioration even before the onset of detectable proteinuria. To our knowledge this is the first study that concluded the significant increment of Cystatin C in type 2 DM patients before the appearance of other biochemical evidence pertaining to renal function impairment.

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