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Assessing Validity of Serum Cystatin C for Predicting Metabolic Syndrome

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Abstract: Serum concentration of cystatin C a marker of glomerular filtration has been associated with Cardiovascular Disease (CVD). The aim of this study was to evaluate cystatin C as a marker of diabetic kidney disease in normoalbuminuric diabetic patients without Chronic Kidney Disease (CKD). The study population consisted of 65 subjects with metabolic syndrome and 32 subjects free of metabolic syndrome (control group). HDL-C, LDL-C, blood urea, triglycerides, glucose, HbA1c, serum cystatin C and serum creatinine were measured in both groups. GFR was calculated in both groups using Cockrofta Gault equation. Metabolic syndrome presented higher cystatin C levels than normal samples (0.98 8 0.26 1.24 8 0.24 $p<0.05$). In the binary logistic regression, the presence of diabetes and metabolic syndrome was significantly associated with elevated cystatin C levels. Diabetic patients also presented a slightly greater creatinine (1.11 8 0.09 1.04 0.15 $p<0.05$). The results suggest that cystatin C may be a marker for metabolic syndrome and may identify a certain degree of renal dysfunction even when serum creatinine does not exceed normal level.

Key words: Creatinine, cystatin C, renal dysfunction, metabolic syndrome

INTRODUCTION

The metabolic syndrome or syndrome x (Reaven) is a combination of several factors which may share a common aetiology and each of which is a risk factor for cardiovascular disease. Depending on the definition used such as WHO and NCEP the metabolic syndrome may include measures of general obesity (as reflected by Body Mass Index (BMI), defined as weight in kilograms divided by height in meters squared), central obesity (as reflected by Waist Circumference (WC) or waist:hip ratio (WHR), dyslipidaemia (as reflected by low high-density lipoprotein (HDL)-cholesterol and/or high triglyceride levels], hyperglycaemia, high blood pressure and resistance to the action of insulin (Reaven, 1988; Balkau and Charles, 1999; Expert Panel on Detection Evaluation and Treatment of High Blood Cholesterol in Adults, 2001; WHO, 1999). The risk of diabetes and cardiovascular disease associated with clustering of these factors is increased and it is important to measure and if appropriate, to treat the other factors when abnormal levels of one factor are identified. The increasing prevalence of obesity across the world will result in increasing prevalence of the metabolic syndrome. This has important implications for future patterns of prevalence of diabetes and cardiovascular disease and their complications in both developed and less developed countries. Although, cardiovascular disease mortality is declining, it is uncertain whether increasing diabetes prevalence will reverse this trend because people with diabetes are at higher absolute risk of cardiovascular disease (Grundy *et al*., 2004; Sattar *et al*., 2003; Schwartz *et al*., 2000; Sharma and Considine, 1998; Briley and Szczech, 2006).

Cystatin C is a low molecular weight protein that functions as an excellent inhibitor of cystatin C proteases (Filler *et al*., 2005). We verified that increased cystatin C may be a more sensitive indicator of renal dysfunction than conventional creatinine based measures.

MATERIALS AND METHODS

In this case-control study witch lasted 1 year a total of 65 subjects who were diagnosed with diabetes for at least one year prior to our study in Mehrad Hospital with high blood pressure (>_130/_85 mmHg) and BMI >25 kg m^{-2} were included in our metabolic syndrome group. 22 healthy subjects with normal blood pressure, BMI<25 kg m^{-2} and normal blood glucose levels were included in our control group. Age range in our study population was 35 to 65 years. Blood was drawn from subjects after 12-14 h over night fasting. Cholesterol, HDL-c, LDL-c, triglycerides, glucose and blood urea was measured using Technicon RA-1000 USA. We use WHO

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criteria for biochemical factors Serum cystatin C was measured using ELISA method. The reference interval for creatinine is 0.5-1 mg dL^{-1} HbA1c was measured by chromatography method. GFR was calculated by the cochcroft-gault equation.

Statistical analyses: The statistical analyses were performed with SPSS (Statistical Package for the Social Sciences), version 16. Data were analyzed using One-way Analysis of Variance, Duncan One-Sample Kolmogorov-Smirnov Test Pearson's Correlation Coefficient statistical software programs. All values are expressed as the mean and Standard Deviation (SD). The p-value under 0.05 is significant.

RESULTS

Sixty five patients and 32 controls were included in this study. Mean serum cystatin C concentration was significantly higher in metabolic syndrome group compared with the control group (p = 0.001) whereas serum creatinine concentration showed no significant difference between two groups.

Clinical characteristics of study population is given in Table 1 based on results obtained there was no significant age difference between two groups. Metabolic syndrome group showed significantly higher HbA1C, glucose, triglyceride, whereas HDL-c level was significantly lower in metabolic syndrome group. Glomerular filtration rate showed no significant difference between two groups (Table 1).

To obtain sensitivity and specificity of cystatin C we used the rock chart (Fig. 1). This sensitivity shows Cys-C evaluation is able to detect an earlier stage of decreased Glomerular Filtration Rate (GFR) than other parameters (serum creatinine, creatinine clearanced etc.) and it is considered particularly useful in patients with a high risk of developing nephropathies.

Attention to charts cystatin C cotpoint 0.98 with sensitivity of 0.80 and spesivity of 65.6 was calculated. The correlation between cystatin C and GFR and creatinine and GFR were calculated with Pearson's Correlation Coefficient (Fig. 2). The relationship between sCys-C and GFR, creatinine and GFR was analyzed using Pearson_s correlation coefficients. A $p<0.05$ was assumed as significant.

Figure 2 Correlations between 1/cystatin C and measured Glomerular Filtration Rate (GFR) (left) and 1/serum creatinine (right).

DISCUSSION

The metabolic syndrome is combination of several factors which may share a common etiology and each of which is a risk factor for renal disease. For example obesity has been shown to be an independent risk factor for CKD (chronic kidney disease) (Hoehner *et al*., 2002; Hsu *et al*., 2006) and treating obesity might stabilize renal function (Agnani *et al*., 2005) or reverse early hemodynamic abnormalities and glomerular dysfunction (Chagnac *et al*., 2003). Obesity can effect renal dysfunction in several ways: excess excretory load, renal sodium retention, hyperinsulinemia, insulin resistance, or renal lipotoxicity (Armstrong, *et al*., 2005). Obesity has been contributed with a type of focal segmental glomerulosclerosis called obesity-related glomerulopathy

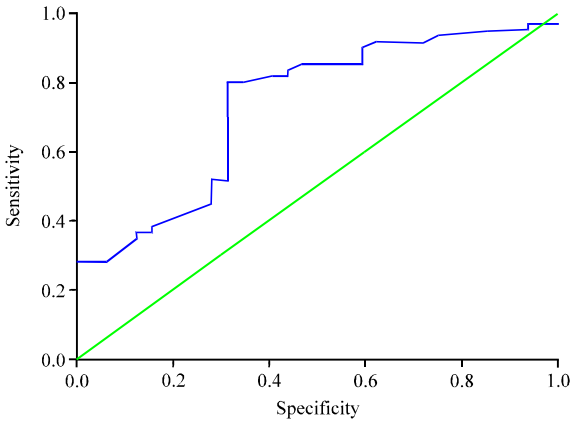

Fig. 1: Sensitivity and specificity of cystatin C

Table 1: Clinical characteristics of study population

Parameters	Overweight (n = 36)	Diabetes (n = 33)	Controls (n = 32)
Age (years)	48.72±9.68[a]	47.33±6.35[a]	45.62±7.67[a]
HbA1C (%)		7.1±0.72	5.47±0.79
Glucose (mg dL^{-1})	120.63±10.4[b]	148.73±49.63[a]	90.84±15.67[c]
Blood urea (mg dL^{-1})	32.83±10.72[a]	37.75±11.46[a]	31.62±8.24[a]
GFR	89.95±10.86	88.42±13.07	95.01±11.31
LDL (mg dL^{-1})	108.58±35.20[a]	110.30±21.13[a]	108.41±22.01[a]
BMI	28.1±4.05	25.52±4.14	23.93±1.67
Triglyceride (mg dL^{-1})	225.89±48.83[a]	205.15±44.16[b]	141.00±27.24[c]
HDL (mg dL^{-1})	41.05±8.90[b]	39.42±8.60[b]	52.65±5.78[a]
Diastolic pressure	91.50±6.84	93.60±4.94	79.78±7.78
Systolic pressure	147.94±30.83	157.03±25.03	113.59±19.79

[a-c]Means with significant differences, A $p<0.05$ was assumed as significant

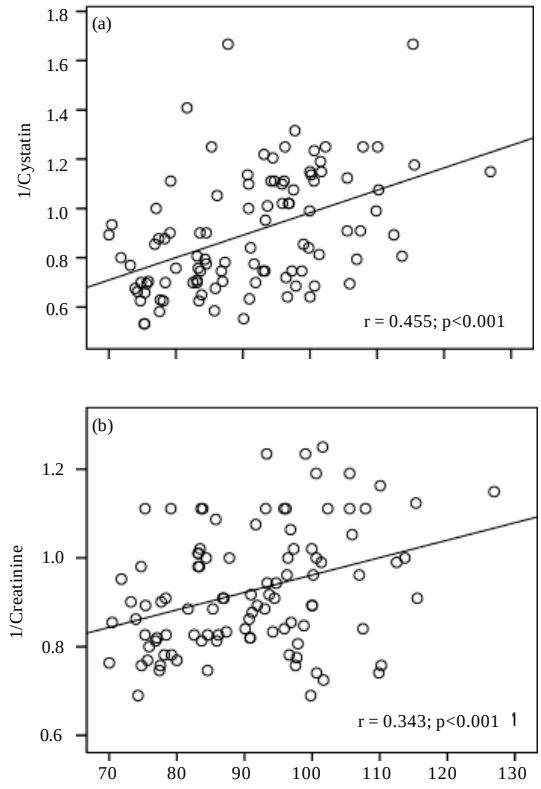

Fig. 2(a-b): Correlations between (a) 1/cystatin C and measured glomerular filtration rate (GFR) and (b) 1/serum creatinine

(Kanıbham *et al*., 2001) all which could facilitate developing of glomerulosclerosis. Insulin resistance also may have a direct role in the pathogenesis of renal injury, as a consequence of stimulating the sympathetic nervous system and the reninsangiotensin-aldosterone system. Microalbuminuria has a direct pathophysiological link to insulin resistance, its relation to the syndrome by sheer associations with other metabolic abnormalities is largely unknown. Microalbuminuria is also a predictor of cardiovascular morbidity and mortality in diabetes (Sowers, 2004).

CONCLUSION

CVD is the primary clinical outcome of metabolic syndrome. Additionally, risk for type 2 diabetes is higher and diabetes is a major risk factor for CVD. Chronic kidney disease is now recognized as a risk factor for CVD and several studies have shown an independent and graded relationship between the degree of kidney dysfunction and risk for CVD. Data from the general population suggest that cystatin C level has a stronger association with CVD outcomes than does creatinine concentration or estimated GFR, especially in elderly persons. The cystatin C level also had a stronger risk relationship with mortality than did creatinine concentration and creatinine clearance, as estimated by using the Cockcroft-Gault equation. We conclude that serum CysC has greater sensitivity in detecting reduced GFR in CKD than serum creatinine. However, further studies are necessary to compare CysC concentrations and CysC-based equations and to clarify which one can better detect small reductions in kidney function within the normal range. The determination of plasma CysC levels is more expensive than routine plasma creatinine determination and the absence of very significant advantages could explain its limited use in daily clinical practice. Therefore, before these CysC-based equations are included in routine clinical practice.

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