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International Journal of Current Research
Vol. 9, Issue, 10, pp.59255-59258, October, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

ASSESSMENT OF CYSTATIN C AS EARLY BIOMARKER FOR DIABETIC NEPHROPATHY IN SUDANESE WITH TYPE II DIABETES

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ARTICLE INFO

Article History:
Received 14th July, 2017
Received in revised form
08th August, 2017
Accepted 18th September, 2017
Published online 31st October, 2017

Key words:

Cystatin C,
ACR,
Creatinine,
Diabetic type 2.

ABSTRACT

Background: One of long-term complication of diabetes mellitus is diabetic nephropathy, which affect kidney and other organs. Suggestion and evaluation of its early diagnostic markers is a goal of many researches to help in providing highly efficient biomarkers.
Objectives: This study aimed to assess cystatin c as early biomarker for diabetic nephropathy in Sudanese with type2 diabetes, in comparison with ACR
Methodology: It is a Descriptive cross sectional study, conducted during the period from March to July 2015 in 72 patients with type2 diabetes mellitus, the serum cystatin c, serum creatinine and spot unrine for ACR tested. Then, the Generated data analyzed using the statistical package (SPSS).
Result: Plasma cystatin c level higher in albuminuric than normal urine group. It is directly proportional to ACR and it is early raise than creatinine, also it positively correlate to duration of diabetes.
Conclusion: Cystatin c has diagnostic efficiency similar to that of ACR in detecting albuminuria. Furthermore it can detect nephropathy earlier than ACR.

Citation: Amira Ahmed Hamid, Maissa. K. Albagir and NassrEldin M.A.Shrif, 2017. "Assessment of cystatin c as early biomarker for diabetic nephropathy in sudanese with type ii diabetes", *International Journal of Current Research*, 9, (10), 59255-59258.

INTRODUCTION

The Diabetes number of people with diabetes is increasing due to population growth, aging, urbanization and the increasing prevalence of obesity and physical inactivity, According to the World Health Organization (WHO), the prevalence of diabetes for all age groups worldwide was estimated to be 2.8% in 2000 and 4.4% in 2030 (Wild *et al*., 2004). In patients with type 2 diabetes screening for diabetic nephropathy must be initiated at the time of diagnosis, since >7% of them already have micro albuminuria at initial presentation (Adler *et al*., 2003). Diabetic kidney disease (DKD) is one of the most prevalent chronic complications of diabetes and the most common single cause of end-stage renal failure (National Kidney Foundation, 2013). Chronic kidney disease (CKD) is defined by having more than 3 months of decreased GFR or evidence of kidney damage (Kidney Disease: Improving Global Outcomes (KDIGO) 2013). GFR cannot be measured directly; it can be assessed by clearance measurements or estimated from serum levels of endogenous filtration markers, such as creatinine or cystatin C (Stevens *et al*., 2006; Levey *et al*., 2014). SCr has been used as a cost-effective and practical marker of kidney function for decades, despite severe limitations due to both biological and analytical variability (Husdan and Rapoport, 1968). But some of biological factors such as age, gender, ethnicity and nutritional habits substantially influence serum creatinine levels, while partial tubular reabsorption and secretion of creatinine further compromise its use as the glomerular filtration marker (Levey *et al*., 2015). Moreover, Nobuko Harita *et al.* (2009), hypothesized that, lower serum creatinine is associated with an increased risk of type 2 diabetes since skeletal muscle is a major target tissue of insulin and a lower volume of skeletal muscle would mean fewer target sites for insulin which causes increase in insulin resistance, this leads to the development of type 2 diabetes (DeFronzo *et al*., 1985). The variation in calibration of the creatinine assay has an adverse impact on the performance of eGFR to estimate GFR (Coresh *et al*., 2002) particularly at low levels of serum creatinine and it has been found to defecient to detect mild renal impairment, evenwhen used with prediction equations (Nielsen *et al*., 1999). Thus creatinine may be not suitable for nephropathy detection. Albuminuria is a well-known predictor of poor renal outcomes in patients with type 2 diabetes and in essential hypertension (Keane *et al*., 2003). It is preferred to measure ACR and PCR (protein-to-creatinine ratio) to albumin and total protein concentration is to overcome variation in urine concentration and dilution. Many studies show high correlations between urine ACR and PCR in untimed "spot" samples with AER and PER (protein excretion rate) in timed

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urine specimens (National Kidney Foundation, 2002). And in comparison to creatinine concentration of Cystatin-C IS not affected by sex, age, or muscle mass (Coll *et al*., 2000), and according to shimizu Serum cystatin C was better than s-Creatinine in terms of sensitivity and specificity. It appears that the levels of serum cystatin C may predict early prognostic stages of patients with type 2 diabetic nephropathy (Shimizu *et al*., 2003). This study evaluated cystatin c in comparison with albumin creatinine ratio for early diagnosis of diabetic nephropathy.

MATERIALS AND METHODS

This is a qualitative Descriptive cross sectional study with Randomize sample, to assessment of cystatin C in early diagnosis, prognosis of renal diseases in diabetic patients in Khartoum state. Heparinized 72 plasma samples collected to estimation of cystatin c, creatinine, With inclusion criteria is duration of diabetes more than 5 years, and, exclusion criteria is rheumatic diseases, malignancy, cardiac diseases and drug history of taking steroids and anti-hypertension drug. In addition, spot urine sample for ACR demonstration, with exclusion criteria isUTI and hematuria. To estimate creatinine in urine and blood use Jaffs reaction by kinetic technique using biosystems BTS-35o spectrophotometer, and immune-tarbometric assay by MISPA-i2 instrument for cystatin in blood and urine albumin. Then the ACR calculated and Generated data will analyze using the statistical package (SPSS).

RESULTS

Diabetic type 2, 72 patients are included in the study, the baseline characteristics of them are shown in Table 1. Patients were categorized into 3 groups depending on their urinary albumin excretion evaluated using the urine albumin/creatinine ratio (ACR mg/mmol): the macroalbuminuric, microal buminuric and no albuminuric groups. Serum creatinine was normal in all patients and did not differ between urine albumin categories. In Pearson's correlation analysis, both the serum level of cystatin C and ACR were related to age, (P vale< 0.05) and also positively correlate to duration of diabetes, (R =0.57, P value < 0.05). A significant positive correlation between cystin c and ACR is found (Figure 1). Cytatin c level mean is significantly higher in albuminuric (mean=1.42) than normal group (mean=0.64), (P. value =0.00). When performed ROC analyses to define the diagnostic profile of the serum level of cystatin C for detecting albuminuria it showed an AUC of 0.92 with a cutoff value of 0.96 (sensitivity, 80.0%; specificity, 89%) (Figure 2). And when when performed ROC analyses to define the diagnostic profile of ACR for detecting plasma cystin c level higher than normal it showed an AUC of 0.899 with a cutoff value of 3.1 (sensitivity100%; specificity 44%) (Figure 3). When performed ROC analyses to define the diagnostic profile of the serum level of cystatin C for detecting microalbuminuria it showed an AUC of 0.93 with a cutoff value of 0.96 (sensitivity22%; specificity100%) (Figure 4). But when optimized the cut off value to 0.64 the sensitivity improved to 77% and specificity 93%. And when performed ROC analyses to define the diagnostic profile of ACR for detecting plasma cystin c level higher than normal in microalbuminuria it showed an AUC of 0.83 with a cutoff value of 3.1 (sensitivity100%; specificity 46%) and when optimized cut off value to 15.9 the sensitivity is 83% and specificity is 90% (Figure 5)

Table 1. Baseline characteristic of patients

Gender	%
Males	48.6
Female	51.4
Duration of diabetes	%
5-10 years	75
11-15 years	22.2
16-20 years	2.8
Urine albumin	%
No albuminuria	36.1
Microalbuminuria	50
Macroalbuminuria	13.9

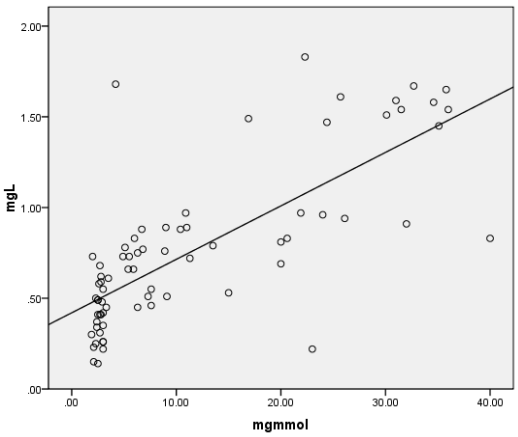

Figure 1. Correlation of plasma cystatin c level and ACR. R=0.751.P.vaLue=0.000

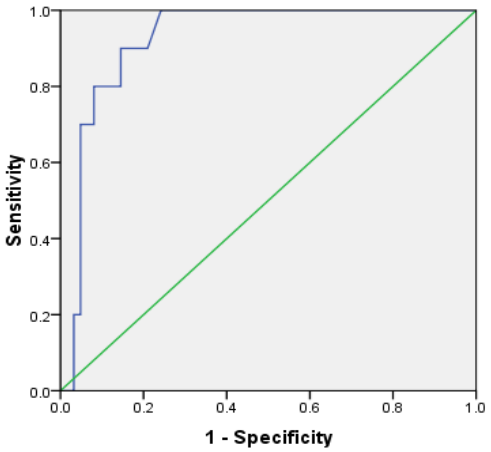

Figure 3. Diagnostic profile of the serum level of cystatin C for detecting albuminuria. AUC = 0.92. (cutoff value o= 0.96, sensitivity, 80.0%; specificity, 89%)

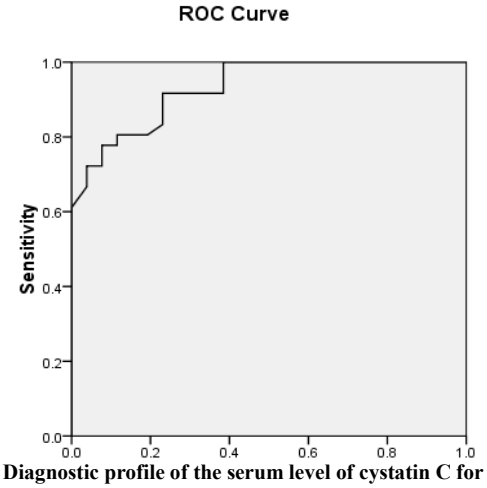

Figure 4. Diagnostic profile of the serum level of cystatin C for detecting microalbuminuria. AUC =0.93 (cutoff value = 0.96, sensitivity22%; specificity100%)

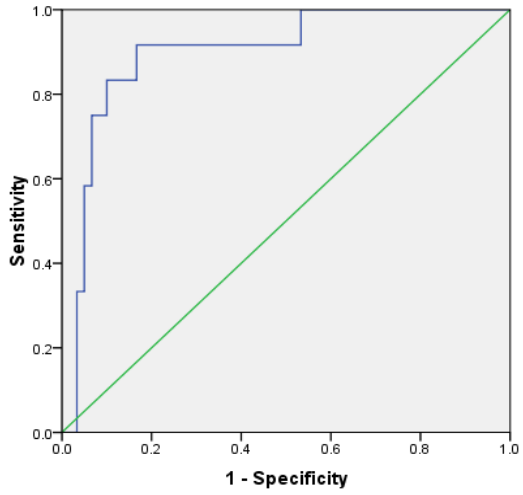

Figure 5. Diagnostic profile of acr for detecting plasma cystin c level higher than normal. AUC = 0.899. (cutoff value = 3.1, sensitivity100%; specificity 44%)

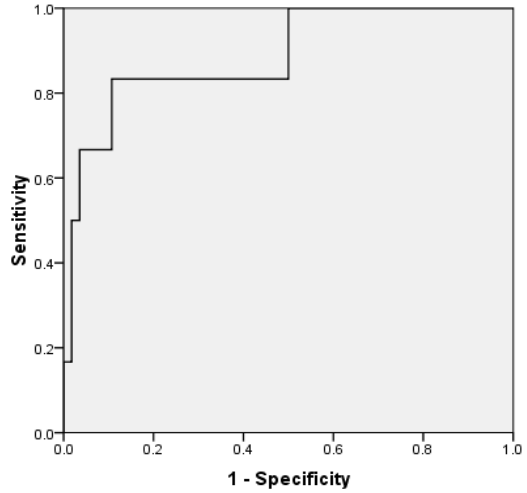

Figure 5. Diagnostic profile of ACR for detecting plasma cystin c level higher than normal in microalbuminuria. AUC = 0.83 (cutoff value of 3.1, sensitivity 100%; specificity 46%)

DISCUSSION

Diabetic nephropathy is the most frequent single cause of end stage renal disese (Ritz and Zeng, 2011). Even when diabetes is controlled, the disease can lead to chronic kidney disease and kidney failure (Dabla, 2010). Earlier detection will not only help in the clinical management of patients but also spur new research into therapies for kidney disease (Wu and Parikh, 2008). Microalbuminuria is now a standard of care to screen annually for the presence of microalbuminuria in all patients with DM (Jeon *et al*., 2011). This study categorize patients into normal, micro and marco according to the ACR as summerized in Table 1. But impaired renal function may be present even in the patients with normal urinary albumin excretion rate (Hojs *et al*., 2006). This suggests a need to screen patients many years before the onset of microalbuminuria. The ideal GFR marker should be an endogenous molecule which, being produced at a constant rate, is cleared solely by the kidneys via free glomerular filtration, with being neither secreted by tubular cells, nor reabsorbed into peritubular circulation (Westhuyzen and Cystatin, 2006), so this study plasma cystatin c is measured and evaluated since it has been proposed as efficient renal biomarker. In this study serum creatine level was not differ significantly between abl categories. A significant positive correlation between cystin c and ACR is found (Figure 1) and same result is obtained by Yun Kyung and *et al*. (2011). In Pearson's correlation analysis, the serum level of cystatin C and acr were related to age, (P vale< 0.05). And also positive Correlation of ACR and cystatin c to duration of diabetes present (R value 0.57) with (P value < 0.05). Cytatin c level mean is significantly higher in albuminuric than the normal group. Cytatin c level mean is significantly higher in microalbuminuric versus norm-albumiac group (P vale =0.00). The means of cystatin c differ significantly in normoal buminuria vs macroalbuminuria, $P < 0.001$) which confirm stud done by Gupta and *et al.* (2017). These values of Cystatin C suggesting it has similar differentiating properities to ACR as an early marker of diabetic nephropathy. The the National Kidney Foundation define microalbuminuria as an ACR between 30 to 300 g/mg in both men and women (Keane and Eknoyan, 1999). These guidelines do not take into account sex and age and ethnic differences in creatinine excretion so this study compared the diagnostic efficiency of cystin versus ACR. When performed ROC analyses to define the diagnostic profile of the serum level of cystatin C for detecting albuminuria it showed an AUC of 0.92 with a cutoff value of 0.96 (sensitivity, 80.0%; specificity, 89%). And when when performed ROC analyses to define the diagnostic profile of acr for detecting plasma cystin c level higher than normal it showed a marked decrease specificity with AUC of 0.899 with a cutoff value of 3.1 (sensitivity100%; specificity 44%). When performed ROC analyses to define the diagnostic profile of the serum level of cystatin C for detecting microalbuminuria it showed an AUC of 0.93 with a cutoff value of 0.96 (sensitivity 22%; specificity 100%) but when optimized the cut off value to 0.64 the sensitivity improved to 77% and specificity 93% which suggests follow up of plasma cystatin c may give early sign o f nephropathy even within normal range. This confim Bruce *et al* conclusion that serial measures of serum cystatin C accurately detect trends in renal function in patients with normal or elevated GFR and provide means for studying early renal function decline in diabetes (Pucci *et al*., 2007). And when performed ROC analyses to define the diagnostic profile of acr for detecting plasma cystin c level higher than normal in microalbuminuria it showed an AUC of 0.83 with a cutoff value of 3.1 (sensitivity100%; specificity 46%) and when optimized cut off value to 15.9 the sensitivity is 83% and specificity is 90%, this optimized cut off value is higher than the minimum value used in microalbuminuria definition. This result can be interpreted by the facts that; urine creatinine concentrations differ between men and women and between different racial/ethnic groups (Holly *et al*., 2002). Therefore, standardizing urine albumin concentrations to creatinine (*i.e.*, ACR may underestimate microalbuminuria in subjects with higher muscle mass (men) and possibly in certain racial/ethnic groups, or overestimate it in subjects with lower muscle mass (women) (Holly *et al*., 2002). This suggests that cystatin -C acts as a marker even before microalbuminuria begins and same result is obtained by Jeon and *et al*. (2013).

Conclusion

Cystatin c is an efficient diagnostic marker for renal impairment concerning diabetic nephropathy. Cystatin c is more sensitive than creatinine and even it is rise before ACR deterioration, then allow timely intervention as predictor for renal disease.

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