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 microalbuminuria at initial presentation (Adler et al., 2003). Diabetic kidney disease (DKD) is one of the most prevalent chronic complications of diabetes and is 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 be deficient to detect mild renal impairment, even when 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 timed “spot” samples with AER and PER (protein excretion rate) in timed
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 is UTI and hematuria. To estimate creatinine in urine and blood use Jaffs reaction by kinetic technique using biosystems BTS-350 spectrophotometer, and immuno-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, microalbuminuric 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>
<thead>
<tr>
<th>Table 1. Baseline characteristic of patients</th>
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<td>Gender</td>
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<td>Macroalbuminuria</td>
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![Figure 1. Correlation of plasma cystatin c level and ACR. R=0.751. P.value=0.000](image1)

![Figure 2. ROC Curve](image2)

![Figure 3. Diagnostic profile of the serum level of cystatin C for detecting albuminuria. AUC = 0.92. (cutoff value = 0.96, sensitivity, 80.0%; specificity, 89%)](image3)

![Figure 4. Diagnostic profile of the serum level of cystatin C for detecting microalbuminuria. AUC =0.93 (cutoff value = 0.96, sensitivity22%; specificity100%)](image4)
Diabetic nephropathy is the most frequent single cause of end stage renal disease (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 macro according to the ACR as summarized 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 an efficient renal biomarker. In this study serum creatinine level was not differ significantly between abl categories. A significant positive correlation between cystatin 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-albuminuric group (P vale =0.00). The means of cystatin c differ significantly in normal buminuria vs macroalbuminuria, (R < 0.001) which confirm the study done by Gupta and et al. (2017). These values of Cystatin C suggesting it has similar differentiating properties to ACR as an early marker of diabetic nephropathy. The National Kidney Foundation define microalbuminuria as an ACR between 30 to 300 g/mg in both men and women (Keane and Eknonyan, 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 of nephropathy even within normal range. This confirm 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.
REFERENCES


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