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Research Article

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Albumin-Creatinine Ratio is More Diagnostic Sensitive than Cystatin-C in Assessment of Diabetic Peripheral Neuropathy

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Abstract

Background: *Diabetic Peripheral neuropathy is one of the most common cardiovascular complications among diabetes mellitus patients and occurs in more than half of the population of diabetic patients world-wide. It is a common cause of foot ulcer, gangrene and amputation among diabetics. Thus, its prevention or early treatment can improve the quality of life of diabetic patients. In a bid to reduce it, various biochemical markers have been evaluated to enable early treatment and amelioration of diabetic neuropathy among diabetes mellitus patients.*

Aim: *Evaluation of the diagnostic relevance of Cystatin-C versus Albumin-creatinine ratio in assessment of Peripheral neuropathy in diabetic type 2 subjects.*

Method: *102 type 2 DM subjects (66 females and 36 males) and 100 control subjects of same age range (40 – 80 years) were recruited for this study which includes 51 subjects with peripheral neuropathy and 51 subjects without peripheral neuropathy. Serum Cystatin-C, Microalbuminuria, Urine creatinine and HBA1c were analysed with standard methods.*

Results: *Cystatin-C, Microalbuminuria, Albumin-creatinine ratio and Glycated haemoglobin were significantly elevated ($P<0.05$) in diabetic subjects compared to the control. Cystatin-C (ng/ml), microalbuminuria (mg/l), albumin creatinine ratio (mg/mmol) and HBA1c (%) is [105.52 ± 45.11; 90.07±20.29; 10.48 ± 4.82; 6.9±1.7] respectively. Microalbuminuria, albumin creatinine ratio showed significant increase ($P<0.05$) in subjects with peripheral neuropathy compared to those subjects without [92.11± 22.82; 35.70±16.35; 2.61±1.1; 6.38±1.79]. The ROC curve shows that Albumin-creatinine ratio showed significant ($P<0.05$) sensitivity to peripheral neuropathy [AUC=0.714] while Cystatin-C showed no significant ($P<0.05$) sensitivity to peripheral neuropathy complication [AUC=0.553].*

Conclusion: *Cystatin-C was found to be deranged in diabetics. However, Albumin-creatinine ratio showed more diagnostic sensitivity for peripheral neuropathy than Cystatin-C.*

Introduction

Diabetic peripheral neuropathy is a long term complication of Diabetes mellitus. It is the most commonly occurring cardiovascular complication among diabetic patient in Nigeria. It's prevalence among diabetic patients are 69.6% in Nigeria [1]. It is the most frequent cause of reduced quality of life among the cardiovascular complications found in diabetes mellitus. It is a common cause of a continuum of foot ulcer, gangrene, abnormal gait, limb amputation and sometimes death. It contributes immensely to reduced quality of life among diabetics. Diabetic Neuropathy is the most common microvascular cardiovascular complication that occurs in diabetic patients and the most common variety is peripheral neuropathy [2]. It's management double or triple health care cost of diabetic management depending on its severity [3]. This takes tremendous toll on diabetic patients especially in developing countries where health care insurance scheme may not exist. Therefore, prevention or delaying the emergence of peripheral neuropathy may improve quality of life and reduce health care cost in diabetics if Diabetic peripheral neuropathy can be detected in its early stage or prior to clinical emergence of signs and symptoms [4]. Hence, recent researches have focused on evaluation of biomarkers to enhance management outcome of diabetic peripheral neuropathy. This is more important in developing country where health care services is at its ebb hence, lack of adequate facilities to aid management of diabetic complications. Therefore, simple screening test may help foster early treatment of diabetic complication especially peripheral diabetic neuropathy which occurs commonly in diabetic patients.

Cystatin-C is a single chain, non-glycosylated basic protein that is produced and secreted by all nucleated cells at a constant rate. It is a protease inhibitor that has been claimed to be a biomarker kidney function and predictor of new onset of cardiovascular diseases or worsening diseases. It has been suggested that Cystatin-C may be elevated in diabetic patients even before the appearance of traditional

Chronic Kidney Disease markers such as albuminuria and creatinine, and can be used as useful marker for detecting nephropathy in patients with normoalbuminuria (early nephropathy). Researches have shown that it may not just be a marker of nephropathy but other cardiovascular diseases. It was found in some study to be significantly elevated in subjects with diabetic peripheral neuropathy than those without [5-7]. Therefore, it has been suggested to be a biomarker of peripheral neuropathy.

The albumin-to-creatinine ratio (ACR) in a single urinary specimen is a widely accepted surrogate of Urinary Albumin Excretion (UAE) and hence marker of early nephropathy. It is increasingly being considered as a marker that predicts chronic complications and mortality in diabetics. Apart from nephropathy, Albumin-creatinine-ratio has been suggested to be a marker of peripheral neuropathy [8]. Albumin-creatinine ratio was found to be risk factors for development of diabetic peripheral neuropathy in newly diagnosed patients [8]. Both Cystatin-C and albumin creatinine ratio elevation have been suggested to serve as markers or risk factor for diabetic peripheral neuropathy therefore, this study will evaluate the diagnostic relevance of Cystatin-C versus Albumin-creatinine ratio in assessment of Peripheral neuropathy in diabetic type 2 subjects.

Materials and Method

Study Design and Population

This is a comparative cross-sectional descriptive study designed to compare Cystatin-C and Albumin-creatinine ratio between diabetic subjects with peripheral neuropathy and those without. The subjects were recruited from two centers; Federal Medical Centre Makurdi and Benue State University teaching, Makurdi, Benue State, Nigeria. The subjects were recruited from the endocrinology unit which manages diabetes mellitus patient. A total 102 diabetics consenting patients participated in the study (59 females and 43 males). Subjects were divided into those that had apparent peripheral neuropathy and no apparent peripheral neuropathy. With the aid of trained interviewers, Michigan neuropathy screening instrument, medical records and Physical examinations the participants were categorized into two groups, those with peripheral neuropathy and those without.

Male and female type 2 diabetes mellitus patients attending medical outpatient clinic between 40-80 years were recruited for this study. Pregnant women, patients with hypoproteinemia patients treated with drugs affecting urinary albumin excretion such as ACE inhibitors in the last 3 months were excluded from the study.

Sample Collection and Biochemical Analysis

About 6mL sample of blood was drawn and early morning urine sample were collected from the participants. The samples were analyzed for HBA1c, Serum Cystatin-C, urine Creatinine and microalbumin. Ethical approval was obtained from the Benue State University Teaching Hospital Makurdi and Federal Medical Centre's Ethical Committee. Informed consent was obtained both verbally and in writing from the participants. Only consenting individuals were recruited. Confidentiality was ensured throughout the study. Number code was allotted to each participant and result obtained from the blood analysis for the study was kept secret such that no person can use the information to trace or know the patient. Each sample was run in duplicate to ensure precision and an average was taken. Quality Control materials were included in every run. The intra assay CV for each run and inter assay CV was measured. Whenever the controls fall out of the control limits ±2SD, the run was repeated and source of error was sought and resolved. Cystatin-C was analysed by ELISA method with Stat-Fax 2100 Awareness technology. Microalbuminuria and Creatinine was analysed with Evolution 3000 semi-automated machine by Biochemical systems International, Italy. HbA1c was done by spectrophotometric method based on boronate affinity chromatography.

Statistical Analysis

Data analysis was done using the statistical package for social sciences (SPSS) windows version 21. Comparison of concentration of Cystatin-C, hbA1c and albumin-creatinine ratio of those with peripheral neuropathy and those without were analyzed with student t-test with mean expressed as mean ± SD. Significance was set at $P<0.05$. Receiver operating characteristic curve of Cystatin-C and albumin-creatinine ratio was compared and statistically analyzed.

Results

The subjects enrolled for this study were 102 which are composed of 59 females and 43 males ranging from 35-80 year old. Table 1 shows that Cystatin-C, Microalbuminuria, albumin- creatinine ratio and HbA1c showed significant increase ($P<0.05$) in subjects with peripheral neuropathy compared to those subjects without peripheral neuropathy. However, Table 2 showed that the ROC curve shows that Albumin creatinine ratio showed significant ($P<0.05$) sensitivity of 71% to cardiovascular complication while Cystatin-C showed no significant ($P<0.05$) sensitivity 55% to peripheral neuropathy. There was a significant increase ($P<0.05$) in Cystatin-C of female when compared to male diabetic subjects. However, table 3 shows that the male diabetics had their albumin-creatinine ratio and microalbuminuria significantly elevated ($P<0.05$) than the female diabetic subjects. There was no significant difference in HbA1c between the male and female subjects. Table 4 shows the mean concentration of microalbuminuria, albumin-creatinine ratio, Cystatin-C and HBA1c across varying age group. Cystatin-C was seen to be statistically ($P<0.05$) increased in those that are >60 years, 46-50 years and 51-55 years compared to those that were between 40-45 years. It was also found to be statistically ($P<0.05$) increased in those that are >60 years, 46-50 years compared to those that were between 46-50 years respectively. Microlbuminuria and albumin-creatinine ratio was found to be significantly ($P<0.05$) increased in those that are 56-60 and >60 years compared to those that are 40-45, 46-50 and 51-55 years respectively. No Significant difference was found with age in HBA1c between the various age group.

Table 1: Serum Cys-C, Microalbumin, Albumin-Creatinine Ratio and Uric Acid Concentrations in Diabetic Subjects with and without Neuropathy (Mean ±SD)

Parameter	Peripheral Neuropathy (n=51)	Nil Peripheral Neuropathy (n=51)	P-Value
Cystatin-C(ng/ml)	105.52 ± 25.11	92.11± 12.82	0.020*
Microalbuminuria	90.07±20.29	35.70±16.35	0.001**
Albumin-Creatinine Ratio(acr) (mg/mmol)	10.48 ± 4.82	2.61±1.1	0.002**
HBA1c (%)	6.9±1.7	6.38±1.79	0.127

* significant at $P<0.05$

Table 2: Area under the Curve of Receiver Operating Characteristic Curve (ROC) For Albumin Creatinine Ratio and Cystatin-C Diagnostic Sensitivity for Peripheral Neuropathy Complication

Test Variable	Area under the Curve	Sig.	Diagnostic Sensitivity(%)
Cystatin-C(ng/ml)	0.553	0.352	55
Albumin-Creatinine Ratio(mg/mmol)	0.714	0.000**	71

* significant at P <0.05
* significant at P <0.05

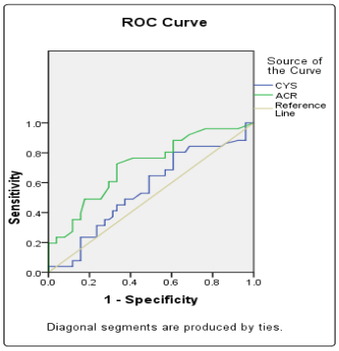

Table 3: Sex Distribution of Serum Cys-C, Microalbumin, Albumin-Creatinine Ratio in Type II Diabetes Mellitus Subjects

Parameter	Female N=59	Male N=43	P-Value
Cys-C(ng/ml)	108.56±78.83	77±16.29	0.032*
Microalbuminuria (mg/l)	40.01±14.97	64.60±25.64	0.022*
Albumin-Creatinine Ratio(ACR) (mg/mol)	4.83±2.58	7.84±2.2	0.037*
HBA1c(%)	7.29±1.28	7.22±1.32	0.51

* significant at P <0.05

Table 4: Age Distribution of Serum Cys-C, Microalbumin, Albumin-Creatinine Ratio Type II Diabetes Mellitus Subjects

Parameter	40-45 Years (n=8)	46-50 Years (n=10)	51-55 Years (n=18)	56-60 Years (n=20)	>60 Years (n=46)
Cystatin-C(ng/ml)	70.5±14.9^{b,c,e}	89.96±35.5^{c,e}	98.51±10.43^{a,d,e}	90.89±30.4^{c}	110.05±52.1
Microalbuminuria	35.65±14.32^{b,c,d,e} 35.65±14.32^{b,c,d,e}	20.51±9.34^{a,c,d,e}	61.56±21.2^{a,b,d}	98.07±22.87	61.31±16.20
Albumin-Creatinine Ratio(ACR)	2.57±1.23^{d,e}	1.62±1.2^{d,e}	3.9±2.2^{d,e}	12.6±9.5^{e}	6.5±3.4
HBA1c(%)	6.65±1.79	7.32±2.03	7.01±2.82	6.67±1.32	6.39±1.37

a=significant at P <0.05 when compared with 40-45 years; b =significant at P <0.05 when compared with 46-50; c= significant at P <0.05 when compared with 51-55 years; d= significant at P <0.05 when compared with 56-60 years e= significant at P <0.05 when compared with 51-55 years; d= significant at P <0.05 when compared with >60 years

Discussion

Cystatin-C was shown to be significantly elevated in subjects with peripheral neuropathy. Hu, et al. 2014 observed similar finding in Chinese population and inferred that serum Cystatin-C may be a biomarker for peripheral neuropathy [6]. In peripheral neural diseases, Cystatin-C could be released from neurons and affected Schwann cells into endoneurial fluid through the endoneurium. Hence, elevated serum Cystatin-C concentration may indicate diabetic peripheral nerve injury and associated demyelination [6]. Microalbuminuria was also found to be significantly elevated in subjects with peripheral neuropathy compared with those without. This is consistent with a study by Bhavya, et al. 2017 and Bell, et al. 1992 respectively [9]. Hence, microalbuminuria may not be only a biomarker of early nephropathy but also a marker of peripheral neuropathy in diabetic subjects. Initially, it was reported that there is no disparity between Cystatin-C concentrations in male and female. This has been the basis for which Cystatin-C based GFR estimation was said to be better than the creatinine based GFR estimation. But in contrast to the prevailing observation. Several work has reported gender differences in Cystatin-C concentration though the variability is less than that of creatinine. This work shows that Cystatin-C increased significantly (<0.05) in female compared to male subjects. Though, several works rather reported higher level of Cystatin-C in male. This result may have been influenced by the fact that 53 female were compared against 43 males. There is more chances that more females had diabetic complication than male which is a confounding factor.

Conclusion

Cystatin-C was found to be deranged in diabetics and tend to worsen in diabetic peripheral neuropathy. However, albumin-creatinine ratio is more sensitive to peripheral neuropathy. Therefore, may serve as a screening tool not only for diabetic nephropathy but also for diabetic neuropathy.

Recommendation

Albumin-creatinine ratio is a simple biochemical tools which should serve as good biochemical marker of cardiovascular complication. Thus can serve not only for screening of diabetic nephropathy but peripheral neuropathy. Therefore, intermittent screening of diabetic neuropathy with albumin-creatinine ratio may curb early emergence and worsening cases of diabetic peripheral neuropathy among diabetic patients.

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