Scientific Foundation SPIROSKI, Skopje, Republic of Macedonia
Open Access Macedonian Journal of Medical Sciences. 2022 Mar 17; 10(T7):12-15.
https://doi.org/10.3889/oamjms.2022.9249
eISSN: 1857-9655
Category: *T7 - "Neuroscience, Neurology, Psychiatry and Other Health Sciences - 2022"*
Section: *Public Health Education and Training*

OPEN ACCESS

Correlation of Cystatin-c with Albumin Creatinine Ratio for the Diagnosis of Diabetic Nephropathy in Patients with Type 2 Diabetes: A Cross-sectional Study in Medan Indonesia

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Edited by: Sasho Stoleski
Citation: Amelia R, Sari DK, Muzasti RA, Wijaya H. Correlation of Cystatin-c with Albumin Creatinine Ratio for the Diagnosis of Diabetic Nephropathy in Patients with Type 2 Diabetes: A Cross-sectional Study in Medan Indonesia. Open Access Maced J Med Sci. 2022 Mar 17; 10(T7):12-15. https://doi.org/10.3889/oamjms.2022.9249
Keywords: Cystatin-c; Albumin creatinine ratio; Nephropathy complications; Type 2 DM
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Received: 02-Feb-2022
Revised: 07-Mar-2022
Accepted: 13-Mar-2022

Funding: The Ministry of Research and Technology/ National Research and Innovation Agency for the 2021 Fiscal Year by the Research Contract Amendment No. 12/ E1/ KP. PTNBH/2021, dated March 8, 2021
Competing Interests: The authors have declared that no competing interests exist

Abstract

BACKGROUND: Diabetic nephropathy (ND) is one of the main complications of chronic microvascular diabetes mellitus (DM) and the leading cause of the end-stage renal disease (ESRD), accounting for nearly half of all ND cases with ESRD incidence in developed countries. Recently, cystatin C serum has been considered as a new biomarker for the diagnosis of kidney damage. Cystatin-C is an appropriate marker for GFR measurement because it is not affected by age, weight, gender, and protein intake. Early detection of abnormal renal function is essential to slow progression to a further stage of nephropathy or the final stage of kidney disease.

AIM: The aim of the study was to analyze the correlation between cystatin-C and ACR to early detection of nephropathy complications.

MATERIALS AND METHODS: This study uses an observational analytical research design with a cross-sectional approach. The research was conducted on patients with type 2 diabetes mellitus (T2DM) who were visiting the primary health service in Medan that met the inclusion and exclusion criteria. The sample count was 89 respondents. The sampling method is done through consecutive sampling. The source of this research data is primary data, including the results of cystatin-c examination and albumin. Data analysis used Spearman correlation using SPSS for Windows software.

RESULTS: There was a significant relationship between cystatin-C levels and albuminuria ($p<0.05$).

CONCLUSION: Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria and progressive decline of renal function, cystatin-C and albuminuria levels can be used as early detection of nephropathy complications.

Introduction

Diabetic nephropathy (ND) is a major consequence of chronic microvascular illness in type 2 diabetes mellitus (T2DM) and the leading cause of end-stage renal failure (ESRD). Nearly half of all ND patients in industrialized countries are projected to have ESRD [1], and it has also become the leading cause of end-stage renal disease worldwide [2]. Early identification of a decline in renal function is critical for slowing the progression of nephropathy to the next stage or to the ultimate stage of kidney disease [3]. Although serum creatinine, eGFR, blood urea, and urinary albumin are typically used to diagnose and monitor the progression of ND, another marker, namely, cystatin-C, alpha 1-microglobulin, immunoglobulin G or M, angiotensinogen, liver type fatty acid-binding protein and urinary transferrin, serum osteopontin, and urinary retinol-binding protein, can now be used to detect decreased kidney function. Microalbuminuria is also used for ND screening, a well-established marker for detecting kidney disease early [4]. Cystatin C serum has recently been proposed as a potential novel biomarker for the detection of kidney injury. Cystatin C serum has been demonstrated in certain studies to be a more sensitive indicator of GFR decline than serum creatinine [1]. In addition, the urine albumin-creatinine ratio (UACR) can be used to check for kidney injury (albuminuria) [5].

Cystatin-C has been evaluated for its potential to aid in the early detection and development of ND. Various studies have been conducted to assess the Glomerular Filtration Rate (GFR) in Asian multiethnic individuals with chronic renal disease using a combination of cystatin-C and creatinine [3]. Cystatin C levels in the urine are elevated in patients with renal tubule failure. Cystatin-C has a significant positive correlation with GFR and is unaffected by inflammatory conditions or other variables [4]. The purpose of this

study was to determine the relationship between cystatin-C levels and microalbuminuria findings in diabetic patients in Medan.

Materials and Methods

Research design

This is an analytical study using a cross-sectional design that was conducted in Medan.

Ethical approval

The Research Ethics Committee at the University of North Sumatra in Indonesia approved this study (permission number: 280/KEP/USU/2020).

Population and research samples

The research enrolled a group of T2DM patients who sought therapy on a regular basis at a Medan primary health-care facility. The sample size was 89 individuals acquired by consecutive sampling. Patients with T2DM aged 35–65 years who visit primary health-care regularly and are willing to participate in this study, patients had a history of kidney disorders prior to diabetes (e.g., urinary stones, trauma, or other urinary tract disorders with decreased renal function), or if they were diabetic patients who had undergone hemodialysis are not eligible to enroll.

Laboratory examination

The findings of the cystatin-C test, microalbuminuria, and nutritional status are all considered primary data. The ELISA method is used to quantify cystatin-C using a commercial kit named Human Cystatin C ELISA Kit (Cat. No E1104Hu, Brand Bioassay TL). Cystatin C is determined using serum centrifuged at 3000 rpm for 15 min and then accommodated in a microtube. Until the analysis is completed, the serum is kept at a temperature of 20°C. ACR is used to determine albuminuria. ACR is calculated as the ratio of albumin to creatinine concentrations in random urine samples. The immunometric assay test technique is used to determine the ACR concentration in urine. SPSS for Windows is used to examine the data.

Data analysis

SPSS for Windows is used to examine the data. The Kolmogorov–Smirnov test was used to determine normality ($p > 0.05$). Simultaneously, the correlation test for variables is performed using Spearman's non-parametric test ($p < 0.05$) [6], [7], [8].

Results

The results showed that the patients were dominated by 69 women (77.5%). The most age group is 46–55 years number of 29 people (32.6%), and long-suffering from DM type 2 1–5 years as many as 47 people (52.8%). Most of the patients had no family history of suffering from T2DM, which were 53 people (59.6%) (Table 1).

Table 1: Characteristics of DM Type-2 patients (n = 89)

Characteristics	Frequency (people)	Percentage
Gender		2.5
Male	20	
Female	69	
Age group		3.0
<36 years	1	
36–45 years	12	
46–55 years	37	
56–65 years	29	
>65 years	10	
Duration of illness		
<1 year	18	20.2
1–5 years	47	52.8
6–10 years	16	18.0
>10 years	8	9.0

The study then assessed its characteristics based on cystatin-C examination and albumin creatinine ratio (ACR). The average of cystatin C from patients was approximately 2.7 ± 3.8 mg/L and ACR about 164.5 ± 371.6 mg/g. The median value of Cystatin-C was 1.58, and ACR was 26. Spearman test results are $p<0.05$, it can be concluded that cystatin levels are correlated with the levels of ACR values of T2DM patients (Table 2).

Table 2: Correlation cystatin-C and ACR

Parameters	Mean	SD	Median	Min	p
Cystatin-C (mg/L)	2.7	3.8	1.6	0.3	0.003
ACR (mg/g)	164.5	371.6	26.0	3	

Discussion

Diabetic nephropathy is a clinical condition defined by chronic albuminuria and gradual decrease in renal function; the name implies the presence of a certain pattern of glomerular disease. Diabetes mellitus is documented in 20–50% of diabetics and is the major cause of end-stage renal damage [9]. The prevalence rates of 28% in the United Kingdom [10], 44% in the United States, and 38% in Australia [11] substantiate this. The objective of diabetes management is to identify a superior beginning marker for accurately diagnosing early-stage diabetic nephropathy to avoid progression to end-stage renal disease. Thus, early identification of nephropathy in diabetic patients is critical to allow for prompt intervention [12].

Cystatin-C is a low molecular weight protein (13 kDa) that is generated at a consistent rate throughout

the body of nucleated cells, freely filtered through the glomerulus, and metabolized in the proximal tubules, and therefore satisfies the requirements for a glomerular filtration marker [13]. Cystatin-C is an excellent indicator of glomerular filtration rate since it is unaffected by gender, muscle mass, age, or protein consumption [14]. Cystatin-C is also more considered than creatinine clearance and creatinine clearance because there is no urinary reservoir, increased sensitivity to the slightest perturbation of glomerular filtration, allowing for early detection and treatment, is continuously produced by all body cells, completely reabsorbed by tubules for later catabolization, and is not secreted by re-tubules. Arceo *et al*. (2019) found through a meta-analysis that cystatin C serum is a superior and cost-effective biomarker that may be utilized for the early detection of diabetic nephropathy. Cystatin-C can be used to evaluate kidney function, progression, and the prediction of adverse consequences in individuals with type 2 diabetes [12].

The albumin creatinine ratio (ACR) has been proposed as a tool for screening and diagnosing renal disease. Microalbuminuria screening is critical because it enables interventions aimed at preventing diabetic nephropathy and is included in daily treatment for diabetic patients to monitor the progression of kidney disease and to evaluate therapeutic effects (30–300 mg per day) to macro albuminuria (more than 300 mg per day), which affects 25% of patients within 10 years of being diagnosed with diabetes.

In this study, there was a significant relationship between Cystatin-C and albuminuria levels. These results are the following research conducted by Gupta *et al*. (2017). In addition to serum creatinine, cystatin-C serum also has a significant relationship with the group of patients with albuminuria as well as a decrease in glomerular filtration rate. Cystatin-C values in the research were seen to increase even before clinical albuminuria began and, therefore, could act as an early marker of microalbuminuria in detecting nephropathy [14]. In a study by Arceo *et al*., (2019) where a positive correlation was found between cystatin C serum levels and albuminuria. The analysis showed that cystatin-C levels were highest in patients with macro albuminuria and reduced levels in patients with microalbuminuria, and the lowest levels with insignificant differences were found among patients in the control group and normoalbuminuria [12].

The cystatin-C levels were statistically meaningful in the group of patients compared to the control group ($p < 0.001$), but there were no statistically meaningful differences between the normoalbuminuria groups when compared to the control group ($p > 0.05$). There was also a significantly higher average value of cystatin-C in the macro albuminuria group when compared to the normoalbuminuria group and the microalbuminuria group. There was also a significant increase in cystatin C levels in patients with diabetic nephropathy compared to the control group [5]. Similar results can also be found in research conducted by Al-Hazmi *et al*. (2020) that serum levels of cystatin-C increased significantly in diabetic patients with moderate albuminuria and heavy albuminuria when compared to the control group. However, in the study, there was no statistically significant difference between cystatin-C levels in patients with normal albuminuria and the control group [15], [16], [17].

In the study in Nepal, similar results were found that serum levels of cystatin C in T2DM patients increased than in the healthy control group. It is also obtained that serum levels of cystatin C increase in line with urine ACR. Thus, patients with microalbuminuria had higher levels of cystatin C compared to microalbuminuria patients and normal albuminuria cystatin-C is also higher in microalbuminuria patients compared to normal albuminuria [3].

Conclusion

Diabetic nephropathy is a clinical syndrome characterized by persistent albuminuria and progressive decline of renal function. In this study, there was a significant correlation between cystatin C and microalbuminuria to early detection of nephropathy complications in T2DM patients with a value ($p < 0.05$). The analysis showed that cystatin-C levels were highest in patients with macro albuminuria and reduced levels in patients with microalbuminuria. The lowest levels with insignificant differences were found among patients in the control group and normal albuminuria.

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