JEMTAC
Journal of Emergency Medicine Trauma & Acute Care
A PEER REVIEWED JOURNAL

OPEN ACCESS

Research paper

Estimation of cystatin C and inflammation marker levels in type 2 diabetes mellitus patients with microalbuminuria

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https://doi.org/10.5339/jemtac.2022.aimco.16

Submitted: 10 September 2022
Accepted: 15 November 2022

ABSTRACT

Serum cystatin C (CstC) is a type of protein produced by cells at the normal level; when the kidney is in normal condition or function, it inhibits the interstitial cysteine protease. The objective of the current study is to evaluate the levels of CstC and inflammation markers in type 2 diabetes mellitus (T2DM) patients with early diagnosed microalbuminuria (MBA) and find if there is a relationship between CstC and different parameters. Fifty T2DM patients with a mean age of 44.41 ± 6.51 years in the Al-Yarmouk Teaching Hospital were recruited according to the presence of MBA, and they were compared with 40 nondiabetic individuals with a mean age of 42.22 ± 5.33 years as control. Serum CstC, interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) were estimated by enzyme-linked immunosorbent assay. The mean values of serum CstC, IL-6, and TNF-α in the diabetic patients with MBA were all significantly increased compared to those of the nondiabetic individuals ($P < 0.001$). In T2DM patients with MBA, there were positive correlations between serum CstC levels and serum creatinine, creatinine urea, and cystatin-c/creatinine ratio. Similarly, there was a strong positive correlation between serum CstC and serum of the inflammatory markers IL-6 and TNF-α. However, there was a negative association between CstC and the estimated glomerular filtration rate-Larson equation. The results of the current study suggest that serum CstC, IL-6, and TNF-α may potentially serve as biomarkers for the early detection of MAB in patients with T2DM.

Keywords: cystatin C, microalbuminuria, type 2 diabetes, chronic kidney disease, inflammation markers

Cite this article as: ALkhader RAY, Elias NG, Lateef AS, Alkubaisi MR, AlAbdaly AR. Estimation of cystatin C and inflammation marker levels in type 2 diabetes mellitus patients with microalbuminuria. *Journal of Emergency Medicine, Trauma & Acute Care.* 2022(6):16 https://doi.org/10.5339/jemtac.2022.aimco.16

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INTRODUCTION

Chronic kidney disease (CKD) is one of the most common long-term complications of diabetes mellitus (DM) and affects around 20% to 40% of patients.[1] The rising prevalence of CKD is linked with the increase in patients suffering from DM and hypertension.[2] Diabetic kidney disease (DKD) was known as "diabetic nephropathy, defined as persistent clinically detectable proteinuria linked to elevated blood pressure (BP) and decreased glomerular filtration rate (GFR)."[3] DKD may progress to end-stage renal disease (ESRD), necessitating dialysis or kidney transplantation.[4] In patients suffering from type 1 DM (T1DM), the reason for hypertension is usually DKD, and typically BP begins to rise if patients progress from microalbuminuria (MBA) to macroalbuminuria. Nevertheless, hypertension affects approximately one-third of patients suffering from type 2 DM (T2DM) at the time of diagnosis. Consequently, for T2DM, hypertension probably results from numerous factors and can possibly exemplify a component of metabolic syndrome. Regardless of the variations in timing as well as the cause of hypertension in T1DM and T2DM, reports have indicated that hypertension hastens the development of DKD.[3]

Increased excretion of urinary albumin, which is generally considered an early sign of DKD, may possibly be related to a defect in the glomerular membrane filtration, caused by renal endothelial damage as a result of oxidative stress, ischemia, hyperglycemia, and inflammation.[5] Inflammation in the diabetic kidney promotes cell injury along with the evolution of fibrosis, which leads to the advancement of kidney injury. Importantly, the first clinical sign of diabetic kidney injury is the development of MBA in patients with DM. "Microalbuminuria is the last reversible stage by treatment in the course of diabetic kidney injury." The detection of MBA is crucial in the prohibition of ESRD caused by DM.[6] MBA is usually diagnosed when the urinary albumin/creatinine ratio is 30 to 300 mg/g or the excretion of urinary albumin ranges from 30 to 300 mg/day. MBA is considered a prognostic marker of DKD.[7]

Interleukin-6 (IL-6) is a multi-functional cytokine mainly secreted by various cells, for instance, mesangial cells, endothelial cells, fibroblasts, lymphocytes, and monocytes. The role of IL-6 in T2DM is contentious and complicated; nonetheless, numerous studies have established that this cytokine activates various types of inflammatory cytokines and resistance of insulin in the peripheral tissues and apoptosis process in the pancreatic islets.[8,9,10] As a result, IL-6 may be considered a pathological factor as well as an independent risk factor for the weakness of insulin activity and the progression of diabetes.[11]

Tumor necrosis factor-alpha (TNF-α), a cell-signaling protein that is linked with systemic inflammation, is one of the cytokines that instigate the acute phase response. The main role of TNF-α is in the organization of immune cells.[12] TNF-α is synthesized mainly by macrophages/monocytes, although intrinsic resident renal cells have a similar ability to synthesize this cytokine. Importantly, the actions of TNF-α are mediated through two specific transmembrane receptors. After the binding of TNF-α to its two receptors, a number of pathways are activated, which result in the expression of a variety of cytokines, mediators of inflammatory processes, transcription factors, receptors, acute phase proteins, growth factors, and cell adhesion molecules; moreover, it has the ability to mediate necrotic along with apoptotic cell death. Therefore, TNF-α accelerates the synthesis and release of inflammatory cytokines and might participate in the development of DKD.[13]

Serum cystatin C (CstC) is a type of extracellular inhibin that is abundant in the human body fluid and can inhibit interstitial cysteine protease. CstC has a low molecular weight, its production rate is constant, and it can regulate protein hydrolysis outside as well as inside the cell; in addition, it is filtered by renal glomerulus freely and subsequently reabsorbed and metabolized, mainly in the proximal convoluted tubule. More important, the kidney is the only organ to remove it, and at the same time, it is not affected by sex, age, diet, and other factors.[14] Because of its short half-life of about 2 h, CstC reaches the steady state faster than creatinine, whose half-life is 6 h.[15] Estimation of serum CstC is used to measure the kidney function of patients suffering from renal disease. Several recent studies have indicated that CstC is a more accurate marker or at least equivalent to creatinine in predicting renal damage at the early stage; furthermore, it is closely associated with the clinical outcome of dialysis patients. Hence, CstC has a certain value in the diagnosis of DM, heart disease, tumor, kidney disease, and liver cirrhosis.[14]

PATIENTS AND METHODS

Fifty patients with T2DM in the age range of 33–55 years who were in the Al-Yarmouk Teaching Hospital from October 2021 to May 2022 were recruited depending on the presence of MBA, and

they were compared with forty nondiabetic individuals as the control cohort in the range age of 33–55 years.

The questionnaire in this study included age, sex, weight, height, and body mass index (BMI), which were collected from all participants. Laboratory investigations included fasting blood sugar (FBS), glycosylated hemoglobin (HbA1C), total cholesterol (TC), triglyceride (TG), high-density, low-density, and very-low-density lipoproteins (HDL-C, LDL-C, and VLDL), urea, and creatinine. Determination of albumin and Cr in urine was used (Clinitek® Microalbumin kit, reagent strips) to isolate the diabetic patients with MBA. Serum CstC, Serum IL-6, as well as TNF-α were determined by enzyme-linked immunosorbent assay.

Mean BP (MBP) was calculated with the following formula: MBP = Diastolic BP + (Systolic BP – Diastolic BP)/3.[16] The Larson equation was used to determine the estimated GFR (eGFR): eGFR (ml/min) = 77.24 × $SCstC^{-1.2623}$.[17]

RESULTS

Table 1 shows no significant difference in age, weight, height, BMI, diastolic BP, MBP, and serum Cr between diabetic patients with MBA and the nondiabetic control. Systolic BP, FBS, HbA1C, homeostatic model assessment for insulin resistance (HOMA-IR), TC, TG, LDL-C, VLDL, urea, albumin urea, and creatinine urea in diabetic patients with MBA were significantly higher than those in the nondiabetic control, while the serum levels of insulin and HDL-C in diabetic patients with MBA were significantly lower than those in the nondiabetic control.

In Table 2, the results showed that the mean value of the CstC/creatinine ratio in diabetic patients with MBA was 16.19 ± 10.34, which was higher than that of the nondiabetic control (9.25 ± 4.48; $P < 0.05$). On the other hand, the mean value of eGFR-Larson equation in diabetic patients with MBA was 3.39 ± 2.17 mL/min, which was lower than that of the nondiabetic control (9.27 ± 3.80 mL/min; $P < 0.05$).

Table 1. Clinical and biochemical characteristics of patients with T2DM and nondiabetic control.

Clinical parameters	T2DM with MBA Mean ± SD	Nondiabetic control Mean ± SD	*P*-value
No.	50	40	/
Sex (M/F)	25/25	20/20	/
Age (years)	44.41 ± 6.51	42.22 ± 5.33	0.116
Weight (kg)	80.31 ± 14.16	82.84 ± 9.3	0.232
Height (cm)	151.26 ± 9.52	144.41 ± 8.63	0.112
BMI (kg/m^2)	27.5 ± 3.70	23.23 ± 2.51	0.183
Systolic BP (mmHg)	15.07 ± 1.78	13.64 ± 1.58	0.05*
Diastolic BP (mmHg)	9.35 ± 1.54	8.51 ± 1.32	0.401
MBP (mmHg)	14.11 ± 3.02	9.45 ± 2.17	0.06
FBS (mg/dl)	166.7 ± 22.20	82.13 ± 4.15	0.01**
HbA1C%	8.81 ± 2.11	4.64 ± 1.32	0.05*
Insulin (μU/ml)	18.79 ± 2.56	22.34 ± 2.11	0.01**
HOMA-IR	6.23 ± 1.71	2.24 ± 1.17	0.01**
TC (mg/dl)	255.21 ± 16.12	178.10 ± 8.91	0.05*
TG (mg/dl)	167.27 ± 16.2	95.33 ± 19.20	0.04*
HDL-C (mg/dl)	40.50 ± 5.70	55.55 ± 3.61	0.05*
LDL-C (mg/dl)	156.32 ± 18.8	89.53 ± 12.30	0.02*
VLDL (mg/dl)	40.18 ± 5.20	18.60 ± 4.81	0.05*
Urea (mg/dl)	59.7 ± 8.1	29.26 ± 6.12	0.01**
SCr (mg/dl)	1.35 ± 0.14	0.88 ± 0.35	0.06
Albumin urea (g/dl)	33.64 ± 12.32	24.29 ± 9.03	0.01**
Creatinine urea (g/dl)	60.45 ± 15.39	30.48 ± 10.64	0.01**

*$P < 0.05$, statistically significant.

**$P < 0.01$, statistically highly significant.

Abbreviations: BMI, body mass index; BP, blood pressure; FBS, fasting blood sugar; HbA1C, glycosylated hemoglobin; HOMA-IR, homeostatic model assessment for insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VLDL, very-low-density lipoproteins; TC, total cholesterol; TG, triglyceride; MBA, microalbuminuria; SCr, serum creatinine; T2DM, type 2 diabetes mellitus.

Table 2. Clinical parameters between T2DM with MBA and nondiabetic control.

Clinical parameters	T2DM with MBA Mean ± SD	Nondiabetic control Mean ± SD	*P*-value
No.	50	40	/
CstC/creatinine	16.19 ± 10.34	9.25 ± 4.48	0.05*
eGFR-Larson equation (mL/min)	3.39 ± 2.17	9.27 ± 3.80	0.05*
CstC (ng/ml)	14.37 ± 5.83	6.23 ± 2.89	0.001**
IL-6 (pg/ml)	86.22 ± 12.35	39.37 ± 7.33	0.001**
TNF-α (pg/ml)	127.25 ± 23.14	77.36 ± 18.62	0.001**

*$P < 0.05$, statistically significant.
**$P < 0.01$, statistically highly significant.
Abbreviations: CstC, cystatin C; eGFR, estimated glomerular filtration rate; IL-6, interleukin-6; MBA, microalbuminuria; TNF-α, tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus.

Table 3. Correction between CstC vs. different parameters in T2DM with MBA.

Clinical parameters	T2DM with MBA *r*	T2DM with MBA *P*
CstC vs. urea	0.143	0.494
CstC vs. SCr	0.588**	0.004
CstC vs. albumin urea	0.089	0.674
CstC vs. creatinine urea	0.533**	0.003
CstC vs. cystatin-c/creatinine	0.595**	0.001
CstC vs. Larson equation	−0.888**	0.0001
CstC vs. IL-6	0.986**	0.0001
CstC vs. TNF-α	0.788**	0.0001

**Significant at $P < 0.01$.
Abbreviations: CstC, cystatin C; IL-6, interleukin-6; MBA, microalbuminuria; SCr, serum creatinine; TNF-α, tumor necrosis factor-alpha; T2DM, type 2 diabetes mellitus.

The mean values of serum CstC, IL-6, and TNF-α in the diabetic patients with MBA were 14.37 ± 5.83 ng/mL, 86.22 ± 12.35 pg/mL, and 127.25 ± 23.14 pg/mL, respectively, which were all highly significantly increased compared to those of the nondiabetic control (6.23 ± 2.89 ng/mL, 39.37 ± 7.33 pg/mL, and 77.36 ± 18.62 pg/mL ($P < 0.001$), as shown in Table 2.

As shown in Table 3, in patients with T2DM with MBA, there were positive correlations between the CstC level and serum creatinine (SCr) ($r = 0.588$; $P = 0.004$), creatinine urea ($r = 0.533$; $P = 0.003$), and cystatin-c/creatinine ratio ($r = 0.595$; $P < 0.001$). Similarly, there was a strong positive correlation between the CstC level and inflammatory marker levels of IL-6 ($r = 0.986$; $P < 0.0001$) and TNF-α ($r = 0.788$; $P < 0.0001$). However, there was a negative association between CstC and eGFR-Larson equation ($r = -0.888$; $P < 0.0001$).

DISCUSSION

Hyperglycemia increases the expression of several proinflammatory cytokines, for example, TNF-α and IL-6, which results in a state of chronic subclinical inflammation in diabetes.[18] In the current study, there is an elevated level of CstC in diabetic patients with MBA, which is highly significant in comparison with nondiabetic control. These findings corroborate the findings of other studies.[19,20] In this study, the SCr levels in diabetic patients with MBA were not statistically significantly increased. Accordingly, it can be noted that serum CstC can be considered an earlier marker of DKD compared to SCr. Serum CstC is used in detecting acute renal failure (ARF) and the development of ARF earlier than SCr.[21] Another study demonstrated that serum CstC is a better early predictor of the progression of ESRD in patients with T2DM; in addition, its ability to detect the pathology changes in kidney function is extremely high.[22] Previous reports showed that the rise in serum CstC is more than that of SCr in kidney damage.[23] In the current study, there was a positive relationship between serum CstC and SCr of diabetic patients with MBA. These findings corroborate previous findings of many studies.[19,24] Furthermore, in the current study, there was a positive relationship between serum CstC and cystatin-c/creatinine ratio of diabetic patients with MBA. In contrast, a negative correlation was found between serum CstC and eGFR-Larson equation.

In the current study, serum IL-6 and TNF-α levels were highly significantly increased in the diabetic patients with MBA compared to that of the control. Interestingly, there was a strong positive correlation between serum CstC and serum of these inflammatory markers, IL-6 and TNF-α. Since kidneys can play a role in the clearance of proinflammatory cytokines, like TNF-α and IL-6,[25] the increased serum levels of these two inflammatory markers could likely indicate reduced kidney function. In fact, a significant difference in the eGFR-Larson equation between diabetic patients with MBA and control was observed.

CstC has the potential to increase estimates of GFR since it is believed to be less affected by diet or muscle mass. CstC has many desirable traits as a potential marker of GFR. Two different meta-analyses have reported that "serum cystatin C is superior to serum creatinine as a marker of kidney function."[26,27] Other studies by El-Mesallamy and Navarro et al[28,29] observed an increase in plasma TNF-α and IL-6 in the diabetic patients with MBA in comparison with the nondiabetic control group, which corroborates the results of this study. In contrast, results reported by Cao et al disagree with our data, which demonstrated that there was no statistically significant difference in the plasma levels of TNF-α in diabetic patients with MBA in comparison with nondiabetic control.[30]

CONCLUSION

The results showed that the serum CytC/creatinine ratio was higher, while the eGFR-Larson equation was lower in diabetic patients with MBA than that of the nondiabetic control. The serum level of CstC and inflammation markers IL-6 and TNF-α in the diabetic patients with MBA were elevated as compared to those of the nondiabetic control. These results suggest that serum CstC, IL-6, and TNF-α may potentially serve as biomarkers for the early detection of MAB in patients with T2DM. On the other hand, in diabetic patients with MBA, there were positive correlations between the CstC level and SCr, creatinine urea, and cystatin-c/creatinine ratio. Similarly, there was a strong positive correlation between the CstC level and inflammatory markers IL-6 and TNF-α. However, there was a negative association between CstC and eGFR-Larson equation.

ACKNOWLEDGMENT

The authors are thankful to all patients and doctors who supported us in completing this research.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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