

# Cystatin C Level in Prediabetic and Diabetic Patients

Şafak Akın,<sup>1</sup> Banu Pınar Şarer Yürekli,<sup>2</sup> Neşe Ersöz Gülçelik,<sup>1</sup>  
Jale Karakaya,<sup>3</sup> Miyase Bayraktar,<sup>1</sup> Aydan Usman<sup>1</sup>

<sup>1</sup>Department of Endocrinology and Metabolism, Hacettepe University Faculty of Medicine, Ankara, Turkey

<sup>2</sup>Department of Endocrinology and Metabolism, Ege University Faculty of Medicine, Izmir, Turkey

<sup>3</sup>Department of Biostatistics, Hacettepe University Faculty of Medicine, Ankara, Turkey

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Correspondence: Şafak Akın,  
Rize Eğitim ve Araştırma Hastanesi,  
Endokrinoloji Kliniği,  
İstanbul, Turkey  
E-mail: safakcavus@gmail.com



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## ABSTRACT

**Objective:** Cystatin C is a novel marker of kidney function. Serum Cystatin C has been shown to correlate with the progression of prediabetes and type 2 diabetes mellitus. The aim of this study was to evaluate cystatin C levels in diabetic and prediabetic patients and determine its association with anthropometric measurements and insulin resistance.

**Methods:** Twenty-five patients with diabetes, 17 patients with pre-diabetes and 24 healthy controls were included in the study. Baseline fasting plasma glucose, postprandial glucose, HbA1c, fasting insulin, microalbuminuria, renal function tests, liver function tests, and lipid profile were estimated. Body mass index (BMI) was calculated.

**Results:** Diabetic patients had higher body mass index (BMI) than controls ( $p=0.01$ ). Serum cystatin C levels were similar between the three groups ( $p>0.05$ ). Sex and/or smoking had no effect on cystatin levels. Higher cystatin C levels were negatively associated with microalbuminuria. Cystatin C levels were correlated with BMI and HOMA-IR in pre-diabetic patients ( $p=0.039$  and  $p<0.05$ , respectively) but not in diabetic patients or controls, when adjusted for age and gender.

**Conclusion:** Serum cystatin C levels are associated with BMI and insulin resistance in prediabetic patients. These results suggest that higher BMI levels are associated with high cystatin C levels, which is predictive of future risk of diabetes mellitus.

## INTRODUCTION

Type 2 diabetes is a disease which causes important morbidity, and mortality. Early intervention during prediabetic period may significantly delay or prevent development of type 2 diabetes. Adipose tissue is an important factor in the progression of prediabetes to diabetes. Epidemiologic studies have demonstrated an increase in cystatin C levels in obesity.<sup>[1]</sup> Cystatin C which is a protease inhibitor is filtered through glomeruli, and reabsorbed by proximal tubuli, and degraded. Some studies have demonstrated superiority of plasma cystatin C over creatinine in the prediction of glomerular filtration rate.<sup>[2,3]</sup> Recent studies have demonstrated that cystatin-C is not only a sensitive biomarker for renal dysfunction, but it is also associated with insulin resistance, and obesity. Recently, cystatin-C

has been shown to predict type 2 diabetes.<sup>[4]</sup> Besides in “Western New York” health study, higher cystatin C level has been shown to be a predictive factor in the progression from normal fasting blood glucose to prediabetes.<sup>[5]</sup>

In this study we aimed to evaluate the association between cystatin-C levels with anthropometric measurements, and insulin resistance in prediabetic, and diabetic patients.

## MATERIAL AND METHODS

Patients with type 2 diabetes ( $n=25$ ), prediabetes ( $n=17$ ), and 24 healthy controls were included in the study. The study protocol was approved by the Ethics Committee of Hacettepe University School of Medicine. Impaired glucose tolerance was accepted as prediabetes. Baseline fasting plasma glucose (FPG), postprandial glucose (PPG), HbA1c,

fasting insulin, microalbuminuria, renal function tests, liver function tests, and lipid profile were estimated. Waist circumference, body weight, and height were measured according to standard protocol. Body mass index (BMI) was calculated by dividing body weight (kg) by square of height (kg/m<sup>2</sup>). "Homeostasis Model of Assessment-Insulin Resistance" (HOMA-IR) were calculated based on the formula [fasting plasma glucose (mmol/L) × fasting insulin (mmol/L)/22.5]. Serum cystatin C was measured with ELISA test, and using commercially available kit (Biovdor, Czech Republic).

Data were analyzed using SPSS 16.0 software for Windows. Data were presented as mean±SD (standard deviation). For the comparison of variables among three groups, One Way Anova (Post Hoc Bonferroni correction) was used for variables with normal distribution, and for those asymmetrical distribution Kruskal-Wallis test was employed. For the comparison of categorical variables Pearson chi-square test was used. P<0.005 was accepted as the level of statistical significance.

## RESULTS

Study population consisted of 25 (M/F: 7/18) diabetic, 17

(M/F: 6/11), prediabetic patients, and 24 (M/F: 2/22) control subjects. Basic demographic, and laboratory values of the participants were presented in Table I. Serum cystatin C levels in control, prediabetic, and diabetic groups were 0.93±0.13, 0.89±0.16, and 0.96±0.16 mg/L, respectively (p=0.311). Cystatin C levels were comparable between female, and male participants. BMI, waist, and hip circumference, and HOMA-IR values were higher in the diabetic group when compared with the control group (p<0.05). Smoking status did not differ between groups (p=0.49). Any intergroup difference was not detected as for systolic, and diastolic blood pressure measurements (p=0.33, and p=0.51, respectively). A significant intergroup difference did not exist as for creatinine levels (p=0.25). When adjusted for age, and gender, cystatin C levels in prediabetic patients correlated with BMI, and HOMA-IR (p=0.039, and p<0.05, respectively).

## DISCUSSION

This study has demonstrated the presence of a significant correlation between cystatin C levels, BMI, and HOMA-IR values in the prediabetic group. Reutens et al. have revealed that cystatin C is an independent predictor of diabe-

**Table I.** Demographic and laboratory data of the participants

	Groups									p
	Control (n=24)			IGT (n=17)			DM (n=25)			
	Mean±SD	Min.	Max.	Mean±SD	Min.	Max.	Mean±SD	Min.	Max.	
Age (year)	44.13±13.1	16	66	48.06±9.07	29	64	53.52±8.18	38	67	0.025
BMI (kg/m <sup>2</sup> )	27.33±4.23	20	37	29.73±4.65	21	37	32.74±5.45	23	46	0.002
Waist circumference (cm)	89.36±14.72	70	119	96.69±11.48	75	109	103.28±7.99	86	124	0.002
SBP (mmHg)	121.25±11.72	99	156	124±13.67	103	151	125.24±7.71	110	140	0.336
DBP (mmHg)	79.5±8.5	56	106	79.47±6.96	60	90	81.2±6.17	70	90	0.519
FPG (mg/dL)	89.38±6.47	79	100	104.71±12.02	77	124	141.76±44.36	90	260	<0.0001
PPG (mg/dL)	98.16±14.47	68	125	140.24±29.93	94	197	157.28±60.99	89	336	<0.0001
Insulin (μU/mL)	10.95±3.81	0.72	18	14.98±10.32	5.5	49	17.69±12.18	3.5	50	0.160
Homa-IR	2.41±0.86	0.16	4.12	3.76±2.5	1.54	11.25	6.8±6.78	1.81	30.81	0.002
T. Chol. (mg/dL)	194.05±31.25	142	275	194.94±24.27	147	227	167.96±47.22	13	242	0.051
TG (mg/dL)	127.36±77.64	44	363	139.69±52.92	74	223	169.08±95.18	51	436	0.179
HDL (mg/dL)	56.39±14.06	32	88	48.29±7.37	34	67	45.94±12.1	23	76	0.018
LDL (mg/dL)	112.82±22.4	73	164	125.5±25.35	81	160	99.76±27.63	54	162	0.017
BUN (mg/dL)	12.42±3.15	7	20	13.94±3.21	6	18	14.39±2.9	9	19	0.047
Creatinine (mg/dL)	0.71±0.13	0.5	0.99	0.7±0.15	0.5	0.95	0.76±0.14	0.39	0.99	0.250
CystatinC (mg/L)	0.93±0.13	0.7	1.2	0.89±0.16	0.6	1.2	0.96±0.16	0.7	1.3	0.311

DM: Diabetes mellitus; IGT: Impaired glucose tolerance; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; T.Chol: Total cholesterol; Homa-IR: Homeostasis Model of Assessment-Insulin Resistance.

tes in patients with larger waist circumference, increased fat mass, and insulin resistance.<sup>[6]</sup> In this cohort study, use of cystatin C could predict risk of diabetes better in the group with only central adiposity, and insulin resistance. However this correlation did not exist in patients with decreased fat mass. In the Framingham Offspring study a correlation between cystatin C levels, and BMI was found.<sup>[7]</sup> Cystatin C is released in higher concentration in omentum, and subcutaneous fat tissue<sup>[1]</sup> When compared with non-obese individuals two or three times higher amounts of cystatin C secretion were demonstrated from adipose tissue explants.<sup>[1]</sup> This finding suggest the presence of a probable interplay between cystatin C, and cathepsins playing a role in adipogenesis.<sup>[8]</sup> In obesity many biocative molecules released from adipose tissue may be responsible from the development of cardiovascular disease, and disordered homeostasis of glucose. Cathepsin family (cathepsin K, L, and S) are newly discovered potential molecules. Inhibition of cathepsins may decrease cardiovascular risk. Increased serum cystatin C in obesity may have a protective role through inhibition of cathepsin production.<sup>[8]</sup>

Some studies cited in the literature have indicated that cystatin C might be a predictor of metabolic syndrome.<sup>[9–11]</sup> Apart from obesity, inflammation, and oxidative stress may be other etiologic factors which induce increases in cystatin-C levels. Induction of cystatin C mRNA, and protein synthesis by oxidative stress has been demonstrated in many studies.<sup>[11]</sup>

The relationship between renal dysfunction defined with decreased glomerular filtration rate (GFR), and development of diabetes has been demonstrated.<sup>[12]</sup> This condition might be related to insulin resistance,<sup>[13]</sup> increased renal glukoneogenesis,<sup>[14]</sup> endothelial dysfunction and/or chronic inflammation, oxidative stress<sup>[14,15]</sup> and activation of the renin-angiotensin system.<sup>[16]</sup> In the prediction of the presence of early renal dysfunction serum cystatin C has been thought to be more definitive parameter than serum creatinine.<sup>[17–19]</sup> In recent investigations, the correlation between cystatin C, and obesity, hypertension, and insulin resistance which is closely related to diabetes has been suggested.<sup>[10]</sup> In our study cystatin C levels were comparable in diabetic, prediabetic, and control groups, and we have also demonstrated a positive correlation between cystatin C levels, BMI, and insulin resistance in the prediabetic group.

Scarce number of patients in groups constitute a limitation of this study. This cross-sectional study does not indicate the presence of cause-effect relationship. Therefore prospective studies are needed to clarify this issue.

A complex relationship exists between adiposity, cystatin C, and glycemic homeostasis. It is not absolutely certain whether cystatin C can be a predictive biomarker for impaired glucose tolerance, and developing diabetes. Further

studies which will clarify, and evaluate this complex issue are needed.

#### Authorship contributions

Concept: Ş.A.; Design: Ş.A., B.P.Ş.Y.; Data collection &/or processing: Ş.A.; Analysis and/or interpretation: Ş.A., J.K., N.E.G.; Writing: Ş.A.; Critical review: Ş.A., N.E.G., M.B., A.U.

#### Conflict of interest

None declared.

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## Diyabetik ve Prediyabetik Bireylerde Sistatin C Düzeyi

**Amaç:** Sistatin C böbrek fonksiyonunun yeni bir belirteçidir. Serum sistatin C'nin prediyabet ve tip 2 diabetes mellitus progresyonuyla korele olduğu gösterilmiştir. Bu çalışmanın amacı, diyabetik ve prediyabetik hastalarda sistatin C düzeylerini değerlendirmek ve antropometrik ölçümler ile insülin direnci arasındaki ilişkiyi saptamaktır.

**Gereç ve Yöntem:** Diyabetik 25 hasta, prediyabetik 17 hasta ve 24 sağlıklı kontrol çalışmaya alındı. Başlangıç açlık plazma glukozu, post prandial glukoz, HbA1c, açlık insülin, mikroalbuminüri, böbrek fonksiyon testleri, karaciğer fonksiyon testleri ve lipid profili ölçüldü. Bel çevresi, vücut ağırlığı ve boy standart protokole göre ölçüldü. Vücut kitle indeksi (VKİ) hesaplandı.

**Bulgular:** Diyabetik hastalarda kontrol grubuna göre VKİ daha yüksekti ( $p=0.01$ ). Serum sistatin C düzeyleri üç grup arasında benzerdi ( $p>0.05$ ). Cinsiyet ve/veya sigara içilmesinin sistatin seviyeleri üzerinde herhangi bir etkisi görülmedi. Yüksek sistatin C düzeyleri mikroalbuminüri ile negatif ilişkili idi. Yaş ve cinsiyete göre ayarlama yapıldığında prediyabetik hastalarda sistatin C düzeyleri, VKİ ve HOMA-IR ile korelasyon gösterdi (sırasıyla,  $p=0.039$  ve  $p<0.05$ ).

**Sonuç:** Prediyabetik hastalarda serum sistatin C düzeyleri VKİ ve insülin direnci ile ilişkilidir. Bu sonuçlar, daha yüksek VKİ düzeylerinin gelecekte diyabet riskini öngören yüksek sistatin C seviyeleri ile ilişkili olduğunu düşündürmektedir.

**Anahtar Sözcükler:** Diyabet; prediyabet; sistatin C.