RESEARCH ARTICLE

Serum carbohydrate antigen 153 and renal function in patients with type 2 diabetes mellitus

You-Fan Peng¹ | Hao Lin² | Man-Man Han¹ | Ling Li¹

¹Department of Endocrinology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

²Department of Clinical Science and Research, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, China

Correspondence

Ling Li, Department of Endocrinology, Zhongda Hospital, School of Medicine, Southeast University, Nanjing, Jiangsu, China.
Email: liling_79@sina.com

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Objective: The aim of our study was to investigate the correlation between serum carbohydrate antigen 153 (CA153) and renal function in patients with type 2 diabetes mellitus (T2DM).

Methods: A total of 184 patients with T2DM were included, and renal function was assessed by the modification of diet in renal disease (MDRD) formula adjusted coefficient of the Chinese people.

Results: Serum CA153 concentrations were positively correlated with blood glucose (BG) and glycated hemoglobin (HbA1c) ($r = .204$, $P = .005$; $r = .165$, $P = .025$) in patients with T2DM. There was a negative correlation between serum CA153 and estimated glomerular filtration rate (GFR) ($r = -.229$, $P = .002$) in whole patients with T2DM; similarly, the correlations were observed in both women and men ($r = -.228$, $P = .028$ for women, $r = -.231$, $P = .028$ for men). Multiple linear regression analysis suggested that serum CA153 was still significantly correlated with estimated GFR ($\beta = -0.286$, $P < .001$).

Conclusions: Serum CA153 is negatively correlated with estimated GFR in patients with T2DM, and serum CA153 may be a potentially useful clinical biomarker to assess renal function in the study population.

KEYWORDS

glomerular filtration rate, serum carbohydrate antigen 153, type 2 diabetes mellitus

1 | INTRODUCTION

With the rapid increase in patients with type 2 diabetes mellitus (T2DM) in the worldwide context, a chronic kidney disease caused by T2DM has an increasing burden of morbidity and mortality.¹ Chronic kidney disease is related to atherosclerosis and increases a risk of cardiovascular disease in patients with diabetes mellitus.² Chronic kidney disease is a main cause to increase premature death in patients with T2DM.³ In clinical laboratory, early diabetic kidney disease is often implied and determined by an increased microalbuminuria and reduced glomerular filtration rate (GFR) in patients with T2DM.⁴ The estimated GFR is the most widely used index to assess the variation of kidney function in clinical practice.

Serum carbohydrate antigen 153 (CA 153) is a product of the mucin 1 (MUC1) gene.^{5,6} MUC1 as a transmembrane glycoprotein

is expressed on the surface of most epithelia in various organizations,⁷ and MUC1 is called CA153 in the blood circulation.⁸ A line of evidence attested that inflammation might be associated with the expression of MUC1 in cell surface in patients with Sjogren's syndrome⁹; indeed, previous studies have suggested that several inflammatory cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) could upregulate the expression of MUC1 gene.¹⁰ For another, it is reported that glycosylation inhibitor can suppress the MUC1 glycosylation, and the expression of MUC1 is a more highly in glycosylated cell surface.¹¹ Nevertheless, the processes of inflammation and glycosylation have been suggested to be linked with decreased renal function in patients with T2DM.¹²⁻¹⁴ Thus, we supposed that there was a correlation between serum CA153 and estimated GFR in patients with T2DM.

2 | METHODS AND PATIENTS

A total of 184 patients with T2DM were included in the retrospective study, and the diagnosis of all patients with T2DM was defined in accordance with the criteria of World Health Organization (1999). Patients with known hepatic impairment, active infection, uncontrollable hypertension, malignant tumor, and mental disease were excluded. The study was approved by the local ethical committee and was performed according to the Declaration of Helsinki.

2.1 | Renal function assessment

Renal function was assessed by the modification of diet in renal disease (MDRD) formula adjusted coefficient of the Chinese people,¹⁵ the abbreviated MDRD formula: estimated GFR = $186 \times (\text{serum creatinine}^{-1.154}) \times \text{age}^{-0.203} \times 1.233 \times 0.742$ (if female).

2.2 | Laboratory and clinical data

The fasting blood samples were obtained for the laboratory parameters, including total protein (TP), alanine transaminase (ALT), aspartate transaminase (AST), total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A, apolipoprotein B, creatinine (Cr), blood glucose (BG), glycated hemoglobin (HbA1c), and CA153. All tests were accomplished in the identical laboratory.

2.3 | Statistical methods

All statistical analyses were achieved by SPSS software version 16.0. Continuous data were expressed as means $\pm$ standard deviation, and categorical data were expressed as percentages. Pearson's and Spearman's correlation analyses were employed to examine the correlations between serum CA153 and other data appropriately. Multiple linear regression analysis was used to determine the parameters potential correlated with estimated GFR in patients with T2DM. A *P* value of $<.05$ was considered statistically significant.

3 | RESULTS

3.1 | The correlations between serum CA153 and parameters in whole patients with T2DM

Basic laboratory characteristics of all patients with T2DM are listed in Table 1. Serum CA153 levels were found to be positively correlated with Cr ($r = .211$, $P = .004$) in all patients with T2DM, and serum CA153 was positively correlated with BG and HbA1c ($r = .204$, $P = .005$; $r = .165$, $P = .025$) in patients with T2DM; interestingly, there was a negative correlation between serum CA153 and estimated GFR ($r = -.229$, $P = .002$) in whole patients with T2DM, as shown in Table 2.

TABLE 1 The basic characteristics in whole patients with T2DM

Items	T2DM patients
Gender (female/male)	93/91
Age (y)	56.40 $\pm$ 12.53
Total protein (g/L)	64.95 $\pm$ 6.54
Alanine transaminase (U/L)	22.04 $\pm$ 8.17
Aspartate transaminase (U/L)	22.52 $\pm$ 5.59
Creatinine ($\mu\text{mol/L}$)	72.96 $\pm$ 42.67
Fasting blood glucose (mmol/L)	8.12 $\pm$ 4.17
Total cholesterol (mmol/L)	5.00 $\pm$ 1.12
High-density lipoprotein cholesterol (mmol/L)	1.66 $\pm$ 0.46
Very low-density lipoprotein cholesterol (mmol/L)	0.78 $\pm$ 0.55
Triglyceride (mmol/L)	1.72 $\pm$ 1.20
Apolipoprotein A (g/L)	1.28 $\pm$ 0.29
Apolipoprotein B (g/L)	1.08 $\pm$ 0.36
Glycosylated hemoglobin (%)	8.47 $\pm$ 3.14
Glomerular filtration rate (mL/min/1.73 m ²)	126.13 $\pm$ 39.09
Serum carbohydrate antigen 153 (U/mL)	11.38 $\pm$ 4.65

TABLE 2 The correlation between serum CA153 and laboratory parameters in whole T2DM patients

Items	<i>r</i>	<i>P</i> -values
Age	.100	.176
Total protein	.124	.094
Alanine transaminase	.043	.565
Aspartate transaminase	.051	.488
Creatinine	.211	.004
Fasting blood glucose	.204	.005
Total cholesterol	.085	.249
High-density lipoprotein cholesterol	.014	.847
Very low-density lipoprotein cholesterol	.062	.407
Triglyceride	.062	.404
Apolipoprotein A	-.030	.682
Apolipoprotein B	.037	.615
Glycosylated hemoglobin	.165	.025
Glomerular filtration rate	-.229	.002

3.2 | The correlations between serum CA153 and parameters in women and men

We decided to divide the patients with T2DM into genders for detail correlation analysis. Similarly, the negative correlations were observed in both genders between serum CA153 and estimated GFR ($r = -.228$, $P = .028$ for women, $r = -.231$, $P = .028$ for men). Additional, serum CA153 concentrations were positively

correlated with BG ($r = .268$, $P = .010$), Cr ($r = .250$, $P = .016$), TC ($r = .240$, $P = .021$), TG ($r = .239$, $P = .021$), and VLDL-C ($r = .239$, $P = .021$) in women, and positively correlated with Cr ($r = .214$, $P = .042$) in men.

3.3 | Serum CA153 and estimated GFR in multiple linear regression analysis

The serum CA153 and estimated GFR in the population might be affected by some confounders, so the multiple linear regression analysis was used to eliminate these influences. In multiple linear regression analysis after adjustment for gender, age, values of TP, Cr, BG, HbA1c, TC, TG, HDL-C, and VLDL-C, serum CA153 was still significantly correlated with estimated GFR ($\beta = -0.286$, $P < .001$) and correlated with BG ($\beta = 0.298$, $P < .001$) in patients with T2DM in multiple linear regression analysis, as shown in Table 3.

4 | DISCUSSION

CA 153 has been considered as a general tumor marker in clinical practice, especially for breast cancer. Clinical significances of serum CA153, however, are rarely discussed in nontumor diseases. Our study first revealed that serum CA153 was correlated with estimated GFR in patients with T2DM. Furthermore, an additional correlation between serum CA153 and BG was observed in patients with T2DM in multiple linear regression analysis.

Traditionally, serum CA153 has been regarded to be a marker with respect to breast cancer and is correlated with tumor size, nodal involvement, and prognosis.¹⁶ Tumor patients with worse outcome increase the levels of serum CA153.¹⁷ Increased serum CA153 levels have been demonstrated in collagen diseases without evidence of breast cancer such as polymyositis, dermatomyositis, and pulmonary fibrosis.^{6,18} In our study, the reversely relationship between serum CA153 and estimated GFR in patients with T2DM was suggested. Serum CA153, a macromolecular substance, is not filtered into urine by the glomerulus, even in uremia patients.¹⁹ Therefore, the fascinating relationship may be explained by other underlying mechanism in patients with T2DM. For decreased renal function in patients with T2DM, the TNF, IL-6, and high-sensitivity C-reactive protein have been demonstrated to be biomarkers to predict the presence and severity of chronic kidney disease, and systemic inflammation may

be increased in patients with chronic kidney disease, especially in patients with T2DM.^{20,21} The relationship between glycosylation and progression of chronic kidney disease has been established in T2DM,¹² and a higher percentage of glycosylation may result in renal function impairment in both diabetic and nondiabetic subjects.^{22,23} Unfortunately, systemic inflammation and hyperglycemia may alter *MUC1* gene expression in patients with T2DM. First, the expression of *MUC1* gene is regulated by several cytokines including TNF,²⁴ and *MUC1* gene is related to the transcription of inflammatory cytokines by NF- κ B signaling pathway.²⁵ Barrera et al²⁶ found that TNF tended to increase the mRNA expression of *MUC1* gene by mucin-cytokine signaling loop in inflammation environment. Interestingly, the anti-inflammatory properties are observed in knockout mice of *MUC1* gene.^{27,28} In patients with T2DM, low-grade inflammation has been regarded to be a common characteristic²⁹; therefore, inflammation may increase the *MUC1* gene expression in various kinds of cells in patients with T2DM. Second, *MUC1* is composed of five potential glycosylation sites.³⁰ The influence of hyperglycemia on glycosylation has been suggested in the early onset of T2DM.¹² Consequently, we speculate that hyperglycemic environment may activate and aggravate the glycosylation of glycoprotein, which also results in the elevated expression of *MUC1* gene in patients with T2DM. In brief, the serum CA 153, as a circulating *MUC1* antigen, is produced by the *MUC1* gene in human body,^{6,16} and *MUC1* is released into the peripheral blood circulation where it is referred to as CA153.⁸ The overexpression of *MUC1* has been demonstrated to increase the serum CA153 concentrations.³¹ Thus, inflammation and glycosylation induced by hyperglycemic environment may elevate *MUC1* gene expression in various cells, which link the relation between increased serum CA153 and estimated GFR in patients with T2DM. Of course, there are other potential mechanisms to explain this current relationship.

It has been reported that estimated GFR can be served as a predictor of poor outcomes in T2DM patients with acute stroke.³² The variation of GFR is a risk factor of dialysis and death in T2DM patients with chronic kidney disease.³³ Recent study suggested that lower GFR predicted an increase in cardiovascular disease in patients with T2DM.³⁴ In a large cohort of patients with T2DM, reduced GFR has been reported to be a strong predictor of stroke recurrence and all-cause mortality.³⁵ Obviously, the reasonable monitoring and follow-up for GFR are essential in a diverse population of patients, especially in patients with T2DM. In the present study, we observed

TABLE 3 The factors related to serum CA 153 in T2DM patients in multivariable linear regression analysis

	Unstandardized coefficients		Standardized coefficients	
	B	SE	Beta	P-value
Fasting blood glucose	0.332	0.078	0.298	<.001
Glomerular filtration rate	-0.034	0.008	-0.286	<.001
Constant	12.971	1.174	-	<.001

the correlation between serum 153 and estimated GFR in patients with T2DM, based on the above investigations, serum CA153 may be an available marker to reflect renal function in patients with T2DM, and increased serum CA153 may herald a worse prognosis in patients with T2DM.

Several limitations should be noted. First, the statistical power might be limited by a relatively small sample size. Second, the estimated GFR was employed to estimate the renal function rather than more accurate measuring methods such as iothalamate clearance. Third, the current retrospective analysis might result in potential study bias for included individuals, and the T2DM patients were from a single center; these factors might affect the extrapolation of results in various populations and regions. Fourth, we did not assess whether medication use histories such as hypoglycemic agent had the influences on the relationship between serum CA153 and estimated GFR in the population. As a result, the current study suggested that serum CA153 was negatively correlated with estimated GFR in patients with T2DM, and serum CA153 might be a potentially useful clinical biomarker to assess renal function in the study population.

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ORCID

Ling Li <http://orcid.org/0000-0002-7894-8251>

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