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Original Article

Correlation of serum CA199 levels with glycemic control and microvascular complications in patients with type 2 diabetes mellitus

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Abstract: Objective: This study aimed to explore the correlation between glycemic control, microvascular complications and serum glycogen antigen (CA199) in patients with type 2 diabetes mellitus (T2DM). Methods: 519 patients with T2DM admitted to our hospital were included. All patients had CA199 levels measured. Patients were divided into low glycation (LH) group (HbA1C <7.5%), Hyperglycemia (HH) group (HbA1C ≥7.5%), fasting glucose compliance (SF) group (FBG <7.0 mmol/L), high fasting glucose (HF) group (FBG ≥7.0 mmol/L), postprandial glucose compliance (SP) group (PBG <10.0 mmol/L) and high postprandial glucose (HP) group (PBG ≥10.0 mmol/L) and with microvascular complications group, and no microvascular complications group. Division was according to levels of glycated hemoglobin (HbA1C), fasting blood glucose (FBG), 2-hour postprandial blood glucose (2hPBG), and diabetic microvascular complications. Results: CA199 levels were significantly higher in the HH and HF groups than in the LH and SF groups ($P<0.05$); HbA1C and FBG were positively correlated with CA199; CA199 levels were not significantly different between SP and HP groups ($P>0.05$), and PBG was not significantly correlated with CA199 levels. CA199 levels were significantly higher in the group with microvascular complications than in the group without microvascular complications ($P<0.05$); HbA1C was an independent risk factor for elevated CA199. Conclusion: Patients with T2DM and higher CA199 levels need to be evaluated for glycemic status and the presence of microvascular complications. HbA1C is a major risk factor for elevated CA199 levels.

Keywords: Type 2 diabetes, CA199, blood glucose, microvascular complications

Introduction

T2DM is a chronic disease in clinical practice and is significantly associated with the incidence of malignant tumors, among which gastrointestinal tumors, pancreatic cancer, and gastric cancer are the main types [1]. Tumor occurrence is due to the abnormal activation of suppressed proto-oncogenes and suppression of tumor-suppressor gene activity or gene mutation [2]. Insulin-like growth factor I can induce overexpression of oncogenic genes and abnormal cell aging, and also lead to disorders of P53 gene function.

When type 2 diabetes is accompanied by cancer, gastrointestinal tumor is most common category and the incidence of combined pancreatic cancer is also particularly high [3]. At present, T2DM is a major public health problem. According to epidemiologic studies, the number of global cases of T2DM was as high as 30 million in 2018 alone, and about 20 million people died of the disease or its complications [4]. Tumor markers such as CEA, CA199, and CA125 are commonly used clinically to reflect the occurrence and development of gastrointestinal tumors, and they are currently often used in clinical diagnosis and prognosis assessment of patients with gastrointestinal tumors [5]. CA199 is a typical marker for gastrointestinal tumors, and is highly sensitive for pancreatic cancer, and could assist in the diagnosis of rectal cancer, colon cancer and primary liver cancer. It is the first choice tumor marker for detecting tumors of extrahepatic bile duct cancer and pancreatic cancer. Studies have shown that cholecystitis, acute and chronic hepatitis, and pancreatitis can cause elevated CA199 levels, and CA199 levels in T2DM

patients with HbA1C were significantly higher than those without HbA1C [6]. In this study, 519 patients with T2DM were enrolled to explore the correlation between CA199 levels and microvascular complications and glycemic control in glucose metabolism disorders, so as to provide a theoretical reference for future clinical treatment.

Materials and methods

Study subjects

A total of 519 T2DM patients admitted to our hospital from July 2018 to July 2019 were enrolled, including 282 males and 237 females.

Inclusion criteria: patients who were confirmed as T2DM by the 2013 edition of the Guidelines for the Prevention and Treatment of Type 2 Diabetes Mellitus issued by the Chinese Medical Association Diabetes Differentiation [7]. Exclusion criteria: patients with a history of hepatobiliary, pancreatic disease; those with diabetic ketoacidosis; and those who had concomitant tumors were excluded.

Methods

Clinical data: The gender, age, and course of diabetes (years), weight and height, and body mass index (BMI) were collected; The FBG, PBG, basal insulin C peptide, HbA1C, blood lipids and CA199 levels were determined in venous blood. The urine microalbumin (MA) and urine creatinine (Cr) were measured in patients with diabetes with morning urine specimens 2 consecutive times while fundus microscopy, fundus photography, and electromyography were performed. This study has been approved by the Ethics Committee of Pingdingshan University. All study participants provided written informed consent before participating in the study.

Detection and grouping: All patients were categorized according to their metabolic control goals: 74 patients in the low glycemic (LH) group (HbA1C <7.5%), 99 patients in the high glycemic (HH) group (HbA1C ≥7.5%), 73 patients in the fasting glucose compliance (SF) group (FBG <7.0 mmol/L), 100 patients in the high fasting glucose (HF) group (FBG ≥7.0 mmol/L), 68 cases in the SP group (PBG <10.0 mmol/L) and 105 cases in the high postprandial glucose (HP) group (PBG ≥10.0 mmol/L). Glucose was determined by the peroxidase method, basal C-peptide and CA199 by chemiluminescence, HbA1C by high-pressure liquid-phase method, lipids by enzymatic method (GPO-PAP method), urinary MA, urine Cr by immunoturbidimetric assay. Dilated fundus examination was performed by ophthalmologists, and fundus photographs were taken of both eyes under dark room conditions at 45 degrees using fundus cameras. EMG was performed to evaluate the functional status of peripheral nerves. HOMA with modified fasting C-peptide (C-Peptide) were performed to evaluate insulin β-cell function and insulin resistance; insulin resistance index HOMA-IR (C-P) = 1.5 + FPG*FC-P/2800; insulin function index HOMA-islet (C-P DM) = 0.27*FC-P/(FPG-3.5).

Diagnosis of microvascular complications of T2DM: The ophthalmologists diagnosed retinopathy in all patients and divided them into a normal fundus group and a retinopathy group according to the presence or absence of retinopathy. Morning urine samples from T2DM patients were collected to measure Cr and MA values to determine whether the patients were associated with nephropathy. Electromyography was performed to determine whether there was neuropathy in T2DM patients.

Statistical methods

SPSS19.0 statistical software was used for data analysis. Measurement data were tested for normality. The collected data in accordance with normal distribution was expressed as mean ± standard deviation. Comparison between groups was performed by t test; Collected data did not conform to normal distribution was expressed in form of median interquartile range and compared by the Mann-Whitney U Test. Spearman was used to analyze the correlation between the CA199 level and other factors. Logistic multivariate regression analysis was used. $P<0.05$ indicates that a difference was significant.

Results

Changes in baseline data and serum levels between groups

The differences in age, disease duration, BMI, LDL, HDL, TG and TC were not significantly dif-

Table 1. Baseline data (x ± s)

Group		n	Age	Course of disease	BMI	LDL-C	HDL-C	TG	TC
Hb1Ac	HH	99	55.82±9.78	7.59±5.28	24.21±3.46	3.22±1.49	1.11±0.42	2.18±2.54	5.06±1.23
	LH	74	54.85±9.88	6.32±4.67	24.42±3.32	2.88±0.88	1.10±0.32	1.76±1.28	4.62±1.69
	P		0.023	0.001	0.823	0.187	0.796	0.078	0.153
FBG	HF	100	55.01±10.68	8.12±6.18	24.36±3.57	3.18±1.36	1.18±0.49	2.21±2.37	4.83±1.24
	SF	73	56.36±9.78	7.75±6.00	24.29±3.28	3.15±0.86	1.13±0.18	1.73±1.49	4.76±0.87
	P		0.014	0.032	0.856	0.428	0.119	0.218	0.583
PBG	HP	105	57.57±9.14	10.77±5.95	24.15±3.56	3.37±1.45	1.14±0.41	1.74±0.78	5.16±1.14
	SP	68	58.14±8.87	9.02±5.86	23.78±1.84	3.28±0.81	1.25±0.26	1.79±1.81	5.08±0.84
	P		0.038	0.279	0.535	0.661	0.817	0.566	0.431

FBG, fasting blood glucose; PBG, 2-hour postprandial blood glucose.

Table 2. Effects of different HbA1C, FBG, and PBG levels on serum CA199 levels {median (quartile)}

	HbA1C		FBG		PBG	
	HH	LH	HF	SF	HP	SP
CA199	14.58 (10.39, 27.05)	10.38 (6.89, 16.22)	14.26 (9.73, 25.80)	13.31 (9.12, 22.60)	11.59 (7.82, 21.4)	11.26 (6.25, 22.01)
Z	-3.382		-2.009		-0.407	
P	≤0.001		0.045		0.665	

FBG, fasting blood glucose; PBG, 2-hour postprandial blood glucose.

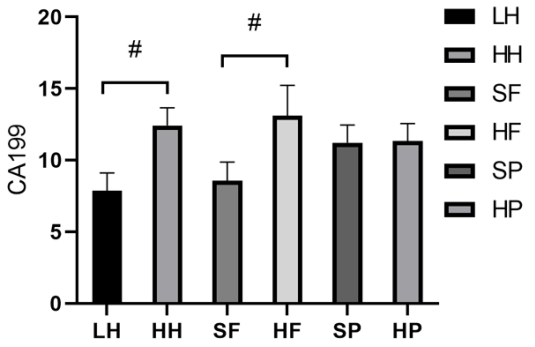

Figure 1. Association between groups and CA199 levels. Patients in the SP and HP groups were found to show the same level of CA199 expression (P>0.05). The LH and SF groups had significantly lower CA199 levels than the HH and HF groups (P<0.05). # represents a significant difference between groups.

ferent (P>0.05) but were comparable between the groups (**Table 1**). CA199 levels were significantly higher in the HH and HF groups than in the LH and SF groups (P<0.05). Serum CA199 levels were not different between HP and SP groups (P>0.05, **Table 2**; **Figure 1**).

Observation of CA199 levels in each group

Patients in the group with microvascular complications had at least one of the conditions of neuropathy, retinopathy or diabetic nephropathy, and their CA199 levels were significantly higher than those in the group without microvascular complications (P<0.05). When the above three microvascular complications were grouped separately, the CA199 levels still conformed to the above trend and the difference was significant (P<0.05, **Table 3**).

Correlation of serum CA199 with various indicators

Spearman showed a positive correlation between CA199 and those with T2DM with HbA1C (r = 0.346, P = 0.002) and FBG (r = 0.298, P<0.001) (r = 0.246, P = 0.003). Beta cell function, PBG and insulin resistance were negatively correlated with CA199 levels (P> 0.05, **Table 4**; **Figure 2**).

Multifactor regression analysis of factors affecting CA199 levels

Multiple logistic regression analysis showed that HbAIC was an independent risk factor for elevated CA199 (P = 0.015, **Table 5**; **Figure 3**).

Discussion

In recent years, there has been a significant increase in the number of T2DM patients who have pancreatic, renal and breast cancers, and

Table 3. Comparison pf CA199 levels in T2DM patients with microvascular complications

	Positive	Negative	*P*-value
Microvascular complication	15.68 (7.99-26.42)	10.73 (7.47-14.28)	0.003
Diabetic nephropathy	18.87 (10.38-29.06)	11.64 (7.36-20.28)	0.002
Diabetic retinopathy	13.66 (9.24-25.43)	11.66 (7.63-21.84)	0.015
Diabetic peripheral neuropathy	14.59 (8.29-22.01)	10.77 (7.62-14.55)	0.002

Table 4. Correlation of clinical variables with CA199

	CA199	*P*-value
Age	r = 0.108	0.153
Duration of illness	r = 0.144	0.079
BMI	r = 0.068	0.359
HbA1C	r = 0.346	0.002
FBG	r = 0.404	<0.001
PBG	r = 0.072	0473
HOMA-IR	r = 0.238	0.083
HOMA-islet	r = -0.086	0.104
TC	r = 0.062	0.525
TG	r = 0.035	0.715
LDL-C	r = 0.066	0.510
HDL-C	r = -0.099	0.827

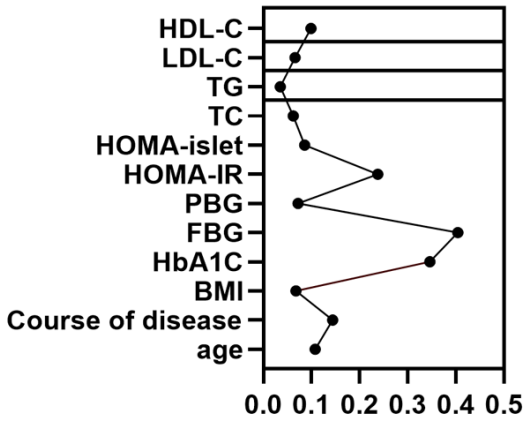

Figure 2. Correlation between CA199 levels and basic clinical data of the included patients. HbA1C and FBG levels were significantly associated with CA199, but were negatively correlated with PBG, disease duration, age, PBG, TC, TG, LDL-C, HDL-C, and insulin resistance.

the relationship between T2MD and malignant tumors has been noticed by many scholars [8]. It has been found that the incidence of endometrial cancer and hepatobiliary pancreatic cancer is significantly higher in patients with T2DM than in patients without diabetes [7, 9]. The mechanism of malignancy caused by T2DM has not yet been clarified. Experiments have confirmed that insulin resistance, hyperglycemia, and hyperinsulinemia are the main influencing factors in the development of malignancy [10, 11]. CA19-9, also known as sialylLewisA, is a tetrasaccharide that is usually attached to O-glycans on the surface of cells. It has been widely used as a clinical aid in the diagnosis of malignant tumors, and CA199 levels show a high sensitivity for gastrointestinal tumors [12, 13]. It has been found that CA199 levels are significantly elevated when pancreatic exocrine function is impaired, with maximum values up to 683-fold [14, 15]. Serum CA199 levels were measured in 20,655 healthy persons and the average concentration of CA199 levels in healthy people was 6 U/ml, while CA199 levels in patients with T2DM were significantly higher than those in normal people [12, 16]. When CA199 levels are elevated in T2DM patients, it is necessary to exclude the possibility of pancreatic cancer, and the cut-off value is 57.14 U/mL [17, 18].

In this study, serum CA199 was collected from 519 patients with T2DM, and groupings were performed on basis of HbA1C, FBG, and 2hPBG to study the characteristics of elevated serum CA199 levels in T2DM patients and their associated influencing factors. This study found that the serum CA199 levels in the HH and HF groups were higher than those in the LH and SF compliance groups ($P<0.05$). Spearman's correlation analysis also showed that CA199 was positively correlated with HbA1C and FBG. Logistic regression analysis found that HbA1C was the main risk factor for increased CA199 levels, which confirmed the obvious correlation between CA99 and glucose control. A controlled study of patients with diabetic ketoacidosis found that the CA199 level in patients with diabetic ketoacidosis was significantly higher than that in healthy controls, and the CA199 levels of patients increased with the aggravation of the patient's condition, indicat-

Table 5. Multifactor regression analysis of CA199 levels

Variable	β	SE	Wald X^2	t	P	95% CI
Constant	2.445	6.154		0.378	0.514	7.54-22.34
HbA1C	0.864	0.283	0.116	2.363	0.015	1.41-3.78
Serum albumin	-0.184	0.148	-0.031	-1.211	0.221	-1.14-0.81
FBG	0.682	0.189	0.204	3.151	0.000	1.00-1.45

FBG, fasting blood glucose.

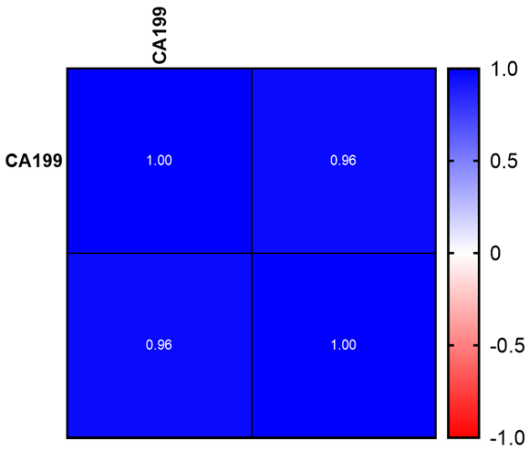

Figure 3. Multifactorial regression analysis. HbA1C was the main risk factor for elevated CA199 level, whereas FBG and serum albumin were negatively correlated with elevated CA199 level.

ing that the increase of CA199 levels in T2DM patients may not be related to malignant tumors but to regulation of blood glucose [19]. Another controlled study on patients with T2DM and patients with malignant tumors and diabetes found that there was no significant difference in the levels of CA199 between the two groups of patients, while the levels of CA199 in patients with malignant tumors alone were significantly lower, which further confirmed the correlation between CA199 and blood glucose [20].

When the serum CA199 level is higher than 6 U/ml in T2DM patients, the glycemic control of the patients should be evaluated, and if the glycemic control does not reach the goal and the CA199 level is higher than 6 U/ml, the CA199 should be re-tested after blood glucose level returns to normal. If the CA199 level is still not lowered and increased to or <57.14 U/ml, then the patients should be examined for tumor [18, 21, 22]. Serum CA199 levels were found to be negatively correlated with pancreatic β-cell function and insulin resistance in patients with T2DM, showing that pancreatic endocrine function is independent of hyperglycemia. The present study found that the CA199 levels in T2DM patients with microvascular complications were higher than those without microvascular complications (P<0.05). The CA199 levels in T2DM patients with microvascular complications such as neuropathy, diabetic nephropathy and retinopathy were significantly higher than those without microvascular complications (P<0.05), indicating that those with elevated CA199 levels need to be further screened for microvascular complications. This index may indicate whether high glucose toxicity has affected diabetic microvasculature.

In summary, HbA1C and FBG were positively correlated with CA199 levels in patients with T2DM, and HbA1C was an independent risk factor for elevated CA199 levels. The innovation of this study is to explore the differences in CA199 levels of patients with different T2DM lesion types by grouping according to different indicators, which provides certain clinical reference for the diagnosis of T2DM patients. At the same time, the risk factors of the changes in CA199 levels of T2DM patients were also analyzed, providing a clinical reference for follow-up clinical research. The limitation of this study is that it analyzed only the differences in CA199 levels of patients with different T2DM and different conditions, but did not conduct in-depth exploration of its mechanism. Targeted molecular biology research should be done in the next step, so as to provide a detailed reference for the treatment of patients with T2DM.

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Disclosure of conflict of interest

None.

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