The serum levels of tumor marker CA19-9, CEA, CA72-4, and NSE in type 2 diabetes without malignancy and the relations to the metabolic control

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ABSTRACT

Objectives: To investigate whether there is a difference in carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), carbohydrate antigen 72-4 (CA72-4), and neuron-specific enolase (NSE) between diabetic and non-diabetic patients.

Methods: A retrospective analysis was performed in 268 type 2 diabetic patients and 95 non-diabetic ones, and their serum levels of CA19-9, CEA, CA72-4, and NSE were compared in our endocrine ward at the Tianjin Fourth Central Hospital, Tianjin, China during the period from January to June 2015. The diabetic patients were divided into 4 groups based on glycosylated hemoglobin (HbA1c) levels to investigate the relationship between levels of tumor markers and glucose status.

Results: Diabetic patients had higher levels of tumor markers than non-diabetic subjects (CA19-9: 13.0 versus 7.25U/mL, p=0.000; CEA: 2.55 versus 2.25 ng/mL, p=0.012; CA72-4: 1.95 versus 1.50U/mL, p=0.001; NSE: 11.64 versus 10.22ng/mL, p=0.000). CA19-9 levels increased in a stepwise manner with poor diabetes status. CEA levels were increased in patients with HbA1c ≥9% and CA72-4 elevation was predominant in patients with poor glycemic control (HbA1c ≥11%). NSE levels were not associated with metabolic parameters.

Conclusion: Serum levels of CA19-9, CEA, CA72-4, and NSE were elevated in type 2 diabetes; however, only CA19-9, CEA, and CA72-4 levels were associated with hyperglycemia.

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Tumor markers are widely used as a screening tool for malignancy. However, clinically it has been observed that diabetic patients without malignant disease have elevated levels of tumor markers, especially for carbohydrate antigen 19-9 (CA19-9), carcinoembryonic antigen (CEA), carbohydrate antigen 72-4 (CA72-4), and neuron-specific enolase (NSE). Therefore, it has been inferred that elevated levels of CA19-9, CEA, CA72-4, and NSE are associated with non-malignant conditions. Serum levels of tumor markers are elevated in acute and chronic inflammation and in other inflammatory conditions.[1] Type 2 diabetes has been recognized as an inflammatory disease, and numerous studies have shown that diabetic patients have elevated serum levels of CA19-9, which is associated with metabolic control, pancreatic β-cell function, and insulin resistance.[2-4] Moreover, compared with non-diabetic controls, serum levels of CEA and NSE are elevated in type 2 diabetic subjects.[5,7] However, few studies have reported differences in serum levels of CA72-4 between diabetic and non-diabetic patients. Hence, we conducted this retrospective analysis to investigate whether there is a difference in CA19-9, CEA, CA72-4, and NSE levels between diabetic and non-diabetic patients without malignancy. Furthermore, we explored the metabolic factors associated with these 4 tumor markers in diabetic patients.

Methods. A total of 313 diabetic patients were hospitalized in our endocrine ward at the Tianjin Fourth Central Hospital, Tianjin, China during the period from January to June 2015. The patients who were measured tumor marker levels and had no any coexistent diseases related to high tumor marker levels were included. Exclusion criteria were as follows: malignant disease, acute stroke, hepatic and nephritic function failure, acute infection, history of abundant alcohol intake, thyroid diseases and digestive system diseases. Eventually, 268 type 2 diabetic patients (38-82 years) were enrolled. The 95 non-diabetic inpatients without malignancy who were measured the tumor marker levels for other reasons were as the control group. A retrospective analysis of the medical records of all subjects was performed. Approval from our local ethics committee was obtained. We analyzed

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such variables as CA19-9, CEA, CA72-4, and NSE levels, fasting plasma glucose (FPG), 2 hours plasma glucose (2 hPG), Hemoglobin A1c (HbA1c), serum lipid, C-reactive protein, fasting C-peptide (FC-p), and other diverse clinical characteristics. Body mass index (BMI, weight [kg] ÷ square of height [m^2]) was calculated. The smoking index included the number of cigarettes smoked per day and the years smoked. Serum levels of CA19-9, CEA, CA72-4, and NSE were measured using chemiluminescence assays (Roche Diagnostics GmbH, Sandhofer Strasse 116, D-68305 Mannhei). Normal ranges were 0-39 U/mL for CA19-9, 0-10 ng/mL for CEA, 0-6.9 U/mL for CA72-4, and 0-15.2 ng/mL for NSE. Serum triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and lowdensity lipoprotein cholesterol (LDL-C) were measured by enzymatic procedures using an autoanalyzer (Hitachi 7600-020, automatic analyzer, Japan). C-reactive protein was measured by immunoturbidimetry (Beckman Coulter. Inc, USA). Serum levels of fasting C-peptide were measured by radioimmunoassay (Northern Biotechnology Research Institute, China). To evaluate the degree of insulin resistance and β-cell function in diabetic patients, the modified homeostasis model assessment index (HOMA) was used. Because many diabetic patients were treated with exogenous insulin, the index was calculated using the following equations: HOMA-IR = 1.5 + (fasting plasma glucose [FPG, mmol/L] × FC-p [pmol/L] ÷ 2800) and HOMA-B% = 0.27 × FC-p [pmol/L] ÷ (FPG [mmol/L] – 3.5).

Statistical analysis. The data was collected from the electronic medical record system. All analyses were performed using the Statistical Package for Social Sciences software version 11 (SPSS Inc., Chicago, IL, USA). Variables are described as mean ± standard deviation or as the median and the interquartile range. The Student's t-test was used for normally distributed variables and the Mann-Whitney U test was used for variables with skewed distributions. One-way analysis of variance (ANOVA) was used for multi-group comparisons, and a post-hoc test was used for multiple comparisons of 2 quartiles. Correlation between parameters was determined using Spearman's correlation coefficient. To determine the degree of correlation between tumor markers and parameters, multiple linear regression analysis was performed. All reported *p*-values were 2-tailed and a value of $p<0.05$ was considered statistically significant.

Results. There were no significant differences in

Table 1 - Clinical characteristics and tumor marker levels of type 2 diabetes compared with non-diabetic subjects.

Variables	Controls (non-diabetic) n=95	Type 2 diabetes n=268	*P*-value
Duration of DM (year)	-	5.00 (13.00)	-
Age (year)	61.45 ± 10.86	60.52 ± 9.64	0.436
BMI (kg/m^2)	25.6 ± 3.6	24.6 ± 3.2	0.430
Serum creatinine	61.0 ± 15.9	64.3 ± 19.0	0.263
C-reactive protein	5.13 (3.63)	5.16 (5.21)	0.255
Smoking index	0 (0,1000)	0 (0,2700)	0.422
FPG (mmol/l)	4.98 (0.85)	9.91 (4.98)	0.000
2 hPG (mmol/l)	7.49 (1.27)	18.26 (5.80)	0.000
HbA1c (%)	4.80 (0.95)	9.90 (3.20)	0.000
TC (mmol/l)	4.89 (1.30)	5.02 (1.53)	0.072
TG (mmol/l)	1.52 (0.92)	1.77 (1.40)	0.340
LDL-C (mmol/l)	2.90 (1.00)	3.08 (1.21)	0.040
HDL-C (mmol/l)	1.18 (0.39)	1.05 (0.29)	0.020
CA19-9 (U/ml)	7.25 (7.99)	13.0 (15.9)	0.000
CEA (ng/ml)	2.25 (1.82)	2.55 (2.38)	0.012
CA72-4 (U/ml)	1.50 (1.37)	1.95 (2.50)	0.001
NSE (ng/ml)	10.22 (2.79)	11.64 (5.34)	0.000

Data are presented as mean ± standard deviation or median (interquartile range). Smoking index is expressed as median (minimum, maximum). Diabetic mellitus, BMI - body mass index, FPG - fasting plasma glucose, 2 hPG - 2 hours plasma glucose, HbA1c - glycosylated HemoglobinA1c, TC - total cholesterol, TG - triglyceride, LDL-C - low-density lipoprotein cholesterol, HDL-C - high-density lipoprotein cholesterol, CA19-9 - carbohydrate antigen 19-9, CEA - carcinoembryonic antigen, CA72-4 - carbohydrate antigen 72-4, NSE - neuron-specific enolase

the following variables between the diabetic and non-diabetic patients: age, gender ratio, BMI, creatinine and C-reactive protein levels, smoking index, and TC and TG (**Table 1**). LDL-C levels were higher while HDL-C levels were lower in diabetic patients compared with control subjects (p<0.05). Moreover, the average levels of CA19-9, CEA, CA72-4, and NSE were all significantly higher in patients with type 2 diabetes than in control subjects (CA19-9: 13.0 [15.9] versus 7.25 [7.99] U/mL, p=0.000; CEA: 2.55 [2.38] versus 2.25 [1.82] ng/mL, p=0.012; CA72-4: 1.95 [2.50] versus 1.50 [1.37] U/mL, p=0.001; NSE: 11.64 [5.34] versus 10.22 [2.79] ng/mL, p=0.000).

To determine the relationship between levels of tumor markers and glucose control, the diabetic patients were divided into 4 groups based on HbA1c level, as follows: group 1 (HbA1c <7%), group 2 (7% ≤ HbA1c < 9%), group 3 (9% ≤ HbA1c < 11%), and group 4 (HbA1c ≥11%). The glycemic control characteristics of the participants are listed in **Table 2**. There was a stepwise increase in CA19-9 levels with poor diabetic status, from groups 1 to 4 (group 1: 6.34 [8.13], group 2: 10.37 [12.69], group 3: 12.08 [12.68], and group 4: 18.39 [21.22] U/mL, p=0.000). CA19-9 levels were significantly higher in groups 2, 3, and 4 than in the control group. The CEA levels in groups 3 and 4 were higher than those in the control group, with group 4 having the highest levels. Moreover, group 4 had significantly higher CA72-4 levels than the other groups (p<0.05). The NSE levels of all diabetic groups were higher than those of the control group (p<0.05). Interestingly, we found no significant differences in the NSE levels of groups 2, 3, and 4 (p>0.05).

Correlation and regression analysis in diabetic patients. The CA19-9 was positively correlated with TC, TG, FPG, 2hPG, HbA1c, and HOMA-IR and was negatively correlated with HDL-C and HOMA-B% (**Table 3**). In a multiple linear regression analysis, TG

Table 3 - Correlation analysis between serum carbohydrate antigen 19-9 level and metabolic parameters.

Variable	Correlation coefficient (r)	*P*-value
Age (year)	-0.007	0.889
Duration (year)	-0.102	0.097
TC (mmol/l)	0.140	0.011
TG (mmol/l)	0.178	0.001
LDL-C (mmol/l)	0.074	0.183
HDL-C (mmol/l)	-0.120	0.030
FPG (mmol/l)	0.383	0.000
2hPG (mmol/l)	0.376	0.000
HbA1c (%)	0.434	0.000
HOMA-B% (C-p)	-0.165	0.049
HOMA-IR (C-p)	0.222	0.008

TC - total cholesterol, TG - triglyceride, LDL-C - low-density lipoprotein cholesterol, HDL-C - high-density lipoprotein cholesterol, FPG - fasting plasma glucose, 2 hPG - 2 hours plasma glucose, HbA1c - glycosylated HemoglobinA1c, HOMA-B% - homeostasis model assessment-measure of β-cell activity, HOMA-IR - homeostasis model assessment insulin resistance

Table 2 - Clinical characteristics and tumor marker levels of the diabetic patients of different HbA1c groups.

Variable	Non-diabetic (n=95)	Group1 (HbA1c <7%)(n=25)	Group2 (7≤HbA1c<9%) (n=74)	Group3 (9%≤HbA1c<11%) (n=86)	Group4 (HbA1c ≥11%) (n=83)	*P*-value
Duration (year)	-	5.00 (13.25)	8.00 (13.00)	7.00 (13.00)	2.00 (10.00)	-
Age (year)	61.45±10.86	60.16 ± 7.59	61.35±9.14	59.32±10.26	61.13±10.00	0.61
BMI (kg/m^2)	24.6±3.23	25.20 ± 2.92	27.06±3.87[b]	25.88±3.76[c]	24.16±3.10[c,d]	0.00
FPG (mmol/l)	4.98 (0.85)	6.51 (1.82) [a,c,d]	7.81 (3.02)[a,b,d]	10.97 (4.28) [a,b,c]	12.20 (4.77)[a,b,c,d]	0.00
2hPG (mmol/l)	7.49 (1.27)	13.10 (3.07) [a,c,d]	15.73 (4.42)[a,b,d]	18.59 (4.54) [a,b,c]	21.43 (6.48) [a,b,c,d]	0.00
HbA1c (%)	4.80 (0.95)	6.50 (0.65) [a,c,d]	8.00 (1.10)[a,b,d]	10.10 (1.02)[a,b,c]	12.30 (1.45) [a,b,c,d]	0.00
TC (mmol/l)	4.89 (1.30)	4.73 (1.39)	4.90 (1.17)	5.12 (1.69)	5.01 (1.14)	0.16
TG (mmol/l)	1.52 (0.92)	1.72 (0.89)	2.03 (1.80)	1.66 (1.27)	1.61 (1.09)	0.57
LDL-C (mmol/l)	2.90 (1.00)	2.71 (1.27)	2.96 (1.39)	3.20 (1.21)	3.23 (1.14)	0.18
HDL-C (mmol/l)	1.18 (0.39)	1.16 (0.27)	1.04 (0.30)	1.03 (0.30)	1.03 (0.21)	0.10
CA19-9 (U/ml)	7.25 (7.99)	6.34 (8.13)	10.37 (12.69)[a]	12.08 (12.68) [a,b]	18.39 (21.22) [a,b,c,d]	0.00
CEA (ng/ml)	2.25 (1.82)	1.57 (2.21)	2.23 (2.45)	2.23 (2.05)[a,b]	3.26 (2.91) [a,b,c,d]	0.00
CA72-4 (U/ml)	1.50 (1.37)	1.44 (2.33)	1.81 (1.80)	2.19 (2.70)	2.06 (3.28) [a,c,d]	0.01
NSE (ng/ml)	10.22 (2.79)	14.20 (9.89)[a]	11.61 (4.28) [a,b]	11.53 (5.38) [a,b]	11.66 (5.39) [a,b]	0.00

Data are presented as median (interquartile range) or mean ± standard deviation,[a] p<0.05 versus Non-diabetic group, [b] p<0.05 versus group1,[c] p<0.05 versus group2, [d] p<0.05 versus group 3. BMI - body mass index, FPG - fasting plasma glucose, 2 hPG - 2 hours plasma glucose, HbA1c - glycosylated HemoglobinA1c, TC - total cholesterol, TG - triglyceride, LDL-C - low-density lipoprotein cholesterol, HDL-C - high-density lipoprotein cholesterol, CA19-9 - carbohydrate antigen 19-9, CEA - carcinoembryonic antigen, CA72-4 - carbohydrate antigen 72-4, NSE - neuron-specific enolase

and HbA1c were significantly associated with CA19-9 levels (TG: β=2.679, 95% CI: 1.300-4.058, *p*=0.000, and HbA1c: β=2.000, 95% CI: 0.501-3.499, *p*=0.009). Moreover, CEA was positively correlated with FPG (r=0.236, *p*=0.000), 2hPG (r=0.241, *p*=0.000), HbA1c (r=0.312, *p*=0.000), and the smoking index (r=0.196, P=0.001), and was negatively correlated with HOMA-B% (r=-0.167, *p*=0.045). The smoking index and HbA1c levels significantly affected CEA levels (β=0.001, 95% CI: 0.001-0.002, *p*=0.001, and β=0.262, 95% CI: 0.111-0.412, *p*=0.001). The CA72-4 was positively correlated with FPG (r=0.194, *p*=0.000), 2hPG (r=0.133, *p*=0.015), and HbA1c (r=0.174, *p*=0.002). However, NSE was not significantly correlated with any variables.

Discussion. There were differences in the levels of tumor markers between diabetic and non-diabetic subjects. The CA19-9, CEA, and CA72-4 levels were principally influenced by the state of glycemic control, whereas NSE levels were not.

Consistent with previous studies, subjects with type 2 diabetes had higher CA19-9 levels compared with non-diabetic subjects, and CA 19-9 levels were associated with HbA1c levels. However, other variables including age, the duration of diabetes, and LDL-C were not correlated with CA19-9 levels. Previous reports have shown that patients with poor metabolic control (ketoacidosis and hyperglycemic coma) have increased CA19-9 levels; however, these were reversible and subsequently decreased after successful metabolic control.[9,10] In our study, the highest CA19-9 level was 108.05 U/mL; this patient was female with new-onset diabetes (FPG 9.31 mmol/L, 2hPG 18.03 mmol/L, and HbA1c 12.9%), and abdominal computed tomography revealed faint hypodensity at the pancreatic head (not shown). Chen et al[10] previously reported a case with reversible high blood CEA and CA19-9 levels in a diabetic and hyperglycemic patient, and similar to our case, this patient also had faint hypodensity at the pancreatic head.

The mechanisms underlying CA19-9 elevation in patients with type 2 diabetes remain unclear. The CA19-9 is expressed by the exocrine pancreas, and it has been used as a sensitive marker to screen for pancreatic exocrine damage. Pancreatic islet histology in type 2 diabetic patients is associated with an inflammatory process involving the exocrine pancreas.[11] Moreover, mildly elevated blood lipase and amylase levels are associated with faint hypodensity at the pancreatic head in hyperglycemic patients, resulting in a subclinical and mild form of insulitis. This insulitis results from the activation of the innate immune system by metabolic stress and is mediated by interleukin (IL)-1 signaling. Moderately elevated glucose concentrations (11 mmol/L) are sufficient to induce transcriptional activationof IL-1 expression in pancreatic islets.[12] Similarly, previous research has shown that free fatty acids also promote aninflammatory response.[13] Thus, islet inflammation induced by hyperglycemia or hyperlipidemia may be responsible for the elevation of CA19-9 levels.

We found a significant association between CEA and CA72-4 levels and hyperglycemia. The CEA levels were associated with moderate hyperglycemia (HbA1c ≥9%), while CA72-4 elevation was predominant in patients with HbA1c levels ≥11%. The patient with the highest CA72-4 level (189.9 U/mL) was a female with new-onset diabetes and severe hyperglycemia (FPG 15.20 mmol/L, 2hPG 22.70 mmol/L, and HbA1c 12.90%), which was similar to the case with the highest CA19-9 value in the present study. The CEA and CA72-4 are highly glycosylated cell surface glycoproteins that are expressed on the surface of inflammatory cell serving as adhesion molecules.[2] Some studies have demonstrated that CEA levels are elevated in inflammatory-related conditions, such as metabolic syndrome.[14] Moreover, a previous study reported an association between CEA levels and oxidative stress markers.[6] Hyperglycemia can influence free radical formation, which may eventually lead to increased oxidative stress. Severe oxidative stress along with poor glycemic control may induce increased CEA expression. However, the correlation between CA72-4 elevation and local insulitis remains unknown and warrants future investigation.

Neuron-specific enolase is a soluble protein enolase enzyme of the glycolytic pathway that promotes the conversion of 2-phosphoglycerate into phosphoenolpyruvate. It is found predominantly in neurons and neuroendocrine cells and is a reliable marker of neuronal tissue damage.[15] We found that NSE levels were significantly higher in type 2 diabetic patients than in non-diabetic subjects, which is in accordance with a previous study.[7] Unexpectedly, 19.4% of diabetic patients had abnormal NSE levels, and most were not the same patients as those with abnormal CA19-9, CEA, and CA72-4 levels. Moreover, NSE levels were not associated with FPG, 2hPG, HbA1c, or other metabolic parameters. Thus, it could be presumed that the mechanism underlying NSE elevation is different than that underlying CA19-9, CEA, and CA72-4 elevation. In a previous study, elevated NSE levels were closely associated with peripheral neuropathy in diabetic patients.[7] In contrast to the central nervous

system, which is protected by the blood-brain barrier, the peripheral nervous system is more vulnerable and readily exposed to toxins. Chronic exposure to hyperglycemia or related ischemia/hypoxia can lead to peripheral neuropathy, which is characterized by neurodegeneration and neuroregeration. During this process, the synthesis of NSE may increase. However, future research is necessary to elucidate these effects.

This study had limitations. First, it was retrospective in nature, and included only a small number of patients from a single center. Moreover, no follow-up data were obtained after anti-diabetic treatment in the hyperglycemic patients. Next, diabetic neuropathy status was not assessed; thus, the mechanism underlying elevated NSE levels was not determined. Future studies are required to determine the effects of inflammation, oxidative stress, and diabetic complications on the elevation of tumor markers in serum.

In conclusion, we demonstrated that serum levels of CA19-9, CEA, CA72-4, and NSE were elevated in diabetic patients without malignancy. The CA19-9, CEA, and CA72-4 levels were affected by glycemic control and HbA1c status; therefore, they should be measured after successful metabolic control. In contrast, elevated NSE levels were not associated with glycemic control. Overall, the levels of these 4 tumor markers should be interpreted carefully in diabetic patients.

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