Correlation between carbohydrate antigen 199 and glycemic control in patients with type 2 diabetes mellitus

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To the Editor: Type 2 diabetes mellitus (T2DM) is a common complex metabolic disorder. Previous studies have reported that T2DM patients posed a risk for pancreatic carcinogenesis.[1] Carbohydrate antigen 199 (CA 199) is the biological link among the diseases, and patients with chronic pancreatitis possibly have higher levels of CA 199 than healthy individuals, and chronic pancreatitis has been confirmed to be a risk factor of diabetes mellitus.[2] Thus it is also a symbol for pancreatic tissue damaged that possibly caused by diabetes. So far several mechanisms for the relationship have been proposed, such as increscent inflammation, abnormal metabolic state, insulin resistance, endoplasmic reticulum stress, misadjustment of autophagy, and so on.[1] Haemoglobin A1c (HbA1c) is the most important laboratory parameter indicating glycemic control in T2DM patients. The general target of HbA1c is $\leq 7\%$ for good glycemic control, while HbA1c values over 7% show poor glycemic control.[3]

Researchers have found that serum CA 199 is associated with an obviously increased risk of diabetes among the Chinese population, whether the serum levels of CA 199 involving with glycemic control of T2DM remains unknown. Therefore, in our study, we aimed to explore the association between CA 199 and HbA1c in T2DM patients.

We retrospectively analyzed the data that included 527 T2DM patients (241 females and 286 males) and 208 nondiabetic healthy controls (96 females and 112 males) visiting the Tianjin First Center Hospital. Patients were recruited between 2015 and 2016. The study protocols conform to the guidelines of the Tianjin First Center Hospital Ethics Committee. We excluded patients if they had a history of tumor, heart failure, thyroid disease, acute or chronic infection, pregnancy, chronic liver disease, dialysis, blood disease, or anemia. Patients with immune-related diseases such as systemic lupus erythematosus, rheumatoid arthritis, and those receiving anticoagulants were also excluded.

The blood samples of patients and healthy controls were collected at admission. White blood cell (WBC), neutrophil, lymphocytes, platelets, hemoglobin, platelet distribution width (PDW), and red blood cell distribution width (RDW) count were measured on a Cell-Dyne counter (Bio-Clinical System, Abbott, Chicago, Illinois, USA). CA 199 and HbA1c levels were determined using commercial ELISA kits (Merck, Darmstadt, Hesse, Germany). Total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and creatinine in serum were measured using an Abbott Aeroset auto-analyzer with original kits. All analyses were carried out with SPSS 16.0 (International Business Machine, Armonk, New York, USA). Results are expressed as mean ± standard deviation unless otherwise stated. Comparisons of parametric data of the two groups were conducted using independent samples *t* test. Comparisons of non-parametric data between two groups were performed by Mann-Whitney *U* test. Categorical variables were compared by the Chi-square test. Logistic regression analysis was used to evaluate the predictors of HbA1c. Those variables with $P < 0.1$ by univariate analysis were included in the multivariate logistic regression analysis model and the respective odds ratios (OR) with 95% confidence intervals (CI) were calculated. The capacity of the CA 199 value in predicting HbA1c levels was analyzed using receiver operating characteristics (ROC) curve analyses. The statistically significant difference was set at the P value < 0.05.

Patients and healthy control characteristics are shown in Supplementary Table 1, http://links.lww.com/CM9/A23. RDW was significantly higher in T2DM patients compared to healthy controls ($P < 0.001$), and simultaneously, PDW and TC were both higher in T2DM patients than healthy controls ($P = 0.046$ and $P = 0.035$, respectively). There were no significant differences were observed

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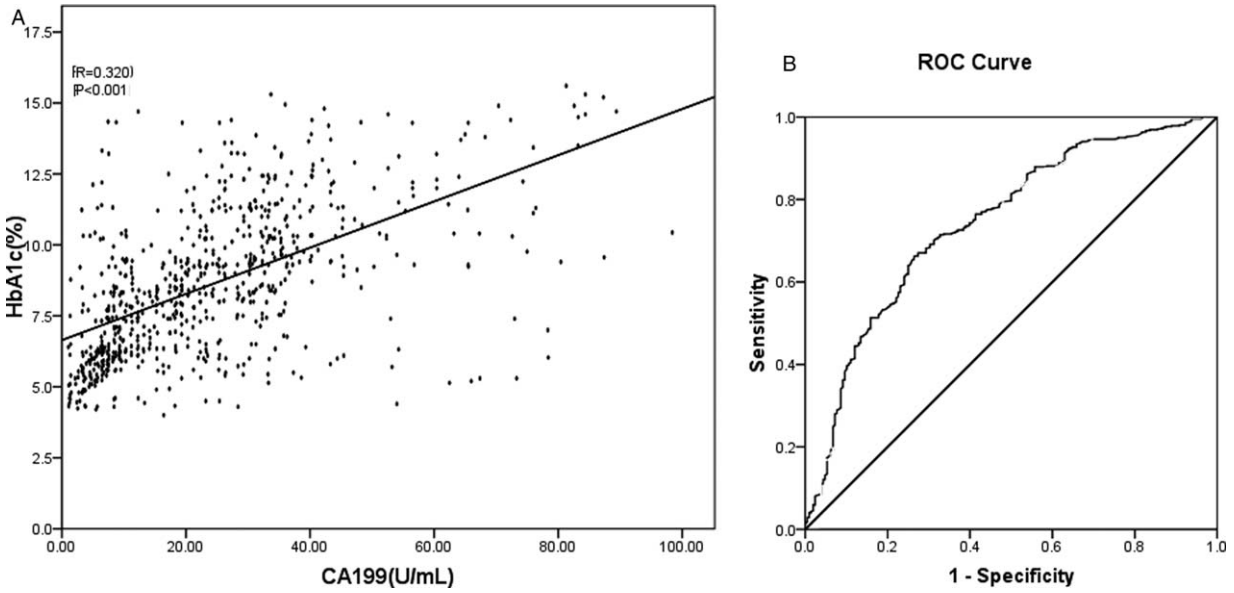

Figure 1: Correlation graph of CA 199 with HbA1c in T2DM patients. Regression analysis showed the CA 199 was positively correlated with HbA1c level ($r=0.320$, $P<0.001$; $n=527$; A). Receiver operating characteristic curve of CA 199 for HbA1c levels. Area under the curve value was 0.744 (95% CI: 0.572–0.736, $P<0.001$; B). CA 199: carbohydrate antigen 199; CI: confidence interval; HbA1c: haemoglobin A1c; ROC: receiver operating characteristics; T2DM: type 2 diabetes mellitus.

between both groups regarding the neutrophil, lymphocytes, platelets, hemoglobin, or WBC count. The data showed higher RDW ($P=0.038$), lymphocyte ($P<0.001$), PDW ($P=0.039$), and TC ($P=0.021$) in HbA1c > 7% group than HbA1c ≤ 7% group, whereas, no other significant differences were noted [Supplementary Table 2, http://links.lww.com/CM9/A23].

The mean CA 199 level was higher in the diabetes group (43.64 ± 18.54 U/mL) than that in the control group (13.74 ± 11.92 U/mL, $P<0.001$). Compared to the control group, patients with HbA1c ≤ 7% group (34.45 ± 21.12 U/mL) also showed higher CA 199 level ($P=0.015$). Regression analysis showed that the CA 199 was positively correlated with HbA1c level ($r=0.320$, $P<0.001$) [Figure 1A]. Significant univariate predictors of HbA1c level were lymphocyte, CA 199, RDW, PDW, and TC. Using multivariate logistic regression analysis, we found that CA 199 (OR = 2.146, 95% CI 1.143–7.613, $P<0.001$), RDW (OR = 1.152, 95% CI 0.651–3.256, $P=0.037$), and TC (OR = 1.026, 95% CI 0.893–1.098, $P=0.044$) were independent predictors of HbA1c level. The results of multivariate logistic regression analysis are presented in Supplementary Table 3, http://links.lww.com/CM9/A23. We also analyzed the diagnostic properties of CA 199 using ROC curves [Figure 1B]. Area under the curves (AUC) values from the ROC curve analysis for CA 199 was 0.744 (95% CI: 0.572–0.736, $P<0.001$).

Our results showed that average CA 199 levels were significantly higher in the T2DM group than the healthy control group. And there was a significant association between serum CA 199 levels and HbA1c level in T2DM patients.

It has been elucidated that diabetes is a chronic inflammatory disease of the pancreas, and it happens due to the destruction of islet beta cells leading to reduce insulin secretion or insulin resistance.[4] The inflammation of pancreas is a progressive phenomenon in diabetes mellitus. Patients with chronic pancreatitis often lead to endocrine pancreatic dysfunction, and about 50% of patients with pancreatitis blood glucose were elevated. Meanwhile, they were found to have greater serum levels of CA 199 than healthy people.[5] This is perhaps one of the important reasons why serum levels of CA 199 elevated in patients with diabetes.

Hyperglycemia has multiple effects on the red blood cells and blood platelet, comprising of decreased deformability and life span. Nada[6] investigated the association between RDW and HbA1c level in diabetes patients. Their study suggested that in patients with HbA1c > 7% group, there was significantly higher RDW than good glucose controlled diabetic patients. Consistent with their study, our results showed that higher RDW in HbA1c > 7% group than HbA1c ≤ 7% group. PDW gives an indication of the distribution of platelet size. Jindal *et al*[7] found that PDW was significantly increased in patients with diabetes, and it was higher in patients who developed microvascular complications. Consistent with their study, we found that PDW values were significantly higher in T2DM patients compared with control individuals. PDW values of diabetic patient groups increased according to glycemic control levels. RDW and PDW have been investigated for many diseases, while there are few studies that have been conducted on RDW, PDW, and glycemic control.

Benhamou *et al*[8] have investigated the relationship between CA 199 and diabetes mellitus in 51 adult patients, and they concluded that the levels of CA 199 increased in acute metabolic situations, which significantly correlated with blood glucose concentration in diabetic patients. While Banfi *et al*[9] have reported that there was no correlation between CA 199 and glycemia in diabetes. However, there is greater randomness and variability of

blood glucose concentration compared with serum HbA1c, which to reflect the total three months glycemic control levels, so the CA 199 and HbAlc relatively strong correlation than blood glucose. In our study, we found that CA 199 levels were higher in the T2DM group than the healthy control group. Regression analysis showed the CA 199 was positively correlated with HbA1c level.

Based on the results obtained from our study, we found that CA 199 plays a role in glycemic control in T2DM patients. RDW and PDW were obviously associated with glycemic control. Finally, due to our study was the retrospective study, further investigations are also required to highlight the relationship between CA 199 and glycemic control.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Conflicts of interest

None.

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