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Serum ErbB2 concentration positively correlated to the glycemic variations in newly diagnosed Type 2 diabetic patients

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Evidences indicate that elevated levels of circulating ErbB2 are closely associated with increased incidence of diabetes. However, the relationship between ErbB2 concentration and glycemic variations (GV) in type 2 diabetic (T2D) patients remains elucidated. The aim of this study was to assess whether there is an association between serum ErbB2 concentration and GV in newly diagnosed T2D patients. This was a three-center, and observational study. Between April 2019 and July 2019, a total of 106 newly diagnosed T2D patients were recruited. All recruited subjects were admitted as inpatients and received anti-diabetes agents free during the study period. At baseline, fasting serum was collected for ErbB2 measurement and all recruited patients were subjected a prospective CGM for at least 3 days. The primary endpoint was the relationships between ErbB2 concentrations and GV in T2D patients. Data of a total of 95 subjects who met the inclusion criteria were analyzed at the endpoint. Subjects were divided into quartiles according to their serum ErbB2 concentrations. We observed that subjects with an elevated level of ErbB2 had a higher value of GV in terms of mean amplitude of glucose excursion (MAGE), standard deviation of mean glucose (SDMG), and the coefficient of variation (CV%) than those with lower levels (all $P < 0.05$). Multiple linear regression analyzes after adjusting for confounder factors indicate that serum ErbB2 levels were significantly positively correlated with the MAGE ($\beta = 0.664$, $t = 7.218$, $P < 0.01$), SD ($\beta = 0.469$, $t = 5.125$, $P < 0.01$) and CV% ($\beta = 0.337$, $t = 4.442$, $P < 0.01$), respectively. Our data indicated that diabetic patients with higher ErbB2 concentrations may have large GV, which is an independent risk factor for microvascular and macrovascular complications.

The ErbB2/HER2 oncoprotein, a member of the receptor of tyrosine kinases, is a transmembrane protein, that consists of the internal tyrosine residues, the transmembrane portion, and the external extracellular domain (ECD)[1,2]. Homo- or heterodimerization leads to ErbB2 activation, which initiates a multiple of downstream signaling pathways that regulate cell proliferation, apoptosis, and differentiation[3]. Various studies have shown that serum ErbB2/HER2 concentration elevation is a specific marker for a variety of cancers, such as breast cancers[4,5], ovarian, bladder, salivary gland, endometrial, pancreatic, and non-small-cell lung cancer[6]. Studies have also indicated that tumor patients with ErbB2 amplification or overexpression have an enhanced risk of poorer prognoses[7].

Epidemiological studies have shown that diabetic patients have a potentially increased risk of increase in incidence of cancers[8], and pre-diagnosed diabetic patients with tumors had an increased in all-cause and cancer-related mortality compared with individuals with normal glucose metabolism individuals[9,10]. The underlying biological mechanisms between the two heterogeneous, chronic and progressive diseases may be a partial reason for the two conditions to share the same metabolic risk factors, such as aging, obesity, and diet[8]. The links between diabetes and cancer are further strengthened by activation of the insulin receptor, insulin-like growth

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factor receptor (IGFR)[11] and ErbB2[12]. Studies have demonstrated that ErbB2 plays a role in controlling lipid metabolism[13] and is involved in impaired glucose metabolism[14]. This Fuels the idea that ErbB2 may be a bridge between diabetes and cancers, in that anti-diabetic agents may be a somewhat beneficial therapy for patients with cancer[15]. This hypothesis was confirmed by an in vitro study that found glucose-lowering agent metformin has an anti-cancer effect by mTOR/p70S6K1-sensed reactive oxygen species downregulating HER2 expression[12].

Recently, a population-based cohort study confirmed that elevated levels of ErbB2 are associated with an increased incidence of diabetes[16]. Continued efforts have been made to suppress rapid glycemic variations in patients with type 2 diabetes (T2D)[17]. Large glucose fluctuations in patients with diabetes may have implications for the risk of long-term diabetic complications[18,19]. The underlying mechanisms might be acute glucose fluctuations, more specifically, the triggering of oxidative stress by acutely increased postprandial blood glucose levels[20]. However, the effects of serum ErbB2 concentrations on the glycemic variation in patients with T2D have not yet been elucidated.

Therefore, we performed a three-center, observational study using continuous glucose monitoring (CGM) to assess the relationship between ErbB2 concentrations and glucose variations in patients with T2D.

Methods

This was a three-center, observational study. Between April 2019 and July 2019, 106 newly diagnosed patients with T2D were recruited from the following institutions in China: Department of Endocrinology, Yancheng No. 1 People's Hospital, The Fourth Affiliated Hospital of Nantong University, Department of Endocrinology, Nanjing Pukou Central Hospital, Pukou Branch Hospital of Jiangsu Provence Hospital, and Zhimaying Community Health Service Center, Qinhuai District, Nanjing. The inclusion criteria were the following patients: (1) newly diagnosed patients with T2D random blood glucose less than 22.2 mmol/L; (2) $HbA_{1c} < 12.0\%$; (3) aged between 18 and 80 years; and (4) body mass index (BMI) 21 to 35 kg/m^2. The exclusion criteria were the following patients: (1) admission blood glucose higher than 22.2 mmol/L; (2) with chronic kidney or liver disease, and/or (3) diagnosed with maturity-onset diabetes in the young[21,22]. The study was approved by the ethics committee of Yancheng No. 1 People's Hospital, The Fourth Affiliated Hospital of Nantong University, China. Written informed consent was obtained from all the patients. The methods, including all relevant details, were conducted in accordance with the Declaration of Helsinki guidelines.

All recruited patients were admitted as inpatients and were not treated with anti-diabetic agents during the study period. Oral glucose tolerance tests were performed at 8 a.m. the day after admission using 75 g glucose diluted in 100 mL water, and serum samples for the measurement of HbA_{1c}, glucose, insulin, and C-peptide levels were obtained at 0, 30, and 120 min after glucose loading. Insulin concentration was measured using an insulin radioimmunoassay kit (Beijing Technology Company, Beijing, China). HbA_{1c} values were measured using a DiaSTAT HbA_{1c} analyzer (Bio-Rad, Hercules, CA, USA). C-peptide and glucose concentrations were measured centrally at the central laboratory of Yancheng No. 1 People's Hospital. Fasting ErbB2 concentrations were measured using a commercially available quantitative enzyme-linked immunosorbent assay kit (Oncogene Science, Inc., Uniondale, NY, USA; Bayer AG, Leverkusen, Germany) according to the manufacturer's instructions.

After collection of the baseline data, prospective CGM (Sof-sensor, CGMS-Gold, Medtronic plc, LA, CA, USA) was performed for 3 d, as described previously[23,24]. Briefly, the subcutaneous glucose sensor was embedded in the abdomen on day 1 at approximately 4 p.m. and was removed on day 4 at 4 p.m. During the CGM period, at least four finger-stick readings were entered for calibration every day. After the sensors were removed, CGM data were recorded by the investigators, as described previously[23–25]. The patients were instructed to maintain moderate activity while having breakfast, lunch, and dinner at 7 a.m., 11 a.m. and 5 p.m., respectively. Their meals consisted of carbohydrate, proteins, and fats in 55%, 17%, and 28% ratios, respectively.

The readings delivered from the CGM were recorded by the researchers. The 24-h mean glucose concentration (MG), the standard deviation of MG (SDMG), the coefficient of variation (CV%), the incremental area under the curve (AUC) of glucose concentrations above 10.0 mmol/L or the incremental area over the curve (AOC) less than 3.9 mmol/L, and the time in range (TIR) of glucose levels ranged from 3.9 to 10.0 mmol/L, and the hourly MGs were calculated by researchers. The mean amplitude of glucose excursion (MAGE) was calculated manually, as previously described[23,24]. In addition, β-cell function and insulin sensitivity were assessed using the homoeostasis model assessment B (HOMA-B), HOMA-insulin resistance (IR)[21,26] and the Matsuda index[27,28].

The primary endpoint was the relationship between ErbB2 concentrations and glucose variations in patients with T2D. The differences in 24-h MG, SDMG, incremental AUC (glucose > 10.0 mmol/L), incremental AOC (glucose < 3.9 mmol/L), TIR, hourly MG, β-cell function, and insulin sensitivity in patients with different ErbB2 concentrations were also analyzed.

Statistical analysis. The normal distribution data were presented as mean ± SD. Statistical analysis was performed using the SPSS software (version 17.0; IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to verify data distribution. A test was performed to compare the ratio differences between the two groups. All of the repeated data were analyzed via a two-way analysis of variance between groups, followed by the Bonferroni–Dunn post hoc test. P-values were two-tailed, with a significance level of 5%. Multiple linear regression analyses were performed to assess the correlation between ErbB2 and MAGE.

Ethics approval and consent to participate. The study was approved by the ethics committee of Yancheng No. 1 People's Hospital, The Fourth Affiliated Hospital of Nantong University, China. All patients gave written informed consent. The methods were conducted in accordance with the Declaration of Helsinki guidelines, including any relevant details.

Items	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
Number	23	24	24	24	–
Male	11	15	16	11	0.66
Age	54.6 ± 10.8	52.1 ± 12.5	56.7 ± 8.9	53.2 ± 12.0	0.78
BMI	23.3 ± 5.6	24.1 ± 6.0	25.0 ± 8.4	23.9 ± 7.2	0.81
HbA1c	9.0 ± 2.0	9.5 ± 4.6	8.8 ± 1.7	9.3 ± 2.5	0.82
Waistline	78.1 ± 28.4	74.6 ± 20.1	82.3 ± 19.6	75.8 ± 23.0	0.79
Waist-to-hip	0.8 ± 0.4	0.8 ± 0.2	0.8 ± 0.3	0.8 ± 0.2	0.92
Triglycerides	1.2 ± 1.3	1.4 ± 1.0	1.4 ± 1.5	1.8 ± 1.3	0.04*
Cholesterol	4.6 ± 1.5	5.4 ± 1.2	5.3 ± 1.8	5.8 ± 1.1	0.03*

Table 1. Baseline characteristics of subjects across 4 quartiles of ErbB2 concentrations. Data were presented as means ± SD. *Age* (years); *BMI* body mass index (kg/m^2), *HbA1c* glycated hemoglobin (%), Waistline (cm), *Waist-to-hip* waist-to-hip ratio (%), Triglyceride (mmol/L), Cholesterol (mmol/L). *P < 0.05 (both Quartile 1 vs. Quartile 4).

Items	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
Number	23	24	24	24	–
24-h MG	8.7 ± 1.9	8.6 ± 3.2	8.3 ± 1.2	8.2 ± 2.1	0.18
SDMG	1.6 ± 1.1	1.9 ± 1.8	2.2 ± 1.0	2.6 ± 1.3	0.03
MAGE	5.4 ± 2.1	5.7 ± 1.2	6.4 ± 1.0	7.1 ± 2.6	0.01
CV%	18.4 ± 12.3	22.7 ± 20.5	26.7 ± 21.6	31.7 ± 21.6	0.02
TIR	72.1 ± 28.0	64.3 ± 21.1	42.9 ± 31.4	35.6 ± 23.2	0.00
AUC > 10.0	0.3 ± 0.4	0.5 ± 0.2	0.6 ± 0.3	0.8 ± 0.2	0.00
AUC < 3.9	0.3 ± 0.0	0.2 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.23

Table 2. Glycemic profiles in recruited subjects across 4 quartiles of ErbB2 concentrations. Data were presented as means ± SD, *P < 0.05. *24-h MG* 24-h mean glucose concentrations (mmol/L), *SDMG* 24-h standard deviation of mean glucose concentrations (mmol/L), *MAGE* 24-h mean amplitude of glycemic excursions (mmol/L), *CV%* the coefficient of variation (%), *TIR* time in range from > 3.9 mmol/L to < 10.0 mmol/L (%), *AUC* > 10.0 *mmol/L* the incremental AUC of glucose level above 10.0 mmol/L (mmol/L*Day), *AUC* < *3.9 mmol/L* the incremental AUC of glucose less than 3.9 mmol/L (mmol/L*Day).

Consent for publication. Written informed consent for publication was obtained from all participants.

Results

Baseline characteristics. A total of 106 patients newly diagnosed with T2D between April 2019 and July 2019 were screened for eligibility at the following institutions in China: Department of Endocrinology, Yancheng No. 1 People's Hospital, The Fourth Affiliated Hospital of Nantong University; Department of Endocrinology, Nanjing Pukou Central Hospital, Pukou Branch Hospital of Jiangsu Provence Hospital; and Zhimaying Community Health Service Center, Qinhuai District, Nanjing. Eleven patients were excluded from the analysis, five due to having capillary glucose concentrations above 22.2 mmol/L and six due to having readings of CGM missing for at least 10%. The remaining 95 patients who met the inclusion criteria (53 men and 42 women, aged 55.1 ± 7.6 years, BMI 24.7 ± 3.6 kg/m^2, and HbA1c values 9.2 ± 1.8%) were analyzed at the endpoint. We observed that patients with newly diagnosed T2D had ErbB2 concentrations ranging from 13.2 ± 3.8 to 6.3 ± 2.2 ng/ml.

Glycemic variations in subjects with different ErbB2 concentrations. We analyzed data from day 1 to day 3 of CGM at the endpoint because CGM has an infiltration phage at the beginning of the monitoring period and a sensor expires phage at the end of the monitoring period, which might not be reliable according to the manufacturer's instructions. The included patients were subjected to CGM at 1600–1500, yielding 751 ± 76 glucose readings per patient.

To observe whether patients with various ErbB2 concentrations had the same glycemic variations, the patients were assigned into quartiles according to their serum ErbB2 concentrations. Demographic data were comparable across the four groups, as shown in Table 1. The differences in glycemic variation are presented in Table 2. We observed that patients with an elevated level of ErbB2 generally had a higher value of GV in terms of MAGE, SD, and CV% (all P < 0.05) than did those with lower levels (Table 2).

In the present study, our CGM data showed that the 24-h SDMG, MAGE, CV%, and the incremental AUC of glucose above 10 mmol/L were progressively and significantly amplified alongside ErbB2 levels in patients newly diagnosed with T2D. As expected, patients in the higher quartiles of ErbB2 levels were significantly fewer in the TIR group than in the lower quartiles (Table 2).

Items	Quartile 1	Quartile 2	Quartile 3	Quartile 4	P value
Number	23	24	24	24	–
C-peptide 0	2.8 ± 0.1	2.7 ± 1.3	2.2 ± 0.3	2.2 ± 1.1	0.23
C-peptide 30	3.8 ± 1.7	3.2 ± 0.5	2.9 ± 3.2	2.8 ± 2.7	0.42
C-peptide 120	5.2 ± 2.3	5.4 ± 0.8	5.4 ± 1.1	5.1 ± 2.7	0.36
HOMA-B	19.1 ± 15.4	20.3 ± 21.0	21.7 ± 17.2	18.9 ± 16.6	0.66
HOMA-IR	2.1 ± 2.3	2.6 ± 1.1	3.4 ± 1.0	3.8 ± 1.1	0.04*
Mastuda Index	116.8 ± 81.5	107.1 ± 22.7	96.3 ± 12.8	85.0 ± 33.9	0.03*

Table 3. The β-cell function and insulin sensitivity in recruited subjects across 4 quartiles of ErbB2 concentrations. Data were presented as means ± SD, *P < 0.05. *C-peptide 0* C-peptide 0 min (ng/mL), *C-peptide 30* C-peptide 30 min (ng/mL), *C-peptide 120* C-peptide 120 min (ng/mL), *HOMA-B* the homoeostasis model assessment B, *HOMA-IR* the homoeostasis model assessment IR.

In addition, we did not observe statistically significant differences in the 24-h MG and incremental AOC of hypoglycemia across the quartiles in the recruited patients. In addition, no hypoglycemic episode (defined as finger-stick glucose < 3.9 mmol/L and/or symptomatic hypoglycemia) was reported during the study period. However, our CGM data demonstrated that six patients in the highest quartile and one patient in the third quartile experienced hypoglycemic episodes (defined as CGM glucose reading < 3.9 mmol/L), with hypoglycemic durations ranging from 10 to 60 min. We did not observe hypoglycemic episodes delivered by CGM in patients in the other two quartiles.

Relationships between ErbB2 concentration and glycemic variations. Multiple linear regression analyzes were performed to assess the correlation between ErbB2 and MAGE. Our data indicated that HbA1c, age, BMI, ErbB2, FBG, MG, HOMA-IR, SDMG, sex, smoking habits, C-reactive protein (CRP), systolic blood pressure, and low-density lipoprotein (LDL) cholesterol remained significant in the stepwise regression analysis. The standardized regression coefficients were 0.516 (t = 6.27, P < 0.01), 0.496 (t = 6.112, P < 0.01), 0.464 (t = 5.634, P < 0.01), 0.433 (t = 5.535, P < 0.01), 0.283 (t = 3.218, P < 0.01), − 0.201 (t = − 3.482, P < 0.05) and 0.175 (t = 2.387, P < 0.05), respectively. After controlling for HbA_{1c}, age, BMI, ErbB2, FBG, MG, HOMA-IR, SDMG, sex, smoking habits, CRP, systolic blood pressure, and LDL cholesterol, the ErbB2 concentration was still significantly positively correlated with MAGE 0.664 (t = 7.218, P < 0.01). Similarly, ErbB2 concentration was significantly positively correlated with SD (β = 0.469, t = 5.125, P < 0.01) and CV% (β = 0.337, t = 4.442, P < 0.01).

Relationships between ErbB2 concentration and β-cell function/insulin sensitivity. We also observed the relationship between ErbB2 concentration and β-cell function/insulin sensitivity in patients with different ErbB2 levels. Our data showed that patients with higher ErbB2 concentrations exhibited an increase in HOMA-IR values and induction of the Matsuda index (Table 3). However, there were no differences in the HOMA-B values across the quartiles of ErbB2 concentrations. Multivariate analysis controlled for age and BMI to determine the relationships between ErbB2 concentration and β-cell function and insulin sensitivity. Our data showed that ErbB2 values were significantly negatively correlated with HOMA-IR (β = 0.422, t = 4.117, P < 0.01) and Matsuda index (β = 0.317, t = 2.885, P < 0.05). We did not observe a statistically significant relationship between ErbB2 concentration and β-cell function.

Relationships between ErbB2 concentration and lipid profiles. Furthermore, because ErbB2 control lipid metabolism[13]. we assess the relationship between ErbB2 concentration and lipid profiles in patients with different ErbB2 levels. We found that the patients in the highest ErbB2 concentration group had statistically significant increases in triglycerides and cholesterol values than did those in the lowest ErbB2 concentration group (both P < 0.05).

Discussion

In this observational study, we found that patients with newly diagnosed T2D with higher serum ErbB2 concentrations exhibited increased glycemic variations with respect to MAGE, SD, and CV% than did the patients with lower serum ErbB2 concentrations. Multivariate linear regression analyses of the whole study population revealed that serum ErbB2 concentration was positively correlated with glycemic variations, and this association remained significant after adjusting for potential confounding factors, such as age, sex, and BMI. Our data also showed that patients with T2D with higher serum ErbB2 concentrations had an increase in IR in terms of the HOMA-IR and Matsuda index than did those with lower ErbB2 concentrations.

It was well-documented that ErbB2 is been widely investigated as an oncogenic marker and the predictor of cancer prognosis[7]. There is a close association between metabolism and IR, which prompts the confirmation of a possible link between ErbB2 and glucose metabolism in future studies. Recent in vivo and in vitro studies have observed a role beyond the oncogenesis of ErbB2, with regard to the relationship between ErbB2 and diabetes[15]. Fatty acid synthase (FASN) activity may partly account for the link between ErbB2 and diabetes because the overexpression of ErbB2 through a phosphatidylinositol 3'-kinase-dependent pathway promotes the expression of FASN[29]. Studies have provided ample evidence indicating that circulating FASN is a candidate biomarker for

the diagnosis and prognosis for diabetes[30], and it has been associated with insulin action, glucose metabolism, and resistance in the development of T2D[31]. A study performed by Fernandez-Real et al.[32] found that serum ErbB2 concentrations were positively associated with IR in obese persons, indicating that ErbB2 might play a role in the pathophysiology of diabetes[32]. Furthermore, other studies have provided strong evidence supporting the notion that higher serum ErbB2 levels may rely on ErbB2, leading to an increase in IR[32], and hyperglycemia[32,33]. As with previous studies, our data showed that patients with T2D higher serum ErbB2 concentrations had an increase in IR in terms of HOMA-IR and Matsuda index compared to those with lower ErbB2 concentrations. However, we did not observe any difference in HOMA-B across the quartiles in any of the recruited patients.

A significant increase in serum ErbB2 concentrations along with the deterioration of glucose metabolism was observed[33]. Ashfaque et al. found that serum ErbB2 levels were significantly higher in patients with T2D than in those with impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), and those with IFG and IGT had a higher ErbB2 compared to those with normal glucose tolerance, after adjusting for age, sex, and body mass index[33]. In the present study, we did not have data regarding the differences in ErbB2 concentrations in populations with different glucose metabolism conditions. However, we observed that diabetic patients with higher ErbB2 levels had larger GV than did those with lower serum ErbB2 concentrations. Microvascular and macrovascular complications are mainly[34,35], or at least partially[35,36], dependent on hyperglycemia. Postprandial glucose increase is a well-know independent risk factor for cardiovascular disease[37], as is chronic hyperglycemia, which may trigger oxidative stress[20], and induce an overproduction of peroxynitrite and nitrotyrosine in patients with T2D[20,38,39].

We also analyzed the relationship between serum ErbB2 concentrations and GV, β-cell function, and IR. As with a previous study[32,33], our multivariate linear analysis after adjusting for the confounding factors, patients with higher ErbB2 values had higher HOMA-IR values and decreased Matsuda index values. We did not observe a correlation between ErbB2 values and β cell function in the present study. Notably, our data showed that serum ErbB2 concentrations were strongly positively correlated with GV (MAGE, SD, and CV%). However, we do not have data to support these observation, and future studies are needed to ascertain the underlying mechanisms of ErbB2 that lead to amplified glycemic fluctuations.

Diabetic patients must achieve HbA_{1c} target values before physicians can prescribe glucose-lowering agents[40]. However, HbA_{1c} does not provide sufficient evidence of daily glucose variations[18,19]. Studies have demonstrated that glucose variations, especially large MAGE, are independent risk factors for long-term diabetic complications in T2D[18,19]. The underlying mechanisms may be the reason by acute glucose variations triggering multiple factors, that impair the epithelial cells[20].

This study had certain limitations. First, a correlation between HbA1c and glycemic variation has been reported in previous studies[22]. In agreement with our findings, it would be more logical that patients with higher ErbB2 values exhibited higher HbA1c concentrations. However, there was no positive correlation between ErbB2 levels and HbA1c concentrations. We speculated that the following two reasons may have impaired this correlation: (1) our recruited patients had moderate HbA1c concentrations, ranging from 8.1 to 14.1%, with only six patients exhibiting an HbA1c concentration higher than 10%; (2) the sample size was moderate, which may have been the primary reason for the decrease in the possibility of the correlation. Second, we did not observe a significant difference in serum ErbB2 concentration between non-diabetic and diabetic patients.

In conclusion, our data indicated that diabetic patients with higher ErbB2 concentrations may have large GV, which is an independent risk factor for microvascular and macrovascular complications.

Data availability

The data sets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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Author contributions

Y.-Q.S., and X.C. contributed to the conception and design of the study. T.C., and Y.H., contributed to the Conduct/data collection. X.H. contributed to data analysis. F.-F.L. contributed to manuscript writing. Y.-Q.S. and Y.M.L. final approval of the manuscript.

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Competing interests
The authors declare no competing interests.

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