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Research Article

The C-peptide correlations and effect on the glycemic variability parameters in patients with type 2 diabetes

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Abstract. Background and aims:Glycemic variability is an important aspect of glycemic control -linked to the development of diabetes chronic complications. Endogenous insulin secretion varies widely among patients with type 2 diabetes (T2DM) and might be an important factor involved in the control of glycemic variability. Material and method:We included data from 53 patients with T2DM and complete continuous glucose monitoring (CGM) recording (first 24 hours of recording starting from the midnight after insertion with no pause in recorded values). Endogenous insulin secretion was assessed by C-peptide levels. We collected from patients' medical charts data on age, gender, anthropometric parameters - weight, height, body mass index (BMI), visceral fat area (VFA) and percent of body fat (PBF), diabetes duration and treatment, HbA1c and C-peptide levels. The following glycemic variability parameters were calculated:mean level of 24h interstitial glucose value (MG);median glucose value (MedG);standard deviation (SD);percentage coefficient of variation (%CV);weighted average of glucose values around 100 mg/dl (M100);J index;percentage of glucose values above 180 mg/dl (%above180) or below 70 mg/dl and 54 mg/dl (%below70 and %below54);mean amplitude of glycemic excursion (MAGE);fractal dimension (FD);continuous overall net glycemic action (CONGA) at 1, 2, 4 and 6 hours. Results:Mean age of patients included in the analysis was 55.6±8.96 years and median duration of diabetes 4 years (0;9.75 years). Median C-peptide value was 2.71 ng/ml (1.91;3.89) and mean HbA1c was 8.29±1.90%. C-peptide quartile correlated significantly with body weight (r=0.520, p<0.001), BMI (r=0.481, p<0.001), VFA (r=0.338, p=0.013), M100 (r=-0.294;p=0.032), J index (r=-0.271;p=0.050), % above126 (r=-0.275;p=0.046), CONGA-1 (r=-0.332, p=0.015) and CONGA-2 (r=-0.298, p=0.030). Patients in the lowest C-peptide quartile had significantly higher values of mean glucose levels (180.69 mg/dl vs. 141.37 mg/dl, p=0.017), J index (50.50 vs. 30.77, p=0.020), % above126 (93.73% vs. 59.03%, p=0.013) and % above180 (49.65% vs. 15.97%, p=0.026) and significantly lower weight (79.2 kg vs.101.8 kg, p=0.004), BMI (28.2 kg/m2 vs. 34.8 kg/m2, p=0.002) and VFA (133.9 cm2 vs. 155.00 cm2, p=0.048) than patients in highest quartile. Conclusions:Endogenous insulin secretion was correlated with weight, BMI, VFA and better glycemic control, expressed as HbA1c value or time spent in hyperglycemia, and few other glycemic variability parameters evaluated by CGMS.

Key Words: C-peptide, type 2 diabetes, glycemic variability, continuous glucose monitoring

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Introduction

Current clinical practice guidelines recommend the use of glycemic profile by self-monitoring of blood glucose (SMBG) and HbA1c value (American Diabetes Association 2018) for the assessment of glycemic control in patients with type 2 diabetes mellitus (T2DM). For selected T2DM patients a continuous glucose monitoring (CGM) system can be useful to further improve glycemic control and for safety reasons (e.g. hypoglycemia unawareness) (American Diabetes Association 2018). CGM measures the glucose concentration from subcutaneous interstitial fluid (which correlates with blood glucose concentration) and provides a profile of 288 measurements per day. Beyond the role in glycemic control in T2DM, in a recent published study was also demonstrated that the use of 25 indices of glycemic variability calculated on CGM recording can distinguish healthy persons from those with impaired glucose tolerance with an accuracy of 91.4% (Acciaroli et al 2017).

Although HbA1c was showed to be an important risk factor for microvascular diabetes complications (Manley 2003), wide glycemic variability was linked to oxidative stress and impaired endothelial function (Ceriello & Ihnat 2010), even in those with HbA1c levels within target recommended by guidelines (Constantino et al 2017).

In the recent years numerous studies showed that glycemic variability is an important aspect of glycemic control. Variation of glycemic values over either a short or a long time period, expressed as standard deviation (SD) and HbA1c variation, have been linked with the risk of development and progression of diabetic retinopathy (Hsu et al 2015). Variation of HbA1c has been also associated with diabetic peripheral neuropathy (Su et

al 2018) and with the risk of atrial fibrillation development in T2DM (Gu et al 2017). Recent data showed no association between high variation of glycaemia (measured as mean amplitude of glycemic excursion - MAGE) and microvascular complications in patients with T2DM;however, mean glucose value and time spent in hyperglycemia (values above 180 mg/dl) was significantly correlated with microangiopathies (Sonoda et al 2018). Causes of increased glycemic variability in patients with diabetes, other than carbohydrate intake, can be:hypoglycemia (Takeishi et al 2017), antihyperglycemic treatment (Yin et al 2018; Dandona 2017), presence of dawn phenomenon (Roman et al 2016), higher age and lower body mass index (BMI) (Takeishi et al 2017), longer duration of diabetes (Takeishi et al 2017). On the other hand, some indices of glycemic variability are independent predictors of hypoglycemia (Monnier et al 2011;Rama Chandran et al 2018).

Endogenous insulin secretion varies widely among patients with T2DM and might be an important factor involved in the control of glycemic variability in these patients.

Our objective was to evaluate correlations between C-peptide and glycemic variability parameters, recorded using a continuous glucose monitoring system in patients with T2DM.

Material and method

This is a retrospective study in which we included data of 53 T2DM patients who had a complete CGM recording (first 24 hours of recording starting from the midnight after insertion with no pause in recorded values) and C-peptide measurement available. We collected from patients' medical charts data on age, gender, anthropometric parameters - weight, height, body mass index (BMI), visceral fat area (VFA) and percent of body fat (PBF) measured by bioimpedance (InBody720, Biospace, Korea), diabetes duration and treatment, HbA1c and C-peptide levels. The CGM was performed using the professional iPROTM device (Medtronic, Northridge, CA), in a blinded manner. The iPRO was placed on and removed from the patient by a trained member of the medical staff, in the abdominal area. The parameters of glycemic variability were calculated using the method described by Czerwoniuk D et al. (Czerwoniuk et al 2011). The glycemic variability indices calculated based on CGM readings were (Czerwoniuk et al 2011):

- mean level of 24h interstitial glucose value (MG) and standard deviation (SD) - an index of the dispersion of data around mean blood glucose;
- percentage coefficient of variation (%CV) is the ratio of SD of the glucose values to mean of the glucose values. This parameter describes the magnitude sample values and the variation within them;
- M100-weighted average of glucose values provides a measure of stability of glycaemia in comparison with an arbitrary assigned glucose value, initially set to 100 mg/dl;
- J index is a measure of quality of glycemic control based on the combination of information from the mean and SD calculated as 0.001 × (mean + SD);
-percent of glucose values above or below a given threshold measured as the percentage of hyperglycemia (levels over 126 mg/dl and 180 mg/dl) and hypoglycemia (levels below 70 mg/dl and 54 mg/dl);

Table 1. The baseline characteristics of patients included in the study

Parameter	Study group (n=53)
Age, years	55.6±8.96
Women, n (%)	18 (33.9)
Duration of diabetes, years	4 (0;9.75)
HbA1c, %	8.29±1.90
C-peptide, ng/ml	2.71 (1.91;3.89)
Weight, kg	91.1 (77.6;98.8)
BMI, kg/m^2	30.99±5.54
PBF, %	33.96±9.32
VFA, cm^2	148.4 (120.7;171.9)
Insulin therapy, n (%)	12 (22.64)

- mean amplitude of glycemic excursion (MAGE) - calculated based on mean of differences between consecutive glucose values picks and nadirs, only for differences greater than SD. The small variations are excluded. MAGE provides a measure of intra-day, high amplitude, glucose variability;
- fractal dimension (FD) - describes glucose variability of high frequency and small amplitude;
- continuous overall net glycemic action (CONGA) at 1, 2, 4 and 6 hours (CONGA -1, -2, -4, -6) which shows glycemic variability within a predetermined time window. It is an indicator of within-day glucose variability;

HbA1c values were assessed in the same laboratory by high-performance liquid chromatography (Cobas Integra 400Plus, Roche Diagnostics). C-peptide concentrations were determined by automatic immunology analysis (Cobas e 411, Roche Diagnostics).

The study was conducted according to the World Medical Association Declaration of Helsinki and national legislation regarding the conduct of retrospective clinical trials. A previous written Inform Consent was provided by every patient for the CGM procedure as required by clinic's Standard Operating Procedures.

Statistical analysis was carried out using SPSS-PC 15.0 software (SPSS Inc., Chicago, IL, USA). Distribution of variables was tested with Kolmogorov-Smirnov test. Statistical data is presented as mean ± standard deviation (SD) for normally-distributed variables, median (1st quartile;3rd quartile) for variables with abnormal distribution and percentage for categorical variables. Student t-test was used to compare variables with normal distribution, and Mann-Whitney U test for variables with abnormal distribution. The correlation between variables was assessed by Pearson correlation coefficient for variables with normal distribution and Spearman correlation coefficient for variables with abnormal distribution. The level of significance was set at 0.05.

Results

We collected data from 53 T2DM patients, 55.6±8.96 years old, a median duration of diabetes of 4 (0;9.75) years and a median C-peptide concentration of 2.71 (1.91;3.89) ng/ml. Twenty-two patients (41.5%) were newly diagnosed and they had no pharmacotherapy during CGM recording. From the remaining 31 patients, 21 (67.74%) received metformin, 9 (29.03%) sulphonylurea, 7 (22.58%) incretin-based therapy and 12 patients

Table 2. The baseline characteristic of patients included in the study according to C-peptide quartiles

Parameter	1st Quartile	4th Quartile	p
Age, years	56.77±9.04	55.54±8.24	0.72
Women, n (%)	6 (46.2)	4 (30.8)	0.511
Duration of diabetes, years	4 (0;10)	0 (0;7)	0.123
HbA1c, %	9.09±2.38	7.55±0.95	0.047
C-peptide, ng/ml	1.13 (0.69;1.64)	4.80 (4.02;7.19)	<0.001
Weight, kg	79.2 ±15.92	101.8 ±25.67	0.004
BMI, kg/m²	28.2±5.12	34.8 ±5.69	0.002
PBF, %	30.80±9.94	38.31 ±9.10	0.056
VFA, cm²	133.9 (106.6;179.1)	155.0(147.3;239.5)	0.048
Insulin therapy, n (%)	4 (30.8)	4 (30.8)	1

Table 3. Glycemic variability parameters according to C-peptide quartiles

Parameter	1st quartile	4th quartile	p value
MG, mg/dl	180.69±67.13	141.37±33.89	0.017
Median glucose value, mg/dl	180.5±75.79	135.0±37.40	0.033
SD, mg/dl	35.95±12.34	29.79±14.57	0.179
%CV	17.22(15.21;23.09)	17.03(11.10;25.98)	0.707
M100, mg/dl	22.88(8.78;66.52)	7.34(0.52;17.41)	0.012
J index, mg/dl	50.50(32.68;83.70)	30.77(15.62;42.20)	0.02
%above126 mg/dl, %	93.73(50.69;100)	59.03(13.89;87.15)	0.013
%above180 mg/dl, %	49.65(12.15;98.26)	15.97(0;40.97)	0.026
MAGE, mg/dl	107.18±34.66	79.84±38.77	0.07
FD, mg/dl	1.05(1.03;1.06)	1.05(1.04;1.08)	0.336
CONGA1, mg/dl	28.87±10.21	21.20±8.33	0.047
CONGA2, mg/dl	42.56±14.91	31.39±14.62	0.066
CONGA4, mg/dl	49.16±15.41	40.40±22.62	0.26
CONGA6, mg/dl	50.06±17.38	42.93±24.87	0.405

Table 4. The correlations of the C-peptide with glycemic variability parameters

Parameter	ρ	p
MG, mg/dl	-0.247	0.062
Median glucose value, mg/dl	-0.238	0.074
SD, mg/dl	-0.228	0.101
%CV	-0.19	0.172
M100, mg/dl	-0.259	0.041
J index, mg/dl	-0.249	0.061
%above126 mg/dl, %	-0.238	0.086
%above180 mg/dl, %	-0.236	0.088
%below70 mg/dl, %	-0.175	0.21
%below54 mg/dl, %	-0.119	0.394
MAGE, mg/dl	-0.262	0.058
FD, mg/dl	0.131	0.349
CONGA1, mg/dl	-0.337	0.014
CONGA2, mg/dl	-0.234	0.028
CONGA4, mg/dl	-0.219	0.092
CONGA6, mg/dl	-0.179	0.2

Table 5. Correlations of the C-peptide quartile with glycemic variability parameters

Parameter	ρ	p
MG, mg/dl	-0.267	0.054
Median glucose value, mg/dl	-0.249	0.072
SD, mg/dl	-0.237	0.088
%CV	-0.146	0.297
M100, mg/dl	-0.294	0.032
J index, mg/dl	-0.271	0.05
%above126 mg/dl, %	-0.275	0.046
%above180 mg/dl, %	-0.246	0.076
%below70 mg/dl, %	-0.152	0.276
%below54 mg/dl, %	-0.087	0.536
MAGE, mg/dl	-0.249	0.072
FD, mg/dl	0.175	0.209
CONGA1, mg/dl	-0.332	0.015
CONGA2, mg/dl	-0.298	0.03
CONGA4, mg/dl	-0.221	0.112
CONGA6, mg/dl	-0.162	0.247

(38.70%) were treated with insulin. The baseline characteristics of the patient included in the study are presented in Table 1. Baseline characteristics of the patients according to quartiles of C-peptide concentration are presented in Table 2.

Patients with a C-peptide concentration in the lowest quartile had statistically significant higher values of mean and median glucose value, M100, J index, % time spent in hyperglycemia (% above 126 mg/dl and 180 mg/dl), and higher CONGA1 than those in the highest quartile (Table 3).

C-peptide concentration was not correlated with age (ρ=0.115, p=0.413), gender (ρ=0.115, p=0.413), duration of diabetes (ρ=-0.258, p=0.091), HbA1c (ρ=-0.230, p=0.104), or insulin therapy (ρ=-0.025, p=0.859), but was significantly correlated with anthropometric parameters - weight (ρ=0.518, p<0.001), BMI (ρ=0.535, p<0.001), PBF (ρ=0.343, p=0.012), and VFA (ρ=0.409, p=0.012).Correlations of C-peptide concentration and glycemic variability parameters are presented in Table 4. There was a significant correlation with M100 and CONGA1 and CONGA2.

The C-peptide quartiles were not correlated with age (ρ=0.083, p=0.556), gender (ρ=0.139, p=0.323), duration of diabetes (ρ=-0.253, p=0.097), HbA1c (ρ=-0.235, p=0.097), or with insulin therapy (ρ=-0.039, p=0.787), but were significantly correlated with weight (ρ=0.520, p<0.001), BMI (ρ=0.481, p<0.001), and VFA (ρ=0.338, p=0.013). No correlation between C-peptide quartile and PBF was observed (ρ=0.255, p=0.065). The correlations of C-peptide quartile and glycemic variability parameters are presented in Table 5. There was a significant correlation with M100, J index, % above 126mg/dl, CONGA1 and CONGA2.

Discussion

Type 2 diabetes is a chronic disease with progressive failure of insulin production from the pancreatic beta-cells. In our study the C-peptide plasma concentration, a parameter evaluating endogenous insulin secretion from pancreatic beta-cells, was not correlated with diabetes duration or age. An explanation for this observation might be that the patients included in our study had a short duration of T2DM (median of 4 years) and relatively young age (55.6±8.96). In our study patients with C-peptide in the highest quartile had a significantly higher BMI and VFA than those in the lowest quartile. These results are in line with previous reports in patients with T2DM. Thunander et al showed that C-peptide levels increased in parallel with BMI levels in patients with newly diagnosed diabetes (Thunander M et al 2012). Similar results were reported by Sonwane et al in patients with T2DM treated with hypoglycemiant agents (Sonwane A et al 2018). Also, previous research reported higher insulinemia in persons with higher visceral fat (Gautier JF et al 1998). A hypothesized mechanism of these associations is insulin resistance which leads to increased endogenous insulin secretion to overcome this state (Sonwane A et al 2018).

Another important finding of our research is the correlation of C-peptide levels with several glycemic variability parameters and glycemic control. Higher C-peptide levels and quartiles were correlated with lower glycemic variability within predetermined time window (as assessed by M-100, CONGA1 and CONGA2) and better glycemic control. J index, another parameter for glycemic variability which measures the quality of glycemic control based on the combination of information from the mean glucose levels and SD, was significantly lower in patients from the highest C-peptide quartile compared with those from the lowest one. Additionally, C-peptide quartiles were negatively correlated with time spent with glycemia over 126 mg/dl. In our study the percent of time spent in hyperglycemia (measured as % above 126 mg/dl and above 180 mg/dl) was significantly lower in patients with C-peptide in highest quartile. Similar negative associations between C-peptide levels and glycemic variability parameters were previously reported in other studies in patients with T2DM. In a study enrolling 106 patients with T2DM evaluated by CGMS it was observed that low C-peptide index (fasting C-peptide X fasting plasma glucose/100) was associated with the highest postprandial glucose levels (Takeishi et al 2017). In another study enrolling 399 patients with T2DM (168 non-insulin treated and 231 insulin treated) also investigated by CGMS it was showed that fasting C-peptide levels were negatively correlated with markers of glycemic variability, but only in insulin treated patients (Jin SM et al 2014).

Although it has been agreed that glycemic variability is an important factor associated with glycemic control and risk of micro- and macrovascular complications in patients with diabetes (Caprnda M et al 2017; Ceriello A et al 2010;Constantino S et al 2017), its use in clinical practice is limited by the lack of agreement on the 'best' parameter(s) of glycemic variability associated with the risk of diabetes chronic complications and mixed results of studies on the association of these parameters with diabetes complications. %CV, describing the magnitude of glycemic excursions, is another parameter proposed for use in clinical practice to assess glycemic variability (Monnier et al 2017;Gomez et al 2018). In our sample there was no correlation between C-peptide level and %CV and no difference was observed in %CV values between the lowest and the highest C-peptide quartile. Monnier et al also showed that acute glucose fluctuation during postprandial hours, measured as mean amplitude of glycemic excursions (MAGE) has a more important effect on activation of oxidative stress than chronic hyperglycemia (Monnier et al 2006) in patients with T2DM. In our study MAGE was not correlated with C-peptide levels.

Conclusions

The C-peptide plasmatic level was correlated with weight, BMI, VFA and better glycemic control, expressed as HbA1c value, mean/median glucose value and percent of time spent in hyperglycemia. Our results suggest that endogenous insulin secretion may play an important role in glycemic control and may prevent, in some extent, glycemic excursions and glycemic variability.

Conflict-of-interest statement

DMC received speaker fees from AstraZeneca and Sanofi. AEC declares speaker fees, sponsorships and consultancy fees from AstraZeneca, Sanofi, Eli Lilly, Servier, Merck Sharpe&Dhome, Mylan, Novo Nordisk, Amgen. CB declares speaker fees, sponsorships, and consultancy fees from AstraZeneca, Sanofi, Eli Lilly, Servier, Merck Sharpe&Dhome, Meda Pharmaceuticals, Novartis, Amgen, Unilever, and Danone. GR declares speaker fees from AstraZeneca, Sanofi, Eli Lilly, NovoNordisk, Servier, Merck Sharpe&Dhome, Mylan, and Berlin Chemie,

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