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Взаимосвязь вариабельности уровня глюкозы и функции почек у больных сахарным диабетом 2 типа на базис-болюсной инсулинотерапии

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Цель. *Определить взаимосвязь вариабельности уровня глюкозы (ВГ) с функцией почек у больных сахарным диабетом 2 типа (СД2), получающих базис-болюсную инсулинотерапию.*

Материалы и методы. *Обследована 101 женщина с СД2, 47–79 лет, со скоростью клубочковой фильтрации (СКФ) >30 мл/мин/1,73 м². У 45 женщин инсулин комбинировался с метформином. Средняя гликемия, стандартное отклонение (SD), средняя амплитуда колебаний гликемии (MAGE), индекс длительного повышения гликемии (CONGA), индекс лабильности (LI), J-индекс, индекс риска гипогликемии (LBGI), индекс риска гипергликемии (HBGI), показатель M-value, среднечасовая скорость изменения гликемии (MAG) рассчитаны на основе результатов «слепого» непрерывного мониторинга уровня глюкозы. Установлена распространенность эпизодов снижения уровня глюкозы в интерстициальной жидкости (≤3,9 и ≤2,8 ммоль/л) продолжительностью не менее 20 минут.*

Результаты. *У больных с СКФ 30–44 мл/мин/1,73 м² HBGI, J-индекс, MAGE и M-value были достоверно ниже по сравнению с пациентами с более высокой фильтрацией (все p<0,05); LBGI не зависел от СКФ. Слабые положительные корреляции выявлены между СКФ и HBGI, J-индексом, M-value и MAG. В многофакторном регрессионном анализе СКФ являлась независимым предиктором MAG (p=0,04). Не зафиксировано достоверных различий в распространенности эпизодов низкого уровня глюкозы между больными с различными градациями СКФ.*

Заключение. *У женщин, больных СД2 и получающих базис-болюсную инсулинотерапию, параметры ВГ связаны с функцией почек. Больные с хронической болезнью почек 3б стадии имеют меньшую ВГ, преимущественно в гипергликемическом диапазоне, по сравнению с больными с более высокими значениями фильтрации.*

Ключевые слова: *сахарный диабет 2 типа; хроническая болезнь почек; вариабельность глюкозы; непрерывный мониторинг глюкозы; гипогликемия*

The relationships between glucose variability and renal function in type 2 diabetes patients on basal-bolus insulin therapy

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Aim. *To assess the relationship of glucose variability (GV) and renal function in patients with type 2 diabetes on basal-bolus insulin therapy.*

Materials and methods. *We observed 101 females with type 2 diabetes, aged 47–79 years, with a glomerular filtration rate (GFR) >30 mL/min/1.73 m². Insulin was combined with metformin in 45 of these women. The mean glucose and standard deviation, continuous overlapping net glucose action, lability index, J-index, low blood glucose index (LBGI), high blood glucose index (HBGI), M-value and mean absolute glucose (MAG) were calculated based on the results of blinded continuous glucose monitoring. The prevalence of episodes of low interstitial glucose (<3.9 and 2.8 mmol/L) of at least 20-min duration was estimated.*

Results. *Patients with a GFR of 30–44 mL/min/1.73 m2 had significantly lower HBGI, J-index, MAG and M-value compared with those with better filtration (all p < 0.05); LBGI was not dependent on GFR. The GFR values were weakly and positively correlated with HBGI, J-index, M-value and MAG. Multiple regression analysis showed that GFR is an independent predictor of MAG (p = 0.04). No significant differences were found in the prevalence of episodes of low interstitial glucose between patients with different GFR ranges.*

Conclusions. *GV parameters are related to renal function in type 2 diabetic women on basal-bolus insulin therapy. Patients with stage 3b chronic kidney disease have reduced GV, predominantly in the hyperglycaemic band, compared with those with better filtration.*

Keywords: *type 2 diabetes; chronic kidney disease; glucose variability; continuous glucose monitoring; hypoglycaemia*

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The study of glucose metabolism in renal insufficiency remains one of the most topical issues of diabetology. The kidneys are important suppliers of glucose into the circulation, particularly under post-prandial conditions [1]. The majority of the hormones that regulate the hydrocarbonic metabolism are also processed by the kidneys. The development of chronic kidney disease (CKD) is accompanied by complex hormonal and metabolic shifts that change the endogenous secretion of insulin as well as sensitivity to this hormone [2]. The literature provides an overview on the role of the accumulation of uraemic toxins with biguanide-like characteristics, gastroparesis, hyperparathyroidism, vitamin D deficiency and other factors in the changes in glucose homeostasis in patients with CKD [3]. The reduced filtration function of the kidneys leads to changes in the pharmacokinetics and pharmacodynamics of most hypoglycaemic preparations, which also changes glycaemic control [4].

It is necessary to determine the regularity of the changes in the glycaemic variability (GV) in renal insufficiency to develop optimal strategies of hypoglycaemic therapy in patients with diabetes mellitus (DM) and CKD. In the last two decades, significant progress has been made in the development of methods for evaluating GV in patients with DM [5, 6]. In particular, new approaches to GV analysis have been suggested based on the logarithmic transformation of glycaemic curves and ranking stratification of glycaemia values. Continuous glucose monitoring (CGM) has significantly extended the possibilities for methods of evaluating glucose excursions in different ranges. From generalised data, GV is associated with the development of microvascular complications in type 2 DM (DM2) [7]. The features of GV in patients with DM on dialysis have been previously shown [8]. The correlations between GV and renal function in patients with DM at pre-dialysis CKD stages have not yet been studied. Insulin therapy is a generally recognised as the risk factor of hypoglycaemia in patients with DM2 [9]; thus, evaluation of glucose excursions in patients with DM2 on insulin therapy with different levels of renal function is of great interest.

Aim

To assess the relationship between GV and renal function in patients with DM2 on basal-bolus insulin therapy

Materials and methods

We observed 101 post-menopausal women with DM2 aged 47–79 years (mean: 65 years). Most of the examined patients showed DM complications and comorbid conditions, including arterial hypertension (n = 99), diabetic retinopathy (n = 87), stages 1–3 of CKD (n = 85), polyneuropathy (n = 101), lower limb macroangiopathy (n = 66) and ischaemic heart disease (n = 47).

All examined patients received insulin in the basal-bolus mode, and in those with no contraindications, insulin was combined with metformin (n = 45). Patients who received other hypoglycaemic preparations were not included in the present study. In the majority of examined patients, basal insulin was administered in the form of long-acting insulin analogues such as glargine (n = 71) or detemir (n = 7). The remaining patients (n = 23) were on neutral protamine Hagedorn (NPH) insulin. Ultra-rapid-acting insulin analogues (n = 54) or rapid-acting insulin (n = 47) were used for the bolus insulin. The level of glycohaemoglobin A1C (HbA1c) varied from 6.7% to 11.7% (median: 8.5%).

The glomerular filtration rate (GFR) was determined from creatinine levels via the CKD–EPI equation (2009); in morbidly obese patients, the Rehberg–Tareev test was used for this. After determining GFR, the examined patients were divided into three groups: 1) GFR ≥60 ml/min/1.73 m2 (n = 45); 2) GFR 45–59 ml/min/1.73 m2 (n = 35) and 3) GFR 30–44 ml/min/1.73 m2 (n = 21). Considering that half of the examined patients were >65 years (for whom filtration values of 60–89 ml/min/1.73 m2

Table 1

Clinical characteristics of patients with DM2 showing different GFR levels

Index	GFR, ml/min/1.73 m2		
	≥60 (n = 45)	45–59 (n = 35)	30–44 (n = 21)
Age, years	62 (58; 67)	67 (63; 71)*	68 (64; 75)*
Body mass index, kg/m2	32 (29.4; 36.5)	31.2 (28.9; 33.9)	32.8 (29.3; 38.4)
Waist circumference, cm	102 (87; 123)	103 (99; 109)	100.5 (96; 113)
Waist circumference/hip circumference	0.93 (0.86; 0.98)	0.93 (0.86; 0.97)	0.93 (0.89; 0.98)
Duration of DM from the time of diagnosis, years	15 (10; 19)	19 (14; 23)*	16 (11; 22)
Duration of insulin therapy, years	8 (4; 11)	7 (5; 15)	8 (4; 11)
Insulin dose, unit/kg/day	0.74 (0.6; 0.9)	0.74 (0.5; 0.82)	0.76 (0.5; 1.0)
HbA1c, %	8.5 (7.6; 9.7)	8.4 (7.6; 9.6)	9.0 (7.5; 10.7)
Number of patients on analogues of long-acting insulin, n (%)	35 (78)	26 (76)	17 (81)
Number of patients on analogues of ultra-rapid-acting insulin, n (%)	27 (55)	17 (45)	10 (48)

* Significant difference with the group of patients with GFR ≥60 ml/min/1.73 m2.
The data are presented as medians (25; 75 percentile).

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could be considered normal), the patients with GFR ≥60 ml/min/1.73 m2 were considered to be one group.

The clinical and laboratory characteristics of the groups are presented in Table 1. The patients with GFR <60 ml/min/1.73 m2 were older than those from the other groups. The duration of insulin therapy, mean daily doses of insulin and HbA1c levels were not significantly different among the three groups. Part of the patients on insulin analogues was also commensurable. Thirty patients with GFR >60 ml/min/1.73 m2 and 15 patients with GFR 45–59 ml/min/1.73 m2 received metformin therapy.

CGM was conducted using professional glycaemia monitoring systems, and retrospective data analysis was performed using Medtronic MiniMed Paradigm MMT-722 and Medtronic iPro2. The systems were calibrated using blood plasma at least four times a day. According to CGM consensus guidelines [10], the first 2 h of monitoring is an unstable calibration period; therefore, the data collected during this period were excluded from analysis. The mean amount of CGM data subjected to analysis accounted for 48.7 h per person (interquartile range: 42.5–69.8 h).

GV parameters were calculated using the EasyGV calculator (version 9.0) [11]. The following parameters were determined: standard deviations (SD), continuous overlapping net glycaemic action (CONGA), lability index (LI), J-index, low blood glucose index (LBGI), high blood glucose index (HBGI), mean amplitude of glycaemic excursions (MAGE), mean absolute glucose (MAG) and M-value index. The characteristics of the calculations and diagnostic value of the indicated indices have been described in recent reviews [5, 6]. Principally, for a number of these parameters, the general GV is reflected by the SD, LI, MAGE and MAG indices; HBGI, J-index and CONGA are more related to hyperglycaemia; LBGI is more sensitive to hypoglycaemia and the M-value index characterises the 'quality' of the glycaemic control. Calculator settings were adapted for the CGM data. To calculate CONGA, which represents the SD of the sum of glycaemia differences for the indicated time periods, a 2-h period was chosen. The same period was chosen for LI calculation (sum of squares of the difference between the results of two successive glucose measurements, averaged over a certain period of time). We chose 6.67 mcmol/l as the 'ideal' glycaemic level to calculate the M-value index.

In addition to GV indices calculations, we analysed the episodes of low interstitial glucose (LIG) . At the same time, we analysed the episodes of glucose levels of ≤3.9 and ≤2.8 mcmol/l. The minimum duration of the episodes was taken as 20 min [12]. The frequency of LIG episodes was calculated as the ratio of the number of persons who experienced one or several episodes in the first 24 h of the analysed record to the total number of examined patients in the study population.

The present study was approved by the local ethics committee (based on the Scientific Institute of Clinical and Experimental Lymphology). All patients provided written informed consent to participate in this study.

Statistical data analysis was conducted by means of STATISTICA 10.0 (StatSoft, Tulsa, OK, USA). Considering the fact that the distribution of most of the studied signs differed from those of normal ones, non-parametric statistical methods were applied. Intergroup differences were evaluated using the Mann–Whitney U test (two independent groups) and Kruskal–Wallis ANOVA (three groups). Comparison of binary sign frequencies was conducted using the χ^2 test (two independent groups) and exact Fisher's test (three groups). Correlation of the signs was studied using Spearman's rank correlation analysis and multifactorial single-step regression analysis. Signs that were not normally distributed underwent logarithmic transformation before they were included in the regression analysis. The critical significance level for the statistical hypotheses was 0.05. The data are presented as medians (25; 75 percentiles).

Results

According to the CGM data, the mean glucose levels in patients with a GFR of 30–44 ml/min/1.73 m2 were not significantly lower than those in the examined patients

Table 2

GV indices in patients with DM2 showingwith different GFR levels

Parameter	GFR, ml/min/1.73 m2			Significance of the differences among the groups		
	≥60 (n = 53)	45–59 (n = 44)	30–44 (n = 22)	p1–2	p2–3	p1–3
Mean glycaemia, mol/l	8.6 (7.2; 9.9)	8.4 (7.2; 9.9)	7.6 (6.9; 8.5)	0.40	0.24	0.06
SD, mol/l	2.2 (1.9; 2.8)	2.6 (2.0; 2.9)	2.2 (1.7; 2.6)	0.46	0.08	0.25
CONGA, mcmol/l	7.5 (6.5; 9.1)	7.3 (6.4; 9.0)	6.8 (6.1; 7.7)	0.52	0.27	0.12
LI, (mcmol/l)2/h	2.5 (1.6; 3.3)	2.4 (1.6; 3.5)	1.8 (1.4; 2.3)	0.91	0.03	0.07
J-index, mcmol/l2	36.6 (32.8; 48.6)	38.5 (27.7; 50.6)	29.8 (25.9; 39.7)	0.52	0.04	0.02
LBGI, st. units	1.0 (0.2; 4.0)	1.7 (0.7; 3.8)	1.9 (0.7; 3.3)	0.33	0.75	0.74
HBGI, st. units	6.3 (4.6; 9.0)	6.6 (4.4; 9.7)	4 (3.0; 7.3)	0.87	0.03	0.02
MAGE, mol/l	4.5 (3.6; 5.6)	5.0 (3.7; 6.2)	3.7 (3.4; 5.1)	0.26	0.02	0.05
M-value, st. units	6.7 (4.2; 14)	6.4 (3.5; 11.6)	3.3 (2.5; 5.6)	0.75	0.04	0.01
MAG, mcmol/(l × h)	2.4 (1.8; 3.1)	2.1 (1.7; 2.7)	1.9 (1.3; 2.9)	0.08	0.35	0.05

p: Significance of the differences among the groups: group 1 (GFR ≥60 ml/min/1.73 m2), group 2 (GFR 45–59 ml/min/1.73 m2) and group 3 (GFR 30–44 ml/min/1.73 m2). The data are presented as medians (25; 75 percentiles).

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with higher filtration rates (Table 2). The patients with a GFR of 30–44 ml/min/1.73 m2 showed lower GV indices, reflecting hyperglycaemia (HBGI and J-index), general variability (MAGE and MAG) and the quality of the glycaemic control (M-value). The index reflecting hypoglycaemia risk (LBGI) was low in all groups of examined patients (<2.5 in most of the patients) and did not depend on GFR. GV parameters in the patients with a GFR of 45–59 ml/min/1.73 m2 did not significantly differ from those in the group of patients with a GFR of ≥60 ml/min/1.73 m2.

In patients receiving analogues of long-acting insulin (mainly, glargine), we observed lower GV in terms of the MAG parameter in comparison with the examined patients on NPH insulin: 2.0 (1.6; 2.8) versus 2.7 (2.1; 3.3) mcmol/l × h, respectively (p = 0.001). When comparing GV parameters in patients receiving glargine and those on NPH insulin therapy, lower differences in LI (p = 0.03) and MAG (p = 0.0007) were revealed in the glargine group. No differences were found in the GV indices between patients receiving human rapid-acting insulin and those receiving analogues of rapid-acting insulin. No influence of metformin was found on GV parameters.

HbA1c levels correlated positively with the mean interstitial glucose levels (r = 0.27, p = 0.008) as well as with CONGA (r = 0.26, p = 0.01) and J-index (r = 0.22, p = 0.03). Weak positive correlations were found between GFR and some GV parameters, including J-index (r = 0.21, p = 0.02), HBGI (r = 0.2; p = 0.03), M-value (r = 0.22, p = 0.02) and MAG (r = 0.26, p = 0.005). In models of multifactorial regression analysis using GV indices as the dependent parameters and clinical parameters (age, body mass index, DM duration, daily insulin dose, HbA1c levels and GFR) as the independent parameters, we found a significant effect of GFR on the MAG index (b = 0.23, R2 = 0.2, p = 0.04).

The frequency of episodes of reduced interstitial fluid levels, which were determined using CGM data, is presented in Fig. 1. The tendency of increasing number of patients with episodes of ≤3.9 mcmol/l as filtration renal function reduced (p = 0.07). Although the number of patients who experienced episodes of LIG ≤3.9 mmol/l turned out to be in the GFR of 30–44 ml/min/1.73 m2 group, the total duration of these episodes within 24 h was shorter in this group compared with that in patients with a GFR of ≥60 ml/min/1.73 m2 (r = 0.05). Part of the patients who experienced episodes of LIG ≤2.8 mcmol/l did not significantly differ between the groups (p = 0.42).

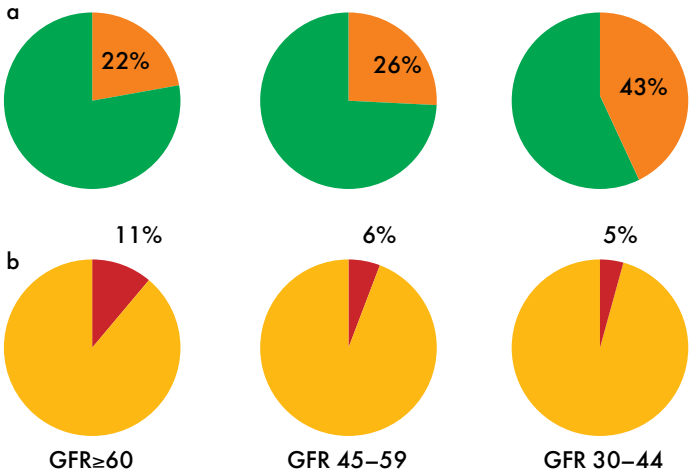

Fig. 1. Part of the patients who experienced episodes of LIG ≤3.9 μmol/l (a) and ≤2.8 μmol/l (b) among the examined patients with different GFR levels.

Discussion

This paper highlights the correlations among GV parameters and renal function in patients with DM2 at stages 0–3 CKD. To provide more homogeneous sampling, only women on basal-bolus insulin therapy alone or in combination with metformin (if there were no contraindications against it) were included in the present study. This study was performed under inpatient conditions, which ensured relative homogeneity of the patients' daily routine and type of nutrition. To evaluate GV, we used a wide range of parameters characterising the amplitude and frequency of glucose excursions in the hypo- and hyperglycaemic ranges.

Contrary to our expectations, we found reductions in a number of GV parameters in patients with stage 3b CKD. At the same time, significant differences were found between patients with a GFR of 30–44 ml/min/1.73 m2 and those with higher filtration values in terms of the parameters reflecting glucose excursions, mainly in the hyperglycaemic range (HBGI and J-index), as well as the parameter reflecting general variability (MAGE). In multifactorial analysis, we revealed a significant influence of GFR on MAG, the index reflecting the glycaemia change rate.

For proper comparison of GV parameters in patients with different levels of renal function, it is necessary to consider other modifying factors, primarily the features of hypoglycaemic therapy. We found lower GV values (LI and MAG) in patients on glargine that those in the patients on NPH insulin. Previously, Shestakova M.V. et al. reported lower amplitudes of glycaemia excursions in DM2 and DM1 patients receiving glargine insulin as compared with those receiving NPH insulin on haemodialysis [4]. A reduction in GV has been found after switching from NPH insulin to glargine [13]. We must note that in our study, part of patients on insulin analogues as well as the mean daily doses of insulin did not significantly differ among the groups of patients with different levels of renal function. As seen from the clinical characteristics of the three groups and the results of the multifactorial analysis, the differences in the GV indices among the three patient groups cannot be explained by insulin therapy conditions alone.

The phenomenon of the reduction and even disappearance of hyperglycaemia in the normalisation of the HbA1c levels has been described in patients with DM and uraemia as well as in DM patients on haemodialysis. We suggest the term 'burnt-out diabetes' to describe this phenomenon [3, 14]. The mechanism of the disappearance

of the hyperglycaemia in patients with DM having CKD has not been adequately studied. Protein-energy malnutrition, which develops in some patients on dialysis, plays a certain role in the reduction of the glucose level [15]. According to our data, GV reduction in the hyperglycaemic range in patients with DM becomes obvious at the 3b stage of CKD. We suggest the following hypotheses to explain the phenomenon of GV reduction.

The kidneys are an important participant in glucose homeostasis. In healthy individuals, under fasting conditions, about 20%–25% of the glucose released in the bloodstream is formed in the kidneys by means of gluconeogenesis (15–55 g per day) [16]. In patients with DM2, as compared with healthy people, triple the amount of glucose is released into the circulation because of the activation of renal gluconeogenesis [17]. The regularities of the changes in glucose production by the kidneys in patients with CKD have not yet been studied. Presumably, GV reduction in patients with reduced renal function is a consequence of the a reduction in the numbers of functioning nephrons' which, in turn, leads to decreased levels of glucose released into the bloodstream.

Another hypothesis is that GV reduction in CKD is the consequence of decreased sensitivity to endogenous and exogenous insulin, leading to decreased glycaemic fluctuations. The reduction of sensitivity to insulin in CKD may be explained by the development of chronic inflammation, increased volume of visceral fat, disorders in adipokine secretion, vitamin D deficiency, effects of oxidative stress, anaemia, metabolic acidosis, reduction of physical activity or other factors [18]. The association between insulin sensitivity and CKD dynamics in patients with DM2 has not yet been studied. In patients with arterial hypertension, previous researchers have observed decreased insulin sensitivity in patients with GFR reduced to <50 ml/min/1.73 m2 [19] as well as in patients with primary renal pathology having a GFRof <60 ml/min/1.73 m2 [20].

In the present study, we confirmed the rather high frequency of LIG episodes found in a previous study using CGM data from patients with DM2 on insulin [21]. Despite the similar daily dose of insulin and the absence of metformin, the mean glucose levels obtained from the CGM data in patients with a GFR of 30–44 ml/min/1.73 m2 turned out to be lower than those in the patients from other groups. This unexpected result may be explained by prolongation of the effect of insulin preparations. Evidently, a simultaneous increase in insulin resistance and increase in the duration of the insulin effect allow us to explain the absence of increased hypoglycaemic risk (judging by the frequency of LIG episodes and LBGI) that we found in patients with stage 3b CKD.

The present study has some limitations. Due to the single-stage (cross-sectional) design, the causal effects can only be discussed as hypotheses. Further, GV parameters were calculated using short-term CGM data. In addition, the study did not include patients at stages 4–5 CKD, which would likely have allowed us to predict future GV changes. At the same time, this paper represents the first study of GV parameters evaluated using CGM in patients with DM2 having differing levels of renal function, and regularities of GV changes in patients with DM having CKD may be clarified in future studies.

Conclusions

In women with DM2 on basal-bolus insulin therapy, GV parameters are related to renal function. Patients with stage 3b CKD have reduced GV, particularly in the hyperglycaemic band, as compared with those with higher filtration rates.

Information on financing and conflict of interests

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Information of author contribution: V. V. Klimontov provided the idea and design of the study and writing the text; N. E. Myakina performed data collection and processing and writing the text.

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