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METABOLOMIC PROFILING OF PATIENTS WITH GESTATIONAL DIABETES MELLITUS

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ABSTRACT

Relevance. Pregnancy in women with carbohydrate metabolism disorders is classified as a high-risk group for early reproductive losses, obstetric complications, and perinatal morbidity, despite undeniable progress in understanding the pathogenesis, timely correction, and prevention of complications in this cohort of women.

Aim: To study the metabolomic profile of amino acids in women with gestational diabetes mellitus (GDM) to identify potential biomarkers for predicting obstetric and perinatal complications.

Materials and Methods: The study involved 50 pregnant women in the third trimester: 25 with GDM (GDM group) and 25 without GDM (control group). The concentration of 26 amino acids in a morning urine sample was determined for all participants, with analysis performed on the Agilent 1200 HPLC chromatographic system. Statistical processing of the data was carried out using IBM SPSS v. 26.

Results: Three significant metabolites — valine, lysine, and glutamine — were identified. In GDM group, lysine levels were 5.3 times lower, valine 2 times lower, and glutamine 1.61 times lower compared to the control group. These changes may reflect GDM pathogenesis and predict complications.

Conclusion: To enhance the effectiveness of diagnosis, individual management of pregnant women, and prevention of complications in women with GDM, it is important to consider the reduction in concentrations of key amino acids such as valine, lysine, and glutamine, which can serve as predictors of carbohydrate metabolism disorders.

Keywords: gestational diabetes mellitus, biomarkers, metabolomics, early diagnosis, pregnancy complications.

INTRODUCTION

Pregnancy is associated with various adaptive processes. Most metabolic changes are normal physiological responses. However, in some pregnant women, these changes may be disrupted, leading to complications such as the development of gestational diabetes mellitus (GDM). GDM arises from hormonal changes during pregnancy when the placenta releases hormones that decrease the cell's responsiveness to insulin [1]. According to published data, disturbances in the quantity and quality of proteins in a woman's diet during the pre-gravid phase and pregnancy can directly influence the development of GDM [2]. Amino acids are the main building blocks of proteins and are classified as essential and non-essential [3]. All amino acids serve as a dietary foundation for ensuring normal glucose and lipid metabolism and maintaining endocrine balance [4]. In the study by K. Sakurai et al. (2019), it was found that glutamine and ethanolamine serve as informative markers for predicting GDM [5]. F. Han et al. (2024), studying the concentrations of amino acids associated with the risk of developing type 2 diabetes mellitus (T2D), found that the most informative ratio was that of glutamine to glutamic acid (Gln/Glu), which inversely correlates not only with the likelihood of developing T2D but also predicts disease progression [6].

Thus, the content of amino acids in biological fluids, including urine, reflects the condition of the body during pregnancy and may serve as potential biomarkers for the risk of GDM.

AIM

The aim of the study was to investigate the metabolomic profile of amino acids in pregnant women with gestational diabetes mellitus and to identify potential biomarkers for predicting obstetric and perinatal complications.

MATERIALS AND METHODS

A prospective study was conducted at the Perinatal Center of the Kaluga Regional Hospital (Kaluga, Russia). The study included 50 pregnant women in the third trimester, who were divided for two groups: GDM group — 25 women with gestational diabetes mellitus (GDM) and the control group — 25 women without GDM. In the third trimester of pregnancy, a single morning urine sample was collected from all women for the analysis of the metabolomic profile of amino acids. Amino acid concentrations were determined using the Agilent 1200 HPLC chromatographic system. The study focused on 26 amino acids: arginine, valine, histidine, methionine, threonine, leucine, lysine, isoleucine, tryptophan, phenylalanine, alanine, asparagine, aspartic acid, glycine, glutamine, glutamic acid, serine, taurine, tyrosine, ornithine, citrulline, homocysteine, cystine, alpha-aminoadipic acid, alpha-aminobutyric acid, and gamma-aminobutyric acid. Statistical analysis was performed using IBM SPSS 26.0 software.

RESULTS

The results of the study on the metabolomic profile of urine in pregnant women showed that the total amino acid content in urine was reduced in the presence of GDM: in the GDM group this value was 931.5 (Q1–Q3: 658–1020.6) mmol/mol creatinine, while in the control group it was 1197.4 (Q1–Q3: 710.9–1290.8) mmol/mol creatinine, no statistically significant differences were found ($p=0.09$). Statistically significant differences between the groups were found for the concentrations of valine, lysine, and glutamine in the urine of pregnant women. The concentration of valine in the GDM group was 2.32±0.66 mmol/mol creatinine, and in the control group it was 4.37±2.08 mmol/mol creatinine ($p=0.027$); for lysine, 12.41±9.73 and 42.18±15.75 mmol/mol creatinine respectively ($p<0.001$); and for glutamine, 31.62±11.12 mmol/mol creatinine and 51.34±18.14 mmol/mol creatinine respectively ($p=0.012$). Additionally, it was found that the glutamine/glutamate (Gln/Glu) ratio in the GDM group was 4.32 (Q1–Q3: 3.49–5.05), while in the control group it was 9.48 (Q1–Q3: 5.22–11.3), with a significance level of $p=0.008$.

The evaluation of the discriminative ability of GDM development based on the concentration of valine in the urine of pregnant women using ROC analysis (Fig. 1) showed that valine is a statistically significant predictor of GDM (AUC=0.850; 95% CI: 0.658–1.000, $p=0.013$). The cut-off threshold value for valine, which corresponded to the highest value of the Youden index, was 3.370 mmol/mol creatinine. GDM development was predicted when the valine concentration was below this value. The sensitivity and specificity of the obtained predictive model were 100.0% and 75.0%, respectively.

When evaluating the discriminative ability of GDM development based on the concentration of lysine in the urine of pregnant women in the third trimester using ROC analysis, the following curve (Fig. 2) was obtained, which showed that lysine is a statistically significant predictor of GDM (AUC=0.963; 95% CI: 0.863–1.000, $p=0.001$). The cut-off threshold value for lysine concentration in urine, corresponding to the highest Youden index, was 20.620 mmol/mol creatinine. GDM development was predicted when the lysine concentration was below this value. The sensitivity and specificity of the obtained predictive model were 90.0% and 100.0%, respectively.

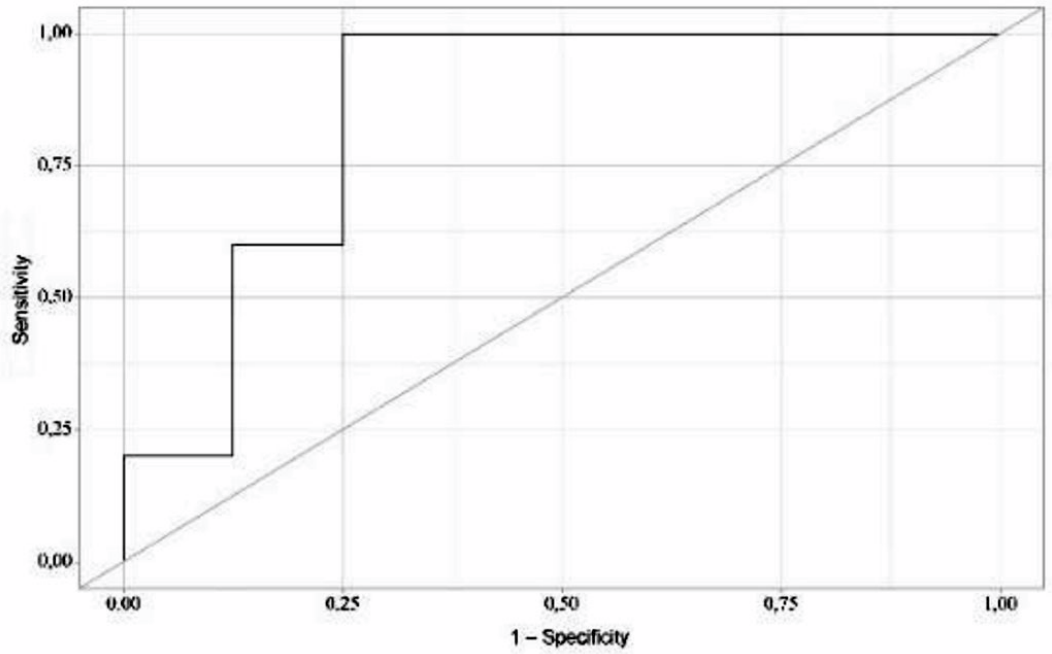

Fig. 1. ROC curve for valine concentration indicators.

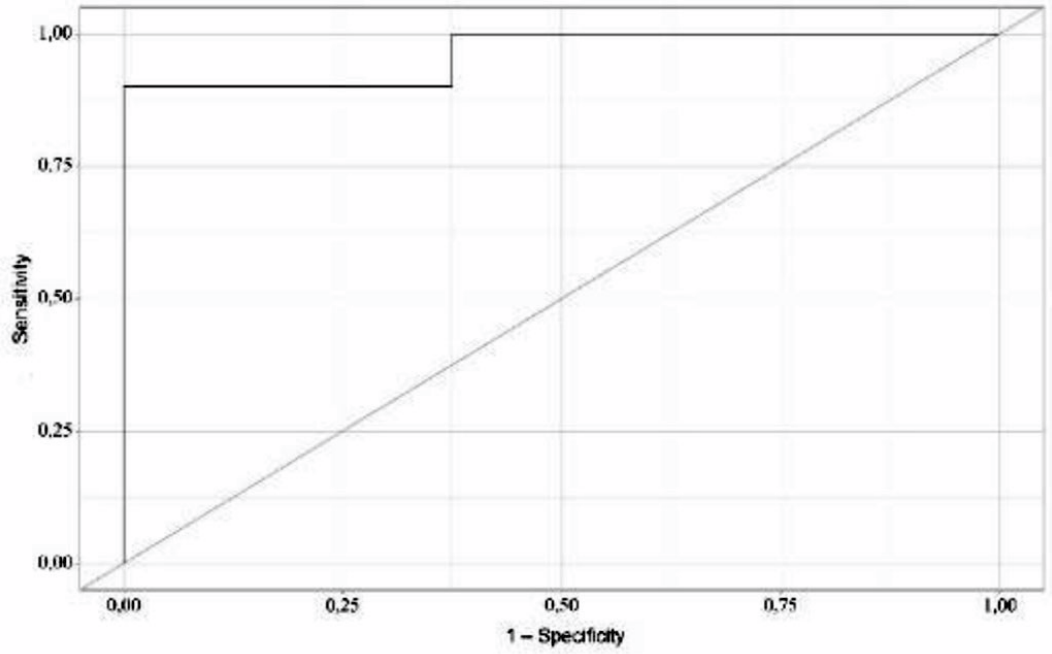

Fig. 2. ROC curve for lysine concentration indicators.

When evaluating the discriminative ability of the absence of GDM based on the concentration of glutamine using ROC analysis, the following curve (Fig. 3) was obtained, which showed that glutamine is a statistically significant predictor of GDM (AUC=0.838; 95% CI: 0.638–1.000, p=0.016). The cut-off threshold value for glutamine, corresponding to the highest Youden index, was 43.340 mmol/mol creatinine. The absence of GDM was predicted when the glutamine value was higher than or equal to this value. The sensitivity and specificity of the obtained predictive model were 75.0% and 90.0%, respectively.

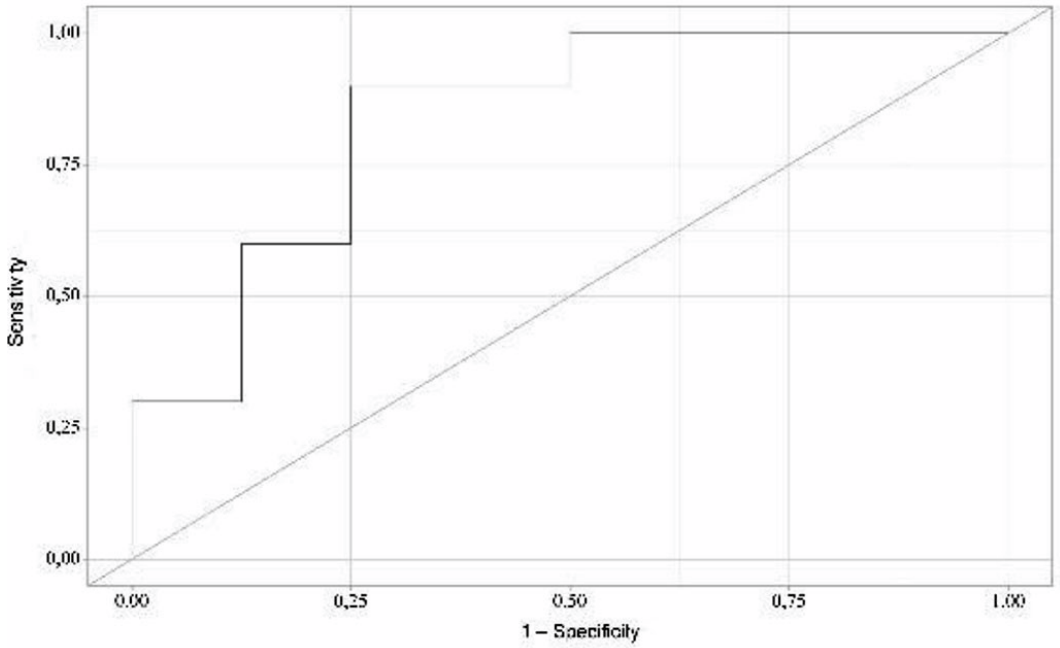

Fig. 3. ROC curve for glutamine concentration indicators.

DISCUSSION

The obtained data indicate significant changes in the metabolic profile in GDM, including decreased levels of amino acids such as valine, lysine, and glutamine. These changes may be of considerable importance for the pathogenesis of the disease, as amino acids play a key role in metabolic exchange, insulin sensitivity, and energy balance in both the mother and the fetus.

A decrease in valine levels may indicate dysfunction in the enzymes regulating BCAA (branched-chain amino acid) catabolism, leading to mitochondrial dysfunction and impaired energy metabolism, which contributes to insulin resistance.

Lysine is involved in protein synthesis and carbohydrate metabolism. Its deficiency can lead to changes in lipid metabolism, the development of dyslipidemia, and hypertension, which increase risks in GDM.

Glutamine, a key regulator of nitrogen balance, is also important for gluconeogenesis and cell proliferation. Its decrease is associated with disturbances in glucose homeostasis and increases the risk of hyperglycemia, as well as complications such as fetal growth restriction and preterm labor.

Thus, the results of the study confirm amino acid disturbances in GDM; however, further research, including studies in the pre-gravid phase and the first trimester of pregnancy, is necessary to confirm their prognostic value.

CONCLUSION

The key to effective prediction and prevention of obstetric and perinatal complications in GDM is the identification of informative biomarkers of metabolic changes occurring in pregnancy. To improve the efficiency of diagnosis, individualization of pregnancy management, and prevention of complications in women with GDM, it is essential to consider the reduced concentrations of key amino acids such as valine, lysine, and glutamine, which may serve as predictors of carbohydrate metabolism disturbances.

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