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PATHOGENETIC SIGNIFICANCE OF ADIPONECTIN, LEPTIN AND RESISTIN IN THE DEVELOPMENT OF INSULIN RESISTANCE IN PREGNANT WOMEN WITH OBESITY AND TYPE 2 DIABETES

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Analysis of scientific publications shows that the most important role in the development of insulin resistance accompanying metabolic syndrome is played by adipose tissue hormones-adiponectin, leptin and resistin. The article presents the results of a study conducted to study the role of adiponectin, leptin and resistin in the development of insulin resistance in pregnant women with abdominal obesity and type 2 diabetes mellitus. The results of the study demonstrate the relationship of metabolic and hormonal changes in the examined patients against the background of carbohydrate metabolism disorders. It has been shown that pregnant women with abdominal obesity and type 2 diabetes mellitus have insulin resistance and hyperinsulinemia. In these patients, there was a decrease in the level of adiponectin and an increase in leptin, and there were no differences in the level of resistin in the blood serum. Against the background of insulin resistance, the insulin level and the HOMA-IR index had a negative relationship with the level of adiponectin and resistin and a positive relationship with the level of leptin. The revealed correlations with insulin and the HOMA-IR index allow us to regard a decrease in adiponectin secretion and an increase in leptin production as a component involved in the formation of insulin resistance and metabolic syndrome in pregnant women with abdominal obesity and type 2 diabetes mellitus.

Key words: pregnant women, insulin resistance, adiponectin, leptin, resistin.

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ПАТОГЕНЕТИЧНЕ ЗНАЧЕННЯ АДИПОНЕКТИНУ, ЛЕПТИНУ ТА РЕЗИСТИНУ У РОЗВИТКУ ІНСУЛІНОРЕЗИСТЕНТНОСТІ У ВАГІТНИХ ЖІНОК З ОЖИРІННЯМ ТА ЦУКРОВИМ ДІАБЕТОМ 2 ТИПУ

Аналіз наукових публікацій показує, що гормони жирової тканини – адипонектин, лептин та резістин – відіграють найважливішу роль у розвитку резистентності до інсуліну, що супроводжує метаболічний синдром. У статті представлені результати дослідження, проведеного для вивчення ролі адипонектину, лептину та резістину у розвитку резистентності до інсуліну у вагітних жінок з абдомінальним ожирінням та діабетом 2-го типу. Результати дослідження демонструють взаємозв'язок метаболічних та гормональних змін у досліджених пацієнтів на тлі дисфункції вуглеводного метаболізму. Показано, що у вагітних жінок з абдомінальним ожирінням та діабетом 2-го типу спостерігаються інсулінорезистентність та гіперінсулінемія. У цих пацієнтів відмічено зниження рівня адипонектину та підвищення лептину, а також різницю рівня резістину в сироватці крові. На тлі інсулінорезистентності рівень інсуліну та індикатора HOMA-IR мав негативний зв’язок з рівнем адипонектину та резістину та позитивний із рівнем лептину. Виявлені кореляційні взаємозв'язки з інсуліном та індексом HOMA-IR дозволяють розглядати зниження секреції адипонектину та збільшення продуктів лептину, як компонент, що бере участь у формуванні резистентності до інсуліну та метаболічного синдрому у вагітних з абдомінальним ожирінням та діабетом 2-го типу.

Ключові слова: вагітні, інсулінорезистентність, адипонектин, лептин, резістин.

According to modern concepts, the main links in the pathogenesis of metabolic syndrome are insulin resistance and abdominal obesity [2, 10]. Adipose tissue has not only an energy function, but is also an active endocrine and paracrine organ. Adipose tissue synthesizes and secretes a large number of biologically active peptides, the so-called adipocytokines, which act both locally and systemically, and affect various links of homeostasis [1, 3, 5, 13, 14]. Adipocytokines are involved in the regulation of energy metabolism and tissue sensitivity to insulin. Violation of the regulation of adipocytokines is reflected in such metabolic and endocrine changes as an increase in body weight and the amount of adipose tissue, insulin resistance [10].

Adiponectin increases the sensitivity of peripheral tissues to insulin, increases fat oxidation, reduces the level of free fatty acids in the blood serum, reducing the intracellular content of triglycerides in the liver of muscle tissue [4, 12]. Leptin is an important secretory peptide that activates the oxidation of fatty acids, thereby regulating the mass of adipose tissue [6]. Resistin affects fat metabolism according to the feedback principle: on the one hand, its concentration increases with differentiation of adipocytes, on the other-resistin suppresses adipogenesis [11].

At the present stage, the biological and pathophysiological effects of adiponectin, leptin and resistin in the human body have not been fully clarified and this issue remains a topic of discussion. The importance of adipocytokines in the formation and progression of obesity and insulin resistance is discussed.

The purpse of the study was to study the pathogenetic significance of adiponectin, leptin and resistin in the development of insulin resistance in obese pregnant women.

Material and methods. A total of 244 patients participated in the study. The studied patients were divided into 2 groups comparable in age: group 1 (n=125) -pregnant women with abdominal obesity; group

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2 (n=39) pregnant women with type 2 diabetes. The control group included 80 pregnant women who did not have a burdened obstetric and gynecological history.

The average age of women in group 1 was 29.0±0.44 years, group 2–30.3±0.90 years, control group – 25.7±0.47 years. Anthropometric studies conducted once in the 1st trimester included measurements of height, body weight, waist circumference (WC) and hips circumference (HC). Calculated the ratio WC / HC and body mass index (BMI). Obesity was diagnosed based on the calculation of the BMI index according to the Quetelet formula: BMI = body weight (kg) / height (m^2). The control group included women with a BMI from 18.5 to 25 kg/m^2. Obesity was regarded as abdominal with a waist circumference of more than 80 cm and an WC / HC ratio of ≥0.85.

To study carbohydrate metabolism, the concentration of venous blood glucose and fasting immunoreactive insulin was measured. To assess the degree of insulin resistance, a small homeostasis model (Homeostasis Model Assessment–HOMA) was used to determine the HOMA-IR index, which was calculated using the formula: HOMA-IR = [insulin, mcunit /ml x glucose, mmol/l] /22.5. A HOMA-IR value greater than 2.7 is considered as the presence of insulin resistance. Another criterion for insulin resistance is the calculation of the CARO coefficient according to the formula: CARO = [glucose, mmol/l/insulin, mcunit /ml]. CARO values below 0.33 indicate insulin resistance. The serum levels of adiponectin, leptin and resistin were studied by enzyme immunoassay.

Laboratory studies were conducted in 29 patients of group 1, 9 patients of group 2 and 80 women of the control group. Blood sampling from patients was performed in the morning strictly on an empty stomach from the ulnar vein.

Statistical data analysis was carried out using the MedCalc statistical software package for biomedical research. The evaluation of the obtained results was carried out by methods of statistical description and verification of statistical hypotheses. To compare normally distributed quantities, the Student's t – test was used, in the case of a difference in the distribution from the normal, the nonparametric Mann-Whitney criterion (U-criterion) was used. The data for the parametric distribution are presented in the form of the mean measured value and the standard error (M±m). The evaluation of the strength and relationship between phenomena or signs was carried out using the Pearson pair correlation coefficient. The critical value of the level of statistical significance (p) when testing null hypotheses was assumed to be 0.05.

Results of the study and their discussion. According to the results of the anthropometric examination, in pregnant women with obesity and type 2 diabetes, the BMI significantly exceeded the control values ($p<0.05$) (Table 1).

Table 1

Anthropometric indicators in pregnant observation groups

Anthropometric parameter	group 1 (n=125)	group 2 (n=39)	Control group (n=80)
Age, years	29.0±0.44* (19–39)	30.3±0.90* (19–39)	25.7±0.47 (17–39)
Height, cm	162.2±0.48 (147–174)	160.3±0.99 (145–171)	160.6±0.59 (148–171)
Weight, kg	100.4±1.12*# (69–136)	84.7±3.11* (54–138)	62.1±0.87 (46–82)
BMI, kg/m^2	38.2±0.44*# (24.7–52.2)	33.0±1.20* (22.8–48.9)	24.1±0.34 (17.8–32.5)
WC, cm	89.2±0.69*# (68–101)	85.7±1.52* (69–101)	73.4±0.48 (67–84)
HC, cm	98.7±0.72* (80–116)	96.7±1.47* (81–115)	88.1±0.65 (76–103)
WC / HC	0.90±0.004* (0.78–0.99)	0.89±0.008* (0.79–0.98)	0.83±0.004 (0.76–0.90)

Note:* $p<0.05$ compared to the control group; # $p<0.05$ relative to the comparison group

In the control group, the BMI values corresponded to the norm – 24.1±0.34 kg/m^2. As can be seen from the presented data, in pregnant women of the two observation groups, the average body weight was higher than the control values ($p<0.05$). Also, in pregnant women of these two groups, the WC was more than 80 cm, and the WC/O ratio was more than 0.85, which made it possible to diagnose abdominal type of obesity in them. The presence of abdominal obesity in pregnant women of group 1 was characterized by a significantly higher BMI (38.2±0.44 kg/m2) and WC (89.2±0.69 cm) compared with group 2 patients with type 2 diabetes mellitus (33.0±1.20kg/m2 and 85.7±1.52cm, respectively) ($p<0.05$).

Overweight and obesity are naturally accompanied by a decrease in tissue sensitivity to insulin and hyperinsulinemia. The study of carbohydrate metabolism in pregnant women with obesity revealed the following features. According to the results of the study of carbohydrate metabolism indicators (table 2), it was found that in the 1st group of women with abdominal obesity, the plasma glucose level was

5.90±0.016mmol/l and significantly exceeded the same index of the control group – 4.62±0.018 mmol/l (p<0.001). The level of glycemia in the group of patients with type 2 diabetes mellitus (5.87±0.027 mmol/l) also significantly exceeded the same index of the control group (p<0.001) (Table 2).

Table 2

Indices of carbohydrate metabolism in women of the examined groups (M±m) (min-max)

Indices	Monitoring groups		
	Group 1 (n=29)	Group 2 (n=9)	Control group (n=80)
Insulin, mcME/ml	16.0±0.57* (11.7–21.3)	15.0±0.76* (12.7–19.0)	8.9±0.16 (7.0–11.5)
Glucose, mmol/l	5.90±0.016* (5.76–6.05)	5.87±0.027* (5.75–6.01)	4.62±0.018 (4.36–4.90)
Index HOMA-IR, unit	4.20±0.25*	3.91±0.78*	1.82±0.17
Index CARO, unit	0.36±0.12*	0.39±0.14*	0.52±0.11

Note: the differences are significant in relation to the control group: * – p<0.001

Insulin resistance (HOMA-IR>2.7) was detected in women of both observation groups, which was accompanied by hyperinsulinemia. The fasting serum insulin level in pregnant women with abdominal obesity was 16.0±0.57 μm/ml, in pregnant women with diabetes mellitus – 15.0±0.76 μm/ml and was 1.7-1.8 times higher than in patients of the control group (8.9±0.16 μm/ml, p<0.001).

The HOMA-IR insulin resistance index in group 1 patients was 4.20±0.25 units, in group 2 patients – 3.91±0.78 units. and was significantly higher than in women of the control group (1.82±0.17 units, p<0.001). The CARO coefficient in the examined women was slightly higher than the quantitative criterion of insulin resistance and amounted to 0.36±0.12 units. in patients of group 1 and 0.39 ±0.14 units – in group 2. In women of the control group, the mean value of this index was equal to 0.52±0.11 units. (p<0.001).

The mean levels of adiponectin, leptin and resistin among all groups of examined patients showed the following. In pregnant women of the control group, the level of adiponectin in the blood ranged from 23.5 to 34.1 mcg/ml and averaged 28.7±0.37 mcg/ml. In pregnant women with abdominal obesity and diabetes mellitus, there was a decrease in blood adiponectin relative to the control values. Slightly more pronounced hypoadiponectinemia was detected in group 1 patients (21.2±0.63 mcg/ml, p<0.001). The mean level of adiponectin in group 2 was 25.4±0.93 mcg/ml (p<0.05). Adiponectin levels in pregnant comparison groups did not significantly differ.

A study of the serum leptin content in pregnant women with abdominal obesity revealed its increase by 2.5 times compared with the control group (40.5±2.66ng/ml versus 16.5±0.61 ng/ml, p<0.001). In patients with diabetes mellitus, the leptin level was 30.4±1.99 ng/ml, which also exceeded the control values (p<0.001). The level of leptin was slightly higher in obese patients compared to pregnant women with diabetes mellitus (p<0.001). Apparently, this is due to the presence of an increased mass of adipose tissue that actively synthesizes leptin. In pregnant women of the 1st group with a higher BMI, the value of the leptin/BMI coefficient was 1.06±0.064 units, in pregnant women of the 2nd group – 0.92±0.016 units, in the control group – 0.68±0.017 units (p<0.001).

There were no changes in the concentration of resistin in pregnant women of both observation groups in comparison with the control group. In group 1, the resistin level ranged from 3.35 to 6.68 ng/ml, the average value was 4.91± 0.198 ng/ml. In group 2, the resistin level ranged from 3.11 to 6.29 ng/ml, the average value was 4.35±0.327 ng/ml. In the control group, fluctuations in its level ranged from 3.43 to 6.62ng/ml, the average value was 4.66±0.083 ng/ml, but the differences between the groups were statistically insignificant (p>0.05).

Our results indicate that in the observed pregnant women, the dysfunction of adipose tissue is determined, which is manifested by the expression of leptin and a decrease in the level of adiponectin. The calculation of the association of expression levels of the studied adipocytokines for each group of patients was presented by us in the form of an index index: index=adiponectin/√leptin x resistin.

The results of the evaluation of the association of these adipokines showed that for the control group, this index was equal to 3.27± 0.16. In the 1st observation group, the value of this index was 1.51±0.09 (p<0.001), in the 2nd group – 2.21±0.11 (p<0.001). A significant decrease in this index in the groups of pregnant women with abdominal obesity and diabetes mellitus may indicate a shift in the balance of adipose tissue hormones. Taking into account the data obtained by us, indicating an increase in the level of leptin, the absence of significant changes in the level of resistin, as well as a decrease in the level of adiponectin, it can be assumed that the imbalance of adipocytokines detected by us using the integral index is determined primarily by the expression of adiponectin and leptin.

Adiponectin plays an important role in the regulation of carbohydrate metabolism in insulin-sensitive tissues. A decrease in the level of adiponectin in pregnant women with abdominal obesity is one of the causes of insulin resistance. In group 1 patients, there was a significant feedback between the level of adiponectin and insulin (r=-0.163, p<0.05) and the HOMA-IR index (r=-0.323, p<0.05). This indicates

that already at the stage of impaired glucose tolerance against the background of hyperinsulinemia and insulin resistance, the level of adiponectin decreases. In group 2 patients, there was also a significant feedback between the level of adiponectin and insulin (r=-0,134, p<0.05) and the HOMA-IR index (r=-0.448, p<0.05).

Leptin secretion is closely related to glucose and insulin metabolism. In obese patients, a statistically significant direct correlation was found between the level of leptin and insulin (r=0.402, p<0.05), as well as between the level of leptin and the value of the HOMA-IR index (r = 0.16, p<0.05), which indicates a certain involvement of leptin in the mechanisms of insulin resistance development. In patients with diabetes mellitus, a significant relationship was established between the level of leptin and insulin (r = 0.128, p<0.05) and the HOMA-IR index (r= 0.234, p<0.05).

Among the metabolic indices, the level of resistin had a negative correlation with the level of insulin (r= – 0.216, p<0.05) and the HOMA-IR index (r= -0.366, p<0.05) in obese pregnant women. In patients with diabetes mellitus, there was also a significant feedback between the level of resistin and insulin (r = -0.389, p<0.05) and the HOMA-IR index (r= -0.542, p<0.05). At the same time, the results of various clinical studies are contradictory and ambiguous. Some authors have identified correlations between the level of resistin, glucose, immunoreactive insulin and HOMA-IR [7, 8], other authors have not found this relationship [9], which does not allow us to unambiguously judge the role of resistin in the development of insulin resistance.

The obtained results demonstrate the relationship of metabolic and hormonal changes in the examined patients against the background of carbohydrate metabolism disorders. It has been shown that pregnant women with abdominal obesity and type 2 diabetes mellitus have insulin resistance and hyperinsulinemia. In these patients, there was a decrease in the level of adiponectin and an increase in leptin, and there were no differences in the level of resistin in the blood serum. Against the background of insulin resistance, the insulin level and the HOMA-IR index had a negative relationship with the level of adiponectin and resistin and a positive relationship with the level of leptin. The results of the study once again confirm the opinion of other researchers [2, 4, 7, 8] about the role of adipocytokine status in the development of obesity and insulin resistance.

Conclusion

The results obtained indicate the development of adipose tissue dysfunction in obese pregnant women, which is manifested by leptin expression and a decrease in adiponectin levels. There were no changes in the level of resistin. The revealed correlations with insulin and the HOMA-IR index allow us to regard a decrease in adiponectin secretion and an increase in leptin production as a component involved in the formation of insulin resistance and metabolic syndrome in pregnant women with abdominal obesity and type 2 diabetes mellitus.

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