UDC 616.379 – 008.64 – 078: 57.08' 175.8

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APELIN-ADDITIONAL MARKER OF INSULIN RESISTANCE

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Abstrakt

The purpose of the present study was to determine the correlations between the state of carbohydrate metabolism and concentrations of apelin in blood of patients with type 2 diabetes mellitus with different phenotypes. Materials and methods: a total of 32 patients with type 2 diabetes mellitus with different phenotypes (13 men, mean age 56,77 ± 1,79 years) were examined. The control group included 20 healthy individuals. Results: the significant elevation of adipocytokine apelin level was found. The significant correlations between body mass index, apelin and the parameters of carbohydrate metabolism were defined. Conclusions: the increased levels of apelin and connection between this adipocytokine and anthropometric parameters, as well as the indices of carbohydrate metabolism suggest that the elevated body weight contributes to activation and strengthening of impact mechanisms of adipose tissue hormones on metabolic status.

Key words: type 2 diabetes mellitus, apelin, body mass index, increased body weight.

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АПЕЛИН - ДОПОЛНИТЕЛЬНЫЙ МАРКЕР ИНСУЛИНОРЕЗИСТЕНТНОСТИ

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Аннотация

Цель исследования – изучение взаимосвязей между показателями углеводного обмена, концентрациями апелина в плазме крови у больных сахарным диабетом типа 2 с различным фенотипом.

Материалы и методы. Было обследовано 32 больных сахарным диабетом типа 2 с различным фенотипом (13 мужчин, средний возраст 56,77 ± 1,79 лет). Контрольную группу составили 20 практически здоровых лиц.

Результаты. Выявлены значимые повышения содержания этого адипоцитокина и наличие значимых корреляционных связей между индексом массы тела, апелином и показателями углеводного обмена.

Выводы. Повышенные уровни апелина в крови, а также связь этого адипоци-токина с антропометрическими показателями и показателями углеводного обме-на дает возможность предположить, что при повышенной массе тела активируются и углубляются механизмы влияния гормонов жировой ткани на метаболический статус при сахарном диабете типа 2.

Ключевые слова: сахарный диабет типа 2, апелин, ИМТ, повышенная масса тела.

Obesity and metabolic syndrome (MS) are considered as a global epidemic of noninfectious genesis [2]. MS occurs in 17.9% of men up to 40 years old and in 43.7% of men between 40 and 55 years in Ukraine and Europe. The incidence of MS is much lower in women and occurs in 7.1% up to 40 years and in 19.9% aged from 40 to 55 years [1].

MS is a cluster of disorders such as insulin resistance (IR), dyslipidemia, visceral (abdominal) obesity, hyperinsulinemia, arterial hypertension, impaired glucose tolerance and type 2 diabetes mellitus (T2DM), nonalcoholic fatty liver disease and other.

It is known, that adipose tissue is an endocrine organ that consists of certain cells – adipocytes that produce the hormone-like substances – adypocytokines. The main physiological role of adypocytokines is the storage of triacylglycerols during the periods of excess calorie intake and mobilization of this reserve in those periods when expenses exceed the supply. The regulation of these processes in adipose tissue is under the direct influence of hormones, cytokines and other factors that are involved in the metabolism of energy [3].

According to current data, a lot of the signal substances are synthesized in the white adipose tissue, including leptin, TNF-α [7], interleukin-6 (IL-6), interleukin-8 [7] and the corresponding soluble receptors. The number of newly discovered substances, which are secreted by adipocytes, is constantly increasing and includes angiotensinogen, angiotensin II, plasminogen activator inhibitor-1 (PAI-1), adiponectin, apelin.

It should be noted that inflammatory changes depend on location of the adipose tissue. The concentration of some adypocytokines and the activity of some enzymes in visceral fat is higher than in the subcutaneous adipose tissue. The production of PAI-1, angiotensinogen, IL-6 dominates in visceral fat (compared to subcutaneous adipose tissue). Besides, the higher ratio of androgens/estrogens and a greater activity of 17-hydroxysteryddehydrogenase is more common for visceral fat. The production of adiponectin and leptin, the higher activity of aromatase prevails in the subcutaneous adipose tissue compared to visceral fat.

The increase of volume of visceral adipose tissue leads to the systemic release of resistin and proatherogenic interleukin. The increased levels of circulating cytokines are associated with the development of IR in muscle tissue. The study which investigated the distribution of adipose tissue (according to magnetic resonance imaging) and functions of microvasculature (by videomicroscope) found that inflammatory condition of the body is associated with visceral obesity and depletions of the microvasculature [4].

Thus, white adipose tissue is in the center of the system of autocrine, paracrine and endocrine signaling substances. There are several evidences that deregulation of the synthesis and secretion of adypocytokines impacts the development of metabolic diseases such as MS, T2DM. Thus, adypocytokines can serve as a link through which obesity and IR become risk factors for T2DM.

The pathological relationship between obesity and T2DM is confirmed by many studies. The 9-fold increased risk of T2DM in men with a body mass index over 30 kg / m^2 demonstrates this relationship particularly evidently [4]. Approximately 80% of patients with T2DM have abdominal obesity [4]. The particular importance in the development of these pathologies is given to the metabolic disorders.

Along with the known pathogenetic aspects of T2DM, there are several factors that have been insufficiently studied, among them – the effects of hormones of adipose tissue (adypocytokines).

Apelin is an adypocytokine, known for its ability to influence the metabolism. Several studies have shown that apelin is secreted by adipose tissue cells of mice and humans [3]. It has been proven that high levels of apelin in plasma and its increased expression by adipose tissue have been determined in laboratory animals with obesity, hyperinsulinemia and hyperglycemia, as well as in persons with obesity and hyperinsulinemia and / or with T2DM.

Therefore, the promising area of research is to investigate the role of adypocytokines in the pathogenesis of obesity and T2DM. Timely detection of these disorders contributes to improving the results of diagnosis of this disease, especially in the presence of increased body weight.

The purpose of the present study was to determine the correlations between the state of carbohydrate metabolism and concentrations

of apelin in the blood of patients with type 2 diabetes mellitus with different phenotypes.

Materials and methods. A total of 32 patients with T2DM with different phenotypes (13 men, mean age 56,77 ± 1,79 years) were examined in the Department of Endocrinology at Kharkov Regional Hospital. The control group included 20 healthy individuals.

The following parameters were determined in the examined patients: body weight, height with subsequent calculation of body mass index (BMI) using the formula:

$$BMI\ (kg/m^2) = weight\ (kg) / height\ (m^2)$$

For the purpose of our research all patients were tested for serum glucose by glucose-oxidase Somogyi-Nelsone assay with a standard method; the level of glycosylated hemoglobin (HbA1c) was determined by kinetic method using «DAC-Spectro Med»; the level of immunoreactive insulin (IRI) – ELISA method using «DRG» set of reagents. The evaluation of IR was performed according to homeostasis model assessment (HOMA) using the formula: HOMA-IR = IRI, mcU/ml * serum glucose, mmol/L / 22,5. The content of apelin (C-Terminus peptide) was determined by immune-enzyme assay using «Raybiotech» set of reagents.

The examined patients were divided into 2 groups that differed by the level of BMI: 1st group – patients with T2DM with normal body weight (n=15), 2nd group – patients with T2DM with increased body weight (n=17).

The correlation analysis was performed between all studied parameters according to their distribution law using Statistica 6.0 licensed program.

During this clinical study we followed the safety precautions for the patients' health, protection of their rights, human dignity and ethical standards in accordance with the principles of the Helsinki Declaration of Human Rights, the European Convention on Human Rights and Biomedicine, and applicable laws of Ukraine.

Results. While comparing the received data, we found significant differences between selected groups not only in comparison with the control group, but also between the patients of the 1st and 2nd groups. The details are shown in the table.

Table

Mean values of indices in the studied groups

Investigated indices	Control group (n=20)	Group 1 (n=15)	Group 2 (n=17)
Age, years	42.55±0.73	55.07±2.89	57.5±2.3
Duration of T2DM, years	-	12.13±1.54	10.1±2
Gender (male/female)	10/10	7/8	6/11
BMI, kg/m²	21.75±0.2	23.18±0.4*	29.9±0.7*/**
Serum glucose, mmol/l	4.98±0.06	8.68±0.53*	8.91±0.34*
HbA1c, %	5.83±0.07	7.24±0.16*	7.3±0.23*
IRI, mcU/ml	3.7±0.29	9.21±0.47*	13.3±0.75*/**
HOMA-IR	0.82±0.06	3.67±0.33*	5.39±0.45*/**
Apelin, pg/ml	171±8.2	262.8±8.3*	296.7±9.2*/**

Note: *-significantly (p<0.05) differs from control group; **– significantly (p<0.05) differs from 1st group

The revealed disorders of carbohydrate metabolism demonstrated that the most difficult achievement of compensation of carbohydrate metabolism was observed in the 2nd group of patients (T2DM and overweight), despite an increase of carbohydrate derangements in all study groups of patients. The levels of apelin significantly increased in patients with T2DM and were higher in patients with increased body weight, which indicated the probable participation of this adypocytokine in the pathogenesis of T2DM and its progression in the presence of increased body weight.

The presence of statistically higher levels of apelin in patients with IR and T2DM confirms the connection of this adypocytokine with the insulin signaling pathway. In other words, insulin is able to control the secretion of apelin and to affect the metabolism due to indirect effects.

The largest increase of apelin was observed in patients with T2DM and overweight, which indicated a reliable involvement of this adypocytokine in the pathogenesis and progression of T2DM in the presence of increased body weight.

The close correlations between indices of carbohydrate metabolism (Fig. 1, Fig. 2) were found in patients with T2DM with different phenotype, and were particularly pronounced between all indices of carbohydrate metabolism in 2nd group with T2DM and overweight. As we can see, increased body weight is an additional risk factor for development of disorders of carbohydrate metabolism, which affects the course and progression of pathological changes in T2DM.

The positive correlations between adypocytokine apelin and indices of carbohydrate metabolism were found in both groups of T2DM.

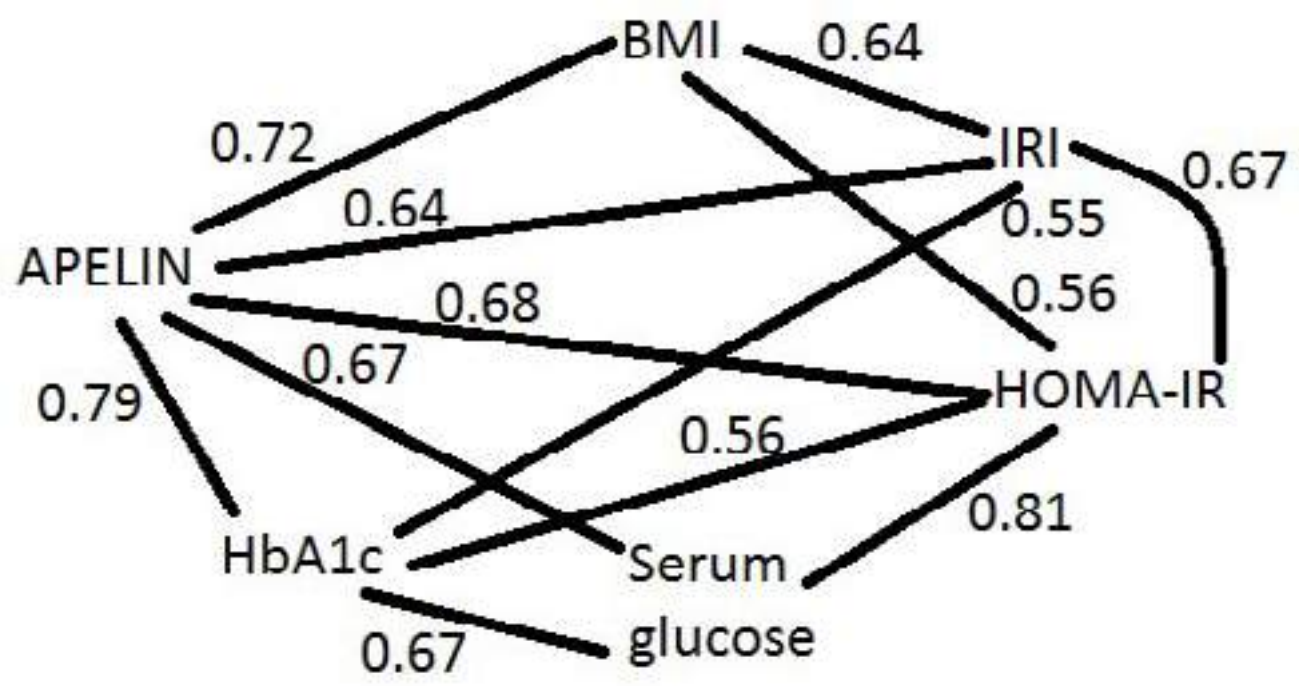

Figure 1. ***Correlations between BMI, apelin and indices of carbohydrate metabolism in 1st group.***

These relations were somewhat weaker or absent in the group of patients with T2DM with normal body weight. The increasing trend of these interactions was found in the group of patients with T2DM and overweight.

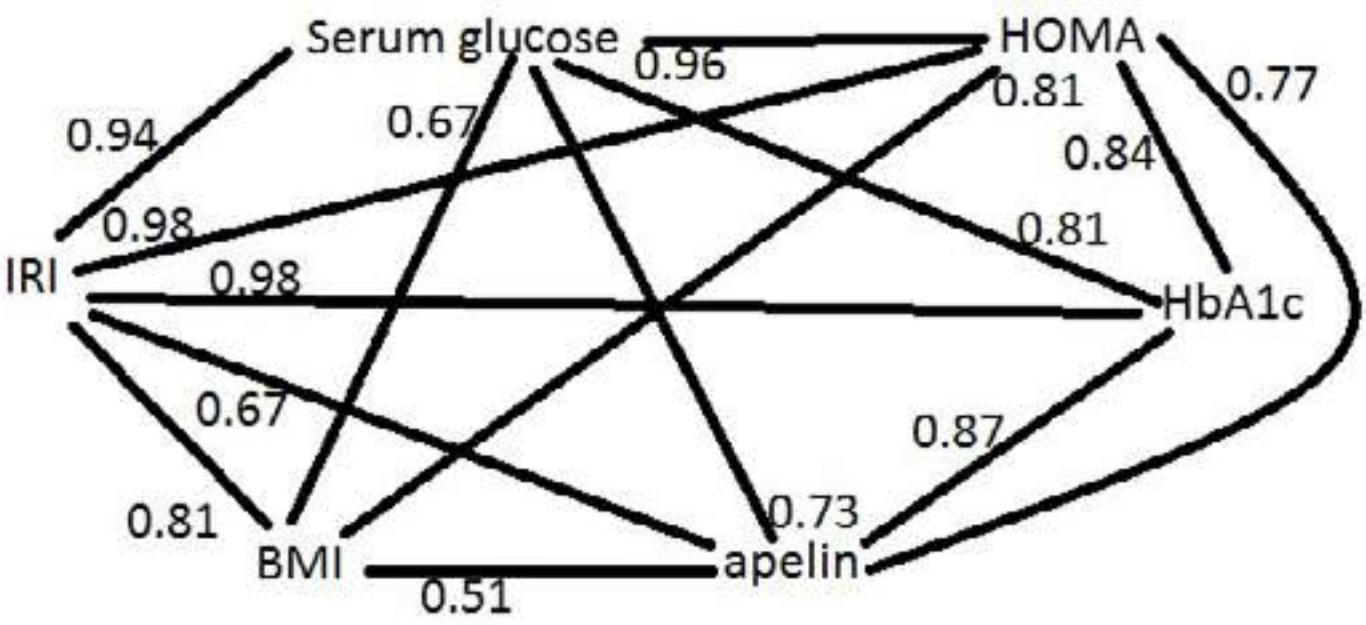

Figure 2. ***Correlations between BMI, apelin and indices of carbohydrate metabolism in 2nd group***

According to some authors, insulin is directly involved in the mechanisms of the regulation of apelin synthesis [4], namely controlling gene expression in adipocytes, which are responsible for the synthesis of apelin, as evidenced by the presence of significant positive correlation between levels of apelin and IRI in our research, with higher interdependence in patients with overweight. The given above data allow to consider apelin as auxiliary diagnostic marker of IR.

The results of the study revealed an increased level of apelin in the serum of all patients with T2DM with different phenotypes, which is associated with slower metabolism that negatively impacts the body as a whole, promotes the development and deepening of late complications. It also is a factor of poor compensation of carbohydrate metabolism, resulting in worsening and progression of T2DM.

Conclusions

1. The moderately increased levels of indices of carbohydrate metabolism and apelin were found in patients with T2DM and normal body weight.

2. The significantly increased levels of apelin were found in patients with T2DM and overweight, while the levels of carbohydrate metabolism indices increased moderately. Probably, hyperapelinemia is an additional indicator of progression of metabolic changes and aggravation of IR in patients with T2DM with BMI over 25.0 kg/m^2.

3. The significant correlations between BMI, carbohydrate metabolism and apelin in both groups may indicate the interpotentiating role of these factors in the progression of T2DM, which deepens in patients with increased body weight.

Prospects for future research

The continuation of studies in this area should be aimed at establishing the other equally important factors of occurrence and progression of T2DM. It is necessary to continue the further research in this area, in particular when phenotype changes are present.

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