

# ADIPONECTIN AND LEPTIN INDICES IN PATIENTS WITH CHRONIC PANCREATITIS

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**Key words:** chronic pancreatitis, adipocytokines, adiponectin, leptin, insulin resistance

## **Introduction**

Adipose tissue is more often considered as a separate organ, taking part in the role of pathogenesis development of many diseases and secreting a significant number of biologically active peptides (adipocytokines), which act both on a local (autocrine/paracrine) and systemic level [1]. Adiponectin, leptin and resistin are referred to the main adipocytokines.

Adiponectin reduces the level of glucose production by the liver, increases glucose utilization and oxidation of fatty acids in muscles, inhibits expression of adhesion molecules and proliferation of smooth muscular cells of the Vessels, and also suppresses conversion of macrophages into foam cells (lipophages), retards proatherogenic processes in the cells of the liver and pancreas (P) and has antiinflammatory effect [1]. Adiponectin plasma level is lower in patients with diabetes mellitus type II (DM 2) than in people without it [4]. AMPH-kinase activation under adiponectin influence reduces insulin resistance (IR), and data, obtained in a large population research Hoorn, including 2484 participants at the age of 50–75 years, testify to the fact that high levels of adiponectin are associated with less risk of the development of tolerance disorders to glucose and DM 2. Adiponectin concentration is reduced according to obesity development [10].

Leptin, peptide hormone of adipose tissue, is responsible for energy metabolism, metabolism and state of hunger and satiation. Leptin receptors are mostly represented in hypothalamus as well as on the cells of hypothalamus, lungs, endothelium muscles and  $\beta$ -cells of the P [6]. Leptin plays a significant role in appetite reduction, decreases food consumption and use of fats in energy metabolism.

An increase of leptin content is observed under conditions of obesity (though in a part of person with obesity this index is in health), excessive feeding, excessive quantity of rich food in dietary intake, administration of insulin, glucocorticosteroids, estrogens, hyperproduction of endotoxins and cytokines [3].

The role of adipokines in the development of pancreatic diseases is intensively studied, and pancreatic injuries are considered as original cause of the development of metabolic disorders that lead to obesity and DM type 2. IR is connected with functional pancreatic insufficiency as a result of secretory dysfunction of islet apparatus, an increase of lipid peroxidation activity due to hypoxic processes in the gland [7, 9].

Thus, main adipocytokines play a certain role in dietary intake behavior, psychological state of the patients suffering from chronic pancreatitis (ChP) because of the system of glucocorticoids, sexual, thyroid hormones in carbohydrate metabolism. These systems influence on the course of not only metabolic but hormonal processes both in case of exacerbation and clinical course remission at the disease onset and sufficient prescription of the course, and may also influence upon clinical course of the disease itself in every concrete case.

**The aim of research** is to investigate the indices of adiponectin and leptin in the patients with ChP.

### **Materials and methods**

32 patients aged from 27 till 71 with ChP were examined during the period of exacerbation. That is persons of the middle age and elderly patients prevailed by age structure, persons of the middle age ( $49,0 \pm 7$  years) predominated according to statistical data. There were 22 women (68,75%) and 10 men (31,25%) among them. According to anamnesis data it was established that prescription of ChP constituted 5-12 years in the majority of patients, acute condition of the disease was 1-2 times a year, and in this connection they were administered in-patient care. The majority of the patients connected exacerbation with malnutrition (using rich, fried food, alcohol and aerated drinks, fresh shortening). Chronic recurrent pancreatitis (ChRP) was observed in 8 patients (25%). Concomitant gastroenterologic pathology (chronic

noncalculous cholecystitis, chronic gastroduodenitis) was revealed in 12 patients (37,5%) and 10 patients (31,25%) had ischemic heart disease. Control group consisted of 20 apparently healthy persons. Diagnosis of ChP was verified according to the order of MPH of Ukraine №271 from 13.06.2005 [5]. All patients under research underwent a careful examination using generally accepted clinical, laboratory and instrumental investigation. To diagnose ChP determination of  $\alpha$ -amylase activity of the blood serum (Karavei amyloclastic method) and urine diastase, was carried out, external secretory function of P was estimated by the content of fat in the feces (according to the method of Van de Kramer) and coprogram data (estimation was carried out by the method of L. V. Kozlovska and O. Y. Nikolayev). Besides, biochemical investigation included determination of blood glucose on an empty stomach, activity of alanineaminotransferase (ALT), aspartataminotransferase (AST), alkaline phosphatase (APh), content of general bilirubin, proteinogram, coagulogram.

Structural change of the P were revealed by means of ultrasonographic investigation ("Aloka" SS-630 (Japan). Sizes of P and its parts (head, body, tail), clearness of circuits, homogeneity of the structure, exogeneity, diameter of Wirsung's duct, presence of pseudocysts, calcification were estimated. P structural state was evaluated by Cambridge classification [2], determining degrees of the process difficulty and giving a certain ball to every degree. P health (0 balls) — its sizes are in health, size of the main pancreatic duct (MPD) is about 2 mm, parenchyma is homogeneous. Questionable changes (1 ball) — dilatation of the MPD to 2-4 mm, sizes of P are in the limits of 1-2 norms, parenchyma is not homogeneous. Mild changes (light degree — 2 balls) — two or more signs of the following MPD — 2-4 mm, insignificant increase of P sizes, parenchyma heterogeneity, P circuits are not distinct. Moderate change (a process of median difficulty, 3 balls) — small cysts (less than 10 mm), irregular MPD, acute focal necrosis, rise of exogeneity of MPD walls, uneven circuits of the P. Significant changes (4 balls, difficult degree) — some of the signs cited above and also one of more following signs: cysts are larger than 10 mm in diameter, intraductal defects of filling, pancreatic calculus (pancreatic

calcification), obstruction or stricture of MPD, evident dilation or irregularity of MPD, invasion into neighbouring organs.

When it was necessary the patients were administered gastroduodenofibroscope (IDFS), roentgenologic investigation of the stomach and duodenum.

Besides, antropometric examination was carried out too: stature (m), body mass (kg) were defined, body mass index (BMI, kg/m) was calculated according to Kettle formula.

Determination of leptin and adiponectin level in the blood was carried out by the method of immunoenzyme analysis using such sets of reagents: Leptin Elisa (Diagnostics Biochem Inc.), AssayMax Human Adiponectin Elisa Kit. Statistical processing of the results obtained was carried out using "Statistica for Windows version 8.0 programme" with calculation of confidence intervals.

### **Results of research**

Having analyzed the main complaints of the patients, data of physical investigation and the results of supplementary methods of examination, it has been revealed that ChP clinical course is defined by the formation and progression of such syndromes: pain syndrome (in 85,3% of patients), dispeptic one (in 62,3% of patients), outersecretory insufficiency of P (46,8% patients). Pain syndrome was characterized by intermittent aching, dull pains, sometimes of belting character with irradiation to the left and right hypochondrium, back, which increased at the patient's dorsal position and decreased in sitting position and forward inclination of the body. There is brightly pronounced pain syndrome in case of ChRD: pains are more intensive, acute, stablign, more often belting with irradiation to the back, and at ChP exacerbation dispeptic syndrome, accompanied by lowering or absence of appetite, eructation, nausea, vomiting which does not give relief prevailed in complaints. Outerexcretory maldigestion insufficiency declared itself by (bloating and gurgling, pancreatogenous diarrhea 2-3 times a day with parridge — like stool excretion of fatty brightness with undigested food debris).

Estimation of anthropometric data has shown that 26 patients (81,25%) had normal body weight (within the limits of 19-24,9 kg/m), and there was a body weight

deficit ( $BWD < 18,9 \text{ kg/m}$ ) in 6 patients (18, 75%). It should be noted that BWD was more often observed in alcohol abused men.

There was a moderate leukocytosis with a shift of leukocytic formula to the left, somewhat accelerated ESR in general blood analysis of all patients. Glucose levels in the blood are higher in the patients with ChP in comparison with the group of apparently healthy persons, although in the limits of statistical standard ( $4,44 \pm 0,18 \text{ mmol/l}$  and  $4,35 \pm 0,20 \text{ mmol/l}$ , accordingly).

Taking into consideration USD criteria of ChP changes of the gland echogenicity were observed mostly in the form of the areas of increase and decrease of echo signal (87,5%), dilatation of pancreatic duct more than 2 mm (43,75%). Changes of sizes have been revealed only in 6,25%, mainly due to an increase of the head of P.

When carrying out the analysis of adiponectin level its ranges have been determined: median and interquartile range in the patients with ChP made up 1,95 ng/ml (the 25th percentile — 1,2 ng/ml, the 75th percentile — 3,1 ng/ml), in the control group — 2,85 ng/ml (1,65 — 4,2 ng/ml). Patients with ChP were divided into 2 subgroups. In the first subgroup, consisting of 23 (71,88%) patients under study, adiponectin level (median and interquartile range) made up 1,5 ng/ml (the 25th percentile — 1,0 ng/ml, the 75th percentile — 2,3 ng/ml). Men of normal body weight with more evident clinical symptoms (more intensive abdominal pain, alternation of dispepsia and constipation, nausea and vomiting) predominated in this group. Signs of P fibrosis prevailed according to USD results. In the second subgroup — 9 patients (28,12%) median and interquartile range made up 3,6 ng/ml (the 25th percentile — 3,3 ng/ml, the 75th percentile — 3,7 ng/ml), patients with BWD were included to this group.

Decrease of adiponectin level in the majority of patients may be explained by the presence of chronic inflammation of little intensity, exhausting its protective anti-inflammatory activity, insulin resistancy (hyperglycemia, hyperinsulinemia) due to the same immune chronic inflammation, which may indicate the risk of DM type a development, despite the absence of obesity sings. Such presumption is confirmed by

literary data that adiponectin suppresses activity of macrophages and myelomonocytes, inhibits synthesis of antiinflammatory cytokines TNF- $\alpha$  [11]. Considering antiinflammatory effect of the given adiponectin it is possible to assume that it plays a certain role in the organism defence from the progression of chronic inflammation in a latent course and formation of atherogenic dyslipidemia, since IR and atherogenic dyslipidemia have in their development a close connection with chronic immune inflammation.

Estimating leptin content in the patients' blood it has been revealed that median and interquartile range made up 10,2 ng/ml (the 25th percentile — 5,4 ng/ml, the 75th percentile — 27,05 ng/ml). The given patients were divided into three subgroups. In the first group consisting of 14 persons (43,75%) median and interquartile range made up 5,05 ng/ml (the 25th percentile — 2,9 ng/ml, the 75th percentile — 5,7 ng/ml), not distinguishing from the control meanings, in the second group — 8 patients (25%) — 17,7 ng/ml (10,2 — 18,8 ng/ml), in the third one — 10 persons (31,25%) — 31,5 ng/ml (28-33 ng/ml), that in 3-5 times exceeded indices in the group of apparently healthy persons. Leptin level was somewhat lower in comparison with the sick persons (median 7,5 ng/ml and interquartile range 5,5-12,0 ng/ml) in practically healthy persons. It is possible to explain such range of indices in these groups of patients by the presence of concomitant biliary pathology, ischemic heart disease, where metabolism and energy metabolism are impaired, atherogenic dyslipidemia and insulinresistancy progress influencing on leptin receptors in hypothalamus, vessels endothelia and  $\beta$ -cells of P (may be promoting the development of lipoidosis interstitium of the gland) [8].

### **Conclusion**

The obtained results of adiponectin and leptin indices in patients suffering from chronic pancreatitis confirm their changes depending upon the evidence of clinical symptomatology, intensity of chronic immune inflammation, concomitant pathology and clinical course of chronic pancreatitis. Adiponectin indices decreased in the majority of cases, but leptin indices increased concerning indices of apparently healthy persons, not having obvious connection with obesity.

### **Perspectives of further research**

It is obvious that some cytokines, for example TNF-  $\alpha$ , IL-6, C-reactive protein increase leptin level, maintaining, in such a way, chronic inflammation of little intensity, that is one of the main links of chronic pancreatitis pathogenesis, therefore we consider expedient to investigate the levels of the given indices in such patients. So long as, some physiological factors, such as age, gender, may significantly influence on the levels of circulating adiponectin and leptin, it should have estimated the content of adipokines data depending on gender peculiarities.

## References

1. Косыгина А. В. Адипоцитокіни в науковій і клінічній практиці / А. В. Косыгина // Ожирение и метаболизм. — 2011. — № 1. — С. 32–39.
2. Крилова О. О. Методи візуалізації підшлункової залози та стан панкреатобіліарних проток у хворих на хронічний панкреатит / О. О. Крилова // Сучасна гастроентерологія. — 2011. — № 4 (60). — С. 45–53.
3. Лептин та його роль у внутрішній патології / О. М. Радченко, О. Р. Слаба, Н. С. Бек, Л. М. Радченко // Мед. гідрол. та реабіл. — 2011. — № 4. — С. 101–109.
4. Майоров А. Ю. Состояние инсулинорезистентности в эволюции сахарного диабета 2 типа : автореф. дисс. на соиск. науч. степени докт. мед. наук: спец. 14.00.03 «Эндокринология» / А. Ю. Майоров. — М., 2009. — С. 25–27.
5. Наказ МОЗ України № 271 від 13.06.05 р. — К., 2005. — 146 с.
6. Патологіологічна роль ожиріння у розвитку захворювань підшлункової залози / І. В. Лещенко, В. Г. Шевчук, С. А. Суходоля, Т. М. Фалалєєва // Вісник Вінницького національного медичного університету. — 2013. — № 2, Т. 17. — С. 499–504.
7. Христич Т. М. Можлива роль функціонального стану підшлункової залози у розвитку та прогресуванні метаболічного синдрому / Т. М. Христич, Т. Б. Кендзерська // Мистецтво лікування. — 2006. — № 4. — С. 53–58.
8. Христич Т. Н. Дисметаболические формы хронического панкреатита / Т. Н. Христич, Т. Б. Кендзерская, И. В. Трефаненко // Сучасна гастроентерологія. — 2004. — № 6 (20). — С. 79–84.
9. Nonalcoholic fatty pancreas disease / A. Mathur, M. Marine, D. Lu [et al.] // HPB (Oxford). — 2007. — Vol. 9. — P. 312–318.
10. Prognostic value of adiponectin for cardiovascular disease and mortality / J. M. Dekker, T. Funahashi, G. Nijpels [et al.] // J. Clin. Endocrinol. Metab. — 2008. — Vol. 93, No 4. — P. 1489–1496.
11. Tilg H. Adipocytokines: mediators linking adipose tissue, inflammation and immunity / H. Tilg // Nature Rev. Immunol. — 2006. — Vol. 6. — P. 772–783.

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Article presents the results of determining the levels of main adipocytokines (adiponectin and leptin) in patients with chronic pancreatitis, depending on the severity of clinical symptoms, intensity of low-intensity chronic inflammation and progression of chronic pancreatitis. The increase of leptin and adiponectin reduction is detected in a group of patients as compared with a group of almost healthy persons.