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# THE ROLE OF CHRONIC PANCREATITIS IN METABOLIC DISORDERS OF BONE TISSUE AND THE FORMATION OF OSTEOPOROSIS

***Mirzaeva Gulchehra Payzullaevna***
*Tashkent medical academy*
*Department of faculty and hospital therapy № 2, nephrology and hemodialysis*

**Abstract.** The paper presents the results of the study of bone tissue metabolism in 49 patients with chronic pancreatitis. It is shown that the development of the disease, its chronic and recurrent character of course with violation of excretory and incretory function of the pancreas contributes to the formation of osteopenic syndrome, which is confirmed by changes in the content of bone tissue markers (bone isoenzyme of alkaline phosphatase and tartrate-resistant acid phosphatase), as well as bone mineral density according to densitometric study. The obtained results are recommended to be used in the correction of therapeutic measures (diet, calcium preparations, bisphosphonates) in patients with chronic pancreatitis.

**Key words:** chronic pancreatitis, bone tissue metabolism, osteopenic conditions.

## INTRODUCTION

Chronic pancreatitis (CP) belongs to those diseases of internal organs, which by prevalence, increase in morbidity, temporary loss of working capacity and cause of disability are considered from the position of an important socio-economic problem. In the structure of digestive organs morbidity CP makes up 5-9%, and in general clinical practice it occurs in 0.2-0.6% of cases. In the world over the last few decades, the statistics of patients with chronic pancreatitis has increased many times. In addition, this disease has significantly “grown younger”: the average age of such a patient has decreased by 11 years - from 50 to 39. At the same time, the contribution of alcoholic pancreatitis has significantly increased - the previous 40% increased to 75% [6,12].

In Uzbekistan, a more intensive growth of morbidity has been noted. Thus, the prevalence of pancreatic gland (PG) diseases among adults has increased threefold over 10 years, and among adolescents - more than fourfold; and the proportion of women has increased by 30%. This trend is associated with the increase in alcohol consumption, including low-quality alcohol, reduction of food quality and general standard of living [12,18].At the same time, it is noted that the values of morbidity rates are constantly growing due to the improvement of diagnostic methods - the recent emergence of new methods of imaging of the pancreas with high resolution, allowing to detect CP at earlier stages of disease development [7]. However, it is stipulated that against the background of improved diagnostics of the main pathological process developing in the organ, complications are quite often formed, which are caused not only by inflammatory changes or fibrosis development in the gland, but also by other links of pathogenesis, triggering this process.

Among such complications, secondary osteoporosis (SO) is considered, the occurrence of which is associated not only with impaired digestive processes, but also with impaired synthesis of hormones, particularly insulin [3,10,14]. Considering OP as an independent nosological form, all points to many potentiating factors and conditions contributing to its development. Thus, in uncomplicated CP the change in bone tissue metabolism is associated with impaired absorption of calcium and vitamin D in the intestine against the background of cavity digestion disorders - maldigestion and malabsorption develop. In this case, bone tissue remodelling may be a consequence of both low calcium intake and increased calcium excretion [14,16,17]. In a number of earlier studies the role of calcium in the secretory process of digestive glands was established. It has been shown that the production of calcium ions and enzymes in the pancreas proceeds in parallel. Released calcium triggers enzyme secretion and opens channels in the plasma membrane permeable to Ca2+, C1~, K+ ions, thus leading to depolarisation of cell membranes. Consequently, an insufficient amount of calcium in serum will favour its release from the depot - bone tissue [1,5,21]. In addition, the resulting hypodynamia also favours the precipitation of calcium salts, which in 72% of cases leads to calcification of the pancreas. There is also an inverse relationship: the presence of calcification in the duct of the PG can potentiate the development of CP. High pressure is created in the duct, as a result of which the stone can move, and it will disrupt the integrity of the epithelium and proteolytic enzymes will penetrate to the unprotected acinose (secreting) cells and digest them [10,12]. Consequently, calcium imbalance in the body can not only trigger the pathological process in PJ, form the exacerbation of the disease and lead to its progression, but also contribute to the development of osteoporosis [1,14].

Purpose of the study. To determine the state and role of calcium metabolism in the organism of CP patients and to determine the mechanisms of secondary osteoporosis formation.

Materials and methods of the study. There were 49 patients with CP under observation, the average age of which was 38,2±4,5 years, and duration of the disease - from 2 to 14 years. Women (59,2%) prevailed among the examined patients. In 57,1% of cases (28 patients) formation of CP was preceded by diseases of biliary tract; in 42,9% (21 patients) - by alcohol abuse. In addition to conventional laboratory tests and coprological examination we determined the level of faecal elastase (a marker of the state of excretory function of PG), the content of glycosylated haemoglobin in blood serum; we performed glucose tolerance test, which allowed to estimate the incretory function of the organ. The activity of the pathological process in the gland was assessed by determining the levels of proinflammatory cytokines - IL-1β and TNF-α (Protein Contour reagent kit, St. Petersburg). Among biochemical markers of bone tissue remodelling, two groups of studies are considered for OP diagnosis: the first group includes calcium-regulating parathyroid and thyroid hormones, active metabolites of vitamin D3, the main function of which is to maintain the calcium level in the body. The second group of markers controls bone formation and resorption, i.e. the results of osteoclasts and osteoblasts [2,4]. Bone synthesis markers are represented by osteocalcin, type I collagen peptides, total alkaline phosphatase and its bone isoenzyme [8,9,13].

As a marker of bone tissue synthesis, we studied the content of bone isoenzyme of alkaline phosphatase (BAP); bone resorption - by the content of tartrate-resistant acid phosphatase (TRAP) in blood [4,11]. The activity of these enzymes was determined by biochemical method (Bodansky's method). The determination of the content of both enzymes is based on the determination of the amount of phosphate that is released after incubation of the enzyme with sodium glycerophosphate for one hour at 37°C. The bone tissue condition was tested using ultrasound method - densitometry (Achilles Express GE LUNAR device, USA, 2010), which allows to estimate the possibility of osteoporetic conditions by the state of bone mineral density (MPDT) - the heel bone was examined - [18,20]. This non-invasive method is based on the measurement of sound propagation velocity in bone and provides a qualitative

assessment of the state of trabecular bone tissue and its architectonics. The following parameters are assessed during densitometry:

- ultrasound propagation velocity (m/s), which depends on bone density;

- broadband attenuation of ultrasound (BAU) - an index that characterises the loss of ultrasound intensity in the medium and assesses the state of bone trabeculae: their number, size and spatial orientation of trabecular bone tissue, the presence of microdamage;

- bone density or stiffness index, which characterises bone density and is calculated taking into account the two previous parameters;

- T-criterion (deviation of bone mineral density of a given patient from the average value of this indicator in healthy elderly patients of the corresponding sex)

- Z-criterion (deviation from the values in groups of people of the same age, sex and body weight as the patient).

In clinical practice, individual bone mineral density is compared to a reference database, and assessed using T- and Z-criteria. Control results of biochemical and instrumental methods of research were obtained during the examination of 50 practically healthy individuals, and the control group was filled according to the principle of structural proportionality.

Statistical processing of the obtained results was carried out using one- and multivariate analysis of variance (packages of licensed software "Microsoft Excel", "Stadia.6.1 prof", "Statistsca").

Research results and their discussion. The diagnosis of chronic pancreatitis was established at the previous stages of diagnostics and treatment of the examined patients using the approved "Clinical protocols of medical care for patients with chronic pancreatitis". The glucosotolerant test allowed in 28.6% of cases (14 patients) to establish a violation of the incretory function of the pancreatic duct, which led in 9 patients to the development of insulin resistance, and in 5 cases - to diabetes mellitus. At elastase test (by the level of faecal pancreatic elastase-1), characterising the excretory function of the PG, a mild form of extrasecretory insufficiency was established in 16 cases (32,7%), of medium severity - in 33 (67,3%). At ultrasound examination of the PG moderately expressed fibrosis of the organ parenchyma (31 patients) with irregularity of its structure, jagged contour and reduction of the gland size were noted. With predominance of inflammatory changes in the gland (18 patients), decrease of tissue echogenicity, blurred contour, increase in the size of the gland or its part, dilation of the virsung duct were determined. IL-1β content in serum of patients with CP was 73,2±4,6 pg/ml with norm 19,7±0,8 pg/ml, and TNF-α level exceeded the norm 3,1 times - up to 63,1±1,8 pg/ml, with control - 20,3±0,8 pg/ml ($P<0,05$). It should be noted that the values of these parameters correlated with the etiological factor of the disease: in its alcoholic genesis IL-1β was 58.9±2.3 pg/ml, and TNF-α - 51.4±2.1 pg/ml; in biliary genesis - 82.1±2.1 pg/ml and 71.1±2.4 pg/ml, respectively. The direct dependence of the indicated parameters on the degree of severity of external secretory function of PG was also established: at its mild degree the indicated cytokines were slightly higher than at the average degree of severity ($P>0,05$). When studying the activity of bone tissue synthesis marker it was found that the pathological process in PG was accompanied by a decrease in BMSCF to 41,3±2,1% (normal - 65,2±5,1%, $P<0,05$). At the same time, in the age group up to 35 years old the level of CRP corresponded to 52,7±4,6%, and after 35 - 34,6±2,1%. There was also noted a correlation between CSFBF and sex of patients: in women this index was slightly lower than in men.

When studying the values of bone tissue resorption, an increase in its activity was found, which was manifested by an increase in the level of TRKF up to 3.41±0.2 units of Bodansky with the control - 0.92±0.14 units. Moreover, if at the age up to 35 years this index was 1.73±0.2 units, then after 35 years - 3.57±0.17 units. TRCF levels also had a direct dependence on the sex of patients, but did not correlate with the etiological factor of the disease. It was not possible to note changes in the indicated values

taking into account the duration of anamnesis, which can be explained by the following by a small number of patients (up to 5 years - 13 patients: 6-10 years - 21 and more than 11 years - 15). There was also no dependence of the studied parameters on duration, frequency of exacerbations, incretory function of PG and etiological factor of the disease.

Thus, in patients with CP there are changes in bone tissue remodelling parameters with imbalance of bone synthesis and resorption processes, the result of which is the formation of systemic osteodeficiency.

Apparently, this condition is caused not only by impaired digestive processes arising from the insufficiency of the enzymatic function of the gland, but also by the activation of the

Ultrasound diagnostics of bone tissue state allowed to establish a decrease in bone mineral density (BMD) in 73.5% of patients (36) with CP, with osteopenia in 15 cases and osteoporosis in 21 (Table). Thus, the decrease in the activity of pancreatic enzymes in CP can occur as a result of a vicious circle development: impaired enzyme production in PG in chronic pancreatitis leads to impaired calcium absorption in the intestine. In turn, decrease of total and ionised calcium in blood serum decreases production of PG enzymes, because enzymatic activity of PG is provided by the presence of calcium ions directly involved in enzyme synthesis. I.e. a situation is created, when replenishment of calcium lacking for formation of enzymes in PG occurs at the expense of its leaching from bone tissue. Consequently, hypocalcaemia is the trigger mechanism that increases the resorption processes in bone tissue, thereby contributing to the development of OP.

**Conclusions.**

The development and course of CP leads to the formation of symptoms of maldigestion and malabsorption, which reduces the absorption of calcium and vitamin D in the intestine and thus favours its withdrawal from the depot.

Chronic recurrent pathological process in the pancreas is a factor contributing to the disruption of bone tissue remodelling processes due to both impaired intake of this macronutrient into the body and its increased excretion. The development of osteopenic conditions in patients with chronic pancreatitis is the basis for correction of dietary measures and prescription of replacement therapy. Further study of the role of some genetic markers in the development of osteoporosis in patients with chronic pancreatitis is planned.

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