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Research Article

Structural and Functional Condition of Bone Tissue in Patients with Chronic Pancreatitis, Considering the Polymorphism of Vitamin D and Lactase Receptor Genes

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Abstract

Osteoporosis is characterized by deterioration of bone structure and low bone mass, which leads to bone fragility and increased risk of fracture. Osteoporosis is a serious public health problem because of its potentially serious consequences for both patients and the health care system. Chronic pancreatitis is a progressive inflammatory disease that leads to exocrine and endocrine dysfunction. Exocrine dysfunction leads to a decrease in the production of digestive enzymes of the pancreas, which results in improper absorption and malabsorption of nutrients, leading to nutrient deficiency, thereby creating the conditions for the development of secondary osteopenic conditions.

Keywords: Osteoporosis; Osteopenic Conditions; Chronic Pancreatitis; Vitamin D Receptor Gene; Lactase Gene

Abbreviations

CP: Chronic Pancreatitis; OP: Osteoporosis; VDR: Vitamin D Receptor; LCT: Lactase Gene; PCR: Non-polymerase Chain Reaction; BMD: Bone Mineral Density; DEXA: Dual-energy X-Ray Absorptiometry; CCP: Pearson χ-square Test; CMU: Non-parametric Mann-Whitney Test

Introduction

In recent years, there has been an increase in people with pathology of the musculoskeletal system, which is associated with the spread of so-called "calcium-dependent" diseases and a significant increase in the relative number of people of older age groups. Pancreas is one of the organs of the digestive tract, which works in the presence of calcium ions. Thus, the synthesis of pancreatic enzymes requires the presence of the specified macronutrient; insulin synthesis and activation also occur under conditions of calcium intake [1].

The development of CP is accompanied by impaired exocrine and endocrine function of the body. Disorders of calcium homeostasis due to lack of calcium intake due to dietary restrictions are considered to be factors contributing to the chronicity of the disease. That is, several factors of the internal and external environment will contribute to the development of calcium deficiency. Among them are the following: the patient's age, female gender (especially in the pre- and menopausal stage), dietary restrictions, intestinal malabsorption due to exocrine insufficiency; concomitant, competitive in need of calcium diseases (hypertension, coronary heart disease, kidney disease, intestinal diseases, etc.) [2,3]. Thus, the recurrent nature of the pathology leads to depletion of the body's calcium pool and requires its constant replenishment.

That is, in chronic pancreatitis due to impaired exocrine function of the pancreas there is a vicious circle: insufficient synthesis of enzymes of the gland prevents the absorption of certain types of food, which blocks the flow of calcium into the body, and lack of the latter inhibits the synthesis of enzymes and insulin. Thus, conditions for the development of calcium deficiency are created, the correction of such conditions is carried out through the intake of calcium from the bones: conditions for the development of osteoporotic conditions are formed.

OP or osteopenic conditions are characterized by changes in bone structure and low bone mass, which leads to bone fragility and increased risk of fractures [4]. Osteoporosis is considered a serious problem because of its potentially serious consequences for both patients and the health care system as a whole [5].

The formation of osteoporosis in chronic pancreatitis was first introduced in 1997, when the authors of the study showed that 21% of patients with CP develop OP. Since then, several studies have shown different prevalence of OP in patients with CP: from 5% to 39% [1]. In this case, it is appropriate to assume that patients with CP are at risk of developing osteoporotic conditions. However, to date, no international consensus regulations recommend assessing the condition of bone tissue in CP.

According to the literature, an important role in the diagnosis and prediction of bone metabolism disorders is played by the study of candidate gene polymorphism, which in certain relationships can affect not only the development of osteopenic conditions, but also determine the timing of this complication [6,7]. Currently, more than 9 genes are known, the polymorphic changes of which "contribute" to the development of OP. These include VDR and LCT [8-11].

Thus, the problem of secondary osteopenic syndrome in people suffering from CP is very relevant and requires a scientific search for the most effective methods of diagnosis, treatment and prevention.

Purpose of the Study

Determination of the role of vitamin D receptor gene and lactase gene polymorphism in the risk of developing osteopenic conditions in patients with chronic pancreatitis.

Materials and Methods of Research

The study included 40 patients with CP (main group) and 40 healthy individuals (control group). The groups did not differ in age - 33.2 ± 2.1 and 32.9 ± 3.1 years old, respectively, and sex (dominated by men - 53.4% and 54.3%, respectively). The duration of a history of CP was in the range of 2-15 years with an interquartile range of 4-7 (IR) years, with a medial tendency - 5 years.

Each patient was given written consent to conduct the study, in accordance with the recommendations of ethical committees on biomedical research, Ukrainian health legislation, Helsinki Declaration 2000, European Community Directive 86/609 on human participation in biomedical research.

The diagnosis of CP should be verified by a comprehensive assessment of patient complaints, history, results of clinical, laboratory and instrumental research methods using the M-ANNHEIM scoring system [12]. The course of CP corresponded to the active stage of the disease with impaired excretory function of the body of mild and moderate severity. Patients with incretory disorders of the pancreas were not involved.

Determination of polymorphism of VDR and LCT genes was determined using PCR using Litech kits on the amplifier "Rotor - Gene 6000" in real time.

Diagnosis of BMD was performed using DEXA, which was performed on the device HOLOGIC Explorer QDRW Series Bone Densitometer.

The obtained data were processed in the statistical environment STATISTICA 13.0. The tables were analyzed using CCP test. CMU was used for distributions other than normal.

Research Results and their Discussion

In the main group, 15 patients (37.5%) had a mild degree of excretory insufficiency and 25 (62.5%) - moderate. During the densitometric study, it was found that the change in BMD was registered in 25% of 40 patients with CP: signs of osteoporosis (OP) were confirmed in 4 people (10% of 40 patients), and osteopenia - in 6 (15%) cases.

When analyzing the anamnesis data, it was found that 4 people (10%) with CP indicated fractures of the extremities. Only 1 such

patient was in the control group (4%). However, these statistics were the result of the surveyed contingent - young people with a sedentary lifestyle.

We analyzed chromosomal aberrations in the gene for vitamin D receptors - VDR and lactase genes (LCT) to establish the possible dependence of anamnestic and clinical parameters on the polymorphism of these genes.

Genetic testing of VDR showed that in the main group and the comparison group, the distribution of genotypes was different (Table 1).

Receptor gene genotype VDR	Control group (n=40)	Main group (n = 40)
bb	48,6%	22,5%
Bb	24,3%	42,5%
BB	27,1%	35,0%

Table 1: Distribution of vitamin D receptor gene genotypes in the examined patients.

Thus, the unfavorable allele B was registered in 77.5% of cases in patients with isolated CP. In almost healthy individuals, the frequency of allele B registration corresponded to 51.4%. That is, this figure was 1.5 times higher in patients with CP. At the same time, the frequency of unfavorable homozygous explosive genotype prevailed in the main group of subjects - 35.0% against 27.1% - in the control group. Changes in the polymorphism of the VDR gene, which affected the frequency of lesions of the musculoskeletal system (CCP, $\chi2 = 20.81$, $p < 0.01$) and had a statistically significant dependence in the distribution of alleles between groups (CCP, $\chi2 = 30.08$, $p < 0.01$). The distribution of the genotype of the VDR receptor gene considering osteopenic changes in bone tissue in the main group of persons corresponded to the following indicators: bb - genotype - 1 patient with osteopenia; Bb genotype - 1 person with osteoporosis and 2 - with osteopenia; and BB genotype were recorded in 3 and 3 persons, respectively. At the same time, the history of fractures based on gene polymorphism were distributed as follows: 1 patient was in the group of persons with bb-polymorphism, 1-had Bb-genotype and 2 - BB-polymorphism of the VDR gene. That is, the B allele in the polymorphism of the vitamin D receptor gene in the densitometric study was registered in 90% of cases (9 patients out of 10), and in the registration of fractures there were 33.3% (3 out of 9) of such patients. These numerical ratios confirm the thesis that in young people the formation of fractures can be influenced not only by genetic factors but also phenotypic components.

Testing of frequencies of genotypes and alleles of the LCT gene in the control group corresponded to the following results: TT genotype was registered in 19.2% of cases (n = 15), CT genotype - in 32.1% (n = 25) and SS genotype - in 48.7% (n = 38) people. The main group with isolated CP had the following distribution of genotypes (Table 2).

Type of gene polymorphism LCT	CC	CT	TT
Control group	12,5 % (5)	37,5 % (15)	50 % (20)
Main group	55% (22)	27,5% (11)	17,5% (7)

Table 2: Frequency of distribution of genotypes of the LCT gene in patients with CP.

Therefore, changes in the polymorphism of the LCT gene in patients with CP and almost healthy individuals were statistically significant (CCP, $\chi2 = 26,16$, $df = 4$, $p = 0,00003$).

According to several studies, it was found that in the variant of the norm in the homozygous form of SS polymorphism of the LCT gene corresponds to lactose intolerance in adults. However, an unfavorable variant of the TT polymorphism of the LCT gene shows good lactose tolerance. In individuals with a heterozygous form of CT polymorphism, lactose intolerance is formed with the participation of additional factors and the amount of lactose consumed [11].

Thus, more than 2/3 of patients with CP had the C allele, the presence of which can be considered as an unfavorable factor in the formation of lactose intolerance. At the same time, no significant changes in the polymorphism of the LCT gene by the SS genotype in healthy individuals were found, which can most likely be explained by the congenital nature of this pathology. The increase in the number of patients with CP and SS genotype (55% vs. 12.5% in the control) is probably the result of "loss" of lactase-secreting function of the pancreas in the formation of the disease.

Changes in the polymorphism of the LCT gene were compared with the frequency of lesions of the musculoskeletal system. Bone fractures in the anamnesis in patients with CP were registered in 3 cases, which corresponded to the genotypes of SS (2 patients - 67%) and CT (1 - 33%). In the control group, a bone fracture was registered in 1 person with the CT genotype. Thus, CP is accompanied by an increase in the risk of developing osteopenic conditions by more than 2 times.

Conclusions

- The course of chronic pancreatitis can be considered as a predictor of the formation of osteopenic conditions.
- One of the prerequisites for the formation of osteopenic conditions in patients with chronic pancreatitis is the adverse effects of calcium-dependent disease.
- Progression of chronic pancreatitis increases the risk of osteoporotic conditions by more than 2 times.
- The presence of osteopenic changes in patients with chronic pancreatitis may be due to polymorphism of the vitamin D receptor gene with a predominance of adverse B alleles.
- The course of chronic pancreatitis is often accompanied by lactose intolerance, which can be the result of both genetic aberrations and "loss" of lactose-secreting function in pancreatic lesions.

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