Diagnostic and prognostic value of polymorphism of candidate genes of secondary osteoporosis in patients with chronic pancreatitis and hypertension

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Key words: chronic pancreatitis, hypertension, vitamin D gene, lactase gene, osteoporotic conditions

The study of the characteristics of the combined course of a number of diseases of internal organs is due to their mutually reinforcing negative influence, the need to make corrections to diagnostic and therapeutic measures. Their combination increases the risk of atypical clinical manifestations, torpid to conventional therapy and the early development of complications. One of these complications is secondary osteoporosis, the occurrence of which is associated with many chronic non-infectious diseases of internal organs [12]. Developing structural and functional changes in the bone tissue are not only a compensatory response to an increased need of the body for calcium ions, but also an independent factor in the further progression of the disease when these pathologies are combined. Among such nosologies, attention is drawn to chronic pancreatitis (CP) and hypertension (HT), which are considered in the context of calcium-dependent diseases, i.e. their course leads to an increase in the need for calcium ions.

Diagnosis and treatment of CP is one of the priorities of modern gastroenterology [7]. This is due to the growth of its share in the general structure of diseases of the digestive system (10.5%), an increase in the initially chronic course with frequent recurrence, difficulties in early diagnosis and treatment tactics, the development of early complications (up to 30%), low treatment efficiency and high frequency of combination with other visceral pathology [1]. The high level of temporary disability and primary disability (up to 15%) indicates the medical and socio-economic problem of CP in our country [13].

In recent years, the question of priorities in the etiology of CP has been reviewed: biliary pathology, as the cause of the disease began to occur somewhat less

frequently, and excessive alcoholic “stress” is detected in almost 40% of these patients [7, 13]. The development of CP is accompanied by a violation of all types of metabolism, and in combination with hemodynamic instability in hypertension, conditions are created for the progression of nosology and the formation of complications [4].

Clinicians have discovered a relationship between the lesion of the pancreas (PJ) and changes in the cardiovascular system for a long time, but the mechanism of these interactions is not completely clear. HT is considered as a frequent comorbid state in patients with CP.

About 12 million of the population of Ukraine has HT [5]. According to official statistics, in 2016, in the country, arterial hypertension (AH) was reported in 47.3% of men and 46.3% of women. In 27% of patients who come to medical institutions with various diseases of internal organs, HT is also registered [3].

Damage to the vascular wall in HT leads to the formation of endothelial dysfunction with the accumulation of many active substances, and among them — proinflammatory cytokines [8]. Thus, HT not only leads to hemodynamic changes, but also due to generalized vascular spasm can cause impaired microcirculation in various organs and systems, as well as maintain the inflammatory component of the pathogenesis of concomitant nosological forms [6]. In this regard, it can be assumed that the adherence to the HT of any disease of internal organs will impede the achievement of clinical remission and, therefore, a long period of time there will be a need for active therapeutic measures.

The next adverse factor in the combined course of CP and HT is their need for calcium ions: with CP, their role in the synthesis of pancreatic enzymes has been proven, and with HT, the need for increased consumption as a result of an imbalance in the sodium-calcium-calcium pump. This “joint” pathogenetic link determines the direction of the search for a mechanism to meet the arising needs. The absorption of calcium ions in CP is severely limited: the majority of patients do not use in the diet of dairy products — the main suppliers of calcium in the body; in addition, the

development of malabsorption hinders the process of its absorption. In this case, the need is filled by the receipt of calcium from the bone tissue.

Inadequate calcium intake and its increased consumption in CP and HT leads to metabolic disorders in bone tissue, thereby creating the prerequisites for the development of secondary osteoporotic conditions. The formation of secondary osteoporosis (OP) is not only a consequence of the increased need for calcium, but also the result of possible genetic aberrations of candidate genes [2].

According to the literature, an important role in the diagnosis and prediction of impaired bone tissue metabolism is played by the study of the polymorphism of candidate genes, which, under certain relationships, can influence not only the development of OP, but also determine the timing of this complication. Currently, we are talking about 9 genes that "contribute to" the development of this complication. Among them consider the genes of vitamin D (VDR) and lactase (LCT) [9, 11].

Maintaining calcium homeostasis is an important aspect of bone mineralization [10]. Vitamin D regulates calcium homeostasis through vitamin D receptors (VDR), which promote calcium intake [9]. The LCT gene encodes the amino acid sequence of the lactase enzyme. This enzyme is produced in the small intestine and is involved in the breakdown of lactose. Polymorphism of this gene affects the production of lactase and, thus, is involved in the processing and absorption of dairy products, which are a depot of calcium [11, 16]. Consequently, an unfavorable genetic background (we are talking about a combination of the corresponding genotypes of candidate genes) can lead to early development of complications, namely, the formation of secondary OP.

Aim of research is to study the role of gene polymorphism of vitamin D receptors (VDR) and lactase gene (LCT) in the risk of developing osteopenic conditions in patients with comorbidity of CP and HT.

Materials and methods of research. 110 patients with CP were examined, which made it possible to form two groups: the main group — 70 people with combined CP and HT and the comparison group — 40 patients with isolated CP. The groups did not differ in age: 33.2±2.1 (main) and 32.9±3.1 years (comparisons) and

sex (men prevailed — 53.4% and 54.3%, respectively). The history of CP history was 2–15 years with an interquartile range of 4–7 (IR), with a medial tendency of 5 years. Anamnesis of HT varied from 3 to 17 years with IC — 4–8 years and medial tendency — 5 years. In 27 cases, HT preceded the formation of CP, and in 19 patients, CP debuted. The remaining 24 patients could not determine the previous disease. Benchmarks were obtained by examination of 78 healthy individuals, identical in age and sex to selected groups.

Written consent was obtained from each patient to conduct the study, as recommended by the ethical committees on biomedical research, the legislation of Ukraine on health care and the 2000 Helsinki Declaration, and the European Society Directive 86/609 on the participation of people in biomedical research.

When making a diagnosis of hypertension, the recommendations of the European Society for Arterial Hypertension (ESH) (2009) and the recommendations of the working group on arterial hypertension of the Ukrainian Association of Cardiologists for the prevention and treatment of arterial hypertension (2012), taking into account the classification of the degree and stage of hypertension, the risk of hypertension (risk stratification to assess the prognosis of hypertension). The value of blood pressure (BP) was assessed using the Unified Clinical Protocol for medical care in hypertension. All patients with hypertension were stage II and had grade 2 hypertension with a relatively mild course of the disease. The diagnosis of CP was verified through a comprehensive assessment of patient complaints, anamnesis, clinical, laboratory and instrumental findings using the M-ANNHEIM point system [15].

The excretory function of the pancreas was assessed when determining the content of pancreatic elastase-1 in the serum of patients — enzyme immunoassay using commercial test systems of the company ScheBo (Germany) on the enzyme immunoassay analyzer Labline-90 (Austria). The course of CP in both groups corresponded to the active stage of the disease with impaired excretory function of the organ of mild and moderate severity. Patients with incremental disorders of the pancreas were not involved in the work.

Ultrasound diagnostics, both during the hospital stay and during the previous stages of treatment, confirmed the development of CP with the presence of inflammatory and/or fibrous sites in the gland. These results were evaluated as diagnostically positive when supported by the appropriate clinical picture of the disease.

The polymorphism of the VDR and LCT genes was determined by setting up the polymerase chain reaction (PCR) using Litech kits (Russia) on a Rotor-Gene 6000 amplifier (Australia) in real time.

As an instrumental method for diagnosing osteoporotic conditions, dual-energy X-ray absorptiometry (DEXA) was used, which was performed on a HOLOGIC Explorer QDRW Series Bone Densitometer (USA).

The obtained data was processed in the statistical environment STATISTICA 6.0. Contingency tables were analyzed using the Pearson χ-square (CCP) test. For distributions other than normal, the non-parametric Mann-Whitney test (CMU) was used.

Results and discussion. Given the content of fecal pancreatic elastase, patients with CP were distributed as follows. In the main group, 27 patients (38.6%) had a mild degree of excretory insufficiency and 43 (61.4%) — of moderate severity. In the group with isolated CP, this distribution corresponded to 15 (37.5%) and 25 (62.5%) individuals.

A densitometric study showed that out of 110 patients with CP, changes in bone mineral density (BMD) were recorded in 33 cases (30%). At the same time, in the main group of such patients there were 32.9%, and in the group with isolated CP — 25%. When allocating patients with regard to osteoporotic manifestations, it was found that the signs of osteoporosis (OP) with combination of CP and HT were confirmed in 11 individuals (15.7% of 70 patients), and osteopenia in 12 cases (17.1%). In the comparison group, these indicators corresponded to 4 (10% of 40 patients) and 6 (15%) observations.

At the same time, an analysis of the anamnesis data showed that both in the main group of individuals and in the comparison group, patients pointed to

previously suffered fractures of the extremities (29–41.4%) and 4 (10%), respectively. However, this statistic was not always combined with the indices of BMD, namely, changes in the main group of individuals during the densitometric study were less common — 23 vs. 29. This discrepancy appeared to be the result of the peculiarity of the surveyed population — young people with a mobile lifestyle and possible traumatic situations.

As the candidate OP genes, we analyzed chromosomal aberrations in the vitamin D receptor gene (VDR) and the lactase gene (LCT) to determine the possible dependence of anamnestic and clinical indicators on the polymorphism of these genes.

Genetic testing of the VDR gene showed that in the group of individuals with isolated CP and when combined with HT, the distribution of genotypes was different (Table 1).

Table 1

Distribution of genotypes of the vitamin D receptor gene in the examined patients

VDR gene genotype	Control group (n=78)	Main group (n=70)	Comparison group (n=40)
bb	24.3%	15.7%	22.5%
Bb	48.6%	32.9%	42.5%
BB	27.1%	51.4%	35.0%

Thus, the unfavorable allele B was recorded in 77.5% of cases in patients with isolated CP, and when joining HT, the number of such patients increased to 84.3%. In practically healthy individuals, the frequency of registration of allele B corresponded to 75.7%. This indicator almost corresponded to the group of persons with isolated CP, however, there were 1.7 times more patients with the pathological BB genotype among patients. At the same time, not only the total expression of individuals with the pathological allele B (84.3%) prevailed in the main group of patients, but also the "contribution" of the homozygous genotype BB — 51.4% versus 27.1% in the control. Changes in the polymorphism of the VDR gene, which influenced the frequency of lesions of the osteo-articular system (CCP, $\chi 2 = 20.81$, $p<0.01$) and had

a statistically significant dependence in the distribution of alleles between groups (CCP, $\chi 2 = 30.08$, $p<0.01$).

The distribution of the genotype of the VDR gene, taking into account osteoporotic changes in bone tissue in the main group of individuals, corresponded to the following indicators: bb — 2 patients with osteopenia had the genotype; Bb genotype — 4 with osteoporosis and 3 — with osteopenia and the BB genotype — 7 and 7, respectively. At the same time, the history of fractures with regard to gene polymorphism was distributed as follows: 5 patients were in the group of individuals with bb-polymorphism, 9 had Bb-genotype and 15 had BB-polymorphism of the VDR gene. The allele B in the polymorphism of the vitamin D receptor gene was registered in 91.3% of cases with a densitometric study (21 patients out of 23), and 79.3% of cases were registered with fractures of such patients (23 out of 29). These numerical ratios confirm the thesis that in young people, the formation of fractures can be influenced not only by a genetic factor, but also by phenotypic components.

When comparing these genotypes with the clinical symptoms of the disease, it was found that with an unfavorable BB genotype in the main group of patients, dyspeptic syndrome was expressed, with nausea on an empty stomach (19 people), abdominal distention in the afternoon (38), impaired stool to 2–3 once a day (27), “crashing in the stomach” (29). Thus, the progression of the process was reflected in a shift in the distribution of alleles towards the BB genotype. It should be noted that no relationship was found between genetic polymorphism and the degree of pancreatic excretory insufficiency.

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

Table 2

Frequency of distribution of the genotypes of the LCT gene in patients with CP and HT

LCT gene			

polymorphism type	CC	CT	TT
Control group	48.7% (15)	32.1% (25)	19.2% (38)
Patients with CP	55% (22)	27.5% (11)	17.5% (7)
Patients with CP and HT	55.7% (39)	28.6% (20)	15.7% (11)

Consequently, changes in the polymorphism of the LCT gene in patients with CP and with the combination of CP and HT had a statistically significant nature (CCP, $\chi 2 = 26.16$, df = 4, p = 0.00003).

According to a number of studies, it was established that under the normal variant in the homozygous form of the CC, the polymorphism of the LCT gene corresponds to lactose intolerance in adults. At the same time, the mutant variant of the TT polymorphism of the LCT gene reveals a good tolerance of lactose. In individuals with a heterozygous form of CT polymorphism, lactose deficiency is formed with the participation of additional factors and the amount of lactose used [14].

Thus, more than half of patients with CP had an allele C, the presence of which can be considered as an unfavorable factor in the formation of lactose deficiency. At the same time, there were no significant changes in the polymorphism of the LCT gene for the SS genotype in both healthy individuals and pancreatic disease, which can most likely be explained by the congenital nature of this pathology. Some increase in the number of patients with CP and SS-genotype (55% and 55.7% versus 48.7% in control), apparently, is the result of the "loss" of lactase-secreting function of the pancreas during the formation of the disease.

Clinically, lactose deficiency was diagnosed in 48 patients (68.6%) of the main group and 23 individuals (57.5%) of the comparison group. In determining the prevalence of lactose deficiency in the examined patients, taking into account the polymorphism of the LCT gene, the following relationships were established (Table 3).

Table 3

The prevalence of lactase deficiency in the examined patients, taking into account the polymorphism of the LCT gene

LCT gene polymorphism type	CC	CT	TT
CP (p=40)	16 (40%)	5 (12.5%)	2 (5%)
CP+HT (p=70)	34 (48.6%)	13(18.6%)	1 (1.4%)

The “protective genotype” of TT in patients with chronic pancreatitis in relation to lactase deficiency was “effective” in only 2 out of 7 patients, and when attaching HT, in 1 out of 11 individuals.

Polymorphic variants of the LCT gene were not associated with the history of history of CP and HT, morphological changes in the pancreas according to ultrasound diagnosis and its excretory function.

The study did not reveal reliable results of the dependence of the polymorphism of the lactase gene (LCT) with mild and moderate severity of pancreatic excretory insufficiency.

Changes in the polymorphism of the LCT gene were "comparable" with the frequency of lesions of the osteo-articular system. Bone fractures in history were recorded in 38 patients (34.5%), among whom 35 (31.8%) belonged to the main group; 8 of them (23%), CT genotype — 12 (34%) and CC — 15 (43%) were carriers of the TT genotype. In the comparison group, fractures were recorded in 3 cases, which corresponded to the SS genotypes (2 patients — 67%) and CT (1 — 33%). Thus, comorbid pathology (CP and HT) is accompanied by an increase in the risk of developing osteopenic conditions by more than 4 times.

By comparing the pathological VDR and LCT genes of the entire sample of patients (188 people: 110 patients with CP and 78 practically healthy people), we obtained the distribution of frequencies of a statistically significant nature (CCP, $\chi 2 = 21.92547$, df = 4, p = 0.00021). Namely, the coincidence in the heterozygotes Bb and CT was 37.88% (66/188), in terms of BB and CC homozygotes — 45.57% (36/188). The coincidence of Bb and CC was 21.21% (14/188), BB and CT — 31.65%

(25/188). The distribution of frequencies in patients with isolated CP (40) also had a statistically significant character (CCP, $\chi 2 = 10.69637$, df = 4, p = 0.03020). The coincidence in the heterozygote of Bb and CT was 25% (4/40), in homozygotes for BB and CC — 60% (9/40). The distribution of Bb and CC corresponded to 31.25% (5/40), BB and ST — 33.33% (5/40).

When comparing these genotypes with the clinical symptoms of the disease, it was found that if the alleles B of the VDR gene and C coincide, the alleles of the LCT gene in the group of individuals with isolated pancreatitis were marked by severe pain and dyspeptic syndromes. The pain syndrome was characterized by a long attack (more than 2 hours) of dull pain in the left hypochondrium and epigastric region with irradiation to the back. Patients noted nausea and more often single vomiting on an empty stomach, abnormal stool up to 2–4 times a day, pronounced persistent flatulence. Also in these patients there was a shortage of body weight.

Comparison of pathological alleles in the group of patients with CP and HT did not have a statistically significant nature. The coincidence of Bb and ST heterozygotes was 36.36% (4/70), and BB and CC homozygotes — 49.09% (27/70). The distribution of Bb and CC corresponded to 54.55% (6/70), BB and ST — 29.09% (16/70). When HT was attached, patients with the coincidence of the pathological alleles of the indicated genes (B and T) were observed: a persistent increase in blood pressure during exacerbation of CP against the background of pain syndrome, lasting from 2 to 3–3.5 hours, arising in the left hypochondrium with irradiation to the back, with variety manifestations of dyspeptic syndrome (nausea, vomiting, bloating and rumbling in the abdomen, impaired stool). There was dizziness, periodic unsteadiness when walking, cardialgia and arrhythmias. The reduction of abdominal pain was not accompanied by a normalization of hemodynamic parameters — a delay of BP control was observed on average for 2–3 days.

Conclusions. The course of CP, as well as its combination with HT, can be considered as a predictor of the formation of osteoporetic states. In this case, one of the prerequisites for their formation can be considered an unfavorable combination of

calcium-dependent diseases, coming both to an increased consumption of this macrocell (HT) and to an increase in its consumption in CP.

The presence of osteopenic changes in patients with combined CP and HB may be due to the polymorphism of the vitamin D receptor gene with the prevalence of unfavorable B alleles.

Comorbidity of HT and CP increases the risk of developing osteoporotic conditions by more than 4 times. CP is often accompanied by lactose deficiency, which may be the result of both gene aberrations and the loss of lactose-secreting function in the presence of pancreas.

Prospects for further studies on these issues related to the rationale for the directions of individualized therapeutic correction for the prevention of the risk of osteopenic conditions in people with comorbid CP and AH.

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Study of features of the combined course of a number of diseases of internal organs is caused by their mutually enhancing negative influence and need to correct diagnostic and therapeutic measures. Among such nosologies, attention is drawn to chronic pancreatitis (CP) and hypertension. Their comorbidity increases a risk of atypical clinical manifestations, torpid to conventional therapy and early development of complications. One of these complications is secondary osteoporosis. Developing structural and functional changes in the bone tissue are not only a compensatory response to an increased need for calcium ions, but also an independent factor in further disease progression when these pathologies are combined. An important role in the diagnosis and prediction of impaired metabolism of bone tissue is played by the study of the polymorphism of candidate genes, which can affect not only the development of osteoporosis, but also determine the timing of this complication to certain extent. Vitamin D (VDR) and lactase (LCT) genes are considered among them.

Aim of research is to study the role of gene polymorphism of vitamin D receptors (VDR) and lactase gene (LCT) in the risk of developing osteopenic conditions in patients with comorbidity of CP and hypertension.

Materials and methods. 110 patients with CP were examined, which made it possible to create two groups: main group — 70 people with comorbid CP and hypertension, and comparison group — 40 patients with isolated CP. Control group included 78 healthy individuals. All patients were representative by age and sex. The state of the bone tissue was determined by conducting double-energy X-ray

absorptiometry (DEXA). Polymerase chain reaction was used to study the polymorphism of the vitamin D receptor (VDR) and lactase (LCT) genes.

Results. Majority of patients in the main group (84.3%) had an unfavorable B-allele, in contrast to the comparison group, where this index was equal to 77.5% of cases. Changes in the VDR gene polymorphism, which influenced the frequency of lesions of the osteo-articular system, were stated. Lactose insufficiency (LI) was found out in more than half of the patients with CP (57.5%). Upon comorbidity of CP and hypertension, number of such patients increased (68.6%), which could be considered as a result of impaired vascular pancreatic regulation. At the same time, LI occurred against the background of normal (C/C) polymorphic variants of the LCT gene. Almost a third of patients (35.7%) had osteopenic states, but they were not associated with the lactase gene polymorphism. Comparing the pathological VDR and LCT genes of the entire sample of patients (188 people), we obtained the frequency distribution of a statistically significant nature (CCP, $\chi 2=21.92547$, df=4, p=0.00021). Namely, the coincidence of Bb and CT heterozygotes was 37.88%, and that of BB and CC homozygotes was 45.57%. The coincidence of Bb and CC was 21.21%, BB and CT — 31.65%. Frequency distribution in patients with isolated CP (40) also had a statistically significant character (CCP, $\chi 2=10.69637$, df=4, p=0.03020). Coincidence in the heterozygote of Bb and CT was 25%, and that of homozygotes for BB and CC — 60%. Distribution of BB and CC corresponded to 31.25%, BB and CT — 33.33%.

Conclusion. It was stated that upon CP, as well as in its comorbidity with hypertension, osteoporotic conditions might be formed. Combination of calcium-dependent diseases (CP and hypertension) and the vitamin D receptors gene polymorphism with a predominance of unfavorable B-allele could be the cause of such conditions. At the same time, the risk of developing osteoporotic conditions increases 4 times. Course of CP is often accompanied by LI, which may be the result of both gene aberrations and loss of lactase-secreting function in a given disease.