Mechanisms of implementation of osteopenic conditions in patients with combined course of chronic pancreatitis and hypertensive disease

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Key words: chronic pancreatitis, hypertension disease, vitamin D receptor gene, biochemical markers of osteoporosis (total acid phosphatase and tartratre-resistant acid phosphatase), osteopenic conditions

Introduction. At the present stage of observation and treatment of patients, one of the main problems is the problem of the combination of chronic non-infectious diseases. The term "comorbid diseases" or "comorbid conditions" has often become commonplace, due to the predominance of individuals with the combined course of the most common and socially significant diseases of the internal organs [1]. This interest of the medical community in combining the course of diseases has several reasons. First, the comorbidity of diseases makes it difficult to determine the pre-existing at this stage of the disease, that is, it requires definition of the leading components of pathogenesis in this case. Secondly, it is discussed the possibility of using medicines that can be combined in such cases. Third, the combined course of diseases can contribute to a significant progression of each of them, the prolongation of the period of aggravation of the process and the formation of complications.

Among such diseases, which can often be combined with each other, require the development of a plan of diagnostic and therapeutic measures, have a negative effect on the formation of complications, is chronic pancreatitis (CP) and hypertension (HT).

According to statistical calculations, chronic pancreatitis — one of the most common diseases of the gastroenterological profile [12]. It is diagnosed in 10.5% of patients with diseases of the digestive system; while quite often it is a question of its primary-chronic course with frequent relapses [4]. At the same time, many practitioners noted difficulties in the initial stage of diagnosis due to the atypical course of the pathological process with early development of complications (up to 30%), low effectiveness of therapeutic measures and a high frequency of combination with other

diseases that alleviate the manifestations of CP [1]. In this case, the high level of temporary disability and primary disability causes the formation of not only medical but also socio-economic problems in the country [2].

Significant prevalence of the disease, long-term nature of the course, the tendency to frequent recurrence and its occurrence in young people contribute to the frequent combination of CP with other diseases of the internal organs [10].

One of these unfavorable combinations can be considered lesions of the pancreas and the cardiovascular system, in particular, HT.

The emergence of hypertension is associated with conditions that at some stage combine adverse genotypic and phenotypic attitudes. There are quite a few genetic markers that can affect blood pressure, but none of them causes all the varied clinical manifestations of the disease. The most studied of these are the angiotensin-converting enzyme genes and nitric oxide [8]. This is due to the proven properties of ACE and nitric oxide to affect the vascular system. Among the phenotypic preconditions for the formation of HT are: lifestyle, chronic stress, the presence of false habits (smoking and alcohol abuse), malnutrition, low physical activity, increased use of caffeine and deficiency of vitamin D [7, 9, 13]. The presented factors of risk of HT in the overwhelming majority can be considered as etiological factors of CP, that is, the combination of CP and HT happens not only due to their significant prevalence, but also similar etiopathogenetic units.

Systemic vascular defeat with the formation of endothelial dysfunction, one of the mechanisms of which is the interaction of pro- and anti-inflammatory immune mechanisms, cell membrane damage as current changes in the composition of fatty acids, and the imbalance of the POL-AOS processes, the effect of diseases on the macro-elemental composition of the organism (with HT- due to changes in the redistribution of indicators of potassium-sodium-calcium mechanism, and in the case of CP — a violation of the absorption of calcium), vitamin balance (lack of vitamin D as a result of intake and absorption) can be considered as a role pathogenetic links of the fields HT and CP [3]. In this case, it can be assumed that the common pathogenetic links can increase and contribute to the occurrence of complications, not

only due to their combination, but also provoked by each nosological form. Such complication in the comorbidity of CP and HT is osteoporotic states [11].

Osteoporosis (OP) is the most common metabolic disease manifested as a violation of the quality of bone tissue and increased risk of fractures. OP occupies leading positions in the structure of morbidity and mortality all over the world. If the recent occurrence of osteopenic conditions was considered as a factor in age-related changes, today they are observed in young people with different diseases and conditions, among which predisposed diseases of the endocrine system, the gastrointestinal tract, rheumatic diseases, scarcity conditions due to lack of calcium and vitamin D in food, etc. [6].

The combination of CP and HT takes place against the backdrop of structural and genetic changes, that is, the commonality of the pathogenetic mechanisms causes the burdened course of both diseases, which necessitates the development of a systematic approach to the study of genetic and biochemical markers in this group of patients.

Aim of study is to establish the features of the comorbid course of CP and hypertension, to optimize the diagnosis of osteoporotic conditions by studying the content of biochemical markers of OP (total acid phosphatase (TAP) and tartrate-resistant acid phosphatise (TRAP)) and polymorphism of the vitamin D receptor genes (VDR).

Materials and methods of research. The study involved 110 patients, which were divided into two groups: the main (70 people for CP in combination with HT) and the comparison group (40 persons — for isolated CP). The composition of the groups did not differ by age (33.2±2.1 and 32.9±3.1 years) and gender (women accounted for 72.9% and 70% respectively). The history of CP was within 2-15 years with an interquartile magnitude of 4-7 (IR) years, with a medial tendency of 5 years. The history of HT ranged from 3 to 17 years with the same inflammatory magnitude (4-8 years) and the medial tendency of 5 years.

The control group included 70 practically healthy persons, representative of age and sex.

During the diagnosis of chronic pancreatitis, they relied on the "Clinical protocol for the provision of medical care to patients with chronic pancreatitis", approved by the order of the Ministry of Health of Ukraine No. 271 dated 13.06.2005 and updated by order number 638 dated 10.09.14. Diagnosis of arterial hypertension (AG) was established taking into account the recommendations of the European Society for Arterial Hypertension (ESH) (2009); recommendations of the Working Group on Arterial Hypertension of the Ukrainian Association of Cardiologists for the prevention and treatment of hypertension (2012), taking into account the classification of the degree and stage of hypertension, the risk of hypertension (stratification of risk for estimating AG prediction).

To determine the polymorphism of the gene of the receptors of vitamin D (VDR), a set of reagents from the firm "Litech" (Russia) was used — the polymerase chain reaction method for real-time amplification using fluorescence labels on the six-channel analyzer Rotor-Gene ™ 6000 (Corbett Research, Australia)

General and tartrate-resistant acid phosphatase were determined by biochemical method using commercial sets of firm DAC — Spectromed (Moldova) using biochemical analyzer "Lablin-80" (Austria).

Statistical processing of the obtained data was carried out by analysis of the connection tables using the software package of Statistica Basic Academic 13 for Windows. The statistical significance of the result was evaluated using the Pearson Xi-square test (KHP).

Results of research and discussion. All patients in the main group had HT stage II and grade 2 severity with a relatively mild course of the disease.

The excretory function of the software on the level of fecal pancreatic elastase-1 corresponded to a mild severity of 27 patients (38.6%) of the main group and 15 (37.5%) of the comparison group. The average severity was recorded in 43 (61.4%) and 25 (62.5%) patients, respectively. Persons with impaired digestive function of the gland were not involved in the work.

To study the relationship between the levels of the biochemical markers of the OP, the presence of the pathological VDR gene and fractures in patients of both groups,

the rates of total acid phosphatase and non-prostatic acid phosphatase (tartrate-resistant acid phosphatase) have been transformed on the orderly scale by comparison with the reference values. Measurement intervals in control group patients (70 people) were considered to be the reference values. Thus, the norm interval for the general CF was 2.2-4.8 U/L and the non-prostatic CF was 1.6-3.9 U/L. Subsequently, for the marker of each patient, the ratio of the marker indicator with the reference values on the scale «N» was determined — the norm, «NN» — lower than the norm, «VN» — higher than the norm and the percentage of this gradation in each group.

The indicators of total acid phosphatase in the HCV group were 95% (38), followed by the distribution of alleles of the VDR gene: the genotype bb was 7 individuals (18.4%), BB — 14 (36.8%), Bb — 17 (44.8%). In 5% of patients (2 persons), the PKF score was within the norm ("N") and corresponded to genotype bb. At the same time, fractures of the bones of different localization in the history were noted in 3 patients (8%) from the subgroup "VN", which in all cases were carriers of the genotype BB.

In the group of people with CP and HT, the total acid phosphatase level was higher than normal in 100% of patients (70 people). In this case, the genotype bb occurred in 15.7% of cases (11 people), BB — 32.9% (23 persons) and Bb — 51.4% (36). There were 35 patients (50%) in the history of bone fractures in the history of the subgroup VN, of which 4 persons (11.4%), BB — 18 (51.4%), Bb — 13 (37.1%) were carriers of the genotype bb,)

Indicators of the content of TRKF in the group of patients with CP were higher than the norm in 30% of patients (12 persons) in the distribution of the genotype of the VDR gene: the Bb genotype had 25% (3 persons) and BB — 75% (9). At the same time, in the subgroup "VN" fractures were in one patient (8%) with genotype BB. In 50% of patients (20 people), the indicator was within the norm with distribution of the genotype bb — 40% of cases (8 people); Bb genotype had 35% (7 people) and BB — 25% (5); in the subgroup "N" fractures were in one patient (5%) with the genotype BB, in 20% (8 people) was lower than the norm ("NN"). Genotype bb was

recorded in 12.5% of cases (1 person); Bb-genotype had 87.5% (7 people). In the "NN" subgroup, one patient also had a fracture (13%) that had a B genotype. In the patients of the main group, the indicators of non-prostatic acid phosphatase had the following values: 67.1% of patients (67 people) were higher than normal; Percentage variations in the polymorphism of this gene were as follows: genotype bb was 2.1% (1 person), VB — 40.4% (19 people) and Bb — 57.5% (27). In 25.7% of patients (18 persons), the NSC rate was within the normal range. Percentage variations in the polymorphism of this gene were as follows: the genotype bb was noted in 33.3% (6 persons), BB — 22.2% (4 persons) and Bb — 44.5% (8). In 7,2% (5 persons), the NSC content was lower than the rate with fluctuations in the polymorphism of this gene: bb — 80% (4 persons), BB — 0%, and BB — 20% (1). In the subgroup "VN" in patients with comorbidity of CP and HT fractures were 35 patients (50%), of which carriers of genotype bb — 3 persons (8,6%), VV — 19 (54,3%) and Bb — 13 (37.1%). In the subgroups "N" and "NN", no patient had any fractures in history. At the same time, such a division was statistically significant (Pearson's "$\chi 2$" criterion, $p=0.01$).

Based on the results of the study of the polymorphic VDR gene, control patients were divided into three groups. The b-genotype carriers belonged to the first group (17 persons — 24.3%), to the second one they were carriers of the genotype Bb (34-48.6%)), and the third group was presented by 19 patients (27.1%) — carriers of the BB genotype. Thus, the overwhelming majority of patients with CP, burdened with HT (84.3%), had a pathological B-allele, but in the comparison group, the B-allele was recorded in 77.5% of cases, while in the control group it was 75.7%. Changes in the polymorphism of the VDR gene affected the frequency of bone and articular lesion involvement. Thus, the presence of bone fractures in the history was recorded in 39 patients (35.5% of 110 people with CP), of which 35 patients belonged to the main group and 4 to the comparison group. Dependence was statistically significant (KHP, $\chi 2=20.81$, $p <0.01$). These results were the basis for determining the possible dependence of anamnestic and clinical parameters on the polymorphism of the VDR gene. Thus, there was a statistically significant

dependence in the distribution of alleles of the VDR gene from the group (KHP, $\chi 2=30.08$, $p < 0.01$). Indicators of the content of PKF and TRKF in individuals with a combination of CP and HT were 8.7±2.3 U/L and 5.1±2.3 U/L respectively, and in the comparison group — 6.9±3.0 Od/L and 3.5±2.1 O/l. Thus, levels of PKF and TRKF exceeded norms.

Conclusions. A combination of chronic pancreatitis and hypertension is a characteristic increase in the number of individuals with the V-allele of the VDR gene (84.3% of cases), whose carriers exceed the risk of osteopenic states formation. The combined course of chronic pancreatitis and hypertension is accompanied by fluctuations in the content of biochemical markers of bone metabolism — common acid phosphatase and non-prostatic acid phosphatase, the content of which correlates with the polymorphism of the gene of the receptors of vitamin D. Increasing the content of total acid phosphatase and non-prostatic acid phosphatase in blood serum in patients with comorbidity of hypertensive disease and chronic pancreatitis more often occurs against the background of the unfavorable B-allele of the polymorphism of the VDR gene.

The combination of chronic pancreatitis and arterial hypertension is the basis for an early diagnosis of osteoporotic complications.

Perspective. The promising direction of the study is the study of other genetic markers of osteoporosis with comorbidity of chronic pancreatitis and hypertension.

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The comorbidity of chronic pancreatitis (CP) and hypertensive disease (HD), which are often combined with each other, can be considered as predictor states of the complication formation. This is due to the intersection of individual pathogenic links, which are enhanced by their combination. As such a complication, it is possible to consider osteoporotic conditions, leading to metabolic disturbances of bone tissue with quantitative and qualitative changes. The emergence of secondary osteoporosis (SO) is not only phenotypically but also genetically conditioned, which is the basis for studying the gene aberrations of "osteopenically directed genes" and determining the content of SO biochemical markers.

Aim of study: to establish the features of the comorbid course of CP and hypertension, to optimize the diagnosis of osteoporotic conditions by studying the content of biochemical markers of OP (total acid phosphatase (TAP) and tartrate-resistant acid phosphatise (TRAP)) and polymorphism of the vitamin D receptor genes (VDR).

Materials and methods of research. To solve this problem, 110 patients with CP were examined and further divided into 2 groups: treatment group — 70 persons with CP and hypertensive disease (HD), and the comparison group — 40 patients with isolated CP. These groups were representative by age and sex. The condition of bone tissue was studied in assessing the content of indicators of total acid phosphatase (TAP) and non-prostatic acid phosphatase (TRAP) in blood serum. At the same time, VDR was determined.

Results. It was found that the vast majority of patients in the treatment group (84.3%) had an unfavourable B-allele; against the comparison group — 77.5% of events.

Changes in the VDR gene polymorphism affected the incidence of the osteoarticular system (CCP, $\chi 2 = 20.81$, $p < 0.01$) and had a statistically significant relationship in the distribution of alleles between groups (CCP, $\chi 2 = 30.08$, $p < 0.01$). The parameters of TAP and TRAP in patients with combined course of CP and CP were 8.7±2.3 U/L and 5.1±2.3 U/L, respectively, and in the comparison group — 6.9±3.0 U/L and 3.5±2.1 U/L. Thus, the content of TAP and TRAP exceeded the control in the treatment group by 2.5 (TAP) and 1.9 (TRAP) times ($p<0.01$) and in the comparison group by 2.0 (TAP) and 1.3 TRAP) times ($p<0.01$), which allowed us to state the development of osteopenic conditions. The distribution of alleles of the VDR gene was characterized by the predominance of the B-allele and was "supported" by changes in the biochemical markers of osteoporosis, which led to the development of osteopenicconditions in such individuals. Thus, the combination of CP and CP is an unfavourable factor in the development of osteoporosis and the basis for early detection of osteoporetic changes.

Conclusions. In the combined course of CP and arterial hypertension, there is an increase in the number of persons with the B-allele of the VDR gene (84.3% of cases), the carriers of which have a high risk of osteopenia. With the comorbidity of CP and HD, there are fluctuations in the content of TAP and TRAP, correlating with VDR. Increase in the content of TAP and TRAP in patients with CP and HD often occurs against the background of an unfavourable B-allele of the VDR gene. Combined course of CP and HD is the basis for early diagnosis of osteoporotic complications.