PATHOGENETIC LINKS OF THE COMBINED COURSE OF CHRONIC PANCREATITIS AND HYPERTENSIVE DISEASE AND THEIR ROLE IN THE FORMATION OF COMPLICATIONS

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The combined course of many of the most common chronic diseases of internal organs, each of which is socially significant and can determine the quality of life, requires other diagnostic and therapeutic approaches. Among such nosological forms, the comorbidity of which aggravates the clinical picture of the disease and the prognosis, one can consider hypertensive disease (HD) and chronic pancreatitis (CP).

The prevalence of hypertensive disease in a digital recalculation on the planet's population can be considered as an epidemic, which is registered in all countries and regions, at any age, regardless of gender, race and social identity. Patients with HD make up about 12 million of the total population of Ukraine, however, according to many researchers, these data are incomplete and do not reflect the true picture of its prevalence [7]. According to official statistics, in 2016 HD was recorded in 47.3% of men and 46.3% of women in the country [6]. Also, HD is registered in 27% of patients who visit medical institutions with various diseases [2]. The affection of the vascular wall in HD leads to the formation of endothelial dysfunction with the accumulation of many active substances and proinflammatory cytokines among them [12]. Thus, HD not only leads to hemodynamic changes, but also due to generalized vasospasm can cause a violation of microcirculation in various organs and systems, as well as maintain an inflammatory component of the pathogenesis of concomitant nosological forms [8,11]. In this connection, it can be assumed that the accession of any disease of internal organs to HD will make it difficult to achieve clinical remission.

Chronic pancreatitis is one of the nosological forms, which is often observed in patients with HD. In recent years, the issue of priorities in the etiology of CP has been reviewed: biliary pathology, as the cause of the disease has become less common, and excessive alcohol "load" is detected in almost 40% of such patients [1,6,9]. Development of CP is accompanied by a violation of all types of metabolism, and in combination with the instability of hemodynamics in HD, conditions for the progression of nosology malfunctions and the formation of complications are created [9]. Among such complications it is possible to consider secondary osteoporosis (SO), the occurrence of which may be due to increased intake (II) and/or insufficient absorption (IA) of calcium in the small intestine [3,10].

In addition, in recent years, the issues of genetic predisposition to the formation of various clinical forms are being considered. However, in none of the diseases the existence of a single gene that provokes its development and course has been proven [4].

Objective - study of the relationship between the polymorphism of the gene of vitamin D receptors (VDR) and biochemical markers of bone metabolism (osteocalcin, tartrate-resistant acid phosphatase, total acid phosphatase) in the risk of osteoporosis in patients with chronic pancreatitis and hypertensive disease.

Material and methods. 110 patients with CP were examined, in 70 cases it occurred in combination with HD (main group). The comparison group included 40 patients with CP without hypertensive disease. Both groups were comparable in age (33.2±2.1 years and 32.9±3.1 years, respectively) and gender (women mounted to 72.9% and 70% respectively). The duration of the history of CP was between 2-15 years with an interquartel swing (IS) of 4-7 years and a median trend of 5 years. The diagnosis of CP was established at the previous stages of treatment and was verified with a comprehensive assessment of complaints, data of anamnesis, clinical and laboratory and instrumental research methods.

The duration of the history of HD was recorded in the range of 3-17 years; IS scope corresponded to 4-8 years, the medial trend was 5 years.

The diagnosis of arterial hypertension (AH) was established taking into account the recommendations of the European Society for Hypertension (ESH) (2009); recommendations of the working group on arterial hypertension of the Ukrainian Association of Cardiologists on the prevention and treatment of hypertension (2012), taking into account the classification of the degree and stage of hypertension, the risk of hypertension (risk stratification for assessing AH prediction).

Indicators of the standard of biochemical and genetic studies were obtained by examining 70 practically healthy persons of the same sex and age.

Instrumental diagnosis of OP was performed using an ultrasound densitometer or X-ray examination with the dual-energy X-ray absorptiometry (DEXA) method.

Osteocalcin in the blood serum was examined by an enzyme immunoassay using commercial test systems "IDS" ("ELISA", USA).

Total and tartrate-resistant acid phosphatases (TRAP) were determined by a biochemical method using commercial DAC-SpectroMed kits (Moldova).

Polymorphism of the gene of vitamin D receptors (VDR c.IVS7 + 283 G> A) was studied in the polymerase chain reaction using "Litech" kits (Russia) in real time on a six-channel Rotor-Gene™ 6000 analyzer (Corbett Research, Australia).

The statistical processing of the results was carried out using the STATISTICA software package. When analyzing the conjugacy tables, the Pearson criterion χ-square (QCP) was determined; for comparison of unbound samples of continuous scale indicators, the nonparametric Mann-Whitney criterion (CMC) was used.

Results and their discussion. A densitometric study showed that out of 110 patients with CP, changes in bone mineral density (BMD) were recorded in 33 (30%) cases. In the main group, signs of osteoporosis (OP) were confirmed in 11 persons (15.7%), and osteopenia - in 12 (17.1%) cases. In the comparison group, these rates corresponded to 10% and 15%.

Based on the results of testing the polymorphic VDR gene, the control group had the following distribution: carriers of the bb genotype - 17 (24.3%) persons; carriers of the Bb-genotype-34 (48.6%) and carriers of the BB-genotype - 19 (27.1%) patients. In the group of patients with CP, gene polymorphism corresponded to: 9 (22.5%) individuals, 17 (42.5%) and 14 (35%). In the combination of CP and HD, the changes in the polymorphism of this gene were as follows: 11 (15.7%) patients, 23 (32.9%) and 36 (51.4%), respectively. Thus, the overwhelming majority of patients with CP, aggravated with HD (84.3%), had a pathological B-allele, compared to the comparison group - 77.5% of cases.

To determine the relationship between the levels of biochemical markers of OP, the presence of pathological VDR gene and

fractures, the parameters of osteocalcin, total acid phosphatase (TAP) and tartrate-resistant acid phosphatase (TRAP) were transformed into ordinal scales by comparison with reference values. The limits of the reference values were the measurement intervals in the control group (70 patients).

Thus, the content of osteocalcin in the control group ranged from 14.7 to 26.0 ng/ml; the normal range for TAP was 2.2-4.8 U/l and TRAP was 1.6-3.9 U/l. In the future, for the marker of each patient, the ratio of the marker indicator to the reference values on a scale "N" is the norm, "BN" is below the norm, "AN" is above the norm and the percentage composition of this gradation in each group were indicated.

In the group of patients with isolated pancreatitis, the average osteocalcin content was 26.1±0.8 ng/ml. At the same time, the norm values were recorded in 27 (67.5%) patients with the following allele distribution: genotype bb – was in 6 (22.2%) persons, BB - 7 (25.9%), Bb - 14 (51.9%). A decrease in the level of osteocalcin to 17.1±0.4 ng/ml was observed in 4 (10.0%) patients, one of whom had a fracture of the upper limb in an anamnesis. Genotype BB was determined in 3 cases and Bb in one. Elevated levels of osteocalcin (37.9±0.8 ng/ml) were found in 9 (22.5%) patients, two of whom had fractures of the limbs. In this case, the genotype bb was in a third of patients (3), BB - in 44.5% (n=4) and Bb - in 22.2% (n=2).

When combined CP and HD, the level of osteocalcin averaged over the group was 22.1±0.64 ng/ml. A half the patients with the following genotypes has its normal value: bb - 34.3% (12 of 35), Bb - 37.1% (13) and BB - 28.6% (10), 2 of whom had fractures. Elevated levels of osteocalcin were recorded in 12 (17.1%) patients - 11 of them had fractures in the anamnesis and the distribution of the genotypes corresponded to: Bb - 83.3% (10) and BB - 16.7% (2). The content of osteocalcin was lower than normal in 23 (32.9%) cases followed by polymorphism of the VDR gene: bb - 8.7% (2), Bb - 17.4% (4), BB -73.9% (17), 16 of them had fractures in the past.

The parameters of total TAP in patients with CP corresponded to the level of "above the norm" ("AN") in 95% of the observations (n=38) followed by the distribution of VDR gene alleles: 7 (18.4%) patients had genotype bb, BB - 14 (36.8%), Bb-17 (44.8%). In 2 (5%) of patients the TAP index was within the norm ("N") and corresponded to the genotype bb. In this case, fractures of bones of different localization in the anamnesis were noted in 3 (8%) observations from the subgroup "AN", which in all cases were carriers of the genotype BB.

In the group of patients with CP and HD, the total acidic phosphatase was higher than normal in all patients. At the same time, the bb genotype was found in 11 (15.7%) of cases, BB – 23 (32.9%) and Bb – 36 (51.4%). Bronchial fractures in the "AN" subgroup were in 35 (50%) patients, of which 4 (11.4%) were carriers of the bb genotype, BB - 18 (51.4%), Bb - 13 (37.1%).

The level of TRAP in the group of patients with CP was higher than the norm in 12 (30%) of patients, while the distribution of the VDR genotype was consistent with the Bb genotype in 3 (25%) patients and BB – 9 (75%). At the same time, in the "AN" subgroup, only one (8%) patient with the BB genotype had a fracture. In 20 (50%) persons, the TRAP index was in accordance with the norm, and the distribution of genotypes: bb – 8 (40%) of cases; Bb genotype – 7 (35%) and BB – 5 (25%). In the subgroup "N", one (5%) patient with the BB genotype had a fracture. In a fifth (20%) of patients, the level of TRAP was below the norm ("BN"). In this case, the bb genotype was recorded in 1 (12.5%) of cases and the Bb genotype - in 7 (87.5%). One patient of this group with BB-genotype had an indication of fracture of the upper limb in an anamnesis.

In the patients of the main group, TRAP rates were higher than the norm in 47 (67.1%) of cases with the following distribution of VDR gene polymorphism: bb genotype was in 1 (2.1%) patient, BB - 19 (40.4%) and Bb - 27 (57.5%). In 18 (25.7%) patients, the content of TRAP was within the normal range with gene polymorphism of 6 (33.3%), 4 (22.2%) and 8 (44.5%), respectively. In 5 (7.2%) of cases, the level of TRAP was below the norm with variations in the polymorphism of this gene: bb – 4 (80%), BB - 0% and Bb – 1 (20%).

In the subgroup "AN", 35 (50%) patients indicated a history of fractures in the history of combined CP and HD, of which 3 (8.6%) were the carriers of bb genotype, BB - 19 (54.3%) patients and Bb - 13 (37.1%). In the subgroups "N" and "AN" there were no indications for the fractures of the limbs. At the same time, this distribution had a statistically significant character (Pearson Chi-square, $\chi 2 = 20.81$, $p<0.01$).

Based on the results of the study of the polymorphic VDR gene, control subjects were divided into three groups: carriers of the bb genotype were found in 17 (24.3%) of cases, Bb-genotype – 34 (48.6%) and BB-genotype - 19 (27.1%).

Changes in the polymorphism of the VDR gene influenced the incidence of lesion of the osteoarticular system. For example, fractures of bones of different localization in the history were recorded in 39 patients (35.5% out of 110 examined with CP), 35 of them belonged to the main group and 4 - to the comparison group, while the dependence was statistically significant (Pearson Chi-square, $\chi 2 = 20.81$, $p<0.01$). These results served as the basis for establishing a possible relationship between anamnestic and clinical data and polymorphism of the VDR gene.

Thus, a statistically significant dependence was revealed in the distribution of alleles of the VDR gene from a group of patients (Pearson Chi-square, $\chi 2 = 30.08$, $p<0.01$). The revealed regularities are represented by the column diagrams in Fig. 1.

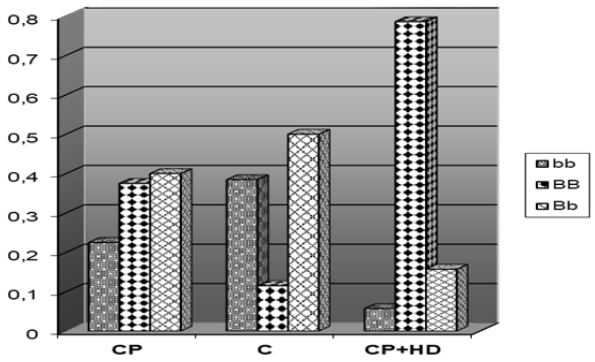

Fig.1. The distribution of alleles of the VDR gene in the main group (CP + HD), comparison group (CP) and control (C)

The parameters of the content of TAP and TRAP in individuals with combined course of CP and HD 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. The graphically presented distributions are represented by box charts of the triads "median, interquartile range, sample sweep" in Figs. 2 and 3.

Thus, the levels of TAP and TRAP were 2.5 and 1.9 times higher than those of the main group (Mann-Whitney U Test, U = 866.0, $p <0.01$), and in the comparison group 2.0 (TAP) and 1.3 (TRAP) times, respectively (Mann-Whitney U Test, U = 821.0, <0.01), which allowed to state the development of osteopenic conditions. Genetic redistribution of the alleles of the VDR gene with predominance of the B-allele was "supported" by changes

in biochemical markers of osteoporosis. Also, a decrease in the content of osteocalcin in the blood serum of patients with comorbidity of CP and HD (32.9%) occurred more often against the background of an unfavorable B-allele of polymorphism of the VDR gene (30%). Thus, the combined course of CP and HD is an unfavorable tandem in the development of secondary osteoporosis and the basis for early osteoporotic screening.

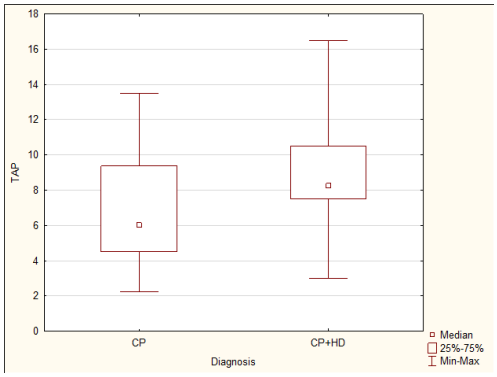

Fig. 2. Indicators of the content of TAP in the main group (CP+HD) and the comparison group (CP)

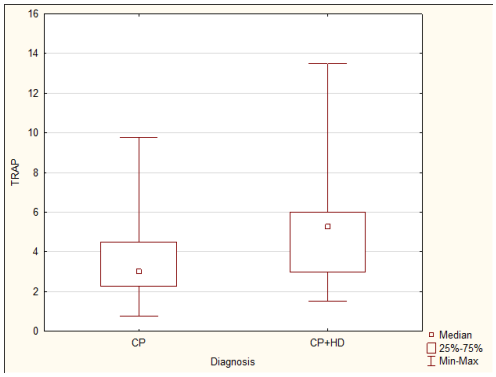

Fig. 3. Indicators of the content of TRAP in the main group (CP+HD) and the comparison group (CP)

Conclusions. The combined course of chronic pancreatitis and hypertensive disease is characterized by an increase in the number of individuals with V-alleles of the VDR gene (84.3% of cases), whose carriers have an increased risk of osteopenic conditions.

The combined course of chronic pancreatitis and hypertensive disease is accompanied by changes in the content of biochemical markers of bone tissue metabolism (osteocalcin, total bone phosphatase and tartrate-resistant acid phosphatase), the content of which correlates with the polymorphism of the gene for vitamin D receptors.

The combined course of chronic pancreatitis and hypertensive disease is the basis for early diagnosis of osteoporotic complications.

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SUMMARY

PATHOGENETIC LINKS OF THE COMBINED COURSE OF CHRONIC PANCREATITIS AND HYPERTENSIVE DISEASE AND THEIR ROLE IN THE FORMATION OF COMPLICATIONS

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Objective the purpose of the study the relationship between the gene polymorphism of vitamin D receptors (VDR) and biochemical markers of bone metabolism in the risk of osteoporosis in patients with chronic pancreatitis (CP) and hypertensive disease (HD).

110 patients with CP were examined, in which it proceeded against the background of HD in 70 cases, and in 40 cases it was isolated. The polymorphism of the VDR gene, the content of osteocalcin, total acid phosphatase (TAP), and tartrate-resistant acid phosphatase (TRAP) were studied to determine the possible effect of these parameters on the course of the disease and the formation of complications.

The obtained results show that in persons with combined course of CP and HD, a decrease in serum osteocalcin content (bone tissue synthesis index) and an increase in the content of TAP and TRAP - markers of bone destruction were revealed. The polymorphism of the VDR gene was characterized by the predominance of individuals with the B-allele, against which the reliability of changes in biochemical markers of osteoporosis was noted, which can be considered as a predictor of the development of osteoporotic conditions.

The combined course of CP and HD is characterized by an increase in the number of persons with B-alleles of the VDR gene (84.3%), the carriers of which have an increased risk of osteopenic conditions. Reduction of osteocalcin content, increase in the level of TAP and TPKF in the blood serum of patients with HP and HD often occur against the background of an unfavorable B-allele of VDR gene polymorphism. Combined course of CP and HD is the basis for early diagnosis of secondary osteoporosis.

Keywords: chronic pancreatitis, hypertensive disease, vitamin D receptor gene, biochemical markers of osteoporosis, osteopenic conditions.

РЕЗЮМЕ

ПАТОГЕНЕТИЧЕСКИЕ ЗВЕНЬЯ СОЧЕТАННОГО ТЕЧЕНИЯ ХРОНИЧЕСКОГО ПАНКРЕАТИТА И ГИПЕРТОНИЧЕСКОЙ БОЛЕЗНИ И ИХ РОЛЬ В ФОРМИРОВАНИИ ОСЛОЖНЕНИЙ

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Целью исследования является изучение взаимосвязи между полиморфизмом гена рецептора витамина D (VDR), биохимическими маркерами метаболизма костной ткани и риском развития остеопороза у больных хроническим панкреатитом в сочетании с гипертонической болезнью.

Обследовано 110 пациентов с хроническим панкреатитом (ХП), среди них в 70 случаях панкреатит протекал на фоне гипертонической болезни (ГБ) и в 40 - изолированно. Исследовали полиморфизм гена VDR, содержание остеокальцина, общей кислой фосфатазы (ОКФ) и тартратрезистентной кислой фосфатазы (ТРКФ) с определением возможного влияния данных показателей на течение заболевания и формирование осложнений.

Полученые результаты выявили, что у лиц с сочетанным течением ХП и ГБ отмечается снижение содержания остеокальцина в сыворотки крови (показатель синтеза костной ткани) и повышение содержания ОКФ и ТРКФ - маркеров костной деструкции. Полиморфизм гена VDR выявлен преимущественно у лиц с В-аллелем, на фоне которого отмечены достоверные изменения биохимических маркеров остеопороза, что следует рассматривать в качестве предиктора развития остеопоротических состояний.

У большинства лиц (84,3%) с сочетанным течением ХП и ГБ выявлено наличие В-аллеля гена VDR, носители которого характеризуются повышенным риском формирования остеопенических состояний. Снижение содержания остеокальцина, повышение уровня ОКФ и ТРКФ в сыворотке крови пациентов с ХП и ГБ чаще происходит на фоне неблагоприятного В-аллеля полиморфизма гена VDR. Сочетанное течение ХП и ГБ является критерием ранней диагностики вторичного остеопороза.

რეზიუმე

ქრონიკული პანკრეატიტის და ჰიპერტონული დაავადების თანმხლები მიმდინარეობის პათოგენეტიკური რგოლები და მათი როლი გართულებების ჩამოყალიბებაში

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კვლევის მიზანს წარმოადგენდა კორელაციის განსაზღვრა ვიტამინ D რეცეფტორის გენის პოლიმორფიზმს, ძვლოვანი ქსოვილის მეტაბოლიზმის ბიოქიმიური მარკერების და ოსტეპოროზის განვითარების რისკს შორის ავადმყოფებში ქრონიკული პანკრეატიტით და ჰიპერტონული დაავადებით.

გამოკვლეულია 110 პაციენტი ქრონიკული პანკრეატიტით (ქპ), მათ შორის 70 შემთხვევაში პანკრეატიტი მიმდინარეობდა ჰიპერტონული დაავადების (ჰდ) ფონზე, ხოლო 40 შემთხვევაში - იზოლირებულად. გამოკვლეულია ვიტამინ D რეცეფტორის (VDR) გენის პოლიმორფიზმი, ოსტეოკალცინის, საერთო მჟავეფოსფოტაზის (სმფ) და ტარტრატრეზისტენული მჟავეფოსფოტაზის (ტრმფ) შემცველობა, მათი შესაძლებელი ზემოქმედების განსაზღვრით დაავადების მიმდინარეობაზე და გართულებების განვითარებაზე.

მიღებულმა შედეგებმა აჩვენა, რომ ქრონიკული პანკრეატიტით და ჰიპერტონული დაავადების თანმხლებით პაციენტებში აღინიშნება ოსტეოკალცინის შემცველობის დაქვეითება სისხლის შრატში და სმფ-ს და ტრმფ-ს - ძვლის დესტრუქციის მარკერების მატება. VDR გენის პოლიმორფიზმი ახასიათებს ძირითადად В-ალელის მატარებელ პირებს, მის ფონზე აღინიშნება ოსტეოპოროზის ბიოქიმიური მარკერების სარწმუნო ცვლილებები, რაც შესაძლებელია განიხილებოდეს, როგორც ოსტეოპოროზული მდგომარეობის განვითარების პრედიკტორები. ქპ-ს და ჰდ-ს შერწყმული მიმდინარეობით ავადმყოფები ხასიათდებიან VDR გენის В-ალელის მაღალი მაჩვენებლებისთ, რაც მიუთითებს ოსტეოპენური მდგომარეობის განვითარების მაღალ რისკებზე. ქპ-ს და ჰდ-ს შერწყმული მიმდინარეობა წარმოადგენს მეორადი ოსტეოროზის ადრეული დიაგნოსტიკის რიტერიუმს.