УДК: 616.71-007.234-008.9+575.191
DOI 10.21886/2219-8075-2021-12-1-6-13

# The role of genetic and metabolic disorders in osteoporosis

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Osteoporosis is a progressive multifactorial systemic disease of the skeletal system characterized by the damage of the microarchitectonics of the bone tissue, which leads to the occurrence of low-energy fractures and impairment of the quality of life of individuals. The risk factors for the development of osteoporosis include smoking, which inhibits calcium absorption in the intestine and not only contributes to the reduction of bone density but also acts as a predictor of bronchopulmonary pathology. The systemic inflammation that develops in patients with chronic obstructive pulmonary disease, associated with the production of interleukins (IL)-6, IL-1, IL-8, and tumor necrosis factor – α, stimulates osteoclast-mediated bone resorption and a low level of osteoprotegerin closes the circle. In clinical practice, the determination of markers of bone resorption is required. This is a tartrate-resistant acid phosphatase, the 5β fraction of which signals the end of the resorption process; these are hydroxypyridine crosslinks – pyridoline (PYD) and deoxypyridoline, that stabilize the bone collagen molecule. Genetic factors also play an important role in the development of osteoporosis. The presence of the GG genotype or the G allele of the 283 A> G polymorphism (Bsml) of the VDR gene is a predictor of osteoporosis of the lumbar vertebrae L1-L4. The substitution of cytosine for thymine (C> T) in exon 17 of the calcitonin gene (CALCR) at position 1340 leads to the substitution of the amino acid proline (CCG) for leucine (CTG) at position 463 of the receptor protein molecule and affects bone density. But the most phylogenetically ancient mechanism for regulating the development and maintenance of tissue homeostasis by controlling cell proliferation, differentiation, migration, and apoptosis is the Wnt signaling pathway (SP-Wnt). Alterations in Wnt signaling observed in cases of genetic mutations cause various diseases of the human skeleton. A systematic literature search was carried out using the Scopus, PubMed, Web of Science databases.

**Keywords:** osteoporosis, osteoprotegerin, gene polymorphism, review.

**For citation:** Vasilyeva L.V., Bezzubtseva E.N., Gosteva E.V., Evstratova E.F. The role of genetic and metabolic disorders in osteoporosis. *Medical Herald of the South of Russia.* 2021;12(1):6-13. (In Russ.). DOI 10.21886/2219-8075-2021-12-1-6-13.

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# Роль генетических и метаболических нарушений при остеопорозе

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Остеопороз — это прогредиентное мультифакториальное системное заболевание скелета, характеризующееся нарушением микроархитектоники костной ткани, приводящее к возникновению низкоэнергетических переломов и ухудшающее качество жизни индивидуумов. К факторам риска развития остеопороза относят курение, которое за счёт ингибирования всасывания кальция в кишечнике не только способствует развитию снижению плотности костной ткани, но и является предиктором возникновения бронхолёгочной патологии. Развивающееся при хронической обструктивной болезни легких системное воспаление, связанное с выработкой интерлейкинов (ИЛ)-6, ИЛ-1, ИЛ-8, фактора некроза опухоли α, стимулирует остеокластопосредованную резорбцию костной ткани, а низкий уровень остеопротогерина замыкает порочный круг. В клинической практике требуется определение маркеров резорбции костной ткани. Это и тартрат-резистентная кислая фосфатаза, 5β фракция которой сигнализирует об окончании процесса резорбции; это и гидроксипиридиновые сшивки (пиридолин (PYD) и деоксипиридолин), придающие стабилизацию молекуле костного коллагена. В развитии остеопороза не последнюю роль играют и генетические факторы. Наличие генотипа GG или аллеля G полиморфизма 283 A> G (Bsml) гена VDR является предиктором остеопороза поясничных позвонков L1-L4. Замена цитозина на тимин (C> T) в экзоне 17 гена кальцитонина (CALCR) в положении 1340 ведёт к замене аминокислоты пролина (CCG) на лейцин (CTG) в положении 463 молекулы белка-рецептора и влияет на плотность кости. Но наиболее филогенетически древним механизмом регуляции развития и поддержания гомеостаза тканей за счёт контроля пролиферации, дифференциации, миграции и апоптоза клеток является сигнальный путь Wnt (СП-Wnt). Изменения в передаче сигнала Wnt, наблюдаемые при генетических мутациях, вызывают различные заболевания скелета человека. Системный поиск литературы проводился по базам данных Scopus, PubMed, Web of Science.

**Ключевые слова:** остеопороз, остеопротогерин, полиморфизм генов, обзор.

**Для цитирования:** Васильева Л.В., Беззубцева Е.Н., Гостева Е.В., Евстратова Е.Ф. Роль генетических и метаболических нарушений при остеопорозе. *Медицинский вестник Юга России.* 2021;12(1):6-13. DOI 10.21886/2219-8075-2021-12-1-6-13.

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*Osteoporosis* is a progressive multifactorial systemic disease of the skeletal system that is manifested by a decrease in the bone mass and characterized by the damage of the microarchitecture of the bone tissue, which leads to the brittleness of the bones [1].

According to the World Health Organization, around 75 million people around the world suffer from osteoporosis. The main risk group (around 80%) is represented by menopause women, i.e. the disease is associated with age-related changes in metabolic processes. Thus, the risk of its development should be defined after 45 years old. In industrially developed countries, senile osteoporosis is widespread in men and women after 70 years old. Drug-induced secondary osteoporosis or associated with different pathology is also widespread. It is expected that annually the rate of femoral neck fractures will increase from 1.7 mln (1990) to 6.3 mln by 2050 [2].

The risk factors for the development of osteoporosis can be divided into genetically-related (non-modifiable) and modifiable. The role of genetic predisposition is doubtless, as well as the influence of such external factors as vitamin D deficit, lack of protein in food, hypodynamia, low body weight, glucocorticoid therapy, external breathing disturbances, smoking [3].

Smoking increases the risk of osteopathic fractures of different localization by 1.29 times, femoral neck fractures – by 1.8 times [4] because of disturbances in osteogenesis that result from a decrease in the intestinal absorption of calcium [5]. The density of bone tissue in smokers (more than 20 packs/years) is 16% lower in comparison with non-smokers [6]. The risk of vertebra and femoral bone fracture in smokers is higher than in non-smokers. In ex-smokers, the parameters of the mineral density of bone tissue T were 0.064 units higher per every 10 years of remission [7]. Smoking not only contributes to a decrease in the density of bone tissue but is also a predictor of the development of bronchopulmonary pathology, which in turn, induces pulmonogenic osteopenias.

The rate of occurrence of osteopenia in patients with chronic obstructive pulmonary disease (COPD) varies from 60 to 75.9%. The study included 95 patients with COPD (30 women and 65 men). The mean age of patients was 54.2±1.4 years old, the duration of the disease was from 4 to 22 years old. A decrease in forced expiratory volume in 1 second was associated with a decrease in the density of bone tissue ($r = -0.86$, $p < 0.01$) [8]. Systemic inflammation in patients with COPD, associated with the development of interleukins IL-6, IL-1, IL-8, and TNF-α, stimulates osteoclast-mediated resorption of the bone tissue [9]. Apart from the specified anti-inflammatory cytokines, a lot of attention is paid to the factors that were united in the system of "osteoprotegerin (OPG) – receptor activator of nuclear factor kappa-B ligand" that regulate bone resorption in the norm and pathological condition [10].

OPG is a glycoprotein from the family of tumor necrosis factor (TNF) that is produced by the osteoblastic cells [11]. The mechanism of its action is in the neutralization of the receptor activator of nuclear factor kappa-B ligand (NF-kB)- RANKL. Thus, the interaction between the activator of NF-kB- RANK receptor and its RANKL ligand on the surface of pre-osteoclasts is blocked, which leads to the inhibition of the final stage of osteoclast differentiation and bone resorption [12]. In 43 out of 55 patients with COPD, osteopenic syndrome was diagnosed: the level of OPG in the serum was lower than in the control. An increase in the severity of COPD was characterized by a lower level of OPG. Besides, there was an inverse correlation between the level of TNF-α and myelin basic protein. At the same time, the content of TNF-α positively correlated with the level of β-CrossLaps [10].

β-CrossLaps are C-terminal telopeptides that are formed after the degradation of collagen type I that represents 90% of the organic matrix of bones. In the norm, minor fragments of collagen formed after bone degradation get into the bloodstream and are excreted with the kidneys. In patients with osteoporosis, collagen type I is destructed in great amounts, so the number of collagen fragments in the blood increases [13–14]. Patients with COPD have a sharp increase in the level of CrossLaps (CL-component of C-terminal telopeptide collagen type I) nearly by 3 times in comparison with the control group [8].

Markers of degradation are represented by a tartrate-resistant acid phosphatase (TRAP) (osteoclast-regulating protein) and free products of degradation of collagen type I: pyridolin (PYD), deoxypyridolin (DPD), N-terminal telopeptide, and cross-linked C-telopeptide [15].

TRAP from the family of acid phosphatases has been a cytochemical marker of osteoclast functioning since 1959 [16, 17]. Its effect is in the transcellular transport of microbubbles with the products of bone degradation [18–20]. Presently, there are five different forms of this enzyme.

They are produced by tissues (spleen, bone tissue, prostate) and cells (platelets, erythrocytes, macrophages). All five isoforms are suppressed by L(+)-tartrate, except for isoenzyme-5. There are two types of TRAP-5: 5α-containing sialic acid expressed by macrophages and 5β-containing acid that is synthesized only by osteoclasts, directly reflects their activity, and is measured by the colorimetric method [21, 22]. Besides, TRAP-5β dephosphorylates osteopontin and bone sialoprotein, disturbs their links with integrins $\alpha_v\beta_3$, and signals the end of resorption [21].

A molecule of bone collagen is stabilized by hydroxypyridine cross-links of PYD and DPD that are formed during the extracellular maturation of collagen [23]. During disorganization of the bone tissue, the cross-links get broken and their fragments get into the bloodstream and excreted with the urine [24, 25]. It should be mentioned that the level of cross-links reflects the degradation of only mature collagen and not newly formed, and the content of PYD and DPD does not depend on the character of the nutrition. PYD and PDP have a high affinity to skeletal tissues. Even though PYD is detected in the cartilaginous tissue, ligaments, and vessels, and DPD – primarily in the bone tissue and dentine, their presence indicates destruction of the bone tissue because the level of metabolism in bones is higher than in the above-mentioned tissues. Presently, the detection of these cross-links is possible by a highly-sensitive method of liquid chromatography with mass-spectrometry and a silicon dioxide column [26].

Radioimmunoassay is used for the evaluation of the level of amino and carboxyterminal telopeptides (NTX(NTP) and CTP(CTX), respectively) that are the terminal parts of a collagen molecule. CTP (CTX) have 4 isoforms (α-L form, β-isomeric peptide (β-L)), and α- and β- D-isomers. The measurement of NTX(NTP) is based on the evaluation of monoclonal bodies to antigen determinant of α-2 collagen chain. The identification of these forms provides information on the age-related changes in the metabolism of the skeleton of the healthy population and patients with connective tissue diseases [27].

Disorders in the formation of collagen in the bone tissue manifested as a decrease in the number of cross-links in collagen chains were revealed in *in vivo* and *in vitro* studies in patients with a high level of homocysteine [28]. The Hordaland Homocysteine Study [29] that included 2639 women and 2127 men aged 65 to 67 years old revealed an increase in the risk of femoral neck fractures in women with a high level of homocysteine (≥15 μM) in comparison with women with a low level (<9.0 μM). This is explained by the fact that hyperhomocysteinemia can be associated with a polymorphism of methylenetetrahydrofolate reductase, MTHFR (type C677T: TT), which exerts a negative effect on nervous, vascular, and endothelial cells, osteoblasts, and osteoclasts through an enhancement of the oxidative stress and increase in the level of the final products of glycation that lead to a decrease in the bone strength [30, 31].

It is difficult to underestimate the importance of vitamin D (VD) in the maintenance of adequate mineralization of bone tissue and skeleton formation. This vitamin regulates more than 2000 genes in a human organism [32]. In the skin, under the effect of ultraviolet light with wavelength 290–315 nm, Vitamin D3 is synthesized out of 7-dehydrocholesterol. In plants, vitamin D2 is synthesized through a modification of ergosterol. VD that gets absorbed with food and synthesized in the skin undergoes a series of transformations in the liver under the influence of 25-hydroxylase of mitochondria (CYP 27A1) and microsomes (CYP2R1) with the formation of calcidiol and ergocalcidiol. In the proximal sections of kidney tubules, these molecules turn into calcitriol and ergocalcitriol (active hormonal forms of VD). It was noted that the intensity of the formation of active forms directly depended on the level of protein that binds VD and albumin, which are synthesized in the liver and transport metabolites of VD. It can be concluded that disorders in the protein synthesizing function lead to a deficit of transport proteins, and as a result, to a deficit of VD and osteopenia [32, 33].

As it was mentioned before, the final stage of the activation of VD metabolites is performed in the kidneys. This process is catalyzed by a mitochondrial enzyme from a cytochrome P450 family 1α-hydroxylase (CYP 27B1). The activity of CYP 27B1 and synthesis of VD by the kidneys are stimulated by parathyroid hormone and insulin-like growth factor. The mechanisms of resistance to vitamin D depend on the level of 1α-hydroxylase because calcidiol converted by CYP 274B1 to calcitriol is required for the establishment of the links with the receptors of VD in the target organs for the formation of the gene response through the formation of X-receptor complex that induces the expression of calcium cationic canals in the intestinal epithelium [34].

The influence of a genetic factor in the development of a decreased bone density was studied by several authors [13, 34, 35, 36]. One of the gene candidates for the development of osteoporosis is a polymorphism of the gene receptor of vitamin D (VDR). This gene is localized in the chromosome 12q13.11 and contains a number of mononucleotide polymorphisms, including polymorphism Bsml. A total of 525 women in postmenopause were examined [35] (38–88 years old). The study [35] on the association of genotypes and alleles of polymorphism 283 A > G (Bsml) of the gene VDR showed that genotype GG or allele G of the polymorphism 283 A > G (Bsml) of the gene VDR was a predictor of osteoporosis of lumbar vertebra L1-L4. However, there was no association of this polymorphism with a decrease in the density of the bone tissue of the proximal section of femoral bones and the distal section of the antebrachium revealed. This discrepancy can be explained by the prevalence of the spongy material in the proximal sections of the femoral bones and distal sections of the antebrachium, and in the lumbar vertebra – trabecular substance.

Polymorphism of the gene receptor of calcitonin (CALCR) is also considered as a genetic predictor of osteoporosis [37]. Calcitonin is a hormone that is synthesized in the parafollicular cells of the thyroid body and regulates calcium and phosphorus metabolism in the organism. Bone tissue is a target organ for calcitonin and the inhibition of bone resorption is the main activity. CALCR occupies site 7q21.3 and codes the isoform-1 of a highly-sensitive receptor for calcitonin. A replacement of cytosine with thymine (C>T) in the exon 17 of the gene CALCR in position 1340 leads to a replacement of proline (CCG) with leucine (CTG) in position 463 in a molecule of protein receptor and influences the density of bones [38, 39]. It was established that allele C of the polymorphism of the gene CALCR leads to a decrease in the bone density, and the risk of osteoporosis depends on the physiological condition of the organism (adolescents, pregnant or lactating women) [37].

The genes of bone tissue remodeling also include the gene of lactase LCT (LPH) 13910 T>C and the gene of collage COL1A1 2046 G>T [36]. The function of the gene LCT (LPH) is the coding of the amino acid structure of the lactase that is synthesized in the small intestine and is necessary for lactose (milk sugar) splitting. Usually, this enzyme functions in children. In adults, it is not produced, which leads to intestinal disorders associated with lactose intolerance. Mutation in the site LCT (LPH) 13910 leads to a disturbance in the regulation of transcriptional activity of the lactase gene, while a normal variant of polymorphism C correlates with a decrease in the production of lactase in adults and a mutant T – with its maintenance. Thus, homozygotes in the allele C cannot digest lactose and homozygotes in the allele T can. Women in the post-menopausal period who have allele C are prone to osteoporosis and require a prescription of calcium-based drugs [36].

The role of COL1A1 is in the coding of protein sequence α1 of the collagen chain of type I. Multimorphism of COL1A1 is characterized by a replacement of guanine with thymine, which leads to disturbances in the site of binding for the factor of transcription in the area of the first intron. In patients with allele T (especially homozygote) of this polymorphism, idiopathic osteoporosis develops. Heterozygotes in the allele G/T have the lowest mineral density of bone tissue in comparison with homozygotes G/G [36]. Ninety-seven women with osteoporosis (49 Russians and 48 Buryats aged 50 to 80 years old) were studied. In the group of Buryat women, an accumulation of a recessive allele A of the gene VDR (Bsm1 c.IVS7G> A) was observed, which increased the risk of osteoporosis in individuals. Allele C of polymorphism (LCT) -13910 T>C was associated with the development of osteoporosis among Buryat women. When Buryat women had allele A in the gene VDR Bsm1 c.IVS7G> A and the allele C of lactase LCT -13910 T>C, they had a higher risk of the development of osteoporosis than Russian women. Genotypes G/T and T/T of the gene polymorphism COL1A 12046 G-> T were associated with the development of osteoporosis among the population of both nationalities.

However, a special role in the regulation of bone homeostasis is occupied by one of the most ancient phylogenetically formed mechanisms – Wnt, signaling pathway (SP-Wnt), which controls the bone tissue due to the influence on the process of differentiation of mesenchymal stem cells, stimulation of replication of pre-osteoblasts, inhibition of apoptosis of osteoblasts and osteocytes [40–42].

First, the role of SP-Wnt was mentioned in the regulation of the bone tissue density in 2001, when such an osteoporosis syndrome as pseudoglioma was revealed, which was characterized by a combination of a decrease in the mineral density of the bone tissue, retinal detachment, and cataract. This syndrome is inherited by an autosome-recessive type due to a mutation in the gene LRP5 in the 11$^{th}$ chromosome, which leads to a decrease in bone formation due to inhibition of SP-Wnt [43]. Mutation in the allele LRP5 can initiate the development of juvenile osteoporosis. The study included 235 Finnish men aged 18.3 to 20.6 years old. Only polymorphism A1330V LRP5 was significantly associated with the parameters of bones. In comparison with patients with genotype AlaAla (n = 215), patients with genotype AlaVal (n = 20) had the bone mineral content (BMC) of the lower part of the femoral neck P = 0.029 and bone mineral density (BMD) P = 0.012, BMC of trochanter P = 0.0067 and BMD P = 0.015, and general BMC of the femoral bone (P = 0.0044) and BMD (P = 0.0089) [44].

The antagonists of SP-Wnt also include one of the representatives of the DAN glycoprotein family (differential screening selected gene aberrant in neuroblastoma) – sclerostin [45]. Sclerostin is synthesized by osteocytes and binds with the receptor of lipoproteins of very low density 5 (LRP5; main membrane-associated cofactor of the Wnt-signal pathway) on their surface, as well as closely interacts with the coreceptor LRP6. Such interaction leads to SP-Wnt blocking and thus, the impossibility of osteoblastogenesis [46].

Specialists in practical healthcare need to be able to use and interpret the above-mentioned markers for the evaluation of the mineral density in patients with a predisposition to osteoporosis. During the past years, a lot of biochemical, molecular, and genetic factors have been studied in the development of osteoporosis. A special direction in these studies is the genetic regulation of bone remodeling. For this reason, this area is perspective in practical application for the diagnostics and treatment of osteoporosis.

***Finansing.*** *The study did not have sponsorship.*

**Финансирование.** Исследование не имело спонсорской поддержки.

***Conflict of interest.*** *Authors declares no conflict of interest.*

**Конфликт интересов.** Авторы заявляют об отсутствии конфликта интересов.

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**Authors contribution**

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Gosteva E.V. — editing and approval of the final version of the article;

Evstratova E.F. — editing and approval of the final version of the article.

*Получено / Recived: 26.01.2021*
*Принято к печати / Accepted: 01.03.2021*