

REVIEWS

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Osteoporosis: Genetic Determinants and Relationship with Cardiovascular Disease

Osteoporoza – uwarunkowania genetyczne i związek z chorobą sercowo-naczyniową

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation;
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Abstract

Osteoporosis has become one of the major public health problems, affecting about two hundred million people worldwide, including one third of all postmenopausal women. The paper presents a review of the current literature concerning the pathophysiology and the most common genetic and environmental determinants that account for the individual predisposition to age-related osteoporosis. Particular emphasis is placed on the specific linkage between the causative factors of osteoporosis and atherosclerotic cardiovascular disease (*Adv Clin Exp Med* 2013, 22, 1, 119–124).

Key words: osteoporosis, candidate genes, cardiovascular disease.

Streszczenie

Osteoporoza stała się jednym z głównych problemów zdrowotnych, dotykając około 200 milionów ludzi na świecie, w tym jedną trzecią kobiet w okresie pomenopauzalnym. Praca przedstawia przegląd aktualnego piśmiennictwa dotyczącego patofizjologii osteoporozy oraz najczęstszych uwarunkowań genetycznych i środowiskowych, które odpowiadają za osobnicze predyspozycje do ujawnienia się objawów osteoporozy związanej z wiekiem. W artykule szczególną uwagę zwrócono na występowanie związku przyczynowo-skutkowego między czynnikami wywołującymi osteoporozę i miażdżycową chorobą sercowo-naczyniową (*Adv Clin Exp Med* 2013, 22, 1, 119–124).

Słowa kluczowe: osteoporoza, geny kandydaci, choroba sercowo-naczyniowa.

Osteoporosis is the most common chronic skeletal disorder. It has a multifactorial etiology and is expressed by a progressive loss of bone substance, impairments of bone microarchitecture and an increased risk of so-called “fragility fractures” [1, 2].

Phenotypic expression of osteoporosis is assessed with indices describing the quality of bone tissue, such as bone mineral density (BMD), broadband ultrasound attenuation (BUA) and velocity of sound (VOS), which characterize over 80% of bone deterioration [3].

Osteoporosis develops when bone resorption occurs too rapidly or the replacement process is too slow. Resorption of bone tissue is a result of ongoing interactions between osteoblasts and osteoclasts. Osteoclasts, originating in the bone marrow from monocyte/macrophage with the help of transcription factor PU.1, degrade bone matrix. Osteoclast proliferation is mediated, besides many other proteins, by the receptor activator of NF-κB (RANK), which is an osteoclast receptor, combined with the receptor activator of NF-κB ligand (RANKL), an osteoblast cytokine. In turn, RANKL initiates the differentiation

of osteoclasts in the presence of macrophage colony-stimulating factor (M-CSF). RANKL then activates the tumor necrosis factor receptor-associated factor 6, c-Fos and calcium signaling pathways necessary for the induction of the nuclear factor of activated T cells (NFAT) c1. NFATc1 is the crucial transcription factor for osteoclast differentiation. In addition to calcineurin-NFATc1, calcium signaling activates the calcium/calmodulin activated kinase-cyclic AMP-response element binding (CaMK-CREB) protein pathway, which plays a key role in osteoclastogenesis. Also, osteoprotegerin (OPG), which can capture RANKL before it is linked to RANK, suppresses bone resorption [4–6].

Osteoporosis is becoming one of the major public health problem. Nowadays about two hundred million people worldwide, including one-third of all postmenopausal women, suffer from osteoporosis that subsequently leads to fragility fractures in about 40% of the affected women and in up to 30% of the affected men. For women at age 50, the lifetime risk for hip fracture related to osteoporosis is 17.5%, 16% for vertebral fracture and 16% for Colles' fracture; for men, the same risks are 6%, 5%, and 2.5% respectively [1, 2, 7].

A study of 862 perimenopausal women (242 African Americans, 384 Caucasians, 117 Chinese and 119 Japanese) performed by Greendale et al. revealed that BMD loss began one year before menopause, and then decelerated but did not cease two years after the last menstruation. The cumulative 10-year BMD loss was estimated by the authors as 10.6% [8]. In Poland, the incidence of hip fractures among women is about 50 cases per 10,000, and the female: male ratio is estimated as 1.6. It is worth emphasizing that hip fracture (called often the "last fracture") is the third most common direct cause of death among patients over 65, after cardiovascular disease and neoplasms [6].

According to the International Osteoporosis Foundation (IOF) guidelines, osteoporosis risk factors can be divided into: (1) modifiable factors depending mainly on lifestyle, like poor nutrition, vitamin D deficiency, low body mass index (BMI), smoking, alcohol overuse, inadequate physical activity and frequent falls; and (2) fixed factors, which cannot be modified, such as ethnicity, age (above 65 years), small stature, female gender, a family history of fractures, hormonal status (menopause in women, hypogonadism in men) and some kinds of long-term therapy (glucocorticoids, anticoagulants, antiepileptics) [1].

It should be emphasized that the clinical manifestation of osteoporosis results from the complex interrelations between environmental and genetic determinants that account for an individual predisposition to the disease.

Genetic Determinants of Osteoporosis

Knowledge of the genetic factors responsible for osteoporosis can be crucial not only for disease prevention but also for inventing novel therapies. However, as Marini and Brandi stated: "Classic age-related osteoporosis is a multifactorial heterogeneous disorder and its exact genetic bases are still unknown" [1]. Epigenetic regulative factors, gene-gene and gene-environment interactions make the situation even more obscure: Sometimes different genetic and environmental factors may result in the same osteoporotic phenotype, but it is also possible that individuals predisposed genetically never become osteoporotic, and, conversely, people without predisposing alleles can develop age-related osteoporosis [1].

According to various authors, studies on twins and families affected by osteoporosis indicate that inter-individual variations in BMD are determined by genetic factors in 50–85% of the cases [9, 10], and BMD heritability varies with different skeletal sites [11]. Surprisingly, the heritability of fragility fractures, as confirmed by family history, seems to be independent of BMD and is probably influenced by other factors, such as bone geometry, bone turnover or the risk of falling [1].

In turn, it was clearly demonstrated that such bone features, like quantitative ultrasound properties, femoral neck geometry, and bone turnover markers range are controlled by genetic factors [3].

According to Ralston et al., segregation analyses in families revealed that the regulation of BMD and other osteoporosis-related phenotypes mentioned above is polygenic, and is determined by polymorphisms (common genetic variants) in multiple genes, each with a relatively minor effect, rather than by mutations in a few genes. Ralston et al. state that there are about 20 million known polymorphisms in the human genome. However, polymorphisms have modest effects on gene function, acting by altering the protein structure of the gene product or by changing gene expression. It is assumed that several common conditions, including osteoporosis, result from the combined effects of many hundreds of polymorphisms [2].

Only very severe rare forms of osteoporosis are inherited as the result of mutations in single genes, according to Mendel's rule. Among these monogenic bone diseases associated with abnormal (diminished or increased) bone mass are osteogenesis imperfecta (genes COL1A1 and COL1A2), osteopetrosis and sclerosteosis (two very rare conditions) and estrogen receptor deficiency (mani-

fested by osteoporosis and tall stature; caused by mutations of gene ESR1) [2, 10].

Candidate gene association studies have been widely used in seeking the genetic background of osteoporosis. Such studies have identified several polymorphisms connected with BMD, bone characteristics and the risk of fragility fracture. As Ralston and Uitterlinden wrote, candidate gene association studies “involve analyzing polymorphic variants in candidate genes with a role in bone biology and relating carriage of a specific allele (or haplotype) to a quantitative trait or disease” [1]. A list of the most important candidate genes for osteoporosis was created, based mainly on the results of the European Genomos (Genetic Markers for Osteoporosis) study. Genomos is a European multicentric consortium that collected over 25,000 Caucasian subjects from 18 European centers (including Poland), using prospective genotyping with cross-center standardization for the isolation of osteoporosis candidate genes. Within this project, data on fractures incidents, bone densitometry measurements, information on risk factors and DNA analyses from blood samples are collected [1, 11, 12].

About 150 candidate genes related to osteoporosis have been identified, and the list of them is available on the Hugenet website (<http://www.hugenavigator.net/>) [1].

Osteoporosis-related genes, well-documented in large-scale studies, include the genes encoding collagen type I (COLIA), vitamin D receptor (VDR), estrogen receptor (ESR), androgen receptor (AR), aromatase (CYP19A1), lipoprotein receptor-related protein 5 and 6 (LRP5, LRP6), sclerostin (SOST), transforming growth factor β 1 (TGFB1), interleukin-6 (IL-6), and insulin growth factor-1 (IGF-1) [1, 13, 14]. The most significant genes associated with increased susceptibility to osteoporosis are presented in the next section.

The COLIA1 Gene

Collagen type I is the essential protein of bone matrix, consisting of α 1(1) and α 1(2) protein chains encoded by the COLIA1 and COLIA2 genes, respectively. Researchers have mainly focused on a G/T polymorphism within intron 1 of the COLIA1 gene that creates a binding site for the transcription factor Sp1 [1, 9]. The T allele is connected with increased synthesis of the collagen I α 1 chain, which causes an imbalance between the α 1 and α 2 chains and consequently a reduction of bone mineralization [15]. The T/T genotype appears to be associated with reduced BMD, increased age-related bone loss, and a higher risk of fracture as a result of impaired bone density and

quality [1]. In addition, two other polymorphisms have been detected in the promotor region of the COLIA1 gene that are in linkage disequilibrium with the Sp1 polymorphism [16]. In a study on a large cohort of the British females, Stewart et al. found that haplotypes defined by the three polymorphisms mentioned have stronger effects on BMD than the individual single-nucleotide polymorphism (SNP) [17].

It was reported by Jin et al. that the promotor and intron 1 polymorphism of COLIA1 gene interact with each other to regulate gene transcription [18].

The VDR Gene

The VDR-vitamin D endocrine system is crucial to the regulation of calcium-phosphate homeostasis, increasing the absorption or reabsorption of calcium at almost all the epithelia that are involved in Ca^{+2} transport. Vitamin D is derived from nutritional sources or synthesized in the skin with the help of UV-B light; and it requires both 25- and 1- α -hydroxylation, which occurs mainly in the kidneys, to be transformed to the active hormone 1,25-(OH) $_2$ D. As Bouillon et al. wrote: “An important role of 1,25-(OH) $_2$ D is to regulate calcium absorption in the intestine and reabsorption in the kidney” [19]. Vitamin D deficiency leads to a bone, growth plate and tooth phenotype known as rickets (before puberty) or osteomalacia (in adults) [19].

The polymorphisms of the VDR gene that have been extensively analyzed are the BsmI, ApaI, and TaqI polymorphisms in the 3' UTR of the gene, the FokI polymorphism in exon 2 and the Cdx2 polymorphism in the promotor region of the gene [20].

The VDR gene alleles were extensively tested in association studies as potential candidates for genetic susceptibility to osteoporosis in relation to BMD, but with time the association appeared to be rather weak [9], with the exception of the Cdx2 polymorphism [20].

In Marini's opinion, considering the conflicting findings and data that have so far been published on the VDR gene, interest in this field should be focused on meta-analyses rather than single association studies alone [1].

The ESR Gene

Estrogens exert an important influence on the acquisition and maintenance of bone mass, thus the estrogen receptor gene ESR1 seemed to be an obvious candidate for the genetic regulation of bone turnover. As Marini and Brandi wrote:

“Most studies have focused on the (TA) n repeat microsatellite in the promoter region and on the PvuII and XbaI single nucleotide polymorphisms (SNPs) in the intron 1” of the ESR gene [1, 21].

Albagha et al. reported positive associations between haplotypes defined by PvuII and/or XbaI polymorphisms and bone mass loss in a population of 3,000 postmenopausal women [22]. In a study by van Meurs et al., in turn, when ESR polymorphisms were analyzed together as haplotypes, significant associations of haplotypes with decreased spinal BMD and with an increased risk for spinal fracture were detected in women, but not in men [23]. Regarding the pathomechanism, Ralston suggested that the ESR intron polymorphisms may affect gene transcription and hence regulate expression of the estrogen receptor in target tissues [9].

IL6

There is evidence that in postmenopausal women, the increase of IL6 and other proinflammatory cytokines related to the decline of estrogen are associated with bone loss. The most common polymorphisms connected with enhanced bone resorption have been described in the promoter region of the IL6 gene [1].

Ferrari et al. proposed that this genetic predisposition is specific for middle-age women because IL6 gene polymorphisms affect bone mass only after menopause, through a molecular mechanism induced by the estrogen deficiency [24].

LRP5 and LRP6

The LRP5 and LRP6 genes are co-receptors for the Wnt/beta catenin signaling pathway that regulates osteoblast activity and therefore bone formation [1, 6].

The Genomos study investigators analyzed polymorphisms of both the LRP5 and LRP6 genes in over 30,000 Caucasian subjects and found that only the Met667 and Val1330 alleles of the LRP5 gene were associated with reduced BMD and increased risk of fractures [25].

With time, it became evident that the osteoporosis candidate gene association studies were, as Marini and Brandi noted, providing results because of “inadequate population sampling, ... lack of standardized genotyping methods, gene-gene interactions, linkage disequilibrium with other trait-causing polymorphisms in a nearby locus, epigenetic and/or posttranscriptional gene expression regulation” [1].

A novel and very promising approach has appeared along with genome-wide association

analyses (GWASs) using chip technologies and the achievements of complete sequencing of human genome. GWASs are based on simultaneous analyses of huge numbers of single-nucleotide polymorphisms spread at locations throughout the genome. This technique enables the identification of quite new loci and/or genes associated with a susceptibility to osteoporosis [9, 26]. Over 60 quantitative trait loci (QTLs) related to bone metabolism, located in all chromosomes except for chromosome Y, have been identified through GWAS studies [27]. GWAS analyses have revealed some quite new candidate genes for osteoporosis, like bone morphogenetic protein 2 (BMP2) [28], latent transforming growth factor beta binding protein 2 (LTBP2) [29], and the signal transducer and the activator of transcription 1 (STAT1) [30]. GWASs have also confirmed the crucial role of the gene TNFRSF11B, which encodes osteoprotegerin, a natural inhibitor of bone resorption [31].

However, Ralston (2010) warned that GWAS markers are designed to seek common alleles, and some rare polymorphisms contributing to a given trait could be overlooked [9]. The same opinion was expressed by Marini and Brandi, who pointed out that “new candidate genes must be verified by follow-up population-based association studies and functional studies” and that “caution should be taken in the interpretation of replication/confirmation of the results since some genomic region could eventually be proven to be a false positive” [1].

Osteoporosis and Cardiovascular Disease

For a long time osteoporosis and atherosclerotic cardiovascular disease (CVD) have been considered two independent conditions closely related to aging process. Interestingly, recent evidence indicates that these two diseases have a similar physiopathological and genetic background [19, 32, 33]. The main role in this common pathogenesis is played by calcium metabolism, which affects both bone mineralization and the development and progression of arteriosclerosis – it is known that over 90% of atherosclerosis fatty plaques undergo calcification. It has been proven that elderly people often manifest a deficiency of calcium and vitamin D, which, through parathormon (PTH) stimulation, could cause calcium mobilization from bones, leading to lower BMD, a higher risk of fractures, and simultaneously intensified calcification of arteries [1, 34].

Moreover, many cells that play an important role in the cardiovascular system, like vascular endothelial cells, cardiomyocytes, vascular smooth

muscle cells and monocytes/phagocytes, have been found to express VDR and respond to vitamin D with cell-specific gene regulation [19].

Several clinical studies have linked even mild vitamin D deficiency with many conditions that are considered common cardiovascular risk factors, such as hypertension, obesity, type 2 diabetes mellitus, metabolic syndrome, prothrombotic state and vascular calcifications [19, 35, 36].

An increased risk of CVD is specifically observed in vitamin D-deficient patients with chronic renal failure, who demonstrate enhanced atherosclerotic lesions with evident arterial stiffening and reduced flow-mediated dilatation [37].

It is worth noting, after Bauillon et al., that not only vitamin D deficiency, but also vitamin D excess due to exogenous overdosing or endogenous overproduction can result in vascular and valvular calcifications and subsequent organ failure [19]. Therefore, there is a justified need for carefully optimizing vitamin D administration.

Osteoporosis and CVD share a common genetic background, which is evidenced, for instance, by osteoprotegerin and RANKL, which regulate osteoclast activation and are simultaneously involved in vascular calcification and atherosclerosis [38]. Also, bone morphogenetic protein (BMP2) is active in osteoblastic differentiation through Runx2 expression, and atherosclerotic lesions show increased expression of BMP2 and Runx2, as compared to normal arteries [34].

Another common pathogenesis of osteopo-

rosis and CVD is age-related estrogen deficiency, which stimulates the generation of pro-inflammatory cytokines (IL1, IL6 and TNF α), enhancing the expression of adhesion molecules on leukocytes and endothelial cells and facilitating the development of atherosclerosis plaques. Moreover, a lack of estrogen contributes to a decrease in osteoprotegerin production, with subsequent calcium mobilization from bones and an increased risk of calcification of atherosclerosis lesions [1, 34].

As Yamaguchi et al. showed, elevated LDL and low HDL cholesterol, accepted as one of the most significant risk factors for atherosclerosis, are also connected with low BMD and vertebral fractures in postmenopausal women, which may explain the coexistence of atherosclerosis and osteoporosis in patients with dyslipidemia [39].

In a recent paper, Nielson et al. (2012) offered an interesting insight into the complex relations between a susceptibility to osteoporosis and body weight. In the past, it was commonly accepted that older people with a low BMI are at increased risk of bone fractures. However, the authors presented data indicating that obesity, being a serious factor leading to atherosclerosis and CVD worldwide, is also related to a higher risk of bone fractures, although the pathomechanisms of this link remain unclear [40].

All the intriguing interrelations between osteoporosis and CVD that have been briefly reviewed here surely need further specific studies to identify their common causative risk factors and genetic determinants.

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