

## REVIEW

# Osteoporosis Complicating Some Inborn or Acquired Diseases

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Received July 13, 2018

Accepted September 13, 2018

**Summary**

Osteoporosis in chronic diseases is very frequent and pathogenetically varied. It complicates the course of the underlying disease by the occurrence of fractures, which aggravate the quality of life and increase the mortality of patients from the underlying disease. The secondary deterioration of bone quality in chronic diseases, such as diabetes of type 1 and type 2 and/or other endocrine and metabolic disorders, as well as inflammatory diseases, including rheumatoid arthritis – are mostly associated with structural changes to collagen, altered bone turnover, increased cortical porosity and damage to the trabecular and cortical microarchitecture. Mechanisms of development of osteoporosis in some inborn or acquired disorders are discussed.

**Key words**

Osteoporosis • Celiac disease • Phenylketonuria • Crohn disease • Rheumatoid arthritis • Hyperthyreosis

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**Introduction**

It is known that the low bone density and high bone fragility increase risk of fractures and often complicate many endocrinopathies and metabolic disorders (primary hyperparathyroidism, hyperthyroidism, hypercortisolism, diabetes mellitus of type one and type two, growth hormone deficiency, diabetes insipidus and others). Osteoporosis is also associated with chronic diseases of a non-hormonal

nature. Strong detrimental effects on the skeleton have been recorded from chronic inflammatory diseases, such as rheumatoid arthritis, psoriasis, ankylosing spondylitis, pemphigus vulgaris, systemic lupus erythematosus (Briot *et al.* 2017, Barake *et al.* 2017). The compensation and treatment of these diseases will slow the loss of bone mass and may reduce the risk of fracture. Diseases, which deteriorate the skeleton can outbreak in childhood or they are acquired during adulthood. The article discusses the pathogenesis of osteoporosis complicating selected internal disorders, including cirrhosis of the liver, chronic hepatitis and chronic obstructive pulmonary disease. Straub *et al.* (2015) characterize this osteoporosis as an „accident of inflammation“. Recent data and literature search were obtained in PubMed.

**Inborn metabolic diseases associated with bone deterioration***Celiac disease*

Celiac disease (gluten-sensitive enteropathy, non-tropical sprue) affects approximately 1 % of the population in Europe and the USA (Hernandez and Green 2006). It is to be expected, with the availability of modern serological methods performed in the risk groups, that there is going to be an increase in the number of patients with an adult variant of celiac disease. It is essentially a genetically determined autoimmune hypersensitivity of the intestinal cell to gluten. It affects the mucous membrane of the small intestine by inflammation, induces villous atrophy and widening or hyperplasia of the crypt, which leads to nutrient malabsorption (Briani *et al.* 2008). Histological changes

in the intestinal mucosa usually occur with a daily dose of gluten exceeding 10 mg (Akobeng and Thomas 2008).

#### *Genetics of celiac disease*

It was observed that celiac disease is often bound to the class II HLA system (chromosome 6p21). In around 50 % of Danish population were HLA DQ2/DQ8 positive and therefore potentially risky for celiac disease (Karhus *et al.* 2018). Similarly, approximately 90 % of celiac patients have a DQ2 or DQ8 haplotype, as compared with only 40 % of general population (McAllister *et al.* 2018). The polymorphism beta57 in the HLA-DQ8 gene amplifies the T-cell activation and it is associated with an increased sensitivity of the body to gluten. Symptomatic carriers of the HLA-DQB1\*02 genotype have high titers of antibodies against transglutaminase I. Moreover, the HLA system may also be associated with some extraintestinal autoimmune diseases that occur more frequently with celiac disease than in unaffected populations. Children suffering from both celiac disease and type 1 diabetes are more likely carriers of the HLA-DQ 2/8 gene than children with isolated celiac disease or healthy children (Lewandowska *et al.* 2018). The genes common to celiac disease and type 1 diabetes were identified at chromosomes 1q31 and 6q25. Other risk genes for both diseases were localized at chromosomes 3p21, 18p11, 2q33 and 12q24 (Verdu and Danska 2018). The MAG12 gene, which is responsible for intestinal damage in celiac disease, was also identified with the method GWAS (Genome-wide Association Study), which could identify other genes common to celiac disease and associated autoimmune disease and could thus contribute to the early diagnosis of these diseases (Abadie *et al.* 2011). Moreover, recently epigenetics and microbiota appeared to be further potent factors, affecting disease manifestation and targeting therapeutic procedures (Dieli-Crimi *et al.* 2015).

The first manifestations of the disease can occur in childhood, more often in early adulthood in diarrhea and malabsorption syndrome, in slowing growth, loss of weight, and children's total lag behind their peers. There are increasing cases being diagnosed in adulthood or even over 60 years of age, when classical manifestations are not fully expressed, and malabsorption syndrome and increased bone loss are mostly attributed to the physiological aging. In adulthood, the manifestations of the accompanying diseases – most commonly autoimmune diseases (diabetes mellitus of type one,

chronic thyroiditis, connective tissue disease) often highlight celiac disease. The prevalence of seropositive celiac disease is about 28 % in general population (Juneau *et al.* 2018). Therefore, screening is recommended for celiac disease in all patients with autoimmune disorder. In celiac disease, a higher incidence of other extraintestinal diseases (T-cell lymphoma, herpetiform dermatitis, neuropathy, Sjögren's syndrome, male infertility, or hypochromic hypsideremic anemia) has been observed. Extremely serious complications of celiac disease include osteoporosis and osteomalacia with subsequent fractures. Decreased bone density was observed in 50 % of children with histologically verified celiac disease. The low peak bone mass achieved in adolescence is the cause of low traumatic fractures in adulthood (Abadie *et al.* 2011). In any way, quality of life is deteriorated in all celiac patients (Martinez-Martinez *et al.* 2018).

#### *Mechanisms of the development of osteoporosis in celiac disease*

The basic causes of the accelerated loss of bone mass are chronic inflammation and malabsorption (Bianchi and Bardella 2008). Inflammatory cytokines IL-1 $\alpha$ , IL-1 $\beta$  and TNF- $\alpha$  produced by the intestinal mucosa activate the bone resorption and accelerate the loss of bone mass. The relationship of cytokines to the skeleton is also probably determined genetically. Moreover, it is also interesting to note the evidence of a higher incidence of osteoporosis in other healthy relatives of patients with celiac disease, who had higher IL-1 $\beta$  levels (Stazi *et al.* 2008). The inflammation-activated bone resorption is further stimulated by overproduction of parathyroid hormone, which is the result of hypocalcemia caused by insensitivity of inflammatory intestinal mucosa to 1,25(OH) $_2$  vitamin D and by malabsorption of calcium and vitamin D (Cashman 2008). Other factors may also contribute to acceleration of bone loss in patients with celiac disease, such as a history of multiple pregnancies or prolonged hypoestrinism and hyperprolactinemia in men. Individuals simultaneously suffering from a deficit of somatotropin or sarcopenia – the factors that damage the stability of bone mass – also have a higher risk of osteoporosis. Also, patients who are on long-term medications that activate the axis RANK/RANKL/osteoprotegerin, such as glucocorticoids, carry an increased risk.

### *Laboratory detection of gluten-sensitive enteropathy*

From the point of view of the prevention of osteoporosis and other complications of celiac disease, the early detection of the disease is important, using gliadin, transglutaminase and endomysial IGA antibodies. Determination of antibodies is indicated, for example, in patients with unexplainable secondary hyperparathyroidism, or in premenopausal women with osteoporosis not responding to conventional anti-resorptive therapy. The final diagnosis of celiac disease is reliably confirmed by an intestinal biopsy. The expensive determination of genetic markers to identify patients at risk of osteoporosis is still only theoretical.

### *Prevention and treatment for bone disorder in celiac disease*

A basic step in the prevention of osteoporosis is the treatment of celiac disease, which consists in the timely introduction of a gluten-free diet. This alone often leads to the normalization of levels of 25(OH) vitamin D and parathyroid hormone, and then to an increase in bone density. A gluten-free diet is also recommended for children in long latency. If there is not an adequate rise in vitamin D levels, calcium and cholecalciferol substitution is indicated. Prospects for the future are specific proteases, which reduce the toxicity of gluten, or the inhibitory immunomodulator recombinant alpha-gliadin. Currently, the effect of larazotide (AT-1001) is being examined (Khaleghi *et al.* 2016). This synthetic peptide works as a permeability regulator, which (under condition of normal calcium-phosphate homeostasis) regulates the function of the intestinal epithelial cells in celiac disease. The effect is conditioned by more severe loss of bone mass, non-specific anti-resorptive treatment with bisphosphonates or the monoclonal antibody against RANK should be considered (Miller 2009).

Altogether, celiac disease is not a rare autoimmune disorder affecting the intestinal mucosa, which occurs in genetically disposed individuals. It is often associated with other extra-intestinal diseases predominantly of an autoimmune nature. The fundamental mechanisms by which celiac disease damages the bone are inflammation and malabsorption. The most serious consequence for the integrity of the skeleton is the disease when it manifests in childhood, when it causes insufficient development of the peak bone mass. However, even 'mute' forms of disease in adults and older persons can accelerate the physiological loss of bone mass and may lead to the formation of secondary

osteoporosis and/or osteomalacia. The early detection of the disease and its objective treatment can prevent the development of pathological fractures. However, it is necessary to bear in mind that laboratory tests on celiac disease have a low specificity and sensitivity, therefore their practical applicability is limited.

### *Phenylketonuria (PKU)*

PKU is a hereditary, autosomal recessive metabolic disorder caused by mutation in the PAH gene for phenylalanine hydroxylase. Although it is typically diagnosed in children, it may also deteriorate the adult skeleton (Sumánszki *et al.* 2017). In the liver, in the presence of a tetrahydrobiopterin cofactor, the phenylalanine hydroxylase degrades the amino acid phenylalanine to 5-hydroxytryptophan (serotonin). The mutation in some of the 13 exons, in the intron or the promoter region of the PAH gene (548 mutations in total have been described) or in the tetrahydrobiopterin gene (1-2 % of cases) leads to a slowdown in the metabolism of phenylalanine to 5-hydroxytryptophan. The phenylalanine concentration in blood and tissues is abnormally high, while the level of 5-hydroxytryptamine is low. The effect of this deviation is the attenuation of the synthesis of neurotransmitters (serotonin and dopamine), which leads to severe brain damage that dominates in this disease. Some mutations in the gene may cause only a mild form of phenylketonuria, when the level of phenylalanine in the blood just slightly exceeds the upper limit of the standard (normal range 50-110  $\mu\text{mol/l}$ ).

### *Hyperphenylalaninemia and the skeleton*

Although PKU is mostly diagnosed in children, a study on a small number of probands showed that osteopenia in phenylketonuric men and women aged 20-30 was confirmed in 39 % of cases, osteoporosis in 6.5 % (Modan-Moses *et al.* 2007). The primary cause of the bone metabolic disorder in phenylketonuria is the direct effect of phenylalanine, which will accelerate the conversion of mononuclears to osteoclasts. In the experimental study, however, the association of phenylketonuria and osteopenia was not clearly confirmed. Although the risk of osteopenia in phenylketonuria is not high, this disease can significantly slow down the development of bone mass in children with delayed puberty, with an inadequacy of growth factors and active metabolites of vitamin D, or an imbalance in soft tissue composition. Because the

peripheral quantitative computer tomography (pQCT) in phenylketonurics showed a decreased value in the density of the trabecular bone (even at normal DXA values), it can be assumed that phenylketonurics have primarily reduced bone quality and strength. Bone metabolism with phenylketonuria is likely negatively influenced also by the deficiency of 5-hydroxytryptamine, which alone has an osteoanabolic effect. Furthermore, pQCT is able to analyze not only deterioration of bone metabolism, but also neuromuscular abnormalities (Choukair *et al.* 2017). Thus, the most reliable information on the function of skeletal damage in phenylketonuria is provided by pQCT.

In pediatric patients, the 17 quantitative ultrasound (QUS) can also be used, which shows the low values of mineralization and cortical thickness in suspected cases. Z-score SOS (speed of sound) and broad-band ultrasound attenuation (BUA) negatively correlated with the plasma level of phenylalanine. The method is also suitable for long-term monitoring of the state of the skeleton. The current bone remodeling activity can be monitored by measuring bone formation and bone resorption markers, always with respect to the age of the patient.

The basis of the treatment is the consistent control of phenylalaninemia, which is based on the strict restriction of natural proteins containing phenylalanine and on the supplementation of neutral synthetic acids, glycomacropeptide and calcium. The decrease in phenylalanine levels may be achieved by administering tetrahydrobiopterin (Van Spronsen and Enns 2010). However, inadequate amino acid intake in patients with PKU may increase the detrimental effects on the skeleton. The impact of the suppressed production of serotonin, which itself, under physiological conditions, activates new bone formation, needs to be analyzed.

The early detection of phenylketonuria has paramount importance, and if it is carried out in the context of screening for congenital diseases, it can prevent not only severe mental retardation, but also poor skeletal development in children and subsequent osteoporosis in adulthood (van Wegberg *et al.* 2017, Sumaily and Mujamammi 2017). The aim of the research is also the study of the bone metabolism focused on PKU in adult and elderly suspected populations. Apart from the substitution of phenylalanine hydroxylase, that would restore enzyme activity, gene therapy holds promise for the future. Thus, untreated phenylketonuria may cause the insufficient development or the accelerated loss of the bone mass and therefore also the increased risk of

fractures. Pathogenesis of this form of osteopenia/osteoporosis has a complex nature (first the direct effect of hyperphenylalaninemia and further nutritional deficiency, mainly inadequate amino acid intake) (Hochuli *et al.* 2017).

### **Further inflammatory gastrointestinal diseases, complicated by osteoporosis**

#### *Crohn disease and ulcerative colitis*

36 % of patients with Crohn disease and 32 % with ulcerative colitis showed osteopenia, and 15 % with Crohn disease and 7 % with ulcerative colitis showed osteoporosis. Due to the overexpression of inflammation cytokines, such as IL13, IL-1 $\beta$  and IL4, bone resorption markedly increases in inflammatory bone diseases (IBD), although bone formation is unchanged, or inhibited, partly as a result of treatment with glucocorticoids and malnutrition (Krela-Kaźmierczak *et al.* 2016). In steroid-free bowel inflammation in remission, Bastos *et al.* (2017) still found low bone mass with Z-score -2.0 at L1-L4, which indicates that factor(s) responsible for bone loss in active IBD may have a long-lasting effect on the skeleton. Osteopenia/osteoporosis is caused by inflammation alone together with malnutrition and glucocorticoid treatment. To identify bone microarchitecture in patients with IBD, peripheral quantitative computer tomography (pQCT) is recommended, which usually correlates with the severity of IBD (Maratova *et al.* 2017).

Besides inflammatory gastrointestinal diseases, the skeleton is deteriorated by gastrectomy status, short bowel syndrome or state of achlorhydria (e.g. induced by the treatment with proton pump derivatives) (Krela-Kaźmierczak *et al.* 2015). Serious metabolic disease complicated by osteoporosis is also inborn or secondary-acquired hypolactasia leading to milk intolerance, increase in bone turnover, reduced BMD and osteoporotic fractures. This mostly autosomal recessive disease, which may have a severe impact on calcium and vitamin D homeostasis, may be associated with TC-13910 polymorphism. Deleterious effect of milk intolerance on BMD was described in a population of Northern Europe (Kull *et al.* 2009).

New prospects in the therapy of IBD consist in biological therapy, such as monoclonal antibodies against TNF or special small molecules, which easily penetrate into inflammation tissues (reviewed by Douda 2018).

### *Rheumatoid arthritis*

The current cause of osteopenia/osteoporosis is inflammatory joint disease – especially rheumatoid arthritis (RA), but also other rheumatoid diseases, such as lupus erythematosus, systemic sclerosis, ankylosing spondylitis or psoriasis, which all are characterized by inflammation and limited mobility leading to irreversible structural damage of the affected joints and the skeleton. A specific association develops between autoimmunity and the skeleton, in which antibodies recognizing citrullinated proteins and rheumatoid factor become powerful osteoclast activators triggering bone loss (Schett 2017). The hyperactivity of antibodies and proinflammatory cytokines (IL-1, IL-6 and IL-17) in RA stimulates above all the synthesis of RANKL in chondrocytes, which results in periarticular activation of bone resorbing osteoclasts (Braun and Schett 2012). A typical radiological finding is periarticular bone thinning with characteristic marginal erosions, whose repair is slowed down as a result of diminished bone formation. In RA, the direct effect of inflammation on the bone is enhanced by glucocorticoid therapy, malnutrition, physical inactivity and muscle atrophy. Continuing hyperactivity of bone resorption induces the acceleration of cortical bone loss, the expansion of the endosteal circuit and the reduction of bone strength. At this time, bone deterioration has not only a focal, but also a systemic character due to accelerated bone loss, but also microstructure damage. Children with RA, mainly those with late onset of puberty have a poor development of peak bone mass (Burnham 2012). Among adults, there is most risk of osteoporotic fracture in postmenopausal women and patients with other severe diseases (e.g. cardiacs, patients with obstructive pulmonary disease and diabetics) and/or those living in harmful environment (smokers, alcoholics). Genetic analysis holds some promise for the future, as it will allow the prediction of the risk of osteoporosis in RA. A study conducted in 350 women (200 diagnosed with RA) found an association between bone density of the hip and variations in genes for VDR (polymorphism BsmI) and OPG (polymorphism A163G). Female carriers of the G allele (in the A163G polymorphism) also have simultaneously a significantly higher risk of RA and osteoporosis (Hussien *et al.* 2013). The similar association was also described in white population by Mencej-Bedrac *et al.* (2009).

The basis of prevention and treatment of osteoporosis complicating RA is the suppression of

inflammation, supplementation of vitamin D, calcium and menatetrenone (vitamin K2). According to the European guidelines for osteoporosis from 2009, in postmenopausal women, who are receiving glucocorticoids at doses above 7.5 mg prednisone daily for more than three months and who are achieving a DXA score below -2.0, anti-resorptive medication at the start of treatment with glucocorticoids is recommended. Teriparatide shows osteoanabolic effect, which could slow down the development of bone erosions in these patients. Promise for the future holds biological therapy with anti RANKL antibody-denosumab. Both these treatment have only transitory effects and thus the treatment should be followed by the course of further antiresorptive therapy.

The loss of bone mass is also observed in autoimmune diseases, such as systemic lupus erythematosus. Osteoporosis in this disease is related to the detrimental effect of lupus itself and to frequent vitamin D deficiency. A strong causal effect on the skeleton is attributed to long-term glucocorticoid treatment (Edens and Robinson 2015). In patients with some other autoimmune diseases, such as systemic sclerosis, vitamin D deficiency plays an essential role in the development of the disease and osteoporosis (Szamosi *et al.* 2017).

### **Endocrine and metabolic diseases associated with accelerated bone loss**

#### *Hyperthyroidism*

A number of endocrine disorders are complicated by osteopenia/osteoporosis. Bone deterioration is very serious in chronic hyperthyroidism, and, in particular, in the life-long treatment with high (suppressive) doses of thyroid hormones. Triiodothyronine at physiological concentrations acts directly on the skeleton *via* specific receptors on osteoblasts. It stimulates osteoblastic activity and it has a key importance for the linear growth and development of peak bone mass in children. In adulthood, thyroid hormones promote the mineralization of bone and improve its quality. In euthyroid postmenopausal women, the tyrosine concentration positively correlated with the number of progenitor bone cells in circulation. Belsing *et al.* (2010) recorded low bone density in the femoral and lumbar spine in premenopausal women with Graves' disease. When euthyreosis was obtained, the bone density normalized, but after 18 months of discontinuation of

thyrostatic action, the BMD decreased again in negative correlation with serum thyroxin levels. Bone loss and decline of bone strength in hyperthyroidism are induced by an increase in IL-6 and cathepsin K and partly *via* the physiological decrease in TSH levels, as the later hormone is a relatively strong bone anabolics (Mysliwiec *et al.* 2011, Zhang *et al.* 2014). The correlation study in euthyroid postmenopausal women noted the significant reciprocal relationship between serum TSH levels and some parameters of osteoresorption (Zofkova and Hill 2008). Furthermore, TSH in rats and under certain experimental condition also prevents bone resorption (Dumic-Cule *et al.* 2014). As osteoporosis induced by hyperthyroidism is not only a problem of postmenopausal women, the aim of the treatment is to achieve permanent remission of hyperthyroidism independently of the age or gender. The skeletons of patients with thyroid carcinoma, who are treated with high doses of thyroid hormones over a long period, are extremely endangered. The bone response is proportional to the dose of hormone, particularly in women with hypoestrinism, chronic inflammatory diseases, smokers and alcoholics. Treatment with thyrostatic pharmaceuticals slows the loss of bone mass or accelerates its growth in children. The treatment of severe osteoporosis in hyperthyroid patients – except thyreostatics – is based on the administration of anti-resorptive drugs. Inhibitors of cathepsin K are a future prospect.

### Further weighty endocrine and/or metabolic diseases threatening the skeleton

#### *Diabetes mellitus*

Type 1 and the type 2 diabetics are very often affected by osteoporotic fractures, which reduce the quality of life of the patients, similar to other major diabetic complications (Vokó *et al.* 2017). The pathogenesis of skeletal damage in diabetics differs in individual patients, mainly depending on the type of disease. While type 1 diabetes, the bone density value is markedly decreased, diabetics with type2 have impaired bone quality, even at normal or elevated bone density. Botushanov and Orbetzova (2009) showed the relative risk of hip fracture in women with type 1 diabetes to be higher (RR: 8.9) than for women with type 2 diabetes (RR: 2.0). Therefore, the fracture risk is higher for type 1 diabetics.

The pathogenesis of osteoporosis in diabetes has a complex nature and it is partly outlined by Montagnani

*et al.* (2011). Hyperglycemia itself has a toxic effect on osteoblasts, as it reduces their sensitivity to  $1.25(\text{OH})_2\text{D}$ . In addition, it stimulates the proadipocytic transcription factor PPAR $\gamma$ , thus it activates adipogenesis to the detriment of osteogenesis. The bone quality in diabetics also damages the storage of glycosylation products and pathological cross-bridges in collagen, which is related to oxidative stress. Decreased bone formation is the crucial mechanism leading to reduced bone mass in diabetics. Bone metabolism is also negatively influenced by a low level of insulin, IGF-1 and IGF-2, high levels of proinflammatory cytokines, as well as by hyperinsulinemia in type 2 diabetes. The negative effect of oxidative stress and increased homocysteine levels on the skeleton in diabetics is also discussed (Tariq *et al.* 2018, Samadi *et al.* 2018). Adipokines inflammatory factors, TNF- $\alpha$ , interleukin-6 and CRP in patients with complicating osteoporosis were significantly higher than in those without osteoporosis (Chen *et al.* 2017). Thus, increased inflammatory response, an abnormal lipid spectrum in the blood and a change in adipokines increase the risk of osteoporosis in patients with diabetes mellitus. The bone quality in diabetes could also be endangered by prolonged diabetic neuropathy, microangiopathy and hypercalciuria (Montagnani *et al.* 2011). In type 2 diabetes, there is also speculation about the detrimental effect of sclerostin, which inhibits Wnt/ $\beta$ -catenin signaling, and thus the function of osteoblasts (Graat-Verboom *et al.* 2012). Influence of the hormones of the skeleton was reviewed in detail by Zofkova (2015). Another negative factor is treatment with some antidiabetics. While metformin has a beneficial effect on the skeleton (it reduces the deposition of glycosylation products in bone), the thiazolidinediones have a negative effect because they direct to the differentiation of the mesenchymal progenitor cell in favor of adipogenesis. The final products of glycation (AGE) and pentosidine become the candidate markers of fracture risk in diabetics. Prevention of fractures in diabetics is based on strict glycemic control, supplementation of calcium and vitamin D, and permanent monitoring of the bone density. In cases of osteoporosis, antiresorptive therapy is mostly indicated. Besides teriparatide, promising for the future are derivatives of incretin-glycogen like peptide (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which control glycemia and directly activate the process of new bone formation.

### *Protoporphyrin*

Osteoporosis or osteopenia are frequent in patients with erythropoietic protoporphyria (metabolic disease characterized by increased photosensitivity due to accumulation of protoporphyrin IX). Vitamin D deficiency and weight-bearing exercise correlates with low BMD was observed in these patients (Biewenga *et al.* 2017). Thus, pathogenesis of bone deterioration in protoporphyria is most probably complex.

### *Hyponatremia*

Hyponatremic patients showed a markedly higher rate of hip fractures. Mild long-term chronic hyponatremia (89 days duration) is independently associated with hip fracture risk in older humans (Ayus *et al.* 2016). However, correction of hyponatremia did not lead to a decline in hip fractures. The causal association between hyponatremia and low bone mass remains questionable.

### *Unusual effects of endogenous uric acid on the skeleton*

Interestingly, uric acid has a positive effect on bone metabolism in obese subjects, in whom the serum osteocalcin directly and independently correlates with serum uric acid. Some authors attribute the protective effect of uric acid on the skeleton to the antioxidant properties of normal levels of uric acid (Pirro *et al.* 2017). On the other hand, De Pergola *et al.* (2017) observed that the association between serum uric acid and BMD (mostly in the femur in postmenopausal women) is partly explained by the confounding effect of adiposity, the role of which remains to be further analyzed.

### *Chronic obstructive pulmonary disease (COPD) and bone health*

Osteoporosis occurs more frequently in patients with COPD than in the rest of the population. Female smokers are the highest risk group. In smokers, according to Bon *et al.* (2011), radiographic emphysema is a strong, independent predictor of low BMD. Later authors assessed cancellous and cortical bone mineralization density distribution in a small group of postmenopausal smokers. The frequency of osteoporotic fractures increased depending on the stage of the disease and mostly correlated with parameters of functional lung examination. Osteoporotics with moderately advanced disease (CT II) had higher residual lung volume than patients without osteoporosis expressed as a percentage of total pulmonary capacity (RV% TLC) (Graat-Verboom *et al.* 2012). In a group of 85 patients with COPD, compressive

fractures were found in 35 % of patients, where the number of fractures strongly correlated with the vital lung capacity and with forced expiratory volume (FEV<sub>1</sub> s) (Szymanski *et al.* 2002). Compressive fractures of the vertebrae further aggravate pulmonary ventilation and lead to acute exacerbations of COPD. The frequency of these exacerbations is (in addition to PaO<sub>2</sub>) an independent predictor of a decrease in bone density. The primary cause of skeletal involvement in COPD is ventilator disorder and a high frequency of acute inflammatory exacerbations of the disease. Pathogenesis of osteopenia in COPD is complex. Significant associated factors are nicotine, reduced mobility and the loss of muscle mass, respiratory acidosis and systemic inflammation with a negative influence of interleukins and pre-existing osteopenia. Also, administration of glucocorticoids, negatively affects the skeleton (Sanel *et al.* 2016). Key factor in accelerating bone loss in COPD is vitamin D deficiency. Thus, fracture prevention in COPD is based on anti-inflammatory treatment, supplementation of vitamin D, rehabilitation, and permanent monitoring of bone density.

Caffarelli *et al.* (2016) followed osteoporosis in 58 patients with idiopathic pulmonary fibrosis, where correlation between BMD in the femoral region and respiratory parameters were found, at first between BMD and FVC % or DLCO %. Vertebral fractures usually lead to worsening of respiratory parameters in these patients.

## **Cardiovascular diseases associated with osteoporosis**

### *Chronic heart failure (CHF)*

Fractures complicating cardiac failure are relatively frequent. Mazziotti *et al.* (2012) reported in patients with chronic heart failure a prevalence of thoracic vertebral fractures – 31 %. Leistner *et al.* (2012) assume that the molecular basis of accelerated loss of bone mass in cardiac patients is the activation of RANKL. In a group of 153 people (123 of whom suffered from chronic heart failure), a subgroup of cardiac patients had higher RANKL/osteoprotegerin ratios. The authors, using multivariate regression analysis, found, that the independent predictors of the RANKL level were the duration and severity of heart failure. Thus, it appears that bone catabolism is almost inevitably associated with CHF. In CHF, many other factors that predispose to the origin of osteoporosis, affect the skeleton: older age, vitamin D deficiency and hyperparathyroidism, oxidative stress, decreased kidney function, the high activity of the

renin-angiotensin-aldosterone system, often diabetes mellitus and frailty syndrome. For the prevention of osteoporosis in cardiac patients, thiazide diuretics and spironolactone should be preferred to the loop diuretics that increase urinary calcium loss. Attention should be paid to the treatment of osteoporosis in cardiac patients, particularly because the fractures increase their mortality.

#### *Other cardiovascular diseases and osteoporosis*

Veronese *et al.* (2017) in a meta-analysis of 28 studies with more than 1 million participants found a small, but significantly increased risk of cardiovascular disease, such as coronary artery disease and cerebrovascular accident in subjects with low BMD. Krynytska *et al.* (2017) in 33 men with coronary heart disease found structural and functional changes of bone tissue in the lumbar spine in 49.2 % of patients complicated by stage II-A chronic heart failure. Osteoporosis was found in 16.9 % of patients. The association between the skeleton and vascular system could be explained by biological links between the RANKL/RANK/OPG axis and Wnt/ $\beta$ -catenin signaling working in both systems. In other words, a key role in the association is most probably played by both osteoprotegerin and sclerostin (Karajewska-Wlodarczyk 2017). Further large studies on this topic are needed.

#### *Calcification processes as a potential cause of osteopenia/osteoporosis*

Osteoporosis is very often associated with increased calcification of the abdominal aorta and carotids. Calcified plaques were significantly correlated with osteoporosis. Low doses of supplements do not seem to influence vascular calcifications (Lampropoulos *et al.* 2016). Negative bone remodeling in patients with vascular calcification is probably a consequence of reduced bone formation without activation of OPG-RANKL axis (Pennisi *et al.* 2004).

According to some authors, osteoporosis often complicates calcium urolithiasis (Lampropoulos *et al.* 2016). 20 % of calcium stone formers have osteopenia and 7 % osteoporosis. Although normal DXA declines with increasing age, osteoporosis is more prevalent and more pronounced in older patients (over 60 years of age) with nephrolithiasis (Bijelic *et al.* 2016). On the other hand, Sakhaee *et al.* (2017) did not find any association between urine calcium and BMD in patients with calcium nephrolithiasis in a large group of males and estrogen treated females. Thus, the authors presume that

mechanisms other than hypercalciuria cause osteoporosis in kidney stone formers.

#### *Cirrhosis of the liver and/or chronic hepatitis*

Complication of cirrhosis with osteoporosis is very common (50 %), in chronic active hepatitis 9.1 % (Bedimo *et al.* 2016). Fractures are often two fold in patients with chronic liver disease (Handzlik-Orlik *et al.* (2016). It occurs especially in the final stage of the disease or early after liver transplantation. The toxic effects of high levels of bilirubin and bile acids to osteoblasts, which leads to a slowing of the formation of new bone, is amplified by the direct influence of alcohol (Gonzalez-Calvin 1993). The key pathogenetic factors leading to bone loss are decreased production of 25-OH vitamin D, hypovitaminosis K and low levels of IGF-1 and overproduction of interleukin-1 and interleukin-6 (which activate RANKL) (Handzlik-Orlik *et al.* 2016). Suboptimal serum vitamin D is frequently observed in HIV/AIDS patients treated with anti-retroviral pharmaceuticals (Mastaglia *et al.* 2017). Epidemiologic studies suggested a three-fold increased fracture incidence in patients coinfecting with HIV/hepatitis C virus even before development of cirrhosis (Bedimo *et al.* 2016, Weitzmann *et al.* 2016) (see below).

Hepatic osteodystrophy is present in about 15-52 % of cases of primary biliary cirrhosis, which depends on the severity and duration of the disease and degree of cholestasis (Glass and Su 2016). According to Handzlik-Orlik *et al.* (2016), activated bone remodeling could be normalized by inhibitors of bone turnover, or by liver transplantation. Patients with chronic biliary cirrhosis usually slow the metabolism of cholecalciferol to the active metabolites of vitamin D. They initially may have normal DXA values, but the bone density measured by peripheral quantitative computed tomography (pQCT) usually indicates an early decrease in geometric and volumetric parameters in both cortical and trabecular bone. Upala *et al.* (2017) published a meta-analysis of the association between non-alcoholic fatty liver disease and BMD. Other meta-analysis involving 1,276 participants, of whom 638 had non-alcoholic fatty liver disease, showed no significant difference in BMD between subjects with fatty liver disease and controls. Due to a certain controversies, further clinical studies are required. The basic therapeutic approach in osteoporotic subjects with cirrhosis of the liver or chronic hepatitis is to optimize the nutrition and supplementation of calcium and active metabolites of vitamin D.



### *The role of chronic infections with HIV, HCV or HBV in development of osteopenia/osteoporosis*

Fracture risk increases mainly in elderly patients with untreated chronic hepatitis induced by long-term infection due to accelerated bone resorption (increased activation of RANKL) and deterioration of bone microstructure. Moreover, in hepatitis B and hepatitis C infected subjects a crosstalk between virus activity and the patient's immune system has been observed (Biver *et al.* 2017). Lower serum IGF-1 and IGFBP-3 have been found in subjects with osteoporosis of the proximal femur complicating hepatitis C infection than in those without osteoporosis (Raslan *et al.* 2010). Furthermore, bone metabolism in infected patients treated with anti-retroviral pharmaceuticals is additionally deteriorated by suboptimal serum vitamin D (Mastaglia *et al.* 2017). Unfortunately, antiviral pharmaceuticals (anti HBV and anti HIV) themselves may also be toxic to the skeleton. Thus, the harmful effect of virus infection on bone appears to be very complex (Biver *et al.* 2017).

### *Chronic renal failure*

Hemodialyzed patients with vertebral fractures have significantly reduced BMD and usually reduced trabecular bone score (TBS) compared to those without fractures (Yavropoulou *et al.* 2017). Brunerova *et al.* (2016) found normal TBS only in 1/3 of patients in a group of 59 patients treated with hemofiltration. Low BMD and high risk of vertebral fractures were also observed in a major study of postmenopausal women with mild renal dysfunction (Kaji *et al.* 2010). Nevertheless, renal osteopathy is a very serious separate chapter that goes beyond the scope of this article. Here it is worth mentioning the causal effect of not too much frequent renal tubular acidosis (RTA I) on bone homeostasis. A significant proportion of patients with osteopenia or osteoporosis had incomplete RTA I. The furosemide test in this inborn disease is able to suggest a defect in H<sup>+</sup>ATPase or Na<sup>+</sup> reabsorption in the cortical collecting tubules (Weger *et al.* 2000). The precise detrimental effect of RTA I on bone mass remains to be identified.

## **Further selected states complicated with osteoporosis**

### *Frailty syndrome*

Conditions associated with frailty are muscle atrophy, low strength, falls and fractures markedly increasing mortality and morbidity (Suh and Lyles 2003).

Frailty syndrome also belongs to a group of diseases which include anorexia nervosa, neoplasias, sarcopenia, dialysis patients, all of which are endangered by fractures (Gielen *et al.* 2017).

### *Beta-thalassemia and sickle cell anemia*

Osteoporosis complicates beta-thalassemia major, similar to sickle cell hemolytic anemia (mutations in the beta globin genes), which synthesizes abnormal hemoglobin S. Bone demineralization was detected in nearly 93 % of these patients, mainly at the femur (Baldini *et al.* 2010). Pathophysiological significance in osteoporosis induced by thalassemia is most probably multifactorial, partly attributed to severe growth hormone deficiency (measured in 27.9 % of subjects using GHRH plus arginine analysis. IGF-I (but not IGF-II) was low in 86.3 % of thalassemic patients (Scacchi *et al.* 2016). No correlations were found between growth hormone peak and osteocalcin and/or telopeptides. In the case of sickle cell disease osteoporosis develops in the context of nutrient deficits, including vitamin D. Effectivity of treatment with vitamin D, has not been extensively studied (Soe *et al.* 2017).

## **Conclusion**

Osteoporosis in chronic diseases is very frequent and pathogenetically varied. It complicates the course of the underlying disease by the occurrence of fractures, which aggravate the quality of life and increase the mortality of patients from the underlying disease. This report deals with the most common and, from the point of osteoporosis, the most risky diseases. However, accelerated bone loss with fracture risk may accompany a number of other serious diseases. The secondary deterioration of bone quality in chronic diseases, such as type 2 diabetes, chronic kidney disease and chronic obstructive pulmonary disease and a number of metabolic and inflammatory disorders – are mostly associated with structural changes to collagen, altered bone turnover, increased cortical porosity and damage to the trabecular and cortical microarchitecture (Yamaguchi 2016). Accelerated bone loss with fracture risk may be accompanied by other states, such as chronic pancreatitis, cystic fibrosis and/or neurological disorder. The Global Longitudinal Study of Osteoporosis in Women (GLOW), conducted in over 52,000 subjects, has shown strong associations between fracture risk and Parkinson's disease (Ishizaki *et al.* 1993). At increased risk for osteoporosis

are adults with cerebral palsy. From the point of prevention of bone loss in neurological diseases, Whitney *et al.* (2018) emphasize importance to maintain musculoskeletal mass and function during the lifespan.

A frequent mechanism leading to deterioration of bone mass in some states, such as diabetes mellitus, atherosclerosis, menopause or chronic kidney diseases and life style diseases (including sleep habits) may be oxidative stress (Notsu and Yamaguchi 2013, Sasaki *et al.* 2016). Osteoporosis in women with breast cancer associated with ovarian suppression and chemotherapy treatment and the disease alone, due to tissue infiltration or metastatic processes could also be mentioned here (Biarese *et al.* 1996).

A consideration of all comorbidities could predict the risk of fractures and early prevention of osteoporosis, which consists in the compensation the underlying disease (treatment of inflammation, metabolic or hormonal disorders), in the adjustment of nutritional

deficiency, supplementation of vitamin D and calcium and correction of homeostasis of trace elements (Zofkova *et al.* 2017), as well as the rehabilitation of physical activity. Anti-resorptive therapy (using bisphosphonates, denosumab, raloxifene), or administration of teriparatide is indicated in the cases of manifest secondary osteoporosis. For inborn diseases, such as celiac disease and phenylketonuria, specific procedures are recommended for the prevention of low peak bone mass and subsequent osteoporosis in adulthood.

### Conflict of Interest

There is no conflict of interest.

### Acknowledgements

This work was supported by the project (Ministry of Health, Czech Republic), for conceptual development of research organization 00023761 (Institute of Endocrinology, Prague, Czech Republic).

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