Osteoporosis is a multifaceted disorder provoked by a complex interaction of genetic, endogenic and exogenic factors, significantly affecting not only the locomotor apparatus’ mechanics but rather the life quality and longevity [6]. As of today, 200 million people across the world are suffering from osteoporosis and almost 9 million have osteoporotic fractures [6, 7]. From 17 to 80 % cases of osteoporosis have a secondary genesis [17].

The 2014 guidelines published by the Osteoporosis International list the following causes of secondary osteoporosis associated with nervous system diseases: epilepsy, multiple sclerosis, stroke, spinal cord injury, Parkinson’s disease and muscular dystrophy. These disorders vary considerably in terms of their pathogenesis (vascular, neurodegenerative, autoimmune, traumatic etc.), course (acute, chronic), clinical picture; however, all of these conditions provoke a complex of disorders resulting in a bone loss.

Nervous system pathologies affect the bone turnover in an unidentified way; however, there are key mechanisms contributing, to a certain extent, to a secondary osteoporosis afflicting the neurological patients.

Such mechanisms include:

• Lack of axial loading due to a long-term lying position (immobilization),
• Muscle weakness and restricted mobility,
• Vitamin D deficiency,
• Disorders of bone turnover’s nervous regulation.

Immobilization affects the bone tissue in various ways. The study involving 11 healthy volunteers (9 men and 2 women aged 34 ± 11 years) followed them for 12 weeks of bed rest, analyzing their calcium homeostasis, turnover markers, and bone histological parameters. After 12 weeks of immobilization, bone mineral density (BMD) values of lumbar spine decreased by 2.9 % (p = 0.09), while the hip BMD measured at the level of trochanter major – by 3.8 %, (p = 0.002). The bed rest also provoked a rapid and significant increase of Calcium and Phosphorus rates in the urine, as well as a significant rise of Calcium in the blood serum. By contrast, the parathyroid hormone (PTH) and Vitemin D rates decreased significantly, though the mean values remained normal.

The histological bone study revealed a moderate suppression of trabecular bone formation (from 3.1 ± 1.3 to 1.9 ± 1.5 %, p = 0.01) and an increased resorption of both trabecular and cortical bone. The serum bone markers (osteocalcin, bone-specific alkaline phosphatase and propeptide of type I procollagen (PICP)) did not vary significantly. By contrast, the bone resorption markers (hydroxyproline, deoxypyridinoline and urinary N-telopeptide of type I collagen (NTx), as well as serum C-terminal telopeptide of type I collagen (CTX-I)) showed a prominent increase during the immobilization and returned to their initial rates after a week of a suspended immobilization.
Thus, the bone tissue reacts to a lack of axial load by a rapid and sustained growing of resorption rates as well as by a less significant bone formation [64]. Due to these facts, the early verticalization and patients’ activation is an efficient prevention of osteoporosis in the patients affected by the neurological pathologies.

It is very difficult to analyze the influence of a reduced muscle strength and spasticity on the bone tissue, as these factors determine the physical performance and mobility.

The Vitamin D role in the osteoporosis development is well-researched. The patients affected by the neurologic pathologies are less often exposed to the sunlight due to their restricted mobility and thus increasingly develop the Vitamin D deficiencies. Furthermore, the Vitamin D deficiency has been proved a contributing factor of numerous neurological disorders’ genesis.

Nervous system and regulation of bone remodeling

Osteoblasts and osteoclasts are regulated by the systemic hormones, namely PTH, Vitamin D (1,25(OH)₂D₃), calcitonin, glucocorticoids, sex steroids etc. Furthermore, the association between the body mass and BMD values has been confirmed, suggesting a common regulator for the body and bone mass. The most promising option is a leptin, regulating body mass via hypothalamus and its receptors [16].

The bone cell function is also regulated by the factors produced either by the bone cells proper, or by their immediate environment. These autocrine and paracrine factors include cytokines, growth factors and prostatic hormones. To the same extent as most homeostatic functions, the bone remodeling regulation is affected by the endocrine and paracrine mechanisms, as well as by the sympathetic nervous system. The bone cells have functioning receptors to several neuro-osteogenic factors [59]. The ‘bone neuromediators’ include noradrenaline, neuropeptide, endocannabinoids, dopamine, serotonin, calcitonin gene-related peptide (CGRP) etc. The sympathetic nervous system (SNS) is referred to as a neural pathway of osteoblast function and bone mass regulation [27].

The histological studies show that the bone and periosteum are innervated by numerous sensory and sympathetic fibers, whose density is maximal around the growth plates and in the long trabecular metaphyses. The human osteoblasts and osteoclasts have adrenergic receptors (ARs) and neuropeptide receptors, suggesting a dynamic neuro-endocrine central regulation of bone turnover via adrenergic systems. The sympathomimetic influence on the bone formation and resorption is executed by β- and β-ARs acting on osteoblasts and osteoclasts, respectively [16].

The experiment reveals the adrenalin’s ability of osteoclast genesis stimulation by the reversal of the receptor activator of the osteoblast-produced nuclear factor kappa-κ ligand (RANKL) and osteoprotegerin (OPG)’s interaction.

The increased sympathetic nervous system (SNS) activity results in an increased bone resorption marker rate and a decreased leptin rate, suppressing cortical bone formation. Thus, an adrenergic stimulation increases the osteoclast number and activity, simultaneously suppressing the osteoblast function, and reverses the formation and resorption rate ratio, promoting osteoporosis development.

This mechanism of osteoporosis development was among the key ones in several clinical situations:

• Using β₁-adrenoreceptor antagonists (ex., broncholitics to treat bronchial asthma) results in a 2-fold increase of hip fracture risk,
• Regional osteoporosis development attending a reflex sympathetic dystrophy syndrome (RSD) characterized by a hyperactivity of adrenergic pathways,
• Loss of bone mass and stress fracture risk increase in athletes using the legal β₁-adrenoreceptor agonists for anabolic muscle effect and catabolic fat tissue effect. Despite the confirmed sympathetic nervous system (SNS)’s role in osteoporosis development, the appropriateness of β-AR blocker use in osteoporosis treatment and prevention is not substantially proved [24].

Unfortunately, the patients suffering from secondary osteoporosis are brought to osteologist’s attention usually following the fracture, and often this fracture is not the first one the patients had.

Osteoporosis in stroke patients

Acute brain blood circulation disorders may occur at any age; however, it is more common in the older age groups, and a half of stroke cases affect people over 70 years [1, 13, 53]. Thus, this group already has an elevated risk of osteoporosis and fractures. The stroke patients have a hip fracture risk which is 2-4 times higher than the one of general population [38]. Following the hip fracture, survival and mobility recovery rates of stroke patients were much lower than of other groups. 4 % of patients who have undergone intervention after the hip fracture, develop a stroke during 1 year after the intervention, while 5 % of stroke patients suffer a proximal hip fracture during 1 year after the stroke; this statistics underlining a similarity of risk factors [45]. A high fall risk is undoubtedly one of the key fracture risk contributors [37].

Over 80 % of fractures are caused by the falls of stroke patients. Among the stroke patients with hip fractures, 66 % were falling to their side at the hip, most commonly to the paresis side, explaining the preponderance of fracture localizations at the paresis side - 82 % [30]. Furthermore, the paretic upper limb triceps’ weakness prevents fall’s impact attenuation. However, it is not only the increase of falls frequency that the fracture risk is associated with. The stroke patients have their BMD values which are lower than the general population ones [5, 15, 19, 33]; however, when and how this reduction occurs is disputable. The 2 SD BMD decrease at the proximal hip bone site increases the falls-related fracture risk of the
stroke occurs by 7 times [30]. The mean time before the first fracture occurs is, on average, 24 months.

The BMD of healthy adults remains the same or decreases at the annual rate of 0.5 % by the menopause onset; however, after the menopause, the bone loss grows by 1.5 % every year [1]. During the 1st year after the stroke, the bone loss at the paretic limbs grows by 12-17 % [38]. The BMD decrease is also registered at the intact side; however, it is smaller than on the damaged one [2]. According to the peripheral CT data, the trabecular bone loss measured at the 4 %-radius site of the paretic limb 12 months after the stroke was 14 % in men and 9 % in women. At the femoral neck, it was 11 % in men and 13 % in women. The loss of cortical bone measured at the 20 %-radius site was 4 % and 2.5 %, respectively [41].

There are many determinants of bone loss after stroke: immobilization term [38], hemiplegic severity [37], postmenopausal duration in women [52], as well as the low body mass in the per-stroke period and lateverticalization (over 2 months after the stroke) [24].

The greatest bone loss develops during the first years after the stroke. Later on, such factors as a low rate of functional recovery [41], ongoing immobilization, Vitamin D deficiency [37], anticoagulants (Warfarin) [48] and anticonvulsants [18] may promote a further bone loss. All the above-mentioned facts prove that the stroke patients have a high risk of osteoporosis and its severe complications, namely hip fractures.

**Osteoporosis and Parkinson's disease**

Osteoporosis and Parkinson's disease (PD) are both age-related disorders affecting patients of one age group. Parkinson's disease is a chronic progressive brain disease, predominantly associated with black substance dopaminergic neuron degeneration, Alpha-synuclein (S) protein accumulation and intracellular inclusions (Lewy bodies), manifesting itself through a combination of hypokinesia and rigidity, resting tremor and postural instability, as well as a large array of non-motor features – mental, autonomous, sensory etc. [3].

The Global Longitudinal Study of Osteoporosis in Women showed that a fracture risk association with Parkinson's disease was more significant than that of any other attending pathologies [25].

The postural instability and gait disruptions related to Parkinson's disease bring up the falls risk: 60.5 % of PD patients fall no rarer than once a year, while 39 % have recurrent falls and 33 % of falls lead to fractures [8]. The fracture risk of PD patients exceeds the risk of controls by 2-4 times in various populations [56, 62]. It is well-known that 90 % of fractures in the elderly are related to falls [56].

However, not all fractures in these patients are falls-related; for instance, the vertebral fractures bear no association with falls [36]. The key predictor of fragility fractures is a low BMD [43]. Although the studies of PD patients’ BMD last for over 25 years, the number of new reports is growing. In the newly published one, osteoporosis is referred to as “a concealed non-motor face” of Parkinson's disease, as its role in aggravating motor and non-motor symptoms is revealed and the urgency of its treatment is emphasized in PD patients [46]. The falls risk is partially dependent on the disease manifestations and the tool of falls risk reduction is treating Parkinson's disease, while the tool of BMD improvement and associated falls risk reduction may be implemented only after a correct diagnostics [3, 62].

Many studies report that the BMD of PD patients is significantly lower than that of controls [46, 51, 56, 61]. The frequency of low BMD detection is 60-90 % [49, 51]. Besides, the BMD of PD patients is lower than the one of controls by 7-20 % [31, 49]. Despite all the above-mentioned factors, bone tissue studies are not obligatory for the PD patients.

The impaired mobility is one of the key factors explaining the BMD loss and increased fracture risk of PD patients. The tremor positively affects the BMD, while the immobilization and functional disorders do it negatively. Various vectors of PD symptom influence on bone tissue explain the differences in findings. For instance, the bone tissue is constantly exposed to the mechanical stimulation due to the muscle contraction and body movements. In response to the mechanical loading, its remodeling rate is activated. The osteocytes, bone tissue cells, due to the mechanical loading stimulate osteoblast and osteoclast activity [14]. On one hand, the reduced mobility suppresses osteocyte activity; on the other, an increased muscle tension and tremor intensify it. According to some studies, the BMD of PD patients reflect the duration and severity of the disease [4], while according to others, there is no such reflection [23].

Among the key promoters of BMD loss there are malnutrition, low body mass index (BMI), Vitamin D deficiency, muscle strength and mobility reduction, increased homocysteine rate due to the elevated doses of levodopa (L-DOPA) [61].

Body mass, namely fat mass, loss is one of the non-motor autonomous Parkinson’s disease’s symptoms [39]. Body mass loss in the PD patients was described as early as in 1817, when the first report by James Parkinson was published. The recent findings show that the PD patients have BMI which is much lower than the control, and depends on the severity of disease. Furthermore, the parameters of fat and lean mass are also reduced [39, 42].

The studies of Vitamin D’s role in genesis and prognostication of Parkinson’s disease are ongoing. Vitamin D is an essential risk factor of osteoporosis and osteomalacia. As of today, it is confirmed that the PD patients’ Vitamin D rates in blood serum are significantly lower than those of general population; however, the variations of this parameter due to the disease’s progressing and treatment are under scrutiny [40, 48].

**Bone mineral density of multiple sclerosis patients**

Another neurological disorder also associated with an elevated fracture risk is a multiple sclerosis (MS), characterized by a classical triad of symptoms; damaged pyramidal tracts (mobility impairments), coordinative
dysfunction and visual impairment. Unlike the above-mentioned conditions, this disorder predominantly affects the young individuals. The MS patients have a higher osteoporosis and fragility fracture risk due to the glucocorticoid treatment, immobilization and Vitamin D deficiency [29, 34]. On examining 9346 MS patients, the researchers found that 2501 (27.2 %) patients had a reduced BMD, over 15 % reported a history of fractures after 13 years (n = 1482), among them 685 (46.2 %) had multiple fractures, 522 (35.2 %) had forearm fractures, 165 (11.1 %) reported vertebral fractures, while 100 (7.4 %) had a femoral neck fracture [44]. Among the recruited MS patients with a history of fractures, 746 (55 %) took Calcium supplements, 858 (68.8 %) – Vitamin D and 334 (22.5 %) – bisphosphonates [44].

The BMD changes were revealed not only in the elderly, but also in the young patients. Similarly to other disorders, the early studies associated the reduced BMD with immobilization; however, later on the researchers started to consider other factors. In our opinion, the bone tissue changes and their mechanisms in the MS patients are not completely clear. The MS patients under 50 years had a significant correlation between the femoral neck BMD and age, as well as between their BMD and physical activity, the age of MS onset and BMD [55]. The study confirmed that the low BMD predominates among the young patients, so this group should pay a special attention to their bone tissue.

While studying the osteoporosis risk factors, independent of immobilization, the researchers revealed a significantly lower Vitamin D and osteocalcin concentration, along with significantly higher PTH, alkaline phosphatase, pyridinoline and deoxypyridinoline, in the MS patients whose mobility was retained. The lumbar spine, femoral neck and trochanter major BMD were much lower than those of the controls. The significant negative correlation was found between the disease’s duration and BMD. Significant correlation was also revealed between the overall functional independence and femoral neck and trochanter major BMD, as well as a negative correlation between EDSS and lumbar spine BMD, together with all the hip BMD measurements. As to the blood serum remodeling markers, they didn’t reveal any significant associations, other than Vitamin D and lumbar spine BMD. Thus, the disease’s duration and reduced functional performance are the key factors affecting the BMD of MS patients. Together with a reduced functional performance, Vitamin D and secondary PTH growth promote the BMD changes in MS patients [57].

While in the general population osteoporosis and an increased osteoporosis-related fracture risk reveal themselves in men about 10 years later than in women, the MS male patients have a fracture risk which is significantly higher than the one of the MS female patients belonging to a similar age group [63].

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References


