Senile osteoporosis:
Modern view of the problem

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Abstract. The article summarizes the data on senile osteoporosis and presents a clinical case of this disease. The reference sources on peculiarities of bone remodeling in senile osteoporosis are summarized; low bone formation takes place against the background of a pronounced bone resorption. The article also presents pathomorphological features of bone tissue remodeling resulting in pronounced impairments of the compact bone, which increase the risk of fracture. Vitamin D plays a significant role in the complex mechanism of senile osteoporosis. The data on the combined effect of vitamin D and parathormone on bone remodeling are summarized. The paper presents data on other cumulative effects of senile osteoporosis development. Against the background of ageing-associated systemic changes, calcium and vitamin D deficiency, increased pro-inflammatory cytokine expression, localized bone disorders develop. An important link to the development of senile osteoporosis is an increased marrow adipose tissue with an intensified adipogenesis, resulting in a decrease of osteoblasts due to the toxic effects of adipokines, reduced differentiation and proliferation of osteoblasts. Age-associated immune-related mechanisms of inflammation, indirectly affecting the bone, are considered. Peculiarities of the senile osteoporosis diagnostics by means of bone mineral density assessment tools are described. Despite the successes achieved in the study of senile osteoporosis development mechanisms, further research is required to explore local and systemic factors affecting bone tissue which are involved in the development of this disease.

Keywords: senile osteoporosis; bone remodeling; bone mineral density assessment

Senile osteoporosis, known as the second type of systemic osteoporosis, occurs after the age of 70-75 years [1-3]. Along with other osteoporosis types, it results in a bone fragility with an increased fracture risk. Senile osteoporosis is more frequently associated with women; the overall ratio of disease prevalence distribution is one man to every two women. Some authors consider senile osteoporosis to be a principal geriatric syndrome [4].

The senile osteoporosis has the risk factors which are similar to other osteoporosis types: i.e. probable low bone peak achieved by 30 years. The disease generally occurs due to chronic conditions, long-term use of medications negatively affecting the bone tissue, smoking and other risk factors. However, the principal factor of senile osteoporosis is a specific bone turnover occurring due to the age-related systemic changes, namely due to the hormonal dysfunction.

Vitamin D and parathyroid hormone

The key component of senile osteoporosis pathogenesis is Vitamin D whose deficiency may be provoked by its reduced supplementation or skin production promoted by an insufficient insolation [5]. The senile osteoporosis pathogenesis is also mainly attributed to 1.25(OH)D3 receptor deficiency in the bone cells, intestine etc., as well as probable Vitamin D receptor’s gene polymorphism. The Vitamin D active metabolite deficiency is tapering down with age due to the involutionary changes in kidneys and a reduced activity of 1α-hydroxylase enzyme. This enzyme is regulated by a range of factors, namely the parathyroid hormone (PTH) influencing the bone remodeling at various levels. One of the key physiological Vitamin D functions is the secretion and synthesis control. The PTH secretion is growing due to a low Calcium blood rate (secondary senile hyperparathyroidism) and dimin...
ishing under increased rates of Calcitriol whose receptors are located in the parathyroid gland cells [1, 6]. The hypogonadism developing with age is also promoting the bone loss in 20–30% elderly population, resulting in a secondary hyperparathyroidism. With advancing age, malabsorption causes the Calcium rate decrease, bone remodeling rate acceleration. The above-mentioned factors account for the fact that senile osteoporosis attending hyperparathyroidism is considered one of the key mechanisms of its pathogenesis [4].

**Bone remodeling in senile osteoporosis patients**

The principal pathophysiological mechanisms for all the osteoporosis cases involve the negative bone remodeling, i.e. imbalance of bone resorption to bone formation. The senile osteoporosis is associated with an increased resorption. The proliferation and differentiation disorders involve multiple factors in case of this condition. With ageing, the bone formation rates diminish, the fatty tissue rate in the bone marrow increases, mesenchymal stromal cells progress from osteoblastogenesis to a predominant adipogenesis [6–8] inducing the osteoblastic different cell changes, i.e. their proliferation and activity drops (Fig. 1) [7, 9].

Furthermore, the age-related changes of bone tissue may be considered systemic negative changes due to Runx2 suppression. The Runx2 is in charge of osteoblast differentiation, while an increased Peroxisome proliferator-activated receptor-γ (PPARγ) results in the accelerated adipogenesis rates (Fig. 1) [10].

One has performed a genome analysis of gene expression during the mesenchymal stromal cell differentiation [11]. The Id4 gene is a leading candidate for control over the differentiation of these cells towards either adipocytes or osteoblasts. The Id4 gene suppressed expression promoted adipocyte differentiation, while the high rate of Id4 gene expression in the mesenchymal stromal cells resulted in osteoblast differentiation and lessening of adipogenesis rates. Furthermore, the Id4-mutant mice demonstrated abnormal lipid drop accumulation in bone marrow and bone formation activity disorders. Based on the increased rate of adipocytes in bone marrow and its obesity-induced changes, one claims senile osteoporosis to be a type of lipotoxic condition, which favors bone marrow fattening and confers its toxicity to osteoblasts [7, 12]. Under the cumulative adipocyte and osteoblast cultivation, adipocytes were confirmed to slow down the osteoblast activity and their survival, probably due to the adipokine and fatty cell release [13]. However, the role of increased adipocyte numbers pervading the bone marrow is debatable; this is why, the researchers are still making further studies into the issue. Using the SAM-P6 mice for a senile osteoporosis model, one has detected in their bone marrow a low rate of osteoglycine biosynthesis, weakening the mesenchymal cell ability of differentiation towards osteogenesis [10]. It is well-known that normal or increased osteoglycine rates may suppress the α2 adipogenesis marker gene expression and promote Wnt5b, RUNX2 osteoblast differentiation, osteocalcin, alkaline phosphatase and collagen (Colla1) gene expression, reducing the PPARγ2 adipogenesis marker expression. The described findings testify to the fact that osteoglycine plays an important role for senile osteoporosis development, regulating the osteo- and adipogenesis gene expression, while its increasing rates may be a potential target for therapeutic intervention [10]. One of the possible age-related changes provoking osteoporosis is presented in Fig. 2.

The osteoporosis risk increases due to the reduced localized regulators of osteoblast environment - IGF-1, IL-11, TGF-β, BMP, whose biosynthesis diminishes with age. One has also detected the key role of inflammation within the senile osteoporosis development; along with immunological mechanisms, inflammation is a determinant of bone resorption [14] (Fig. 2). It is well-known that a great number of cytokines and growth factors take part in functional activity and osteoblast/osteosteat viability regulation. The anti-inflammatory cytokines are critical inflammatory mediators which are affecting osteoclast modulation in a direct or indirect way. These are interleukins 1 and 6 (IL-1, IL-6), tumor necrosis factor-α (TNF-α), RANKL molecule of TNF family etc. [8, 12, 15]. There are important immune-regulating mechanisms controlling the bone loss and formation balance. First and foremost, T-cells are indirectly affecting osteoclasts, predominantly via the suppressed osteoprotegerin (OPG) and increased cytokine expression, which stimulates the RANKL-induced proliferation and osteoclast activation. RANKL is affecting the RANK osteoclast receptor; after

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**Figure 1. Cellular changes due to senile osteoporosis (adapted from [4])**
its activation, the signals are transmitted via the receptor-associated tumor necrosis factor (TRAFs), probably TRAF6. This is one of the better researched mechanisms considered primary for osteoclastogenesis and age-related resorption, respectively (Fig. 3).

Furthermore, the chronic T-cell activation results in a counter-regulatory mechanism disorders, among them antiviral cytokine interferon–γ (IFN–γ) suppressing osteoclast development and activation via ubiquitin-proteasome pathway (UPP), causing protein degradation in osteoclasts [16]. The T-cells are also activating inflammatory molecule biosynthesis affecting the osteoporosis development and deteriorating the bone formation [3].

**Other factors**

There are data on probable senile osteoporosis pathogenesis which is initiated by zinc deficiency. Based on the experimental and clinical data, one was exploring the following mechanism of zinc deficiency effect on the increased endogenous heparin rate, probably due to the fatty cell degranulation and heparin release intensifying the destructive action of E prostaglandin on bone [17]. It is possible that the endogenous heparin and E prostaglandin are PTH co-factors, and they both accentuate the PTH action in senile osteoporosis pathogenesis.

It is suggested that the Kloto gene is osteoporosis-contributing factor, slowing down the ageing rate due to the tyrosine phosphorylation, insulin and IGF-I [12, 18]. The authors claim that it is a new systemic factor regulating age-related bone mass, while the age-related expression may provoke the senile osteoporosis. For the first time it was established that mice with Kloto gene mutation have osteopenia, cortex formation disorders, identical to the cortex changes of patients with senile osteoporosis. In the remodeling there is a prevailing bone formation decrease and resorption increase, reflecting the osteopenia with a low rate of bone turnover. Based on the pathophysiological studies, one may present new evidence of senile osteoporosis pathophysiology, which may be used to develop the treatment regimen.

Thus, within the senile osteoporosis mechanism there are several pathogenic links which have an interconnected effect.
Morphological bone changes

With postmenopausal osteoporosis, the trabecular bone is primarily affected, while with senile osteoporosis, the pronounced changes are observed in the compact bone due to an increased porosity. The study of hip bone heads obtained from the senile osteoporosis patients aged 55–82 years. The authors confirmed that within the femoral neck cortex there are osteons of various forms and sizes, bone plates surrounding the central channel, they are irregularly located, the osteocyte density between bone plates is low [19]. Most osteocytes have pyknotic hyperchromatic nuclei. The osteon central channels are increased and deformed. This is why the increased cortical porosity is a hip bone fracture risk.

The cortical bone loss results from two simultaneous though opposite processes: subperiosteal layering and bone resorption predominant in the endosteal fragment, and significantly growing with age. After the fourth decade of life, there is a decrease of periosteal bone formation and an increase of remodeling units within the endosteum, resulting in a linear cortex porosity increase, its thinning-down attended by the cortical bone loss [20]. This process is considered to be independent from hormonal effect and closely related to the potential ageing mechanisms [21].

With disease development, the density and thickness of bone trabeculae go down. Due to the low osteoblast density, the trabecular microfracture regeneration slows down, increasing the tendency of low-energy vertebral fractures. The intrab trabecular spaces get filled up with yellow bone marrow and individual hemopoietic cells.

Clinical manifestations of senile osteoporosis

The most frequent senile osteoporosis symptom is an acute or chronic back pain. The patients report weakness, stiffness, kyphosis, height reduction and vasomotor disorders [1]. The pain generally occurs upon standing for a long period of time. The back pain attacks are associated with spinal deformations, increased muscle tone, nerve root compression [1].

Among the senile osteoporosis complications, there are vertebral body fractures resulting in a height reduction, progressing kyphosis; they are attended by pain and physical, mental and/or social functioning deficiency. The back-hunching and kyphosis provoke breathing and walking disorders, height reduction by 10-15 cm, while with physiological ageing the height reduces only by 2-5 cm.

Patients with senile osteoporosis have an increased fracture risk in those skeletal areas where the cortical bone predominates, namely the femoral neck, pelvis, proximal shoulder and proximal tibia [3].

The estrogen and Vitamin D active metabolite deficiency promotes the bone mineral density (BMD) reduction, provokes muscle weakness, nerve-muscle coordination disorder which may account for an increased frequency among the elderly or old people and reduced defense mechanisms in case of injuries.

The range of facts about senile osteoporosis is expanded by the SIRT6 Knockout (KO) mice. All of them had age-related osteoporosis referred to as senile [22]. The basal SIRT6 gene expression was detected in the mice bone marrow, which was also supported by the human experiments. It was found out that SIRT6 takes part in the bone formation processes: from stromal bone to osteocyte. Mice who had no SIRT6 gene revealed changes in the trabecular network structure and cortical bone, bone turnover disorders which were similar to the age-related manifestations of human osteoporosis. The KO mice have undergone the bone formation’s suppression, their BMD decreases. One has additionally cultivated the primary stromal cells of SIRT6 animal’s bone marrow. As a result, one has detected suppressed osteoblastogenesis, increased osteoclastogenesis with an increased number of minor osteoclasts. Those data expanded our view of senile osteoporosis pathogenesis.

Senile osteoporosis diagnostics

At the first stage, one should collect anamnesis including the risk factors. One should also use questionnaires if possible.

The senile osteoporosis diagnostics may be performed by means of spine X-ray in a lateral projection. At the spine X-ray, one frequently detects the reduced height of vertebrae with a wedge deformation. The compressive deformation is detected much more rarely. The special feature of senile osteoporosis is an increased height of intervertebral disks attended by the deformations and multiple tears of hyaline endplates.

The BMD evaluated by dual-energy X-ray absorptiometry (DXA) is one of the most popular diagnostic assays for osteoporosis. The bone densitometry allows measuring the BMD at various skeletal sites in order to confirm the osteoporosis and to control the treatment efficacy after the anti-resorptive drug use.

While selecting the BMD measurement sites for the senile osteoporosis patients, one suggests two options: in order to diagnose and treat the condition, one should measure the femoral neck BMD or spine BMD [23]. While ageing, the senile osteoporosis patients suffer from the pronounced changes of locomotor spine apparatus: end-plate osteophytes are being formed, degenerative changes are present in the facet joints, the vertebral bodies decrease due to the height reduction and compression fractures. The patients may also have a spondylolisthesis, bone sclerosis areas, degenerative manifestations of intervertebral disks resulting in the reduction of their sizes [24].

The study involving 630 middle-aged women (73.3 ± 6.9 years) revealed that degenerative spine changes are associated with an increase of lumbar spine BMD values [24]. Based on the findings which were obtained, the authors consider femoral neck BMD to be more informative than lumbar spine BMD for the senile osteoporosis confirmation in the elderly women. Other researchers are also supporting this idea [25, 26]. However, there is a study involving 395 subjects aged 67-89 years; the patients’ BMD was measured by DXA along with anterior, median and posterior height, as well as anterior-posterior vertebral size (L1-L5) and 6 intervertebral disks (T12-L1, to
Senile osteoporosis: clinical case

The patient A. is 85 years old. She complains of thoracic and lumbar spine pain, persisting during 5 years, and height reduction.

The patient denies having conditions and disorders with a confirmed effect on bone tissue, namely rheumatoid arthritis, an increased function of thyroid and parathyroid gland, ovariomnetrual disorders and a history of ischemic heart disease and cerebral stroke, i.e. present osteoporosis may be used for an early screening of elderly patients.

Table 1. Characterization of two primary osteoporosis types [29]

| Index                          | Type I (postmenopausal) | Type II (senile) |
|-------------------------------|-------------------------|-----------------|
| Age (years)                   | 51-75                   | > 70            |
| Gender-related frequency (M:F)| 1:6                     | 1:2             |
| Bone type                     | Trabecular              | Trabecular and compact |
| Bone loss rate                | High                    | Low             |
| Typical localization and fracture character | Vertebrae (compression fractures). Distal radius | Vertebrae (multiple wedge, rarely – compression fractures). Hip bone |
| Parathyroid hormone rate      | Reduced                 | Increased       |
| Calcium absorption            | Reduced                 | Reduced         |
| Vitamin D metabolite activity | Secondary reduction     | Primary reduction |
| Principal causes              | Menopause-related factors | Ageing-related factors |

Conclusions

The cumulative effects of ageing, Calcium and Vitamin D deficiency attributed to various causes, such as osteoblast dysfunction, increased bone resorption attended by the osteoclast stimulation and suppressed osteoblast function, immune-associated inflammatory processes indirectly affecting the bone, sexual hormone dysfunction, promote the senile osteoporosis development. A key link in the senile osteoporosis development is obesity-related changes of bone marrow and an increased adipogenesis promoting a decrease of osteoblasts and bone remodeling disorders. Despite the achievements of senile osteoporosis mechanism studies, one requires a further in-depth analysis of localized and systemic factors affecting the bone tissue and promoting the development of this condition.
Figure 4. Bone mineral density of the lumbar spine (A), proximal hip (B), total skeleton (C)
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Сенільний остеопороз: сучасний погляд на проблему

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Резюме. У статті узагальнені сучасні знання щодо сенільного остеопорозу і наведені клінічний приклад пацієнта з даним захворюванням. Наведені дані літератури щодо особливостей ремоделювання кістки при сенільному остеопорозі, патоморфологічних особливостей перебування кісткової тканини, які приводять до виражених порушень компактної кістки, що піддається ризик переломів.

Ключові слова: сенільний остеопороз; ремоделювання кістки; оцінка мінеральної щільності кісткової тканини; оцінка мінеральних запалень, індукованих віком, які опосередковано впливають на кістку.

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