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Osteosarcopenia in rheumatoid arthritis treated with glucocorticosteroids – essence, significance, consequences

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Abstract

Rheumatoid arthritis (RA) is one of the most common rheumatic diseases, associated with co-occurrence of serious side effects. This study discusses the problems associated with chronic RA, well-known as osteoporosis, but also recently recognized as sarcopenia. Relationships between sarcopenia and rheumatic diseases are not yet fully understood. Co-occurrence of osteoporosis and sarcopenia, referred to as osteosarcopenia, is becoming increasingly important. The overlap of the effects of RA and osteosarcopenia and the adverse effects of glucocorticosteroids leads to progressive impairment of the musculoskeletal system, increasing the risk of falls, fractures, institutionalization and death, and it is a source of dramatic socioeconomic burden on society. Very limited options for effective treatment of developed osteosarcopenia, as well as the severity of complications caused by it, advocates for the need of broad education and raising public awareness, especially among health care workers, in order to implement the prevention of osteosarcopenia as early as possible.

Key words: osteoporosis, sarcopenia, osteosarcopenia, glucocorticosteroids.

Introduction

Rheumatoid arthritis (RA) is one of the most common rheumatic diseases, becoming more widespread and increasingly recognized. The analysis of Global Burden of Disease study 2017 resulted in conclusion that there were 19,965,115 globally prevalent cases of RA in 2017. The global age-standardized point prevalence and annual incidence rates of rheumatoid arthritis has increased by 7.4% and 8.2%, respectively, from 1990 [1]. The global age-standardized prevalence rate was increasing with age and was higher in women, peaking between 70 to 74 years in men and 75 to 79 years in women [1].

The lack of causal treatment and the associated chronic nature of the disease, its nuisance to patients and patients' family are the rising problems in the aging societies of highly developed countries. The situation is aggravated by the co-occurrence of serious side effects associated with RA treatment, especially from the use of systemic steroids, which, despite the introduction and increasing use of disease-modifying drugs, continue to be the primary therapeutic option in a significant percentage of patients, especially the elderly.

The overlapping of the effects of chronic inflammation, the side effects of treatment along with the increase in age of multimorbidity and reduction of reserves and adaptability of the human body promotes disability, dependence on caregivers and institutionalization of RA patients in the elderly. The consequence of these facts will be an increasing burden on already poorly fit health care systems and an increase in their operating costs.

This study indicates problems that occur in the course of RA, both those well known as osteoporosis, but also those that appeared, or actually been noticed and appreciated relatively recently, such as sarcopenia and osteosarcopenia. Both these phenomena seem to be closely related to each other and affect the musculoskeletal system, which together with the ligaments and bone connections constitute the human motor apparatus.

The overlapping of the effects of an inflammatory disease such as RA and complications in the form of osteosarcopenia, as well as undesirable effects of drugs,

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especially glucocorticosteroids, leads to a significant progressive impairment of the locomotor system.

Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic autoimmune disease in which there is inflammation of many joints, joint cartilage and bone damage [2]. It is currently recognized, that RA is dependent on various genes and under the influence of many environmental factors. In etiopathology, cells equipped with a specific Toll-like receptor (TLR) presents overreactivity, which plays a key role in the non-specific (innate) immune response that triggers the immune system and the cytokine cascade.

The essence of the disease is a chronic inflammatory process involving various cell populations and biologically active molecules. Pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, as well as IL-17 and IL-23 are responsible for the formation of helper lymphocyte (Th) populations. Among the numerous cell populations that affect immune processes of CD4+ and CD25+ lymphocytes need to be enumerated.

A key element is also the proteolytic enzymes, including metalloproteinases and agrekanases that degrade cartilage and bone. These enzymes are also activated by pro-inflammatory cytokines. The osteoclastogenesis-related system represented by the RANK/RANKL ligand receptor plays an important role in bone destruction [3].

The variety of processes occurring in RA affects the complex picture of the disease with the individual, often difficult to modify, course. While the changes in tissue structures and the production of inflammatory cells are characteristic, the disease progresses with the exacerbations and numerous relapses despite the use of pharmacological therapies. The methods of treatment lead to a reduction of cell hyperreactivity in various mechanisms.

On one hand, we observe processes that suppress inflammation leading to fibrosis, on the other, we deal with lymphatic infiltrates with high biological activity. Despite the increasing use of disease-modifying antirheumatic drugs (DMARDs), such as methotrexate and leflunomide, and despite the known severe side effects of chronic, systemic glucocorticosteroid therapy (GC), a significant proportion of patients, especially the elderly, are still being treated with GC.

Osteoporosis

One of the most recognized and well-described complication in the course of RA and the use of chronic steroid therapy is osteoporosis. According to the definition, it is a chronic disease characterized by low bone mass and progressive damage to bone microarchitectonics, which reduces their mechanical resistance and increases susceptibility to fractures. (Post-steroid osteoporosis is a secondary form).

As the population ages, osteoporosis becomes a growing public health problem. According to the report of the European Foundation for Osteoporosis and Musculoskeletal Diseases and the Polish Society of Orthopedics and Traumatology "Osteoporosis – Silent Epidemic in Poland" Krakow 2015, there were 2,710,000 people with osteoporotic fractures in 2010 in Poland. The projected increase due to aging of the population, is forecasted at 3,239,564 in 2025 and 4,098,898 in 2035 [4].

The pathogenetic mechanisms of osteoporosis cause disturbance of bone tissue homeostasis as a result of disturbances in the regulation of osteogenic and osteoblastic processes as well as calcium and phosphate metabolism, which are responsible for maintaining proper bone structure and regeneration.

Bone tissue homeostasis is subject to constant hormonal regulation by polypeptide hormones: mainly parathyroid hormone (PTH), but also by calcitonin, insulin, somatotropin, and thyroid hormones; steroid hormones: the active form of vitamin D, glucocorticosteroids and sex hormones; and local factors: insulin-like growth factors (IGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), platelet-derived growth factor (PFGF), interleukin 6 (IL-6), prostaglandins (PGE-2) and tumor necrosis factor (TNF) [5].

Chronic persistent excess of glucocorticosteroids leads to acceleration of bone-fat processes due to a direct decrease in activity, prolonged puberty and shortening of osteoblast survival, and at the same time to increase of activity and prolongation of osteoclast survival. Glucocorticosteroid therapy move pluripotent bone marrow cells from the osteoblast line towards other cell lines, especially fat ones [6], and additionally accelerate their apoptosis due to the increased degradation of actin fibers, a cytoskeleton protein, which deficiency causes change in the shape of cells and its elimination from the body [7].

In addition, in the mechanism of disorders of calcium ions absorption in the gastrointestinal tract and reduction of calcium ions reabsorption in the renal coils, the secondary hyperparathyroidism and an increase synthesis of PTH occur. This leads to normalization of serum calcium concentration by increased reabsorption of calcium in kidneys, but also by increasing bone turnover, as a result of which demineral foci appear in bone tissue [5–7].

On the other hand, an excess of glucocorticosteroids inhibits bone formation by reducing the rate of collagen and non-collagen protein synthesis, such as osteocalcin or alkaline phosphatase, and decreasing the activity of

bone growth factors such as IGF-1, IGF-2, IL-1 or PGE-2, and reducing mineralization the emerging bone matrix due to stimulation of collagenase III – a metalloproteinase causing collagen breakdown [7].

Glucocorticosteroid therapy promotes osteoclastogenesis by stimulating the expression of transmembrane gene RANKL protein, which belongs to the TNF protein superfamily. It is produced in bones by osteoblasts and stromal cells. Its main role is, after binding to the RANK receptor, to stimulate osteoclast differentiation in bone tissue and inhibit their apoptosis.

In turn, GC inhibition of the osteoprotegrin (OPG) gene further enhances osteoclastogenesis. OPG is a soluble receptor protein from the TNF superfamily, structurally similar to the RANK receptor, with high affinity for RANKL, which competitively binding RANKL protein inhibits osteoclastogenesis [8]. The resulting disproportion between the amount of bone tissue resorbed and newly formed in each subsequent cycle of the undergoing remodeling, causes the formation of small perforations, disruption of bone beam continuity and, as a consequence, fractures.

This process mainly applies to trabecular bone tissue, which undergoes intense metabolic changes, but can also affect cortical bone (compacted), especially at later stages. Osteoporotic changes appear at the latest in the bones of the skull cover [6, 9].

Despite significant awareness of the problem of osteoporosis, both among medical staff and a growing number of patients, still only between 3.7% [4] and 10% [10] of patients suffering from osteoporosis in Poland are currently being treated, which will certainly contribute into the increased number of pathological fractures, disability and future deaths. This indicates the need for a broader implementation of effective prevention and treatment programs for osteoporosis.

Sarcopenia

Recent scientific reports indicate the development of another complication in the course of rheumatoid arthritis, which is sarcopenia. It is a relatively new disease entity, first recognized by the WHO and marked with its own ICD-10 code in October 2016 [11].

Sarcopenia (greek: sarx – meat, paenia – deficiency), is a muscle disease that is characterized by generalized and progressive loss of strength, quality and mass of skeletal muscles. Although the loss of muscle mass with age is a physiological process associated with aging, the excessive muscle loss that impairs physical performance is considered a pathology.

Sarcopenia was first described in 1988 by Rosenberg et al. [12] as an age-related decrease in lean body mass affecting patient mobility, nutrition and independence. The accelerated development of sarcopenia research began after 2010, when the unified criteria for the recognition of sarcopenia were published for the first time under the consensus of the European working group on sarcopenia (EWGSOP). The rapidly growing amount of scientific research required a re-meeting of the working group in 2018 (EWGSOP2) to update the original definition to reflect the accumulated new scientific data from the last decade [13].

Currently, sarcopenia is diagnosed on the basis of muscle strength tests (e.g. hand-grip, chair stand test), assessment of the number of skeletal muscles expressed in the index of skeletal muscle mass of the limbs (appendicular skeletal muscle mass index – ASM) examined with dual energy X-ray absorptiometry (DXA) or bioimpendance (BIA) and physical performance assessment (e.g. gait speed, 400 m walk test).

Sarcopenia is associated with an increased risk of health complications, physical disability, social dependence and accelerated death due to falls and fractures. Its occurrence depends on many risk factors accumulating with the passage of years, the most important of which are age, low physical activity, whether as a result of life habits or disability in the course of diseases of the skeletal system, associated diseases, especially those with cachexia as a result of increased catabolism, long-term inflammatory processes, malnutrition in both neoplasmic processes and chronic diseases, hormonal imbalances and better understood side effects of some groups of drugs. In the recent years, there are increasing number of reports assessing the risk of death associated with the occurrence of sarcopenia.

Yalcin et al. [14] conducted an observational study in 170 nursing home residents in Turkey. A mortality rate was 44% (18) of sarcopenic patients, whereas participants without sarcopenia has 15% (15) mortality rate after 2 years of follow up. After adjusting for confounding factors, sarcopenia was associated with increased mortality due to all causes among older nursing home residents in Turkey. Similar results were obtained during 6-months follow-up of 122 nursing home patients in Italy. Sarcopenic residents were more likely to die compared with those without sarcopenia [15].

Sarcopenia can be divided, due to etiology, into primary sarcopenia, which depends almost exclusively on age, and secondary sarcopenia, in which, in addition to age, comorbidities play a significant role. As a primary disease it occurs mainly at the elderly, while its secondary form occurs in many clinical conditions with chronic inflammation.

One of the chronic conditions potentially being the most common cause of secondary sarcopenia is

rheumatoid arthritis due to the chronicity of the accompanying inflammatory process and the associated physical activity limitation. There are number of new studies suggesting the relationship between sarcopenia and rheumatic diseases, but their etiopathological mechanisms and cause-effect relationships are not yet fully understood. Currently, in many centers around the world, research is focused on explaining the relationship between sarcopenia and rheumatic diseases.

According to a study published in Modern Rheumatology, a significant proportion of RA patients develop sarcopenia as a result of several overlapping factors such as aging, malnutrition and cachexia, joint damage, and long-term illness. The results of these studies showed that the incidence of sarcopenia was 37.1% in the RA group, and the incidence of sarcopenia increased with age: in patients aged 40–49 years it was 14%, in patients aged 80–89 years increased to 78.6% [16]. The authors of this study point out the difficulties occurring during the performance of the handshake test due to joint deformities and pain associated with RA patients.

Vlietstra et al. [17] emphasize the relationship between fatigue and a decrease in physical activity in patients with RA, which can lead to a decrease in strength and function, and consequently to a decrease in muscle mass and accelerate the risk of developing sarcopenia.

A study by Munro et al. [18] conducted on 97 patients with RA showed a negative correlation of C-reactive protein and ESR levels with the muscle mass of these patients. One of the studied pathogenetic mechanisms of sarcopenia is the effect of chronic steroid therapy. As a result of the catabolic action of GC, there is a gradual loss of mass and a decrease in muscle strength as a consequence of the degradation of muscle fiber proteins through the activation of the ubiquitin-proteasome intracellular system.

One of the main side effects of GC is insulin resistance. As a result of the increase in insulin resistance in the mechanism of accumulation of intracellular free fatty acids, increase in the concentration of circulating free fatty acids, and disruption of the insulin signal and direct interaction of GC with cellular insulin receptors and glucose transporters, there is a decrease in muscle glucose consumption [19, 20].

A decrease in muscle mass, promotes a further increase in insulin resistance. Moreover, glucocorticoids-mediated increase of gluconeogenesis by a direct hepatic stimulation is playing a part in increasing insulin resistance because insulin is the primary suppressor of hepatic glucose production, especially in the presence of dietary glucose [20]. This creates a vicious circle mechanism, similar as in the metabolic syndrome.

Another factor that may affect the development of secondary sarcopenia is osteocalcin protein deficiency, which, in addition to affecting bone mineralization, plays a positive, hormone-like effect that increases insulin sensitivity of muscle cells and on testosterone production [21]. Previous studies show significant suppression of its synthesis by glucocorticosteroids, even by about 50% [22].

In the CHIKARA study conducted on RA patients, Yamada et al. [23] showed a relationship between age, BMI and use of GC, and the risk of sarcopenia. Of 68 patients without sarcopenia, 9 of them (13.4%) developed sarcopenia during one year follow-up. Average glucocorticosteroids dose of ≥ 3.25 mg/day was a significant factor in sarcopenia occurrence. These reports certainly require further research on a larger patient population, but seem to confirm the important role of long-term steroid therapy in the etiopathogenesis of sarcopenia.

Osteosarcopenia

In recent years, increasing importance has been associated with the adverse phenomenon of co-occurrence of osteoporosis and sarcopenia, referred to as osteosarcopenia (OS). It turns out that there is a strong relationship between muscle strength and bone mineral density [24]. The results suggest that pre-sarcopenia and sarcopenia are associated with abnormal bone mineral density (BMD) and are associated with an 8-fold higher risk of lowering BMD in pre-sarcopenia and 9-fold in sarcopenia [25].

Bering et al. [26] proved that in patients with chronic hepatitis C, low ASM is an independent prognostic factor for low BMD. This phenomenon can be explained by the dependence of higher BMD on greater physical activity, which results in the increased bone load and, consequently, its remodeling towards a stronger bone, adequate to withstand increased loads. In sarcopenia, muscle mass and fitness are reduced, which leads to a decrease in the activity of patients. As a consequence of the reduction in load, bone remodeling occurs towards a lower density, adequate to the reduced loads.

Lowered BMD increases the risk of fractures and sarcopenia increases the risk of falls, which results in an increased frequency of fractures and as a consequence, makes patient less mobile, which in turn causes further atrophy of untrained muscles, deteriorating the patient's overall psychophysical fitness. This is how the mechanism of the vicious circle of osteosarcopenia is created. This mechanical interaction known as "mechanostat hypothesis" was described by Frost [27] in 2003. Newer studies also suggest an additional paracrine or endocrine form of mutual communication between

bone and muscle tissue, through which they coordinate each other's mass [28].

Osteosarcopenia occurs mostly in the elderly population, exposed to frailty syndrome, and dramatically increases the risk of falls, fractures, institutionalization, and higher socioeconomic costs. Patients with osteosarcopenia have a 3.5-fold higher risk of fractures that is significantly higher than in patients with only sarcopenia or osteoporosis [29]. Osteosarcopenia is also associated with an increased risk of mortality.

Yoo et al. [30] in their studies involving 324 patients showed an annual mortality rate of 15.1% for patients with osteosarcopenia, while in patients with osteoporosis alone it was 5% and 10.3% in patients with sarcopenia alone. The 1-year risk of death after hip fracture in patients with OS is 1.8 times higher than in patients without osteosarcopenia, and arthritis is associated with OS significantly more often [31].

Conclusions

The mutual overlap of osteoporosis and sarcopenia pathomechanisms in the course of rheumatic diseases and the use of steroids may suggest that the risk of osteosarcopenia during chronic use of GC in rheumatic diseases, is significantly higher than in healthy seniors. One might even be tempted to state that osteosarcopenia will only be a matter of time. Despite the fact that therapies for osteoporosis treatment are developed and available for use, the achievements of medical care systems to date, where, according to Polish reports, only between 3.7% to 10% of patients suffering from osteoporosis are currently being treated, suggest a wide field for development.

On the other hand, pharmacological attempts to treat sarcopenia undertaken so far prove to be unsatisfactory. The fact that both of these conditions can worsen each other, supports the identification of patients at risk of developing osteosarcopenia as soon as possible in order to apply prevention promptly in order to prevent its development.

The demographics of the aging societies of developed countries and the increasing prevalence of both civilization and rheumatic diseases threatens to dramatically increase the socio-economic burden of societies on the consequences of pathological fractures and their complications. That is why it is so important to broaden public awareness, and especially medical staff in terms of osteosarcopenia, as well as the health consequences that it brings, in order to strive to increasingly widen the implementation of effective preventive measures due to the dramatic deterioration in the quality of life of patients and very high costs of patient care in which it develops.

The authors declare no conflict of interest.

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