COMMON PATHOGENETIC MECHANISMS AND THERAPEUTIC INTERVENTIONS IN ASSOCIATED DEGENERATIVE DISEASES

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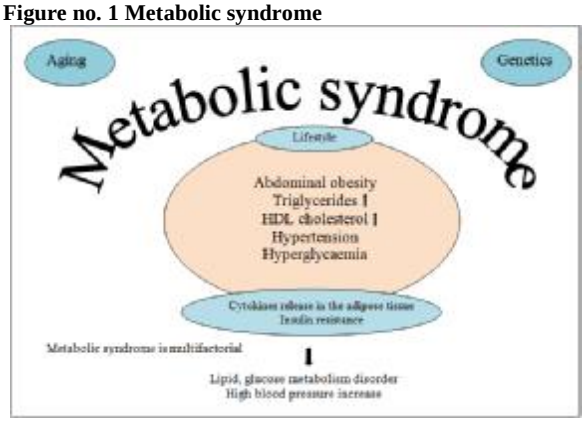
Abstract: *Specialized data indicate an increased incidence and frequent association of degenerative diseases which cannot be attributed solely to old age, but which can be explained by pathogenic mechanisms common to these diseases. Current research suggests that metabolic syndrome (MS) and atherosclerosis (ATS) is associated with osteoporosis (OP) and favours the progression of osteoarthritis (OA). Specialized literature considers MS as the connecting element. Systemic inflammation plays an important part, being essential in the pathogenesis of degenerative diseases. Optimal therapy should act simultaneously at both cardiovascular and skeletal level, current research being focused on this.*

Metabolic syndrome is associated with obesity, dyslipidemia, hypertension and hyperglycemia. Metabolic syndrome is multifactorial and results from aging combination with genetic factors and lifestyle, low physical activity and excessive caloric intake. The release of cytokines in the adipose tissue contributes to insulin resistance which induces the disorder of lipid, glucose metabolism and high blood pressure. Because of these disorders, metabolic syndrome is associated to cardiovascular morbidity and mortality (figure no. 1).

Figure no. 1 Metabolic syndrome



Although increased body mass index was correlated with increased bone mineral density, it has been shown that metabolic syndrome is actually associated with a reduction in bone mass and increased fracture rate, as well as an increased incidence of osteoarthritis.(1,2,3)

It has been demonstrated that systemic inflammation holds a central place in the pathogenesis of osteoarthritis, metabolic syndrome and atherosclerosis. Substances called adipocytokines are released in the adipose tissue, that in terms of their effect are the following:

- pro-inflammatory adipocytokines: TNF-alpha, IL-6, leptin, plasminogen activator inhibitor (PAI-1), angiotensinogen, resistin and C-reactive protein (CRP); they are mediators of endothelial damage and atherosclerosis, maintaining at the same time, the cartilage and bone destructive process;
- anti-inflammatory adipocytokines: nitric oxide (NO) and adiponectin, which have protective, anti-atherosclerotic role.

Excess proinflammatory cytokines secreted in the adipose tissue cause endothelial damage and the development of atherosclerosis and maintain cartilage and bone destructive process.(4)

The association between osteoporosis and atherosclerosis, respectively atherosclerotic calcification, is supported through the similarity of bone and vascular mineralization process.(5,6)

The interrelation between the reduction in bone mineral density and vascular calcification process is incompletely elucidated. An important part is played by vitamin K deficiency, which is common to atherosclerosis and osteoporosis and vitamin D deficiency, which is associated with a significant increase in cardiovascular disease.(7)

Currently, it is considered that the vascular calcification is an active, organized and regulated process, largely similar to the process of bone formation or bone remodeling.

Vascular calcification supposes the osteogenic differentiation of vascular cells with osteoblastic potential, osteoid matrix production in vascular structures and subsequent mineralization. The process involves the intervention of complex, intercellular and molecular signaling systems, found in bone formation.(8)

Stimuli for phenotypic osteogenic differentiation of the vascular cells are the inflammatory status, oxidized lipids and oxidative stress. In the atherosclerotic plaque, there are present bone regulatory proteins - osteopontin (OPN), bone morphogenetic proteins (BMPs), matrix Gla-protein (MGP, matrix- Gla proteins), osteoprotegerin (OPG), Receptor activator of nuclear factor-kappa B ligand (RANKL). They are expressed by vascular cells (endothelial cells, monocytes / macrophages, T lymphocytes, vascular smooth muscle cells (VSMCs), calcifying vascular cells (CVC) etc.).(9)

One of the regulation systems is the RANK / RANKL / OPG system, which has a major importance in bone and immune biology. Recent data support the involvement of this system in the vascular biology, respectively in the vascular

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calcification process.(10,11)

Gene transcription-activating factor (TGF-β) has a dual effect (opposite) at vascular and bone level, resulting in mineralization amplification in both types of tissue: decline in the RANKL / OPG relation at bone level favours bone mineralization through the inhibition of osteoclastic resorbtion, and the increase of RANKL / OPG ratio at vascular level promotes vascular calcification through the stimulation of osteogenic differentiation and calcification of the vascular smooth muscle cells (VSMC).(12,13)

The most frequent combination found in the elderly is high blood pressure, vascular wall calcification and reduction in bone mineral density.(14) In this context, the renin-angiotensin system plays an important part as a central regulator of blood pressure and fluid and electrolyte balance and having physiological function in bone remodelling.(15) Angiotensin II is regarded as a negative regulator of bone turnover and bone mass through AT1 receptors, as demonstrated by clinical studies.(15)

Regarding the correlation between diabetes and osteoporosis, study results indicate diabetes as a risk factor in the onset of osteoporosis and osteoporotic fractures.(16) Osteoporosis occurs through:

- decrease bone formation due to lack of insulin;
- calcium loss through urine, accompanying glycosuria;
- involvement of innate abnormalities;
- increased bone resorption by insufficiently specified mechanisms.(16,17)

Frequent association of arthritis with diabetes mellitus may be explained by the fact that the hyperglycemia is a joint degradation trigger. Locally, increasing glucose concentration increases glycation end products, the production of proinflammatory mediators, resulting in cartilage matrix alteration, modification of subchondral bone quality and the activation of chondrocytes and synoviocytes. Systemic toxicity determines a low degree of inflammation that aggravates arthritic process. Neurotoxicity within diabetes brings about neuromuscular deficiency that destabilize and exacerbate joint arthritis.(18)

Atherosclerosis favours the development of osteoarthritis as vascular damage from subchondral bone may accelerate the degenerative articular process through the alteration of cartilage nutrition and through the ischemic direct effect on the bone. Thus, the mechanical properties of the bone are altered, reducing the ability to absorb mechanical shocks and increasing cartilage susceptibility to damage. In addition, dyslipidemia may cause disorganization of the articular metabolism.(19)

Obesity promotes the development of osteoarthritis inducing chronic inflammation by increasing the synthesis of proinflammatory cytokines in the adipose tissue, all these being capable to initiate the synovial inflammation. Obesity also causes functional joint overloading of the bearing joints (especially, the knees) favouring the destruction of cartilage.(4)

Due to common pathogenic mechanisms presented in the literature, arthritis and osteoporosis fall among the components of the metabolic syndrome.(20,1)

The management of associated degenerative diseases should aim each condition separately, the ideal treatment being considered that with concomitant action, cardiovascular and skeletal. Pharmacological and non-pharmacological means used are:

- treatment of the metabolic syndrome: statins;
- treatment of osteoporosis - vitamin D;
  - antiosteoporotic agents;
- treatment of osteoarthritis: calcium, vitamin D, chondroprotectives;
- hygienic-dietary regime;
- means of medical rehabilitation.

Statins inhibit the enzyme 3-hydroxy-3 methylglutaryl coenzyme A reductase (HMG-CoA reductase) involved in the synthesis of cholesterol. At the same time, they accelerate bone morphogenetic protein-2 expression, an important mediator of osteoblast differentiation and bone formation. Studies have shown that statins significantly reduce the risk of fracture, and through their anti-inflammatory and antiateroscerotic effect, they could modulate calcium redistribution between arteries and bones.(21)

Vitamin D plays an important part in vascular and bone protection.(22) Vitamin D deficiency increases the risk of falls and fractures, hyperparathyroidism secondary with increased bone resorption, vascular calcifications and the significant increase in cardiovascular disease. It is, therefore necessary in the elderly, a daily intake of 800 -1000UI.(7)

Bisphosphonates reduce bone resorption and the risk of fracture. In addition, they have the potential to reduce the atherosclerotic process by interfering with the synthesis of cholesterol, systemic inflammation and oxidative stress. Most animal studies show a clear anti-atherogenic activity of bisphosphonates. Instead, clinical trial data are not consistent or conclusive, given the high affinity of bisphosphonates for bones, which prevents the accumulation in other tissues, the concentration required to exert a pharmacological clear effect. At the same time, nitrogen-containing bisphosphonates can reduce cardio-vascular calcifications.(21)

Medical rehabilitation, especially physical therapy aims at:

- preventing and treating atherosclerotic cardiovascular diseases;(23)
- preserving bone mass, reducing bone loss and fracture risk, caused by falls;(24)
- maintaining or restoring mobility, joint stability and ability, strength and muscle composition.

Conclusions:

Metabolic syndrome, atherosclerosis, osteoporosis and arthritis have similar biochemical and inflammatory profile, which determines their frequent association. Searching for the development of therapeutic strategies, is therefore encouraged, to have both cardiovascular and skeletal effects. Among the drugs that can simultaneously increase bone mineral density and reduce the progression of atherosclerosis, we can mention bisphosphonates, statins, vitamin D, beta-blockers and possible, anti-RANKL antibodies.

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