Risk of osteoporosis in endocrine disorders and celiac disease

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Summary. Osteoporosis is characterized by a loss of bone mass; the bones become less dense, fragile and prone to fracturing. It is regulated by endocrine-environmental factors with the genetic component accounting for 70% of an individual's variation in bone mass density (BMD). Pathological conditions such as celiac disease (CD) exacerbate the process of bone loss and the presence of osteoporosis in celiac subjects may be the only sign of undiagnosed CD. The interleukins IL-1α and IL-1β are stimulators of bone resorption; the relatives of celiac patients shown the increased IL-1β supporting the genetic susceptibility. In women osteoporosis is indirectly associated with early menopause and amenorrhea, while in men it is associated with hypogonadism and GH deficit. The direct effect on the bones of CD is secondary to poor absorption of calcium and vitamin D. These endocrine and non-endocrine factors exert their effects on bones by modulating the RANK/RANK-L/OPG system.

Key words: osteoporosis, celiac disease, menopause, hypogonadism, micronutrients.

Riassunto *(Rischio di osteoporosi nei disordini endocrini e nella malattia celiaca)*. L'osteoporosi è una patologia caratterizzata da perdita di massa ossea; l'osso diventa meno denso, fragile e soggetto a fratture. È regolata da fattori endocrino-ambientali; la componente genetica incide per il 70% nelle variazioni individuali della densità della massa ossea (BMD). Condizioni patologiche come la malattia celiaca (MC) aggravano il processo di perdita dell'osso e l'osteoporosi nei soggetti celiaci può essere il solo segno di MC silente. Le interleuchine IL-1α e IL-1β sono stimolatori del riassorbimento osseo; i parenti di pazienti celiaci mostrano un incremento del IL-1β confermando la suscettibilità genetica. Nelle donne l'osteoporosi è indirettamente associata con la menopausa precoce ed amenorrea, mentre negli uomini all'ipogonadismo ed al deficit di GH. L'effetto diretto della MC sull'osso è evidenziabile dal malassorbimento di calcio e vitamina D. Questi fattori endocrini e non endocrini esercitano il loro effetto sull'osso modulando il sistema RANK/RANK-L/OPG.

Parole chiave: osteoporosi, malattia celiaca, menopausa, ipogonadismo, micronutrienti.

As the increase in lifespan brings to light diseases that were previously not clinically detectable, osteoporosis has become an issue of worldwide significance.

Bone is a mineralized tissue consisting of an organic matrix of collagenous fibers (proteins) dispersed throughout an inorganic mass of minerals (calcium hydroxyapatite). Osteoporosis is a quantitative and qualitative alteration in the components of this tissue, in which the process of demineralization becomes intense and prolonged and minerals are used up more quickly than they can be replaced, to the point where bones become fragile and break easily [1].

Variations in the alimentary and endocrine systems in both women and men have a fundamental role in the development of osteoporosis: if these variations are combined with an inappropriate lifestyle (*e.g.*, inadequate physical exercise, alcohol abuse or smoking), pathologies such as hyperparathyroidism, thyrotoxicosis and/or the use of drugs such as antipsychotics or corticosteroids, the risk of osteoporosis is increased [2]. All of these factors are able to interact with the systemic signs of celiac disease (CD).

For genetically predisposed individuals, CD is a permanent gluten intolerance, a protein presents in many cereals such as wheat, barley and rye; for which the only treatment currently available is lifelong adherence to a gluten-free diet (GFD: only sure treatment for CD). The disease is a chronic enteropathy featuring with villous atrophy, crypt hyperplasia and lymphocytosis in which fundamental in inflammatory processes occur in the proximal part of small intestine mucosa. Osteoporosis and CD are often found together and both are modulated by genetic and environmental factors, confirming their multifactorial etiopathogenesis [3]. The incidence of osteoporosis is higher in celiac subjects (3.4%)

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than in the population as a whole (0.2%) and this disease is an important extra-intestinal sign of CD. Bearing in mind that approximately 1% of the total population has CD, the screening of patients with idiopathic osteoporosis for CD is advisable [4]. In subjects who are also affected by endocrine-reproductive disorders, themselves a major risk factor for osteoporosis, this screening acquires even more importance.

In women the risk of osteoporosis is linked in particular to the fall in estrogen levels; as well as being important in reproduction and for bone integrity, estrogens are also essential for various physiological processes implicated in the development and progression of numerous diseases mediated by the estrogen receptors (ER), a mechanism that forms the basis for numerous therapeutic interventions [5].

The biological effects, mediated through the interaction between estrogen and ERα and ERβ, are expressed as a form of protective action in which bone turnover is inhibited, with a consequent reduction in both resorption and the formation of new bone [6].

Estrogen deficiency leads to calcitonin-induced hypocalcemia and secondary raised PTH, with a decisive effect on the homeostatic regulation of bone turnover. By promoting the interaction of calcitonin and PTH, estrogens thus regulate calcium homeostasis and bone turnover. In addition, patients with resection of the small intestine also show low levels of 25-hydroxyvitamin D (25(OH)D) associated with increased PTH and decreased BMD values [7]. This is of particular interest when we consider that this part of the intestine is the target of CD, a factor that makes a common pathogenetic mechanism for the two diseases all the more plausible.

The importance of the RANK/RANK-L/OPG system in bone remodeling is increasingly evident, on account of its interaction with hormones (PTH, TSH, estrogens, corticosteroids, androgens), vitamin D and some cytokines (IL-6, TNF-α). Both PTH [8] and TSH [9], in particular, influence bone homeostasis through the RANK/RANK-L/OPG system by regulating osteoclast production. Overproduction of IL-6 and TNFα are also seen in CD-related intestinal damage, suggesting the influence of this system also in celiac disease [10].

The risk of osteoporosis is higher in women with CD, which has both an indirect and a direct impact. Indirectly, CD leads to early menopause [11] and amenorrhea, both of which are themselves risk factors for osteoporosis. In some women other factors such as prolonged breast-feeding and frequent pregnancies may represent a risk of early osteoporosis and dietary supplements of calcium and vitamin D are recommended in these cases [3]. These are stages in which latent CD may be reactivated in women who have followed a GFD for some time, suggesting the possibility that changes in the endocrine and immune systems associated with pregnancy and puerperium, such as increased levels of PRL, may in turn lead to changes in BMD [12].

Another indirect effect of osteoporosis is the presence of clinical and subclinical hyperthyroidism, which lead to a decrease in bone mass [13]. Because of their endocrine and environmental implications, these thyroid disorders are among the pathologies most commonly associated with CD [14]. This is important when we consider that thyroid diseases also affect reproduction and can lead to spontaneous abortions, neonatal mortality, retarded fetal growth and congenital abnormalities.

The direct effects of CD in increasing the risk of osteoporosis include not only general malabsorption, but also deficiencies of specific micronutrients that are fundamental to normal female and male reproductive development, as well as to the regular growth and maintenance of bone tissue: this is particularly true of calcium and vitamin D, in which CD women are deficient [3]. A shortage of these micronutrients may also occur with secondary hyperparathyroidism caused by CD. Calcium levels are linked to those of estrogens, which decrease with the menopause; indeed, hormone replacement therapy (HRT) is known to improve calcium levels. Approximately 20 million women worldwide use HRT, and while its beneficial effects for osteoporosis and menopausal symptoms are known, the well-documented higher risk of breast tumors in these subjects cannot justify its long-term use. Besides, several recent trials have indicated that HRT carries a higher risk of cardiac and cerebral events, contradicting its protective effects on the cardio-and cerebrovascular systems [15]. However, among women 50 to 59 years old, estrogen therapy on coronary-artery calcification has helpful outcome because of complex biologic effects through multiple pathways [16].

In this regard, the consumption of soy (gluten-free cereal) isoflavones (natural substances similar to estrogen) is gaining importance, but their therapeutic efficacy should be carefully assessed in order to verify possible chronic effects of these substances and to establish risk-benefit ratios for each stage of the lifespan. This is even more important when we consider that osteoporosis is associated with genetic-environmental pathologies such as CD and the use of soy isoflavones, which albeit gluten-free nonetheless contain estrogen-like substances, should be carefully evaluated.

Other vitamins and minerals, besides calcium and vitamin D, are needed for the development and maintenance of bone mass and for normal metabolism and bone turnover as well as for their ability to improve BMD. If these nutrients are administered from adolescence, particularly in CD patients, they could help to prevent the onset of osteoporosis. Of these micronutrients, vitamin K and zinc are of special interest since their deficiency in pregnant women can harm the skeletal system of fetus [3].

The presence of osteoporosis in men is correlated mainly with the effect of GH and hypogonadism. GH stimulates an increase in muscle mass and the formation of bone tissue [17] and its deficiency is

evident in the low stature of celiac children, who nonetheless are able to resume normal growth after a year following a GFD, particularly if this is associated with hormone therapy [18]. With regard to hypogonadism, osteoporosis is heavily influenced by steroid hormone homeostasis, in which CD can be an additional osteoporotic risk factor. Celiac men are at greater risk of infertility and hypogonadism, while a GFD improves both sperm count and sperm motility. This points to the existence of an imbalance in the hypothalamus-pituitary-testis axis and demonstrates the importance of nutritional deficiencies as factors involved in dysfunctions of the endocrine system, which is sensitive to changes in nutrition. The significance of hypogonadism lies also in its association with increased levels of PRL, which in men result both in fertility disturbances, erectile dysfunction and loss of libido and, as is the case with women, in altered BMD [12]. In addition, both adult and child celiacs who do not adhere to a GFD have increased serum PRL levels; this could be used as a marker for the active disease, assuming it plays a role in the modulation of intestinal damage. Increased levels of PRL may also influence normal skeletal development, given that in men altered pituitary function due to other causes such as, for example, tumors or drugs, leads to bone loss. Adherence to a GFD is nonetheless able to reverse these hormone changes [2], further confirming the importance of early diagnosis in all cases of clinical uncertainty such as unexplained male osteoporosis and/or hypogonadism. A proper GFD needs then to be followed in order to avoid damage both to the reproductive system and to bones, bearing also in mind that, as already noted, CD causes deficiencies of specific micronutrients such as vitamin A, with effects on spermatogenesis and testosterone (T) secretion. A deficiency of retinols influences three major types of adult and fetal testicular cells, while a fall in T production not only leads to atrophy of the accessory sex organs, but also damages muscle and bone tissues [3]. The use of T-based therapy for the prevention and treatment of osteoporosis is controversial, but [19] may benefit osteoporotics with evident hypogonadism and probably also those with CD, with which hypogonadism is often associated. These considerations acquire greater importance in older men with late-onset CD, for whom damage to bones is more serious and the risk fracture greater, for whom vitamin D and calcium supplements are highly recommended.

The use of pharmacological therapy (for example bisphosphonates) for the prevention and treatment of osteoporosis in postmenopausal women has long been recognized. The use of these agents has been traditionally based on date obtained predominantly from postmenopausal women and cases glucocorticoid-induced osteoporosis, but data are becoming increasingly available to justify their use in osteoporotic men. Moreover, there are evidence that treatment with risedronate increases BMD and reduces hip fractures in elderly men [20].

In conclusion, increased risk of osteoporosis should not be considered as an isolated factor, but as part of a more generalized endocrine-environmental imbalance with possible serious effects on health on account of its influence on a fairly broad range of tissues and functions of which metabolism and bone structure are a major target. This risk of osteoporosis is further increased if the imbalance is accompanied by CD, which also causes problems for both male and female reproductive systems on account of deficiencies of important micronutrients.

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