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*REVIEW*

# Osteoporosis in celiac disease and in endocrine and reproductive disorders

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## Abstract

As the increase in lifespan brings to light diseases that were previously not clinically detectable, osteoporosis has become an issue of worldwide significance. The disease is marked by a loss of bone mass; the bones become less dense, fragile and more prone to fracturing. Because it is regulated by endocrine and environmental factors, osteoporosis presents a multifactorial etiopathogenesis, with the genetic component accounting for 70% of an individual variation in bone mass density (BMD), the principal determinant, with age, of fracture risk. Pathological conditions such as celiac disease (CD) exacerbate the process of bone loss, so that the occurrence of osteoporosis in celiac subjects is of particular note: indeed, the screening of osteoporosis patients for this disease is advisable, since it may be the only sign of undiagnosed CD. An increase in interleukin IL-1β, of the IL-1 system, in the relatives of celiac patients confirms the genetic predisposition to osteoporosis and its presence is evidence of an association between the two conditions. The direct effect on the bones of CD is secondary to poor absorption of calcium and vitamin D. In women osteoporosis is indirectly associated with early menopause and amenorrhea, and it may follow prolonged breast-feeding and frequent pregnancies, while in men it is associated with hypogonadism and GH deficit. These endocrine and non-endocrine factors exert their effects on bones by modulating the RANK/RANK-L/OPG system. An appropriate lifestyle from adolescence onwards, together with early diagnosis of and treatment for CD and primary and secondary endocrine pathologies are important for the prevention of damage to the bones.



**Key words:** Osteoporosis; Celiac disease; Menopause; Estrogens; Hypogonadism; Micronutrients

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## INTRODUCTION

Osteoporosis has only recently been accorded the clinical importance that its evolution and potential health impact deserve. Thanks to considerable increases in life expectancy this pathology is becoming more visible, and is now treated as a serious public health issue, as well as one of social and economic importance.

Osteoporosis generally manifests in late middle age, but its causes are rooted in the years of development[1]: a lower peak of bone mass in the first 20 years of life can influence the evolution of this disease in later years. The impoverishment of bone mass may become irreversible and lead to serious disability necessitating long-term assistance and treatment, with increasing social and economic costs: for these reasons prevention is of fundamental importance. Prevention should be initiated early on, particularly during adolescence, when calcium ingested with food is absorbed by the organism and contributes effectively to consolidating bone density; it is also important that children and young people engage in regular physical activities from the earliest schooldays through to the completion of secondary schooling. In diseases such as osteoporosis an individual's gender, race and constitution, as well as variations in complex endocrine systems associated with factors such as the menopause, aging and the presence of other pathologies,

can all interact with the lifestyle to determine its onset[2].

In order better to understand the changes in endocrine-environmental factors that can cause damage to bone tissue, the following brief description of its physiology and pathology may be helpful.

## THE PHYSIOPATHOLOGY OF OSTEOPOROSIS

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. In this it differs from osteomalacia, which is marked by qualitative alterations due to mineralization defects of the proteinic matrix.

The organic and inorganic matrix, together with the cells (osteoblasts, osteoclasts, osteocytes, lining cells) make the biodynamic units of the process of remodelling and resorption, the basic multicellular units (BMU).

The particular characteristic of bone tissue is that during an individual's lifetime it is subject to processes of transformation that can be summarized in the following stages:

- -the stage of bone mass increase that parallels growth in stature;
- -the stage of consolidation marked by a slow but steady increase in bone mass, which lasts until 20-25 years of age;
- -the stage at which each individual's peak bone mass is reached and in which the difference between men and women is evident;
- -the stage of decline in which bone mass is reduced and which lasts for the rest of an individual's life.

Thus, notwithstanding their apparent solidity, bones are the dynamic and continually evolving sites of two constant and inter-related processes (bone turnover): a slower process of accumulation and a more rapid one of resorption. Then there are the various functions in which calcium is involved: its endocrine function, nerve conduction, muscle contraction, cell metabolism and blood coagulation. Calcium is carried by the blood to and from all bodily tissues, where a dynamic equilibrium is reached between the body's use of calcium and the need to sustain the calcium load. This equilibrium is finely regulated by various endocrine, environmental and genetic factors, responsible for the multifactorial origin of osteoporosis, in which the genetic component plays an important part[3]. Numerous studies performed in recent years to identify the genes and allelic variants involved in osteoporosis have shown its polygenic determinants, but the identity of genes involved has not yet been disclosed. It is estimated that genetic factors account for 70% of individual variations in bone mass density (BMD), the principal determinant, with age, of fracture risk, and that BMD accounts for 70% of bone solidity.

The elucidation of the role of the (IL)-1 interleukin system, localized on chromosome 2q14-21 and comprising IL-α, IL-1β and the IL-1 receptor antagonist (IL-1ra), has shown that IL-α and IL-1β are potent stimulators of bone resorption by inducing the proliferation and differentiation of both osteoclast precursors and mature active osteoclasts[4].

Studies on the allelic variants of the IL-1 system in postmenopausal women of different ethnic origins have revealed the existence of associations between BMD and the system's different genetic polymorphisms. Investigations on the relations between polymorphisms of the IL-1 system and BMD in 220 postmenopausal Korean women aged between 48 and 70 years showed that BMD in those carrying the A2 allele of the IL-1ra gene was significantly lower than that of those who did not carry the allele. Moreover, the A2 allele was more frequent in women with osteoporosis than in those who did not suffer from the disease. There is thus a relation between this allele and BMD; it presumes that polymorphism of the IL-1ra gene is an important genetic factor that affects the BMD of Korean women[4].

Other studies have identified regulators of bone remodelling, such as the Ciz gene (Castor-interacting zinc finger protein), which could also possible be used as therapeutic targets[5] particularly for the treatment of individuals also affected by CD. The existence of an association between the two pathologies was demonstrated by a study performed by Taranta *et al*[6], in which the authors showed the presence of a cytokine imbalance affecting bone metabolism in the sera of celiac patients and the direct effect of these sera on bone cell activity *in vitro*. They found an increase in IL-1β and in tumor necrosis factor alpha (TNF-α) in all patients, while patients who did not follow a gluten-free diet (GFD: only sure treatment for CD) also had increased IL-6 and IL-18 and an additional increase in TNF-α. These findings suggest that the loss of BMD could be caused partly by this imbalance, which directly affects osteoclastogenesis and osteoblast activity.

Besides cytokines, parathyroid hormone (PTH), estrogens, androgens, corticosteroids and vitamin D all affect bones by modulating the receptor activator of nuclear factor B/receptor activator of nuclear factor B-ligand/osteoprotegerin (RANK/RANK-L/OPG) system[7].

The RANK-L is the final mediator of the cytokine (IL-1, TNF, IL-6) and hormone (PTH) network. This soluble polypeptide is produced by osteoblasts and expressed on their cell membrane and binds with high affinity to its specific RANK receptor, present in hemopoietic osteoclast precursors of bone marrow and on the membrane of osteoclasts. OPG is a polypeptide of 380 amino acids that is produced in several cell types, including those of the immune system and osteoblastic stromal cells, and has been identified as the soluble biological RANK-L inhibitor able to contrast its osteoclastogenetic, pro-resorption and anti-apoptotic effects on mature osteoclasts[8]. OPG is thought to act as a 'decoy' receptor, competing with the specific RANK receptor to inhibit RANK-L/RANK binding[7].

The importance of the increase in IL-1β is supported by its presence in relatives of celiac patients, confirming

the genetic susceptibility for bone loss pathogenesis[9]. Other studies of families and twins have produced further evidence that genetic factors play a significant role in osteoporosis and that they affect not only BMD but also skeletal geometry and bone turnover, with an increased fracture risk[3].

In addition to pathologies such as, for example, Cushing's disease and prolactinomas, other factors can indirectly affect bone homeostasis. One of these is stress due to physical strain, which produces a cytokine and hormonal imbalance. Strenuous physical exercise leads to an imbalance in which the central nervous system and the hypothalamus-pituitary-suprarenal axis react by increasing catecholamines, cortisol and the activation of corticotropin-releasing hormone (CRH) neurons, with consequences for gonad function. IL-6, growth hormone (GH) and prolactine (PRL) are also activated. It is worth emphasizing that physical exercise in men not only increases muscle mass but also has an indirect effect on bone structure. In female athletes the so-called 'exercise-related reproductive dysfunction' may be present, the consequences of which may include not only osteoporosis but also amenorrhea, infertility, food-related disorders, coronary disease and "euthyroid sick" syndrome[10].

As we have already seen, the phase of decreasing body mass, which continues throughout the lifespan, is a physiological fact: there nonetheless exist risk situations which, by interacting with the balance of hormonal (e.g. estrogen deficiency), nutritional (e.g. calcium deficiency) and environmental (e.g. lifestyle) factors, accelerate bone loss and can harm the organism[11]. Because bones are highly susceptible to interference, it is very important to maintain this balance which, together with genetic equilibrium, helps to preserve bone health. Pathologies such as celiac disease (CD), which manifests when genetic and environmental factors interact, can affect this equilibrium and increase the risk that an individual will develop bone diseases such as osteoporosis and osteomalacia[12].

On account of both its frequency (one in four women and one in eight men over 50) and related complications, osteoporosis represents a serious health emergency of considerable economic importance; when it is associated with CD it may cause additional damage to bone health; indeed, screening for CD is recommended for patients with idiopathic osteoporosis[13,14]. If these patients also suffer from endocrine-reproductive disorders, such screening becomes even more advisable, since these disturbances are a significant risk factor for osteoporosis[2].

## SOME ASPECTS OF THE ETIOPATHOGENESIS OF CELIAC DISEASE

While discussing the association between CD and osteoporosis in persons also affected by reproductive problems, it is worth emphasizing certain aspects of the etiology and pathogenesis of celiac disease.

For genetically predisposed individuals, CD is a permanent gluten intolerance, for which the only treatment currently available is lifelong adherence to GFD. The disease is a chronic enteropathy featuring with villous atrophy, crypt hyperplasia and lymphocytosis in which fundamental in inflammatory processes occurs in the proximal part of small intestine mucosa. The adaptive immune pathway is thought to provide the major immune response, but recent evidence has also indicated the involvement of the innate immune system[15]. Besides increased T lymphocytes, other cell types are also increased, including B lymphocytes, NK cells, neutrophils, eosinophils, macrophages and mastocytes. In particular, a chronic recruitment of activated neutrophils is present even in completely normalized remission of CD[16].

In the pathogenesis of CD exposure of the mucosa of the small intestine to gluten leads to hyperproduction of cytokines by T cells, triggering an inflammatory process that includes the release of IL-2, IL-6, IFN-γ and TNF-α and activation of B lymphocytes with production of specific antibodies and the activation of autoimmune mechanisms. IL-15, a mediator of the innate immune system, is thought to be of particular importance in damage to the mucosa and in the persistence of inflammatory processes[17].

CD used to be considered a rare disease typical of infancy, with generalized symptoms of poor absorption combined with chronic diarrhea and slow growth. It is now recognized that along with this classic form of the disease there are other clinical and subclinical forms that may manifest later and in which there may be no intestinal symptoms; these forms can be associated with symptoms affecting the liver, thyroid, skin, reproductive system and bones[18]. The effects of CD on these systems are mediated not only by gluten but also by the combination of other genetic and environmental factors, indicating that CD, like osteoporosis, has a multifactorial pathogenesis[19]. The poor absorption induced by CD leads to deficiencies of nutrients such as iron, folic acid and vitamin K that are essential for organogenesis, of fat-soluble vitamins important for spermatogenesis, and of vitamin D and calcium, essential for the maintenance of bone structure[18]. Osteoporosis deserves particular consideration as a non-intestinal sign of CD; indeed, bone metabolism disorders and a decrease in BMD may be the only signs of otherwise 'silent' CD[20]. In particular, studies have shown that osteoporosis is more serious in individuals also affected by CD[18] and is an important example of a non-intestinal sign of the disease, a factor that acquires additional importance if we consider that 1% of the total population suffers from CD[21]. Osteoporosis is more prevalent in celiac (3.4%) than in non-celiac (0.2%) subjects. In addition, severe cases of CD are accompanied by more severe osteoporosis[13], and celiac individuals who also suffer from reproductive disorders are affected even more severely[2].

In light of the available evidence, it is useful to see how endocrine and reproductive factors interfere in osteoporosis, with special focus on problems associated with CD.

## OSTEOPOROSIS IN WOMEN

For women the risk of osteoporosis is linked primarily to a fall in the production of estrogens, the female

steroid hormones *par excellence*. In order to understand the importance of these hormones, it is useful to emphasize that, as well as influencing reproduction and bone integrity, they are major actors in numerous physiological processes: it is thus no surprise to find that they are implicated in the development and progression of several diseases ranging from various types of tumor (e.g. breast, ovaries, colon-rectum, prostate, endometrium) to neurovegetative and cardiovascular disorders, insulin resistance, lupus erythematosus, endometriosis and obesity. In several of these diseases estrogens act through estrogen receptors (ER), and our understanding of this mechanism forms the basis of a number of treatments[22].

After the menopause the decrease in estrogen is evident in the absence of regular modulation of cellular activity in tissue[2]. 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[23].

Estrogen deficiency promotes calcitonin-induced hypocalcemia and a secondary increase in PTH consistent with the effects of calcitonin in increased bone turnover. By promoting the interaction of calcitonin and PTH, estrogens thus regulate calcium homeostasis and bone turnover[24]. 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[25]. 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 RANK/RANK-L/OPG cytokine system is essential to bone turnover biology; metabolic bone diseases are related to alterations in this system[26]. Functional links between bone remodelling and the immune system in inflammatory processes are also mediated, in part, by the RANK/RANK-L/OPG cytokine system. In these processes, neutrophils play a crucial role; RANK-L is expressed by inflammatory and normal neutrophils, unlike OPG and RANK, which are expressed only by neutrophils exposed to an inflammatory environment. This suggests that neutrophils may contribute to bone remodelling at inflammatory sites where they are present in significantly large numbers[27]. Interestingly in both active and remission CD enhanced neutrophiles infiltration is observed[16]. The risk of osteoporosis is higher in women suffering from CD, which can act both indirectly and directly. The indirect effects of CD include early menopause[28] and amenorrhea[29], two pathologies that are themselves an osteoporosis risk[18]. An early menopause in female patients increases the risk of early development of osteoporosis. Amenorrhea is a major clinical consequence of increased levels of PRLs, which in turn promote disruptions in BMD[30]. In some women other factors such as long periods of breast-feeding and frequent pregnancies may represent a risk of early osteoporosis[31].

In these conditions, latent CD may become manifest or be reactivated in women who have followed GFD for some time, suggesting the existence of immune or hormonal changes peculiar to pregnancy and puerperium[32], such as increased PRL which, as already emphasized, bring changes in BMD[30].

Early menopause should be treated by the immediate adoption of measures to prevent and treat osteoporosis, such as dietary supplements of calcium and vitamin D, physical exercise, not smoking, moderating alcohol consumption and, where necessary, the administration of drugs and/or hormone replacement therapy (HRT). These strategies are necessary to prevent increased fracture risk, largely because most patients are not aware that they have osteoporosis until a fracture occurs[33]. It is also advisable, during critical periods such as pregnancy and breast-feeding, to take calcium and vitamin D supplements[34].

To complete the effects of hormones on bone balance it should be remembered that hyperthyroidism, evident in low serum levels of TSH, is accompanied by a decrease in bone mass[35]. Over treatment for postmenopausal hypothyroidism can lead to a reduction in normal TSH values (0.5-4.0 mU/L), which, by causing subclinical hyperthyroidism, can lead to osteoporosis. It is useful here to remember that thyroiditis may first appear as periods of metabolic hyperfunction leading to hyperthyroidism.

In adults osteoporosis associated with hyperthyroidism is traditionally viewed as a secondary consequence of altered thyroid function[36]. Some studies have provided evidence for a direct effect of TSH on skeletal remodeling mediated *via* the TSH receptor (TSH-R) found on osteoblast and osteoclast precursors. Even a 50% reduction in TSH-R expression produces serious osteoporosis together with focal osteosclerosis (localized bone formation). These studies define a role for TSH as a single molecular switch in the independent control of both bone formation and resorption. In particular, TSH inhibits osteoclast formation and survival by interacting with the RANK-L/RANK system and TNF-α[37].

Because of their endocrine-environmental implications, forms of thyroiditis often occur in combination with CD[38] and are among the pathologies most frequently associated with it. Bearing in mind that forms of thyroiditis can lead to spontaneous abortion, neonatal mortality, retarded fetal growth and congenital malformations[39] and that CD has an important impact on the reproductive system[18], it can be appreciated that the genetic and environmental factors associated with these diseases are correlated. A direct effect of CD is that the process of bone remodeling is increased in these patients in relation to calcium malabsorption, secondary hyperparathyroidism and vitamin D deficiency, with marked bone loss[40].

A further consideration in support of a direct effect of CD in the development of osteoporosis is that patients with this disorder suffer not only from generalized poor absorption but also from a deficiency of specific micronutrients fundamental both to normal male and female reproductive development[18] and to the regular growth and maintenance of bone tissue[12]. The presence of osteoporosis in CD patients, particularly in subclinical cases, thus underscores the significance of a shortage of specific nutritional elements. This is further emphasised by the malabsorption of calcium and vitamin D that affects women with CD. Eastell[41] highlights this fact given that women are affected not only by a lack of estrogens but also by a deficiency of these important

micronutrients in the pathogenesis of osteoporosis. Regarding the loss of calcium it is useful to emphasize that this occurs both as a direct consequence of damage to the mucosa[42] and with secondary steatorrhea, one of the major effects of CD, through a chelating mechanism involving the intraluminal fats[43,44]. All the above considerations assume even greater significance if we remember that, in general, the poor absorption of calcium by postmenopausal women and estrogen-related calcium deficiency unquestionably represent a major risk factor for postmenopausal osteoporosis, as evidenced by improved calcium levels following hormone replacement therapy (HRT). 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[45].

With regard to preventing or slowing the progression of chronic diseases such as osteoporosis and combating the increased risk of breast cancer, the consumption of soy isoflavones is gaining ground, particularly in the US. These natural substances are similar to estrogen in their action; their beneficial effects on bones may be specific to each phase of an individual's life, as well as depend on the number of estrogen receptors and on the endogenous hormonal environment. Menopausal or premenopausal women, who have greater numbers of these receptors, may be more receptive to the therapeutic effects of isoflavones on bone loss than postmenopausal women, in whom estrogen receptors decrease. Studies on pubertal laboratory animals exposed to high levels of soy isoflavones showed negative effects. This is important if we remember that no clinical studies on adolescents are available to confirm or challenge research carried out on animals. Studies should, in any case, be performed on individuals at all stages of the lifespan to identify possible long-term effects of these substances: indeed, this aspect should be the basis of research aimed at assessing the risk-benefit ratio[46]. Bearing in mind that osteoporosis is associated with genetic-environmental pathologies such as CD, the use of soy isoflavones, which albeit gluten-free nonetheless contain estrogen-like substances, should be carefully evaluated.

Alongside calcium and vitamin D, the prevention of osteoporosis through the development and maintenance of bone mass also calls for other vitamins (A, C, E, K) and minerals (phosphorus, fluoride, iron, zinc, copper, boron) that, by improving BMD, are necessary for a normal metabolism[47] and for bone turnover[48]. The administration of these nutrients from adolescence, particularly in individuals with CD, could help to prevent the onset of osteoporosis. Among them, vitamin K merits special attention, given that its deficit in pregnant women can harm the fetus, leading to chondrodysplasia punctata with nasal hypoplasia and spinal cord abnormalities[49]. In menopausal women vitamin K deficiency disrupts bone calcification on account of reduced osteocalcin (GLA) carboxylation[50]. A deficiency of zinc is also particularly important, as this mineral affects BMD through its effect on the ovaries and consequent changes in estrogen levels; moreover, low maternal serum zinc levels are associated with fetal malformations such as neural tube deficit[51]. This suggests that a shortage of these micronutrients may also have a harmful effect on fetal bone metabolism. Because of the direct involvement of CD in the availability of micronutrients, the above factors may be more significant in celiac women who do not follow the GFD correctly or who are unaware they have the disease.

## OSTEOPOROSIS IN MEN

The longer lifespan of humans brings an increased risk of osteoporosis in men and in women, but while in women it is undoubtedly associated with the menopause, in men it is often linked to the effect of GH and hypogonadism[52]. During infancy and adolescence GH stimulates growth and sexual development as well as increasing muscle mass and the formation of bone tissue, while in adults it is important for metabolism in various tissues. The association between CD and GH deficiency is evident in the low stature of celiac children, although after a year on GFD these children will resume normal growth, particularly if the diet is combined with hormone therapy[53,54].

With regard to hypogonadism, osteoporosis is strongly influenced by the homeostasis of steroid hormones[55], changes in which are indicated as one of the commonest causes of this type of pathology[56], while the presence of CD may represent an additional risk factor for osteoporosis[57]. Celiac males are at greater risk of infertility and hypogonadism: indeed, the GFD can improve both sperm count and sperm motility[58]. Gonad dysfunction is caused by a reduction in the conversion of testosterone (T) to 5-alpha-dihydrotestosterone (DHT) resulting from the low levels of 5-alpha-reductase in CD subjects, which disrupts the hypothalamus-pituitary-gonad axis[59]. Hypogonadic males who also have CD are thus more likely to develop osteoporosis, an important consideration if we bear in mind that the malabsorption associated with CD makes this disease *per se* a risk factor for osteoporosis[57]. This further highlights the significance of nutritional deficiencies in these dysfunctions and the sensitivity of the endocrine system to changes in food habits. Another aspect of hypogonadism is its association with increased levels of PRL, which in males lead not only to fertility problems, erectile dysfunction and loss of libido but also, as in females, to altered BMD[30].

Individuals with active CD have increased serum PRL levels, which correlate with the degree of atrophy of the intestinal mucosa and with the serum concentration of anti-endomysial antibodies. The presence of PRL could become a marker for the active disease if it is indeed found to have a role in modulating intestinal damage[60]. High serum levels of PRL are present not only in adults with CD but also in celiac children who do not follow the GFD[61].The above considerations suggest that in these patients the increases in PRL could also affect normal skeletal development, since in men changes in pituitary function from other causes such as, for example, tumors (prolactinoma) and drugs (antipsychotics) lead to osteopenia and osteoporosis. Bone loss in men associated

with hyperprolactinemia and hypogonadism is in fact an indirect effect of increased estrogen levels[62]. It should also be borne in mind that increased levels of PRL not associated with infertility may be indicators of a more general hypothalamus-pituitary imbalance, which may imply an increased risk of osteoporosis in men with CD[18]. The changes in PRL levels are nevertheless reversible if GFD is followed[63]. Other hormones such as GH[64], PTH[65] and Ghrelin also respond in the same way to GFD[66]. These data emphasize the importance of early diagnosis whenever there is a clinical reason to suspect the presence of CD, as for example in otherwise unexplained male osteoporosis or hypogonadism.

Celiac disease leads to a deficiency of specific micronutrients such as vitamin A, which is fundamental for the maintenance of spermatogenesis[67] and T secretion[68]. Retinols appear to act on three main types of testicular cells (Sertoli cells, germ cells and Leydig cells) of both adult and fetus[68]. A decrease in T production leads to atrophy of the accessory sex organs and, because T secretion also induces anabolic effects on these tissues[69], has negative effects on muscle and bone tissue. In addition, low circulating levels of GH lead to an altered body composition, with increased fat and reduced lean body and skeletal muscle mass[70].

Testosterone therapy for the prevention and treatment of osteoporosis in men is still a matter of controversy, but it is probable that osteoporotic men with evident hypogonadism[56], as well as those with CD with which it is often associated, can benefit from this treatment.

Strict adherence to GFD is thus necessary to avoid damage to both the reproductive system and bones. The negative effects on bones are more evident in older men with late-onset CD, for whom the risk of osteoporosis with its attendant fracture risk is greater, particularly in subjects who do not exercise regularly[71] and for whom vitamin D and calcium supplements should be recommended.

The use of pharmacological therapy (for exemple 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[72]. Moreover, there is evidence that treatment with risedronate increases BMD and reduces hip fractures in elderly men[73].

## CONCLUSION

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[41], the risk of osteoporosis is increased[66]. All of these factors are able to interact with the systemic signs of CD[41]. Osteoporosis and CD are often found together and are both modulated by genetic and environmental factors, confirming their multifactorial etiopathogenesis[18,19]. The incidence of osteoporosis is higher in celiac subjects (3.4%) 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[21], the screening of patients with idiopathic osteoporosis for CD is advisable[14]. In subjects who are also affected by endocrine-reproductive disorders, themselves a major risk factor for osteoporosis[2], this screening acquires even more importance.

Increased risk of osteoporosis should not be considered as an isolated factor, but as part of a more generalised endocrine-environmental imbalance with possible serious effects on health on account of its influence on a fairly broad range of tissues and functions and 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.

One important strategy to conserve bone integrity could be the adoption of a suitable lifestyle from adolescence. Early diagnosis of CD is also indispensable so that measures to prevent and treat it, such as GFD, can be initiated in early, thereby averting an increased risk of pathologies such as osteoporosis.

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