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Pathophysiology of osteoporosis: genes, oxidative stress and immunopathogeny. A qualitative systematic review.

(Fisiopatología de la osteoporosis: genes, estrés oxidativo e inmunopatogenia. Una revisión sistemática cualitativa)

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Abstract (english)

The aim of this qualitative systematic review is to describe the most important pathophysiological factors related with genes, oxidative stress, immunophatogeny and others aspects in osteoporosis. We selected Pubmed, Scielo and Google Scholar databases. A total of 7,730 documents were returned, based on different combinations of keywords in English and Spanish. We use the quick reading of titles and abstracts to eliminate the articles unrelated to the proposed expository scheme. A total of 152 papers fulfilled the following validation criteria: descriptive clinical studies, comparative with control group, analytical studies of random assignment, and studies in experimental animals. To evaluate the methodological quality of the clinical studies, the Sackett evidence scale was used, and the list of criteria of Sniekers to analyze the quality of the animal studies were used. A major challenge is the integration of a multitude of signaling pathways and redundant cytokines, oxidative stress, chronic stress, genes, among others, apparently capable of playing an important role, in trying to establish a complete model of the pathophysiology of postmenopausal osteoporosis.

Keywords (english)

Osteoporosis, pathology, oxidative stress, genes, immune system (Source: MeSH).

Resumen (español)

El objetivo de esta revisión sistemática cualitativa es describir los factores fisiopatológicos más importantes relacionados con los genes, el estrés oxidativo, la inmunopatogenia, entre otros aspectos en la osteoporosis. Para lo cual seleccionamos las bases de datos de Pubmed, Scielo y Google Académico. La búsqueda devolvió un total de 7.730 documentos, basados en las diferentes combinaciones de palabras claves en inglés y español. Utilizamos la lectura rápida de títulos y resúmenes para eliminar los artículos no relacionados con el esquema expositivo propuesto. Un total de 152 trabajos cumplieron los siguientes criterios de validación: estudios clínicos descriptivos, comparativos con el grupo control, estudios analíticos de asignación al azar y estudios en animales de experimentación. Para evaluar la calidad metodológica de los estudios clínicos, se utilizó la escala de pruebas de Sackett y se utilizó la lista de criterios de Sniekers para analizar la calidad de los estudios en animales. Un desafío importante es la integración de una multitud de vías de señalización y citoquinas redundantes, del estrés oxidativo, estrés crónico, los genes, entre otros muchos factores, aparentemente capaces de desempeñar un papel

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importante, para tratar de establecer un modelo completo de la fisiopatología de la osteoporosis posmenopáusica.

Palabras clave (español)

Osteoporosis, patología, estrés oxidativo, genes, sistema inmunológico (Fuente: DeCS).

Introducción

For the search of the pertinent information to the subject, we selected the Pubmed, Scielo and Google Scholar databases. A total of 7,730 papers were returned from the following word combinations: in Pubmed the phrase "immunopathology osteoporosis" returned 6 papers, with the words "immune system osteoporosis" were found 1,620 articles, the combination "genes and osteoporosis" assigned 2,357 and finally “Osteoimmunology and osteoporosis” assigned 3 articles, for a subtotal of 4,222 research work. With respect to the Scielo database the phrase "immune system osteoporosis" allowed to identify 4 works, "fisiopatología de la osteoporosis" returned 11 articles, "osteoporosis" 994 articles, "inmunología y osteoporosis" only located 1 work and finally "genes y osteoporosis " allowed the rescue of 18 works, for a subtotal of 1,028 documents. As Google Scholar is a more general search engine the phrase used by us was: "immune system pathophysiology osteoporosis osteoimmunology". This search limited to 2,080 the works found. After the preliminary reading of the titles and the summary in Spanish or English allowed us to eliminate about 98% of the documents. *In vivo* or *in vitro* studies that met the following criteria were selected: a) descriptive clinical studies, comparative with control group, b) analytical studies of random assignment, and c) studies in experimental animals. To evaluate the methodological quality of the clinical studies, the Sackett evidence scales were used and the list of criteria of Sniekers was used to analyze the quality of the animal studies (1, 2).

Osteoporosis is a multifactorial disease, complex, dependent on aspects such as race, nutritional status and immune status, age, genetic predisposition, consumption of medications such as glucocorticoids, anticonvulsants, therapy with other different immunosuppressants to glucocorticoids (such as Cyclosporin A, for example), among others. All this is compounded by stress, depression, underlying diseases such as hyperthyroidism, Cushing's syndrome; the physiological decline of estrogen by menopause, amenorrhoea, testosterone deficiency in men, life habits consistent with excess of tobacco, consumption of alcoholic beverages, just to name the most frequent aspects (Figure 1). Elucidate the etiopathogenesis of the disease in humans is very difficult because of the large number of simultaneous variables that must be controlled; for this reason, alternative models such as *in vitro* cell systems and all ovariectomized murine models (*in vivo* models) offer a great alternative, but it must be considered that a mechanism linked to osteoporosis obtained by *in vitro* experiments could not necessarily be extrapolate to the model *in vivo* (or have the opposite effect, for example) and even more must be validated in humans. The mouse models offer an excellent alternative to study the acute effect of glucocorticoids, but in humans could be totally different. Therefore, searching for new experimental models to study osteoporosis is mandatory. Every day, the topic of pathophysiology in osteoporosis is growing rapidly. However, its causes and signaling pathways and cellular interconnections are not fully understood (3-10).

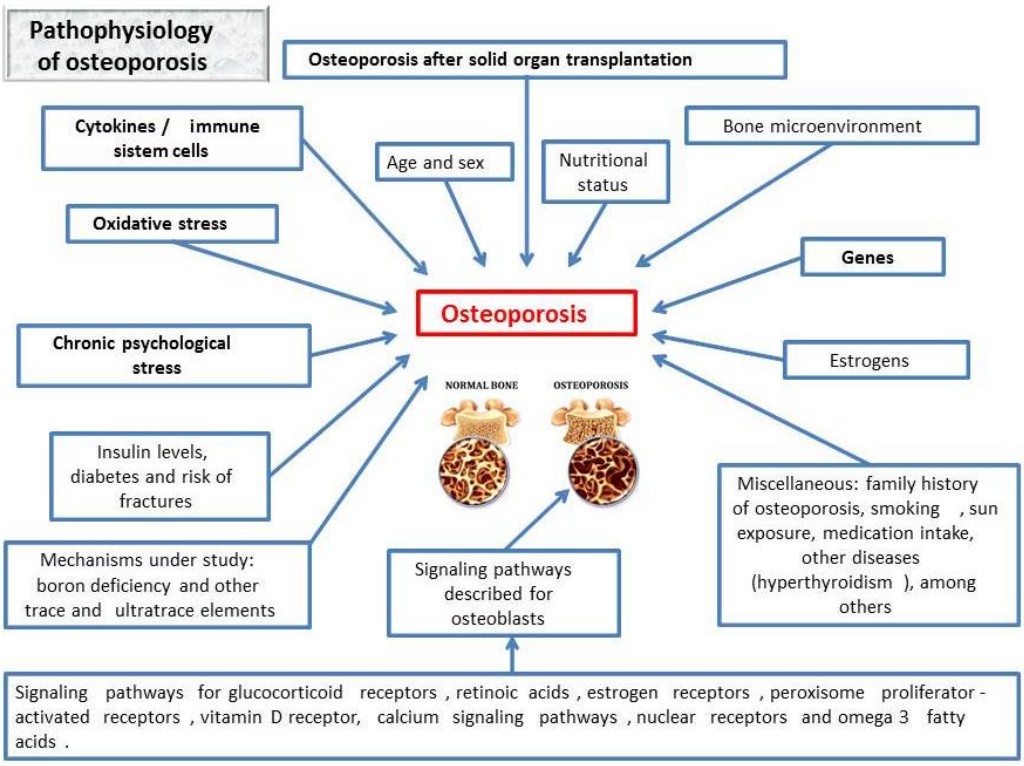

Figure 1. General scheme proposed to describe the pathophysiology of osteoporosis. In bold, the aspects developed in the present review are highlighted

In recent decades, the perception of osteoporosis has changed from an inevitable consequence of aging to a well-characterized, treatable chronic no communicable disease with major impacts on individuals, health systems and societies all over the world. The characterization of its pathogenesis from the hierarchical structure of the bone and the role of its cellular populations (osteoblasts and osteoclasts) and the microenvironment of the latter, the development of effective strategies for the identification of the most suitable candidates for treatment and a growing of effective pharmacological therapies have sustained this evolution (11). The aim of the present qualitative systematic review is to describe the most important pathophysiological factors in osteoporosis.

Osteoporosis after solid organ transplantation

Solid organ transplantation has become an effective and established clinical therapy for end-stage renal disease, liver, heart and lung disease over the last twenty years. However, the improvement in the life quality of patients after transplantation also has brought about the adverse effects of some complications such as osteoporosis and fractures related to it (Figure 2; Figure 3). A fast decrease in BMD and also a marked increase in fracture risk in the first 6 to 12 months after transplantation have been frequently observed (12-14). The percentage of bone loss in renal transplant recipients was 76.05% (200/263). Logistic regression analysis revealed the risk factors of osteoporosis in renal transplant recipients were age older than 50 years old (p=0.01), parent fractured hip history (p=0.001), high dose of corticosteroid (p=0.02) (13). One study found that the overall risk of osteoporosis following a solid organ transplant was 5.14 (95% CI: 3.13-8.43) and the overall risk of related fractures was 5.76 (95% CI: 3.80-8.74). Whereas, in lung transplant recipients an increased risk of osteoporosis and fractures were observed, followed by other organ types (15). As the patient should be treated for life with immunosuppressants to avoid graft rejection (hyperacute, acute or chronic), these drugs are closely linked to BMD decreases, as well as other major risk factor in this group of patients, it is constituted by the previous bone diseases, before transplantation. In this sense the associated immunosuppressants include: glucocorticoids, which primarily affect trabecular bone more than those sites

where cortical bone predominates. Daily doses of 7.5 mg of prednisone are generally considered a significant cause of bone loss, although lower doses have been reported with harmful effects on bone health. In this context, the main pathophysiological mechanism of glucocorticoids is reduction of bone formation due to the suppression of osteoblast differentiation and function and the promotion of osteoblastic apoptosis (12, 16).

Calcineurin inhibitors (a calcium-related protein and its intracellular signaling pathways, present in CD4+ T cells) have been successfully used since the 1980s as useful immunosuppressant in organ transplantation. Two drugs are linked in this particular context to osteoporosis: Cyclosporin A and Tacrolimus (FK506). The pathophysiological mechanism that explains the link between the administration of cyclosporin A to transplanted patients and the genesis of osteoporosis is not completely understood. However, it is well-known the dose-dependent effect and time of administration of the drug. Another relevant aspect is that patients receiving combination therapy with glucocorticoids and cyclosporin A increase the osteoporosis and related fractures risks. Otherwise with the FK506 the effect is known to be due to a bone resorption excess on the formation, related to RANK / RANKL / OPG system imbalance (12, 16-17).

Everolimus and Sirolimus are mammalian rapamycin inhibitors (designated as mTORi) useful in organ transplant recipients. It is well known that mTORi have both an antiproliferative effect and antiangiogenic activities; so their interference with bone metabolism is inevitable (12, 18). Kneissel et al., in 2004 (19) studied the impact of Everolimus in mice, human osteoclasts *in vitro* and in the ovariectomized rat bone. They found suppression in spongy bone, bone resorption and cathepsin K expression by osteoclasts. Sirolimus has been shown to inhibit the formation of osteoclasts both *in vivo* and *in vitro*; therefore, it may have the potential to balance the effects of corticosteroids and immunosuppressive regimens based on calcineurin inhibitors, thus promoting an accelerated osteoporosis development in kidney transplant recipients. Both Everolimus and Sirolimus are considered bone resorption inhibitors which action is the inhibition of calcineurin (20).

Molecular mechanisms involved in osteoporosis

Several regulatory pathways described for

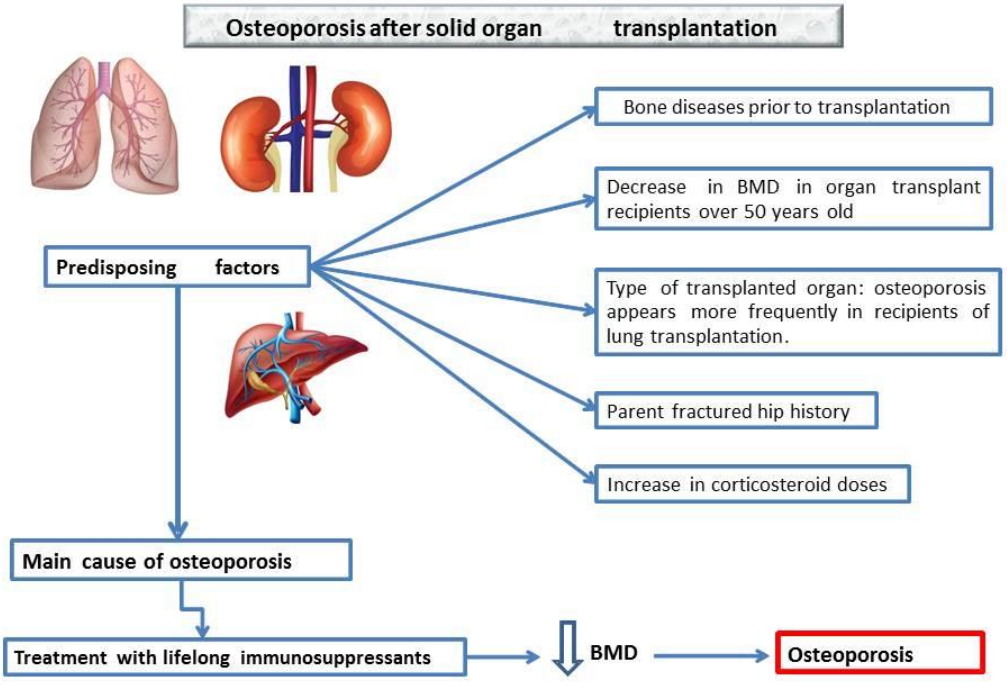

Figure 2. Predisposing factors and main causes of osteoporosis after solid organ transplantation. BMD = Bone mineral density.

osteoblasts have been implicated in osteoporosis: the glucocorticoid receptor signaling pathway, retinoic acid signaling pathway (RAR), the signaling pathway of the estrogen receptor, peroxisome proliferator-activated receptor signaling pathway (PPAR), vitamin D receptor signaling pathway, $Ca2^{+}$ signaling pathway, nuclear receptor coactivators (NCOA), and omega 3 fatty acid signaling pathway. Glucocorticoids are a class of steroid hormones that bind to the glucocorticoid receptors present in each vertebrate cell. They inhibit the proliferation and differentiation of osteoblasts. Glucocorticoids also regulate ion channels. Retinoic acid acts by binding to retinoic acid (RARs) receptors which are members of the nuclear receptor superfamily. The RAR family comprises 3 isotypes: RARα, RARβ, RARγ. RARs act on heterodimeric combinations with retinoid X (RXR) receptors. Retinoic acids are essential for the physiological regulation of a wide range of biological processes including development, differentiation, proliferation and apoptosis. Estrogen is necessary for bone growth and for the development and maintenance of bone health. The cellular responses of osteoblasts and osteoclasts to estrogen are initiated through two high affinity Erα and Erβ receptors. PPARs are members of the nuclear receptor family that can form a heterodimeric complex with RXR and function as transcription factors that regulate the expression of genes. PPARs are involved in important metabolic and inflammatory processes in the control of cell proliferation, differentiation and survival (21).

These last eight signaling pathways were verified with transmission electron microscopy and gene expression profiles for ovariectomized rat bone tissues before and after treatment with strontium gluconate. Based on the network structure and experimental data, the dynamic model predicted that calcium and glucocorticoids signaling pathways are the molecular targets for treatment with strontium gluconate. The results further reveal that in the context of the lack of estrogen pathway signaling, treatment with strontium gluconate may offer a

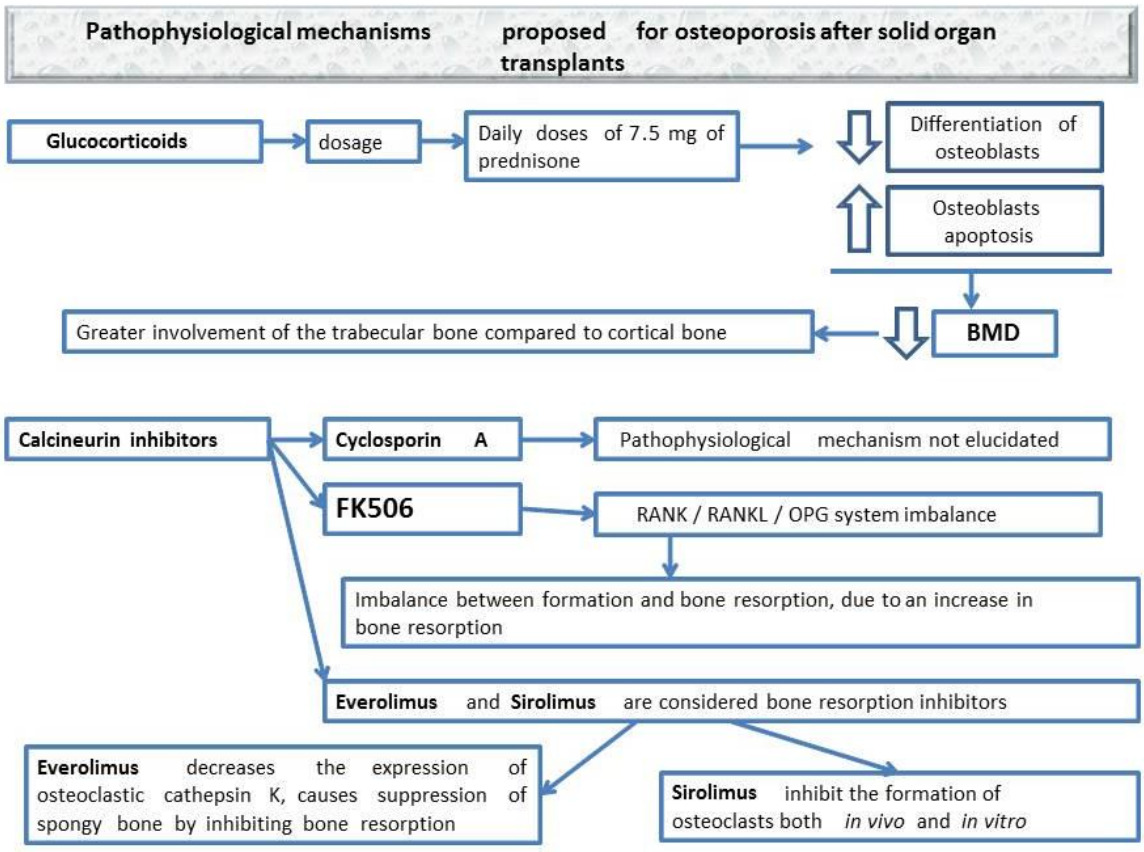

Figure 3. Pathophysiological mechanisms proposed for osteoporosis after solid organ transplants. BMD = Bone mineral density; FK506 = Tracolimus; RANK = Receptor Activator of Nuclear Factor κβ; RANKL = Receptor Activator for Nuclear Factor κβ Ligand; OPG = Osteoprotegerin.

desirable health status for humans (21).

It is important to clarify in this section that strontium salts, in the form of strontium ranelate, are a therapeutic option reserved only for those patients who respond little to nothing to treatment with oral or intravenous bisphosphonates. It is important to emphasize that the reason why Yan et al., 2016 (21) decided to use strontium gluconate is precisely because in this way these researchers managed to reverse the abnormal phenotype observed for osteoblasts, being able to elucidate the particular molecular pathways and then verify a network, which brings enormous advantages for the vision from a global point of drugs that are used for long periods of time in relation to the safety of their use. Strontium ranelate is not the first therapeutic option in osteoporosis treatment. Its use is limited to patients who do not have a history of ischemic heart disease, peripheral arterial disease or cerebrovascular disease. It is also contraindicated in hypertensive patients not controlled, being at the discretion of the clinician its use in osteoporosis patients.

Strontium gluconate exerted an action at the level of osteoblasts (21), while bisphosphonates have mechanisms of action on osteoclasts. Bisphosphoric acid confers to bisphosphonates a high affinity for the bone surface, a low half-life, a very low bioavailability and a profile of low systemic effects unlike other anti-reabsorptives. The high affinity for the bone surface is a great advantage since a minimal amount of the absorbed drug can exert an important effect in the bone remodeling. Inside the osteoclasts, it is the R2 chains that determine the potency and mechanism of action of the drug through the inhibition of the Farnesyl pyrophosphophosphate synthase (FPP-S) enzyme and the Geranyl pyrophosphophosphate synthetase (GPP-S), interfering in osteoclastic activity: cytoskeleton organization, vesicle trafficking, brush edge formation and with prolonged exposure cell apoptosis is also induced. The basic molecular structure of

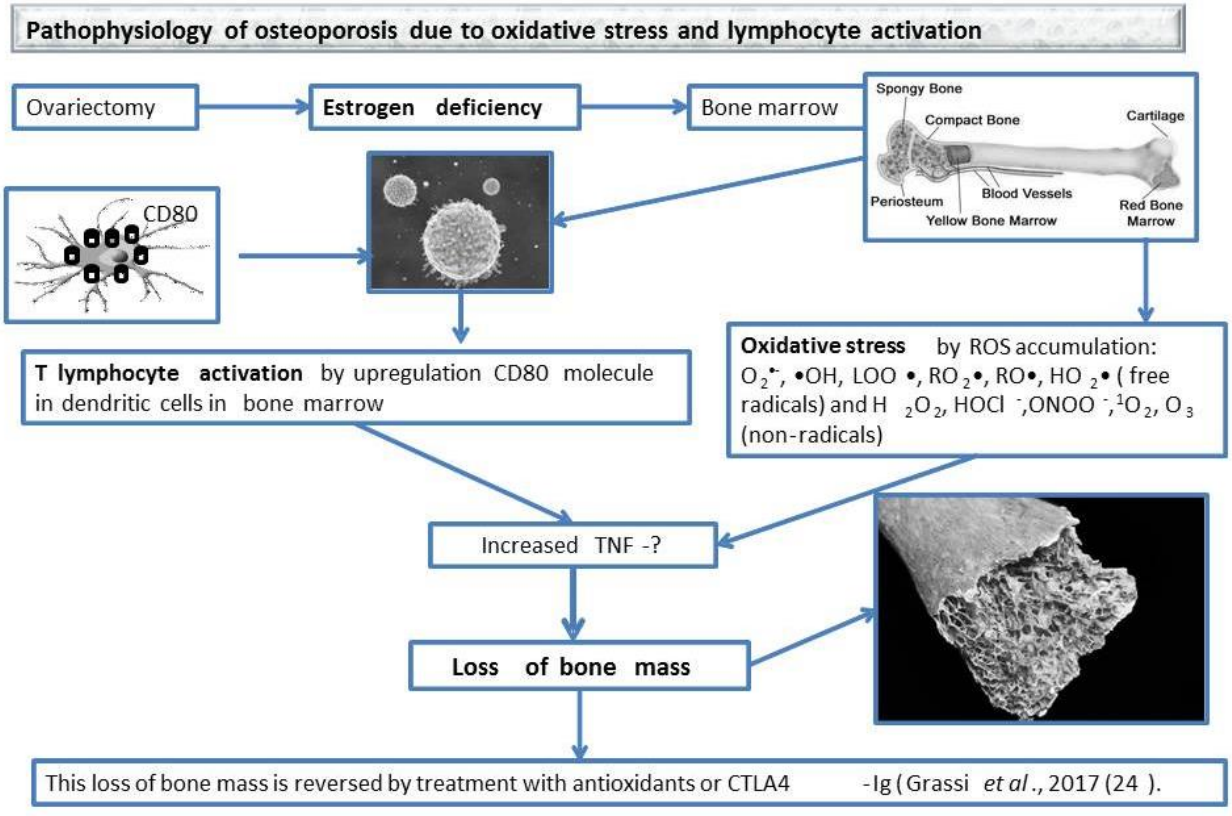

Figura 4. Pathophysiology of osteoporosis due to oxidative stress and lymphocyte activation. Reactive oxygen species (ROS); superoxide anion (O_2•-); hydroxyl radical (•OH); lipoperoxide radical (LOO•); Peroxyl (RO_2•); Alkoxyl (RO•); Hydroperoxyl (HO_2•); Hydrogen peroxide (H_2O_2); Hypoclorous acid ($HOCl^-$); Ozone (O_3); Singlet oxygen ($^1O_2$); Peroxynitrite (ONOO-). Peroxynitrite is also classified as reactive nitrogen species (RNS) in the subgroup of non-radicals; some authors also include it as ROS.

bisphosphonates is similar and the difference lies in the radicals R1 and R2 that give them bone affinity and potency to aminobiphosphonates. The R2 attached to the central carbon is the one that confers the potency to the bisphosphonate and is the one that will produce the enzymatic inhibition at the level of the synthetases, while the R1 gives the affinity to the bone and in the majority of the bisphosphonates is the group hydroxyl that gives you that property. The difference between Aminobiphosphonates lies in the variation of this molecule that will produce in these bisphosphonates a more pronounced effect of suppression of the replacement, so that the higher potency of the new molecules allows a lower dosage. The bisphosphonates that have until now long-term safety data are Alendronate and Risedronate. So we will have to wait for longer clinical trials of the latest-generation drugs that offer more power than those already known to assess their safety and effect on the bone microarchitecture (22).

Oxidative stress and the osteoporosis genesis.

A free radical is an atom or molecule with a single unpaired electron. Examples: nitric oxide (•NO), superoxide anion ($O_2^{\bullet-}$), hydroxyl radical (•OH), lipoperoxide radical (LOO•). Although molecular oxygen (O_2) has two electrons isolated in different orbitals, it is not a free radical. Molecular oxygen, however, reacts rapidly with most radicals, in turn forming other free radicals, which are more reactive and cause selective oxidation of lipids, proteins or DNA molecules (23-24). Most of the radicals that are produced *in vivo* are reactive oxygen species (ROS) or reactive nitrogen species (RNS). RNSs include peroxynitrite (ONOO-), nitric monoxide (NO•) and nitrogen dioxide (NO_2•). Aerobic organisms have developed a complex antioxidant defense system to combat the destructive effects of O_2 products. Unfortunately, this defense system is not perfect and some molecular damage always occurs, leading to disease and aging (23-24).

In 2007, Grassi et al., 2007 (25) demonstrated that increased tumor necrosis factor alpha (TNF-α) production in the bone marrow in response to both oxidative stress and T lymphocyte activation contributes to bone loss by estrogen deficiency; however, it was not known until then whether oxidative stress caused bone loss through T

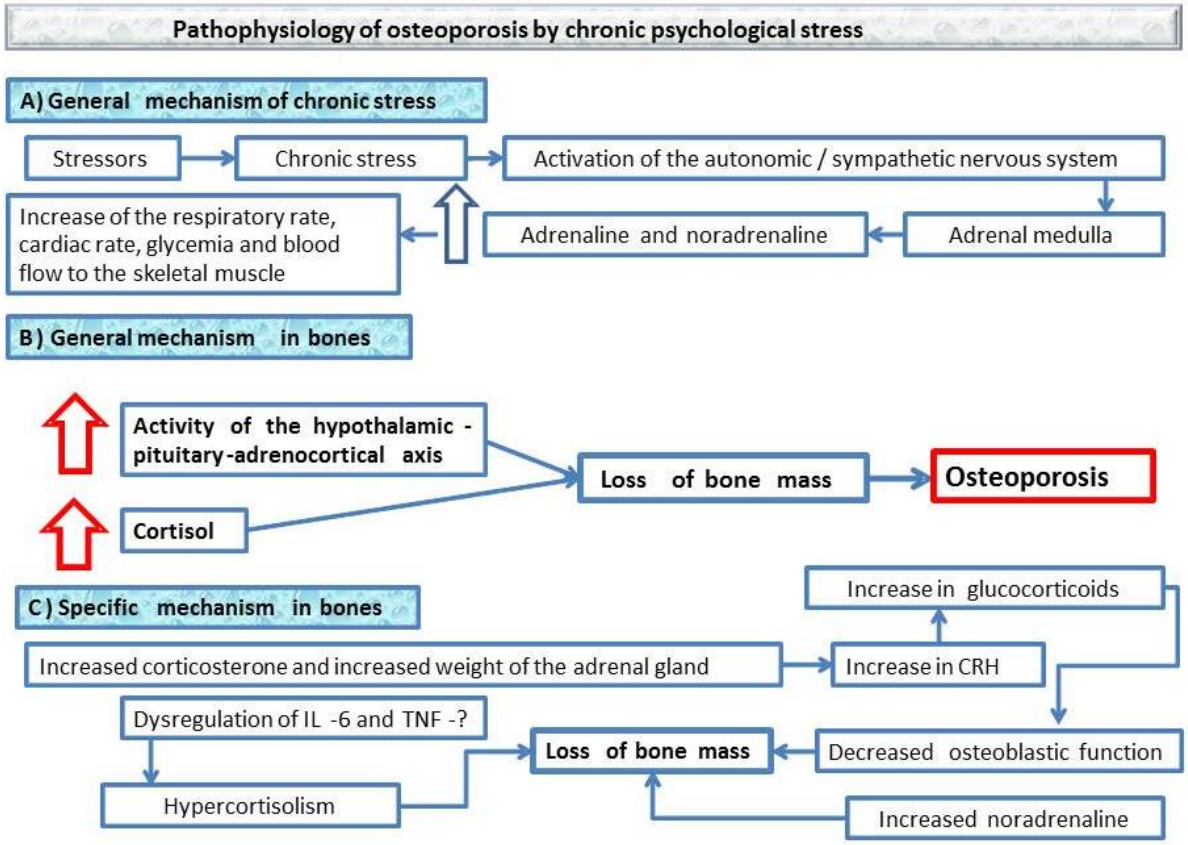

Figure 5. Pathophysiology of osteoporosis by chronic physiological stress. CRH= Corticotropin-releasing hormone; IL-6 = Interleukin 6; TNF-α = Tumor necrosis factor alpha.

lymphocytes (Figure 4). Ovariectomy causes an ROS accumulation in the marrow bone, which is due to increased TNFα production by activated T lymphocytes through the upregulation of the CD80 costimulatory molecule on dendritic cells. Therefore, bone loss is avoided by treatment of ovariectomized mice with antioxidants or CTLA4-Ig, a CD80/CD28 inhibitor.

Chronic psychological stress and osteoporosis.

The chronic psychological stress is a risk factor for osteoporosis. Increased evidence confirms the physiological importance of the central nervous system, especially the hypothalamus, in the regulation of bone metabolism (Figure 5). Both animal and human studies indicate that chronic stress triggers activation of the sympathetic nervous system, which promotes the release of adrenaline and noradrenaline from the adrenal medulla (26-27). Adrenaline and noradrenaline will increase respiratory rate, heart rate, blood glucose concentration, and blood flow to the skeletal muscles (26). Hyperactivity of the hypothalamic-pituitary-adrenocortical axis or hypercortisolemia is considered an important factor for bone loss induced by stress. Several human studies report that blood cortisol levels were elevated in depressed patients, concomitantly with low BMD (28-29). Animal studies also showed elevated levels of circulating corticosterone and adrenal gland weight, accompanied by decreased bone quality in chronic stress mice (30-31). Chronic stress stimulates the hypothalamus to release corticotropin-releasing hormone, which activates the hypothalamic-pituitary-adrenocortical axis and stimulates the secretion of glucocorticoids, which in turn have been shown to be efficient in inhibiting osteoblastic function, causing bone loss (32). In the other hand, studies carried out on animals also showed elevated levels of circulating corticosterone and an increase in adrenal gland weight, accompanied by a decreased in bone quality and in chronic stress mice. Chronic stress is associated with pronounced and durable central and peripheral hypernoradrenergic state (33). Increases in stress-related noradrenaline levels especially within bone tissue could contribute to bone loss and osteoporosis. Elevated noradrenaline levels were confirmed in animal models of chronic stress along with bone loss. In addition, stress-induced bone loss may be partially improved by the β-adrenergic antagonist propranolol, suggesting that the sympathetic nervous system mediates stress-induced bone loss (31). Pro-inflammatory cytokines are also potential stimulators of the hypothalamic-pituitary-adrenocortical axis and may contribute to hypercortisolism in subjects with depression. Chronic psychological stress is associated with dysregulation of inflammatory cytokines, such as interleukin-6 (IL-6) and TNF-α (26, 34-35).

The Genes and Osteoporosis.

Extreme cases of osteoporosis have been served as models to identify genes that could be candidates and indicate susceptibility to the disease. Initially, genes related to imperfect osteogenesis and the Wnt signaling pathway were identified (36). Although most studies have involved small cohorts and some limited genetic approaches, the advent of sequencing is rapidly increasing our ability to establish a molecular diagnosis in these cases. Candidate genes identified in this way are: the *LRP5* gene encoding a Wnt signaling pathway receptor, described in individuals with juvenile osteoporosis, in women with vertebral fractures during pregnancy, and in idiopathic juvenile osteoporosis. In this same Wnt signaling pathway, the genes *DKK1* and *WNT3A* have been identified, which encode an antagonist and a respective ligand of Wnt receptors in patients with juvenile osteoporosis. In this same group the *WNT1* gene whose product is a ligand of the Wnt signaling pathway found in patients with autosomal dominant osteoporosis of early onset could be identified. Finally, in patients with idiopathic osteoporosis and other alterations such as X-linked osteoporosis and postpartum vertebral fractures, the relationship with genes coding for actin-binding proteins and homocysteine metabolic proteins, designated *PLS3* and *MTHRF*, respectively (36-39).

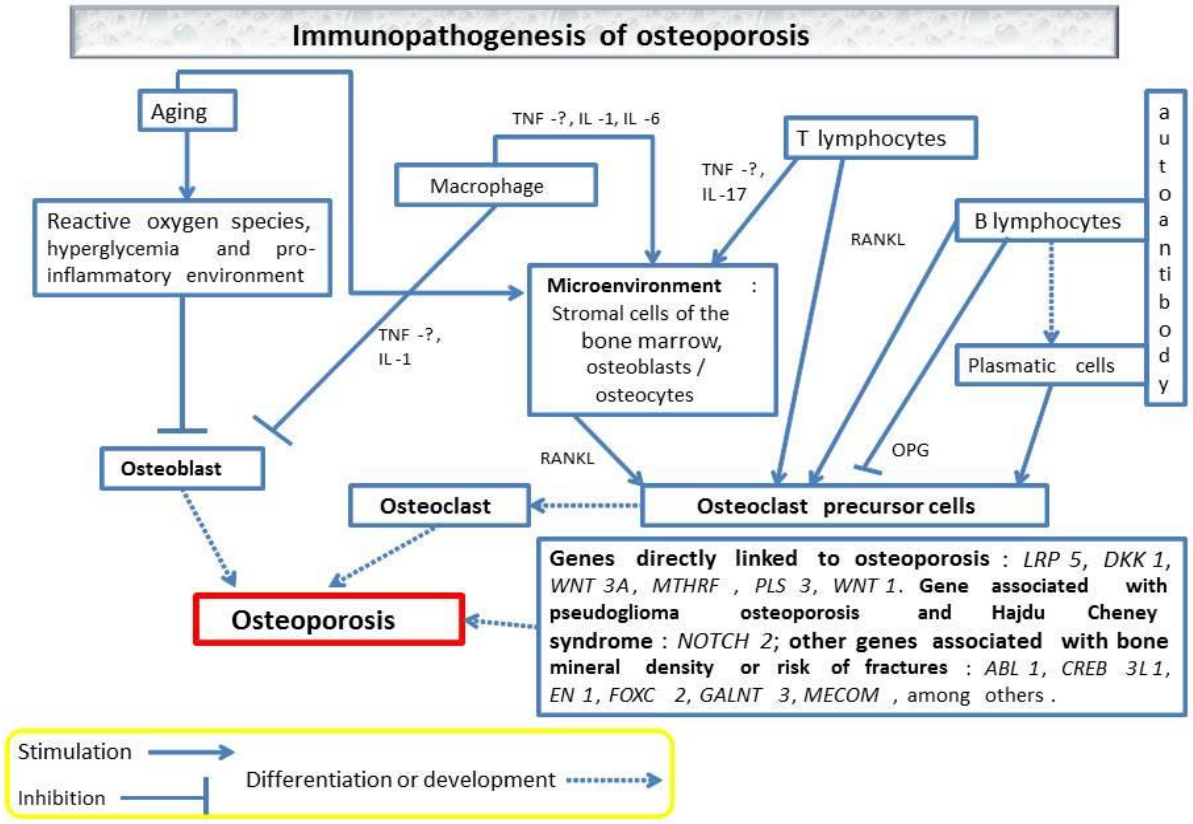

Figure 6. Immunopathology and genes linked to osteoporosis. Source: Taken and modified by Pietschmann et al., 2016 (33); Rocha-Braz and Ferraz-de-Souza, 2016 (35) and Vielma *et al*., 2016 (7). IL-6 = Interleukin 6; TNF-α = Tumor necrosis factor alpha; IL-17 = Interleukin 17; IL-1 = Interleukin 1; RANKL = Receptor Activator for Nuclear Factor κβ Ligand; OPG = Osteoprotegerin.

The study of monogenic diseases with impact on bone resistance has allowed the identification of several mechanisms involved in bone physiology. For example, imperfect osteogenesis, has demonstrated the importance of bone matrix quality of collagen; Van Buchem disease, Hajdu-Cheney syndrome and autosomal recessive osteopetrosis have revealed important signaling pathways (Wnt, Notch and RANK-RANKL-OPG) that regulate bone remodeling; and picnodisostosis has given an idea of the primary action of cathepsin K on the function of osteoclasts. Along with a recently proposed taxonomy of rare genetic disorders of bone metabolism (40), these genes include: *COL1A1, COL1A2, BMP1, PLS3, SERPINH1, SEC24D, TCIRG1, CTSK, NOTCH2, LRP5, SOST*, among many others. Several of candidate genes mentioned above derive from sources with solid experimental support and their link to osteoporosis little and its link with osteoporosis has been gradually established. The last group of genes associated with osteoporosis has been characterized through genome association studies (GWAS), these include: *ABL1, AXIN1, CLCN7, CREB3L1, CTNNB1, DMP1, EN1, FKBP11, FOXC2, SOX4*, among others. In the near future, the concerted effort of clinicians and researchers and ongoing technological progress will shed light on the fundaments genetic of osteoporosis and thus making possible the development of more accurate treatment strategies (36).

Osteoimmunology and immunopathogenesis of osteoporosis

Although osteoimmunology is a relatively new discipline, this field of research has already made significant contributions to the field of biology, bone pathophysiology, and immune system (34). Based on the central role of RANKL / RANK / OPG system in osteoporosis pathophysiology (Figure 6), denosumab a monoclonal antibody directed against RANKL, has been developed. Denosumab inhibits the generation and activity of osteoclasts; in clinical studies, this

antibody decreased bone resorption and increased BMD (41). In postmenopausal women with osteoporosis, denosumab significantly reduced the risk of vertebral, non-vertebral, and hip fractures (42). Up to day, antibodies against sclerostin (an inhibitor of bone formation) are under clinical investigation. In rheumatoid arthritis and other inflammatory arthritis, anti-TNF-α therapies are effective in treating inflammation of the joints. According to the osteoimmunology, antibodies against TNF-α have shown an inhibition effect on bone resorption.

Although the term osteoimmunology has been used since 2000s, the phenomenon of a low-grade systemic chronic inflammatory state associated with aging has been defined as "inflammation-aging" by Claudio Franceschi. And it has been linked to age-related diseases, such as osteoporosis. Given the close anatomical and physiological coexistence of B-lymphocytes and bone-forming units in the bone marrow (in addition to the microenvironment) a role for B lymphocytes in osteoimmunological interactions has long been suspected (34).

This hypothesis seems to be supported by recent findings on B-cell as active regulators of the RANK / RANKL / OPG axis of altered production of RANKL / OPG by B lymphocytes in bone loss is associated with human immunodeficiency virus (HIV) or a modulated expression of related genes with the biology of B lymphocytes in response to estrogen deficiency (34).

Factors that over-regulate the formation of osteoclasts in humans and rodents are TNF-α, a cytokine known to increase the production and activity of the RANKL osteoclastogenic molecule and to potently induce IL-1, IL-6 cytokines and the macrophage colony stimulating factor, regulated in turn by estrogen levels by bone loss induced by ovariectomy. However, the mechanism by which ovariectomy manages to expand the T lymphocyte group of bone marrow was unknown. Until the work of Cenci et al., 2003 (43) whose demonstrated that ovariectomy positively regulates the IFN-γ, by induced class II transactivator, an immune modulator with multiple targets or cell targets, resulting in increased presentation of the antigens enhanced macrophages, enhanced T lymphocyte activation, and extended T lymphocyte life. The positive regulation of the class II transactivator is derived from the increase of the production of IFN-γ by helper or collaborating Th1 cells, resulting in a greater secretion of IL-12 and IL-18 by macrophages. The resulting T cell expansion and bone loss are prevented *in vivo* by both the blocking of T lymphocyte activation induced by the antigen presenting cells and by the silencing of the IFN-γ signaling receptor. Therefore, the increase in IFN-γ-induced class II transactivator expression and the resulting improved T-cell proliferation, and the duration of its useful life or survival, are critical for the bone loss effect associated with estrogen deficiency.

Weitzmann et al., in 2002 (44), demonstrated that ovariectomy improves the production of the IL-7 osteoclastogenic cytokine and that it's *in vivo* neutralization prevents bone loss induced by the surgical procedure. Surprisingly, serum levels of osteocalcin, a bone formation biomarker (7), suggested that the effects of bone reduction by neutralizing IL-7 were due not only to inhibition of bone resorption but also to the stimulation of bone formation. Therefore, because it targets both the osteoclast and osteoblast pathways, IL-7 is a central cytokine in the alteration of the bone turnover characteristic of estrogen deficiency.

Perspectives and final considerations

Osteoporosis has been called "the disease of the century" because of its great impact on public health throughout the world; its etiology has not yet been deciphered. One hypothesis suggests that certain elements such as boron and strontium could participate in a metabolic disease such as osteoporosis (45-46). Much progress has been made in terms of treatment, diagnosis, and especially in eliminating the perception that the disease was a logical consequence of aging. It is now considered as a chemotherapy-treatable disease. To consult a simple model on the immunopathogenesis of the osteoporosis, the reader can consult a previous work of our group Vielma et al., (2016) (7).

In attempting to establish a complete model of postmenopausal osteoporosis pathophysiology the major challenge is the integration of a multitude of redundant pathways and cytokines, apparently capable of playing an important role.

All efforts in the field of basic and applied research in the pathophysiology of the disease will result in an increase in our knowledge of topical topics such as micro RNA and epigenetics. All this effort will result in ensuring a better quality of life for the millions of people who suffer from the disease anywhere on the planet.

Conflict of Interest

The authors declare no conflicts of interest

References

1. Manterola C, Pineda V, Vial M, Losada H, Muñoz S. Revisión sistemática de la literatura. Propuesta metodológica para su realización. Rev Chil Cir. 2003; 55: 204-6.
2. Sniekers YH, Weinans H, Bierma-Zeinstra SM, van Leeuwen JP, van Osch GJ. Review, animal models for osteoarthritis: the effect of ovariectomy and estrogen treatment a systematic approach. Osteoarthritis Cartilage 2008; 16: 533-41. [PubMed] [Google Scholar]
3. Lai CW, Chen HL, Tu MY, Lin WY, Röhrig T, Yang SH, Lan YW, Chong KY, Chen CM. A novel osteoporosis model with ascorbic acid deficiency in Akr1A1 gene knockout mice. Oncotarget 2017; 8: 7357-69. [PubMed] [Google Scholar]
4. Naruse K, Uchida K, Suto M, Miyagawa K, Kawata A, Urabe K, Takaso M, Itoman M, Mikuni-Takagaki Y. Alendronate does not prevent long bone fragility in an inactive rat model. J Bone Miner Metab 2016; 34: 615-26. [PubMed] [Google Scholar]
5. Xu JH, Yao M, Ye J, Wang GD, Wang J, Cui XJ, Mo W. Bone mass improved effect of icariin for postmenopausal osteoporosis in ovariectomy-induced rats: a meta-analysis and systematic review. Menopause 2016; 23: 1152-7. [PubMed] [Google Scholar]
6. Zang Y, Tan Q, Ma X, Zhao X, Lei W. Osteogenic actions of metoprolol in an ovariectomized rat model of menopause. Menopause 2016; 23: 1019-25. [PubMed] [Google Scholar]
7. Vielma JR, Carrero PE, Gutiérrez LV, Delgado Y, Picon D, Chirinos RC. Boro y osteoporosis, tratamiento y biomarcadores de metabolismo óseo. Editorial Académica Española. Primera Edición. ISBN-10: 3841757901. 2016, 188 p.
8. Scalize PH, Bombonato-Prado KF, de Sousa LG, Rosa AL, Beloti MM, Semprini M, Gimenes R, de Almeida AL, de Oliveira FS, Hallak Regalo SC, Siessere S. Poly(Vinylidene Fluoride-Trifluorethylene)/barium titanate membrane promotes de novo bone formation and may modulate gene expression in osteoporotic rat model. J Mater Sci Mater Med 2016; 27: 180. [PubMed] [Google Scholar]
9. Komori T. Glucocorticoid Signaling and Bone Biology. Horm Metab Res 2016; 48: 755-63. [PubMed] [Google Scholar]
10. José Ramón V, Mora Mora M, Marino Alarcón O, Hernández G, Josefina Linares L, Urdaneta Romero H, Arévalo González E. Comparative study of the urinary excretion of boron, calcium, magnesium and phosphorus in postmenopausal women with and without osteoporosis. Invest Clin 2012; 53: 3-15. [PubMed] [Google Scholar]
11. Curtis EM, Moon RJ, Dennison EM, Harvey NC, Cooper C. Recent advances in the pathogenesis and treatment of osteoporosis. Clin Med (Lond) 2015; 15: s92-6. [PubMed] [Google Scholar]
12. Lan GB, Xie XB, Peng LK, Liu L, Song L, Dai HL. Current Status of Research on Osteoporosis after Solid Organ Transplantation: Pathogenesis and Management. Biomed Res Int 2015; 2015: 413169. [PubMed]
13. Zhang Q, Cao K, Hu X, Li H, Wang W, Li H, Xue W, Xu Y, Wang W, Zhang X. Investigation of bone loss and its related factors in renal transplant recipients. Zhonghua Yi Xue Za Zhi. 2015; 95: 2062-5. [PubMed]
14. Song L, Xie XB, Peng LK, Yu SJ, Peng YT. Mechanism and treatment strategy of osteoporosis after transplantation. Int J Endocrinol 2015; 2015: 280164. [PubMed] [Google Scholar]
15. Yu TM, Lin CL, Chang SN, Sung FC, Huang ST, Kao CH. Osteoporosis and fractures after solid organ transplantation: a nationwide population-based cohort study. Mayo Clinic Proceedings 2014; 89: 888-95. [PubMed] [Google Scholar]
16. Hansen KE, Kleker B, Safdar N, Bartels CM. A systematic review and meta-analysis of glucocorticoid-induced osteoporosis in children. Semin Arthritis Rheum 2014; 44: 47-54. [PubMed] [Google Scholar]
17. Gurin L, Gohh R, Evangelista P. Pain syndrome with stress fractures in transplanted patients treated with calcineurin inhibitors. Clin Kidney J 2012; 5: 13-6. [PubMed] [Google Scholar]
18. Schwarz C, Oberbauer R. The future role of target of rapamycin inhibitors in renal transplantation. Curr Opin Urol 2002; 12: 109-13. [PubMed]
19. Kneissel M, Luong-Nguyen NH, Baptist M, Cortesi R, Zumstein-Mecker S, Kossida S, O'Reilly T, Lane H, Susa M. Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts. Bone 2004; 35: 1144-56. [PubMed] [Google Scholar]
20. Westenfeld R, Schlieper G, Wöltje M, Gawlik A, Brandenburg V, Rutkowski P, Floege J, Jahnen-Dechent W, Ketteler M. Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis-implications for post-transplantation bone disease. Nephrol Dial Transplant 2011; 26: 4115-23. [PubMed] [Google Scholar]
21. Yuan R, Ma S, Zhu X, Li J, Liang Y, Liu T, Zhu Y, Zhang B, Tan S, Guo H5, Guan S, Ao P, Zhou G. Core level regulatory network of osteoblast as molecular mechanism for osteoporosis and treatment. Oncotarget 2016; 7: 3692-701. [PubMed] [Google Scholar]
22. Sun S, McKenna CE. Farnesyl pyrophosphate synthase modulators: a patent review (2006 - 2010). Expert Opin Ther Pat 2011; 21: 1433-51. [PubMed] [Google Scholar]
23. Kalyanaraman B. Teaching the basics of redox biology to medical and graduate students: Oxidants, antioxidants and disease mechanisms. Redox Biol 2013; 1: 244-57. [PubMed] [Google Scholar]
24. Vielma JR, Bonilla E, Chacín-Bonilla L, Mora M, Medina-Leendertz S, Bravo Y. Effects of melatonin on oxidative stress, and resistance to bacterial, parasitic, and viral infections: a review. Acta Trop 2014; 137: 31-8. [PubMed] [Google Scholar]
25. Grassi F, Tell G, Robbie-Ryan M, Gao Y, Terauchi M, Yang X, Romanello M, Jones DP, Weitzmann MN, Pacifici R. Oxidative stress causes bone loss in estrogen-deficient mice through enhanced bone marrow dendritic cell activation. Proc Natl Acad Sci USA 2007; 104: 15087-92. [PubMed] [Google Scholar]
26. Azuma K, Adachi Y, Hayashi H, Kubo KY. Chronic psychological stress as a risk factor of osteoporosis. J UOEH 2015; 37: 245-53. [PubMed] [Google Scholar]
27. Kvetnansky R, Lu X, Ziegler MG. Stress triggered changes in peripheral catecholaminergic systems. Adv Pharmacol 2013; 68: 359-97. [PubMed] [Google Scholar]
28. Michelson D, Stratakis C, Hill L, Reynolds J, Galliven E, Chrousos G, Gold P. Bone mineral density in women with depression. N Engl J Med 1996; 335: 1176-81. [PubMed] [Google Scholar]
29. Altindag O, Altindag A, Asoglu M, Gunes M, Soran N, Deveci Z. Relation of cortisol levels and bone mineral density among premenopausal women with

major depression. Int J Clin Pract 2007; 61: 416-20. [PubMed] [Google Scholar]
30. Furuzawa M, Chen H, Fujiwara S, Yamada K, Kubo KY. Chewing ameliorates chronic mild stress induced bone loss in senescence-accelerated mouse (SAMP8), a murine model of senile osteoporosis. Exp Gerontol 2014; 55: 12-8. [PubMed] [Google Scholar]
31. Yirmiya R, Goshen I, Bajayo A, Kreisel T, Feldman S, Tam J, Trembovler V, Csernus V, Shohami E, Bab I. Depression induces bone loss through stimulation of the sympathetic nervous system. Proc Natl Acad Sci USA 2006; 103: 16876-81. [PubMed] [Google Scholar]
32. Seibel MJ, Cooper MS, Zhou H. Glucocorticoid-induced osteoporosis: mechanisms, management, and future perspectives. Lancet Diabetes Endocrinol 2013; 1: 59-70. [PubMed] [Google Scholar]
33. Wong ML, Kling MA, Munson PJ, Listwak S, Licinio J, Prolo P, Karp B, McCutcheon IE, Geracioti TD Jr, DeBellis MD, Rice KC, Goldstein DS, Veldhuis JD, Chrousos GP, Oldfield EH, McCann SM, Gold PW. Pronounced and sustained central hypernoradrenergic function in major depression with melancholic features: relation to hypercortisolism and corticotropin-releasing hormone. Proc Natl Acad Sci USA 2000; 97: 325-30. [PubMed] [Google Scholar]
34. Pietschmann P, Mechtcheriakova D, Meshcheryakova A, Föger-Samwald U, Ellinger I. Immunology of osteoporosis: a mini-review. Gerontology 2016; 62: 128-37. [PubMed] [Google Scholar]
35. Kahl KG, Rudolf S, Stoeckelhuber BM, Dibbelt L, Gehl HB, Markhof K, Hohagen F, Schweiger U. Bone mineral density, markers of bone turnover, and cytokines in young women with borderline personality disorder with and without comorbid major depressive disorder. Am J Psychiatry 2005; 162: 168-74. [PubMed] [Google Scholar]
36. Rocha-Braz MG, Ferraz-de-Souza B. Genetics of osteoporosis: searching for candidate genes for bone fragility. Arch Endocrinol Metab 2016; 60: 391-401. [PubMed] [Google Scholar]
37. Hartikka H, Makitie O, Mannikko M, Doria AS, Daneman A, Cole WG, Ala-Kokko L, Sochett EB. Heterozygous mutations in the LDL receptor-related protein 5 (LRP5) gene are associated with primary osteoporosis in children. J Bone Miner Res 2005; 20: 783-9. [PubMed] [Google Scholar]
38. Korvala J, Loija M, Makitie O, Sochett E, Juppner H, Schnabel D, Mora S, Cole WG, Ala-Kokko L, Männikkö M. Rare variations in WNT3A and DKK1 may predispose carriers to primary osteoporosis. Eur J Med Genet 2012; 55: 515-9. [PubMed] [Google Scholar]
39. Fahiminiya S, Majewski J, Roughley P, Roschger P, Klaushofer K, Rauch F. Whole-exome sequencing reveals a heterozygous LRP5 mutation in a 6-year-old boy with vertebral compression fractures and low trabecular bone density. Bone 2013; 57: 41-6. [PubMed] [Google Scholar]
40. Masi L, Agnusdei D, Bilezikian J, Chappard D, Chapurlat R, Cianferotti L, Devolgelaer JP, El Maghraoui A, Ferrari S, Javaid MK, Kaufman JM, Liberman UA, Lyritis G, Miller P, Napoli N, Roldan E, Papapoulos S, Watts NB, Brandi ML. Taxonomy of rare genetic metabolic bone disorders. Osteoporos Int 2015; 26: 2529-58. [PubMed] [Google Scholar]
41. Maldonado-Gonzales E, Pietschmann P. An antibody against RANKL for the treatment of osteoporosis, inflammatory and malignant bone diseases. Wien Med Wochenschr 2010; 160: 458-63. [PubMed] [Google Scholar]
42. Cummings SR, San Martin J, McClung MR, Siris ES, Eastell R, Reid IR, Delmas P, Zoog HB, Austin M, Wang A, Kutilek S, Adami S, Zanchetta J, Libanati C, Siddhanti S, Christiansen C, FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361: 756-65. [PubMed] [Google Scholar]
43. Cenci S, Toraldo G, Weitzmann MN, Roggia C, Gao Y, Qian WP, Sierra O, Pacifici R. Estrogen deficiency induces bone loss by increasing T cell proliferation and lifespan through IFN-gamma-induced class II transactivator. Proc Natl Acad Sci USA 2003; 100: 10405-10. [PubMed] [Google Scholar]
44. Weitzmann MN, Roggia C, Toraldo G, Weitzmann L, Pacifici R. Increasedproduction of IL-7 uncouples bone formation from bone resorption during estrogen deficiency. J Clin Invest 2002; 110: 1643-50. [PubMed] [Google Scholar]
45. Picón-Borregales D, Carrero PE, Gutiérrez-Peña LV, Vielma JR. Relación del estroncio con el metabolismo mineral óseo y la osteoporosis. Una revisión de la literatura. Avan Biomed 2017; 6: 133-43. [Google Scholar]
46. Vielma JR, Picón-Borregales D, Vergara MA, Carrero PE, Gutiérrez-Peña LV. El boro, un elemento benéfico que ayuda a prevenir la osteoporosis en el humano: Una revisión de literatura. Avan Biomed 2017; 6: 216-26. [Google Scholar]

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