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Osteoporosis and Alzheimer´s disease (or Alzheimer´s disease and Osteoporosis)

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Abstract:

Alzheimer's disease (AD) and osteoporosis are two diseases that mainly affect elderly people, with increases in the occurrence of cases due to a longer life expectancy. Several epidemiological studies have shown a reciprocal association between both diseases, finding an increase in incidence of osteoporosis in patients with AD, and a higher burden of AD in osteoporotic patients. This epidemiological relationship has motivated the search for molecules, genes, signaling pathways and mechanisms that are related to both pathologies. The mechanisms found in these studies can serve to improve treatments and establish better patient care protocols.

Keywords:

Alzheimer's disease, osteoporosis, microglia, osteoclast, association, mechanisms.

1.- Introduction:

Alzheimer's disease, like osteoporosis, are two pathologies strongly associated with age and due to the increase in life expectancy and population aging, the appearance of cases for both diseases increases. For some time now, various associations have been found between the two, firstly epidemiological research establishing these associations, followed by studies to try to understand the mechanisms and genes involved that connect both pathologies.

1.1.- Alzheimer Disease:

The incidence and prevalence of Alzheimer's disease (AD) increase dramatically with age. Approximately 80% of patients are older than 75 years. Alzheimer's disease is the most

common cause of dementia, accounting for 60-70% of all cases (World Alzheimer Report, 2018). Dementia is defined as a syndrome characterized by aphasia (progressive decline in language ability) and impairment of multiple brain functions, including memory, thinking, orientation, comprehension, calculation and learning ability (Dementia-WHO 2018). These alterations are due to selective damage to brain regions involved in these processes, such as the hippocampus, the entorhinal cortex, the amygdala and the basal telencephalon. The clinical course of AD usually lasts about 10 years, and death usually occurs from complications secondary to the disease and the debilitation it entails, such as pneumonia, pulmonary embolism, or sepsis (Rabinovici, 2019).

AD presentation can be familial or sporadic. Familial cases account for less than 5% of all AD cases and are characterized by an early onset of symptoms, between 30 and 60 years of age. These early-onset presentation cases can be caused by missense mutations in the amyloid precursor protein (APP) gene or of presenilins 1 or 2, located on chromosomes 21, 14, and 1, respectively, with an autosomal dominant pattern of inheritance. The APP protein, whose role is involved in synaptogenesis and synaptic plasticity, is the precursor of β-amyloid peptides (Aβ) and is cleaved by a group of protease enzymes, including the presenilins (Bekris et.al. 2010). Sporadic or late-onset Alzheimer's disease, defined as having symptoms onset after age 65, most commonly manifests as a progressive amnestic disorder characterized by early and prominent deficits in episodic memory, with varying degrees of executive, linguistic, and visuospatial impairment. The number of patients with Alzheimer's disease in the United States is projected to nearly triple by 2050, with most of the growth attributed to the age group 85 and older. The public health impact of Alzheimer's disease and other forms of dementia cost an estimated $277 billion in the United States in 2018 (Rabinovici, 2019).

However, more than 95% of cases of AD are sporadic and are characterized by a late-onset of symptoms, after 65 years of age. Late-onset Alzheimer's disease is a complex genetic disorder, with an estimated heritability of 60 -80%. The exact cause of Late-onset Alzheimer's disease is not yet known, but different risk factors have been identified, such as mutations in the apolipoprotein E4 gene (Bekris et.al. 2010), environmental factors, trauma and, mainly, aging. It is essential to emphasize that AD is not a normal consequence of aging, but it is the main risk factor for this form of disease.

Genome-wide association studies (GWAS) have provided the identification of some 20 genetic loci involved in bioprocesses of apolipoprotein metabolism and in pathways associated with lipid homeostasis and endocytosis (Giri et al. 2016). In recent years, much attention has been paid to neuroinflammation as a relevant factor in the triggering of Alzheimer's disease (Leng and Edison, 2021; Wang et al. 2022). These types of studies

turn out to be important in order to improve early and personalized treatments. To do this, it is necessary to know the genes and their variants of the different populations of the world. In an interesting work, Dalmasso and collaborators performed the first AD GWAS on populations from Argentina and Chile and found genetic risk variants shared with the European population, while other loci could be considered genetic risk scores of Native American ancestry (Dalmasso et al. 2023).

1.1.A.- Alterations in Alzheimer's disease:

At a macroscopic level, the pathology includes cerebral atrophy, which practically always appears in the clinical phases of this disease and preferentially affects the cerebral cortex, especially in the temporal-parietal areas, the hippocampus and the amygdala (Walsh and Selkoe, 2004). The degree of cerebral atrophy is related to the progress of the disease.

For decades it was proposed that AD is caused by an abnormal accumulation of proteins that make up extracellular senile or neuritic plaques and intracellular neurofibrillary tangles. These aggregates lead to oxidative stress, neuroinflammation, neuronal loss and degeneration (especially in the hippocampus and cortex) and the incorrect functioning of the synapse (LaFerla and Oddo, 2005; Querfurth and LaFerla, 2010).

Other nonspecific lesions, including granulovacuolar degeneration, Hirano bodies, and Lewy bodies, may also appear in the brain of AD patients (Lopez and DeKosky, 2003). All this leads to the interruption of the main afferent and efferent pathways of the hippocampus, which explains, in part, the cognitive deficit observed in this disease (Bigl and Schliebs, 1998; Selkoe, 1999).

1.1.B.- Neuritic plaques:

The amyloid β peptides are normal products of brain metabolism, originating from proteolytic cleavage by a group of enzymes that act sequentially. However, in AD, an imbalance between cleavage and proteolytic synthesis leads to its abnormal accumulation and the formation of extracellular neuritic plaques (Lichtenthaler, 2011). These aggregates exert negative effects on neuronal homeostasis: They promote apoptosis, cause oxidative damage, promote tau protein hyperphosphorylation, have toxic effects on synapses and mitochondria, and also promote local inflammation, triggering microgliosis and astrogliosis (Kurz and Perneczky, 2011).

Although the amyloid hypothesis establishes that the accumulation of Aβ peptide is the primary event of AD, triggering the neurodegenerative changes of Aβ pathology, it is

currently known that this hypothesis cannot fully explain the pathophysiology of the disease, and is seriously questioned as a cause for AD (Hardy and Selkoe, 2002).

1.1.C.- Neurofibrillary tangles:

Tau protein, normally soluble in axons, promotes the assembly and stability of microtubules and transport vesicles. Its activity depends on the state of phosphorylation in which it is found, so the cell carries out a fine regulation of its phosphorylation and dephosphorylation, according to physiological needs. The hyperphosphorylated form of tau loses affinity for microtubules, accumulates, and self-assembles into intracellular neurofibrillary tangles. In AD, hyperphosphorylated tau markedly increases, an imbalance attributed to the activities of kinase and phosphatase enzymes (Kumar, 2015; Wang et al. 2013).

1.2.- Osteoporosis:

Osteoporosis is a disease characterized by a decrease in bone mass and the deterioration of bone macro- and microarchitecture, which can negatively affect the resistance of this tissue and increase the risk of fracture (NIH, 2001) caused by an imbalance between bone formation and resorption (Florencio Silva, 2015) mainly linked to menopause and aging. Although osteoporosis affects both men and women around the world, only 6.3% of men over 50 years of age are affected, as opposed to 21.2% of women (Kanis et al, 2008). Currently, due to demographic changes that include population aging and an increase in life expectancy, osteoporosis incidence is growing significantly, with cases projected to double between 2010 and 2040 (Oden et al., 2015).

Osteoporosis is a disease that does not present symptomatic components until the first fracture occurs. These occur due to fragility and can occur anywhere in the skeleton, the most frequent sites being vertebral bodies, the proximal ends of the femur and humerus, and the distal end of the radius (Kanis et al., 2004; Meton et al., 1999). These fractures cause complex disability, significant morbidity, reduced quality of life, and functional limitations; as well as an economic burden for both patients and health insurance providers (Nuti et al., 2019; Sözen et al., 2017).

They can be classified into primary osteoporosis, which includes juvenile, postmenopausal, male, and senile osteoporosis; and secondary osteoporosis, which is a consequence of different types of medications and diseases (Khosla et al., 2021; Nuti et al., 2019; Sözen et al., 2017).

1.2.A.- Risk factors, costs and frequency:

Different factors are associated with an increased risk of suffering fractures, and they can be categorized as factors that decrease bone mineral density (BMD), factors that are totally or partially independent of BMD, or extraosseous factors that cannot be assessed by BMD. Some examples are genetic load, medication such as glucocorticoids, age, low BMD, family history of fragility fractures and osteoporosis, previous fragility fractures, diseases associated with an increase in fracture risk, certain habits such as smoking or alcohol intake, risk of falls. There is a large increase in the prevalence of osteoporosis in all people over 50 years of age. However, this pathology affects mostly women, who are seven times more likely to suffer an osteoporotic fracture (Berry et al., 2010; Cummings and Melton, 2002).

Osteoporotic fractures have a negative effect by reducing mobility, decreasing quality of life, and increasing mortality (Bleiber et al., 2014; Clynes et al., 2020; Nuti et al., 2019; Qadir et al., 2020; Sanchez, 2010; Ziebart et al., 2019). The prevalence of osteoporosis is growing significantly due to population aging, with projections of a 30% increase in cases from 2010 to 2025 (Kanis et al., 2019). Vertebral fractures are frequently observed prior to hip fractures (Gonnelli et al., 2013), and are usually diagnosed in less than half of the cases (Cooper et al., 1992; Li et al., 2018). These fractures are associated with an increased risk for new vertebral and non-vertebral fractures, as well as increased mortality (Hernlund et al., 2013; Roux et al., 2007). In contrast, fractures involving the distal radius may induce loss of function, but have fairly good recovery and are not associated with increased mortality.

There are different treatment options for osteoporosis (particularly postmenopausal), which can be divided into three broad categories. The first is constituted by antiresorptive agents that decrease bone resorption, and includes: selective modulators of estrogen receptors, calcitonin, bisphosphonates, estrogens, and denosumab (a humanized monoclonal antibody against RANKL (ligand for receptor activator of NF-κB). The second category includes drugs with bone tissue anabolic effects, such as intermittent parathyroid hormone (PTH, teriparatide, abaloparatide) and romosozumab (a humanized monoclonal antibody against sclerostin). The third group includes calcium, vitamin D, and vitamin K supplements (Axelsson et al., 2017; Khan et al., 2015; Mugnier et al., 2019; Schurman et al., 2017).

These treatments have emerged as a new variable to progressively increase osteoporosis-associated costs. Fractures have been shown to cause a significant

economic burden not only in relation to treatment but also to mobility problems associated with them (Bleibler et al., 2013; Bleibler et al., 2014; Burge et al., 2007; Dimai et al., 2012).

Finally, considering osteoporosis as a chronic disease, it is highly relevant to take into account the degree of adherence to the prescribed pharmacological treatment, since reduced compliance could decrease the benefits of treatment and thus its cost-effectiveness (Li et al., 2021).

1.2.B.- Cells involved in bone mineral metabolism:

Risk factors for osteoporosis can induce an imbalance in bone remodeling, a decrease in bone mineral density and/or an increase in bone resorption, thus provoking an increase in fracture incidence. These factors operate via (dys)regulation of different bone tissue cells, such as: mesenchymal stromal cells (MSCs), cells characterized by being multipotent; osteoblasts, derived from MSCs and related to bone formation; osteoclasts, responsible for bone resorption; and osteocytes, responsible for mechanotransduction and maintenance of the extracellular matrix.

1.2.B.i.- Bone marrow MSCs:

Mesenchymal stromal cells are undifferentiated cells from mesenchymal tissues, such as adipose tissue and bone marrow; and they have the ability to self-replicate and differentiate into various phenotypes such as osteoblasts and adipocytes (Keating, 2012). Alterations in MSC proliferation and differentiation can be related to the development of osteoporosis. It has been shown that in older people the number of osteoblasts decreases in bone tissue as the number of adipocytes increases. A similar pattern occurs with the processes of osteogenesis and adipogenesis, due to decreased expression of Runt-related transcription factor 2 (Runx2) and increased expression of Peroxisome proliferator activated receptor γ (PPARγ) (Jiang et al., 2008; Kim et al., 2012). In addition, aged BMSCs show replicative and functional senescence (Mattiucci et al., 2018) which can be due to different causes: telomere shortening, oxidative stress due to high blood sugar levels and/or histone hypermethylation (Infante and Rodriguez, 2018; Li, 2017).

1.2.B.ii.- Osteoblasts:

MSCs proliferate and differentiate into osteoblasts which then carry out bone formation, synthesizing extracellular matrix (mainly type I collagen) and inducing its mineralization by accumulation of calcium phosphate as hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$).

In relation to molecular mechanisms, there are different signaling molecules that are related to the proliferation and differentiation of osteoblasts. Among the main ones we find:

Runx2, osterix (Osx), WNT/β-catenin, and activating transcription factor 4 (ATF4) (Glass et al., 2005; Komori, 2010; Liu and Lee, 2013; Marie, 2008; Soltanoff, 2009).

Another function of osteoblasts is to maintain bone mass by stimulating or inhibiting osteoclasts. In order to induce osteoclastogenesis, a direct contact is necessary between a series of molecules that are expressed in the osteoblast membrane with others that are expressed in the pre-osteoclast membrane. One of these is the RANKL, a member of the tumor necrosis factor (TNF) superfamily, which is expressed on the surface of bone-forming cells and interacts with its receptor RANK expressed by preosteoclasts (Noh, 2020). RANKL is a plasma membrane homotrimeric protein expressed by osteoblasts, osteocytes and stromal cells. When RANKL binds to its receptor in pre-osteoclastic cells, osteoclast formation is promoted. RANKL also inhibits osteoclast apoptosis (Lacey et al., 2012). Likewise, osteoblasts secrete a protein called osteoprotegerin (OPG) that is characterized by negatively regulating the differentiation and maturation of osteoclasts. OPG acts as a high-affinity soluble receptor for RANKL with an affinity approximately 500 times that of RANK (Infante and Rodriguez, 2018). Therefore, the OPG/RANKL ratio is strongly related to the maintenance of bone density and quality.

1.2.B.iii.- Osteoclasts:

Osteoclasts are giant multinucleated cells that degrade bone by secreting proteolytic enzymes and hydrochloric acid, located on the resorbing bone surface. These cells are derived from granulocyte/monocyte progenitor cells (CFU-GM), and reach bone tissue via the bloodstream or by direct migration. As previously mentioned, for osteoclastogenesis to occur, direct contact between RANKL, expressed in the osteoblast membrane, and its receptor RANK in osteoclast precursors is necessary; leading to the activation of the MAPK cascade and consequently the expression of genes involved in the differentiation of osteoclasts (Boyle et al., 2003; Noh et al., 2020; Park et al., 2017). TNFα, an inflammatory cytokine, also promotes osteoclast differentiation by acting synergistically with RANKL. When there is a minimal amount of one, the osteoclastogenic properties of the other are enhanced, although the osteoclastogenic effects of TNFα require constitutive levels of RANKL (Novack and Teitelbaum, 2008; Yokota et al., 2014).

1.2.B.iv.- Osteocytes:

Osteocytes are the most abundant cells in bone tissue, and are regularly located within the bone matrix. They originate from MSCs through the differentiation of osteoblasts, which occurs when they are immersed within lacunae of mineralized matrix. They are cells with a reduced cytoplasm that extends cytoplasmic processes via canaliculi towards the mineralization front, to the vascular space or the bone surface. In turn, through these

processes they can communicate with processes of other osteocytes (Bonewald, 2011; Schaffler and Kennedy, 2012). They also have indirect contact via various signaling molecules with osteoblasts, blood vessel pericytes, and other distant bone cells (Kollmannsberger et al., 2017).

Osteocytes are characterized by acting as mechanosensors, via physical (load-induced) deformation of the bone matrix and changes in the flow of the canalicular fluid induced by deformations of the cell body and its extensions. By translating mechanical signals into biochemical responses, they can regulate bone remodeling through the expression of signaling molecules (Dallas et al., 2013; Li MCM et al., 2006). When load is lacking, as in the case of immobilization, osteocytes release RANKL with the aim of activating bone resorption by forming new osteoclasts, and sclerostin that inhibits osteoblastic bone formation (Infante and Rodriguez, 2018; Robling et al., 2008). A decrease in the efficiency of mechanotransduction can negatively affect bone turnover, and may cause the development of osteoporosis (Li MCM et al., 2021).

2.- Association between Alzheimer's Disease and Osteoporosis:

Both Alzheimer's disease (AD)-associated dementia and osteoporotic fractures are common among the elderly, and their incidence increases with age. In recent decades, epidemiological studies and meta-analyses have been published, showing a global association between these two highly prevalent diseases, and an updated state-of-the-art review of their main conclusions is described below.

2.1.- Epidemiological studies:

In 1987, Buchner and Larson (Buchner and Larson, 1987) wrote one of the first papers to report an increased incidence of fractures in people with AD, studying 157 patients diagnosed with Alzheimer's in Washington, USA. They found, after 3 years of follow-up, a fracture rate of 69/1000 patients/year, while in the general population it was 19/1000 patients/year (fracture rates adjusted for age and sex, obtained from hospital discharge data). In addition, they demonstrated that the frequency of bone fractures increased in those patients with Alzheimer's disease who had toxic reactions to different treatments. In 1996, Johansson and Skoog found in a population of people older than 85 years, that the rate of hip fracture in women with dementia was twice that of the general population (Johansson and Skoog, 1996). Yaffe et al., in 1999, studied more than 8,000 women older than 65 years enrolled in a prospective multicenter study of risk factors for osteoporotic

fractures, and found that osteoporotic women had impaired cognitive function with increased risk of cognitive decline (Yang et al., 2019). Loskutova and her colleagues (Loskutova et al., 2009) studied the relationship between brain volume and cognitive status with whole-body bone mineral density (BMD) in Alzheimer's patients. Regardless of age, sex, regular physical activity, smoking, depression, estrogen replacement, and apolipoprotein E4 carrier status, they found a decrease in BMD in patients with early-stage Alzheimer's disease, correlating BMD with the results of logical memory, delayed logical memory and the selective reminding task, free recall. In this way, they demonstrated that a reduced BMD could be associated with the earliest clinical symptoms of Alzheimer's disease. That same year, Luckhaus (Luckhaus et al., 2009) studied serum biochemical markers of osteoporosis in patients with mild cognitive loss and Alzheimer's disease. They found that the c-terminal fragment of collagen (a marker of bone resorption) was increased both in patients with osteoporosis and in patients with Alzheimer's, as was osteocalcin, which is a marker of bone turnover. Pu et al studied the association between bone metabolic biomarkers, BMD, and early-stage AD in 42 men with AD in China (Pu et al., 2020). They reported that the investigated bone resorption markers were elevated while cortical and proximal tibial BMD were decreased as from the early stages of AD, compared to their control group. In 2020, Başgöz et al conducted a prospective study studying BMD and osteoporosis in more than 360 male and female patients with and without Alzheimer's disease, vascular dementia (VaD), or mixed dementia (AD-VaD) in Istanbul, Turkey (Başgöz et al., 2020). They found that not only AD, but also VaD and AD-VaD were associated with bone loss and osteoporosis in the hip regardless of sex, but not in the lumbar spine. In Pakistan, in 2019, Kumar et al. studied BMD in 150 newly diagnosed AD patients (Kumar et al., 2021). They found that newly diagnosed AD patients had lower serum vitamin D and osteocalcin concentrations and lower BMD when compared with the general population. In 2012, Zhao et al. carried out a meta-analysis study between Alzheimer's disease and fracture risk (Zhao et al., 2012). They found that patients with Alzheimer's have a higher risk of hip fracture and a lower BMD than controls. Six years later, Lv performed another meta-analysis including 8 studies (Lv et al., 2018) pooling data on osteoporosis and bone mineral density with Alzheimer's. They concluded that people with Alzheimer's have a decrease in BMD in the whole body, but especially in the femoral neck, and an increased risk of fracture compared to controls.

From another point of view, Chang et al. studied the risk of dementia in patients with osteoporosis in Taiwan (Chang et al., 2013) finding that they had a risk of dementia 1.46 times greater, and of AD 1.39 times greater, than the control group, both for men and women. Interestingly, osteoporotic patients who received bisphosphonate treatments or

estrogen supplementation had a lower risk of developing dementia than untreated osteoporosis patients. Amouzougan et al carried out a cross-sectional observational study of 2041 osteoporotic postmenopausal women who consulted at the Saint-Etienne hospital, France, evaluating the prevalence of Alzheimer's disease and other dementias (ADD) in this group of women (Amouzougan et al., 2017). They found that the prevalence of ADD in osteoporotic postmenopausal women, especially with a previous fracture of the femur, was higher than the prevalence of ADD in France. In 2018, Kostev and colleagues conducted a 20-year retrospective study of almost 60,000 people in Germany. They concluded that in addition to an increased risk of dementia in osteoporotic women, there was also a 1.3-fold increased risk of diagnosis of dementia in osteoporotic men (Kostey et al., (2018). In Canada, more than 1,700 women older than 65 years were studied from 1997 to 2013 by Bliuc et al. to assess the association between cognitive decline and loss of bone mass (Bliuc et al., 2021). They demonstrated that regardless of age, comorbidity, and education, women presented a rate of cognitive decline associated with bidirectional bone loss, as well as an increased risk of fractures of hips, vertebrae, and other sites within the following 10 years.

All these studies expose several points about the association of these pathologies: i.- deleterious changes in the skeleton (assessed by BMD or by bone turnover markers) occur as from the early stages of AD. ii.- not only can an increase in osteoporosis (and fracture) be observed in the population with AD, there is also an increase in cases of AD in the osteoporotic population. This bidirectional relationship does not allow us to identify which of the two pathologies is the cause and which is the consequence. iii.- The high prevalence of both pathologies worldwide means that this association turns out to be independent of gender, age and geographical location where the population is evaluated.

In order to achieve advances in prevention and improvements in treatment, it is necessary to carry out studies designed to mechanistically explain the association between both pathologies.

2.2.- Mechanisms:

Different studies have attempted to elucidate possible mechanisms explaining the association between AD and osteoporosis. Shan and collaborators demonstrated the importance of osteocalcin (OCN) in the brain after administering it daily intraperitoneally in AD APP/PS1 transgenic mice. After 4 weeks, OCN produced improvements in behavior and cognitive dysfunctions in the mouse model. In addition, OCN improved Aβ loading in

the hippocampus and cortex, improved the function of the brain's neuronal network, and inhibited astrocyte proliferation in the brain. hippocampus of mice with AD (Shan et al., 2023). One of the mechanisms evaluated is the canonical WNT/Dkk1 pathway. WNT is not only essential in embryogenesis, but also during the maintenance and homeostasis of different organs and tissues until adulthood. One of its multiple signaling mechanisms is the canonical pathway involving β-catenin protein, which is degraded in the absence of WNT. When WNT binds to the cell surface receptor complex formed by Frizzled and LDL receptor-related protein (LRP) 5 and 6, β-catenin degradation is prevented, thus allowing its translocation to the nucleus to act as a transcription factor for different genes. The Dickkopf glycoprotein 1 (Dkk1) is an antagonist of WNT with high affinity for LRP 5/6, and acts by preventing the binding of WNT to the receptor complex, thus preventing the translocation of β-catenin to the nucleus (Kikuchi et al., 2022; Li et al., 2010). The canonical WNT pathway has a key role in bone anabolism, favoring osteoblastic differentiation and repressing osteoclastic activity (Kikuchi et al., 2022). Li et al., generated two transgenic mouse models to overexpress Dkk1 (Li et al., 2006). Despite phenotypic differences between the models, both induced a significant decrease in BMD to levels of osteopenia, with a reduction in the number of osteoblasts, in bone histological parameters, and in serum osteocalcin. That same year, Morvan et al. studied bone phenotype in mice knocked out at only one of the Dkk1 loci (Morvan et al., 2006). They found that these animals possess elevated markers of bone formation and an increase in bone mass for both male and female mice. On the other hand, using MC3T3E1 preosteoblastic cells, they found a decrease in the activity of bone alkaline phosphatase activity and mineral deposition in response to Dkk1 in the culture medium. Thus, serum Dkk1 could be important in the regulation of bone anabolism. This point was demonstrated by Butler et al. who studied serum concentration of Dkk1 in patients with decreased BMD, finding a negative correlation between the two (Butler et al., 2011). Dkk1 is not only important in the anabolic regulation of bone tissue, but its increased expression in AD brains has also been shown (Rena et al., 2019). In 2012, Purro et al. studied the relationship between the expression of Dkk1 and the loss of neurons in cultures of neurons obtained from the hippocampus of rats and in sections of the hippocampus of mice. They found that in brain slices there was an increase in Dkk1 mRNA levels and loss of neuronal synapses when exposed to β amyloid peptide. Interestingly, Dkk1 silencing by antibodies neuronal loss was prevented. It has also been suggested that the addition of the amyloid β peptide induces Dkk1, triggering signals for expression of genes linked to AD pathogenesis (Killick et al., 2014). In culture, they demonstrated that Dkk1 decreased synaptic terminals without affecting the viability of neurons (Purro et al., 2012). Furthermore, in the brain, inhibition

of the WNT pathway induces hyperphosphorylation of the intracellular protein TAU by increasing the activity of the enzyme glycogen synthase kinase 3β (GSK3β), provoking intracellular tangles and destabilization of actin microtubules which can lead to neuronal death and AD (Frame et al., 2020). Nonetheless, infusion of Dkk1 into the CA1 region of the hippocampus produced neuronal death of astrocytes in hippocampus and cholinergic neurons in the nucleus basalis magnocellularis. This effect was prevented by administering lithium chloride which inhibits GSK3β (Scali et al., 2006). In 2017, Zhang et al. studied the protective effect of the drug EGb-761 on apoptosis and proliferation of PC-12 cells when exposed to fluoride. They found that the antiproliferative capacity of fluoride was due to increased expression of Dkk1, activation of GSK3 β and decrease of β catenin, effects that were prevented when incubated with EGb761 (Zhang et al., 2017). Thus, WNT-Dkk1 and β-catenin are not only linked to bone homeostasis (regulating osteoblastic and osteoclastic activity), but they are also involved in maintenance, synaptic function and neuronal plasticity during aging, making them potential therapeutic targets for both AD and osteoporosis (Frame et al., 2020; Guo et al., 2016; Jia et al., 2019; Xingzhi et al., 2016).

Oxidative stress can induce deleterious age-related effects on bone metabolism, and has been causally related to postmenopausal osteoporosis. In addition, estrogen deficiency decreases protective mechanisms of bone (and other tissues) against oxidative stress (Bonaccorsi et al., 2018). In postmenopausal women, Akpolat demonstrated an inverse association between BMD and serum levels of thiobarbituric acid reactive substances (TBARS), nitric oxide and folate, showing that all three are risk factors for developing osteoporosis (Akoplat et al., 2013; Manolagas 2010). A recent meta-analysis reported changes in some (but not all) systemic oxidative stress markers in postmenopausal osteoporotic women (Zhou et al., 2016). Postmenopausal women have a higher incidence of AD compared to men of the same age; in addition, women with Alzheimer's have a lower level of estrogen, which demonstrates the neuroprotective effect of estrogen (Jamshed et al., 2014). Recently, Liao and collaborators demonstrated through a cohort study that early menopause turns out to be a risk factor for dementia and Alzheimer's disease (Liao et al., 2023).

Reactive oxygen substances (ROS) have been shown to promote the induction of Forkhead boxO (FoxO) transcription factors in preosteoblastic cells. In the presence of ROS, FoxO is activated by binding to β-catenin in order to favor the expression of genes associated with counteracting the toxic effects of ROS on cells, such as superoxide dismutase, catalase and Gadd45. However, the binding of FoxO to β-catenin makes this protein unavailable as an osteoblastic transcription factor, potentially decreasing osteoblastic bone formation (Amouzougan et al., 2017; Manolagas, 2010). On the other

hand, Lin et al. demonstrated that ROS promotes the differentiation of mesenchymal cells towards the adipogenic lineage instead of the osteogenic lineage, and this could be mediated by decreased activity of SIRT1, a protein involved in cell aging. Interestingly, when a SIRT1 agonist is applied under conditions of oxidative stress, the adipogenesis/osteogenesis imbalance is reversed (Lin et al., 2018). From the point of view of bone catabolism, it has been observed that ROS promotes the expression of RANKL; in addition, certain ROS (such as H_2O_2) can act as second messengers for various signaling pathways that regulate osteoclastogenesis, such as NFκB, MAPK and intracellular Ca^{2+} (Callaway and Jiang, 2015; Manolagas, 2010). In turn, binding of RANKL to its receptor RANK promotes the synthesis of intracellular ROS in osteoclast precursors, activating key genes in osteoclastic differentiation (Lee et al. 2021). AD and other neurodegenerative diseases can also be caused by oxidative stress: excess ROS affect nearby cells by inducing different intracellular events such as mitochondrial damage, alterations in mitochondrial DNA, changes in mineral homeostasis, loss of antioxidant defense systems that can induce alterations in synaptic activity and in the production and release of neurotransmitters. Thus, excess ROS can alter proteins, lipids, mitochondrial dynamics, Ca homeostasis, energy homeostasis, receptor recycling and cell architecture, among others (Mecocci et al., 2018; Sun et al., 2020; Tönnies and Trushina, 2017; Zhao, 2019). Paraoxonases are a family of enzymes produced by the liver that circulate in the bloodstream bound to HDL (High Density Lipoproteins). These enzymes have several functions, all of which are aimed at constituting an anti-atherogenic system, preventing the oxidation of lipids and LDL (Low Density Lipoproteins), and favoring the reverse transport of cholesterol. Recently, Bednarz-Misa et al. studied the levels of Paraoxonase-1 (PON-1) and lipid peroxidation in serum samples from more than 130 patients with dementia (AD, Vascular Dementia and Mixed Dementia). They found an increase in the levels of oxidized lipids and a decrease in the activity of serum PON-1 for all patients (regardless of dementia type). In addition, the levels of both markers correlated with the severity of brain atrophy, as assessed by neuroimaging (Bednarz-Misa et al., 2020).

Although aging strongly influences tissue physiology, young animals are often used to study pathologies that are associated with old age. This is probably one of the main reasons why several preclinical studies have failed to reproduce the events and/or effects of treatments on such diseases (Sun et al., 2020). Recently, in our laboratory we have studied bone metabolism and architecture in a group of 30-month-old rats with impaired memory, comparing it with rats of the same age with a preserved memory state. We found that bone marrow MSCs obtained from the aged rats with impaired memory had a decreased osteogenic capacity, a greater adipogenic potential and an increased capacity

to induce osteoclastogenesis, when compared to aged rats with preserved memory. When we evaluated bone microarchitecture, we found an increase in TRAP activity (osteoclastic activity marker) in long bones and a decrease in trabecular bone area and osteocyte density, together with an increase in marrow adiposity, in rats with non-preserved memory. Interestingly, we also found in the aged rats with impaired memory an increase in both serum TBARS and fatty acid conjugated dienes, indicating greater systemic oxidative stress that could be responsible for both bone alterations and memory impairment (Torres et al. 2021).

There is increasing evidence linking chronic inflammatory conditions such as osteoarthritis and osteoporosis as contributors for the development of AD (although the precise mechanisms remain unclear), and proinflammatory blood cells or components of bacterial structures such as lipopolysaccharides (LPS) may be involved in the activation of microglia leading to morphological and functional changes that can trigger a process of cognitive decline (Culibrk and Hahn, 2020; Wu and Nakanishi, 2015). Recently, Yebo et al inoculated mice with systemic LPS isolated from the bacterium Porphyromonas gingivalis. They found that after 3 weeks the levels of IL-6 and IL-17 increased, observing bone loss in the tibia and memory decline (Yebo et al., 2020).

Amyloid β-peptide (Aβ), derived from the degradation of the amyloid peptide precursor protein, is the main constituent of amyloid plaques and can be found in both spinal fluid and plasma (Fei et al; 2011; Koyama et al., 2012; Nakamura et al., 2018; Song et al., 2011), thus allowing it to reach bone tissue. For this reason, several research groups have studied the effects of Aβ on bone cells and on skeletal metabolism. Both Aβ and its precursor peptide can also be generated in other tissues, as demonstrated by McLeod et al., who found that preosteoblastic cells in vitro and in vivo could produce APP, express γ-secretase and release Aβ (McLeod et al., 2009)**.** Later, and despite their not evaluating its correlation with the cognitive state of patients, Li et al. demonstrated Aβ expression and localization in the osteocyte membrane and extracellular matrix, and amyloid precursor protein on the surface of osteocytes, in osteoporotic bones from both humans and ovariectomized rats, with a negative correlation between Aβ levels and BMD in different patients. In addition, through in vitro tests, they demonstrated that the administration of Aβ to the culture medium promotes the differentiation and activity of osteoclasts (Li et al., 2014). In a subsequent study, they demonstrated through in vitro assays that Aβ promotes osteoclastic activity through an increase in NF-κβ after RANKL binding to RANK, Iκβ-α degradation and phosphorylation of ERK, all key mechanisms in osteoclatic differentiation (Li et al., 2016). Aβ may also induce effects on pre-osteoblastic cells, especially on bone marrow MSCs, although the mechanisms involved are not yet

clear. Yang et al. studied the effect of Aβ on autophagy in rat bone marrow MSCs in culture. They found that exposure of the cells to Aβ, induced an inhibition of cell proliferation with increased autophagy through AKT phosphorylation and decreased mTOR (Yang et al., 2019). On the other hand, Lin et al., using a transgenic mouse model for AD, demonstrated that endogenously produced Aβ suppresses the osteogenic potential of bone marrow MSCs by inhibiting mTOR-dependent autophagy (Lin et al., 2021). Pan and collaborators demonstrated that APP promotes the survival of osteoblasts and bone formation after using App mice (APP-/-) which presented a reduction in trabecular and cortical bone mass through a decrease in bone formation but without changes in resorption. The lack of APP on osteoblasts appears to increase reactive oxygen species in the cells' mitochondria and trigger apoptosis (Pan et al., 2018).

In recent studies, it was shown that RANK/RANKL/OPG proteins are expressed in several types of brain cells such as microglia and oligodendrocyte precursor cells. Although the role of these proteins in the context of the brain is not clear, they could be expressed in the early phase of inflammation by microglia, with RANK/RANKL having a moderating role on TLRs (Toll-like receptor), decreasing neuroinflammation. Additionally, OPG could have an effect on modulating RANKL activity and blocking proapoptotic signals (Glasnovic et al., 2020).

Oligodendrocytes are the myelinating glial cells of the central nervous system (CNS), allowing neurons to have rapid and correct electrical transmission, in addition to providing trophic and metabolic support. The formation of myelin around axons is carried out by oligodendrocyte precursor cells, while its maintenance is the responsibility of mature oligodendrocytes. Different factors such as aging, ROS, neuroinflammation, Aβ, neurofibrillary tangles, promote the degradation or breakdown of myelin, producing neurodegenerative disorders and Alzheimer's disease. Recently, Deep and colleagues demonstrated that age-dependent structural defects in myelin directly and indirectly promote Aβ plaque formation. This dysfunction increases the cleavage of cortical amyloid precursor protein due to the accumulation of the Aβ-producing machinery (Deep et. al., 2023). Because oligodendrocytes could be the cells most sensitive to the physiological changes produced during Alzheimer's disease, oligodendrocyte progenitor cells have become an early therapeutic target in preventing the progression of neurodegenerative diseases (Cai and Xiao, 2015; Han et al., 2022; Maitre et al., 2023). Although its role is not clearly known, OCN was shown to be crucial during brain development and neural cognitive functions. Quian and his collaborators demonstrated, by genetically deleting OCN in mice, that OCN turns out to be a key regulatory mechanism in modulating oligodendrocyte differentiation and myelination, regulating myelin homeostasis in the CNS

(Quian et. al., 2021; Zhang et. al., 2022). In a very interesting work, Elbaz and collaborators found in an in-vivo model that the ablation of the Osterix gene (key gene in the differentiation of mesenchymal cells to osteoblasts) in oligodendrocytes produces changes in the composition of the extracellular matrix and nodes of Ranvier. aberrant. Furthermore, Osterix mutants in adult oligodendrocyte progenitor cells fail to remyelinate normally and maintain myelin (Elbaz et al., 2024).

An interesting system turns out to be the TREM2/TYROBP system (triggering receptor expressed on myeloid cells 2/TYRO protein tyrosine kinase-binding protein). TYROBP is a transmembrane adapter protein that associates with the cell surface receptor TREM2. TREM2 expression is important in microglia cells in the CNS, and after binding to ligand activates a series of intracellular signaling that evokes the immune system. Its function is related to the activation of microglia and to binding, phagocytosis and clearence of Aβ. Mice lacking TREM2 have been shown to possess phagocytic-deficient microglia with impaired lipid metabolism and increased accumulation of Aβ. Both TREM2 and APOE are recognized genetic risk factors for AD. Nguyen and colleagues demonstrated that TREM2 and APOE risk variants are associated with reduced amyloid-responsive microglia (Jorfi et al., 2013; Lee et al., 2021; Nguyen et al., 2020; Sobue et al., 2023). Mutation in one of these genes (TREM2 or TYROBP) induces a condition called polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (PLOSL) which is characterized by cystic, osteoporotic bone lesions and loss of white matter in the brain, leading to spontaneous bone fractures and profound presenile dementia (Paloneva et al., 2023). TREM2/TYROBP are involved in dendritic cell maturation, but also in osteoclast formation (Paloneva et al., 2023; Tomasello and Vivier, 2005)**.** Osteoclasts and microglia are both cells of the macrophage lineage, although located in different tissues with distinct functions. Despite their divergence during development, they share signaling pathways such as TREM2/TYROBP, which is involved in the organization and dynamics of microtubules (Lee et al., 2021). The deficiency of any of the components of the TREM2/TYROBP duo induces accelerated formation of osteoclasts, producing greater bone resorption and osteoporosis in vivo (Otero et al., 2012), and are considered candidate genes for osteoporosis (Xia et al., 2017). TREM2 and TYROBP recruit kinase proteins that, downstream, promote genes for osteoclast activation. On the other hand, in humans it has been shown that loss of function variants of TREM2 or TYROBP cause defective differentiation of osteoclasts with reduced bone resorption in vitro (Lee et al., 2021). In an interesting study, Essex et al. used mice hemizygous for the TREM2 R47H variant ($TREM2^{R47H/+}$) to investigate the role of TREM2 in bone and skeletal muscle loss. They found that this TREM2 variant can cause bone loss and brittleness in female mice

but not in males, probably due to changes in intracellular osteoclast signaling pathways (Essex et al., 2022). On the other hand, missense mutations of TYROBP have been found in patients with AD (Haure-Mirande et al., 2017). TYROBP is key in the activity of microglia and it has been shown that constitutive inactivation of this adapter protein in mice reacapitulates the complement network that is formed in the LOAD brain in humans (Haure-Mirande et al., 2019; Hemmatian et al., 2017). TREM2 has also been found to participate in inflammatory processes, and to interact with other molecules such as APOE (Qin et al., 2021).

3.- Future considerations:

In recent centuries, life expectancy has greatly increased thanks to gerontology, better water and food quality and advances in medicine (Macia et al., 2019; Partridge et al., 2018). Accompanying this increase in life expectancy, fertility rate has been decreasing globally over the last 2 decades (GBD, 2020). Both phenomena lead to continued population aging, increasing the number of cases of osteoporosis and Alzheimer's disease and, therefore, patients with both conditions simultaneously, increasing treatment and medical care costs. In this context, this work turns out to be relevant to provide information to researchers to have a better understanding of both pathologies. Many of the works mentioned here are clear examples in which it is necessary not to see diseases as isolated pathologies and that they may have mechanisms that share or trigger other pathologies, aggravating the patient's health. On the other hand, although there is tangible evidence of the accumulation of misfolded proteins in the brains of people with Alzheimer's, there is currently doubt as to whether this is the main cause of the disease and other diseases could be related and produce both cognitive and bone alterations, in addition to the previously described mechanisms that associate Dementia and AD with osteoporosis (figure 1). It should be noted that the glucose metabolism and the insulin signaling pathway in a brain affected with the pathology are altered, which has suggested that AD is a metabolic disease (Frolich et al., 1998; Hoyer, 2004). Although the exact mechanisms are still unclear, Diabetes mellitus (DM) turns out to be a risk factor for Dementia and Alzheimer's Disease. One of the most studied mechanisms turns out to be given by non-enzymatic advanced glycation products (AGEs), which are a family of molecules that are generated after non-enzymatically controlled glycation of proteins. The AGEs produced on βA make it more aggregable, while on the Tau protein it favors the production of neurofibrillary tangles. Furthermore, the binding of AGEs to their receptor (RAGE) produces oxidative stress, production of proinflammatory cytokines and mitochondrial dysfunction. Another important mechanism turns out to be insulin resistance which can

lead to the phosphorylation of the Tau protein, generating neurofibrillary tangles. Other mechanisms involved turn out to be hypertension, and micro and macro vascular problems (Agrawal and Agrawal, 2022; Akar and Kacar, 2023; Chen et al., 2021; Mooldijk et al., 2022; Yoon et al., 2023). Not only does the insulin resistance produced in Type 2 Diabetes mellitus increase the risk of Dementia and Alzheimer's Disease, Metabolic Syndrome (which occurs due to a combination of insulin resistance, dyslipidemia, obesity and hypertension) has been shown to be a risk factor for dementia in several epidemiological studies (Ezkurdia et al., 2023; Pillai et al, 2013). DM also causes bone involvement, which is known as Diabetic Osteopathy. Chronic hyperglycemia produces AGEs in collagen, the main protein of the bone ECM, producing an increase in the risk of fracture due to a decrease in bone mineral density, changes in bone microarchitecture, a decrease in the rate of bone remodeling with accumulation of damage, increase in spinal adiposity, among other described mechanisms (McCarthy et al., 2001; McCarthy et al., 2013; Romero Diaz, et al., 2021; Wu et al., 2022). It has been described that Metabolic Syndrome, which is an increasingly frequent heterogeneous disorder, could cause a decrease in bone density and an increase in osteoporotic fractures (Felice et al., 2017; Wanionok and McCarthy 2023). Dyslipidemia, which is the imbalance of lipids in the body caused by environmental and/or genetic factors and with a growing prevalence worldwide (Almeida et al., 203), has also been shown to be related to cognitive decline in Alzheimer's disease and to be a risk factor of Osteoporosis (Kan et al., 2021; Wang et al., 2022).

Understanding pathologies as non-isolated entities and that can increase the risk of other pathologies will allow health teams to establish better preventive care and treatments.

In lines with potential therapeutic approaches, in our lab Wanionok and collaborators reported that prolonged treatment with metformin has negative effects on the skeleton in Wistar rats (Wanionok et al., 2024). Interestingly, metformin is currently in phase 3 trials as a treatment for Alzheimer's disease, owing to its role in improving glucose metabolism in the central nervous system and ameliorating cognitive impairment (Buccellato et al., 2023).

Another prospective intervention is eliminating different types of Aβ aggregates, particularly soluble ones, which exert varying degrees of neurotoxicity. An interesting approach involves developing monoclonal antibodies that target specific epitopes or aggregation states of Aβ (Neatu et. al. 2023; Perneczky et. al., 2023; Söderberg et. al., 2023). Recently, two of them, Aducanumab and Lecanemab, gained full and accelerated approval from the US Food and Drug Administration for use in the treatment of AD, while another is currently in phase three trials (Høilund-Carlsen et. al., 2024). However, considering that Aβ can be found not only in the CNS but also in bones and other organs

(Wojtunik-Kulesza et al., 2023), it is important to conduct studies to determine whether this immunotherapy affects bone metabolism, osteoporosis and risk of fractures.

4.- Conclusion:

Several epidemiological studies have shown an association between Alzheimer's disease and osteoporosis, which has motivated different researchers to search for mechanisms that are involved in both pathologies. Some mechanisms are classical for the tissues involved, for example WNT pathway in bone or APP and Aβ in brain, involved in the pathogenesis of Osteoporosis and AD, respectively. Systemic mechanisms such as oxidative or inflammatory states, can trigger both conditions; while other novel mechanisms, such as the TREM2/TYROBP pathway, are still not entirely clear as to how they intervene in the pathogenesis and in the association of both osteoporosis and AD.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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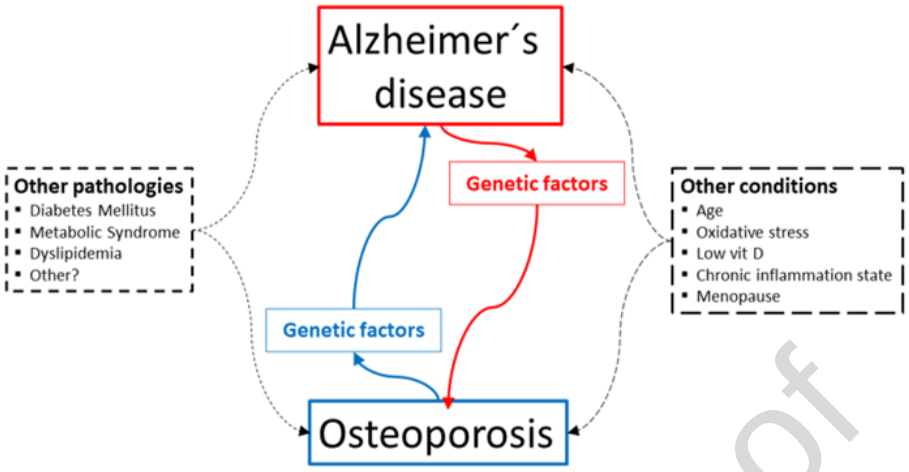
Caption of figure

Figure 1: relationship between AD and osteoporosis and different causes that turn out to be risk factors for both pathologies.

Figure 1



Declaration of Competing Interest

none

Highligths:

- Alzheimer's disease and osteoporosis are two diseases that occur mainly in older people.
- Due to population aging and increased life expectancy, the incidence of both pathologies is increasing.
- An increase in osteoporotic patients in people with AD and an increase in the incidence of AD in people with osteoporosis has been demonstrated, demonstrating a reciprocal relationship.
- There are genetic and molecular mechanisms that are linked to both pathologies.
- Understanding the mechanisms involved can serve to improve prevention protocols and treatments for both pathologies.