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Molecular and cellular mechanisms linking air pollution and bone damage

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Abstract

Air pollution is the second most important risk factor associated with noncommunicable diseases after smoking. The effects of pollution on health are commonly attributable to particulate matter (PM), a complex mixture of particles suspended in the air. PM can penetrate the lower respiratory tract and has harmful direct and indirect effects on different organs and tissues. Direct effects are caused by the ability of PM components to cross the respiratory membrane and enter the bloodstream; indirect effects are systemic consequences of the local airway response. Recent work suggests that PM is an independent risk factor for low bone mineral density and osteoporosis-related fractures. Osteoporosis is a common age-related disease closely linked to bone fractures, with severe clinical consequences affecting quality of life, morbidity, and mortality. In this review, we discuss potential mechanisms behind the association between outdoor air pollution, especially PM, and bone damage. The discussion features four main mechanisms: 1) several different atmospheric pollutants can induce low-grade systemic inflammation, which affects bone metabolism through a specific effect of cytokines such as TNFα, IL-1β, IL-6, and IL-17 on osteoblast and osteoclast differentiation and function; 2) some pollutants, particularly certain gas and metal compounds, can cause oxidative damage in the airway and bone cells; 3) different groups of pollutants can act as endocrine disruptors when binding to the receptors in bone cells, changing their functioning; and 4) air pollution can directly and indirectly cause vitamin D

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deficiency. Characterizing these mechanisms will better define the physiopathology of bone damage, and recognizing air pollution as a modifiable risk factor for osteoporosis will inform environmental policies. Such knowledge will also guide the prevention of fractures due to fragility and help reduce health-related costs.

Keywords

Air pollution; mechanisms; particulate matter; bone damage; fractures; osteoporosis

1. Introduction

1.1. Outdoor air pollution

Air pollution is a global health problem. According to data from the World Health Organization (WHO), 9 out of 10 people worldwide breathe polluted air (World Health Organization, 2018a). Further, outdoor air pollution was estimated to cause 4.2 million premature deaths worldwide in 2016, mostly in low- and middle-income countries. Of all premature deaths related to outdoor air pollution, 58% were due to cardiovascular disease, 18% to respiratory disease, and 6% to lung cancer (World Health Organization 2018b). Hence, air pollution has become the second most important risk factor for noncommunicable diseases worldwide, behind tobacco smoking (Prüss-Ustün, 2019). Growing evidence associates air pollution with damage to most body systems (Schraufnagel, 2019). This review focuses on potential mechanisms underlying the adverse effects of outdoor air pollution on bone health.

Particulate matter (PM) is a major contributor to the effects of pollution on health (World Health Organization, 2018b). PM is a complex mixture of solid and liquid particles suspended in the air. Common chemical components of PM include sulfates, nitrates, ammonium, other inorganic ions (sodium, potassium, calcium, magnesium, and chloride), organic and elemental carbon, crustal material, metals (including cadmium, copper, nickel, vanadium, and zinc), polycyclic aromatic hydrocarbons (PAHs), water, and biological components such as allergens and microbial compounds (World Health Organization, 2013). The most harmful effects of PM are related to small particle size, which has a greater ability to penetrate the lower respiratory tract and enter the bloodstream (Kim, 2015). PM is classified into PM_{10} (coarse) if its aerodynamic diameter is smaller than 10 μm; $PM_{2.5}$ (fine) if it is smaller than 2.5 μm; and $PM_{0.1}$ (ultrafine) if it is smaller than 0.1 μm (Kim, 2015). In 2016, 95% of the world population lived in areas where the environmental levels of $PM_{2.5}$ were higher than the WHO air quality guidelines (Shaddick, 2018).

1.2. Osteoporosis and bone fragility

Bone strength is determined by its composition and structure. Bone is made of a highly organized protein matrix, mainly type I collagen, which provides sites for nucleation of hydroxyapatite crystals. The relative amounts of minerals, water, and organic material, as well as the quality and arrangement of these components, impart the necessary mechanical properties for bone to absorb the energy imposed during loading without structural failure (Currey, 2003). The purpose of bone modeling and remodeling throughout life is to adapt

bone composition and structure to prevailing loads (Seeman & Delmas, 2006). Failure of bone adaptation results in bone fragility, a key cause of fractures and trauma (Cooper, 1993).

Bone mass increases exponentially during puberty and achieves its peak during young adulthood (around age 30); it declines nonlinearly after that, particularly during menopause (Cooper et al., 2008). The peak bone mass, influenced by lifestyle, genetic, and environmental factors, is an important determinant of the risk of osteoporosis during lifetime and bone fractures during late adulthood (Weaver et al., 2016) and it probably plays a key role in bone damage induced by air pollution (Figure 1).

The loss of bone mass can lead to osteoporosis, the most common chronic metabolic bone disease (Sözen, 2017). This bone damage is asymptomatic, so it is often called a “silent disease” (National Institutes of Health, 2018). However, osteoporotic fractures, which develop as a consequence of loss of bone strength, are a significant public health problem (Cooper, 1993) because they have devastating results in terms of decreased autonomy, morbidity, mortality, and health costs (Fonseca, 2014).

In the United States, more than 10.2 million people have osteoporosis, and 43.4 million have low bone density, called osteopenia (National Institutes of Health, 2018; Wright, 2014). By 2025, the annual incidence of osteoporosis-related fractures in the United States is estimated to be more than 3 million cases, with approximately $25.3 billion in treatment costs (Burge, 2007). The consequences of osteoporotic fractures are devastating: one year after a hip fracture, an estimated 40% of patients cannot walk independently, and the five-year mortality rate increases by 20% in patients who experience any bone fracture (Cooper, 1997).

Osteoporosis is diagnosed by measuring bone mineral density (BMD) with dual-energy X-ray absorptiometry (DXA). According to the WHO guidelines, osteoporosis is diagnosed when the femoral neck BMD is 2.5 or more standard deviations (SD) below the mean of the young and healthy population (T-score). Osteopenia is defined as a BMD value within 1 and 1.5 SD below the T-score (World Health Organization, 1994).

Although BMD measurements by DXA have demonstrated their usefulness in determining fracture risk and are the standard for the diagnosis of osteoporosis (Curtis et al., 2017), it is well known that some older individuals may have higher fracture risk without having a T-score below −2.5 SD (Samelson et al., 2019), which could explained because bone strength is determined by both bone mass and bone quality (Link & Heilmeier, 2016). Bone quality is a complex concept that involves aspects such as collagen properties, osteocyte density, and trabecular and cortical microarchitecture (Fonseca et al., 2014). New techniques may allow us to better assess bone quality (e.g., trabecular and cortical microarchitecture, which cannot be evaluated accurately by DXA). Other might include quantitative ultrasound and high-resolution peripheral quantitative computed tomography, bone biopsy, and quantitative computerized tomography (Link & Heilmeier, 2016). Further research on the effect of air pollution by using these technologies will be highly relevant in the field.

2. Air pollution and bone damage

In the 1980s, the first studies were published to indicate a higher incidence of hip fractures in urban areas compared with rural areas [in Norway (Falch, 1985; V. Finsen & Benum, 1987) and Sweden (Jarnlo, 1989; Larsson, 1989; Mannius, 1987; Sernbo, 1988)]. Subsequent studies corroborated this association in Norway and Sweden (Falch, 1993; Finsen, 2004; Jónsson, 1992; Kaastad, 1998) and in other countries such as the United States (Madhok, 1993; Melton, 1999), Australia (Cooley & Jones, 2002; Sanders, 2002) and Switzerland (Chevalley, 2002). This association between urban areas and hip fractures is age- and sex-specific; therefore, demographic differences were discarded from being responsible for these findings. Some researchers argued that differences in lifestyle (Jónsson, 1993) and body composition (Elmståhl, 1993) could explain the association between urban areas and hip fractures, but the results were inconclusive. Other studies found the same association regarding osteoporosis-related fractures in other areas of the body, such as the spine and distal forearm (Cooley & Jones, 2002; Melton, 1999; Omsland, 2011; Sanders, 2002; Søgaard, 2007). Two studies showed a higher incidence of fractures in rural Turkey (Dilsen, 1993) and Australia (Peach & Bath, 1999), and another study did not find differences in the incidence rates in Finland (Lüthje, 1995). However, later reports suggested these results were due to the higher proportion of bone fractures caused by high energy trauma in rural areas in the case of the Turkish study, the small sample size in the Australian study, and recently adopted urban lifestyles (many old people had spent most of their youth in rural areas) in the Finnish study (Brennan, 2010; Cooley & Jones, 2002). Even though the studies did not share a common definition of urban and rural areas, there was a clear tendency toward a higher incidence of fractures in urban areas. Several causal factors were examined, but the possibility that an environmental factor had a significant role in this association was not considered.

Moreover, several studies reported that bone mineral content (BMC) (Gärdsell, 1991; Specker, 2004) and BMD (Filip & Zagórski, 2001; Meyer, 2004; Omsland, 2011; Ringsberg, 2001; Rosengren, 2010, 2012; Specker, 2004; Sundberg, 1997) were lower in urban populations of countries such as Norway, Sweden, Poland, and the United States. Although this association is inconsistent with the mixed results from low- and middle-income countries (Gu, 2007; Li, 2005; Pongchaiyakul, 2006; Pongchaiyakul, 2005a; Pongchaiyakul, 2005b), a meta-analysis by Matsuzaki et al. (2015) suggested that this difference might be due to nutritional deficiencies in rural areas of developing countries. These findings indicated that reduction in bone quality was the main cause of the higher incidence of osteoporotic fractures in urban areas.

Later, Alvaer et al. (2007) observed a negative association between indicators of air pollution ($PM_{2.5}$ and PM_{10}) and total body BMD in older men. In another study, the same authors reported an association between $PM_{2.5}$ and lower distal forearm BMD, with a higher prevalence of self-reported forearm fractures. However, the association was found in male smokers only (Alver, 2010). These studies were significant because they paved the way to considering air pollution as a risk factor for bone fragility and highlighted the need for additional research.

Considering this background, our research group gathered evidence of the association between air pollution and bone damage (Prada, 2017). After analyzing 9.2 million Medicare beneficiaries, we found that older men (>65 years old) from areas with the highest levels of $PM_{2.5}$ had the highest rates of hospital admissions due to osteoporosis-related fractures, regardless of sex and other confounders. Also, during an 8-year follow-up of a cohort of 692 middle-aged men (mean age 47.5 years), we found that the levels of black carbon (BC), a PM component, were related to decreased BMD in several body parts over time, as well as a negative association between BC and parathyroid hormone (PTH) serum levels. These results were consistent with those previously published by Chang et al. (2015), which indicated a higher risk for osteoporosis in people exposed to higher levels of gaseous pollutants (CO and NO_2) in Taiwan, and by Chen et al. (2015), who found that residential proximity to a motorway was related to lower BMD in Mexican Americans. Later, Mazzucchelli et al. (2018) found an association between levels of some gaseous pollutants (SO_2, NO, and NO_2) and incidence of hip fracture in older women from a region in Southern Europe. Likewise, a recent study in India (Ranzani et al., 2020) reported an association between $PM_{2.5}$ levels and a lower BMC in the spine and hip in fully adjusted models.

Although no direct experimental evidence of the susceptibility of different bones to air pollution, Ranzani et al. (Ranzani et al., 2020) have suggested that trabecular bone is more affected than cortical bone. Further research about bone type susceptibility is warranted. On the other hand, although outdoor air pollution has been identified as an independent risk factor for osteoporosis and fractures due to bone fragility, little is known about the mechanisms underlying its association with bone damage. The chemical and physical heterogeneity of PM, which is made up of hundreds of different components, as well as the presence of other atmospheric pollutants not included in this classification (e.g., nitrogen oxides and volatile organic compounds), make it difficult to establish the molecular mechanisms involved in bone damage caused by air pollutants. In this review, we synthesize evidence of the role of different air pollutants in modifying bone homeostasis.

3. Physiopathology of osteoporosis

Bone remodeling depends on the joint action of osteoblasts, the bone-forming cells, and osteoclasts, the bone-resorbing cells. Although bones look inert, they are a highly dynamic organ; they are continuously reabsorbed and remodeled to adapt to mechanical use and repair microdamage (Florencio-Silva et al., 2015). Osteoporosis develops when the balance between bone formation and resorption shifts toward the latter (Kumar, 2014). Two cytokines produced by the osteoblasts and bone marrow stromal cells are essential for osteoclastogenesis: macrophage colony-stimulating factor (MCSF) and receptor activator for nuclear factor κ B ligand (RANKL) (Sipos, 2009). RANK, the receptor of RANKL, is expressed in osteoclast precursors and activates the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a transcription factor inducing the expression of genes stimulating osteoclast formation, fusion, differentiation, function, and survival (Takahashi, 2011). Unlike M-CSF expression, which is constitutive, RANKL expression is inducible and thus has a functional role in the changes in bone metabolism (Takahashi, 2011). Osteoprotegerin (OPG), also produced by osteoblasts and stromal cells, is a natural bait receptor of RANKL, antagonizing its effect. The imbalance between OPG and RANKL

production by osteoblasts and stromal cells is essential in the development of osteoporosis (Marie & Halbout, 2008). With increasing age, osteoblast replication and extracellular matrix synthesis decrease, as do the growth factors in the bone matrix, particularly insulin-like growth factor-1 (IGF-1) (Almeida & O'Brien, 2013; Kumar, 2014), which favors bone loss during aging.

Hormone factors also significantly influence the loss of bone mass. In postmenopausal women, decreased estrogen levels are associated with loss of cortical and trabecular bone (Kumar, 2014). Estrogen deficiency upregulates RANKL (Eghbali-Fatourechi, 2003), an effect mediated by the production of cytokines such as IL-1, IL-6, and TNF (Kumar, 2014). A decrease in estrogens also affects how the stimulation of osteoblast proliferation (Galea, 2013) and OPG production (Bord, 2003).

Furthermore, a sedentary lifestyle contributes to bone fragility. Osteoblasts and osteocytes work as mechanoreceptors by increasing connexin expression after application of mechanical stress, which triggers biochemical signals between both types of cells and increases extracellular matrix synthesis (Datta, 2008). Therefore, a sedentary lifestyle, which reduces osteoblast and osteocyte stimulation, is a significant risk factor in the development of osteopenia and osteoporosis (National Institutes of Health, 2018). To highlight, physical activity, particularly weight-bearing, contributes to bone health as it stimulates bone osteogenesis in osteoporotic patients (Benedetti et al., 2018).

4. Potential mechanisms of bone damage induced by air pollution

4.1. Air pollution promotes low-grade systemic inflammation

Substantial evidence demonstrates that exposure to air pollutants is associated with increased levels of proinflammatory mediators in the systemic circulation of both animals and humans (Araujo, 2010). Exposure to high PM concentrations significantly increases serum levels of monocytes, NK cells, and helper T cells (Pope, 2016), as well as proinflammatory cytokines such as TNFα, MCP-1, IL-8, MIP-1α, IL-6, IL-1β, and GM-CSF in in vitro and in vivo models (Alfaro-Moreno, 2009; Calderón-Garcidueñas, 2013; van Eeden, 2001). A recent high-resolution metabolomics (HRM) study (Liang, 2018) supports the hypothesis that systemic inflammation is an essential mediator of the health effects of air pollutants.

Inflammation induced by PM exposure is likely mediated in part by the response of alveolar macrophages (AM) and airway epithelial cells. Some PM components activate the AM and epithelial cells by signaling of toll-like receptors 2 and 4 (TLR2 and 4) and adaptor protein MyD88. This activation induces the expression of TNFα, IL-6, and IL-8 (Becker, 2005; Huang, 2003; Shoenfelt, 2009). $PM_{2.5}$ components, such as metal pollutants with oxidative activity, polycyclic aromatic hydrocarbons, and bacterial or mycoplasma lipoproteins, are proposed to stimulate TLR2 activation, while the presence of lipopolysaccharides (LPS) in PM_{10} may explain TLR4 activation (Becker, 2005; Shoenfelt, 2009).

Ghio et al. proposed another mechanism by which air pollution exposure induces a systemic inflammatory response: disruption of iron homeostasis by humic-like substances (HULIS), a

mixture of organic compounds in the particles of polluted air. HULIS are formed secondary to atmospheric oxidation of black carbon particles, which are $PM_{2.5}$ components produced as a consequence of fossil fuel and biomass burning (Ghio, 2018). These compounds have a high number of functional groups containing oxygen (e.g., carboxylic and phenolic groups) and promote the formation of stable complexes with metals, particularly iron (Erdogan, 2007). Iron sequestration by HULIS induces oxidative stress, the release of proinflammatory mediators (IL-6 and IL-8), and, finally, apoptosis of airway epithelial cells (Ghio & Cohen, 2005; Ghio, 2016; Ghio, 2015). Ghio et al. (2015) observed that exposure of immortalized human bronchial epithelial cells to wood smoke particles increased the secretion of IL-6 and IL-8, which was related to iron sequestration by the particles. This effect was diminished by preventing the loss of mitochondrial iron with administration of ferric ammonium citrate.

It is likely that additional mechanisms induce systemic inflammation due to particle exposure, and that they are complementary. For example, there is evidence that the aryl hydrocarbon receptor (AhR) signaling pathways have a significant role in particle-induced inflammation (Lawal, 2017). AhR is a key receptor to which several air pollutants bind and will be fully described in the section on endocrine disruptors.

Bone loss, particularly in older people, may be related to low-grade systemic inflammation (Ding, 2008). In a rat model of chronic systemic inflammation induced by LPS, inflammation is associated with systemic bone loss, characterized by low BMD (Smith, 2006). Altered bone remodeling caused by systemic inflammation is characterized by an increase in bone resorption and deficient osteogenesis due to the effect of the inflammatory mediators over osteoclast and osteoblast differentiation and activity (Briot, 2017).

T-cells have an essential role in regulating bone resorption and formation by the activity of specialized cell lines such as Th17 and Treg cells (Briot, 2017). Immunological factors promoting osteoclast activity (and inhibiting osteoblasts) include MCSF, TNFα, IL-1, IL-6, and IL-17 (Briot, 2017). Besides the cytokine-mediated effects, activated T lymphocytes express the membrane marker semaphorin-4D (Sema4D). The binding of Sema4D to the receptor plexin-B1 on osteoblasts inhibits their differentiation by suppressing IGF-1 signaling (Negishi-Koga, 2011).

Cytokines affect bones and are significantly increased by PM exposure. TNFα promotes osteoclastogenesis by stimulating the differentiation of monocytes and macrophages into preosteoclasts (Lam, 2000). Likewise, TNFα increases RANK expression in osteoclast precursors in vivo, as well as MCSF and RANKL in stromal cells and synovial fibroblasts (Kitaura, 2013). Although the RANKL-mediated effect has been the most studied, there is evidence that TNFα induces osteoclastogenesis and bone erosion by RANKL-independent mechanisms (O'Brien, 2016). Finally, as a consequence of the multiple effects of TNFα on bone metabolism, a mouse model of rheumatoid arthritis (RA) revealed that BMD was increased by systemic administration of anti-TNFα antibodies (Saidenberg-Kermanac'h, 2004).

Furthermore, IL-1β directly activates RANK signaling and induces RANKL expression, which promotes osteoclastogenesis and increases bone resorption (Lee, 2010). Pacifici et al.

(1991) conducted a study in premenopausal women who underwent oophorectomy and observed a sustained increase in IL-1β secretion by peripheral blood mononuclear cells, which was associated with a significant decrease in BMD. Systemic IL-1β plays a crucial role in bone loss in diseases such as RA because, even in cases with high levels of TNFα, the absence of IL-1β fully protects against systemic bone resorption (Polzer, 2010).

Although we have mentioned models of RA in animals, mainly to explain the effects of certain cytokines on bone health, it is interesting that RA is also associated with air pollution in humans (Sigaux et al., 2019). While murine models and clinical evidence have demonstrated that corticosteroid treatment in humans has a strong impact on bone health (Whittier & Saag, 2016), corticosteroids can cause additional injury in exposed individuals, including those with RA and other systemic inflammatory diseases.

Cytokines from the IL-6 family are reported to have dual antagonist roles: they sustain bone formation, but can also cause bone loss in several osteolytic pathologies (Blanchard, 2009). The mechanisms involved in osteoclastogenesis induced by IL-6, similar to TNFα, seem to be RANKL- dependent and independent (O'Brien, 2016). Likewise, recent evidence suggests that the variation in IL-6 levels in older adults may help to predict BMD loss (Ding, 2008). Moreover, Wells et al. (2017) found that continuous exposure to an organic dust extract (ODE) induces an increase in IL-6 concentration, with an adverse effect on bone homeostasis mediated by osteoclasts. The same authors found that ODE increases helper T cells with a marked polarization toward proinflammatory Th1 and Th17 phenotypes, which could be the source of systemic IL-6 (Poole, 2012). IL-17 is a cytokine mainly secreted by Th17 lymphocytes and has an important role in bone metabolism because it promotes the release of RANKL by osteoblasts and osteocytes. IL-17 also boosts the osteoclastogenic activity by regulating RANK expression, which increases the sensitivity to RANKL (Adamopoulos, 2010). Finally, parathyroid hormone (PTH) is reported to favor the differentiation of virgin T lymphocytes into Th17 cells. Additionally, this hormone increases the serum levels of IL-17 in both mice and humans (Li, 2015; Pacifici, 2016). Surprisingly, there is evidence that IL-17 increases the sensibility of osteocytes and osteoblasts to PTH (Li, 2019).

In 2,264 children aged 10 years, Liu et al. (Liu et al., 2015) found a positive and significant association between exposure to air pollutants (NO_2, $PM_{2.5–10}$ and PM_{10}) and the levels of two biomarkers of bone turnover: serum osteocalcin (a bone formation marker that reflects osteoblastic activity) and C-terminal telopeptide of type I collagen (CTx, a bone resorption marker). These results are highly relevant because early alterations in bone homeostasis can potentially impair bone mass trajectories, an important contributor to bone resistance in adulthood (Cooper et al., 2008).

Although the association between the local response of the respiratory system, immunological activity, and bone metabolism has only begun to be studied, there is key evidence showing the mechanisms involved in bone damage due to air pollution. This section is an initial approach to understanding the role of the lung-periphery-bone axis in bone damage after exposure to environmental pollutants.

Finally, and in relation to potential effect of household air pollution, Saha et al. has reported that chronic exposure to biomass smoke increased membrane-bound and soluble RANKL and circulating osteoclast precursors but decreased OPG. These findings suggested an increased risk of bone resorption and consequent osteoporosis from household air pollution in women of childbearing age (Saha et al., 2016). More studies are needed to determine the contribution of indoors air pollution on bone mineral density and fracture risk.

4.2. Air pollutants and oxidative stress

Oxidative stress is characterized by the increase in free radicals [reactive oxygen species (ROS) and reactive nitrogen species (RNS)]. The most-studied pollutants concerning intracellular formation of free radicals are ozone (O_3) (Yang & Omaye, 2009), nitrogen oxides (NO and NO_2), and heavy metals (Solleiro-Villavicencio & Rivas-Arancibia, 2018). Reactive species and their damage to cells can modulate the inflammatory response.

These phenomena occur because oxygen reactive species modify signaling pathways; they can oxidize or reduce redox-sensitive amino acid residues (Corcoran & Cotter, 2013). Oxidative modifications change the structure or function of some signaling proteins and keep them active (phosphorylated) (Corcoran & Cotter, 2013), which in turn dysregulates the signaling pathways. Consequently, signal transductions stay active and lead to sustained expression of certain proteins that promote cell proliferation, apoptosis, and inflammatory responses (Solleiro-Villavicencio & Rivas-Arancibia, 2018). Furthermore, ROS can modify the patterns of gene expression because they act on certain transcription factors such as nuclear factor erythroid 2–related factor 2 (Nrf2), activator protein-1 (AP1), NF-kβ, HIF-1α, p53, and FOXO. Many of these transcription factors have oxidation-sensitive cysteine residues in their DNA binding sites. In a state of oxidative stress, reactive species overstimulate transcription factors and, consequently, create a deficit of antioxidant defenses and increase the formation of inflammatory and redox mediators (Farooqui, 2014). Ozone also activates transcription factor NF-κβ, which increases the expression of several proinflammatory cytokines (Rahman & MacNee, 1998).

In addition to the effects of oxidative stress on bone homeostasis mediated by the immune response, several pollutants can directly induce oxidative stress in bone tissues due to their capacity to cross cell membranes. In fact, cumulative oxidative damage may participate in several mechanisms of bone aging (Almeida & O'Brien, 2013). Evidence indicates that mesenchymal stem cells, which differentiate into osteoblasts, chondrocytes, and adipocytes, lose functionality with age due to cumulative oxidative stress (Stolzing & Scutt, 2006). Additionally, activating the peroxisome proliferator-activated receptor gamma (PPARγ) by ligands such as oxidized polyunsaturated fatty acids induces β-catenin degradation, inhibiting Wnt/β-catenin signaling, which is indispensable for osteoblastogenesis (Almeida, 2009; Sharma, 2004).

4.3. Bone damage due to environmental endocrine disruptors

Exogenous chemical substances called endocrine-disrupting chemicals (EDCs) affect hormone activity (Zoeller, 2012). Some EDCs are in polluted air as volatile (VOCs) or semi-volatile (SVOCs) organic compounds in gaseous form or are bound to particles (Darbre,

2018). Fossil fuel and residue burning, industrial activities, volatilization of synthetic chemicals, and other human activities release EDCs into the atmosphere, which produces adverse effects on health (Annamalai & Namasivayam, 2015). Major EDCs include phthalates, polychlorinated biphenyls, polycyclic aromatic hydrocarbons, dioxins, bisphenol A, perfluoroalkyl substances, and alkylphenol ethoxylates (Annamalai & Namasivayam, 2015).

Some EDCs, such as phthalates, are also associated with bone damage. Phthalates are phthalic acid esters that bind to plastics and modulate the properties of materials. Phthalates are used in the production of polyvinyl chloride (PVC) and building materials, among other products. In general, phthalates are not physically bound to polymers, which facilitates their dissemination in the environment (Annamalai & Namasivayam, 2015). Although phthalates are more common indoors, they also abound outdoors (Chen, 2018). Experimental studies link exposure to different phthalates with skeletal deformities and delay in ossification in mice (Ema, 1994; Ema, 1993; McKee, 2006; Saillenfait, 2009; Saillenfait, 2013). Additionally, higher urinary levels of phthalate metabolites are associated with low BMD and a higher risk of osteoporosis in postmenopausal women (DeFlorio-Barker & Turyk, 2016; Min & Min, 2014). In murine models, benzyl butyl phthalate (BBP) and dibutyl phthalate (DBP) can affect the nuclear translocation of fibroblast growth factor 2 (FGF2) in osteoblasts (Menghi, 2001), which is essential for osteoblast function and differentiation (Marie, 2003). Bhat et al. (2013) found that di-2-ethylhexyl phthalate (DEHP) affected in vitro osteoblast differentiation and matrix mineralization in mice. Finally, these compounds can modify the actin structure and induce expression of pro-apoptotic proteins in mouse osteoblasts (Agas, 2007; Marchetti, 2002; Sabbieti, 2009).

Polychlorinated biphenyls (PCBs) are synthetic chemicals used in several industrial and home products. PCBs exhibit high air concentrations in industrial areas and are considered persistent organic compounds (POC) (Kaya, 2012). Twelve PCB congeners (chemical constituents or related chemicals) that bind the aryl hydrocarbon receptor (AhR) are classified as dioxin-like PCBs (DL-PCBs) (Annamalai & Namasivayam, 2015). Serum concentrations of some DL-PCBs (105, 118, and 156) are associated with low stiffness index, a parameter of bone quality, in women (Paunescu, 2013). In another study, DL-PCB 118 was negatively associated with BMD in men (Hodgson, 2008). Evidence shows that PCB 169 (Brankovič, 2019, 2017) and 126 (Alvarez-Lloret, 2009; Lind, 2000) modify bone geometry, biomechanics, and mineral composition in mice. Furthermore, several POC, including many PCBs, are associated with low BMD in mammals (Daugaard-Petersen, 2018a; Daugaard-Petersen, 2018b). However, some studies did not find an association between these compounds and BMD and markers of bone metabolism, as in the case of PCB 153 (Glynn, 2000; Rignell-Hydbom, 2009; Wallin, 2005). Since 209 individual congeners exist, it is difficult to examine the specific effect of each compound on bones (Darbre, 2018). The effect of PCBs on bone is likely mediated by AhR, as we will discuss later.

Polycyclic aromatic hydrocarbons (PAHs), the common chemical components of PM, are a large group of organic compounds that also have potential effects on bone mineralization (Guo, 2018; Zhang, 2016). They are produced by the incomplete combustion of fossil fuels, wildfires, and cigarette smoke. Urinary levels of several metabolites of these compounds

have been associated with low BMD and osteoporosis (Guo, 2018). Moreover, one of these compounds, benzo[a]pyrene (BaP), affects bone integrity in medaka fish (*Oryzias latipes*), a species sharing the basic mechanisms of bone formation with mammals. Fish offspring also exhibit these effects as a consequence of epigenetic changes that modify osteoblast differentiation (Seemann, 2017, 2015). This effect has also been observed in human mesenchymal stem cells exposed to BaP in vitro (Zhou, 2017). Likewise, BaP and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induce osteoclastogenesis in humans by activating the Cyp1 enzymes (Iqbal, 2013). In addition to this double effect in osteoblasts and osteoclasts, there is evidence that BaP enhances vitamin D3 catabolism, with potentially damaging effects on bone homeostasis (Matsunawa, 2009). The mechanisms involved in the biological effects of PAHs and dioxins remain unclear; however, the direct interaction between these compounds and AhR is one of the most studied pathways (Annamalai & Namasivayam, 2015; Machala, 2001; Zhang, 2016).

AhR is a receptor showing a high affinity for several compounds, many of which are found in PM (Mason, 1994). The prototypical AhR ligand, TCDD (DeGroot, 2011; Denison & Nagy, 2003), affects bone microarchitecture and biomechanical parameters in mice (Finnilä, 2010; Herlin, 2013, 2010; Jämsä, 2001; Miettinen, 2005). AhR activation inhibits osteoblast proliferation and differentiation in vitro in mice and humans (Gierthy, 1994; Korkalainen, 2009; Singh, 2000; Watson, 2019; H. Yu, 2014; Yun, 2018, 2017). Likewise, TCDD can inhibit bone healing in rat arthrodesis models (Hsu, 2015), affect the biomechanical properties of bone tissues in Rhesus monkeys (*Macaca mulatta*) (Hermsen, 2008), and interrupt skeletal development in zebrafish larvae (*Danio rerio*) (Burns, 2015). In mouse models, AhR agonists such as 3-methylcholanthrene (3MC) increase bone resorption. Moreover, systemic AhR knockout (AhRKO) mice show increased bone mass and are resistant to bone loss by 3MC due to altered osteoclastogenesis (T. Yu, 2014; T. Yu, 2015). Additionally, 3MC inhibits in vitro osteoblast proliferation and differentiation and in vivo ossification in mice (Naruse, 2002). Moreover, AhR expression in osteoblasts is upregulated due to lead exposure, which in turn increases the sensibility of bone cells to AhR ligands, which could partly explain why lead exposure causes bone damage (Ryan, 2007). Likewise, there is evidence that PAHs in PM stimulate both Th17 differentiation and IL-17 production independent of AhR activation (Castañeda, 2018; van Voorhis, 2013). As mentioned earlier, IL-17 is a crucial inductor of osteoclastogenesis (Adamopoulos, 2010). An inhibitory mechanism between the AhR signaling pathways and the estrogen receptor (ER) has been described (Safe & Wormke, 2003), which could cause the effects of AhR agonists on bone.

Another air pollutant, bisphenol A (BPA), is used to produce polycarbonates and epoxy resins. This compound is considered a xenoestrogen, a synthetic molecule imitating the effects of estrogen. BPA is ubiquitous in the atmosphere, but it reaches its highest concentrations in urban areas (Fu & Kawamura, 2010). This compound is known to bind to estrogen-related receptor gamma (ERRγ) (Matsushima, 2007), which acts as a negative regulator of RUNX2 (Jeong, 2009), an essential transcription factor in the differentiation of mesenchymal stem cells into osteoblasts. Jeong et al. (2009) found that ERRγ inhibition significantly increased osteoblast differentiation, osteocalcin expression, alkaline phosphatase (ALP) activity, and bone mineralization. Binding of BPA to ERRγ has an antiestrogen effect on bone cells, which affects bone metabolism via the RANKL pathway

(Thent, 2018), induces osteoclast and osteoblast apoptosis (Hwang, 2013), and reduces the activation of the Wnt/β-catenin signaling pathway (Leem, 2017). Different skeletal effects are detected in animals exposed to BPA (Chin, 2018; Pelch et al, 2012; Toda et al, 2002). However, an association between BPA exposure and low BMD has not been identified in osteoporotic postmenopausal women (Kim, 2012), nor in healthy premenopausal women (Zhao, 2012). Comprehensive longitudinal studies are needed to verify the association between BPA and bone health in humans.

Polyfluoroalkyl substances (PFASs) are synthetic endocrine disruptors used industrially and widely spread in the atmosphere (Annamalai & Namasivayam, 2015). PFASs exposure can increase *in vitro* bone resorption (Koskela, 2017). Several PFASs have been associated with low BMD and osteoporosis in adults; however, most such associations have been described in women (Khalil, 2016).

Finally, alkylphenol ethoxylates (APEs), another type of EDC, are nonionic surfactants used in the production of plastics, detergents, and paints. Their main components are 4-tert-octylphenol (OP) and 4-nonylphenol (NP), which are both in the atmosphere (Agas, 2013; Annamalai & Namasivayam, 2015). There is evidence that these compounds inhibit osteoclast (Hagiwara, 2008) and osteoblast differentiation (Miyawaki, 2008) and induce osteoblast apoptosis in vitro (Sabbieti, 2011). However, there are no studies in humans that support the potential bone damage induced by these endocrine disruptors.

In summary, several air pollution components considered to be EDCs have proven to produce adverse effects on bone homeostasis in many species. However, the global effect of the mixture of these compounds is unknown. Therefore, another approach has been adopted by researchers such as Novák, who examined the effects of the mixture of these compounds from samples of polluted air (Novák, 2014). In their study, which included PM samples taken from different geographic locations, they found AhR-mediated activity in all samples, which was consistent with the PAH concentrations. When examining the estrogenic effect of different sample fractions, they found contradictory results: weak estrogenic effects, antiestrogenic effects, and no estrogenic effects. These mixed results agree with previous findings (Novák, 2009; Wenger, 2009), and could be explained by the site-specific composition of the mixture. However, as discussed earlier, AhR activation has an inhibitory effect on the estrogen signaling pathways. Thus, due to the presence of several AhR agonists in air pollution, the predominant effect of exposure to atmospheric pollutants could be antiestrogenic (Novák, 2014), with additional damaging effects on bone metabolism.

Some of the mechanisms involved in the antiestrogenic effect of tobacco could be studied regarding air pollutants because their components share similarities. It is thus possible that PM components have, as in tobacco, an antiestrogenic effect mediated by increased levels of sex hormone-binding globulin (Daniel, 1992) and increased hepatic metabolism of estrogens (Michnovicz, 1986), to name a few examples.

4.4. Mechanisms related to metals

Metals are considered as common components of PM (World Health Organization, 2013). The main sources of metals in the atmosphere include industrial and vehicular emissions

(Suvarapu & Baek, 2017). While the introduction of unleaded gasoline has significantly reduced the concentration of lead in ambient air, the concentrations of purely anthropogenic heavy metals, such as cadmium (Cd), chromium (Cr), zinc (Zn), and mercury (Hg), are increasing (Suvarapu & Baek, 2017). (For evidence and reviews of the effect of metal exposure on bones, see Rodríguez, 2018). In this section we will focus on the effects of metals in the air.

Lead (Pb) accumulates in the bones due to its ability to replace divalent cations such as calcium, magnesium, and iron (Rodríguez, 2018). Several studies link Pb exposure to lower BMD in humans (Akbal et al., 2014; Campbell & Auinger, 2007; Dongre et al., 2013; Wong et al., 2015). Higher concentrations of metals (lead, cadmium, and cobalt) have been found in biopsies from the femoral head of osteoporotic subjects, compared with controls, particularly in trabecular bone tissue (Scimeca et al., 2017). Pb was present in 92% of the samples of osteoporotic patients, compared with 20% of controls, with significant differences when comparing the accumulation of two or more elements. Evidence suggests a cytotoxic effect of Pb on bone cells mediated by the induction of oxidative stress (Al-Ghafari et al., 2019).

Moreover, the outbreak of the ‘itai-itai disease’ in Japan due to the Cd poisoning of the Jinzu River revealed the harmful effects of this metal (Aoshima, 2017). Itai-itai disease was characterized, among other clinical findings, by frequent fractures and bone deformities. Recent epidemiological studies have shown an association between low-level Cd exposure and lower BMD and higher incidence of fractures (Engström et al., 2012; Wallin et al., 2016), which correlates with studies in experimental animals (Bhattacharyya, 2009). The Cd effect on bones seems to be mediated, as has been proposed for Pb, by the induction of oxidative stress (Al-Ghafari et al., 2019), increased bone resorption, and impaired calcium absorption (Reyes-Hinojosa et al., 2019). Likewise, an indirect effect due to renal involvement induced by Cd has been proposed (Chen et al., 2011).

Another metal in the atmosphere, mercury (Hg), is produced by industrial processes and coal combustion (Suvarapu & Baek, 2017). In fish, methylmercury exposure decreases the levels of tartrate-resistant acid phosphatase (TRAP) and alkaline phosphatase (ALP), which are, respectively, indicators of osteoclastic and osteoblastic activity (Suzuki et al., 2004; Yachiguchi et al., 2014). Methylmercury induces downregulation in ER and IGF-1 genes (Suzuki et al., 2004). A study in mice demonstrated adverse effects on bone formation parameters during embryonic development, which were counteracted by the administration of vitamin E that prevented lipid peroxidation (Abd El-Aziz et al., 2012). Therefore, bone damage caused by Hg could be associated with oxidative stress and the alteration of the estrogenic signaling and decreased activity of IGF-1, both essential for bone growth.

The main sources of chromium (Cr) are vehicle emissions and coal combustion (Suvarapu & Baek, 2017). Rats exposed to hexavalent chromium (Cr [VI]) showed a decrease in TRAP and ALP activity and an alteration in mandibular growth and dental eruption (De Lucca et al., 2009), similar to the effects of Hg. In vitro studies of osteoblasts derived from human osteosarcoma exposed to Co, Cr (III), and Cr (VI) revealed a synergistic effect (particularly

between Co and Cr) that reduced osteoblast survival and function, determined by ALP activity and surface mineralization (Andrews et al., 2011; Shah et al., 2015).

Arsenic (As) is a metalloid found in industrial emissions and coal combustion (Suvarapu & Baek, 2017). At low concentrations, As inhibits endochondral ossification in rats due to an increase in cartilage thickness of the growth plate (Aybar Odstrcil et al., 2010). In addition, As affects osteoblastic differentiation and function in rats in in vitro and in vivo models, decreasing bone turnover markers (osteocalcin, procollagen type I N-terminal propeptide, and C-terminal cross-linking telopeptide) and BMD and altering bone microstructure (Hu et al., 2012; Wu et al., 2014). Arsenic has shown to induce apoptosis in bone marrow mesenchymal stem cells (BMSC) and rat osteoblasts (Cai et al., 2010; Tang et al., 2009); As is also associated with oxidative stress induction (Chiu et al., 2016).

While the main sources of nickel (Ni) are motor vehicles and coal and oil burning, cobalt (Co) comes mainly from coal burning (Suvarapu & Baek, 2017). Although there are no reports of the effects of these elements on human bones, Kanaji et al. 2014 showed that Ni and Co have a cytotoxic effect (apoptosis and necrosis, respectively) in in vitro mouse osteocytes at a concentration of 0.50 mM. More studies are needed to determine the potential effect of Ni and Co in humans (Kanaji et al., 2014).

In summary, various metals in PM have a proven effect on bones. Although it is difficult to determine their real impact, the concentration and the indirect effect of metals (e.g., through oxidative stress) in the bone matrix can potentially induce bone damage (Rodríguez & Mandalunis, 2018). In addition, the concentration of anthropogenic metals in the atmosphere is increasing, especially in developing countries (Suvarapu & Baek, 2017), and the risk of a potential synergistic effect of metals (Shah et al., 2015) has to be determined.

4.5. Deficient synthesis of vitamin D

Ozone (O_3) is a gas in the stratosphere and troposphere (Leh, 1973). In the stratosphere, ozone protects against the damaging effects of the sun by absorbing UV radiation (Ehhalt, 1999), whereas in the troposphere, whose height ranges from 0 to 7 miles, ozone harms health by acting as an environmental pollutant (Chen, 2007). Tropospheric ozone production depends on the photochemical interaction of nitrogen oxides (NO_x) (Monks, 2015) and VOCs (Duan, 2008). The anthropogenic sources of NO_x and VOCs are fossil fuel and biomass burning, as well as solvent evaporation (Badr & Probert, 1993; Barletta, 2005). Since it absorbs UV radiation, ozone has been proposed by several studies to be responsible for low UVB exposure and deficient vitamin D synthesis. A cross-sectional study of a cohort of 85 postmenopausal Caucasian women in Belgium who lived in rural and urban areas revealed that women who lived in cities were exposed to three times as much ground-level ozone as those living in rural areas (Manicourt & Devogelaer, 2008). Likewise, women living in cities showed higher prevalence of having 25-hydroxyvitamin D levels below 75 nmol/L, even though they had a higher solar exposure index (SEI). This could be the result of low UVB exposure from high tropospheric ozone levels. It is well-documented that UV radiation is essential for the skin to synthesize vitamin D, and its deficiency affects calcium absorption, which in turn leads to bone density reduction and increased risk of osteoporosis-related fractures (Lips, 2001). Some studies show an association between air pollution and

risk of vitamin D deficiency; however, these studies usually combine the values of $PM_{2.5}$, NO_2, and CO. Such studies do not examine the O_3 levels separately (Feizabad, 2017) or do not mention how they measured air pollution levels (Agarwal, 2002; Hosseinpanah, 2010). Thus, studies are needed in which ozone levels are measured individually along with UVB levels and concentrations of serum vitamin D.

Because kidneys participate in vitamin D metabolism, kidney damage is another potential mechanism of bone damage associated with air pollution exposure. A recent review from Afsar et al. collected evidence about the role air pollution has in kidney damage (Afsar et al., 2019). Additionally, atmospheric metal (arsenic, cadmium, lead, mercury, and uranium) exposure is directly nephrotoxic. The effects of renal dysfunction on bones are evident in chronic kidney diseases (e.g., chronic kidney disease-mineral bone disorder [CKD-MBD], formerly called renal osteodystrophy). Although the main potential mechanism behind some air pollution-related effects on bones mediated by kidneys is through vitamin D metabolism and secondary hyperparathyroidism (K. A. Hruska & Teitelbaum, 1995), much more complex interactions may exist, including the presence of inhibitors of the Wnt pathway, such as activin A and Dickkopf 1, essential for osteoclastogenesis (Keith A. Hruska et al., 2017). Further research is needed about the potential interaction of kidney damage in the air pollution-mediated bone damage.

5. Conclusions

Air pollution predominates in urban areas of most parts of the world, particularly in densely populated and industrialized countries. Importantly, air pollution exposure is a risk factor for respiratory, cardiovascular, and bone diseases. Evidence indicates that exposure to air pollutants is associated with induction of a low-grade systemic inflammatory state and oxidative stress, endocrine disruption, and changes in vitamin D metabolism, with potential effects on bone homeostasis. As we have summarized, several components contribute to air pollution-induced bone damage (Figure 2). It is important to insist that, due to the effects of air pollution on various organs and tissues, particularly kidneys (Schraufnagel et al., 2019), other indirect mechanisms of bone damage related to air pollution could exist.

Knowing the mechanisms of bone damage induced by exposure to air pollution will contribute to improved understanding of the physiopathology of bone damage associated with environmental exposure, as well as to implementing new and better prevention strategies. Acknowledging air pollution as a modifiable risk factor for osteoporosis could improve environmental policies, which will have positive effects on bone health, prevent fractures, and reduce health-associated costs. Further research about mechanisms, mixtures and other air pollution components, as well as potential interventions to prevent air pollution-induced bone damage are guaranteed.

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Abbreviation and acronym index

3MC	3-methylcolatren
AhR	Aryl hydrocarbon receptor
ALP	Alkaline phosphatase
AM	Alveolar macrophage
AP1	Activator protein 1
APEs	Alkylphenol ethoxylates
BaP	Benzo[a]pyrene
BBP	Butyl benzyl phthalate
BMC	Bone mineral content
BMD	Bone mineral density
BPA	Bisphenol A
CRP	C-reactive protein
Cyp1	Cytochrome 450, family 1
DBP	Dibutyl phthalate
DEHP	Di-2-ethyl hexyl phthalate
DL-PCBs	Dioxin-like polychlorinated biphenyls
DXA	Dual-energy X-ray absorptiometry
EDC	Endocrine disrupting chemicals
ERRγ	Estrogen-related receptor γ
FGF2	Fibroblast growth factor 2
FOXO	Forkhead box protein O
GM-CSF	Granulocyte and macrophage colony stimulating factor
HIF1α	Hypoxia inducible factor 1α
HULIS	Humic-like substances
IGF-1	Insulin-like growth factor-1
LPS	Lipopolysaccharide
MCP-1	Monocyte chemoattractant protein 1
MCSF	Macrophage colony stimulating factor

MIP-1α	Macrophage inflammatory protein 1α
MyD88	Myeloid differentiation primary response 88
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer
NO	Nitrogen monoxide
NO_2	Nitrogen dioxide
NO_X	Nitrogen oxides
NP	4-nonylphenol
Nrf2	Nuclear factor erythroid 2-related factor 2
O_3	Ozone
OPE	Organic powder extract
OP	4-tert-octylphenol
OPG	Osteoprotegerin
PAHs	Polycyclic aromatic hydrocarbons
PCBs	Polychlorinated biphenyls
PFASs	Perfluoroalkylated substances
PM	Particulate matter
POC	Persistent organochlorine compounds
PPARγ	Peroxisome proliferator activated receptor γ
PTH	Parathyroid hormone
PVC	Polyvinyl chloride
RANKL	Receptor activator of nuclear factor kappa-B ligand
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
Runx2	Run-related transcription factor 2
SEI	Sun exposure index
Sema4D	Semaphorin 4D
SO_2,	Sulfur dioxide
SVOC	Semi volatile organic compounds

TCDD	Tetrachlorodibenzo-p-dioxin
TLR	Toll-like receptor
TNFα	Tumor necrosis factor α
UVB	Ultraviolet radiation B
VOC	Volatile organic compounds

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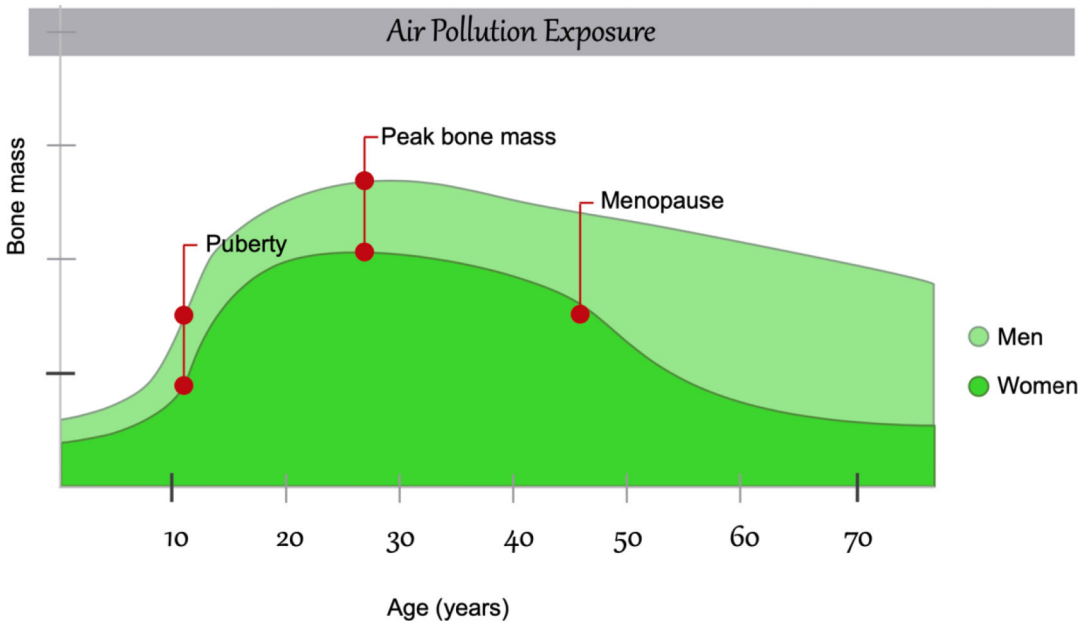

Figure 1. Changes in bone composition over the lifetime and the influence of air pollution.
Air pollution effect is shown before birth, as during pregnancy may also induce molecular changes affecting potentially bone development.

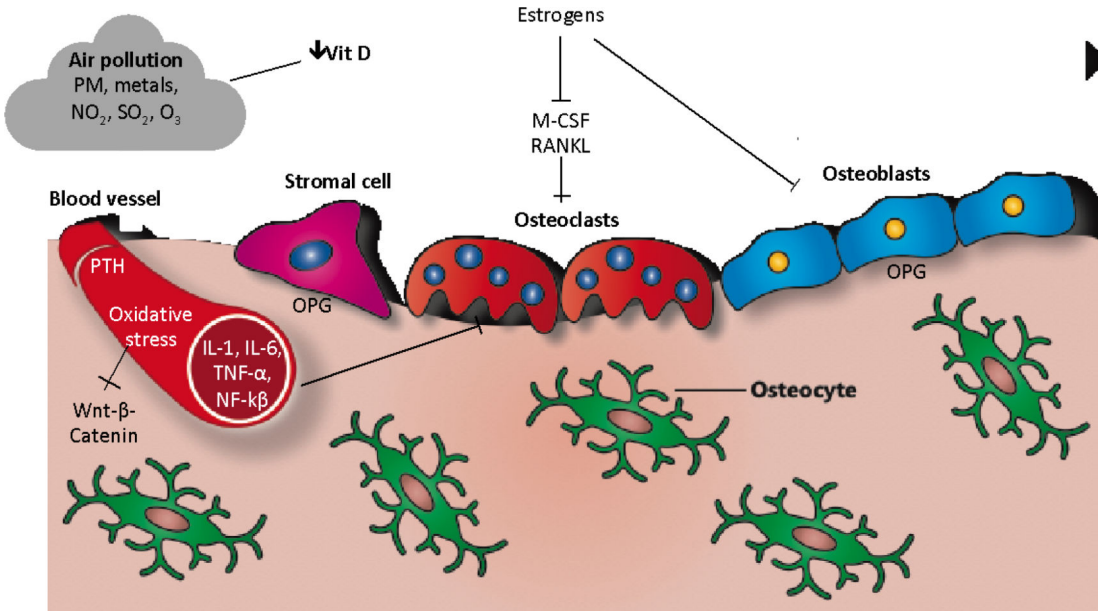

Figure 2. Cellular and molecular mechanisms involved in air pollution-induced bone damage.

PM: Particulate matter; NO_2: Nitrogen dioxide; SO_2: Sulphur dioxide; O_3: Ozone; OPG: Osteoprotegerin, IL: Interleukin; M-CSF: Macrophage colony-stimulating factor; RANKL: Receptor activator of nuclear factor κ B; TNF-α: Tumor necrosis factor-alpha; NF-kβ: Nuclear factor kappa-light-chain-enhancer of activated B cells; PTH: Parathyroid hormone.