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Overview of Traditional and Environmental Factors Related to Bone Health

Juan Carlos Rubio-Gutierrez¹ · Pablo Mendez-Hernández^{2,3} · Yann Guéguen⁴ · Pierre Galichon^{5,6} · Marcela Tamayo-Ortiz⁷ · Karsten Haupt⁸ · Mara Medeiros^{9,10} · Olivier Christophe Barbier¹

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Abstract

Bone mass in adulthood depends on growth and mineralization acquired during childhood and adolescence. It is well known that these stages of life are crucial for bone development, where genetic, nutritional, hormonal, and lifestyle factors play a significant role. Bone loss is normally a natural and slow process that begins years later after the peak bone mass is achieved and continues throughout the lifespan. Lifestyle choices in childhood and adolescence such as minimal physical activity, excessive caffeine or carbonated beverages intake, malnutrition, cigarette use, or high alcohol consumption and other factors like environmental pollutants can also negatively affect bone health and accelerate the bone loss process. The aim of this work is an overview of risk factors associated with inadequate bone health in early life.

Keywords Bone development · Bone health · Childhood and adolescence · Early diagnosis · Growth · Peak bone mass · Bone remodeling · Risk factors

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Abbreviations

ALP	Alkaline phosphatase
Al	Aluminum
As	Arsenic
B	Boron
BC	Black carbon
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body mass index
BUA	Broadband ultrasound attenuation
Ca	Calcium
Ce	Cerium
Cd	Cadmium
CKD	Chronic kidney disease
Co	Cobalt
CO	Carbon monoxide
Cr	Chromium
CRP	C-reactive protein
CTx	C-terminal telopeptide of type I collagen
Cu	Copper
DMP1	Dentin matrix protein
DXA	Dual-energy X-ray absorptiometry
Dy	Dysprosium
Er	Erbium
F ⁻	Fluoride
Fe	Iron
FGF23	Fibroblast growth factor 23
Gd	Gadolinium
GFR	Glomerular filtration rate
Hg	Mercury
ICTP	Type 1 collagen carboxy-terminal telopeptide
IL	Interleukin
K	Potassium
La	Lanthanum
MEPE	Matrix extracellular phospho-glycoprotein
Mg	Magnesium
Mn	Manganese
Na	Sodium
Nd	Neodymium
Ni	Nickel
NO ₂	Nitrogen dioxide
OC	Osteocalcin
OP	Osteoporosis
OPG	Osteoprotegerin
OPN	Osteopontin
P	Phosphorus
PAHs	Polycyclic aromatic hydrocarbons
Pb	Lead
PINP	Procollagen type I N propeptide
PM	Particulate matter
PO ₄ ³⁻	Phosphate
PQCT	Peripheral quantitative computed tomography
Pr	Praseodymium

PTH	Parathyroid hormone
QCT	Quantitative computed tomography
QUS	Quantitative ultrasound
RANKL	Receptor activator for nuclear factor κ β ligand
REEs	Rare earth elements
SD	Standard deviations
Se	Selenium
SI	Stiffness index
Sm	Samarium
Sn	Tin
SOS	Speed of sound
Sr	Strontium
Tb	Terbium
Ti	Titanium
Tl	Thallium
TNF- α	Tumor necrosis factor-alpha
U	Uranium
Yb	Ytterbium
Zn	Zinc

Introduction

Through the years, interest in bone health has grown mainly for the most vulnerable populations: children and the elderly (Curtis et al. 2016). Throughout life, bone metabolism undergoes many changes; early growth stages are also critical for bone's development. During these stages, bone turnover is positive (more bone formation than resorption), reaching peak bone mass by the end of adolescence. Then, bone turnover is kept in balance for up to 50 years, approximately. Conversely, aging is a biological and physiological process where bone turnover becomes negative (more bone resorption than formation) and the loss of bone mass is more prevalent (Hernández-Gil et al. 2006; Yeste and Carrascosa 2015).

Many factors contribute to bone mass accrual and can influence bone health during childhood and adolescence (Fig. 1). Among these factors, genetics, hormones, nutrition, and diet with an adequate Ca and vitamin D supplementation and physical activity play a crucial role (Sharma et al. 2009). Besides, there are other factors that are detrimental for bone development, such as lifestyle [alcohol, caffeine and carbonated beverages' consumption, smoking, sedentarism (Sharma et al. 2009)], obesity (Farr and Dimitri 2018), poverty, demographic area (urban or rural), (Gu et al. 2007), some chronic diseases (kidney diseases, osteosarcoma), and metabolic diseases and environmental factors such as exposure to toxic compounds (metals, air pollutants) (Rodríguez and Mandalunis 2018). Notwithstanding, it is believed that the environmental factors and lifestyles changes are more important than genetics in the determination of bone loss. To avoid spontaneous fractures and osteoporosis (OP) in adulthood, it is essential to acquire correct bone mass in early life periods (Curtis et al. 2016).

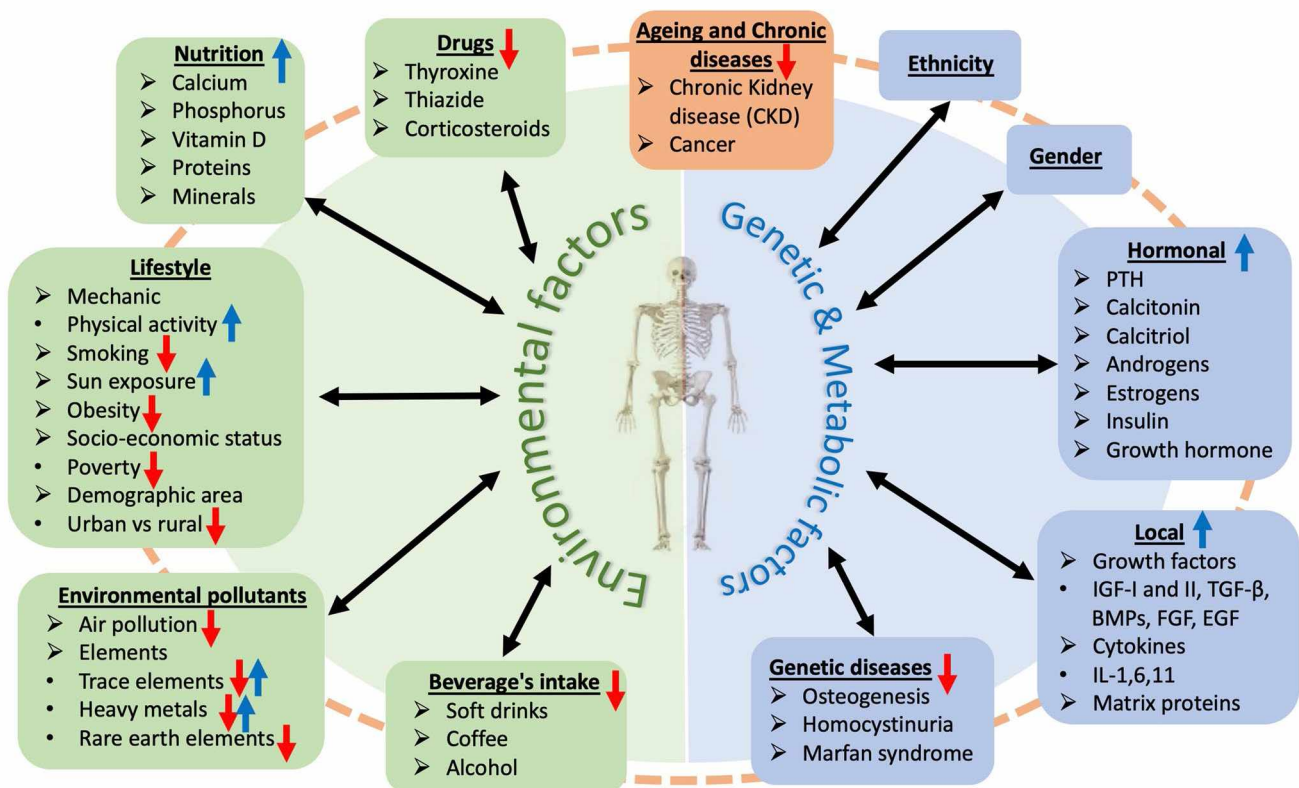


Fig. 1 Determining factors that modify bone mass through resorption and synthesis/formation. Blue arrows show positive effects on bone, red arrows represent the negative effects, and both arrows in one fac-

tor indicate positive and negative effects. Purple letter shows positive effects on bone, red letter represents the negative effects, and gray letter indicate positive and negative effects

Although there are several techniques to assess bone status in adults, in children, these approaches are not standardized due to scarce number (Liu et al. 2015). Nevertheless, bone parameters used to establish reference values represent a challenge and can vary significantly. The differences in values of bone mineral density (BMD, the amount of bone minerals [calcium (Ca) and phosphorus (P)] contained in a certain volume of bone [g/cm^2]), bone mineral content (BMC, bone mineral amount found in a specific area [g]), and concentrations of bone turnover biomarkers depend on factors such as the measurement site, ethnicity, age, gender, and anthropometry, among others (Zhumalina et al. 2020).

The aim of this work is to describe bone health and provide an overview of risk factors associated with inadequate bone health early in life.

Skeletal system

Bone tissue: structure and function

Bone is a mineralized, vascularized, and innervated connective organ arranged in calcified osteoid matrix's tinny lamellae. Lamellae's orientation determines whether the bone is

cortical (80% of total bone mass) or trabecular (the remaining 20%). The set of structured and organized bones forms the skeleton, whose main functions are mechanical (organ protection, solid structure to support the body), metabolic (storage of minerals such as Ca, P, and magnesium (Mg) and fat), and hematopoietic (formation of blood cells) (Hernández-Gil et al. 2005). The skeleton grows as the body grows in length, breadth, mass, and volumetric density (Cooper et al. 2008).

Bone tissue is made up of cells (2%; finding bone-forming cells such as osteoblasts and osteocytes and bone-destroying cells as osteoclasts) and extracellular matrix that is divided into organic (30%; mainly collagen and other non-collagenous proteins in less proportion) and mineral fraction (68%; hydroxyapatite crystals) (Hernández-Gil et al. 2005).

Bone development and mineralization

Bone development and mineralization are continuous processes that begin in utero and continue at different rates during childhood and adolescence until peak bone mass is reached (Yeste and Carrascosa, 2015). There are two high-velocity growth periods, the first between birth and two years of age, and the second during puberty accumulating

approximately 90% of bone mass by this age (Cooper et al. 2008; Liu et al. 2015). Accumulation varies by skeletal region but, on average, is completed by the age of 18 years in girls and 20 years in boys (Sharma et al. 2009).

The consolidation of peak bone mass depends on bone density and bone size, which in turn depends on the mineralization process. It is controlled in two ways: directly (formation of bone cells such as osteoblasts) and indirectly (absorption of Ca and P (Van Driel and Van Leeuwen 2017). In this process, the first step is resorption, where osteoclasts work by degrading the organic matrix and mineral fraction by the secretion of proteases in acidic conditions. Subsequently, osteoblasts fill the gaps with osteoid and other proteins such as alkaline phosphatase (ALP) and osteocalcin (OC), among others. Finally, mineralization begins with Ca and P that precipitate on the organic bone matrix, forming hydroxyapatite crystals (Lalayiannis et al. 2019). The shape and structure of bones are renovated by these two bone metabolism processes, which, apart from replacing old bone with a new one, keep mineral homeostasis, improve vascular distribution, and repair bones' weak areas (Leonard and Zemel 2002).

Factors associated with bone health

Genetics

Genetics is the main factor that determines bone mass and mineralization. The heritable BMD component is between 44 and 88%, while the remaining variability in bone mass is associated with behavioral factors as nutrition and physical activity (Leonard and Zemel 2002). Some family and twin pair studies have proposed a strong genetic component in a predisposition to OP. These studies are focused on the understanding the mechanisms that regulate the cells implicated in bone resorption and bone formation (Levi et al. 2002). Also, studies in different ethnicities suggest that bone mass is determined by height, weight, and bone area (Gu et al. 2007). Black children from South Africa have shown greater bone mass at the femoral neck than that of white children. Similarly, Afro-American children have greater bone area and BMD at all measured sites (lumbar spine, hip, radius, and whole body) than that of white children (Pettifor 2014).

Nutrition, vitamin D, calcium, phosphate, and magnesium intake

Nutrient deficiencies (protein, trace elements, essential nutrients as Ca, P, Mg, vitamin D) play an essential role in determining bone mass, particularly in children and adolescents from developing countries (Pettifor 2014). Intake of fruits and vegetables has a beneficial effect on bone health

due to the skeleton's role in acid–base homeostasis. A diet rich in nutrients such as potassium (K), Mg, vitamin C, fiber, and zinc (Zn) is also associated with increased axial, peripheral, hip, and lumbar spine BMD and less bone loss at the femoral neck. Contrary to this, a vegetarian diet is associated with low serum vitamin D and BMD, the absence of meat being the only associated factor (Burns et al. 2003).

Consumption of meat, fish, and dairy products and oils of animal origin contribute a major source of nutrients such as Ca, P, and vitamin D, which has increased in recent years, especially in developing countries (Gu et al. 2007). In addition, other factors involved with nutrition are economic status, demographic conditions and cultural customs. A balanced diet provides adequate nutrients for most people without the need for expensive supplementation.

Vitamin D

Vitamin D is a hormone that regulates metabolism and Ca^{2+} and PO_4^{3-} homeostasis in the organism (Pettifor 2014). It is a crucial element for bone development and skeletal mineralization, particularly during growth. The primary vitamin D source is through the exposure of skin to sunlight and less common by food sources. Vitamin D has two different forms: vitamin D_2 and vitamin D_3 . When 7-dehydrocholesterol (pro-vitamin D_3) is exposed to UV light, it is transformed to pre-vitamin D_3 (cholecalciferol), while pre-vitamin D_2 (ergocalciferol) is derived from ergosterol in plants. These two previous metabolites are inactive. To be active, both undergo two hydroxylations: hepatic hydroxylation takes place first forming 25-hydroxyvitamin D_2 (ercalciferol) or 25-hydroxyvitamin D_3 (calcidiol). Once they leave the liver, they are distributed to different organs and reach the kidney, where they are filtered in the glomeruli and reabsorbed by the epithelial proximal tubular cells undergoing a second renal hydroxylation by the enzyme 1- α hydroxylase to obtain the active forms of vitamin D: 1,25-dihydroxyvitamin D_2 (ercalcitriol) or 1,25-dihydroxyvitamin D_3 (calcitriol). The process mentioned above is the biosynthesis of vitamin D and its metabolites (Fig. 2). Calcidiol (25[OH]D) is the most commonly measured serum metabolite because it better reflects vitamin D status and is more stable and its half-life is higher compared with calcitriol (25[OH] $_2$ D), (Alshahrani and Aljohani 2013).

Deficiency of vitamin D is caused by many factors such as hereditary diseases of vitamin D, no sunlight exposure, lifestyles, overcrowding, cultural dressing (clothing), air pollution, and drugs. A deficit of vitamin D in children and adolescents is a severe problem for bone health (< 10 ng/mL can cause rickets and osteomalacia). A value < 20 ng/mL is considered as deficiency, between 20 and 30 ng/mL is insufficiency, and between 30 and 60 ng/mL is an indicator of good health (Alshahrani and Aljohani 2013; Farrar et al. 2016).

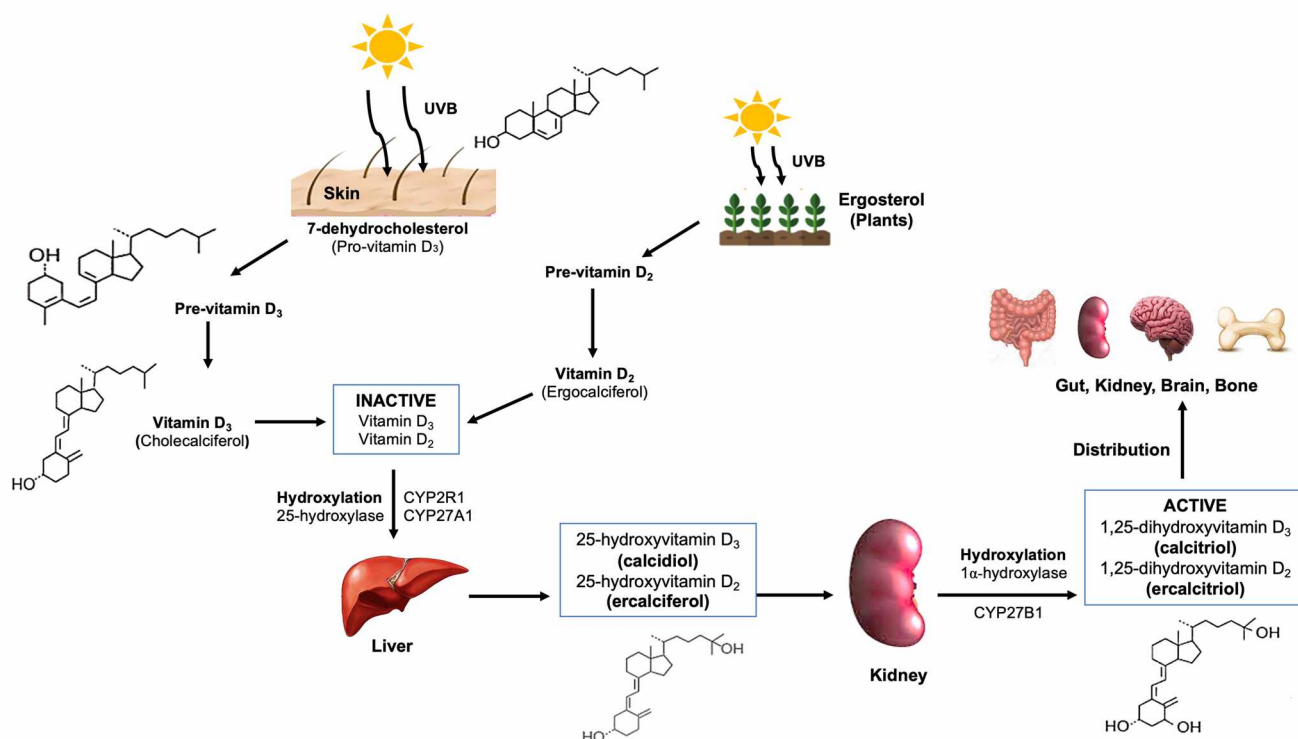


Fig. 2 Biosynthesis of vitamin D and its metabolites

Sunlight exposure Many countries have poor sunlight (countries near the poles, where there are months of darkness). Other countries (the Middle East) have dress customs that interfere with sunlight exposure, especially for women and girls having to use long clothing covering all their body (arms, face, legs). School uniforms have also been associated to lower vitamin D levels (Farrar et al. 2016). In other cities, where pollution is significantly elevated, sunlight exposure is reduced due to this contamination layer. Additionally, nowadays children and adolescents prefer videogames or indoor instead of outdoor activities, plus there is an increased sunscreen use.

Calcium

Ca can be obtained from dairy foods (cheese, milk, yogurt), green vegetables, bread, meat, and fish. 99.4% of Ca in the organism is stored in the bone tissue and is the main component of hydroxyapatite crystals. The storage depends on the amount of Ca ingested, intestinal absorption rate, and urinary clearance (Yeste and Carrascosa 2015). In contrast, homeostasis is mediated through gastrointestinal and renal absorption, modulated by serum vitamin D levels and parathyroid hormone (PTH). Dietary Ca intake can vary, but the average of dairy intake in children and adolescents (1 to 18 years old) has been estimated between 700 and 1,300 mg/day (Pettifor 2014). This mineral intake increases

BMD, especially in the axial skeleton (Burns et al. 2003) and is considered a bone metabolism marker to evaluate bone health (Alghadir et al. 2016). Ca deficiency can trigger severe bone problems as delay in growth, bone fragility, spontaneous fractures, rickets, and OP (Pettifor 2014).

Phosphate

Phosphorus (P) is an essential mineral for bone health. In the human body, the main form of P is phosphate (PO_4^{3-}). 85% of this element is found in bone minerals attached to Ca to form hydroxyapatite. Homeostasis of PO_4^{3-} is maintained by some organs such as kidneys, parathyroid gland, intestine, and bone where PTH, fibroblast growth factor 23 (FGF23, a potent phosphaturic hormone produced by the bone), and vitamin D participate. P requirements are significant because its deficiency is associated with harmful effects on bone and mineral metabolism in humans and animals. In addition, a high amount of the mineral in the organism can cause toxicity, which is also related to some bone alterations such as higher levels of PTH and OC and more bone resorption mediated by osteopontin (OPN, a bone matrix protein).

Nevertheless, P deficiency is rare because it is widely distributed in food as a natural organic form (meats, nuts, seeds, legumes, dairy foods, and grains), inorganic forms as additives, and the body's facility to absorb it. Notwithstanding, its deficiency is more related to defects in renal absorption

of PO_4^{3-} . The adverse effects on human bones because of its deficiency lead to rickets and a delay in growth in children and osteomalacia in adults (Vorland et al. 2018).

On the other hand, a minimal rise over the average serum concentration of P cause increased PTH production and secretion, removing Ca from bones and reducing bone mass. Also, the elevated PO_4^{3-} concentrations promote the secretion of FGF23 through osteocytes. Once in plasma, FGF23 enhances the excretion of PO_4^{3-} in the proximal tubule and the diminution of synthesis of vitamin D_3 due to low regulation of 1α -hydroxylase. During growth periods, the excess of P affects bone mass accrual. These effects have been seen in animal experiments where the group with a high concentration of P reduced body weight, bone mineral content, and bone mineral density. In human studies, the most observed effects due to high dietary P are in bone metabolism, which means that some molecules (bone turnover markers) involved in the process are altered: increased PTH, bone resorption markers (carboxy-terminal collagen crosslinks (CTX), RANKL/OPG), and bone formation markers (osteocalcin). In epidemiological studies, high dietary P has been associated with fracture risk (Vorland et al. 2018).

Magnesium

Mg is essential in the skeleton structure. The concentration of Mg in the human body is approximately 30 g where 50% is stored in bones (Zoroddu et al. 2019). This element is found naturally in a variety of foods such as chocolate, green leafy vegetables, legumes, milk products, nuts, seeds, and whole grains. Homeostasis of Mg is determined by the balance between gastrointestinal absorption and renal excretion (Zaichick et al. 2009). Mg participates in the join up of hard structures through biomineralization (Zoroddu et al. 2019). A high consumption of Mg has been associated with higher BMD, a considerable parameter in the reduction of spontaneous fractures and OP (Alghadir et al. 2016).

Other dietary minerals

The dietary needs of essential minerals for bone development and bone health vary throughout life, being higher during childhood and adolescence and diminishing during adulthood and old age. Some of the essential minerals that significantly correlate with age are Ca, Mg, and P. Other minerals have also shown these changes, such as iron (Fe), Zn, sodium (Na), and strontium (Sr) but with lower significance (Zaichick et al. 2009). A deficiency or an excess intake of elements causes debilitating bone diseases. To better understand the effects of minerals on bone tissue, it is necessary to establish the normal age-related levels of these elements.

Elements involved in bone health

Several elements are widely distributed in the Earth's crust as heavy metals and trace elements. Some of them are essential or beneficial for life, while others are toxic, even at very low doses. At normal environmental levels, the human body manages their toxicity by excretion (ultrafiltration by kidneys) and/or retaining the element in a biochemically inactive form. Most of them accumulate in the skeleton due to the bone being a dynamic tissue undergoing constant remodeling throughout life (Vidaud et al. 2012; Rodríguez and Mandalunis 2018).

Human activities are the major source of pollution. Contaminants such as heavy metals or fluoride (F) can enter the food chain and bioaccumulate in hard and soft tissue that results in a long half-life of the pollutant endogenous source of exposure. Heavy metal intoxication can alter different systems depending on metal type, concentration, and exposure duration (Dermience et al. 2015). Both, the minimum and excess of these elements in the body can alter bone dynamics. Long-term exposure and short exposure to high concentrations induce an imbalance in the bone remodeling process. Some metals have an anabolic effect on bone tissue in low concentrations, such as Zn, copper (Cu), and nickel (Ni). They mostly serve as cofactors for enzymes involved in bone remodeling processes. Other elements, such as cadmium (Cd), arsenic (As), lead (Pb), mercury (Hg), chromium (Cr), aluminum (Al), and F^- , are toxic to bone cells even at low concentrations. Overall, metals can affect bone tissue via two routes: (1) the direct toxicity on bone cells—osteoblasts—inhibiting their differentiation and synthesis activity, leading to an imbalance in the bone remodeling process, decreasing bone formation, and (2) through their accumulation in the bone matrix impairing the extracellular matrix's mineralization (Rodríguez and Mandalunis 2018).

Trace elements Bone integrity is influenced by some trace elements that could have beneficial effects such as boron (B), Fe, Mg, and manganese (Mn), F^- . However, others have the opposite effect as Cd, Pb, and cobalt (Co). Nonetheless, a high intake of certain beneficial elements (F, Zn, Mg) can have toxic effects. The variations between positive or negative effects depend on many factors such as nutrition (amount in the diet and interaction between two or more elements), absorption and metabolism in the body, genetic disposition, age, and gender (Zofkova et al. 2017). A brief description of these trace elements and their effects on bone health is listed in Table 1.

Heavy metals This group of elements is the most critical group of pollutants that affect bone mass, bone metabolism, and bone microarchitecture (Scimeca et al. 2016). To be considered a heavy metal, it must have a density greater than

Table 1 Characteristics of trace elements on bone health

Trace element	Characteristics/positive and/or negative effects	References
Boron (B)	<ul style="list-style-type: none"> • Stimulation of bone growth and bone metabolism and activates active vitamin D production • Beneficial effects on trabecular bone microarchitecture and cortical bone strength • Low levels of B might also reduce bone strength 	Dermience et al. 2015; Zofkova et al. 2017
Cobalt (Co)	<ul style="list-style-type: none"> • Influences bone resorption and bone formation 	Scimeca et al. 2016
Copper (Cu)	<ul style="list-style-type: none"> • Regulation of bone growth and skeletal development, inhibition of osteoclastic bone resorption, and increase in bone strength • Increase in Cu concentration in the body is cytotoxic 	Zofkova et al. 2017; Rodríguez and Mandalunis 2018
Fluoride (F)	<ul style="list-style-type: none"> • At low concentrations, F stimulates osteoblastogenesis and increases bone mass • On the other hand, excessive F causes skeletal fluorosis, bone resorption and inhibits ALP 	Dermience et al. 2015; Zofkova et al. 2017
Iron (Fe)	<ul style="list-style-type: none"> • Stimulation of the synthesis of bone matrix and production of vitamin D • Deficiency of this element is related to low-grade bone mineralization, low BMD, and bone strength • Promotion of osteoclast differentiation, inhibition of osteoblast differentiation and activity, and inhibition of hydroxyapatite crystals growth, altering the crystallinity 	Zofkova et al. 2017; Rodríguez and Mandalunis 2018
Magnesium (Mg)	<ul style="list-style-type: none"> • 60% is stored in the skeleton in the form of hydroxyapatite crystals • Promotion of the mineralization process and with active vitamin D synthesis • Deficiency elevates the osteoclast activity and diminishes osteoblastic activity, which leads to bone loss • A sufficient Mg intake increases bone density. In contrast, excessive intake can alter mineralization and osteoblast differentiation 	Zofkova et al. 2017
Manganese (Mn)	<ul style="list-style-type: none"> • Modulation of the RANKL/OPG ratio in the bone formation process and protective effect on bone tissue • Toxicity due to its high half-life (8–9 years), resulting in an accumulation in bone tissue 	Alghadir et al. 2016; Zofkova et al. 2017
Potassium (K)	<ul style="list-style-type: none"> • High levels of K are associated with stronger bones, higher MBD • In contrast, deficiency in K can deplete calcium in bones 	Dermience et al. 2015
Selenium (Se):	<ul style="list-style-type: none"> • Modulation of bone metabolic turnover in favor of bone formation • Deficiency activates bone resorption and induces adverse effects in bone microarchitecture and BMD 	Zofkova et al. 2017
Zinc (Zn):	<ul style="list-style-type: none"> • Induction of apoptosis of osteoclasts at high concentrations • Beneficial effect on bone integrity due to an increase in osteoblastic activity and synthesis of collagen, contributing to good strength, flexibility, and architecture of the skeleton • Reduction of toxic effects on osteoblasts by Cd and Pb • Deficiency of Zn is related to impairment in bone development 	Alghadir et al. 2016; Zofkova et al. 2017

4.5 g/cm³, and these can be divided into essential heavy metals (Fe, Zn, Cu, Mn, Cr (III), Co, and tin [Sn]) and nonessential heavy metals (Al, Cd, Cr (VI), Pb, thallium (Tl), uranium [U]). The skeleton is considered a long-term compartment for storing these elements (Chang et al. 2018). Some of these elements deposited and stored in the skeleton for long periods are Cd and Pb, which have been proposed as risk factors for OP (Alvaer et al. 2007). In addition, other elements as Cr, Cu, and Co have been investigated to have adverse effects on bone metabolism (Scimeca et al. 2016). Some of the most relevant and studied heavy metals and their negative effects on bone health are presented in Table 2.

Rare earth elements Rare earth elements (REEs) are a group of 17 chemical elements (yttrium, scandium, and the 15 lanthanide elements [lanthanum, cerium, praseodymium,

neodymium, promethium, samarium, europium, gadolinium, terbium, dysprosium, holmium, erbium, thulium, ytterbium, and lutetium]) which have many similar properties, and that often causes them to be found together in geologic deposits. These elements are also metals and have no known biological function. Their use in various industrial processes like ceramics, fluorescent materials, magnets, lasers, superconductors, catalysts, batteries, condensers, and electronic and materials started in the middle of the twentieth century. They have also been used in farmlands as fertilizers (production of phosphate fertilizers has spread a massive amount of REEs into the environment) and animal breeding. However, the attention to health effects due to REEs was addressed until the nuclear era. Human exposure to REEs is through food, drinking water or air, and therapeutic and diagnostic agents (Hirano and Suzuki 1996; Vidaud et al. 2012).

Table 2 Heavy metals/metalloids affecting bone health

Heavy metal/metalloid	Negative effects on bone health	References
Aluminum (Al)	<ul style="list-style-type: none"> • Incorporation into the bone matrix and uptake by osteoclasts during the resorption process where it deposits on trabecular bone surfaces • Inhibition of osteoblast differentiation (decrease in Runx2 expression), bone formation (decrease in the expression of type I collagen and IGF-1), leading to osteoblast apoptosis • Al deposition in bone decreases Ca, Mg, and P levels and diminishes the expression of osteopontin, osteocalcin, and bone sialoproteins inhibiting the bone mineralization process 	Rodríguez and Mandalunis 2018
Arsenic (As)	<ul style="list-style-type: none"> • Competition with the phosphate group in hydroxyapatite crystals, forming apatite arsenate and probably other calcium arsenate crystals, decreasing BMD • Intoxication with arsenic trioxide in vivo decreases osteoclast precursors' maturation and osteoclastic activity, altering the bone resorption process 	Rodríguez and Mandalunis 2018
Cadmium (Cd)	<ul style="list-style-type: none"> • Damage in bone mass and bone quality having a negative effect on growth - Two mechanisms described in bone tissue: <ol style="list-style-type: none"> 1. Cd induction of renal tubular damage decreasing Ca reabsorption in the nephron and leading to hypercalciuria and low BMD, increasing fracture rate risk 2. Osteotoxic effects by impairment of calcium metabolism during osteogenesis and bone homeostasis increasing calciuria and altering calciotropic hormones • Skeletal demineralization in children measured by bone markers suggests that exposure to Cd occurs at relatively low environmental concentrations and/or starts early in life • Inhibition of mineralization and alteration of the collagen matrix and decrease in the expression of markers of osteoblastic differentiation (Runx2, osteocalcin), extracellular bone matrix proteins (type I collagen), and enzymes involved in the mineralization process (ALP), altering the bone formation and mineralization process and increases RANKL expression 	Sughis et al. 2011; Scimeca et al. 2016; Zofkova et al. 2017; Rodríguez and Mandalunis 2018
Chromium (Cr)	<ul style="list-style-type: none"> • Bone damage by oxidative stress and decrease in the OPG/RANKL ratio • Accumulation of Cr (VI) in the femur and generation of a systemic decrease in ALP and TRAP, suggesting an impact on bone formation and resorption • Uptake of Cr (VI) by osteoblasts using membrane transporters and quick reduction to Cr (III) • Both Cr (VI) and Cr (III) decrease ALP activity and mineralization by osteoblasts in cultures 	Scimeca et al. 2016; Rodríguez and Mandalunis 2018
Lead (Pb)	<ul style="list-style-type: none"> • Accumulation in bone tissue (bone matrix), substituting other divalent cations in the body such as Ca²⁺, Mg²⁺, and Fe²⁺ • Association with bone mass deficiency, growth delay, reduced mineralization, increased bone turnover, osteoporosis, and alterations in bone metabolism at low concentrations • Most frequent metal in the bone of osteoporotic patients • In adults, 90–95% of total body lead is stored in trabecular and cortical bone, whereas, in children, 70 to 95% accumulates in the trabecular bone because of its high turnover rate 	Scimeca et al. 2016; Rodríguez and Mandalunis 2018
Mercury (Hg)	<ul style="list-style-type: none"> • Methylmercury decreases calcemia, increases metallothionein synthesis, and decreases estrogen receptor expression, affecting the metabolism of bone cells • Inhibition of osteoclasts and osteoblasts functions 	Rodríguez and Mandalunis 2018
Nickel (Ni)	<ul style="list-style-type: none"> • High concentrations inhibit ALP activity and bone mineralization in in vitro studies 	Rodríguez and Mandalunis 2018

Table 2 (continued)

Heavy metal/metalloid	Negative effects on bone health	References
Titanium (Ti)	<ul style="list-style-type: none"> • Inhibition of osteoblastic differentiation and decrease in the expression of type I collagen, osteopontin, and osteocalcin • Stimulation of osteoclastogenesis and osteoclast activity in the presence of BMP-2 and RANKL 	Rodríguez and Mandalunis 2018
Mixtures of two or more heavy metals	<ul style="list-style-type: none"> • Cd and Cr have similar toxic effects on bone cells, affecting proliferation, size, and shape of osteoblasts, decreasing ALP levels and calcium accretion • Combined accumulation of Pb and Cd is related to low bone quality and a reduction or even an absence of osteoblasts • Accumulation of at least three heavy metals showed low levels of BMD 	Scimeca et al. 2016

There is not much information about REEs and bone health. However, it is known that incorporation of these elements may affect bone quality just like other potentially toxic trace metals do since the bone is the tissue that accumulates more REEs. In bone tissue, REEs have half-lives from a few years up to decades representing an endogenous exposure over time and making its detection easier at low-level and long-term exposures. REE's contents are higher in trabecular bone than in cortical bone (Zaichick et al. 2011).

There are no reports about the assessment of REEs in bone tissue of children and adolescents. Many studies carried out in the 1980s and 1990s in animals exposed to REEs by different pathways have shown that these elements bioaccumulate principally in the skeleton; however, there was no evidence about the kind of bone cells affected (Hirano and Suzuki 1996). More recently, the content of REEs in ribs of deceased subjects has been measured. To estimate the effect of age, two groups were examined (15 to 35 and 36 to 55 years), there was an age-related accumulation of REEs with a statistically significant increase in the content of cerium (Ce), dysprosium (Dy), erbium (Er), gadolinium (Gd), lanthanum (La), neodymium (Nd), praseodymium (Pr), samarium (Sm), terbium (Tb), and ytterbium (Yb) in the older group, but no difference by sex (Zaichick et al. 2011).

Socioeconomic status

In most cases, socioeconomic status drives people's behavior, lifestyle, or what can be obtained with their income. In developing countries, a lower income is frequently associated with an inadequate intake of nutrients (Ca and vitamin D-enriched foods), a lower education level, and lack of health care knowledge (Pettifor 2014). It has also been associated with vitamin D insufficiency, higher values of PTH, lower values of BMD, and a higher prevalence of fragility fractures (Prada et al. 2018).

Lifestyle factors and bone health

Physical activity

Physical activity plays a vital role in determining bone mass due to increased bone density during the bone development process, which occurs in childhood and adolescence. The mechanism is that bone expands in response to the magnitude and direction of biomechanical forces. These mechanical forces on the skeleton arise from muscle, which generates signals that determine bone architecture (Leonard and Zemel 2002). Bone quality is influenced by high intensity, forceful activities, and constant over time. Team sports have shown a high correlation with BMD at calcaneal sites compared with walking or sporadic weight-bearing activities (Sharma et al. 2009).

Studies carried out in older people or postmenopausal women have shown that doing at least 30 min of low-intensity exercise increases the BMD at different skeletal sites (Gu et al. 2007). Aerobic exercise of moderate intensity (jumping or resistive exercise) for 1 h protects bone and cartilage, reduces bone resorption, and increases the rate of bone formation (Alghadir et al. 2016). The type of physical activity or training program, the duration, intensity, and frequency are very important (Farr and Dimitri 2018).

Tobacco smoke or smoking

During cigarette and other tobacco product smoking, their incomplete combustion generates contaminant emissions. Throughout the burning process, a high number of chemical compounds are generated and released into the air. Those related to bone disorders are present in the cigarette smoke's tar fraction. These are two polycyclic aromatic hydrocarbons (PAHs): benzo(a)pyrene and 7,12-dimethylbenz(a)

anthracene, which are also found in diesel engine emissions and automobile exhaust (Alvaer et al. 2007) and in particulate matter (PM), (Prada et al. 2018).

Active smoking is associated with decreased BMD and increased risk of fractures, particularly hip fractures, compared with nonsmokers (Chen et al. 2015; Prada et al. 2018). In addition, some biochemical parameters are affected, such as serum levels of PTH, that are lower in smokers (Prada et al. 2018). Only a few studies have investigated the relationship between passive smoking and bone health in humans. Studies of passive smoking in older people and/or in menopausal women showed an association with decreased BMD and a higher risk of fractures (Holmberg et al. 2011; Chen et al. 2015).

Beverages

Soft drinks intake The deleterious effect from soda intake is secondary to both, increased phosphoric acid of these beverages and a replacement of Ca-rich milk by P-rich carbonated drinks (Pettinato et al. 2006). Sodas contribute to 3.3% of total P intake. Only cola has been studied as a source of additive inorganic P and its effects on bone health. For example, a 20 fl. oz. bottle of cola provides 55 mg of P that is absorbed readily and rapidly, while noncola sodas are P-free. Cola intake is related to altered bone metabolism, low bone density, and fractures even in adolescents, in both genders (Vorland et al. 2018). These beverages also contain sugar and caffeine which contributes to deleterious effect on bone health. The effect of sugar on bone health is an indirect and late effect related to other pathologies (originated by the excess and long-term intake of sugar) such as obesity and diabetes, which trigger kidney disorders in most cases. As mentioned above, this is not immediate, and it may take a long time for the effect on the bone to be seen. Conversely, the adverse effects on bone health due to caffeine are more elucidated and also in some studies have investigated its direct effects on the bone remodeling process. Thus, a section of these effects is described below (3.5.3.3.).

Alcohol consumption Alcohol impairs the proliferation and function of osteoblasts leading to malabsorption, increased renal excretion, and disruption of Ca-regulating hormones such as PTH, calcitonin, and vitamin D metabolites (Sommer et al. 2012). However, alcohol intake may have beneficial or detrimental effects in adults and older people, particularly in postmenopausal women, depending on the dose (Sommer et al. 2012). Low alcohol intake has shown beneficial effects on BMD at different sites: lumbar spine, total body and mid-radius, femoral neck, and lumbar spine (Sommer et al. 2012). Moderate alcohol consumption has been suggested to increase estrogen levels and BMD, decreasing fracture rates. In contrast, high amounts of alcohol have

detrimental effects on skeletal health due to adverse effects on protein and Ca metabolism, direct effect on osteoblasts, and a high predisposition to falls, a risk factor of fractures (Curtis et al. 2016). Long-term alcohol intake has been identified to exert direct and indirect effects on bone turnover and remodeling, leading to decreased BMD and increased risk of fractures (Sommer et al. 2012).

Caffeine Coffee and more recently energy drinks are the major sources of caffeine. Current assessments suggest that the average recommended caffeine intake at all ages is 165 mg/day. Effects of caffeine on bone are more related with increased urinary calcium excretion. To date, there are not many studies carried out in children and adolescents that evaluate the relationship between bone health and caffeine consumption. Although, studies in adults reported that high caffeine intake (> 300 mg/day) was associated with lower cortical and trabecular volumetric BMD in men, also, the rate of bone loss at the spine is higher in high-caffeine consumers; and in some studies, a smaller relationship between high caffeine intake and fractures was observed (Wikoff et al. 2017).

Obesity

Obese children have shown decreased levels of BMD or bone mass compared with nonobese children of similar height. It is not clear whether this decreased BMD is a direct effect of fat on bones or decreased muscle mass or reduced activity levels or a combination of both factors (Borges and Brandao 2006). Excess fat accumulation during this period has been proposed as a risk factor for fractures because of high propensity and significant impact of falls, unhealthy habits, and a sedentary life (Farr and Dimitri 2018). The adipose tissue has multiple effects on bone metabolism. This excess of fat may interfere with bone development and modifies microarchitecture within trabecular and cortical bones. All these effects on bone tissue are observed not only during developmental periods but also in obese adults. Bariatric surgery is an alternative method to control obesity and fat tissue in adults, which has been positively associated with BMD. Also, some hormones (adipokines and leptins) produced by fat impact bone development and enhance osteoblastic proliferation and differentiation (Farr and Dimitri 2018).

Glucocorticoids

Certain medications may also contribute or predispose to bone loss. Some of these are glucocorticoids, calcineurin inhibitors, and chemotherapeutic agents (Borges and Brandao 2006). Mainly, glucocorticoids affect bone negatively by many pathways triggering OP and fractures. These drugs are

especially harmful to bone health because they are associated with diminished bone formation and increased bone resorption (by impairing Ca absorption and increasing urinary Ca loss, leading to secondary hyperparathyroidism). Thus, bone loss is believed to be most rapid in the first few months of therapy with glucocorticoids, which results in a 30% reduction in the total amount of trabecular bone replaced in each remodeling cycle (Leonard and Zemel 2002; Curtis et al. 2016).

Demographic area: urban vs rural

Few studies have investigated the association between home location and the adverse effects on BMD. Most people worldwide live in rural or nonurban regions (Gu et al. 2007). Several studies in western populations have shown that rural people have lower fracture rates (Chen et al. 2015), higher BMD in the distal forearm, and total body (Prada et al. 2018) compared with urban people. In contrast, in eastern countries as China, middle-aged and elderly men and women in urban areas have higher spine BMC, BMD, and bone area and lower rates of fractures than those of rural people (Gu et al. 2007). It has been shown that Asian immigrants in western countries have higher skeletal BMD than that of native Asians, probably due to lifestyle factors and dietary patterns (Gu et al. 2007).

Many factors could explain these controversial results. For example, urban children and adolescents are taller and heavier and have higher body mass index (BMI) and waist circumference than that of people in rural areas. There is more knowledge about healthcare in urban areas, including better nutrition (milk, dairy products, and vitamin D and Ca supplements intake) and higher income, which contribute to better access to these nutritional products, whereas physical activity, smoking, and alcohol consumption are more common in rural areas (Gu et al. 2007). On the other hand, environmental factors such as exposure to compounds related to industrial emissions, automotive exhaust, metals, waste, and many other toxicants generated in urban areas are also related to bone tumors in children (García-Pérez et al. 2017); also, a delay of 2–2.5 years in their bone development compared with their peers, a deficiency in BMD and vitamin D, and some serum bone turnover markers such as osteocalcin, B-cross laps, and procollagen type I N propeptide (PINP) in adolescents have been reported in urban zones (Zhumalina et al. 2020).

Environmental pollutants and bone health and air pollution

Air pollution is one of the most critical and avoidable risks to health globally. Sources include vehicle emissions, industrial combustion, heating of fossil fuels and natural sources such as volcanic emissions, dust resuspension, and wildfires

that have a higher impact in bigger cities than in rural areas (Alvaer et al. 2007). Among the particles found in air pollution are particulate matter (PM_{10} and $PM_{2.5}$), black carbon (BC), carbon monoxide (CO), and nitrogen dioxide (NO_2) (Schraufnagel et al. 2019). Also, in crowded roads (freeways, major roads, etc.), there are significant levels of automotive exhaust that contain relevant contaminants such as PAHs (Chen et al. 2015).

Air pollution can have deleterious effect on bone tissue and alters bone density and mineralization (Chen et al. 2015). There are two potential pathways by which air pollution could affect bone tissue. The first one is that air pollution induces a chronic inflammatory condition, which is characterized by a high level of pro-inflammatory markers like interleukin 6 (IL-6), tumor necrosis factor-alpha (TNF- α), and C-reactive protein (CRP) involved in immune regulation. Higher levels of IL-6 could, in turn, lead to an increase in bone turnover and bone loss (demineralization) and a high risk of bone fractures. The second explanation is related to PAHs in automotive exhausts; however, this mechanism has not been widely studied (Liu et al. 2015; Prada et al. 2018).

In the adult bone, air particles may directly or indirectly affect bone biology and bone mineral loss (Prada et al. 2018), leading to OP and bone fractures (Schraufnagel et al. 2019). For example, total body BMD was inversely associated with $PM_{2.5}$ and PM_{10} but not BMD at the hip. For NO_2 , a similar but not statistically significant association was found (Alvaer et al. 2007). Subjects who live closer to a freeway or crowded road (< 150 m) have lower body BMD and lower pelvic BMD compared with those living far from it (> 150 m) (Chen et al. 2015). Prada et al. (2018) showed that people living in areas with a high concentration and long-term exposure to BC have lower serum PTH levels and increased BMD loss at multiple anatomical sites (femoral neck and ultra-distal radius). $PM_{2.5}$ showed a negative association with BMD, and an association between $PM_{2.5}$ levels and rates of hospital admissions for bone fractures was observed, too (Prada et al. 2018). Also, it has been reported that OP-related bone fractures were common in areas with high concentrations of $PM_{2.5}$, CO, and NO_2 and those markers of increased bone turnover and bone mineral loss were lower with the exposure to ambient BC and $PM_{2.5}$ (Schraufnagel et al. 2019).

The evaluation of bone turnover markers (OC and C-terminal telopeptide of type I collagen [CTx]) was positively associated with coarse particles ($PM_{2.5-10}$), PM_{10} , and NO_2 in older girls compared with boys (Liu et al. 2015). Nevertheless, to characterize bone metabolism changes on the site of exposure to air pollution, more pediatric research is needed. Thus, measurements of serum levels of 25-hydroxyvitamin D [25(OH)D], serum calcidiol (25 OH vitamin D3), and PTH should be included for a better prevention (Calderón-Garcidueñas et al. 2012).

Overview of bone diseases

Rickets

Rickets is a bone disease mainly present in growing children like infants and preschool-aged children (Maricic 2008; Carpenter et al. 2017). It is associated with diminished levels of serum vitamin D, Ca, and/or P and characterized by a delay in the mineralization of growth plates in bones. Nutritional rickets are more common worldwide, not only in infants and children but also in adolescents from developing countries, where low Ca and vitamin D intake are common (Carpenter et al. 2017). Calciopenic rickets and phosphopenic rickets are less common, also associated to a deficiency in Ca, P, vitamin D, PTH, and FGF23 serum levels. Heritable rickets is caused by mutations in genes that encode proteins involved in vitamin D activation and function, P homeostasis, and/or bone mineralization (Carpenter et al. 2017).

Rickets' clinical environment is diverse; it involves skeletal and nonskeletal manifestations that depend on age. Premature birth (<1,000 g or <28 weeks of gestation) is positively associated with an increased risk of developing rickets. Later, during the first year of life, infants can delay the ability to walk. In early childhood, progressive bowing deformities of the legs are observed. Older children can present bone pain and fatigue, and in some cases, fractures are seen. Adolescents show isolated bone pain and proximal muscle weakness (Carpenter et al. 2017).

To confirm rickets' diagnosis, the clinician must set the attention in medical history, physical examination, and biochemical tests, which is finally confirmed by radiography. In some cases, molecular techniques to detect mutations are used (Carpenter et al. 2017).

Osteomalacia

Osteomalacia is one of the most common bone diseases in older people. It is an osteometabolic disease whose primary cause is vitamin D deficiency. However, there are many other causes by which osteomalacia can be developed such as abnormal vitamin D metabolism, use of anticonvulsants and drugs like etidronate, intake of aluminum and fluoride, chronic renal failure, and hypophosphatemia, among others (Maricic 2008; Sitta et al. 2009). At the structural and anatomical level, a deficiency of mineralization of the osteoid matrix in the cortical and trabecular bone is observed (Sitta et al. 2009).

Clinically, early detection osteomalacia considers vitamin D levels. It is also detected when ALP is augmented and is accompanied by normal or diminished serum Ca and P levels and elevated PTH. An adequate supplementation with vitamin D should be considered (Maricic 2008).

Osteomalacia typically presents in the asymptomatic form with radiologic osteopenia or low BMD measured by dual-energy X-ray absorptiometry (DXA). It is symptomatic when proximal muscle weakness and diffuse bone pain are present (Maricic 2008). A final diagnosis for osteomalacia should include the medical history, physical examination, laboratory, and imaging tests. The gold standard in the diagnostic of osteomalacia is the tetracycline-labeled bone biopsy. Osteomalacia must be considered in patients with low BMD and bone pain in the absence of clinical fractures (Maricic 2008).

Osteoporosis

OP is a metabolic bone disease characterized by low bone mass or low BMD and microarchitectural alterations of bone, triggering enhanced bone fragility with increased risk of fractures, particularly in the wrist and the hip (Burns et al. 2003). This disease is also a painful condition that reduces the quality of life (loss of independence) and increases mortality in older people (Borges and Brandao 2006).

Many factors may be involved in the presentation and progression of OP. It has been reported that OP is associated with advanced age, gender (female), race (Caucasian or Asian), low body weight, family history, Ca and vitamin D deficiency, nutrition, use of certain medications (glucocorticoids, thiazide), sedentary life, smoking, and excessive alcohol consumption (Gu et al. 2007; Sommer et al. 2012).

The mechanism by which OP develops is a bit complex, and it depends on many factors and the etiology, but in the end, all of them share a similar way. There are three main common mechanisms in all cases of OP. The first one is by an inadequate reached peak bone mass during early periods of life (insufficient mass and strength). The second and third mechanisms involve the remodeling process (imbalance between bone resorption and bone formation). Thus, the process is carried out in bone multicellular units (BMUs) where osteoclast destroys bone matrix at a higher rate than osteoblast can restore it, leading to low bone density and, consequently, bone fragility.

Nonetheless, the homeostasis of minerals such as calcium, phosphorus, magnesium, and nutrients, like vitamin D, is also relevant in the mechanism of OP. For example, calcium metabolism and vitamin D play a crucial role in bone mineralization, and a deficit of these nutrients leads to reduced bone accumulation. In addition, Ca deficiency activates parathyroid glands to produce PTH, which enhances bone resorption to guarantee enough Ca in the blood (Borges and Brandao 2006; Gu et al. 2007; Sommer et al. 2012).

The diagnostic of OP is based on the measurement of the BMD at different skeletal sites. However, the damage

does not appear in its totality; instead, it progresses as bone damage advances. The World Health Organization defines osteopenia (loss of mineral density in the bone tissue) as a BMD between -1 and -2.5 standard deviations (SD) and OP as $BMD > -2.5$ SD below the mean for normal young adults (Sharma et al. 2009). Although the WHO criteria for OP are not appropriate to use in children, adolescents, and young adults (less than 20 years old), the correct term should be “low bone density for chronologic age” when the Z-score is less than -2.0 (Borges and Brandao 2006). The Pediatric Position Development Conference has used the term “pediatric osteoporosis,” which is defined by any of the following criteria: (a) ≥ 1 vertebral fracture occurring in the absence of local disease or high-energy trauma; (b) low bone density for age and significant fracture history (defined as ≥ 2 long bone fractures before 10 years of age or ≥ 3 long bone fractures before 19 years of age) (Bachrach and Gordon 2016).

Relationship between bone health and the kidney

An adequate physiological function of the kidney is necessary for bone health, metabolism, and development as there is a close and highly complex interaction between them. The kidney regulates Ca^{2+} and PO_4^{3-} homeostasis and is a target of several hormones and cytokines that participate in bone metabolism such as osteoprotegerin (OPG), sclerostin, FGF23, and PTH. Several substances involved in bone formation and remodeling processes are synthesized by kidneys, such as $1,25(OH)_2D_3$, klotho, erythropoietin, and bone morphogenic protein 7 (Wei et al. 2016).

Chronic kidney disease (CKD) is present in up to 15% of the general population and is a major cause for bone disorders. CKD with decreased glomerular filtration rate, regardless of the etiology, causes a decrease in $1-\alpha$ hydroxylation of vitamin D, secondary hyperparathyroidism, and an increase in bone resorption. Also, all the bone abnormalities associated with CKD eventually trigger to a higher rate of fractures (Wei et al. 2016). Additionally, more subtle kidney diseases such as tubular acidosis are also responsible for bone disorders, either through the acidosis or through the urinary loss of elements such as Ca, P, and Mg. Thus, screening populations for kidney diseases at an early stage can contribute to a better bone health. A better and more detailed understanding of the relationship between damaged kidneys and the bone is shown in Fig. 3.

Techniques to evaluate bone health

Imaging techniques

In the past, X-rays were the most frequent technique to assess bone maturation status in children, including significant bone delay (Liu et al. 2015). Nowadays, other imaging techniques have emerged to assess with more accuracy the bone status and less radiation exposure.

Dual-energy X-ray absorptiometry

Dual-energy X-ray absorptiometry (DXA) is the most used technique, considered the gold standard to evaluate bone status. It is a 2-dimensional measurement of the bone referred to as areal BMD (aBMD). The results are presented as T- (comparison of observed aBMD with that of healthy young adults of the same gender) and Z-scores (the SD score based on specific age and genders). T-scores are not appropriate for children and adolescents due to the constant bone turnover (growing period); instead, Z-scores are recommended. The advantages of DXA are its availability, short scanning time, and low radiation exposure; nevertheless, the equipment is expensive, and the images do not distinguish between trabecular and cortical bone (Borges and Brandao 2006). BMD is expressed in arbitrary units (mineral mass/area) and grams per square centimeter (g/cm^2). BMD differs between skeletal sites (Alvaer et al. 2007). In this context, BMD measured with DXA at the hip and spine is considered the gold standard, which has been predictive of fracture risk in adults but not in children (Borges and Brandao 2006). In children, the Z-scores of total body and lumbar spine (L1-L4) are the most used parameters (Bachrach and Gordon 2016).

Quantitative ultrasound

Quantitative ultrasound (QUS) is another technique widely used to evaluate bone density; it is an exploratory and noninvasive method which can be used in young people including neonates. It has many advantages over DXA, such as low cost, speed, portability, and no radiation exposure (Leonard and Zemel 2002). QUS can measure unique skeletal properties that are not quantified in BMD measurements, such as elasticity, and show quantitative and qualitative aspects of bone tissue (Sharma et al. 2009). Its use is limited due to a lack of validated pediatric reference data in different ethnicities. As in DXA, the results are presented as T- and Z-scores; nevertheless, QUS measurements also can be presented as speed of sound (SOS; in meters per second [m/s]),

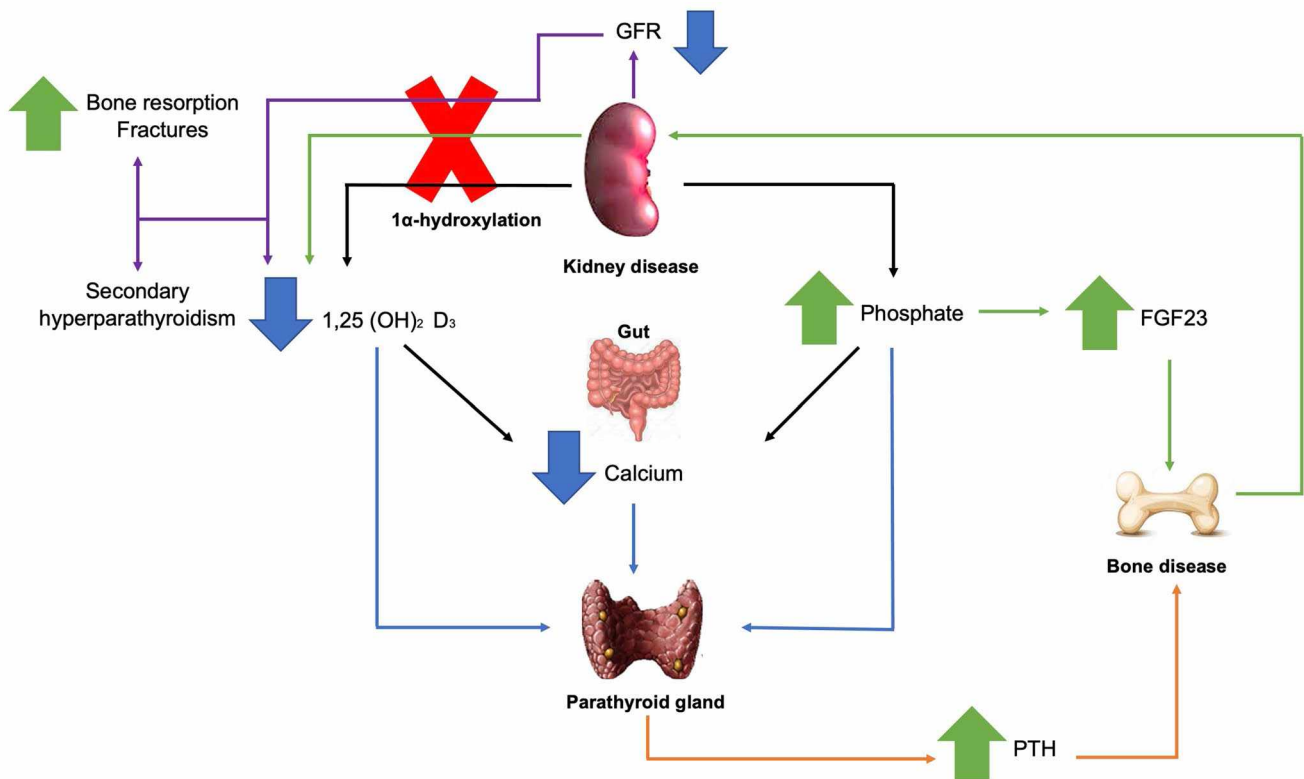


Fig. 3 Proposed mechanism for bone disease through kidney damage. Damaged kidneys cannot carry out the 1α -hydroxylation of 25-hydroxyvitamin D_3 , triggering a decrease in the concentration of 1,25-dihydroxyvitamin D_3 (active vitamin D), secondary hyperparathyroidism, and an increase in bone resorption and rate of fractures. This serum active vitamin D deficiency leads to reduced intestinal calcium absorption. On the other hand, kidney damage also increases tubular phosphate reabsorption, decreasing intestinal calcium absorp-

tion. The triad of low calcium and active vitamin D_3 levels and high phosphate levels stimulate the parathyroid gland to produce large amounts of parathyroid hormone (PTH), mobilizing calcium from bone, leading to bone disease. Also, the elevated phosphate concentrations stimulate the secretion of fibroblast growth factor-23 (FGF23) through osteocytes. Finally, plasma FGF23 enhances the excretion of phosphate in the proximal tubule and the reduction of synthesis of active vitamin D_3 due to the low regulation of 1α -hydroxylase

broadband ultrasound attenuation (BUA; in decibels per megahertz [dB/MHz]), and stiffness index (SI; in percentage [%]) (Pettinato et al. 2006). Both, SOS and BUA relate to bone density and architecture (Leonard and Zemel 2002). Bone density assessed by BUA parameter with ultrasound correlates with age, height, weight, physical activity, and sexual maturity. Also, BUA correlates with DXA measures of bone density in adults and children (Leonard and Zemel 2002). The sites of interest to carry out the QUS measurements are the mid-shaft tibia and distal 1/3 radius. In some studies, a positive correlation between QUS measurements and DXA has been observed (Pettinato et al. 2006).

Other imaging techniques

Nowadays, more complex and sophisticated three-dimensional imaging techniques are being used to evaluate bone health, such as quantitative computed tomography (QCT) and peripheral quantitative computed tomography (pQCT). Both techniques provide more accurate measurements than

BMD measured by DXA in children and adolescents because they can measure volumetric BMD (vBMD; in grams per centimeter cubic [g/cm^3]), the geometry of the bone, and differentiate between cortical and trabecular bones. However, radiation, more prominent equipment types, high cost, and less availability are some of their disadvantages (Pettinato et al. 2006).

Biomarkers for evaluation and early diagnosis

Bone metabolism and turnover markers to detect bone loss signs and predict the risk of fractures are an alternative and supportive method to evaluate bone health (Zhumalina et al. 2020). As observed in studies of adult populations, a negative association between bone turnover markers and bone status has been established. Higher levels of these markers are associated with rapid bone loss, diminish bone strength, and loss of structural elements in bone, contributing to bone fracture (Liu et al. 2015). Markers of new bone formation that correlate significantly with BMD are OC and ALP,

Table 3 Matrix and biomarkers used to evaluate bone health

Group	Biomarkers	Matrix	Upregulated or downregulated
Bone formation markers products of osteoblast metabolism, that reflect the production of type 1 collagen	• Bone-specific alkaline phosphatase (BSAP)	Blood (plasma)	Upregulated
	• N-terminal peptide cleaved from type-III procollagen (PIINP)	Blood (serum)	Upregulated
	• Osteocalcin (OC)	Blood (serum)	Upregulated
	• Procollagen type I N propeptide (PINP)	Blood (serum, plasma)	Upregulated
	• Procollagen type I C propeptide (PICP)		
Bone resorption markers mainly by-products of type 1 collagen breakdown	• Amino-terminal collagen crosslinks (NTX)	Urine / Blood (serum)	Upregulated
	• Carboxy-terminal collagen crosslinks (CTX)	Blood (plasma)	Upregulated
	• Carboxy-terminal telopeptide of type-I collagen (ICTP)	Blood (serum)	Upregulated
	• Deoxypyridinoline (DPD)	Urine	Upregulated
	• Pyridinoline (PYD)	Urine	Upregulated
	• Tartrate-resistant acid phosphatase (TRAP5b)	Blood (serum)	Upregulated
Osteocytic markers can regulate osteoblastic and osteoclastic activity	• Cathepsin-K	Blood (serum)	Upregulated
	• Dentin matrix protein-1 (DMP1)	Blood (serum)	Upregulated
	• Fibroblast growth factor 23 (FGF23)	Blood (serum, plasma)	Upregulated
	• Matrix extracellular phospho-glycoprotein (MEPE)	Blood (serum)	Upregulated
	• Osteoprotegerin (OPG)	Blood (serum)	Upregulated
	• Receptor activator of nuclear factor kappa-B ligand (RANKL)	Blood (serum, plasma)	Upregulated
	• Sclerostin		
Others help to diagnose bone alterations	• Calcium (Ca)	Blood (serum)/urine	Downregulated
	• Magnesium (Mg)	Blood (serum)	Downregulated
	• Parathyroid hormone (PTH)	Blood (serum)	Upregulated
	• Phosphorus (P)	Blood (serum)/urine	Upregulated / Downregulated
	• Vitamin D	Blood (serum)	Downregulated

which are produced by osteoblasts. Bone resorption markers correlated with BMD are deoxypyridinoline and type 1 collagen carboxy-terminal telopeptide (ICTP). These four biomarkers, together with serum PTH, Ca, P, and 25[OH]D, are the most used in the clinical diagnosis of bone alterations (Yeste and Carrascosa 2015). Biomarkers of bone formation and resorption can be measured in blood or urine (Table 3) and reflect bone cells' metabolic activity.

Concentrations of these biomarkers vary depending on age, gender, pubertal stage, and fasting status. Their assessments are not always standardized, so that single or combined biomarkers are not sufficient to diagnose bone mineralization or turnover defects (Lalayiannis et al. 2019). More than one technique is recommended to measure the initial damage and its progression. A bone biopsy might be considered.

Prevention and treatments

Finding children with low bone mass early in life could be an important strategy for preventive and therapeutic efforts to optimize bone accrual and bone strength. The

initial evaluation of bone health must be carried out by a pediatrician, measuring height and weight, considering growth velocity. A patient with decreased height velocity or decreased weight gain over time should raise concern for poor bone health (Borges and Brandao 2006).

Many treatment and prevention protocols to increase bone mass in the general population are available. In children and adolescents, the objective is to reach the adequate bone mass to prevent bone damage in the future. The most basic, safe, available, and recommended intervention in this young population is the supplementation with Ca and vitamin D, which should meet the current recommended daily intake by each age and gender (Bachrach and Gordon 2016). Lifestyle changes such as increasing weight-bearing physical activity play an essential role in the restoration of bone health among children and adolescents. The pharmacological treatment with bisphosphonates, calcitonin, hormone replacement therapy, growth hormone, and cinacalcet, have been proposed for adults as well as children and adolescents (Leonard and Zemel 2002).

Future prospects

Nowadays there are many techniques that help us to diagnose abnormalities in bone quality; nonetheless, new findings and novel molecular techniques need to take relevance for a better understanding of the initiation and progression of the disease. In our opinion, we provide some of the alternatives or options to be carried out:

- Set up bone healthcare programs with long range and ease understanding for people living in communities where the access of information is very scarce.
- Provide more knowledge in the field of clinical research to establish normal values in turnover biomarkers developing more trials.
- Become aware of some key factors aimed at improving bone quality such as diet and nutrition (including well supplementation), physical activity, and exposure to contaminants (metals).

Conclusions

In this work, we have provided an overview of traditional (genetics, nutrition, and physical activity) and environmental factors that can influence bone health. Childhood and adolescence are crucial periods of bone development and acquisition of peak bone mass and, as such, should be monitored by health care providers. Pediatricians and healthcare workers should pay more attention to provide recommendations to maximize bone health in order to avoid adult complications such as spontaneous fractures and OP.

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Declarations

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