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Early bone health: exploring relationship between oxidative stress and skeletal development in newborn infants

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ABSTRACT

Bone health during childhood is critical for proper skeletal development and long-term quality of life. The process of bone formation relies on a balance of mineralization and cellular activity, which is regulated by oxidative stress (OS). While physiological levels of reactive oxygen species (ROS) are important for normal bone cell function and homeostasis, excessive OS can contribute to the development of bone diseases, such as osteoarthritis and osteoporosis. Enzymes like xanthine oxidoreductase are involved in amplifying ROS production, which can lead to cartilage degradation and disrupted bone remodeling. Despite increasing recognition of OS as a risk factor in adult skeletal health, its impact on fetal and neonatal bone development remains underexplored. In vitro and animal model studies, including those using free radicals exposure, have been performed to understand how OS impairs osteogenesis.

This review examines the role of OS in perinatal bone development analyzing key environmental risk factors and the potential long-term consequences of early-life redox imbalance on skeletal health.

The sensitivity of the fetal bone to OS suggests that oxidative damage during this critical period can result in impaired bone growth, low birth weight, and long-term skeletal disorders. Oxidative stress interferes with osteoblast differentiation, enhances adipocyte formation from mesenchymal stem cells, and stimulates osteoclast activity, leading to bone resorption. Clinical studies on the impact of OS on neonatal bone metabolism remain limited. Identifying key risk factors for early-life redox imbalance could be crucial in developing potential antioxidant therapies to support skeletal health during childhood

Introduction

Bone health in children influences overall development and quality of life. The bone matrix is mainly made up of mineral salts, collagen fibres and glycoproteins. While mineral salts, such as calcium and phosphorus, ensure the hardness of the tissue, collagen and glycoproteins provide elasticity.[1,2] Bone tissue, on the other hand, is also composed of three types of continuously active cells: osteoblasts, osteocytes and osteoclasts.

In normal bone homeostasis, reactive oxygen species (ROS) are required for the regulation of cell proliferation, survival, metabolism, apoptosis, and differentiation, being essential for the transmission of cellular signals.[3] However, persistent exposure to high levels of oxidative stress (OS) can cause skeletal diseases. In adults, more and more

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studies are demonstrating the role of oxidative stress in chronic bone diseases, such as osteoarthritis and osteoporosis.[4] Recently, Qiu C et al. demonstrated that the xanthine dehydrogenase (XDH) gene is significantly upregulated in patients with osteoarthritis. The transcription product of the XDH gene is xanthine oxidoreductase (XOR), an enzyme present in two interconvertible forms, XDH and xanthine oxidase (XO), which in turn produce excess ROS/RNS.[5] Elevated intracellular levels of FRs induce chondrocyte dedifferentiation/apoptosis and recruit polymorphonuclear cells, which release proinflammatory cytokines, amplifying the production of ROS and proteases. ROS and proteases, in turn, disrupt cartilage homeostasis, causing extracellular matrix loss, mitochondrial dysfunction, and chondrocyte apoptosis.[6,7] In osteoporosis, ROS contribute to bone mass reduction by altering the functional balance between osteoblasts and osteoclasts.[8] Indeed, on the one hand, ROS promote osteoclastogenesis and increase osteoclast activity, leading to increased bone resorption, on the other hand they trigger osteoblast apoptosis, thus reducing bone formation capacity.[9,10]

The aim of this review is to promote a deeper understanding of the role of oxidative stress in perinatal bone development.

Risk factors of oxidative stress in fetal and neonatal period

Under physiological conditions, oxygen is the final acceptor of high-energy electrons generated in various metabolic processes, leading to the formation of ROS. Reactive oxygen species ROS are most formed from the reaction of oxygen with a single electron, more rarely with two or three electrons.[11] Furthermore, oxygen free radicals (FRs) can combine with nitric oxide (NO) to form reactive nitrogen species (RNS), while in the presence of transition metals, particularly iron, oxygen radicals form hydroxyl radicals.[12]

Although small amounts of ROS/RNS perform beneficial functions as messengers, FRs react with nearby macromolecules, such as lipids, proteins, and DNA, altering their structure and/or function.[13,14]

Oxidative stress results from an imbalance between the production and elimination of ROS/RNS by the antioxidant defense system and has been associated with placental oxidative disorders and neonatal pathologies.[15]

Free radicals (FRs) are present from early pregnancy, contributing to normal embryonic and placental development.[16] At the end of the first trimester, placental maturation leads to an increase in oxygen concentration and an exponential production of FRs. FRs, in turn, regulate the regression of villi from the surface of the chorionic sac, leaving the definitive placenta.[15]

Pregnancy represents a critical window of developmental plasticity, during which embryonic and fetal development can be influenced not only by the inherited genetic makeup but also by a variety of environmental factors.[17] Early intrauterine life is particularly sensitive to perturbations, and adverse conditions during this period have been associated with both immediate complications—such as impaired fetal growth and increased perinatal morbidity—and long-term consequences for the health of the offspring.[18–20]

The concept of fetal programming of adult diseases, first proposed by Barker and colleagues, describes how exposure to suboptimal intrauterine environments can alter the trajectory of fetal development.[18] These alterations represent adaptive responses aimed at enhancing fetal survival in the short term, but they may lead to permanent structural and functional changes in organ systems. As a result, such adaptations can predispose individuals to chronic diseases later in life (Fig. 1).

The availability of nutrients, hormones, and respiratory substrates represents a fundamental determinant of fetal growth and long-term offspring health. The efficiency of nutrient and oxygen transfer is governed by the "placental barrier," which mediates fetal access to these essential substrates. Importantly, maternal nutritional status—whether characterized by undernutrition or overnutrition during early

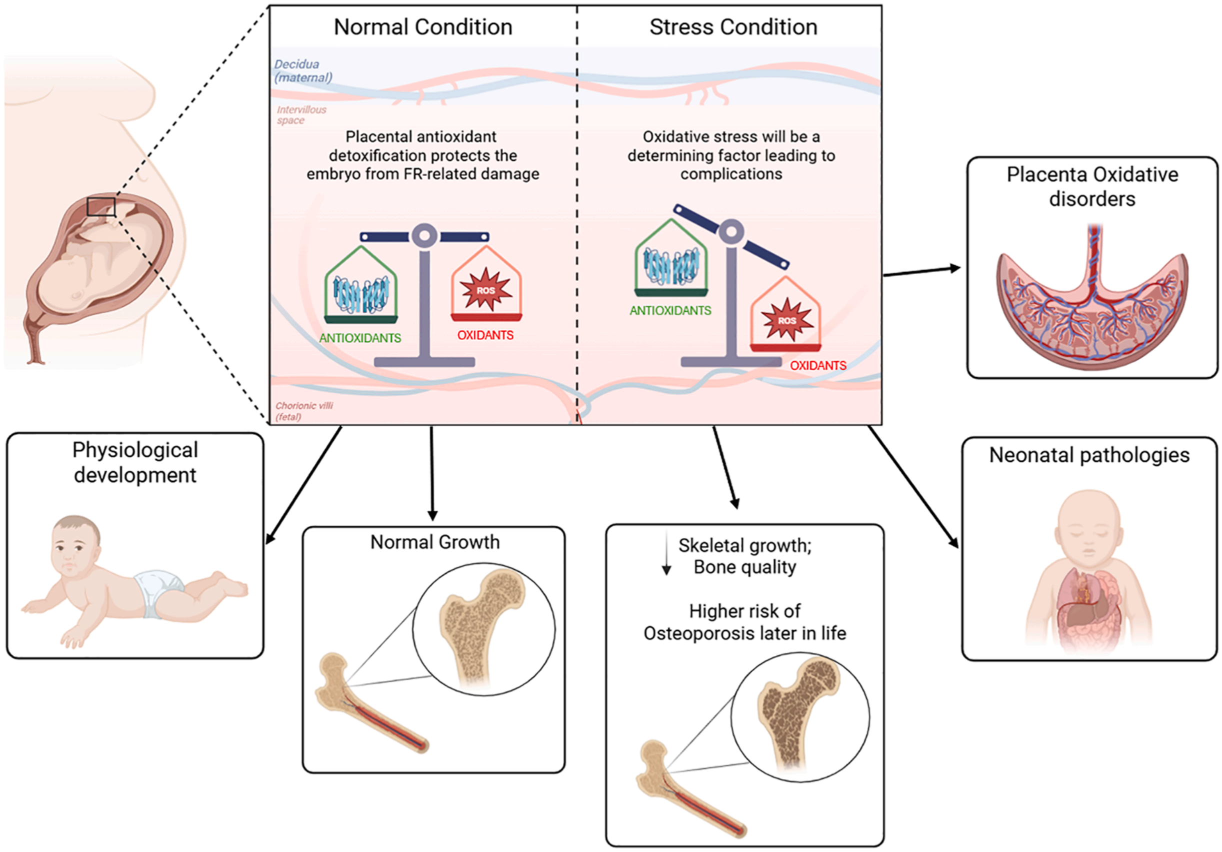

Fig. 1. Overview of intrauterine redox balance and its impact on fetal growth, with emphasis on bone tissue development.

gestation—has been implicated in elevating the risk of cardiovascular and metabolic disorders in offspring later in life[21]

Oxidative stress functions as a central mechanistic link between adverse intrauterine conditions and the programming of chronic disease predisposition. It is hypothesized to act as an initiating molecular signal within the cascade of developmental programming, particularly in the context of poor maternal nutrition[22,23]

Maternal undernutrition can compromise the availability of antioxidant defenses—including vitamins, proteins, and trace elements—thereby impairing antioxidant capacity and shifting the redox balance toward oxidative stress during pregnancy[24]

Conversely, maternal overnutrition—for example, obesity or high-fat diet exposure—induces oxidative stress via chronic inflammatory pathways. Animal studies have demonstrated increased levels ROS and lipid peroxidation markers such as malondialdehyde, alongside reductions in antioxidant enzymes like superoxide dismutase and catalase, in both mothers and their offspring[25,26]

These redox perturbations have been observed across maternal, placental, and fetal tissues, underscoring the transgenerational impact of oxidative dysregulation[23]

Emerging evidence from systematic reviews and meta-analyses supports these findings. For instance, offspring of rodents exposed to maternal high-fat diet exhibit elevated oxidative stress—characterized by increased ROS and malondialdehyde, and diminished antioxidant enzymes—highlighting the programming effects of maternal overnutrition on redox homeostasis in progeny[27]

From a translational perspective, antioxidant nutrient interventions during gestation have shown potential to reprogram and mitigate adverse programming outcomes. In animal models, supplementation with antioxidant nutrients during early life has demonstrated beneficial effects in preventing or attenuating kidney disease, hypertension, and other organ-specific disease phenotypes programmed by oxidative stress[24,28]

Under normal conditions, placental antioxidant detoxification protects the embryo from FR-related damage. However, under stressful conditions, such as preeclampsia and diabetes, oxidative stress will be a determining factor leading to complications such as miscarriage, fetal growth restriction and/or premature rupture of membranes, with the consequent risk of preterm birth[29]

Premature infants, in turn, are at greater risk of oxidative stress and related pathologies. In fact, while a normal increase in FR occurs at birth due to greater exposure to environmental oxygen compared to intrauterine oxygen, prematurity is often associated with the need for ventilation with supplemental oxygen.[30] Moreover, premature infants are more susceptible to oxidative stress because their defenses are weakened.[31]

Perinatal bone development and oxidative stress

Bone formation during embryogenesis occurs in two distinct processes: intramembranous ossification or endochondral ossification. The first, typical of flat bones, begins with the condensation of mesenchymal populations that directly differentiate into bone, while the second involves an intermediate cartilaginous phase.[32] During endochondral ossification, mesenchymal cells differentiate into chondrocytes, which begin to secrete cartilaginous matrices. The cells surrounding the newly differentiated chondrocytes form the perichondrium and stimulate osteoblast differentiation, defining the boundary of bone.[33] The proliferative zone is a site of rapid chondrocyte replication and is composed of three distinct zones: the resting zone, which contains progenitor chondrocytes, the proliferative zone, characterized by differentiating chondrocytes, and the hypertrophic zone, in which mature chondrocytes exit the cell cycle and produce collagen.[34] Postnatal bone growth continues until adolescence. The completion of bone extension is marked by the closure of the metaphysis containing the growth plate, but remodeling continues throughout life due to the balance between osteoblast and osteoclast activity[32] Fig. 2.

It is known that normal fetal growth is the result of a complex interaction between the three components of the maternal-placental-fetal unit and that neonatal bone mass and osteogenesis are positively correlated with placental weight.[35,36] It has recently been shown that preterm infants have lower alkaline phosphatase and osteocalcin levels and higher bone mineral density (BMD) Z-scores compared to controls.[37] Furthermore, in the preterm population, gestational diabetes, preeclampsia, and bronchopulmonary dysplasia were associated with lower total body BMD.[37] This latter finding may be explained by the effect of oxidative stress typical of these conditions on bone development. Indeed, reduced bone density and altered trabecular architecture are thought to result from the fetus's adaptation to a suboptimal environment. A growing number of experimental studies have reported that fetal bone development is extremely sensitive, especially in mid-gestation, when the appendicular skeleton grows rapidly in all dimensions and volumetric densities.[38–42] At this stage, exposure to oxidative stress reduces neonatal size, weight, and growth rate, resulting in low birth weight and an increased risk of skeletal disorders.[39,40] In vitro studies have reported that NO overproduction inhibited osteoblast differentiation.[41] Methylnitrosourea, a known inducer of bone osteogenesis, was shown to alter several key placental proteins that influence placental development and fetal osteogenesis in mice. Methylnitrosourea administration resulted in small fetuses with disproportionately shortened limbs and distal limb malformations.[39] Oxidative stress stimulates the preferential differentiation of mesenchymal stem cells (MSCs) into adipocytes rather than osteoblasts and, on the other hand, directly stimulates osteoclast activity, promoting bone resorption.[40,42]

In vivo and in vitro studies have shown that preterm birth, low birth weight and growth restriction are associated with fetal lipid peroxidation.[29,39,42,43] Preterm infants exhibit higher levels of lipid peroxidation, as revealed by higher plasma isoprostanes and the presence of lipid peroxides, compared to full-term infants.[29,44,45] However, the mechanisms underlying oxidative stress and bone development are still under investigation.

Animal studies show that iron overload resulting from upregulation of iron transporters caused changes in bone microarchitecture.[46,47] Niu et al. recently analyzed the expression of iron transporters (TFR1 and DMT1), iron chelators, and siRNA gene silencing in chick embryos to demonstrate that iron accumulation is critical for the disruption of alkoxyl radical-mediated chondrogenesis.[46] Furthermore, alkoxyl radicals would cause the degradation of the transcription factor SOX9, a key regulator of osteogenesis. Loss of SOX9 ultimately arrests the transduction of signals that drive osteogenesis, thus affecting bone development.[46]

In genetically modified mice overexpressing catalase, early life exposure to hydrogen peroxide (H_2O_2) affected both trabecular and cortical bone.[38] The data suggest that H_2O_2 acts as a negative regulator of osteoblastogenesis and a positive regulator of osteoclastogenesis, even in juvenile phases—highlighting how ROS can influence bone accrual during early growth.

The study by Tompkins et al. demonstrated that microinjection of H_2O_2 into chick embryos alters the expression of antioxidant enzymes and directly influences the expression of proteins key to bone formation, suppressing collagen synthesis. Indeed, H_2O_2-induced OS reduces the expression of osteogenic genes, such as COL1A2, COL2A1, BMP, BGLAP, and RUNX2, resulting in a significant reduction in embryonic length and impaired skeletal growth.[48]

In particular, the alteration of COL1A2 and COL 2A1, induced by OS, leads to an alteration in the collagen type expression ratio in the early differentiation phase with possible future repercussions. Indeed, it is documented that an appropriate collagen type expression profile is essential for bone health and conversely alterations in collagen type expression patterns have been associated with bone pathologies in chickens.[49] BMP instead mediates chondrogenic and osteogenic differentiation, and RUNX2 regulates the proliferation of osteoblast

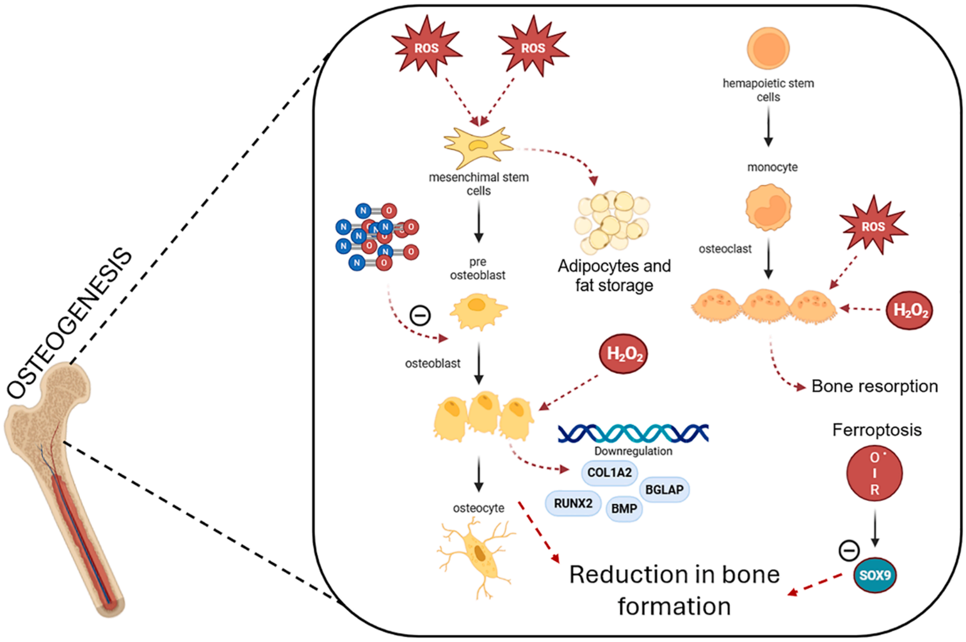

Fig. 2. Schematic rappresention of the cellular and molecular effects of oxidative stress mediators on bone.

progenitors, chondrocyte hypertrophy and the expression of bone matrix proteins, contributing to longitudinal bone growth.[50–52]

Regarding NO, the effect remains controversial to date. In fact, some studies report that NO production has harmful effects by inhibiting osteoblast differentiation, collagen synthesis and promoting chondrocyte apoptosis.[41,53] Conversely, other studies have shown that NO stimulates MSCs towards osteogenic differentiation.[54]

These findings from embryonic and juvenile animal models reinforce the mechanistic plausibility that perinatal oxidative insults exert persistent negative effects on skeletal development.

Translational prospectives: antioxidant approaches during pregnancy

Since OS during the fetal period influences bone metabolism in the newborn, antioxidant nutritional interventions during gestation could attenuate the adverse effects. Macro- and micronutrient supplementation during pregnancy and lactation has been recommended to improve both maternal health and birth outcomes.[24] Of particular interest, previous studies have examined the effects of vitamin K supplementation on bone mineral density and quality, suggesting that vitamin K deficiency in infancy may be a significant predictive factor for osteopenia and increased fracture risk.[55–57] Accordingly, substantial research has focused on the potential of vitamin K intake to positively influence osteoporosis and fracture prevention.[58] However, it remains to be determined whether supplementation with specific antioxidant nutrients during pregnancy and/or lactation confers measurable benefits for fetal and neonatal bone development. Among the various antioxidant nutrients, melatonin (N-acetyl-5-methoxytryptamine) may play a key role. Melatonin is a hormone with antioxidant, anti-inflammatory, and FR-scavenging functions, capable of crossing the placental barrier and entering fetal circulation.[59] As an antioxidant, melatonin reduces ROS levels by acting directly on FRs or indirectly by stimulating antioxidant enzymes (superoxide dismutase, glutathione peroxidase, glutathione reductase and catalase).[60] Melatonin also plays a key role in bone metabolism. Di-Zheng et al. recently demonstrated that melatonin levels correlate with changes in osteoclastogenesis and bone mass in adults, while melatonin supplementation can inhibit bone loss.[61] On the other hand, animal studies have shown that melatonin administration increased bone mineralization capacity and the expression of BMP2 and RUNX2, restoring osteogenic potential while reducing H_2O_2-induced changes.[62] To our knowledge, there are no studies available yet that analyze the effect of melatonin on fetal metabolism.

Conclusions

Normal skeletal development depends on a tightly regulated balance between oxidative and antioxidant mechanisms. Although ROS are essential to physiological cell signaling, excessive ROS levels—demonstrated in several animal models—impair osteoblast differentiation and function while promoting osteoclastogenesis, thereby disrupting bone homeostasis. To date, clinical evidence on the impact of oxidative stress on neonatal and early postnatal bone metabolism remains limited.

A deeper understanding of the oxidative environment during critical windows of development could provide novel insights into the early determinants of bone health. Moreover, redox imbalance in early life may represent a mechanistic link between perinatal exposures and the later emergence of skeletal disorders. In this context, oxidative stress may constitute a missing piece in the complex etiopathogenesis of osteoporosis and adult bone fragility, underscoring the potential long-term impact of early-life oxidative insults on skeletal integrity.

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CRediT authorship contribution statement

Serafina Perrone: Writing – review & editing, Validation, Supervision, Resources, Funding acquisition, Data curation, Conceptualization. **Laura Cannavò:** Writing – original draft. **Virginia Beretta:** Methodology, Investigation. **Elena Scarpa:** Methodology, Investigation, Data curation. **Serena Benedetti:** Visualization, Resources. **Chiara Petrolini:** Visualization, Validation, Investigation. **Vincenzo Raitano:** Visualization, Methodology. **Domenico Corica:** Visualization, Validation. **Tommaso Aversa:** Visualization, Validation. **Maria Cristina Albertini:** Visualization, Validation, Supervision. **Andrea Dall'Asta:**

Visualization, Validation, Supervision. **Maria Elisabeth Street:** Visualization, Validation. **Tullio Ghi:** Visualization. **Silvia Carloni:** Writing – review & editing, Visualization, Validation, Supervision, Data curation. **Malgorzata Wasniewska:** Visualization, Validation, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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