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DNA methylation as a potential mediator between environmental pollutants and osteoporosis; a current hypothesis

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To Editor,

Osteoporosis is a complex non-communicable disease, known as a silent disease, characterized by low bone mass and increased risk of fracture in multiple sites of the body. The worldwide prevalence of osteoporosis is estimated to be 18.3%.[1] As a public health concern, osteoporosis is related to remarkable morbidity and mortality rates as well as huge economic costs for the medical system globally. Osteoporosis is thought to have developmental origins in early life.[2] Some well-known modifiable or non-modifiable risk factors of osteoporosis consist of age, female gender, inactivity, poor diet, stress, and smoking. A growing body of evidence showed that exposure to different classes of environmental pollutants might be related to low bone mass or increased risk of osteoporosis.[3-5] A recent meta-analysis revealed that, unlike mercury, cadmium and lead exposure is associated with an increased risk of osteoporosis or osteopenia (odds ratios = 1.35 and 1.15, respectively).[4] Considering air pollution, in line with other research, a recently published study found that in the UK, exposure to particulate matter 2.5 micrometers or less in diameter ($PM_{2.5}$), nitrogen dioxide (NO_2), and nitrogen oxides (NO_x) is associated with an increased risk of osteoporosis in 422,955 individuals.[6] We had previously summarized the findings on the association of air pollution with bone mass.[7] In addition, emerging evidence indicated the detrimental effects of some environmental chemicals, such as perfluoroalkyl substances (PFASs) and phthalates on bone mineral density.[5] The underlying pathophysiological mechanisms involved in bone response to environmental pollutants are complex and remain to be determined. Those mechanisms include but are not limited to, induction of pro-inflammation, oxidative stress, and endocrine disruption.[4,5] All around the world, humans are exposed to environmental pollutants and are susceptible to their adverse health outcomes.

Epigenetics is the study of heritable changes in gene expression resulting from mechanisms other than changes in the DNA sequence and is crucial in determining spatiotemporal patterns of gene expression.[8] DNA methylation (DNAm) includes the addition of a methyl group to cytosine residues of CpG dinucleotides. DNAm is often linked to turning off genes. This happens when transcription factors that control gene activity are unable to bind to it or when specific proteins that stop gene activity get attracted to it.[9] An accumulating line of evidence supports the pivotal action of epigenetic mechanisms, including DNA methylation, in the influence of environmental chemicals on the disease burden. The effects of epigenetic changes have been linked not only to the prenatal period but also to adulthood. A systematic review proposed a possible role of exposure to cadmium, lead, and persistent organic pollutants (POPs) on DNAm changes.[10] Likewise, a literature review of the last 3 years revealed strong evidence between prenatal metal exposure (especially lead and cadmium) and DNAm signatures. Such an association has been supported for adults as well.[11] Moreover, several air pollutants such as black carbon (BC), particulate matter (PM), ozone (O3), NO_x, and polycyclic aromatic hydrocarbons (PAHs) are found to be linked to changes in DNAm across the life span and adverse health outcomes. i.e., DNAm is thought to be typically lowered after exposure to air pollution.[12] In one study, each 10 μg/m^3 increase in prenatal exposure to particulate matter 10 micrometers or less in diameter (PM_{10}), has been associated with a 1.78% decrease in the placental LINE1 methylation,

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indicating a possible concentration-dependent effect of exposure during early pregnancy.[13] Several Quantitative methods including microarray technologies, bisulfite pyrosequencing, and methylation-specific quantitative PCR (qMSP) have been used to explore DNAm in genomic sites of different tissues.[10] Of note, multiple biological processes, encompassing endocrine disruption, changes in inflammation, oxidative stress, methyl-group availability, and methyltransferase activity, have been proposed as the underlying process linking the environmental chemicals and epigenetic mechanisms. Subsequently, the epigenetic marks may alter the gene expression and the disease risk over time.[14] Epigenetic marks can be passed on when cells divide and are thought to keep the molecular 'memory' of the exposure.[15]

According to the Developmental Origins of Health and Disease (DOHaD) theory, environmental exposures in early life contribute to many chronic diseases in later life. Peak bone mass that greatly affects the chance of getting osteoporosis is thought to be influenced by environmental factors. The epigenetic process is a key candidate mechanism by which the vulnerability to chronic diseases is modified.[16] A recent review article summarized the role of epigenetic mechanisms, including, DNAm in osteogenic differentiation and osteoporosis.[17] Previous studies showed that maternal diet, lifestyle, body build, and vitamin D status during pregnancy are related to bone mineral accumulation in the offspring. In a cohort study on 230 mother-offspring pairs, higher cite specific DNAm changes in the promoter of RXRA gene (effective on vitamin D activation and bone metabolism) in the umbilical cord, were associated with lower bone mineral content in children aged 4 years. The interesting finding was that the methylation in one RXRA site was inversely associated with the maternal vitamin D index.[18] These findings provide clues of epigenetic regulation of bone mineral density in response to exposure to the environment. However, research in this field is scarce and needs to be strengthened by future investigations.

In the context of the abovementioned background, the mediating role of the epigenetic process especially DNA methylation, on bone damage after exposure to environmental pollutants may be hypothesized. To the best of our knowledge, there exist few researches regarding this matter. Future experimental, toxicological, and epidemiological studies are needed to precisely investigate the detrimental effects of exposure to air pollution, heavy metals, and other chemicals on bone mineral density by considering the role of epigenetic processes, notably DNAm (Fig. 1). In light of recent advancements in the technologies used for exposure and DNAm measurement, those prospective studies in the setting of mother-offspring (with large sample sizes and gene-specific methods for DNAm determination), are of paramount value in finding associations. In this context, biological plausibility, reproducibility, strength, and temporal relationships would be warranted. There are multiple targets and pathways related to bone epigenetic modifications, suggested by available evidence, which are potential candidates for future investigations. They

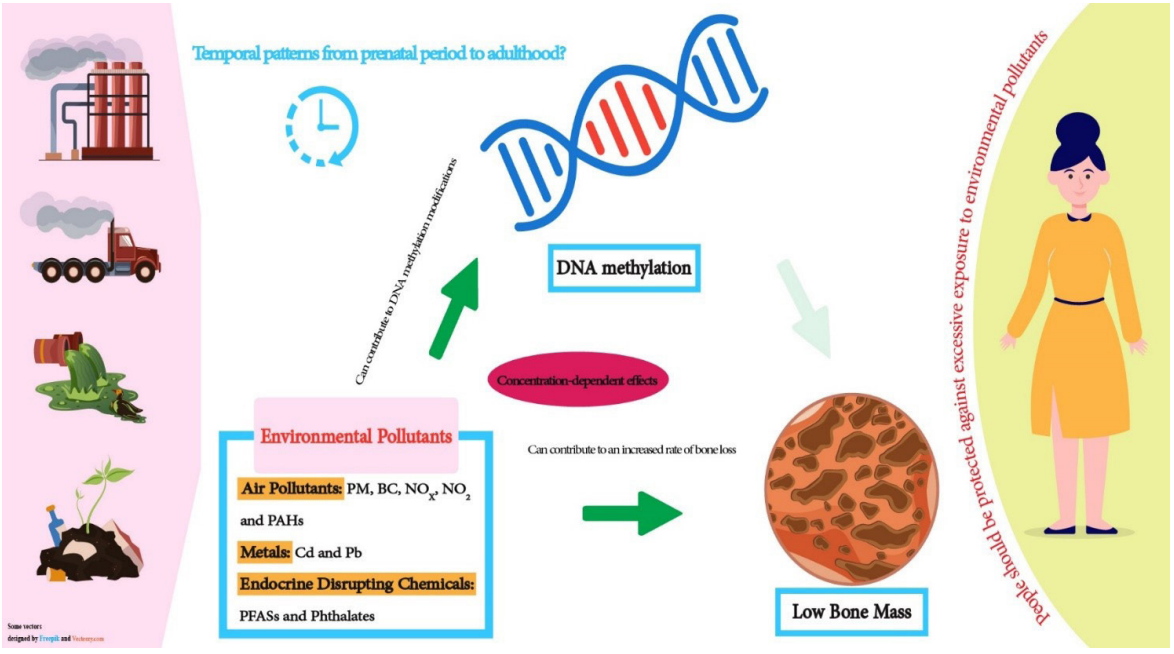

Fig. 1. The potential contribution of exposure to environmental pollutants in decreasing bone mineral density and epigenetic modification (DNA methylation) in humans, is supported by different lines of evidence (dark green arrows). However, the mediating role of DNA methylation change in the bone response to environmental pollutants remains to be fully elucidated in future research with different study designs (bright green arrow). In addition, the dynamic nature and cell-to-cell variability of DNA methylation modifications may grab attention in different studies. PM: Particulate Matter, BC: Black Carbon, NO_x: Nitrogen Oxides, NO_2: Nitrogen Dioxide, PAHs: Polycyclic Aromatic Hydrocarbons, Cd: Cadmium, Pb: Lead, PFASs: Perfluoroalkyl Substances

include but are not limited to, Runt-related transcription factor 2 (RUNX2) and osterix (OSX), bone morphogenetic protein 2 (BMP2), alkaline phosphatase, osteocalcin, Alu Elements, the Wnt/β-Catenin signaling pathway and the osteoprotegerin (OPG)/ receptor activator of nuclear factor-κB ligand (RANKL)/receptor activator of nuclear factor-κB (RANK) signaling pathway.[17]

It is noteworthy that the possible mediation effects of DNAm for the association between environmental pollutants and other chronic diseases are an area of growing research. For instance, NO_2 and PM as air pollutants, affect DNAm at the NXN gene. DNAm at this gene is linked to blood pressure, glucose level, and obesity. Thus, a recent review proposed DNAm as a potential mediator between air pollution and metabolic syndrome.[19] In this work, we tried not to conduct a review study but to outline an evolving thinking of environmental epigenetics of osteoporosis that absolutely would be testable. DNA methylation, as one of the most widely studied epigenetic modifications, is involved in the pathogenesis of aging-bone diseases.[20] We know that the complex interplay between the environment, epigenetics, and genetics, may affect bone modeling and remodeling from the fetal period to adulthood.[21] Therefore, our efforts to better investigate the mechanisms involved in bone response to environmental pollutants, will not only help us in understanding the developmental origins of osteoporosis but also may provide risk assessment tools or biological markers to timely identify individuals with risk of osteoporosis and formulate appropriate preventive programs later on.

Authors' Contribution

Conceptualization: Sadegh Baradaran Mahdavi, Roya Kelishadi.
Investigation: Sadegh Baradaran Mahdavi.
Software: Sadegh Baradaran Mahdavi.
Supervision: Roya Kelishadi.
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Writing–review editing: Sadegh Baradaran Mahdavi, Roya Kelishadi.

Ethical Statement

Not applicable.

Competing Interests

None to declare.

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