Minireview

Maternal nutrition and the developmental origins of osteoporosis in offspring: Potential mechanisms and clinical implications

Jia Zheng[1,*], Qianyun Feng[2,3,*], Sheng Zheng[2,4,*] and Xinhua Xiao[1]

[1]Department of Endocrinology, Key Laboratory of Endocrinology, Ministry of Health, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing 100730, China; [2]Department of Graduate School, Tianjin University of Traditional Chinese Medicine, Tianjin 300193, China; [3]Department of Pediatrics, The Second Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin 300150, China; [4]Department of Spine Surgery, Tianjin Union Medical Center, Tianjin Institute of Spine, Tianjin 300121, China

*These authors contributed equally to this work.

Corresponding author: Xinhua Xiao. Email: xiaoxh2014@vip.163.com

Impact statement

Our review aimed to address maternal nutrition and its implications for the developmental origins of osteoporosis in offspring, that can novelly provide a theoretical basis for the early prevention of osteoporosis.

Abstract

Osteoporosis, the most frequent metabolic disorder of bone, is a complex disease with a multifactorial origin that is influenced by genes and environments. However, the pathogenesis of osteoporosis has not been fully elucidated. The theory of "Developmental Origins of Health and Disease" indicates that early life environment exposure determines the risks of cardiometabolic diseases in adulthood. However, investigations into the effects of maternal nutrition and nutrition exposure during early life on the development of osteoporosis are limited. Recently, emerging evidence has strongly suggested that maternal nutrition has long-term influences on bone metabolism in offspring, and epigenetic modifications maybe the underlying mechanisms of this process. This review aimed to address maternal nutrition and its implications for the developmental origins of osteoporosis in offspring. It is novel in providing a theoretical basis for the early prevention of osteoporosis.

Keywords: Maternal, early life, nutrition, osteoporosis, development, offspring

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Introduction

Osteoporosis, as the most frequent bone metabolic disorder, increases morbidity and mortality of humans. The main characteristics of osteoporosis in bone tissue include lower bone mass and abnormal micro-architecture, resulting in increased risks of bone fracture and fragility.[1] It is a common bone metabolic disease in humans affecting both sexes and all races. It is estimated that the number of osteoporosis in women who were aged more than 50 years will rise to over 10 million by 2020.[2] The prevalence of osteoporosis related fracture is over 1.5 million annually in the United States.[3] Mortality and morbidity rates as a result of hip fractures are substantial and the mortality rate within one year of the fracture is between 5% and 20%.[4] The number of hip fracture is estimated to increase by 240% in women and 310% in men, with 6.26 million hip fractures worldwide in 2050.[5] Vertebral fractures have been called the hallmarks of osteoporosis and tend to occur at younger ages than other fractures. Vertebral fractures can increase the future risks of additional vertebral fractures by 5 to 10 times, and are associated with increased risks of non-vertebral fractures.[6] As a global health concern, osteoporosis dramatically increases social and economic burden throughout the world.[5]

Pathophysiology and etiology of osteoporosis

The skeleton is one of the body's largest organs, composed of mineralized extracellular matrix and bone remodeling unit, with osteocytes, osteoblasts, osteoclasts, and lining cells.[2] Osteoblasts and osteoclasts are the critical participants of bone remodeling. Osteoclasts are a type of bone

cell that degrade the bone matrix, while osteoblast are cells with single nuclei that build bone.[7] The process of bone remodeling cycle is tightly coupled. The rate of bone formation is approximately the same with bone resorption in adulthood. Osteoporosis can occur when bone resorption process is faster than bone formation.[8]

Osteoporosis is a frequent disease with a complicated origin that is influenced by genes and environments. Kung *et al.*[9] reviewed that 63 genes were associated with bone mineral density (BMD) and several phenotypes related with osteoporosis. Both humans and experimental animals showed certain quantitative trait loci were associated with osteoporosis,[10] such as vitamin D receptor (VDR),[11] insulin-like growth factor 1 (IGF-1),[12] and estrogen receptor α genes.[13] However, the role of single gene polymorphism in bone metabolism is less than 1% to 3%.[14] Thus, the pathogenesis and etiology of osteoporosis have not been clearly elaborated.

Recently, it is increasingly clear that early life environment determines the develpoment of diseases in adulthood.[15] Substantial epidemiological and animal studies showed that early life malnutrition can determine the development of a number of cardiometabolic diseases, such as obesity, insulin resistance, type 2 diabetes, cardiovascular diseases, and stroke.[16–19] Environment during early life, especially intrauterine and postnatal nutrition consumption, has long-term metabolic effects in later life. This theory raised interests in the fetal programming of diseases in adulthood and was first proposed in the 1990s, known as "Developmental Origins of Health and Disease (DOHaD)."[20,21] It noted that the adaptive responses in infant can impose long-term risk of diseases in adult.[22] Growing numbers of studies suggest that early life environment determines the risks of metabolic diseases in adult life. However, the associations between maternal and/or perinatal nutrition and osteoporosis in offspring have not been fully elucidated. This review aimed to address early life nutrition and its implications for the developmental origins of osteoporosis in later life.

Early life nutrition and its implication for osteoporosis

Extensive research is focused on fetal origins hypothesis and this hypothesis proposes that early life environment can affect the development of diseases in adulthood, which was known as DOHaD.[23] In recent years, increasing evidence demonstrate that environmental influences during early life can modify the risks of osteoporosis.[24] It demonstrated that bone mineral accrual can be affected by environmental exposures during childhood and puberty. The rate of mineral gain is relatively rapid during early life development. Thus, it provides the possibility that environment plays a significant role in bone metabolism during early life.[25] Thus, increasing evidence suggests that early life environmental and nutrition exposure determine the susceptibility of osteoporosis in later life.

Evidence from clinical studies about maternal nutrition and osteoporosis in offspring

One epidemiological evidence of early life environment and its implication of osteoporosis indicated that body weight at one year was associated with increased bone mineral content (BMC) at the femoral neck and lumbar spine at about 20 year old.[26] Cooper *et al.*[27] showed that the growth rate of infancy was associated with skeletal size in adulthood in a cohort aged about 70 years old. Dennison *et al.*[28] also found that birth weight and body weight at one-year old determined the bone mass when they were aged about 70 years old. A series of clinical studies related to maternal nutrition and the developmental origins of osteoporosis in United States,[29] Finland,[30] Sweden,[31] Norway,[32] Australia,[33] and the Netherlands[34] also demonstrated the same phenomenon. The information of the studis is shown in Table 1.

Vitamin D, an important nutrient, can regulate mineral and bone metabolism. A longitudinal, prospective study in Western Australian found that serum 25(OH)D level of mothers during pregnancy was associated with increased BMC of total body and BMD in their females offspring at 9-year old,[36] and even up to about 20-year old.[35] Antoniades *et al.*[37] showed that the differences in birth weight between twins were significantly related with BMC in a twin cohort-recruited 4008 female twins aged about 47.5 years old. These data implicate the fetal origins of bone health in later life, with the evidence from genetically identical subjects.

Experimental studies in animals about maternal nutrition and osteoporosis in offspring

In addition to the evidence of human studies, animal models also demonstrated that early life nutrition is associated with osteoporosis in adult life. The evidence of animal models is summarized in Table 2. Maternal protein restriction is a commonly used scheme for malnutrition in animal studies. Mehta *et al.*[38] showed that maternal low-protein diet changed the morphology of growth plate and decreased bone mass in adult rats. Lanham *et al.*[39] indicated that maternal protein restriction during pregnancy prediposed lower serum IGF-1 level in four-week-old female offspring and higher serum osteocalcin concentration in four-week-old male and female offspring. It also decreased serum 25(OH)D concentration in 8, 12, and 20-week-old male offspring.[39] Oreffo *et al.*[40] further found that maternal low-protein diet consumption from conception until the end of pregnancy downregulated bone marrow stromal cells proliferation and differentiation in four and eight-week-old offspring.[40] -Jahani *et al.*[41] showed maternal low-vitamin D diet (25 IU vitamin D3 /kg diet) during pregnancy and lactation induced lower VDR expression, and increased offspring colon TNF-α and IL-1β genes expressions, which are known to be involved in osteoclastogenesis. Conversely, Suntornsaratoon *et al.* showed that maternal high dietary vitamin D consumption during pregnancy and lactation period resulted in lower fasting glucose and serum lipopolysaccharide concentrations in male offspring. Maternal vitamin D intake during pregnancy and

Table 1. Human studies of early life nutrition and osteoporosis.

Study ID	Year	Country	Sample size	Mean age	Primary outcomes
Cooper *et al*.[26]	1995	United Kingdom	153 women	21 years	Significant associations between weight at one year and BMC at the lumbar spine and femoral neck; Infant growth and physical activity in childhood are important determinants of peak bone mass in women;
Cooper *et al*.[27]	1997	United Kingdom	189 women and 224 men	63–73 years	Significant associations between weight at one year and BMC at the spine and femoral neck among women, and spine among men; Serum osteocalcin was negatively correlated with BMD;
Dennison *et al*.[28]	2005	United Kingdom	498 eight men and 468 women	About 70 years	Birth weight and weight at one year are independent determinants of bone mass in the seventh decade;
Yarbrough *et al*.[29]	2000	USA	305 postmenopausal women	70 years	Birth weight was positively correlated with BMC at the forearm, hip and lumbar spine;
Mikkola *et al*.[30]	2017	Finland	178 women	60.4 years	Birth length and growth in height before seven years of age were positively associated with femoral neck area and growth in height at all age periods studied with spine bone area;
Callréus *et al*.[31]	2013	Sweden	1,061 young adult women	25.00–25.99 years	Significant correlations were observed between birth weight and total body-BMC, femoral neck-BMC, total hip-BMC, lumbar spine L1-L4-BMC, and lean mass;
Christoffersen *et al*.[32]	2017	Norway	961 participants	15–18 years	Birth weight was positively associated with BMD and BMC at all sites among girls, and birth length was positively associated with BMC in boys;
Hyde *et al*.[33]	2017	Australia	475 pregnant women	29.7–30.3 years	Offspring bone area was associated with maternal diet; Birth length, weight and head circumference correlated poorly with all DXA measures at 11 years at both sites;
Leunissen *et al*.[34]	2008	the Netherlands	312 young adults	18–24 years	Adult weight, lean body mass, fat mass and weight gain during childhood were the main positive determinants for BMD of the total body in early adulthood;
Antoniades *et al*.[37]	2003	London	4,008 white female twins	47.5±12.3 years	Significant relationships were found between the intra-pair differences in birth weight and in BMC;

BMC: bone mineral content; BMD: bone mineral density; DXA: dual energy X-ray absorptiometry.

Table 2. Animal models for the developmental origins of osteoporosis.

Dietary conditions	Species	Period	Age	Main findings	References
Maternal low-protein diet (9% vs. 18% w/w casein)	Wistar rats	Throughout the 21 days of gestation	4, 8, 12, and 20 weeks of age	Serum IGF-1 levels were lower in female restricted diet offspring at 4 weeks of age, and serum osteocalcin was significantly higher at 4 weeks of age in male and female offspring from mothers fed the restricted diet, whereas serum 25-OH vitamin D was significantly lower in restricted diet males at 8, 12, and 20 weeks of age;	Mehta *et al*.[38]
Maternal low-protein diet (9% vs. 18% w/w casein)	Wistar rats	Throughout the 21 days of gestation	8, 12, and 20 weeks of age	Lower serum insulin-like growth factor-1 (IGF-1) and 25(OH)D levels; higher serum osteocalcin in offspring rat;	Lanham *et al*.[39]
Maternal low-protein diet (9% vs. 18% w/w casein)	Wistar rats	Throughout the 21 days of gestation	4 and 8 weeks	Downregulated the proliferation and differentiation of bone marrow stromal cells;	Oreffo *et al*.[40]

(continued)

Table 2. Continued.

Dietary conditions	Species	Period	Age	Main findings	References
Maternal low-vitamin D diet (25 IU vitamin D3/kg diet vs. 5000 IU vitamin D3/kg diet)	CD1 mice	During pregnancy and lactation	3 months of age	Predisposed offspring with reduced vitamin D receptor and increased expression of pro-inflammatory genes in colon in offspring;	Jahani *et al*.[41]
High dietary vitamin D	C57BL/6J mice	During pregnancy and lactation	7 months of age	Improved trabecular bone structure at both the lumbar vertebra and femur in male offspring;	Villa *et al*.[42]
Calcium supplementation	Sprague-Dawley rats	Presuckling for 14 days	3 months of age and 27 weeks	Exhibited increases in trabecular bone mineral density; greater bone elongation in offspring;	Suntornsaratoon *et al*.[43]
High-fat diet	Sprague-Dawley rats	10 weeks before mating and during pregnancy	Gestational embryonic day 18.5	Inhibited bone development, less potential to develop into mature osteoblasts	Chen *et al*.[44]
High-fat diet	Sprague-Dawley rats	12 weeks before mating and during pregnancy	Gestational embryonic day 18.5	Increased in p53/p21-mediated cell senescence signaling, decreased glucose metabolism and decreased osteoblastic cell differentiation and proliferation.	Chen *et al*.[45]
Soy protein isolate diet	Sprague-Dawley rats	continuous diet throughout life	About 6 months of age	Protected against one week post-ovariectomy-associated bone loss, diminished total, trabecular, and cortical bone mineral density loss.	Chen *et al*.46

lactation also improved both femur and lumbar vertebra trabecular bone structure in offspring.[42] Interestingly, presuckling calcium supplements with normal chow diet in lactating rats during pregnancy exhibited greater bone elongation, and increased trabecular BMD in offspring even at the age of 27 weeks old.[43]

In addition to vitamin D and calcium supplements, Chen *et al*.,[44] maternal high-fat diet inhibited embryonic day 18.5 embryos bone development and the development into mature osteoblasts in offspring rats.[44] They further found that high-fat diet obese dams increased cell senescence in embryonic rat osteogenic calvarial cells, with decreased osteoblastic cell differentiation and proliferation.[46]One recent animal study indicated that continuous soy protein isolate diet throughout life protected against one week post-ovariectomy-associated bone loss in rats, with diminished total, trabecular, and cortical bone mineral density loss.[46] Thus, all these evidence indicate that early life nutrition can impact the develpoment of bone health in offspring in later life.

Potential mechanisms underlying maternal nutrition and osteoporosis in offspring

Critical time windows during fetal stage and neonatal stage can impact the growth and development in adult life. Emerging clinical studies and animal experiments indicated that maternal and postnatal nutrition status determines offspring health in adult life. Recently, increasing evidence has strongly demonstrated that epigenetic modifications maybe the underlying mechanisms of fetal metabolism programming.[24] In 1942, the term "epigenetics" was first put forward as a process that can change gene expression and transcription without DNA sequence alteration.[47] Epigenetic modifications are inheritable and it can be passed on to the next generation steadily by cell proliferation, differentiation, and division.[48] The altered gene expressions may contribute to changes in functions of certain genes and metabolic status, that can persist, and even transmit to the next generation.[49] Therefore, epigenetics is supposed to be a potential molecular mechanism of the early life nutrition and the development of osteoporosis in later life.

However, investigations into epigenetic mechanisms between early life nutrition consumption and bone metabolic health are are limited. Calcium and vitamin D are known critical nutrients of bone metabolism. Earl *et al*.[50] showed the effects of maternal nutrition regulate DNA methylation of the promoter region of specific genes, such as placental calcium transporters and VDRs can regulate bone mass in offspring. Circulating cortisol level can decrease bone density and increase bone loss rates in adult life. Lillycrop *et al*.[51] showed that maternal protein restriction during pregnancy decreased DNA methylation of glucocorticoid receptor (GR) gene, with increased GR gene expression and hypercortisolism status. Recently, the Southampton Women's Survey reported that higher perinatal cyclin-dependent kinase inhibitor 2A (CDKN2A) methylation was asscociated with lower bone area, BMC, and areal BMD of whole-body minus head. They further found that each 10% increase in CDKN2A DNA methylation was related with BMC decrease (about 4–9 g) at age 4 years in offspring.[52] However, Fernandez-Rebollo *et al*.[53] indicate that primary osteoporosis was not associated with DNA methylation or epigenetic modifications in blood obtained from 32 patients. That maybe due to the small sample size, stratification of patients by BMD, and variable clinical characteristics. In summary, the aforementioned evidence demonstrates that epigenetic regulation plays

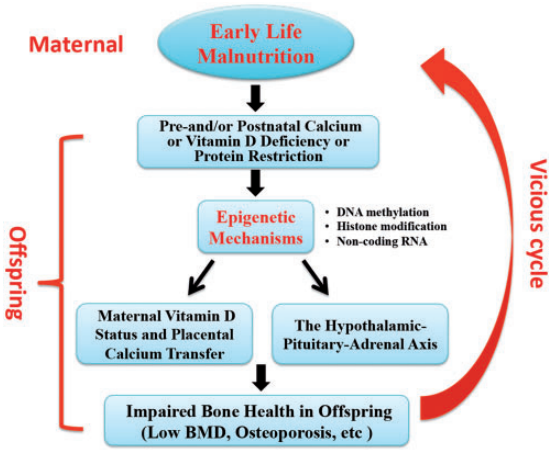

Figure 1. Proposal of an "epigenetic vicious circle" of maternal nutrition and its implication for bone health in offspring. Maternal malnutrition during pregnancy and lactation, including calcium or vitamin D deficiency or protein restriction, can epigenetically regulate gene expressions related with maternal vitamin D status and placental calcium transfer, and the hypothalamic-pituitary-adrenal (HPA) axis. Maternal stress is known to influence the developing HPA axis in the fetus. Thus, epidemiological studies have demonstrated an inverse association between birth weight and fasting plasma cortisol. Indices of the circulating cortisol profile in adult life have also been shown to influence bone density and rates of bone loss. Finally, it can impair bone health in offspring, including low BMD and osteoporosis. If female offspring affected in that way enter reproductive age and become pregnant, they expose their offspring in a similar way to a malnutrition perinatal environment that they were exposed to themselves, thereby closing an epigenetic "vicious intergenerative circle." BMD: bone mineral density. (A color version of this figure is available in the online journal.)

a significant role in the developmental origins of osteoporosis. The proposal of an 'epigenetic vicious circle' of maternal nutrition and its implication for bone health in offspring is shown in Figure 1.

In addition to epigenetic modifications, we propose that hormonal axis maybe an important mechanism and it should be included, especially for the relationship of parathormone (PTH) to calcium and the disturbance of this axis on the mother and thus the offspring. It indicates that placental calcium transport capacity is both regulated by genes and hormones, such as 1,25 $(OH)_2$ vitamin D3, PTH, PTH-related protein (PTHrP), and calcitonin.[54,55] Maternal hyperparathyroidism and hypoparathyroidism appear to be able to increase or decrease the calcium load, and then it can impact the fetus. It shows that lack of fetal parathyroids decreased serum calcium levels and mineralization in mice. Calvi *et al.*[54] further found that PTH and PTHrP affected mineralization of cortical and trabecular bone differentially. Thus, it is proposed that the PTH-calcium hormonal axis maybe an important candidate for fetal bone programming mediation.

Conclusion

In summary, early life stage, especially during perinatal period, is the critical time window for growth and development. Exposure to nutrients during these periods may determine the effects on bone metabolic health in offspring. Emerging evidence has strongly suggested that epigenetic modifications maybe the underlying mechanisms of the developmental origins of osteoporosis. However, the detailed mechanism between epigenetics and osteoporosis has not been fully elucidated yet. Thus, further clinical and basic studies to clarify the potential mechanisms are urgently warranted. We believe that the developmental origins of osteoporosis can novelly provide a theoretical basis for the early prevention of osteoporosis.

Authors' contributions: JZ and QYF collected data, synthesized data and wrote the manuscript. QY F and SZ reviewed and edited the manuscript. JZ and XHX contributed to the design of this review.

DECLARATION OF CONFLICTING INTERESTS

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ORCID iD

Jia Zheng http://orcid.org/0000-0002-6480-3422

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