Bone 50 (2012) 444–451

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review

Influence of pre- and peri-natal nutrition on skeletal acquisition and maintenance ☆

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ARTICLE INFO

Article history:
Received 12 April 2011
Revised 30 May 2011
Accepted 15 June 2011
Available online 24 June 2011

Edited by: Clifford Rosen

Keywords:
Perinatal developmental programming
Genomic imprinting
Caloric restriction
High fat diet
Bone

ABSTRACT

Early life nutrition has substantial influences on postnatal health, with both under- and overnutrition linked with permanent metabolic changes that alter reproductive and immune function and significantly increase metabolic disease risk in offspring. Since perinatal nutrition depends in part on maternal metabolic condition, maternal diet during gestation and lactation is a risk factor for adult metabolic disease. Such developmental responses may be adaptive, but might also result from constraints on, or pathological changes to, normal physiology. The rising prevalence of both obesity and osteoporosis, and the identification of links among bone, fat, brain, and gut, suggest that obesity and osteoporosis may be related, and moreover that their roots may lie in early life. Here we focus on evidence for how maternal diet during gestation and lactation affects metabolism and skeletal acquisition in humans and in animal models. We consider the effects of overall caloric restriction, and macronutrient imbalances including high fat, high sucrose, and low protein, compared to normal diet. We then discuss potential mechanisms underlying the skeletal responses, including perinatal developmental programming via disruption of the perinatal leptin surge and/or epigenetic changes, to highlight unanswered questions and identify the most critical areas for future research.

This article is part of a Special Issue entitled: *Interactions Between Bone, Adipose Tissue and Metabolism.*

Contents

Introduction

Beginning with the observation that individuals born at low birthweight have increased risk of cardiovascular disease [1], there is increasing evidence that early life nutrition influences postnatal health. Both low birthweight [2–10] and high birthweight [11–14] are associated with reduced reproductive and immune function, and significantly higher likelihood of obesity, atherosclerosis, type II diabetes, and the metabolic syndrome in adulthood [15], suggesting that poor intrauterine nutrition might be a risk factor for adult metabolic disease [16,17] (Fig. 1). For example, children of women who were pregnant during the Dutch Hunger Winter of 1944–1945 have increased incidence of obesity, hyperlipidemia, and atherosclerosis if their mothers were impacted by famine during the first trimester; higher rates of pulmonary and kidney disease if during the second trimester; and impaired glucose tolerance if during the third trimester of pregnancy [18–20]. In comparison, children of obese

☆ Funding for this project was provided by NIH F32HD060419, T32DK007028, and RC1AR058389.

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doi:10.1016/j.bone.2011.06.019

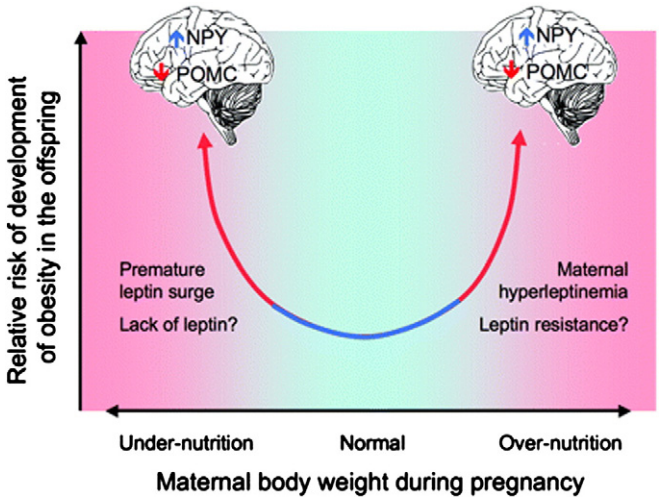

Fig. 1. The relationship between perinatal nutrition and postnatal metabolic disease may be U-shaped, with higher risk of metabolic dysregulation in both perinatal under- and overnutrition.
Adapted from Fig. 1 in Grattan, D. R. Endocrinology 2008;149:5345–5347.

mothers, or those born large for gestational age, are also at increased risk of developing the metabolic syndrome compared to children born at normal birthweight from normal weight mothers, particularly if their mothers also had gestational diabetes mellitus [13].

While these associations are striking, they do not explain why intrauterine nutrition would alter postnatal metabolism, nor reveal the mechanisms involved. The Barker Hypothesis [21], now known as the Developmental Origins of Adult Health and Disease model, posits that the perinatal environment induces lasting changes in physiological parameters such as hormone levels, glucose tolerance, and satiety, a phenomenon known as developmental programming. The hypothesis is that such 'programming' allows offspring to use maternal cues to adapt to the likely postnatal nutritional environment. For example, women born at lower birthweight have lower estrogen levels and are more susceptible to ovarian suppression during energetic stress compared to women born at higher birthweight [22], suggesting restricted perinatal energy availability results in increased sensitivity to adult energetic stress. However, when perinatal and postnatal environments are mismatched, offspring are at increased risk of metabolic disease, a model known as the Predictive Adaptive Response Hypothesis [9,23]. For example, Hales and Barker demonstrated a strong association of low birthweight and type II diabetes risk [4], and proposed that this phenomenon resulted from offspring developing a "thrifty" phenotype in expectation of food scarcity [24]. Similarly, there appears to be a greater risk of obesity in children with low birthweight who exhibit rapid postnatal catch-up growth, compared to children who grow more slowly [25,26], although these relationships are complex [27]. Alternative models include the Maternal Capital Hypothesis, which suggests that offspring exhibit plasticity in early growth in order to match their energetic needs to maternal metabolic resources, and the Intergenerational Phenotypic Inertia Hypothesis, which posits that offspring adapt not to the transient intrauterine nutritional environment, but rather to the mother's long-term energetic history [28–30].

Although there is some support for each of these hypotheses, the idea that the metabolic changes induced by perinatal developmental programming are adaptive is itself a hypothesis. As Ellison and Jasienska [31] point out, such developmental responses may be adaptations, but might also result from constraints on, or pathological changes to, normal physiology. Thus the notion that a given trait is an adaptation is a hypothesis that must be tested against the alternative hypotheses that the trait arose through pathology or constraint. The most rigorous approach for discriminating among these alternatives is to develop falsifiable predictions for each hypothesis – adaptation, pathology, or constraint – that can be evaluated against the data [31]. As an example, we might expect different patterns of changes in offspring body size, bone mass, and body composition in response to maternal caloric restriction depending on whether this response is an adaptation to expected postnatal energy restriction, the result of a constraint on intrauterine energy that is released after birth, or the product of permanent pathological disruption of growth processes (Table 1).

Whether the changes are adaptive or not, it is clear that early life nutrition alters postnatal metabolism, particularly adiposity and glucose tolerance. Recent interest has focused on the possibility that the perinatal environment also affects skeletal health [32]. The rising prevalence of both obesity and osteoporosis, and the identification of common mechanisms linking skeletal and metabolic homeostasis, suggest that obesity and osteoporosis may be related disorders, and moreover that their roots may lie in early life (Fig. 2). Recent studies in mice demonstrate that interconnections of bone and fat, as well as brain and gut, play a major role in postnatal glucose homeostasis, fat mass and bone mass, raising the possibility that these mechanisms also affect human metabolism [33,34]. Osteoblasts and adipocytes derive from the same population of mesenchymal stem cells (MSCs), such that increased commitment of MSCs to the adipocytic over the osteoblastic lineage might shift the balance between fat mass and bone mass [35–37]. Osteoblast-derived uncarboxylated osteocalcin increases insulin sensitivity and reduces fat mass in mice; the adipokine leptin suppresses this effect by favoring carboxylation of osteoblast-derived osteocalcin, decreasing insulin sensitivity and insulin secretion [38,39]. Leptin also reduces murine bone mass by inhibiting the anabolic effects of brain-derived serotonin, and by increasing sympathetic tone via beta-adrenergic receptors on osteoblasts [40–42]. Fat-derived peroxisome proliferator-activated receptor (*Ppar*)-gamma increases marrow fat and decreases bone mass [43], while the protein LDL-receptor related protein 5 (*LRP5*), which plays a crucial role in bone remodeling, increases bone mass by suppressing production of gut-derived serotonin in rodent models [44]. Thus an increase in adiposity has the potential to decrease bone mass, at least in animal models.

How might maternal diet and body composition affect these interactions between offspring bone and fat mass? It is clear that during postnatal life, specific micronutrients, such as Vitamin D and calcium, are essential for proper skeletal development and bone mass acquisition [45,46]. However, the perinatal influences of these micronutrients on skeletal health are more difficult to establish. In addition to micronutrient intake, mothers may be overnourished or undernourished before

Table 1
Expected offspring phenotypes following exposure to perinatal caloric restriction vary depending on whether the developmental responses are adaptive, pathological, or the result of constraint.

Perinatal exposure:	Caloric restriction		
Postnatal response:	Adaptation	Constraint	Pathology
Body size	Smaller than normal, in anticipation of low food availability	Smaller than normal at birth, followed by catch up growth to normal	Smaller than normal at birth, does not recover due to permanent disruption of somatic growth
Bone mass	Lower than normal, but appropriate for smaller body size	Lower than expected for body mass at birth, followed by catch up growth to normal	Lower than expected for body mass at birth, does not recover due to permanent disruption of skeletal acquisition
% Body fat	Higher than normal, in anticipation of low food availability	Lower than expected for body mass at birth, followed by catch up growth to normal	Lower than expected for body mass at birth, but higher than normal postnatally due to permanent disruption of metabolism