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NUTRITION, EXERCISE AND LIFESTYLE (S SHAPSES AND R DALY, SECTION EDITORS)

Energy Balance and Bone Health: a Nutrient Availability Perspective

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Abstract

Purpose of Review Obesity is highly prevalent and is associated with bone fragility and fracture. The changing nutrient availability to bone in obesity is an important facet of bone health. The goal of this article is to summarize current knowledge on the effects of carbohydrate and dietary fat availability on bone, particularly in the context of other tissues.

Recent Findings The skeleton is a primary site for fatty acid and glucose uptake. The trafficking of carbohydrates and fats into tissues changes with weight loss and periods of weight gain. Exercise acutely influences nutrient uptake into bone and may affect nutrient partitioning to bone. Bone cells secrete hormones that signal to the brain and other tissues information about its energetic state, which may alter whole-body nutrient trafficking.

Summary There is a critical need for studies to address the changes that metabolic perturbations have on nutrient availability in bone.

Keywords Energy balance · High-fat diet · Weight cycling · Nutrient trafficking · Bone remodeling · Bone marrow adiposity

Introduction

Maintaining a healthy musculoskeletal system is a critical component of wellness across the lifespan. Nutrition and physical activity are lifestyle factors that contribute to bone quality and quantity, where bone characteristics are altered by the coordinated activity of osteocytes (mechanosensitive bone maintenance cells), osteoblasts (bone-forming cells), and osteoclasts (bone-resorbing cells). Chronic overnutrition and physical inactivity leads to obesity and has a prevalence of epidemic proportions in children, adolescents, and adults [1].

Obesity is associated with metabolic dysfunction, reduced mobility [2, 3], and fracture in youth [4]. In older adults, obesity is linked with a lower risk of fracture at certain skeletal sites [5] (Table 1), but these studies utilized cohorts who were raised during a time in which childhood obesity was rare (i.e., born before 1975). When Generation Xers and Millennials reach older age (> 60 years), cohort studies may reveal a different association between obesity and fracture rates in adults because of the higher proportion of individuals who developed obesity prior to achieving peak bone mass. Since obesity is often associated with physical inactivity and a relatively high intake of fat and sugar, nutritional and exercise management is recommended for improving multiple health outcomes [6, 7].

Bone is a metabolically active organ with its own macronutrient requirements to support healthy bone remodeling [22, 23, 24••]. Glucose is a major energy source for bone, and the skeleton is one of the primary sites for the uptake of fatty acids [25]. Bone appears to have mechanisms in place to communicate or regulate its energetic state, as bone-derived factors help regulate aspects of systemic energy metabolism, such as glucose homeostasis [23, 26, 27, 28]. For bone to store or utilize energy substrates, they must be trafficked to and taken up by bone cells. Nutrient availability to bone is an integral aspect of how diet affects bone health, and this may be influenced by obesity or weight change (Table 1). The purpose of

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Table 1 Alterations in bone and bone marrow adiposity under excessive nutrient availability conditions

Bone	• Reductions in BMD [8, 9] • Increases hyperglycemia in humans [10, 11•, 12, 13] - Reduces BMD - Impairs bone turnover - Impairs mineralization • Reduces bone structure, strength, and mass in mice [14, 15] • Reduces mineral:matrix ratio in HFD fed rats [16] • Increases crystallinity in HFD fed rats [16] • Increase in chylomicron uptake in cortical bone [17] • Increases in lipid accumulation in osteoblasts [18, 19•, 20, 21] • Induction of lipotoxicity leading to apoptosis in osteocytes [19•, 20]
Bone marrow adiposity	• Expansion of marrow adipose volume [21] • Increases in adipocyte differentiation at expense of osteoblast differentiation [18] • Increase in chylomicron uptake in marrow [17]

this narrative review is to provide a unique perspective on how nutrition influences bone health.

Association Between Western Diets and Bone Health

Studies have evaluated the relationship of Western dietary patterns and obesity prevalence with bone health in different ages, cultures, and countries [8, 9]. In North America, Australia, and Europe, long-term consumption of high-fat and high-sucrose diets has been found to be inversely associated with bone quality in humans, such as a decrease in bone mineral density (BMD) and increased bone fragility and fracture prevalence [8, 29]. Health studies in Asia report positive associations in dietary patterns and BMD as Western dietary habits have merged into lifestyles with increasing prevalence [30, 31]. People in China who regularly consume fish, vegetables, and carotenoid have lower incidence of osteoporosis and fractures, when compared to people who consume little to no fish, vegetables, and carotenoid [30]. In addition, postmenopausal women on a Mediterranean diet were found to have superior femoral neck, lumbar spine, and total hip BMD, and a reduction in the risk of hip fracture [32, 33, 34]. In contrast, those who prefer Western-style diets with land-based animal meat, saturated fats, and sugars have increased fracture risk associated with excess adiposity [29, 35]. One of the consequences of obesity is hyperglycemia. Human studies have suggested that skeletal fragility is strongly associated with persistent hyperglycemia [10, 11•]. This is contrary to animal studies in which increases in bone volume fraction and strength have been noted with high sugar intake, although this increase in bone strength may be explained by gains in body weight [36, 37].

There are several major lines of thought explaining how a high-fat diet (HFD) can decrease bone parameters. First is the induction of adipogenesis at the expense of osteoblastogenesis in mesenchymal stem cells, particularly when there is a shortage of n3 fatty acids, which results in reduced bone formation [18]. Second, excess lipid accumulation in osteoblasts and osteocytes negatively influences bone remodeling [19•, 20]. Other important factors include the potential effect of HFD on inflammatory mechanisms, and the association between HFD and high sedentary time [38, 39, 40]. Persistent hyperglycemia also induces an inflammatory response that may decrease BMD and impair bone turnover and mineralization through a decrease in osteoblast migration and mitochondrial biogenesis [12, 13]. What has not been fully established is whether the development of metabolic dysfunction or obesity is a requirement for HFD to have a negative association with bone parameters (Table 2).

Preclinical studies have also demonstrated the effect of HFD with and without obesity on bone health. Animal models under prolonged exposure to a HFD recapitulate an obese state in humans [16, 18, 21, 48]. Dietary fat intake has been positively and negatively associated with osteoclast activity and osteoclastogenesis in bone-remodeling processes [49, 50]. HFD and obesity detrimentally affect bone structure, strength, and mass to a greater extent in skeletally immature mice when compared to mature mice [14, 15]. In addition, mice fed a HFD have increased bone marrow adiposity (BMA) when compared to mice fed a low-fat diet (LFD) or regular-chow diet [18, 21]. There have also been observations of a decreased mineral to matrix ratio and increased crystallinity in male and female rats on a HFD when compared to LFD-fed rats [16]. However, one study found an increase in femur size and whole bone mechanical properties in mice on a HFD [51]. These conflicting results may point to a HFD reducing the microscale bone quality and not whole bone

Table 2 Current gaps in nutrient trafficking changes in bone

What we know about nutrient trafficking	What is unknown
• Glucose and fat are major energy sources for bone [41, 42•, 43, 44]	• Does a caloric restriction suppress or stimulate lipolysis in marrow adipose tissue?
• The skeleton is a primary site for fatty acid uptake [17, 25]	• How does obesity alter glucose uptake in bone, relative to other tissues?
• A HFD suppresses glucose uptake in bone in mice lacking the insulin receptor [45]	• How long does glucose uptake in bone remain elevated after exercise?
• A low fat diet enhances glucose uptake in bone [45]	• What is the role of bone nutrient uptake during weight loss?
• Glucose uptake in bone is increased with exercise [46•, 47]	• Is there a preferential trafficking of dietary fat to marrow versus bone?
	• Can nutrient trafficking into bone be altered by exercise or diet?
	• Does weight loss suppress fat oxidation or lipolysis in bone or bone marrow?
	• Does weight loss from high loading influence nutrient trafficking changes?
	• What is the relationship between bone loading and appetite?

geometry and strength, thus generating the rationale for more studies to investigate microscale bone outcomes. One of the major limitations to preclinical models of obesity in bone health is the use of diets that contain 60% of their kilocalories from fat. These diets do not translate to human dietary conditions. The type of fatty acid in the diet could be driving the resulting effect on bone outcomes independently from the amount of fat consumed. Studies that included diets rich in fat have led to both increases and reductions in BMD, depending on the type of fatty acid content [52, 53]. Diet product numbers and therefore fatty acid types are not always disclosed in published work, but it is critically important for studies to disclose the product numbers of diets used to improve the reproducibility and interpretation of results.

Glucose Uptake and Utilization in Bone

Glucose is essential for osteoblast differentiation and bone formation [26, 46•, 54, 55]. Short-term administration of high-concentration glucose is associated with enhanced bone differentiation and mineralization [13]. Osteoblasts express GLUT1, GLUT3, and GLUT4 [41], indicating that glucose uptake occurs through insulin-independent and insulin-dependent mechanisms [56]. GLUT4 expression increases up to fivefold when primary mouse osteoblasts undergo further osteogenic induction [41]. Glucose uptake and RUNX2, an indispensable transcription factor in osteoblast differentiation, have been shown to have synergistic effects in osteoblastogenesis and bone formation throughout life [57]. Hence, osteoblastogenesis could be compromised if glucose uptake and utilization is impaired [57, 58]. Glucose uptake into bone can be altered with metabolic perturbations. One study demonstrated that glucose uptake into bone is suppressed in mice lacking the insulin receptor in osteoblasts and osteocytes, as well as after being fed a HFD, which may have been due to resistance to insulin-stimulated glucose uptake in bone. It is unknown how quickly glucose uptake in bone is reduced with obesity, relative to other tissues. Glucose uptake into bone was enhanced in the presence of insulin in low-fat diet–fed mice [45].

Multiple studies have demonstrated that bone glucose uptake increases with acute exercise, indicating a short-term need for heightened nutrient availability. For example, an increase in intensity from low to moderate cycling was shown to increase glucose uptake in femoral bone marrow in healthy young men [46•]. Glucose uptake in bone was increased during knee extension exercise [47]. More studies are needed to determine how long glucose uptake in bone remains elevated after exercise and if this is directly impacting bone formation and mineralization by osteoblasts.

It is well established that weight loss improves glucose disposal and hyperlipidemia status [59, 60, 61, 62]. During and after diet-induced weight loss, the liver, skeletal muscle, and adipose tissue undergo metabolic changes that improve nutrient trafficking and can increase appetite, lower energy expenditure, and promote weight regain (reviewed in [63]). In the liver, carbohydrate and lipid metabolism improves, glucose production is decreased, and there is an increase in trafficking of glucose to lipid storage as opposed to glycogen pools [63, 64, 65]. Skeletal muscle facilitates the clearance of excess carbohydrates, thus increasing glucose uptake. This preference for glucose as fuel is associated with the suppression of fat oxidation [66] (reviewed in [63, 65]), and consequently leaves surplus

nutrients to be stored. The induction of lipogenesis by insulin in adipose tissue is restored, and there is a reduction in the average size of adipocytes and an increase in adipocyte number that become prepared to store excess energy [67]. Together, these changes enhance rapid utilization of nutrients, shuttle glucose effectively into tissues, and therefore decrease circulating glucose. The role of bone in nutrient uptake during weight loss remains unknown. Bone is highly dependent on glucose for energy, but the increase in glucose uptake in the liver and skeletal muscle may deplete the glucose availability for bone when carbohydrate intake is very low.

Fat Trafficking and Utilization in Marrow and Bone

Fat trafficking and utilization in bone are most frequently thought of in terms of marrow adiposity, where the marrow cavity is an adipose depot [68]. Marrow cavities are mainly filled with hematopoietic cells at birth, but with aging and menopause, marrow adiposity gradually occupies as much as 70% of long bone cavities [69, 70, 71]. Appendicular skeletal regions are the main adipose storage sites, accounting for over 10% of total fat volume in adults [72•]. Progression of bone marrow adiposity (BMA) occurs during obesogenic conditions, where chylomicrons are cleared from circulation into bone marrow, mediated by perisinusoidal macrophages from endothelial cells [73•]. When radiolabeled chylomicron remnants were intravenously injected into mice, the skeleton (marrow and cortical bone) had the second highest uptake of those remnants [17]. A study found that diet-induced obesity increases the marrow cavity and BMA [74], thus supporting the notion that more lipid is being transported to the bone. On the other hand, BMA volume and adipocyte area have been found to be increased in a calorie-restricted diet compared to a normal diet, which was followed by reductions in trabecular thickness and cortical area fraction [75••]. Diet-induced weight loss decreases BMA in animals and humans [76, 77, 78]. Surgical weight loss and, more specifically, sleeve gastrectomy increases BMA [79, 80]. Although the role of BMA in bone health is unclear, observed reductions in BMA should coincide with the decreases in BMD during weight loss, due to the lack of nutrient availability. Curiously, people who experience anorexia nervosa often have a high BMA [81], adding to the lack of clarity regarding the function of BMA during caloric restriction. The purpose of marrow adiposity is uncertain, but potential functions are as follows.

One potential function of marrow fat includes acting as a local energy source to support the energy requirements of bone turnover or blood cell production, as exercise attenuates BMA accumulation and reduces BMA volume in obese mice [21, 74, 75••]. Also, the marker of fatty acid uptake, CD36, is increased in mice exercising on a normal diet but is reduced in mice exercising on a calorie restriction [75••], thus pointing to the skeleton's ability to shift nutrient uptake in a low-nutrient environment. Despite evidence that BMA is negatively associated with bone microarchitecture and BMD [68], one study indicated that excessive suppression of BMA in caloric restriction was associated with enhanced bone resorption [75••], suggesting that BMA is important for maintaining optimal bone health. Another potential function of bone marrow is to protect osteoblasts, osteocytes, and osteoclasts from excess lipid accumulation. The expansion of BMA from nutrient excess to the degree that ectopic adiposity is accumulating in osteoblasts and osteocytes may explain why an increase in BMA is often accompanied by bone loss. The consequences of prolonged high marrow adiposity are not known and could result in more lipolysis that mimics an insulin-resistant state, along with the release of inflammatory cytokines. The regulation of BMA may differ from other fat depots. Like other depots, obesity is associated with increased BMA. Unlike other depots, marrow adiposity can remain high during periods of prolonged negative energy imbalance, such as in anorexia nervosa [81], suggesting that marrow adipose is resistant to depletion of lipid.

Fat trafficking to osteoblasts, osteoclasts, and osteocytes needs to be considered as well, as cortical bone is a major destination for dietary fat [25]. Fat is an essential energy source for all bone cells [42•, 43, 44, 82]. The ability to oxidize fat may also prevent excess accumulation of lipid. Studies have observed an excessive accumulation of lipids in bone tissue that leads to lipotoxicity that induces apoptosis in osteocytes and affects osteoblast differentiation and function [19•, 83]. Fatty acid delivery was investigated in transgenic mice that lacked central regulators of fatty acid transport and exhibited impairments of fatty acid uptake in the tibia and femur when compared to wild-type mice [25]. Aside from evidence that cortical bone and bone marrow had a similar fatty acid profile [25], it is unclear whether there is a preferential trafficking to marrow versus bone. It is also unclear whether nutrient trafficking can be altered by exercise or diet, but data related to fat trafficking in other tissues yield clues. For example, one study investigating the influence of a HFD on dietary fat trafficking found a preferential disposition to store dietary fat in adipose tissue in obesity-prone rats. Obesity-prone rats were able to clear tracer more rapidly from the plasma and had a decreased $^{14}CO_2$ production following a HFD, suggesting a lowered oxidation of dietary fat. In obesity-prone females on a HFD, there was a decrease in dietary fat tracer oxidation in both the liver and skeletal muscle. This was followed by an increase in triglyceride content in the liver and a decrease in dietary fat tracer in the muscle. Lastly, there was an increase in the tracer in whole-body adipose tissue following HFD, but to a greater extent in obesity-prone rats [84]. These results indicate that an introduction of a HFD alters the way nutrients are trafficked between tissues, and a genetic predisposition to obesity may further amplify these changes. Therefore, the

excess circulating dietary fat as a consequence from a HFD could end up in the bone and in turn influence bone turnover.

With weight loss, skeletal muscle enhances the suppression of fat oxidation [63]. It is undetermined whether weight loss suppresses fat oxidation/lipolysis in bone or bone marrow. If so, then this would likely suppress bone formation, possibly accelerating bone resorption and leading to the bone loss that is frequently observed. So like muscle, the loss of bone mass may preserve the energetic state of the whole body in a way that protects body weight and promotes weight regain. Adipose appears to send signals to the brain that indicate its energetic state [67], and growing evidence that bone is an endocrine organ indicates that bone may do the same.

Bone: an Endocrine Organ with the Power to Regulate Nutrient Availability

The skeleton serves as an endocrine organ that helps regulate nutrient availability and uptake into other tissues [22, 85]. Studies thus far have examined three skeleton-secreted proteins that appear to have endocrine-like functions. Sclerostin, a glycoprotein produced by osteocytes, inhibits bone formation. Interestingly, sclerostin appears to act in an endocrine-like manner and is associated with diet-induced obesity. Specifically, there was a reduction of white adipose tissue and improvements in glucose handling, fatty acid oxidation, and reduced adipocyte de novo fatty acid synthesis in both sclerostin-deficient mice and sclerostin-neutralizing antibody treated mice on a HFD [28].

Recent studies proposed a new osteocyte-dependent mechanism to attenuate the accumulation of fat mass in response to loading, resulting from the observation of reduced body weight and fat mass in animals that received implanted weighted capsules compared to unweighted capsules [86]. The depletion of osteocytes prevented persistent weight loss in mice. Although an osteocyte-mediated reduction of food intake was the proposed means of weight loss, food intake and relative (body weight) VO_2 were only reported in osteocyte-replete animals at 1 time point, and energy balance was never reported. Therefore, it is unclear if osteocyte depletion independently influenced energy expenditure, energy storage, and/or food intake because of the removal of the energy required to detect and respond to loading. It is possible that a weighted capsule creates enough discomfort to reduce appetite. Weight loss was also observed in humans that wore a high-load (11% of body weight) vest for 8 h a day when compared to humans that wore a low-load (1% of body weight) vest [87]. However, rats exposed to simulated hyper gravity did not lose body weight [88]. Importantly, abruptly inserting a weighted capsule in a rodent or a vest on a human creates a form of overload exercise, which can reduce appetite in males and some females [89]. Having a heavier load on the skeleton may increase the energy demand on the osteocytes which may alter nutrient trafficking to the bone and marrow. Further studies are needed to determine the relationship between bone loading, appetite, and energy balance.

Osteoblasts secrete osteocalcin (OCN) and lipocalin-2 (LCN2); these proteins serve different roles as potential hormones to regulate energy balance. Experiments in lean and obese mice demonstrated that bone-derived LCN2 can reduce appetite, improve glucose intolerance, and increase circulating insulin levels [23]. Another study suggests that increases in LCN2 levels in obese mice may counteract metabolic dysregulation and reduce fat mass [24••]. OCN has been shown to stimulate pancreatic islet β-cell proliferation, enhance insulin production and secretion from the pancreas, improve insulin sensitivity in mice, improve glucose tolerance, and prevent obesity in wild-type mice fed a HFD, and this has been reviewed extensively [26, 27]. The question remains why OCN plays a role in endocrine functions similar to insulin, which points to the idea that OCN may be assisting the skeleton to communicate its energetic state or protect its nutrient availability.

Conclusion

Obesity-related overconsumption of food has a negative impact on bone quality. Fat and glucose oxidation are necessary to provide the energy required for bone formation and remodeling processes. However, ectopic lipid accumulation and chronic hyperglycemia in osteoblasts and osteocytes due to chronic overfeeding impair bone formation and adaptations to mechanical loading. These changes may begin with relative differences in nutrient trafficking to bone and other tissues, but bone has been largely omitted from nutrient trafficking studies. Exercise may affect the capacity to take up and oxidize glucose and fat in bone cells, but more studies are needed to support this notion. Further investigations are needed to understand how mechanical and metabolic perturbations alter nutrient trafficking to bone and marrow and subsequently affect glucose and fat oxidation and storage in bone.

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Declarations

Conflict of Interest The authors do not have any further conflicts of interest.

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- • Of importance
- •• Of major importance

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