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Bone quality and strength are greater in growing male rats fed fructose compared with glucose

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ABSTRACT

Optimization of peak bone mass during adolescence is important for osteoporosis prevention. Studies in rodents and humans have demonstrated the harmful effects of sugar intake on bone health. With the high levels of sucrose in the diets of adolescents, it is necessary to understand the influence of glucose and fructose on growing bones. This study compared the effects of dietary glucose and fructose on bone formation, microarchitecture, and strength. Because of the different metabolic effects of glucose and fructose, we hypothesized that their individual effects on bone would be different. Eighteen male Sprague-Dawley rats (age, 60 days) were randomly assigned to high-fructose (n = 9; 40% fructose, 10% glucose) or high-glucose diet (n = 9; 50% glucose) for 12 weeks. Bone measurements included histology and histomorphometry of trabecular bone in the distal femur and a 3-point bending test of the whole tibia. Whole liver mass and postprandial serum glucose, insulin, and triglycerides were used to assess differences in energy metabolism between the diets. There were no differences in food intake, body weight, or visceral adiposity between groups, but fructose consumption led to heavier livers ($P = .001$) and elevated serum triglycerides ($P = .00$). The distal femurs of fructose-fed rats had greater bone volume (bone volume/total volume; $P = .03$), lower bone surface (bone surface/bone volume; $P = .02$), and thicker trabeculae (trabecular thickness; $P = .01$). The tibias of the fructose-fed rats also withstood a greater maximum flexure load ($P = .032$). These results indicate that consumption of the high-fructose diet resulted in stronger bones with enhanced microarchitecture than consumption of the high-glucose diet.

1. Introduction

An estimated 10 million Americans have osteoporosis, whereas another 34 million are at risk for developing the disease because of low bone density [1]. As the population ages, these figures are expected to increase substantially [2]. The predicted rise in prevalence as well as the medical costs ($17 billion in 2005) and poor health outcomes associated with osteoporotic fractures underscore the importance of understanding more about osteoporosis prevention [2,3]. One target for prevention is the optimization of peak bone mass during adolescence [4]. According to a consensus statement by the National Institutes of Health, failure to reach peak bone mass during adolescence is as important as bone loss to the

Abbreviations: BFR, bone formation rate; BMC, bone mineral content; BMD, bone mineral density; BS, bone surface; BV, bone volume; HFS, high-fat sucrose; LFCC, low-fat complex carbohydrate diet; MAR, mineral acquisition rate; MS, mineralizing surface; N.Ob, number of osteoblasts; N.Oc, number of osteoclasts; Ob.S, osteoblast surface; Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.S, trabecular surface; TV, total volume.

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development of osteoporosis [5]. Determinants of peak bone mass include genetics and lifestyle factors such as physical activity and diet [6].

Because diet is modifiable, an understanding of which nutrients affect bone health represents an avenue for osteoporosis prevention. One dietary factor that may influence bone development is the consumption of added sugars. Over the past 3 decades (1978-2003), total sweetener availability in the US food supply has been on the rise. Coincidentally, adolescents consume the greatest amount of added sugars as a percentage of energy intake while also being most vulnerable to the effects of diet on the optimization of peak bone mass [7].

A primary source of added sweeteners in the diets of adolescents is sugar-sweetened beverages such as soft drinks and fruit-flavored drinks [8]. Cross-sectional studies have demonstrated an increased risk of fractures in teenage girls and boys who regularly consume soft drinks [9-12]. Potential explanations for these findings include the displacement of calcium-rich beverages [13] as well as harmful effects from other ingredients such as phosphoric acid and caffeine [14]. Studies that isolate the specific effect of sugar on bone are necessary to clarify the relationship between soft drink consumption by adolescents and fracture risk.

Another important consideration is that because sweetener availability has increased, there has been a shift in the types of sweeteners being used in industry. From 1978 to 2003, sucrose availability decreased by 32.7% (76.5 g/d), whereas the availability of high-fructose corn syrup (HFCS) increased 60.8% (to 74.2 g/d) [7]. HFCS-55, the sweetener used by the beverage industry, is 55% fructose and 42% glucose and 3% polysaccharides [15]. This ratio of fructose to glucose in HFCS-55 differs from the 1:1 ratio found in sucrose. To understand how fructose consumption may affect bone, we compared the specific effects of the monosaccharides fructose and glucose.

Research conducted in both rodents and humans has demonstrated a relationship between fructose and glucose intake and disruptions in bone mineral homeostasis [16-20]. However, few of these studies attempted to quantify the effect of changes in mineral homeostasis in response to consumption of these monosaccharides on specific parameters of bone health. Multiple animal studies have demonstrated deleterious effects of sugar consumption on bone morphology and strength [21-25]. However, the precise influence of the monosaccharides fructose and glucose remains unclear. Recent evidence points to the skeleton as a player in energy metabolism [26]. Therefore, metabolic changes induced by the consumption of high sugar diets have the potential to affect bone mass and quality [27]. The differences in the effects of glucose and fructose consumption on insulin and leptin, hormones that regulate metabolism, have been well documented in both animal and human studies [28-30].

Presently, dietary sugar intake remains high among adolescents, and the development of osteoporosis continues to be a concern for older adults. Although there is evidence of a relationship between sugar intake and bone in the existing literature, the influence of the monosaccharides glucose and fructose on specific bone measures such as bone formation and bone strength remains unknown. A greater understanding of this relationship will provide insight into the role of dietary sugar consumption in the achievement of peak bone mass and, ultimately, the development of osteoporosis later in life. Because of the different metabolic effects of dietary fructose and glucose, we hypothesized that these monosaccharides would have different effects on bone formation, quality, and strength. Bone histology and histomorphometry were used to assess microarchitectural arrangement and bone formation in trabecular bone in 2-month-old male Sprague-Dawley rats, a standard model used in studies investigating the effects of dietary components on bone growth. To determine differences in bone strength, we used a 3-point bending test. Metabolic effects of the 2 diets were assessed by measuring serum glucose, insulin, and triglyceride levels weekly during the 12-week study.

2. Methods and materials

2.1. *Animal model, diets, and study design*

The University of Georgia Institutional Animal Care and Use Committee approved all procedures and protocols used in this experiment. Male Sprague-Dawley rats (aged 60 days, n = 18) were obtained from Harlan Laboratories (Pratville, AL, USA). Upon arrival, the animals were housed individually in clear plastic shoebox cages attached to the BioDAQ Food Intake Monitoring System (Research Diets, New Brunswick, NJ, USA) in a room kept at 21°C with a 12-hour light/dark cycle. The animals were acclimated to the feeding system with ad libitum access to a chow diet (LabDiet PicoLab Rodent Diet 20 5053, Brentwood, MO, USA) and water for 7 days before being randomly assigned to receive a high-fructose diet (n = 9) or a high-glucose diet (n = 9). The animals had ad libitum access to their assigned diets and water throughout the 12-week feeding study.

The high-fructose group received a diet consisting of 20% kcal from protein, 10% kcal from fat, and 70% from carbohydrate: 40% fructose, 10% glucose, and 20% corn starch (Research Diets; No. D02022708). The high-glucose group received a diet consisting of 20% kcal from protein, 10% kcal from fat, and 70% from carbohydrate: 50% glucose and 20% cornstarch (Research Diets; No. D08082606). Both the high-fructose and high-glucose diets supplied 3.8 kcal/g. The compositions of the diets are displayed in Table 1. Food intake was measured continuously, and animal weights were recorded weekly.

2.2. *Bone labeling and tissue collection*

Chlortetracycline hydrochloride (Sigma-Aldrich, St Louis, MO, USA), a fluorochrome used to label bone, was dissolved in water at a concentration of 25 mg/kg. The rats were injected with the solution intraperitoneally at 7 and 2 days before they were killed [31]. The labels allowed for the quantitative measurement of bone formation. After 12 weeks, the animals were killed by decapitation. Epididymal and perirenal fat pads were removed and weighed as a measure of visceral adiposity. The livers were also removed and weighed as an indicator of changes to energy metabolism because of sugar intake. The right hind limb was dissected free, cut at the midshaft of the