Biomedicine & Pharmacotherapy 98 (2018) 191–200

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Osteoporosis is associated with metabolic syndrome induced by high-carbohydrate high-fat diet in a rat model

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ARTICLE INFO

Keywords:
Calcium
Obesity
Hyperglycemia
Hypertension
Dyslipidemia
Bone

ABSTRACT

This study aimed to investigate the bone quality in rats induced with metabolic syndrome (MetS) using high-carbohydrate high-fat (HCHF) diet. Male Wistar rats (n = 14) were randomized into two groups. The normal group was given standard rat chow. The MetS group was given HCHF diet. Diet regimen was assigned for a period of 20 weeks. Metabolic syndrome parameters were measured monthly until MetS was established. Left tibiae were scanned using micro-computed tomography at week 0, 8, 12, 16, and 20 to analyze the trabecular and cortical bone structure. At the end of the study, rats were euthanized and their bones were harvested for analysis. Metabolic syndrome was established at week 12 in the HCHF rats. Significant deterioration of trabecular bone was observed at week 20 in the HCHF group ($p < 0.05$). The HCHF diet also decreased cortical and tissue area significantly ($p < 0.05$), but did not affect cortical thickness and bone calcium content ($p > 0.05$). Femur length and width in the HCHF group were significantly shorter than the normal group ($p < 0.05$). The biomechanical strength test showed that the femur of the HCHF rats could endure significantly lower force, but significantly higher displacement and strain compared to the normal rats ($p < 0.05$). In conclusion, HCHF diet-induced MetS can cause adverse effects on the bone.

1. Introduction

Metabolic syndrome (MetS) is defined as the simultaneous occurrence of at least three conditions including central obesity, hyperglycemia, hypertension, high triglycerides, and low high-density lipoprotein (HDL) cholesterol [1]. As a group, these conditions are often associated with various life-threatening complications, such as cardiovascular diseases, diabetes, stroke, fatty liver, and cancer [2]. Thus, MetS brings about serious healthcare and socioeconomic burden worldwide. Approximately 20% of the adult population in Western countries suffers from MetS [3]. In Malaysia, a cross-sectional survey revealed that the crude prevalence of MetS ranges from 33–43% depending on the definition of MetS [4].

Osteoporosis is a medical condition characterized by the reduction of bone mass and increased risk of fragility fractures [5]. The burden of osteoporosis is increasing significantly by the enormous prevalence, significant healthcare expenditure, chronic pain, long-term disability, and premature death caused by the disease [6,7]. The pathogenesis of osteoporosis is related to sex hormone (oestrogen or testosterone) deficiency and aging. Recent concept of osteoporosis is reflected by impaired microarchitecture of the skeletal resulting from certain unhealthy lifestyle behaviors, diseases or medications.

Metabolic syndrome and osteoporosis seem to be unrelated at the first glance. However, recent investigations on the association between MetS and bone health showed otherwise. According to the literature, increased mechanical loading conferred by high body weight and fat mass in MetS individual protected the bone [8]. Increased adipocyte differentiation inhibited osteoblast differentiation [9] and stimulated pro-inflammatory states to induce bone loss [10,11]. Apart from that, the excessive use of glucocorticoid or mineralocorticoid can cause MetS and bone loss [12,13]. Lipid oxidation associated with dyslipidemia stimulated adipocyte differentiation and suppressed osteoblast differentiation through activation of peroxisome proliferator-activated receptor-γ (PPAR-γ) [14]. The relationship between MetS and bone health in previous human observational studies revealed contradictory findings. Some studies reported a reduction [15–18] while the others reported an increment in bone mineral density (BMD) in MetS subjects [19,20]. The inconsistency may be due to the heterogeneous nature of

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https://doi.org/10.1016/j.biopha.2017.12.042
Received 17 November 2017; Received in revised form 6 December 2017; Accepted 13 December 2017

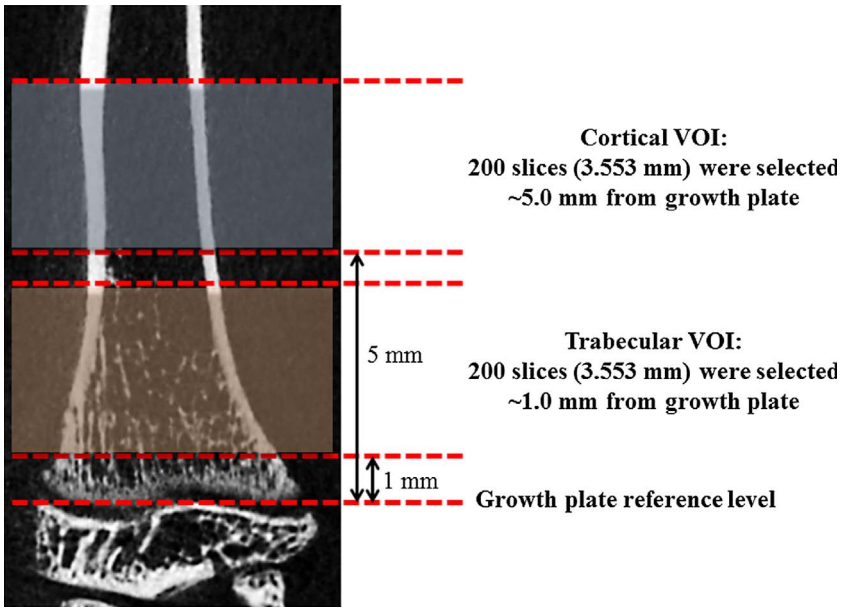

Fig. 1. Volume of interest (VOI) of trabecular and cortical bone chosen for analysis, defined with reference to proximal growth plate level.

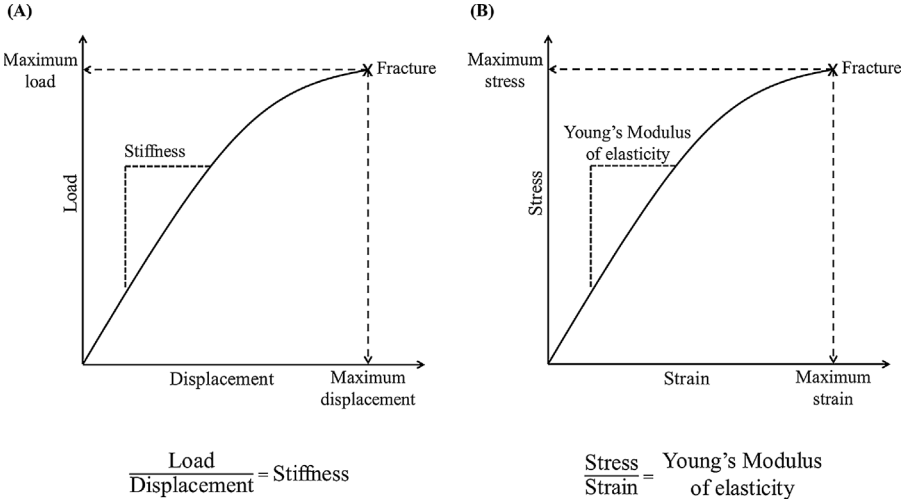

Fig. 2. (A) Load-displacement and (B) stress-strain curve derived from three-point bending test. Load-displacement curve represents the extrinsic (behaviour of whole bone structure) whereas stress-strain curve represents the intrinsic (behaviour of bone tissue) biomechanical properties. The gradient of the curve in the linear region represents the stiffness and Young's Modulus of elasticity, respectively.

MetS, whereby each component exerts different (protective / deleterious) and independent effects on bone [21]. Therefore, the answer to whether osteoporosis is another important consequence of MetS remains ambiguous at this moment.

Researchers have attempted to study the relationship between MetS and bone in a controlled environment using animal models of MetS. An earlier study reported that mice fed with Westernized diet until 30 weeks of age developed MetS. These animals had lower BMD and bone mineral content (BMC) of the whole body, femoral, and vertebral levels [22]. Another in vivo study demonstrated that MetS induced by 16 weeks of high fat diet increased alveolar bone loss, osteoclastogenesis, and inflammation in C57BL/6 mice [23]. However, there was no evaluation of bone structural morphology and biomechanical strength in these studies. The available evidence was still insufficient to conclude the relationship between MetS and bone loss. Therefore, it is necessary to look into other relevant studies on the association between components of MetS (obesity, hyperglycemia, hypertension, or dyslipidemia) and bone loss. The deleterious effects of obesity and hyperlipidemia on bone health have been widely investigated [9,24,25]. A more recent animal study by Mello-Sampayo et al. found that chronic hyperglycemia improved ultrastructure and mechanical properties of cortical bones in ovariectomized rats [26]. For the hypertensive animal model, Lee et al. observed that the spontaneous hypertensive rats had greater trabecular bone mass, volume, and strength compared to normotensive rats [27]. The relationship between MetS and bone health remain obscure because the data from animal studies were heterogeneous. This research gap needs to be bridged for a better understanding of the impact of MetS on the skeleton.

The previous animal studies have several shortcomings. Firstly, the diet adopted in the previous study was not similar with the human diet. Secondly, research on the evaluation of trabecular and cortical bone parameters as well as biomechanical strength from MetS-associated conditions is limited. In this study, we aimed to investigate the bone changes at the microarchitectural level (trabecular and cortical regions), mineral content (calcium), and biomechanical strength in a MetS animal model. These parameters were chosen because they are important in the evaluation of bone quality. The high-carbohydrate high-fat (HCHF) diet adopted to induce MetS in rats in this study was shown previously to mimic the pathogenesis of MetS in human [28,29]. We hope to provide readers a clear picture on the relationship between MetS and osteoporosis using this rat model.