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The effects of palm tocotrienol on metabolic syndrome and bone loss in male rats induced by high-carbohydrate high-fat diet

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ABSTRACT

Inflammation is a possible mediator of the relationship between metabolic syndrome (MetS) and osteoporosis. Palm tocotrienol, an anti-inflammatory agent, has been reported to exert beneficial effects for the treatment of MetS and osteoporosis individually. This study aimed to investigate the potential role of palm tocotrienol in preventing both MetS and bone loss in male rats via alleviating the inflammatory response. In this study, MetS was established in the rats fed with HCHF diet. This was accompanied by bone loss and elevated pro-inflammatory cytokine levels. Supplementation of palm tocotrienol improved MetS parameters, trabecular bone microstructure, bone strength, and reduced pro-inflammatory cytokines in the HCHF rats. A dose-dependent effect of palm tocotrienol was also observed in preventing MetS conditions. In conclusion, palm tocotrienol prevents both MetS and bone loss, possibly through its anti-inflammatory properties.

1. Introduction

Lifestyle-related risk factors including eating behaviours and physical inactivity are the determinants of metabolic syndrome (MetS). The term MetS indicates a constellation of three or more risk factors including abdominal obesity, high blood pressure, high fasting blood glucose (FBG), high triglycerides, and low high-density lipoprotein (HDL) cholesterol (Alberti et al., 2009). Worldwide prevalence of MetS ranges from 8–43% in men and 7–56% in women (Cameron et al., 2004). The incidence of MetS is rising at an alarming rate and has become one of major public health challenges. Metabolic syndrome poses long-term adverse effects on health, particularly with increased risks of cardiovascular disease (Mottillo et al., 2010), type II diabetes (Shin et al., 2013), and stroke (Li et al., 2017). However, the relationship between MetS and osteoporosis remains debatable, whereby both positive and negative associations have been observed in human and animal studies (Chin et al., 2015; Wong, Chin, Suhaimi, Ahmad, & Ima-Nirwana, 2016). Inflammation is a mediator of the relationship between MetS and osteoporosis. Adipose tissue is the common feature for visceral obesity and dyslipidaemia in MetS, which functions as a source of inflammatory mediators such as tumour necrosis factors-α (TNF-α), interleukin-6 (IL-6), interleukin-1β (IL-1β), and C-reactive protein (CRP) (Calder et al., 2011). During hyperglycaemic condition, the accumulation of advanced glycation end-products (AGEs) further contributes to the increase of pro-inflammatory response (Singh, Bali, Singh, & Jaggi, 2014). Subsequently, high levels of inflammatory cytokines promote osteoclast differentiation and bone resorption through activation of receptor activator of NF-κB (RANK)/receptor activator of NF-κB ligand (RANKL)/osteoprotegerin (OPG) pathway (Weitzmann, 2013).

Treatment strategies for MetS focus on lifestyle modifications, such as adopting a healthy balanced diet along with exercising. They are the

Abbreviations: AGEs, advanced glycation end-products; ANOVA, analysis of variance; AUC, area under the curve BMD, bone mineral density; BMI, body mass index; BV/TV, trabecular bone volume; Conn.D, connectivity density; CRP, C-reactive protein; Ct.Ar, cortical bone area; Ct.Ar/Tt.Ar, cortical area fraction; Ct.Th, cortical thickness; DEXA, dual-energy X-ray absorptiometry; DNA, deoxyribonucleic acid; FBG, fasting blood glucose; HCHF, high-carbohydrate high-fat; HDL, high-density lipoprotein; HMG-CoA, 5-hydroxy-3-methylglutaryl-coenzyme A; IL-1α, interleukin-1α; IL-1β, interleukin-1β; IL-6, interleukin-6; LDL, low-density lipoprotein; MCP-1, monocytes chemoattractant protein-1; MetS, metabolic syndrome; NEFA, non-esterified fatty acid; OGTT, oral glucose tolerance test; OPG, osteoprotegerin; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; SMI, structural model index; SEM, standard error of the mean; SPSS, Statistical Package for Social Sciences; STZ, streptozotocin; Tb.N, trabecular number; Tb.Sp, trabecular separation; Tb.Th, trabecular thickness; TNF-α, tumour necrosis factors-α; Tt.Ar, total cross-sectional area inside the periosteal envelope; TRF, tocotrienol-rich fraction; VOI, volume of interest; 3D, three dimensional; μCT, micro-computed tomography

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safest approaches but requires long-term determination and compliance (Kaur, 2014). Alternatively, pharmacological therapies (appetite suppressants and nutrition absorption inhibitors) are used to treat MetS but they are often associated with adverse side effects (Mohamed, Ibrahim, Elkhayat, & El Dine, 2014). Bariatric surgery remains the best option when medications ineffective or the patients presented with comorbid obesity. On the other hand, the common treatments for osteoporosis are hormone replacement therapy (e.g. oestrogen or testosterone) and medications (e.g. bisphosphonates and teriparatide) (Banu, 2013; Kaufman, Lapauw, & Goemaere, 2014), but they also come with various undesirable side effects. Therefore, the search for effective alternative therapies with fewer side effects is ongoing. In addition, despite a potential positive relationship between MetS and osteoporosis (Wong, Chin, Suhaimi, Ahmad, & Ima Nirwana, 2018; Wong et al., 2017c), there is no single treatment to manage both conditions at the same time.

Tocotrienol is a member of the vitamin E family, which can be divided of four distinct analogues: alpha- (α-), beta- (β-), gamma- (γ-), and delta- (δ-) tocotrienol. The main sources of tocotrienol are rice bran, palm, and annatto (Aggarwal, Sundaram, Prasad, & Kannappan, 2010). Palm tocotrienol is extracted and concentrated from red palm fruits (*Elaeis guineensis*). Tocotrienols make up of approximately 75% of the vitamin E in palm oil, of which the majority is γ-tocotrienol (Tan, Sambanthamurthi, Sundram, & Wahid, 2007). The health promoting properties of palm tocotrienol on medical conditions associated with MetS have been widely established for decades in human and animal studies (Wong et al. (2017b)). Administration of tocotrienol-rich fraction (TRF) from palm oil reduced serum cholesterol, low-density lipoprotein (LDL) cholesterol, and glucose levels in hypercholesterolemic subjects (Qureshi et al., 1991). Besides, palm TRF recovered glycaemic status in streptozotocin (STZ)-induced diabetic animals (Budin et al., 2009; Matough et al., 2014; Siddiqui, Ahsan, Khan, & Siddiqui, 2013). More recently, Wong, Poudyal, Ward, and Brown (2012) found that palm TRF reversed all MetS parameters in animals fed with high-carbohydrate high-fat (HCHF) diet, indicated by reductions in abdominal circumference, omental fat, FBG, blood pressure, triglyceride, and non-esterified fatty acid (NEFA) levels. Additionally, palm tocotrienol was previously found to prevent bone loss using animal models (Chin & Ima-Nirwana, 2015, 2012). Supplementation of palm-oil derived tocotrienol at the dose of 60 mg/kg body weight (b.w.) prevented the loss of whole body bone mineral density (BMD) and bone calcium in the femur of dexamethasone-induced osteoporotic rats (Ima-Nirwana & Fakhrurazi, 2002). In an ovariectomized rat model, treatment of palm tocotrienol improved dynamic bone histomorphometric indices and reversed osteoporosis (Soelaiman et al., 2012). Administration of 100 mg/kg b.w. palm tocotrienol for four months conferred better protective effects in the femur by preventing the imbalance in bone metabolism due to free radical damage (Maniam, Mohamed, Shuid, & Soelaiman, 2008). Coincidentally, palm-based tocotrienol has been previously reported to exert anti-inflammatory properties in human (Heng, Hejar, Stanslas, Ooi, & Loh, 2015) and animal studies (Siddiqui et al., 2013). Hence, the investigation on the role of palm tocotrienol in modulating the anti-inflammatory response during MetS and osteoporosis is necessary.

The current research aimed to investigate the effects of palm tocotrienol in preventing bone loss due to MetS. We hypothesize that palm tocotrienol could prevent MetS and the subsequent bone loss and this effect could be mediated by its anti-inflammatory properties. The findings from this study will help to validate the use of tocotrienol as an alternative therapy for MetS and osteoporosis.

2. Materials and methods

2.1. In vivo experimental design

All animal experimental protocols were reviewed and approved by the Universiti Kebangsaan Malaysia Animal Ethics Committee (Code: PP/FAR/2015/IMA/20-MAY/679-JUNE-2015-MAY-2017). The experiment was conducted on inbreed and genetically homogeneous animals (12-week-old male Wistar rats) purchased from Laboratory Animal Resource Unit, Universiti Kebangsaan Malaysia (Kuala Lumpur, Malaysia). They were housed individually at the vivarium (Department of Anatomy, University Kebangsaan Malaysia). The laboratory conditions were maintained at an ambient temperature of 27 °C and alternated 12-h light-dark cycle. Following acclimatization for one week, the rats were randomized into five experimental groups (n = 6/group): baseline, normal, HCHF, 60 mg/kg b.w. palm tocotrienol-treated (HCHF + 60 pT3), and 100 mg/kg b.w. palm tocotrienol-treated (HCHF + 100 pT3) groups. The baseline group was sacrificed upon received. The normal group was given tap water and standard rat chow (Gold coin, Port Klang, Malaysia), which contained sufficient calorie to support growth of the rats. The remaining groups were fed with HCHF diet, which was known to induce early signs of MetS within eight weeks of treatment in rats (Wong et al., 2017a). The HCHF diet was prepared by mixing 175 g of fructose, 395 g of sweetened condensed milk, 200 g of ghee, 155 g of powdered rat food, 25 g of Hubble Mendel and Wakeman salt mixture and 50 mL of water. The drinking water for the HCHF groups was supplemented with 25% fructose. Food and drinks were given *ad libitum*. Palm tocotrienol was administrated orally daily after eight weeks of HCHF diet at the doses of 60 or 100 mg/kg b.w. body weight. The palm tocotrienol, consisting of 21.9% α-tocopherol, 24.7% α-tocotrienol, 4.5% β-tocotrienol, 36.9% γ-tocotrienol, and 12.0% δ-tocotrienol, was a generous gift from Excelvite Sdn Bhd (Chemor, Malaysia). Palm tocotrienol was diluted with tocopherol-stripped corn oil (MP Biomedicals, Solon, USA). All MetS parameters were evaluated at the end of the experiment prior to euthanasia of animals. At the end of the study, the rats were sacrificed. Femurs were harvested and kept under −70 °C for micro-computed tomography (μCT) analysis, calcium content assay, and biomechanical strength analysis. The *in vivo* experimental design was illustrated in Fig. 1.

2.2. Evaluation of metabolic syndrome parameters

2.2.1. Physiological parameters

Food and water intakes were assessed daily. Energy intake was

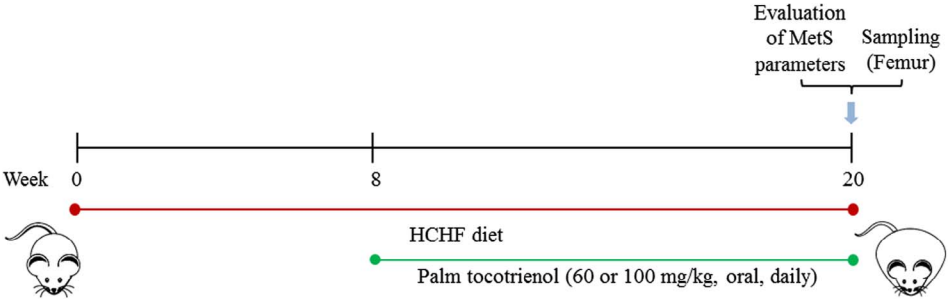

Fig. 1. Animal experimental design of palm tocotrienol (60 or 100 mg/kg b.w.) treatment in HCHF diet-induced MetS rats.

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