

# Direct and Indirect Effect of Honey as a Functional Food Against Metabolic Syndrome and Its Skeletal Complications

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Elvy Suhana Mohd Ramli<sup>1</sup>  
Kumeshini Sukalingam<sup>1</sup>  
Mohd Amir Kamaruzzaman<sup>1</sup>  
Ima Nirwana Soelaiman<sup>2</sup>  
Kok-Lun Pang<sup>2</sup>  
Kok-Yong Chin<sup>2</sup>

<sup>1</sup>Department of Anatomy, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Cheras, Kuala Lumpur, Malaysia; <sup>2</sup>Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Cheras, Kuala Lumpur, Malaysia

**Abstract:** Metabolic syndrome (MetS) refers to the simultaneous presence of hypertension, hyperglycemia, dyslipidemia and/or visceral obesity, which predisposes a person to cardiovascular diseases and diabetes. Evidence suggesting the presence of direct and indirect associations between MetS and osteoporosis is growing. Many studies have reported the beneficial effects of polyphenols in alleviating MetS in in vivo and in vitro models through their antioxidant and anti-inflammation actions. This review aims to summarize the effects of honey (based on unifloral and multi-floral nectar sources) on bone metabolism and each component of MetS. A literature search was performed using the PubMed and Scopus databases using specific search strings. Original studies related to components of MetS and bone, and the effects of honey on components of MetS and bone were included. Honey polyphenols could act synergistically in alleviating MetS by preventing oxidative damage and inflammation. Honey intake is shown to reduce blood glucose levels and prevent excessive weight gain. It also improves lipid metabolism by reducing total cholesterol, triglycerides and low-density lipoprotein, as well as increasing high-density lipoprotein. Honey can prevent bone loss by reducing the adverse effects of MetS on bone homeostasis, apart from its direct action on the skeletal system. In conclusion, honey supplementation could be integrated into the management of MetS and MetS-induced bone loss as a preventive and adjunct therapeutic agent.

**Keywords:** antioxidant, anti-inflammatory, bone, hypertension, hyperlipidemia, hyperglycemia, obesity, osteoporosis

## Introduction

Metabolic syndrome (MetS) is a non-communicable disease characterized by a cluster of medical conditions, such as visceral obesity, diabetes mellitus, dyslipidemia, and/or hypertension, which predispose an individual to cardiovascular diseases and diabetes mellitus.<sup>1</sup> Prevalence of MetS ranges from <10% to as high as 84%,<sup>2,3</sup> affecting 33% of the adult population in the USA between 2003 and 2012 and 25.7% of adults in the Asia-Pacific region.<sup>4</sup> The incidence of MetS often parallels with the onset of obesity and type 2 diabetes, but it is dependent on the diagnostic criteria and definition of MetS used.<sup>5</sup> The underlying etiology of MetS is still not completely understood, but rapid urbanization of developing countries, consumption of unhealthy diet and sedentary lifestyle are known to contribute to MetS.<sup>6</sup> Westernization of lifestyle is closing the prevalence gap between Asian and Western countries.<sup>7,8</sup> Additionally, age, sex, ethnicity, family inheritance (genetic

Correspondence: Elvy Suhana Mohd Ramli  
Department of Anatomy, Faculty of Medicine, Universiti Kebangsaan Malaysia Medical Centre, Level 18, Preclinical Building, Jalan Yaacob Latif, Bandar Tun Razak, Cheras 56000, Kuala Lumpur, Malaysia  
Tel +60 3 9145 8633  
Email elvysuhana@ukm.edu.my

susceptibility), chronic inflammation and gut microbiota are also associated with the onset of MetS.<sup>9–12</sup>

According to the Joint Interim Statement (2009), MetS is diagnosed when a patient has at least three out of five conditions: (1) high fasting blood glucose (FBG) ( $\geq 100$  mg/dL or receiving drug therapy for hyperglycemia); (2) high blood pressure ( $\geq 130/85$  mmHg or receiving drug therapy for hypertension); (3) high serum triglycerides (TG) ( $\geq 150$  mg/dL or receiving drug therapy for hypertriglyceridemia); (4) low serum high-density lipoprotein cholesterol (HDL) ( $< 40$  mg/dL in men or  $< 50$  mg/dL in women, or receiving drug therapy for reduced HDL); and (5) the presence of central obesity [waist circumference  $\geq 102$  cm (40 inches) for Europicid men or  $\geq 88$  cm (35 inches) for Europicid women;  $\geq 90$  cm (35 inches) for Asian men or  $\geq 80$  cm (32 inches) for Asian women].<sup>1</sup> Proper management or prevention of MetS will lower the risk for its complications, including cardiovascular diseases and diabetes mellitus.<sup>10</sup> The current approach in MetS treatment focuses on lifestyle modification or management, such as calorie restriction, low-to-moderate intense and regular aerobic physical activity and resistance training program.<sup>10</sup> The patients will be prescribed medications, such as beta-blockers/angiotensin-converting enzyme inhibitors for hypertension, statins for hyperlipidemia, metformin/glibenclamide for hyperglycemia if lifestyle modifications are insufficient.<sup>13</sup> Although these agents are successful in controlling the components of MetS, concurrent use will lead to the issues of polypharmacy, leading to problems such as high medical expenses, drug interactions, low compliance of the patients.<sup>14</sup> To date, no single treatment targeting all the components of MetS is available in the market.

MetS is associated with oxidative stress and chronic inflammation which underlay various diseases. The cellular catabolism of excess nutrients generates oxidative stress due to mitochondrial dysfunction and endoplasmic reticulum stress, which can subsequently cellular damage and malfunction.<sup>15,16</sup> Adipose secretion of proinflammatory cytokines, such as interleukin (IL)-1, IL-6 and tumor necrosis factor-alpha (TNF $\alpha$ ), and activation of nuclear factor kappa-B (NF- $\kappa$ B) pathway by ligands for Toll-like receptors and receptors of advanced glycation end products produce chronic inflammation in MetS.<sup>17–19</sup> MetS is also linked to hyperactivation of the hypothalamic-pituitary-adrenal axis as a result of increased inflammation and leptin level.<sup>20</sup> These intervening physiological changes give rise to many pathological conditions. For instance, biological toxicity due to oxidative stress and protein glycation could cause

microvascular dysfunction, which subsequently leads to hippocampal neuronal degeneration and cognitive deficit.<sup>21</sup> Oxidative stress, chronic inflammation and hypercortisolism in MetS augment insulin resistance. Hypercortisolism is also implicated in affective disorders, especially depression.<sup>22,23</sup>

The current review focuses on the adverse effects of MetS on bone. Osteoporosis is a metabolic bone disease characterized by a reduction in bone mass and deterioration in bone microstructure, leading to skeletal fragility and increased susceptibility to fracture.<sup>24</sup> It is typically defined in men or women with a bone mineral density (BMD) T-score lower than 2.5 standard deviations of the young adult populations (T-score  $\leq -2.5$ ).<sup>25</sup> Aging, menopause or other secondary factors, such as calcium malabsorption, glucocorticoid treatment, immobility and chronic inflammatory diseases increase the risk of osteoporosis.<sup>26</sup> Accumulated evidence revealed the indirect association of MetS in osteoporosis. Constituents of MetS such as dyslipidemia, abdominal obesity, hyperglycemia and hypertension are co-expressed in individuals with osteopenia or osteoporosis.<sup>27–29</sup> The association of MetS with low BMD and osteoporosis had been demonstrated in systematic review and meta-analysis.<sup>28–30</sup>

Chronic low-grade inflammation and oxidative stress present in MetS play major roles in inducing osteoporosis or bone loss.<sup>28</sup> The inflammatory-related signaling pathways like NF- $\kappa$ B and mitogen-activated protein kinases (MAPKs) are activated during MetS.<sup>31</sup> Activated NF- $\kappa$ B upregulates several downstream proinflammatory mediators such as cyclooxygenase-2 (COX-2), IL-6, IL-12, interferon, TNF- $\alpha$  and inducible nitric oxide synthase.<sup>32,33</sup> Besides, reactive oxygen species (ROS) is generated during MetS due to excessive macronutrients intake and inflammation.<sup>28,34,35</sup> ROS like hydrogen peroxide also reciprocally promotes the oxidative activation and self-amplification of the inflammatory response.<sup>34,35</sup> Eventually, the oxidative stress and inflammation events promote the osteoclastogenesis and inhibit the osteoblastogenesis, thereby affecting bone homeostasis and causing bone loss.<sup>28</sup>

Natural products consumed by humans since antiquity offer safe and economical dietary options to treat or prevent several diseases and complications. They can be used as adjunct treatments to provide more comprehensive prevention or management against each component of MetS including obesity, hyperglycemia and dyslipidemia.<sup>36</sup> Honey is a natural product with health-beneficial effects

due to its potent antioxidant and anti-inflammatory properties. Honey is a sweet viscous fluid stored in wax-form structures called honeycombs after being harvested by honeybees from plants (floral nectar).<sup>37</sup> It is produced through regurgitation, enzymatic activity, and water evaporation in the beehives. Apart from the nectar source, honeybees also collect secretions from insects (belonging to the genus *Rhynchota*) to produce honeydew honey.<sup>37</sup> Honey is composed of at least 181 substances, mainly carbohydrates like fructose (38%) and glucose (31%). It also contains enzymes, amino acids, vitamins, proteins and polyphenols.<sup>38</sup> The antioxidant property of honey is contributed by its polyphenol content, which is comprised of flavonoids (eg, quercetin, luteolin, kaempferol, apigenin, chrysin, galangin), phenolic acids, antioxidant enzymes (eg, glucose oxidase and catalase, CAT), ascorbic acid, and carotenoids.<sup>38–40</sup>

Honey polyphenols are responsible for various pharmacological effects by suppressing ROS formation through inhibition of enzymes or chelating trace elements involved in free radical generation.<sup>41,42</sup> Additionally, honey also exerts anti-inflammatory properties as reported by several *in vitro* and *in vivo* studies.<sup>37,43</sup> In carrageenan-induced inflammation model, honey acts as an anti-inflammatory agent by inhibiting the production of proinflammatory mediators, such as nitric oxide (NO), prostaglandin E<sub>2</sub> (PGE<sub>2</sub>), TNF- $\alpha$ , and IL-6.<sup>43–45</sup> The biological actions of NF- $\kappa$ B, including the activation of transcription and DNA binding activity, are regulated by the acetylation and subsequent nuclear translocation of NF- $\kappa$ B p65 subunit.<sup>46</sup> Honey also inhibits NF- $\kappa$ B inhibitor- $\alpha$  (I $\kappa$ B $\alpha$ ) degradation and subsequently attenuates NF- $\kappa$ B nuclear translocation.<sup>47</sup> Gallic acid, a type of phenolic acids found in honey, also exerts an anti-inflammatory action by suppressing NO, PGE<sub>2</sub> and IL-6 production in lipopolysaccharide-induced RAW 267.4 murine macrophages.<sup>48</sup> Gallic acid inhibits p65 acetylation-dependent activation of NF- $\kappa$ B and the production of inflammatory mediators.<sup>49</sup> All of the bioactive compounds in honey may act synergistically to contribute to its overall anti-inflammatory properties.

The pharmacological properties of honey have been investigated scientifically. Honey has antibacterial properties contributed by its phenolic content, hydrogen peroxide, pH and osmotic pressure.<sup>50</sup> Honey facilitates wound healing, which is a property related to its antioxidant and antibacterial activity and osmotic pressure. Its high viscosity also maintains the moisture of the wound by forming a protective barrier.<sup>38</sup> Recent studies also demonstrated

that honey exerts an antiproliferative effect against cancer cells. This effect is correlated with the phytochemical compounds of honey that activate the mitochondrial apoptotic pathways [62–65].<sup>51–54</sup> The effects of honey on metabolic disorders and skeletal health will be discussed further in later sections.

This review aimed to illustrate the pathogenesis of MetS and its relationship to osteoporosis. It also explores the beneficial effects of honey on each component of MetS and bone against deterioration caused by MetS.

## Methods

A literature search was performed to identify relevant studies reporting the relationship between MetS or each MetS component on bone health. Two databases, ie, PubMed and Scopus, were searched without filtering years, language and type of publications. The search strategy involved a combination of the following sets of keywords, ie, (osteoporosis OR bone) AND (MetS OR hyperglycemia OR dyslipidemia OR hypertension OR obesity). In the subsequent search focusing on the effects of honey on MetS and bone health, the search string used was honey AND (osteoporosis OR bone) OR (MetS OR hyperglycemia OR dyslipidemia OR hypertension OR obesity). We only include original research articles in the current review. Articles were screened prior to their inclusion in this review.

## Honey and Obesity

Obesity is a condition of excessive accumulation of body fat, and it is defined as having a body mass index (BMI)  $\geq 30$  kg/m<sup>2</sup>.<sup>55</sup> Central obesity is reflected by an increase in waist circumference due to the accumulation of visceral adipose tissue.<sup>56</sup> Studies on the effects of obesity on osteoporosis showed contradictory findings. Obesity is traditionally thought to protect the skeleton against osteoporosis by exerting mechanical loading, which stimulates bone formation through decreasing apoptosis, increasing proliferation and differentiation of osteoblasts and osteocytes.<sup>57–59</sup> Wnt/ $\beta$ -catenin signaling pathway is suggested to govern this mechanism.<sup>60,61</sup> Therefore, bone mass increases as a compensatory mechanism to accommodate the greater load.<sup>62</sup> Insulin resistance associated with obesity also causes increased plasma insulin levels, contributing to androgen and estrogen overproduction in the ovary, and reduced production of sex hormone-binding globulin by the liver.<sup>63</sup> The elevation of sex hormone levels reduces osteoclast activity and increases osteoblastogenesis, resulting in increased bone mass.<sup>64</sup>

However, recent reports demonstrated that excessive fat mass is associated with low total BMD and total bone mineral content.<sup>65–68</sup> Obese mice fed with a high-fat diet showed decreased trabecular bone volume and cortical bone growth as revealed by micro-computed tomography (micro-CT) analysis.<sup>69</sup> Another similar study also reported that obesity induced tibial trabecular microarchitectural destruction via increasing bone turnover, but it exerted minimal effects on cortical bone in high-fat diet-fed male mice.<sup>70</sup> Additionally, bone histomorphometric analysis also showed infiltration of adipocytes in the bone marrow of obese mice.<sup>71</sup> These studies showed that obesity could be detrimental to bone health.

Several mechanisms underlying the harmful effects of obesity on the bone have been proposed.<sup>71</sup> Firstly, both osteoblasts and adipocytes are derived from a common pool of mesenchymal stem cells.<sup>72</sup> Agents that inhibit adipogenesis are found to stimulate osteoblast differentiation,<sup>73–75</sup> and those that inhibit osteoblastogenesis could upregulate adipogenesis.<sup>76</sup> Similarly, decreased bone marrow osteoblastogenesis in ageing is usually accompanied by increased marrow adipogenesis.<sup>77,78</sup> This osteoblast-adipocyte shift causes a reduction of the osteoblasts available for osteogenesis.<sup>77,78</sup> Bone marrow adipogenesis eventually leads to the expansion of the marrow cavity and cortical thinning.<sup>79</sup>

Secondly, as adipose tissue undergoes hypertrophy and hyperplasia due to the storage of unused energy, the blood supply to the tissue will reduce.<sup>80,81</sup> A subsequent hypoxia-mediated signaling pathway is triggered. It then further stimulates the production of proinflammatory mediators such as TNF- $\alpha$ , IL-6, leptin, resistin and plasminogen activator inhibitor-1.<sup>6</sup> These proinflammatory mediators induce osteoclast differentiation and bone resorption through receptor activator of NF- $\kappa$ B (RANK)/RANK ligand (RANKL)/osteoprotegerin pathway.<sup>82,83</sup>

Thirdly, bone loss could occur due to the disruption of body energy regulation governed by adipocyte-derived hormones (leptin and adiponectin) and insulin during over-nutrition or obesity. Leptin and adiponectin, which mainly regulate appetite and energy expenditures, also alter bone metabolism.<sup>84–86</sup> These hormones regulate osteoblasts which expressed the leptin, adiponectin and insulin receptors.<sup>87–89</sup> Peripheral leptin improves bone health by increasing estrogen while decreasing cortisol and glucocorticoid level.<sup>90</sup> Besides, systemic administration of leptin to leptin-deficient and wild-type mice results in increased bone growth, skeletal mass and strength.<sup>64</sup> On the other hand, leptin also regulates bone resorption through two

distinct and antagonistic central neural pathways.<sup>91,92</sup> Leptin-mediated sympathetic pathway promotes osteoclastogenesis by increasing the RANKL production by osteoblasts upon binding on the beta 2-adrenergic receptor.<sup>93,94</sup> On the other hand, leptin also induces the production of cocaine amphetamine-regulated transcript (CART, a neuropeptide) in the hypothalamus, which could reduce osteoblast RANKL production.<sup>94</sup>

Protective effects of honey against obesity have been reported in animal studies. Rats fed with long-term and short-term honeydew honey (*Northofagus solandrii*) had a lower percentage of weight gain than those fed with sucrose and mixed sugars diet, although the total energy intake was similar between groups.<sup>95</sup> In addition, dual-energy X-ray absorptiometry analysis showed that rats receiving long-term honey treatment had lower body fat. Nemošek et al (2011) reported that rats given a diet containing 20% carbohydrate from clover honey had markedly lower weight gain and significantly reduced fat pad weight than rats fed with an isoenergetic diet from liquid sucrose.<sup>96</sup> Anti-obesity effects of honey were also reported in randomized clinical trials (RCTs) in humans, whereby subjects receiving a daily 70 g honey for 1 month showed a reduction in body weight, fat weight and body fat percentage along with significantly decreased BMI.<sup>97</sup> In another RCT by Bahrami et al (2009), the addition of honey in the diabetic treatment regime resulted in a significant reduction of the patients' body weight.<sup>98</sup>

The underlying mechanisms of anti-obesity and anti-adipogenic effects of honey are not determined. The gradual reduction of fat mass by honey could be beneficial to the bone as adipose tissues are the primary source of proinflammatory cytokines and leptin. However, bone mass was not assessed in the studies mentioned.

## Honey and Dyslipidemia

Atherogenic dyslipidemia is one of the core metabolic risk factors of MetS. The National Health and Nutrition Examination Survey (NHANES III) reports that 63% of patients with osteoporosis have hyperlipidemia.<sup>99</sup> Individuals with mutations in low-density lipoprotein receptor-related protein 5 have low BMD and multiple spinal fractures.<sup>100</sup> Diet- and apolipoprotein E deficiency-induced hyperlipidemia affects bone health by reducing bone mass and trabecular structural parameters in femur and tibia.<sup>101–104</sup> Micro-CT analysis in hyperlipidemic mice indicated a reduction in bone surface and bone volume with higher cortisol porosity, suggesting skeletal

degenerative changes.<sup>104</sup> Similarly, another study observed cortical and trabecular bone loss of the femur and vertebrae and decreased mechanical strength of the bones in mice with hypercholesterolemia.<sup>105</sup> Proper management of hyperlipidemia was shown to improve bone health status. Various clinical and animal studies reported that cholesterol-lowering statin drugs reduce osteoporosis and fracture risk.<sup>106–109</sup> The stimulatory role of statins in osteoblast differentiation and bone formation has been reported.<sup>110,111</sup>

Biochemical analysis of hyperlipidemic mice displayed increased serum parathyroid hormone (PTH), TNF- $\alpha$ , C-terminal telopeptide of type-1 collagen (a bone resorption marker), calcium, and phosphorus levels.<sup>104</sup> Simultaneously, amino-terminal propeptide of type-1 collagen (a bone formation marker) level was lower in hyperlipidemic mice.<sup>104</sup> You et al (2011) reported that high cholesterol-fed rats showed decreased expression of genes involved in bone formation and increased expression of genes associated with bone resorption.<sup>112</sup> Several bone formation genes are downregulated by high cholesterol diet, including transforming growth factor- $\beta$ , bone morphogenetic proteins (BMPs) and Wnt family genes.<sup>113</sup> Additionally, high cholesterol also increases bone turnover and reduces BMD with the concomitant increase of serum osteocalcin and carboxy-terminal collagen crosslinks.<sup>112,114–117</sup>

Oxidative injury is one of the mechanisms responsible for high-fat diet-induced osteoporosis. Atherogenic high-fat diets increase lipoprotein levels and their oxidative products.<sup>118,119</sup> The lipid oxidation products have been reported to present in the marrow of hyperlipidemic mice.<sup>120</sup> Excessive lipid oxidation products including oxidized low-density lipoprotein attenuate the osteogenic differentiation of mesenchymal stem cells and preosteoblasts in favor of adipogenic differentiation.<sup>82,120–123</sup> Additionally, free cholesterol reduces superoxide dismutase (SOD) activity and increases malondialdehyde (MDA) level, leading to oxidative damages on osteoblasts.<sup>124</sup>

The hypolipidemic effect of honey has been demonstrated by Al-Waili (2004).<sup>125</sup> A significant reduction of total cholesterol (TC) and a decreasing trend of low-density lipoprotein cholesterol (LDL) were observed among honey-supplemented patients with dyslipidemia.<sup>125</sup> In another study, daily 70 g honey for 1 month also significantly lowered the TG level among dyslipidemic patients by 19%, with similar trends of reduction in TC and LDL, despite the lack of statistical significance.<sup>97</sup> Similarly, honey also reduced TC, LDL and TG levels,

and increased HDL (3.3%) in non-dyslipidemic individuals, but the changes were statistically not significant. On the other hand, Hemmati et al (2015) reported that honey (1 and 2 g/kg for 3 weeks) countered the dyslipidemic effects of streptozotocin by normalizing the TC, TG, HDL, non-HDL levels and atherogenic index (TG/HDL).<sup>126</sup> Besides, administration of mad honey at the dose of 50 mg/kg for 3 days significantly reduced TC, TG and very-low-density lipoprotein cholesterol (VLDL) in streptozotocin (STZ)-induced diabetic rats.<sup>127</sup> Mad honey was speculated to act on the parasympathetic nervous system (potentially via M2-muscarinic receptors) to increase the lipid metabolism via insulin release.<sup>127</sup> Another animal study reported that Nigerian honey supplementation for 21 days produced a significant reduction of TG, non-HDL (especially VLDL), cardiovascular risk index (TG/HDL) and coronary risk index (TC/HDL) in rats with alloxan-induced diabetes mellitus (DM).<sup>128</sup> An RCT Bahrami et al (2009) reported that there was a notable decrease in TC, LDL and TG ( $p = 0.000$ ) with increased HDL concentration compared to the baseline level ( $p < 0.05$ ) in diabetic patients after ingesting honey for 56 days.<sup>98</sup>

A diet containing high fructose induces dyslipidemia and exerts pro-oxidant effects in vivo.<sup>129,130</sup> Substituting refined carbohydrate with honey (650 g/kg for 14 days) in the purified diets was reported to reduce TG levels significantly in comparison to fructose-fed rats.<sup>131</sup> At the same time, honey also reduced the lipid oxidation in the heart, marked by a lower thiobarbituric acid-reactive substance level compared with the fructose-fed group.<sup>131</sup> Nemoseck et al (2011) also observed that substitution of sucrose in the rat diet with clover honey (with similar energy density) for 33 days resulted in 29.6% lower TG levels than the sucrose-fed rats.<sup>96</sup> In another study, metabolic effects of 10% honeydew honey (100 g/kg) mixed in diets were compared with sucrose for 365 days. Although there was no significant decrease in TG and LDL, the honey-fed rats had significantly higher HDL levels than the rats on a sugar-free diet and sucrose diet.<sup>132</sup> Apolipoprotein B and TG-rich lipoproteins play a role in developing atherosclerotic cardiovascular disease.<sup>133,134</sup> Pretreatment with 3 g/kg/day of Tualang honey for 45 days in rats with isoproterenol-induced myocardial infarction was shown to normalize cholesterol levels.<sup>135</sup> Serum TC and TG levels were significantly reduced in rats receiving Tualang honey compared to the untreated disease control group.<sup>135</sup> Aziz et al (2017) observed similar results, in which STZ-nicotinamide-induced rats given stingless bee honey (2.0

g/kg for 28 days) showed significant reductions of TC, TG and LDL levels and an increase in HDL level compared to untreated diabetic rats.<sup>136</sup>

Similar to the anti-obesity effect, the underlying mechanism of the hypolipidemic effect of honey remains unclear. Given the hypolipidemic effect of honey, honey could protect the bone against osteoporosis caused by hyperlipidemia. By lowering the blood lipid level, it could reduce lipid oxidation, which is a risk factor of osteoporosis, subsequently preventing bone loss.

## Honey and Hyperglycemia

Diabetic Cohen rats [a non-obese rat model of type 2 DM (T2DM)] demonstrated reduced BMD of distal femur and vertebra compared to normal rats.<sup>137</sup> Prediabetic individuals with impaired FBG and/or glucose tolerance are positively associated with TNF- $\alpha$  level.<sup>138</sup> Upregulation of TNF- $\alpha$ , macrophage-colony stimulating factor (M-CSF) and RANKL caused suppression of bone formation and deterioration of bone strength in STZ-induced diabetic mice.<sup>139</sup> Histomorphometric analysis further revealed the increase in osteoclast numbers in conjunction with osteoclastogenic mediator expression in STZ-induced diabetic mice.<sup>139</sup> On the other hand, STZ-mediated hyperglycemia decreased osteocalcin (a bone formation marker) and Runx2 mRNAs expression with high PPAR- $\gamma$  expression in the bone marrow.<sup>140,141</sup> Besides, a previous study demonstrated an increased glomerular filtration rate and urinary calcium, as well as reduced fractional calcium reabsorption in STZ-induced diabetic rats.<sup>141</sup>

The results of human studies are in parallel with animal studies. Subjects with diabetes demonstrated lower hip BMD in diabetic subjects compared to the non-diabetic. Insulin-dependent DM or type 1 DM (T1DM) often affects younger individuals due to its early onset.<sup>142</sup> Both T1DM and non-insulin-dependent DM or T2DM patients display impaired bone formation, but T1DM patients have a greater fracture risk.<sup>143,144</sup> Surprisingly, BMD was increased in T2DM but not T1DM.<sup>145,146</sup> Apparently, the fracture risk in T2DM patients is independent of the BMD.<sup>147</sup> The underlying reason for this remains unknown. However, conditions like visual disturbance due to diabetic retinopathy and cataract, increased fall risk due to peripheral neuropathy and T2DM treatment may contribute to the fracture risk.<sup>147,148</sup>

Hyperglycemia has direct and indirect detrimental effects on osteoblast function and bone formation. High glucose concentration significantly suppresses mineralization and

osteoblastogenesis and increases the adipogenesis and osteoblast apoptosis in MG63 cells.<sup>149</sup> Insulin and insulin-like growth factor-1 (IGF-1) are humoral factors synthesized by liver and osteoblasts, acting as a vital anabolic signal to promote bone formation.<sup>150,151</sup> Deficiency of insulin and IGF-1 occurs in T1DM, whereby it has been associated with low BMD, low bone size, growth hindrance, and development of osteoporosis.<sup>152–154</sup> Renal glycosuria, which is the indirect effect of hyperglycemia, causes defective reabsorption of both glucose and calcium in the proximal tubule or collecting duct, leading to hypercalciuria and depletion of calcium level in the body, thereby resulting in bone loss.<sup>155,156</sup>

Hyperglycemia also impairs fracture healing by reducing endothelial progenitor cells lining the blood vessels, leading to retardation of the angiogenesis process.<sup>143</sup> This event will hinder the repair process at fracture sites. Decreased BMD and biomechanical strength in DM is negatively correlated with the accumulation of advanced glycation end product (AGE) or non-enzymatic crosslinks within collagen fibers.<sup>157,158</sup> AGEs enhance bone resorption in cultured mouse unfractionated bone cells and induce the mesenchymal stem cell apoptosis, which eventually leads to bone loss.<sup>159,160</sup>

Hypoglycemic effects of honey have been studied extensively through various animal studies and RCTs. Aziz et al (2017) demonstrated a significant reduction of FBG level in rats with partial insulin deficiency induced by combined STZ-nicotinamide upon treated with stingless bee honey (Kelulut honey; 1.0 and 2.0 g/kg/day for 28 days) compared to the untreated diabetic rats.<sup>136</sup> Serum insulin level and pancreatic oxidative status were improved, as evidenced by increased CAT expression and faster pancreatic healing process.<sup>136</sup> The active compound in Kelulut honey, L-phenylalanine was suggested to stimulate insulin release and improve glucose tolerance in diabetic rats.<sup>161</sup>

Besides, treatment with Tualang honey at 1.0 g/kg/day for 28 days significantly downregulated pancreatic MDA level and restored the SOD and CAT activities in STZ-induced diabetic rats.<sup>162</sup> The antioxidant effects of Tualang honey also protected the pancreas from STZ-mediated oxidative damage, leading to significant improvement of FBG in diabetic rats.<sup>162</sup> A similar hypoglycemic effect of honey with a significant reduction in FBG was demonstrated on alloxan-induced diabetic rats upon supplementation of Nigerian honey at 1.0 and 2.0 g/kg/day for 21 days.<sup>128</sup> Additionally, histological analysis

in rats also revealed that honey increased pancreatic  $\beta$ -cells which explains its hypoglycemic effects.<sup>163</sup>

The hypoglycemic effects of honey were replicated in human studies. Unprocessed honey was given orally to 25 T2DM patients at the starting dose of 1.0 g/kg/day and gradually increased by 0.5 g/kg/day every 14 days for a total duration of 56 days. Patients receiving honey experienced a significant reduction of FBG level at the end of treatment than the starting baseline level.<sup>98</sup> In another study, 7 T2DM patients were given honey solution (90 g of honey dissolved in 250 mL of water for 8 weeks) as a substitute for dextrose 30 min before blood sampling for oral glucose tolerance test.<sup>98</sup> The honey-supplemented subjects showed significantly lower blood glucose elevation.<sup>98,107</sup> This finding suggests that substituting honey for sugar might be useful in the management of diabetes if taken in moderate quantities.<sup>131,164,165</sup>

Mechanistically, honey could lower blood glucose by inhibiting  $\alpha$ -amylase and  $\alpha$ -glucosidase activities.<sup>166</sup> Alpha-amylase is an enzyme responsible for the hydrolysis of complex starch to oligosaccharides, whereas  $\alpha$ -glucosidase hydrolyses oligosaccharides, trisaccharides and disaccharides into monosaccharides. Postprandial blood glucose levels can be reduced through the reduction in polysaccharides breakdown and digestion upon the inhibition of these enzymes.<sup>167–169</sup> Krishnasree & Ukkuru (2017) analyzed the antidiabetic activity of honey using in vitro  $\alpha$ -amylase and  $\alpha$ -glucosidase enzyme inhibition assays.<sup>166</sup> *Trigona iridipennis* honey, a type of stingless bee honey, demonstrated the strongest  $\alpha$ -amylase and  $\alpha$ -glucosidase inhibitory properties than other multifloral honey species.<sup>166</sup> This was comparable to standard diabetic therapy by acarbose, especially at the highest honey concentration of 500  $\mu$ g/mL.<sup>166</sup> Furthermore, raw *T. iridipennis* honey had the lowest glycemic index (GI) of 55, making it a suitable sweetener for diabetic patients.<sup>166</sup>

Overall, honey could reduce the blood glucose level through the inhibition of  $\alpha$ -amylase and  $\alpha$ -glucosidase activities and its antioxidant activities. Hence, honey could prevent hyperglycemia and its adverse effects on bone in MetS patients.

## Honey and Hypertension

Hypertension, a multifactorial disease, is one of the components of MetS. Blood pressure is regulated by controlling the diameter of blood vessels through the autonomic nervous system via vasodilation and vasoconstrictions.<sup>170</sup> Sympathetic nervous system activation leads to

vasoconstriction, increased cardiac output and sodium retention by renal tubule that leads to an increase in blood pressure.<sup>171</sup> Besides, obesity is one of the significant factors contributing to hypertension.<sup>172</sup> Obesity is associated with hypertension due to the secretion of leptin by adipocytes, which has been reported to stimulate the sympathetic nervous system.<sup>173</sup> Additionally, diets high in fructose, sucrose and fat have been observed to increase blood pressure and obesity simultaneously.<sup>174,175</sup>

Renal and vascular oxidative stress also contributes to the development of hypertension.<sup>176–178</sup> Oxidative stress causes inflammation of the vascular wall, reduced bioavailability of vasodilatory agent (NO), extracellular matrix alterations as well as increased vascular cell proliferation.<sup>177</sup> Long-term exposure to ROS, especially to hydrogen peroxide, inhibits the antioxidant response due to down-regulation of the Akt and impaired nuclear translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) signaling pathway.<sup>179</sup>

A significant positive relationship between hypertension and bone loss has been suggested. At the same age, spontaneous hypertensive rats (SHR) had lower BMD and bone magnesium content than normotensive Wistar-Kyoto (WKY) rats.<sup>180</sup> Furthermore, SHR exhibited disturbed bone healing with a lower percentage of the trabecular bone area and newly formed bone area compared to WKY rats.<sup>181</sup> Administration of 2% calcium diet (but not 1%) could significantly normalize the BMD of SHR.<sup>180</sup> The BMD of WKY rats was increased by both 1 and 2% calcium diet.<sup>180</sup> This indicates the involvement of calcium loss in hypertension-related bone loss where it could be corrected by optimal calcium supplementation.

Human studies have indicated that hypertension is negatively correlated with BMD.<sup>182,183</sup> Cappuccio et al found that hypertension was associated with increased bone loss at the femoral neck among 34 Caucasian women.<sup>182</sup> A longitudinal study by Yang et al found that women (n=1701) with hypertension had lower BMD at the femoral neck than those without hypertension.<sup>183</sup> A meta-analysis by Ye et al also revealed that essential hypertension caused a significant reduction in BMD of the human body, including the lumbar spine, femoral neck, Ward's triangle, femoral intertrochanteric region, calcaneus and distal forearm.<sup>184</sup> Parallely, Gotoh et al (2005) also demonstrated that the BMD of hypertensive patients was significantly lower than that of normal controls, where BMD was negatively correlated with systolic blood pressure.<sup>185</sup> Therefore, essential hypertension might be a risk factor for low BMD.<sup>185</sup>

Mechanically, osteoporosis and hypertension share similar etiopathology with interactions of genetic and environmental factors. Both diseases are associated with calcium, vitamin D and vitamin K deficiency, high sodium consumption, and low or very high NO levels. Calcium, the main bone mineral, has a significant impact on bone strength and the balance of the bone remodeling process.<sup>186</sup> The significance of calcium metabolism in hypertension and osteoporosis has been reported.<sup>186</sup> Hypertension reduced intestinal absorption of calcium as well as increased calcium urinary elimination.<sup>187</sup> This reduces calcium concentration in the plasma, leading to secondary activation of parathyroid glands and calcium mobilization from the bone into the circulation, resulting in increased bone turnover.<sup>182,188,189</sup>

Honey is beneficial in preventing hypertension through its antioxidant and anti-inflammatory effects. Tualang honey supplementation in SHR at 1 g/kg/day for 12 weeks attenuated renal oxidative stress.<sup>190</sup> It upregulated mRNA, protein expression and nuclear translocation of Nrf2, thus augmenting gene expression of antioxidation enzymes such as CAT and glutathione-S-transferase (GST).<sup>190</sup> Ultimately, the upregulation of these enzymes reduced the oxidative damages in the kidney, restored renal function and subsequently reduced the blood pressure.<sup>174,190</sup> Similarly, the antioxidative properties of Tualang honey were also effective in reducing blood pressure in STZ-induced diabetic SHR.<sup>191</sup> In human studies, administration of 60% honey solution via inhalational route resulted in a marked decrease in blood pressure at 60 and 120 min post-treatment in hypertensive subjects, which indicates immediate blood pressure-lowering effects.<sup>192</sup> Similar instant hypotensive effects of honey have been reported in healthy subjects.<sup>193,194</sup> The underlying mechanism of action of honey in reducing blood pressure is unknown. Honey contains a high concentration of NO, which may contribute to its therapeutic effects on hypertension.<sup>192</sup> Ultimately, the antihypertensive effects of honey could benefit both the cardiovascular and bone health of the patients.

## Honey and Skeletal Health

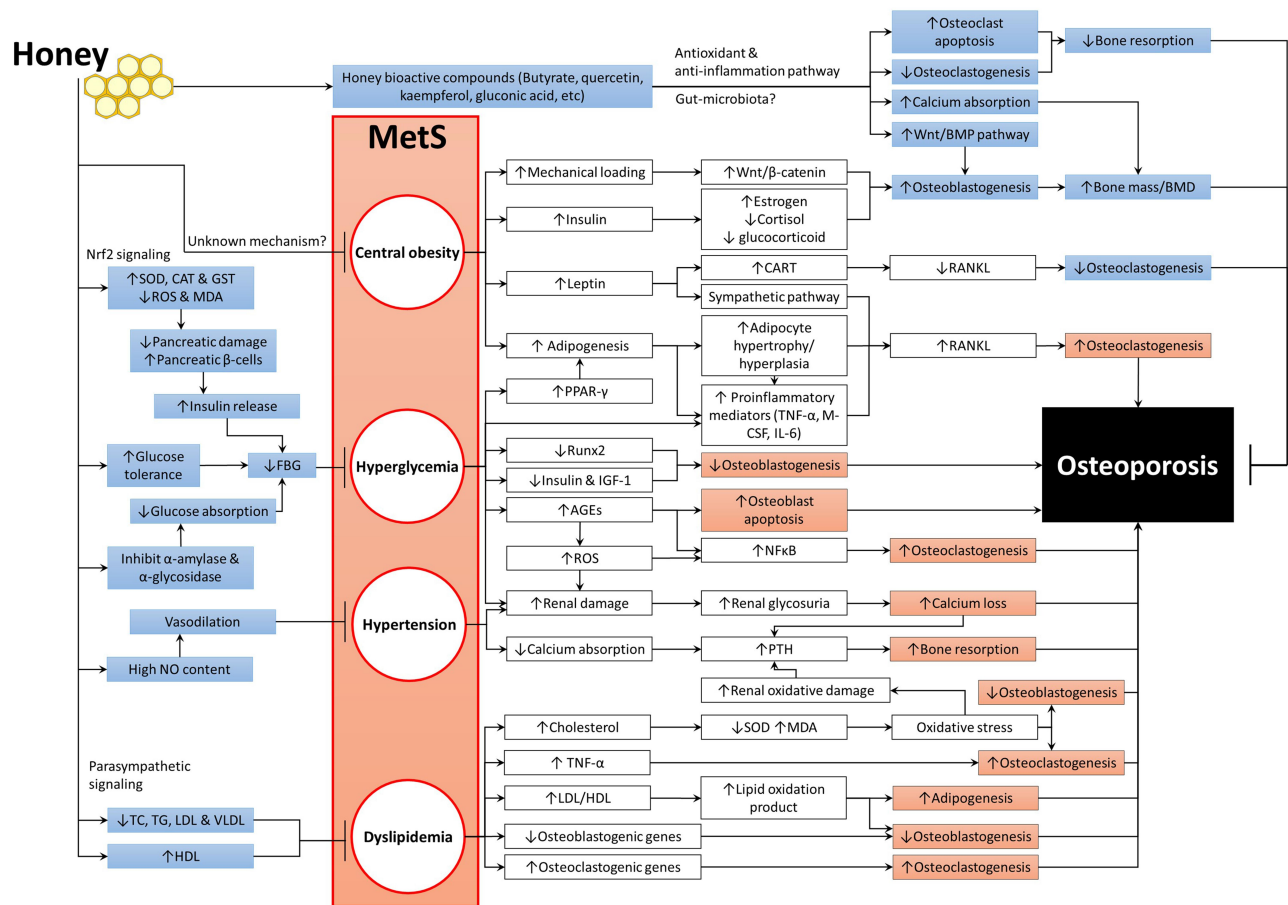
Honey exhibits both antioxidative properties and possesses anti-inflammatory effects, which could be directly beneficial to bone health. Previous studies have shown that honey reduced PGE<sub>2</sub> level and inhibited NO production in rats.<sup>195</sup> Zaid et al reported that two-week consumption of Tualang honey (0.2 g/kg/day) could increase bone density in female

ovariectomized rats, comparable to those of control intact rats.<sup>196</sup> Another study performed by Lily et al showed that the daily intake of Tualang honey at 20 mg/day for 4 months to postmenopausal women was safe and exerted the same effect on bone densitometry when compared to hormone replacement therapy.<sup>197</sup> These positive effects of Tualang honey on bone are probably due to its anti-inflammatory property, antioxidative property, and calcium and gluconic acid content.<sup>198</sup>

A recent study found that Kelulut honey at 400 mg/kg reversed the changes in the femoral bones of rats receiving long-term dexamethasone.<sup>199</sup> Bone structural parameters and osteoblast number in the Kelulut honey treated-group were preserved with a lower osteoclast number compared to the non-treated osteoporotic group.<sup>199</sup> Kelulut honey also reduced the MDA level and augmented SOD activity in dexamethasone-mediated osteoporotic rats.<sup>199</sup> This observation implies that the antioxidant properties of the honey can prevent osteoblast apoptosis by oxidative stress.<sup>199,200</sup>

Several phenolic compounds in honey have been reported contributing to the bone protective effects of honey. Honey contains polyphenols with antioxidant potential, which can increase the differentiation of mesenchymal cells to osteoblasts.<sup>199–202</sup> They also play a role in the cross-talk of signaling pathways, such as Wnt and BMPs, thus promoting mesenchymal cell differentiation to osteoblasts.<sup>203</sup> Flavanols, such as quercetin and kaempferol, could affect bone resorption by directly introducing osteoclasts apoptosis, thus reducing their numbers and bone resorption.<sup>204</sup> They decrease the intracellular ROS in osteoclasts and interact with estrogen receptors in the cells.<sup>204</sup> Parallely, Trivedi et al also found that kaempferol promotes osteoblast function, thus preventing ovariectomized-induced bone loss.<sup>195</sup> Gluconic acid, a major constituent in honey, could enhance calcium absorption in the bone, consequently maintaining bone mass and preventing osteoporosis.<sup>205</sup> It is a major organic acid in honey produced through enzymatic glucose oxidase reaction. In the digestive tract, gluconic acid is then fermented by lactic acid bacteria (*Lactobacillus reuteri* and *L. mucosae*) to produce lactate and acetate, and eventually convert into butyrate by acid-utilizing bacteria (*Megasphaera elsdenii* and *Mitsuokella multiacida*).<sup>206,207</sup> Butyrate is a type of short-chain fatty acid rapidly absorbed by the mucosa of the large intestine. It is reported to have hypoglycemic, antioxidant and anti-inflammatory properties in maintaining gut health and





**Figure 1** The beneficial effects of honey on MetS and bone health.

**Abbreviations:** †, increase or upregulate; ‡, decrease or downregulate; →, promote or induce; ⊥, inhibit or prevent; AGEs, advanced glycation end products; BMPs, bone morphogenetic proteins; CART, cocaine amphetamine-regulated transcript; CAT, catalase; FBG, fasting blood glucose; GST, glutathione-S-transferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; M-CSF, macrophage-colony stimulating factor; MDA, malondialdehyde; MetS, metabolic syndrome; NF-κB, nuclear factor kappa-B; NO, nitric oxide; PPAR-γ, peroxisome proliferator-activated receptor-gamma; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor kappa-B ligand; ROS, reactive oxygen species; Runx-2, Runt-related transcription factor 2; SOD, superoxide dismutase; TC, total cholesterol; TG, triglyceride; TNF-α, tumour necrosis factor-alpha; VLDL, very-low-density lipoprotein.

regulating energy metabolism.<sup>208–211</sup> Additionally, butyrate is also being postulated as the linkage between gut microbiota and bone health.<sup>212–214</sup>

## Conclusions

Understanding the association between MetS and osteoporosis and its mechanisms will help developing therapeutic intervention effective for both diseases. Honey exhibits protective effects against MetS by exerting anti-obesity, antidiabetic, hypolipidemic and hypotensive activities. It has a low GI, which can limit weight gain and prevent the accumulation of fat, thus improves insulin sensitivities and reduces blood glucose levels. Honey can enhance energy and lipid metabolism, which will prevent atherogenesis and attenuate oxidative stress and endothelial dysfunction. The improvement of MetS caused by honey could, in turn,

prevent bone loss. **Figure 1** summarizes the mechanisms of MetS in inducing osteoporosis and the beneficial effects of honey on both MetS and bone health. The anti-inflammatory of honey plays a major role in mediating these biological activities. Therefore, honey has a strong potential to be utilized in the management of MetS and osteoporosis associated with it.

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## Disclosure

The authors report no conflicts of interest in this work.

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