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Research Article

Comparison of Effects of Metformin, Simvastatin and their Combinations with Honey on Obesity Anthropometric Parameters in High-Fat Diet Fed Wistar Rats

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Abstract

Metformin and simvastatin are drugs used to reduce diabesity-related parameters such as weight gain and adiposity in obese type 2 diabetic and obese patients, respectively. The aim of this study was to investigate and compare the effects of metformin or simvastatin and their combination with honey on obesity anthropometric parameters in rats fed high-fat diet (HFD). After 8 weeks of feeding with HFD and sucrose solution (30% w/v), rats were randomly grouped and treated with distilled water, metformin, metformin and honey, simvastatin or simvastatin and honey for 6 weeks. The rats were maintained on HFD during the treatment period. The weight gain, % change in body mass index (BMI) and % change in adiposity index (AI) were significantly ($p < 0.05$ or $p < 0.001$) higher while BMI, body weight/body length (BW/BL) and AI were non-significantly ($p > 0.05$) higher in HFD fed control rats compared with chow fed rats. The weight gain, BMI, % change in BMI, BW/BL, AI and % change in AI in metformin-treated HFD fed rats were comparable to those of HFD fed control rats. Though statistically insignificant ($p > 0.05$), HFD fed rats treated with metformin and honey showed lower weight gain, BMI, % change in BMI, BW/BL, AI and % change in AI. Simvastatin-administered rats had significantly lower BMI ($p = 0.015$), % change in BMI ($p = 0.008$) and % change in AI ($p = 0.026$) compared with HFD fed control rats. In contrast, simvastatin- and honey-treated rats exhibited much significantly lower BMI ($p = 0.002$), % change in BMI ($p = 0.001$) and % change in AI ($p = 0.003$) compared with HFD fed control rats. These findings suggest that simvastatin is better than metformin in attenuating increases in obesity anthropometrics in HFD fed rats. The data also indicate that honey in combination with metformin or simvastatin augmented the ameliorative effects of these drugs on obesity anthropometric parameters in HFD fed rats.

Keywords: *Honey; Metformin; Simvastatin; Body Mass Index; Obesity; High-Fat Diet; Rats*

Abbreviations

HFD: High Fat Diet; BW: Body Weight; BMI: Body Mass Index; AI: Adiposity Index; HMG-Coa Reductase: 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A Reductase; SEM: Standard Error of Mean; ANOVA: Analysis of Variance

Introduction

The incidence of several non-communicable diseases such as cardiovascular diseases, diabetes mellitus, cancer and obesity or diabesity as well as their complications continue to rise unabated [1]. This is in spite of availability of drugs for the treatment of these diseases. The heterogeneous nature of these disorders which are linked to multiple causes including environmental factors provides therapeutic target [1,2]. As a result, multiple therapeutic strategies which target definite pathobiological pathways of some of these diseases are recommended [3]. Diabesity is a new terminology describing the interrelationship between diabetes and obesity. It is now considered as a serious public health issue gradually leading to be an epidemic [4]. Many of the antidiabetic drugs now available and in use do have side effects such as weight gain [3] , but metformin monotherapy is weight neutral. An effective and widely acceptable solution for diabesity is still being awaited. Compared to sugars such as sucrose, honey administration was associated with lower weight gain in healthy rodents [5] though some findings suggested otherwise [6]. Similarly, in overweight, obese or type 2 diabetic patients, honey consumption markedly reduced body weight [7,8]. In animal models of diabetes, administration of honey alone or in combination with antidiabetic drugs improved renal, hepatic and metabolic abnormalities [9-11]. The beneficial effects of combination of antidiabetic drugs with honey on oxidative stress in pancreas and kidney of diabetic rats have also been demonstrated [12,13].

Until recently, there were limited data in the literature on the effect of honey on diet-induced obesity in rodents. Our research group lately reported that honey exerted a suppressing effect on body weight, total weight gain, body mass index (BMI) and adiposity in high-fat diet (HFD) fed Wistar rats [14]. These ameliorative effects of honey on obesity anthropometrics were also recently corroborated in HFD-induced obesity in Sprague-Dawley rats [15]. With available evidence suggesting that honey has a potential to augment the therapeutic effects of synthetic drugs [9,16,17], the prospect of such beneficial effects of honey in combination with drugs used to enhance weight loss and reduce adiposity remains indeterminate. The need to address this uncertainty becomes imperative in view of certain factors such as variances in disease phenotypes (diabetes versus obesity) as well as differences in botanical and/or geographical sources of honey which invariably influence the pharmacological effects of honey [18]. Therefore, this study was carried out to investigate and compare the effects of metformin or simvastatin and their combination with honey on obesity anthropometric parameters in a rodent model of obesity.

Materials and Methods

Animals

A total of 30 male Wistar rats were used in this study. The rats were housed in a well ventilated animal facility (temperature: 25-27°C and light:dark cycle: 12:12-hour). The acclimatization period lasted for at least 2 weeks before the commencement of the study. The rats had unrestricted access to chow and portable water *ad libitum*. The Research Ethics Committee of Ebonyi State University approved the study. The handling of rats was in strict compliance with institutional guidelines on the Use and Care of Laboratory Animals. The rats were administered a HFD (coconut oil and olive oil; 5 ml/kg BW orally) and 30% sucrose solution for 8 weeks.

Preparation of metformin, simvastatin and honey

Metformin (Diabetmin®, Hovid BhD, Malaysia) and simvastatin (TEVA, UK) were dissolved in drinking water and administered at a dose of 200 mg/kg BW and 20 mg/kg BW, respectively. The honey (purchased from a bee farm in Abakaliki, Ebonyi State, Nigeria) was dissolved in portable water (1:1) shortly before it was administered at a dose of 1.0 g/kg BW [14].

Treatment

Body weight and body length of rats were measured before treatment began. The HFD fed rats were randomized into 5 groups consisting of 5 rats. There was no difference in the mean body weight in all the groups. The rats were administered drinking water, metformin, metformin and honey, simvastatin or simvastatin and honey once daily for 6 weeks as follows:

Group 1: Chow fed rats administered 1 mL/kg BW of drinking water
Group 2: HFD fed rats administered 1 mL/kg BW of drinking water
Group 3: HFD fed rats treated with metformin (200 mg/kg BW)
Group 4: HFD fed rats treated with metformin (200 mg/kg BW) and honey (1.0 g/kg BW)
Group 5: HFD fed rats treated with simvastatin (20 mg/kg BW)
Group 6: HFD fed rats treated with simvastatin (20 mg/kg BW) and honey (1.0 g/kg BW)

An hour after the treatment regimens above, the rats were administered HFD. The BMI and AI were estimated. The BMI was calculated based on the formula - BMI = Body weight (g) / body length2 (cm2). The AI was calculated using the formula for Lee index of obesity: AI = cube root of body weight (g) / body length (cm) [19]. The rats were sacrificed under diethyl ether anesthesia.

Statistical Analysis

The data were analyzed using SPSS. Data are expressed as mean ± SEM. One-way analysis of variance (ANOVA) and post hoc Tukey's test were used to identify differences among the groups.

Results and Discussion

Effect of metformin or simvastatin and their combination with honey on weight gain

At the commencement of the study, the initial body weight was comparable among the groups (Data not shown). After 6 weeks of treatment, HFD fed control rats showed significantly ($p < 0.001$) greater weight gain than chow fed rats (Figure 1). The HFD fed rats treated with metformin or simvastatin and their combination with honey gained higher weight than chow fed rats but at different degrees of significant levels ($p < 0.05$, $p < 0.01$ or $p < 0.001$). Compared with the HFD fed control group, none of the agents produced significant suppression of weight gain though their combination with honey tended towards lower weight gain.

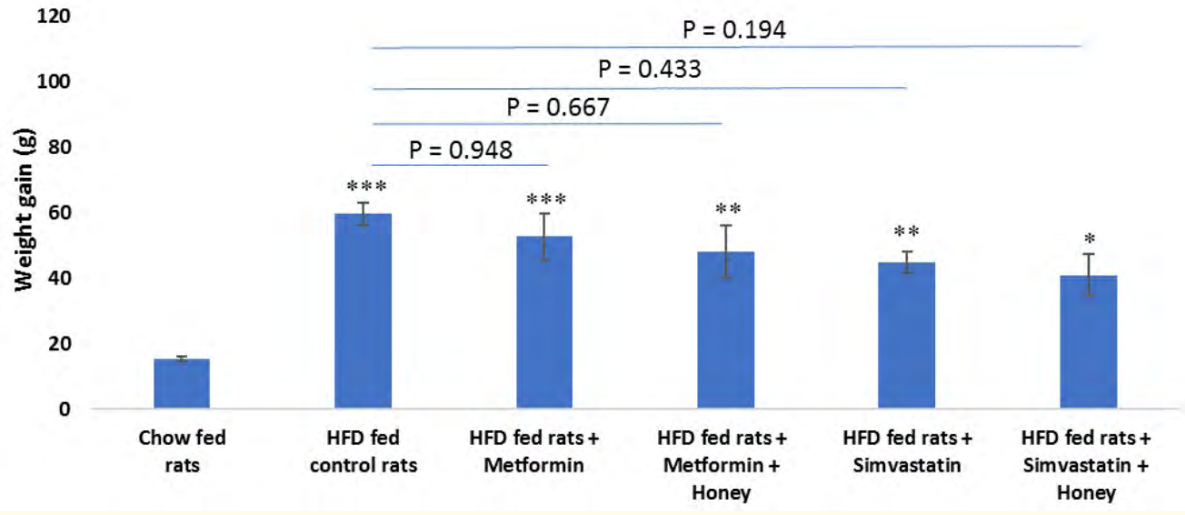

Figure 1: *Effect of metformin or simvastatin and their combination with honey on weight gain after 6 weeks of treatment. * $p < 0.05$, ** $p < 0.01$ and *** $p < 0.001$ compared with chow fed rats.*

Effect of metformin or simvastatin and their combination with honey on body mass index

The HFD fed control rats tended to have greater BMI ($p = 0.056$) compared with chow fed rats (Figure 2). The HFD fed rats treated with metformin did not exhibit lower BMI ($p > 0.05$) compared with HFD fed control rats. Simvastatin-treated HFD fed rats had significantly ($p < 0.05$) lower BMI compared with HFD fed control group. The HFD fed rats treated with simvastatin and honey showed much significantly ($p < 0.01$) lower BMI. Metformin-treated HFD fed rats had significantly ($p < 0.05$) higher BMI than simvastatin- and honey-treated HFD fed rats (Figure 2). In contrast, BMI in metformin- and honey-treated HFD fed rats did not differ significantly ($p > 0.05$) from that of simvastatin- and honey-treated HFD fed rats.

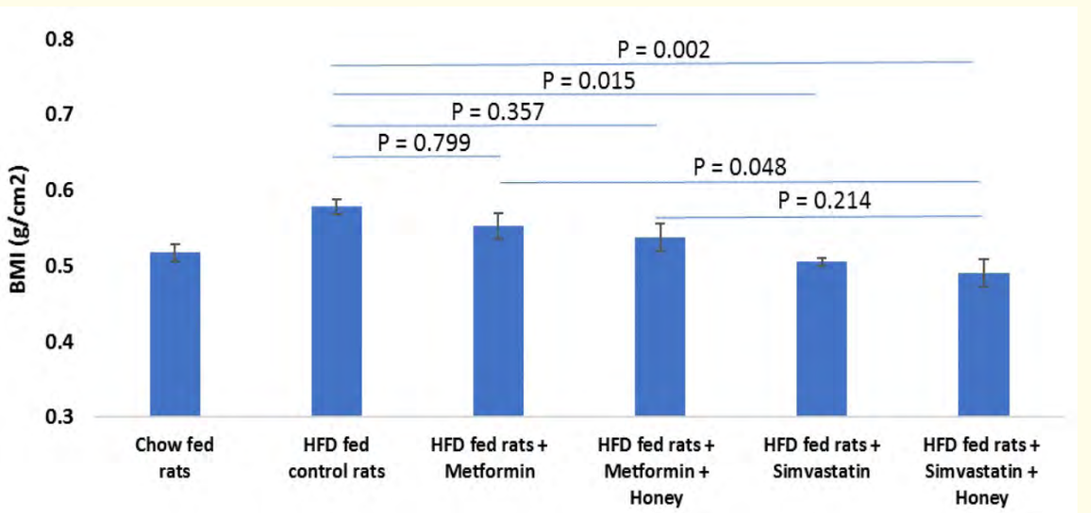

Figure 2: *Effect of metformin or simvastatin and their combination with honey on body mass index after 6 weeks of treatment.*

Effect of metformin or simvastatin and their combination with honey on body weight/body length

The body weight/body length was borderline ($p = 0.053$) higher in HFD fed control rats than in chow fed rats (Figure 3). Metformin or simvastatin did not produce significantly ($p > 0.05$) lower body weight/body length in HFD fed rats compared with HFD fed control group. Though metformin or simvastatin combined with honey also did not lower significantly ($p > 0.05$) body weight/body length in HFD fed rats, the body weight/body length tended to be lower in these groups.

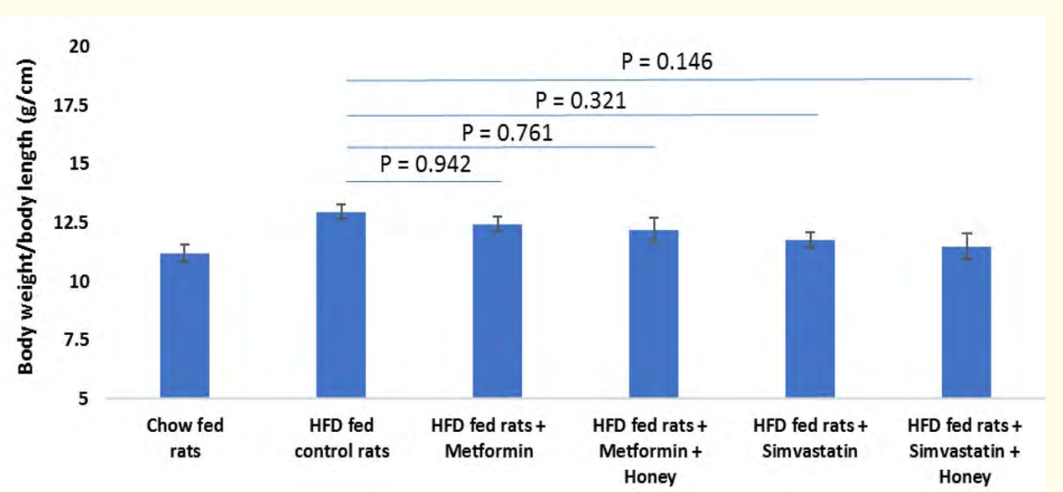

Figure 3: *Effect of metformin or simvastatin in combination with honey on body weight/body length after 6 weeks of treatment.*

Effect of metformin or simvastatin and their combination with honey on adiposity index

The adiposity index (AI) was insignificantly ($p = 0.056$) higher in HFD fed control rats than in chow fed rats (Figure 4). Metformin or simvastatin produced non-significantly ($p > 0.05$) lower AI in HFD fed rats. Though not statistically significant ($p > 0.05$), AI in HFD fed rats treated with metformin or simvastatin in combination with honey tended to be lower.

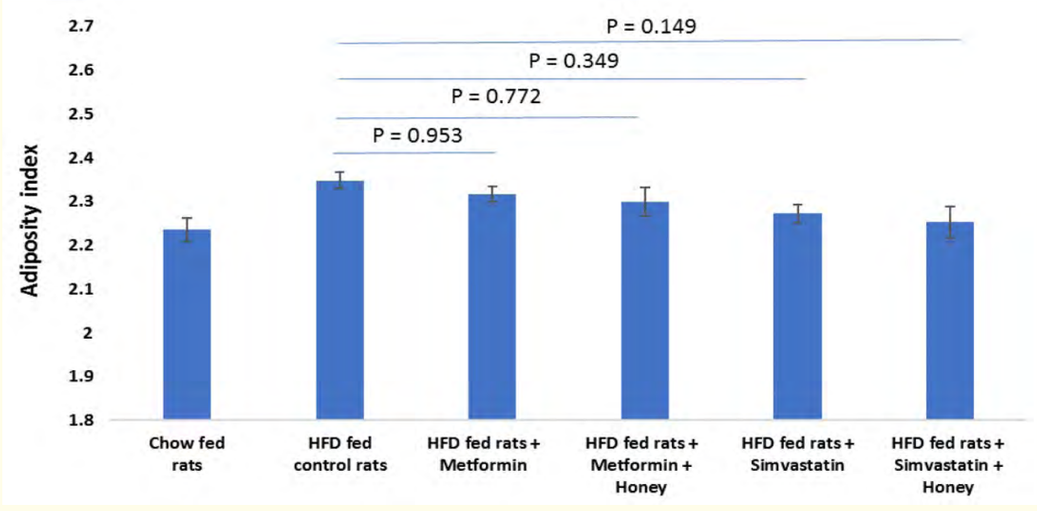

Figure 4: *Effect of metformin or simvastatin in combination with honey on adiposity index after 6 weeks of treatment.*

Effect of metformin or simvastatin and their combination with honey on % change in BMI

The HFD fed control rats had significantly ($p < 0.05$) higher % change in BMI compared with chow fed rats (Figure 5). Administration of metformin or in combination with honey did not significantly ($p > 0.05$) lower % change in BMI. Simvastatin-treated HFD fed rats had significantly ($p < 0.01$) lower % change in BMI compared with HFD fed control. The HFD fed rats treated with simvastatin and honey had much significantly ($p < 0.01$) lower % change in BMI (Figure 5). Metformin-treated group showed borderline ($p = 0.052$) higher % change in BMI compared with HFD fed rats treated with simvastatin and honey. Though % change in BMI in simvastatin- and honey-treated HFD fed rats was lower than in metformin- and honey-treated HFD fed rats, there was no significant ($p > 0.05$) difference between the two groups.

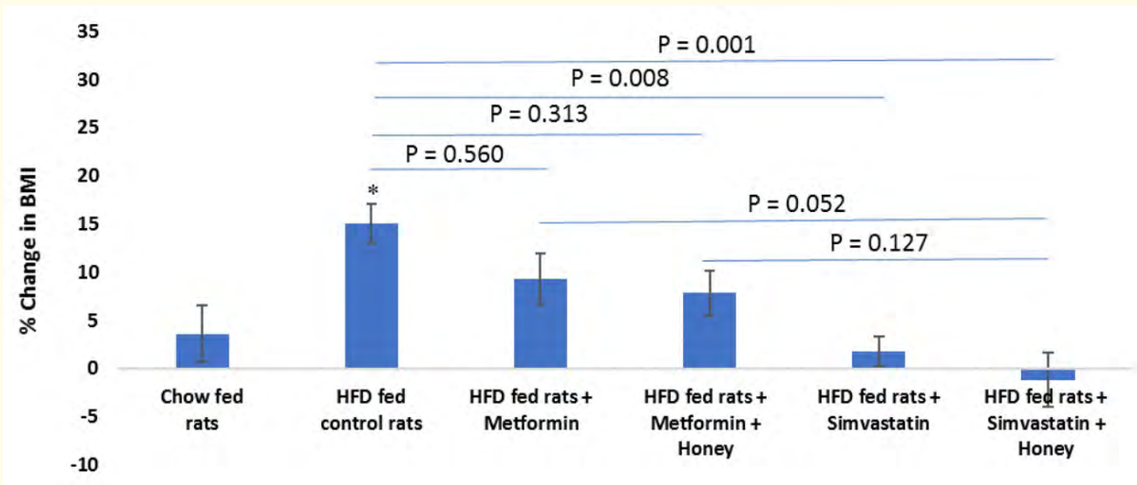

Figure 5: *Effect of metformin or simvastatin in combination with honey on % change in BMI after 6 weeks of treatment.*

Effect of metformin or simvastatin and their combination with honey on % change in adiposity index

The HFD fed control rats had significantly ($p < 0.001$) higher % change in adiposity index (AI) compared with chow fed rats (Figure 6). Rats administered metformin or metformin and honey exhibited non-significantly ($p > 0.05$) lower % change in AI compared with HFD fed control rats. The same groups of rats had significantly ($p < 0.05$ or $p < 0.01$) higher % change in AI compared with chow fed rats (Figure 6). Simvastatin-treated rats had significantly ($p < 0.05$) lower % change in AI compared with HFD fed control group. The % change in AI in HFD fed rats treated with simvastatin and honey was much significantly ($p < 0.01$) lower compared with HFD fed control group. The % change in AI was not significantly ($p > 0.05$) different in metformin- and honey-treated rats and simvastatin- and honey-treated group.

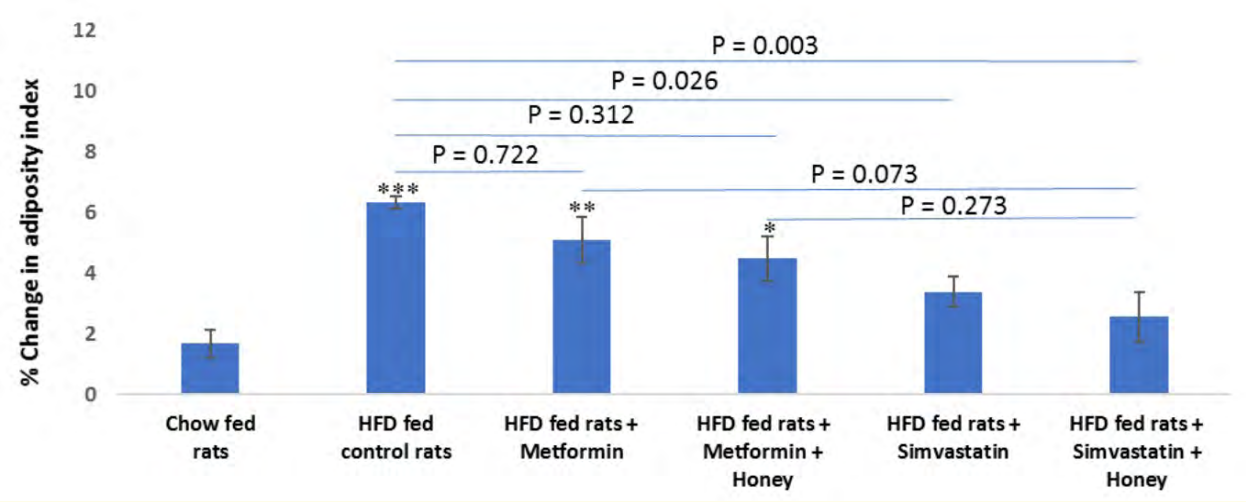

Figure 6: *Effect of metformin or simvastatin in combination with honey on % change in adiposity index after 6 weeks of treatment.*

Metformin and simvastatin are frequently prescribed drugs used to attenuate increases in obesity-related parameters such as weight gain and adiposity in obese type 2 diabetic and obese patients. In a previous study, we have reported that honey at a dose of 1.0 g/kg BW produced considerable amelioration of obesity-associated anthropometric parameters in HFD fed Wistar rats [14]. In this study, we investigated and compared the effects of metformin, simvastatin and their combination with honey on obesity anthropometric parameters in HFD fed Wistar rats. The results revealed that BMI, body weight/body length and adiposity index (AI) were borderline (non-significantly) higher in HFD fed control rats compared with chow fed rats. In contrast, total weight gain, % change in BMI and % change in AI were considerably (significantly) higher in HFD fed control rats compared with chow fed rats. Unlike BMI, body weight/body length and AI, the results of weight gain, % change in BMI and % change in AI provide data on the overall changes in obesity anthropometric parameters during the study period. The fact that these parameters (weight gain, % change in BMI and % change in AI) were markedly greater in HFD fed control rats suggested that obesity deteriorated during the 6 weeks of treatment. These findings agree with data in our previous study [14] and those of other researchers [15].

Our results indicated that obesity anthropometric parameters in metformin-treated HFD fed rats were similar to those observed in HFD fed control rats. That is, administration of metformin did not attenuate increases in obesity-related parameters in HFD fed rats. These data contradict previous findings which demonstrated weight loss-enhancing effect of metformin in HFD fed rats [20]. It is probable to

suggest that the short duration of metformin treatment in this study was responsible for the lack of significant effect of this drug on obesity anthropometric parameters in HFD fed rats. This view is strengthened by results showing that HFD fed rats treated with metformin for 4 weeks showed no diminution of increases in obesity anthropometrics [21]. On the contrary, significant attenuation was observed in HFD fed rats treated with metformin for 7 or 10 weeks [20,21]. This probably suggests that a longer duration of metformin treatment is needed for remarkable amelioration of obesity anthropometric parameters in HFD fed rats. Though statistically insignificant, combination of metformin and honey resulted in lower weight gain, BMI, % change in BMI, body weight/body length, AI and % change in AI in HFD fed rats compared with HFD fed control group. It remains uncertain if longer treatment of HFD fed rats with metformin or its combination with honey would exert marked reduction of obesity-associated parameters. The BMI was significantly higher in metformin-treated HFD fed rats than in HFD fed rats treated with simvastatin and honey. As a result of the combination of metformin and honey, the BMI was lower in metformin- and honey-treated HFD fed rats. Hence, the BMI in metformin- and honey-treated HFD fed rats and simvastatin- and honey-treated HFD fed rats was not statistically significant (comparable). This reduction in BMI can only be attributed to the augmentative effect of honey.

The study showed that simvastatin-treated HFD fed rats exhibited significantly lower BMI, % change in BMI and % change in AI compared with HFD fed control rats. These findings are in agreement with data from previous studies which demonstrated simvastatin ameliorated obesity anthropometric parameters in HFD fed rats [22,23]. Administration of simvastatin and honey to HFD fed rats was associated with much significantly lower BMI, % change in BMI and % change in AI compared with HFD fed control rats. This is an indication of the adjunctive beneficial effect of honey on simvastatin. Simvastatin ameliorates obesity-related parameters via inhibition of HMG-CoA reductase, the rate-limiting enzyme for cholesterol biosynthesis [24]. Unlike simvastatin, the mechanism by which honey attenuated increases in obesity anthropometric parameters as reported in our previous study is unknown. Hence, the mechanism through which honey improved the ameliorative effect of simvastatin in HFD fed rats as demonstrated in this study is worthy of further investigation.

A closer examination of the results on % change in AI revealed that the metformin-treated HFD fed group had significantly ($p < 0.01$) higher % change in AI compared with chow fed rats. The results further revealed that with metformin and honey combination, the increases in % change in AI (as reflected by level of significance, $p < 0.05$) were lower compared with chow fed rats. This means that the administration of metformin and honey combination attenuated the increases in % change in AI towards those of chow fed rats. In contrast, as reported in Figure 6, the increases in % change in AI in either simvastatin-treated or simvastatin- and honey-treated HFD fed rats were comparable (statistically insignificant) to those of chow fed rats. The implication of these findings is that, unlike metformin, administration of simvastatin exerted better ameliorative effect on % change in AI in HFD fed rats.

Amelioration of oxidative stress (antioxidant effect) is one of the pleiotropic effects of honey [25]. Ingestion of high fat diet is associated with oxidative stress [26]. Although oxidative stress status was not evaluated in this study, based on previous findings [12], it is plausible to hypothesize that tissues or organs of HFD fed rats treated with the combination of simvastatin or metformin and honey may have fortified antioxidant status. By and large, the findings of this study add to the existing literature by demonstrating that the adjunctive beneficial effects of honey in combination with synthetic drugs or other therapeutic strategies are not limited to surgical interventions [27], infections [28], cancer [29-31], and diabetes mellitus [9,12,32] but also extend to obesity.

Conclusions

These results suggest that simvastatin is better than metformin in attenuating elevations in obesity anthropometrics in HFD fed rats. Though the ameliorative effects of honey were more remarkable when combined with simvastatin than with metformin, the overall findings suggest honey is a potential adjunct to metformin or simvastatin in HFD fed rats. The mechanism by which honey markedly augmented the ameliorative effect of simvastatin on obesity anthropometric parameters in HFD fed rats requires further investigation. It would be worthwhile to explore the reproducibility of these findings in human obese subjects.

Acknowledgements

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Conflict of Interest

The authors declare that there is no conflict of interest.

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