

Metabolic and Inflammatory Changes with Orlistat and Sibutramine Treatment in Obese Malaysian Subjects

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Introduction: Obesity is associated with numerous health problems, particularly metabolic and cardiovascular complications. This study aimed to assess the effects that, nine months of pharmacological intervention with orlistat or sibutramine, on obese Malaysians' body weight and compositions, metabolic profiles and inflammatory marker.

Methods: Seventy-six obese subjects were randomly placed into two groups. The first group received three daily 120 mg dosages of orlistat for nine months (n=39), and the second group received a once daily 10 or 15 mg dosage of sibutramine for nine months (n=37). Baseline measurements for weight, body mass index (BMI), waist circumference (WC), body fat percentage (BF), visceral fat (VF), adiponectin, fasting plasma glucose (FPG), fasting insulin, pancreatic B cell secretory capacity (HOMA%B), insulin sensitivity (HOMA%S), insulin resistance (HOMA-IR) and serum high sensitivity C-reactive protein (hs-CRP) were performed and repeated during the sixth and ninth months of treatment.

Results: Twenty-four subjects completed the trial in both groups. For both groups, weight, BMI, WC, BF, VF, HOMA-IR and hs-CRP were significantly lower at the end of the nine month intervention. However, there were no significant differences between the two groups for these parameters with nine months treatment. There was a significant decrease in FPG in orlistat group; while fasting insulin and HOMA%B reduced in sibutramine group. For both groups, there were also significant increases in adiponectin levels and HOMA%S at the end of the nine month intervention.

Conclusion: Nine months of treatment with orlistat and sibutramine not only reduced weight but also significantly improved BMI, WC, BF, VF, FPG, adiponectin, fasting insulin, HOMA%B, HOMA%S, HOMA-IR and hs-CRP. These improvements could prove useful in the reduction of metabolic and cardiovascular risks in obese subjects. (J Nippon Med Sch 2017; 84: 125–132)

Key words: high sensitivity-C-reactive protein, insulin sensitivity, obesity, orlistat, sibutramine

Introduction

The prevalence of obesity has increased globally at an alarming rate and is now considered an epidemic. According to the World Health Organizations' global estimates in 2008, there were approximately 35% overweight (BMI ≥ 25 kg/m²) and 12% obese (BMI ≥ 30 kg/m²) adults internationally. In Malaysia, the values were higher, with

44% of adults being overweight and 14% of adults being obese, respectively¹. Obesity is a known risk factor for stroke, diabetes, hypertension, metabolic syndrome, gallbladder disease, coronary heart disease, high blood cholesterol, certain forms of cancer, sleep apnoea and other breathing problems².

Excessive fat storage can cause adipose tissues to in-

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flame through macrophage stimulation³. This leads to the release of free fatty acids (FFAs) into the circulatory system, decreased insulin sensitivity and abnormal release of inflammatory adipokines such as leptin, interleukin 6 (IL-6), tumour necrosis factor α (TNF- α), plasminogen activator inhibitor-1 (PAI-1) and monocyte chemoattractant protein-1^{4,5}. The release of adiponectin, a protective adipokine, also decreases with obesity⁶. Many hope that weight loss can reduce some of these metabolic and inflammatory profiles, potentially diminishing the rates of metabolic and cardiovascular risks in obese subjects. In this study, orlistat and sibutramine were used to reduce the weights of obese adults. Orlistat, a gastrointestinal lipase inhibitor, reduces fat absorption, while sibutramine, a monoamine-reuptake inhibitor, acts to reduce satiety⁷. We previously reported that microvascular endothelial function was impaired in relatively young subjects who were obese; this finding was associated with increased hs-CRP, white blood cell count and serum triglyceride (TG), higher blood pressure (BP), decreased adiponectin and lower high density lipoprotein cholesterol (HDL-C)⁸. After nine months of treatment with orlistat, significant improvements in systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), serum total cholesterol (TC) and microvascular endothelial dependent vasodilatation were observed⁹. The improvement in SBP, DBP and HR in this group may be through reduction in the activities of sympathetic nervous system (SNS) and rennin-angiotensin-aldosterone system (RAS), since obesity is associated with high blood pressure that is probably contributed by the activation of SNS and RAS^{10,11}. Meanwhile, in the sibutramine-treated group of the same study, HR was significantly increased, although no significant changes were seen in BP and microvascular endothelial function. This could be expected, as sibutramine is a selective serotonin, norepinephrine and dopamine reuptake inhibitor, which increases the concentration of these neurotransmitters in the sympathetic synapses.

Currently, there are a lack of reports that compare the effects of orlistat and sibutramine simultaneously in a study on inflammatory and metabolic markers that include fasting insulin level, resistance and sensitivity. In the present study, we focused on the effects that nine months of orlistat- and sibutramine-based treatments had on the metabolic profiles and inflammatory markers (which include adiponectin, FPG, insulin resistance and hs-CRP) of obese Malaysian subjects.

Materials and Methods

Study Design and Subjects

A randomized controlled trial was conducted to examine the effects of orlistat and sibutramine on anthropometry, body composition, BP, lipid profile, adiponectin, FPG, insulin sensitivity and resistance, hs-CRP and microvascular endothelial function in obese subjects. The results and methodologies for BP, lipid and microvascular endothelial function have been presented elsewhere⁹. This report will focus on the results obtained for body composition (WC, BF and VF), metabolic (adiponectin, FPG, insulin, HOMA%B, HOMA%S and HOMA-IR) and inflammatory (hs-CRP) markers.

Obese patients were recruited at the Obesity Clinic in Universiti Sains Malaysia's Hospital. The study protocol had been approved by University Sains Malaysia's Research Ethics Committee (Human) and was conducted according to the principles outlined in the Declaration of Helsinki. All subjects signed an informed consent form before any of the study's procedures were performed.

One hundred and fifty obese subjects with body mass indexes of ≥ 27 kg/m² were screened¹², and a total of 76 subjects were recruited. Subjects were randomly placed into two groups. The first group received three daily 120 mg dosages of orlistat for nine months (n=39), and the second group received a once daily 10 or 15 mg dosage of sibutramine for nine months (n=37). Random allocation into the intervention groups was determined using a computer-generated randomization list, and the study was completed before sibutramine was withdrawn from the market in Malaysia. Subjects included in this study were aged between 18–65 years old, normotensive or controlled hypertensive, had serum low density lipoprotein-cholesterol (LDL-C) <5 mmol/L, were non-diabetic (FPG <6.1 mmol/L) and non-smokers. Subjects with serious acute or chronic diseases such as coronary artery diseases, stroke, or active psychiatric conditions were excluded.

All subjects received healthy lifestyle counselling that included instructions on proper diet and exercise. All patients had at least four consultations with at least one of two of the study's dieticians. Written instructions containing advice on how to increase physical activity were provided; this advice was reinforced every time the patients visited the clinic or attended follow-up examinations with one of the dieticians.

Measurements

Body weight and height were measured using a digital weighing scale (SECA 789, Hamburg, Germany) with an

Table 1 Anthropometrics, body composition, FPG, HOMA%B and HOMA-IR at baseline, 6 and 9 months

Parameters	Baseline		6 months		9 months	
	Orlistat	Sibutramine	Orlistat	Sibutramine	Orlistat	Sibutramine
Weight (kg)	82.77 (14.48)	84.53 (12.09)	78.63 (14.45)	81.25 (12.18)	78.15 (13.73) ***	80.69 (10.80) ***
BMI (kg/m ²)	33.22 (3.93)	34.90 (4.83)	31.55 (4.03)	33.54 (4.89)	31.38 (3.79) ***	33.33 (4.47) ***
WC (cm)	96.23 (10.80)	96.58 (7.82)	92.55 (10.71)	93.46 (7.91)	91.69 (10.71) ***	92.73 (7.44) ***
BF (%)	38.96 (3.42)	40.65 (4.19)	37.75 (3.55)	39.52 (4.42)	37.24 (3.78) ***	39.42 (4.42) **
VF	16.27 (5.73)	17.85 (5.38)	14.40 (5.90)	16.17 (5.60)	14.02 (5.91) ***	16.10 (5.56) ***
FPG (mmol/L)	4.85 (0.60)	4.57 (0.37)	4.65 (0.53)	4.68 (0.53)	4.52 (0.55) *	4.66 (0.51) §
HOMA%B	181.79 (96.20)	142.53 (43.22)	163.98 (76.65)	126.86 (52.46)	157.25 (102.56)	105.31 (59.13) *
HOMA-IR	3.28 (1.91) [^]	1.90 (0.82)	2.66 (1.72)	1.83 (1.08)	2.19 (2.02) *	1.31 (0.93) *

Values presented as mean (SD)

Abbreviations: BMI, body mass index; WC, waist circumference; BF, body fat; VF, visceral fat; FPG, fasting plasma glucose; HOMA%B, Pancreatic B cell secretory capacity; HOMA-IR, Insulin resistance.

[^]Indicates significant difference for baseline characteristics between the 2 groups using independent t-test ($P=0.009$)

* $P<0.05$, ** $P<0.01$, *** $P<0.001$: within group significant effects of time on 9 months intervention using repeated measures ANOVA

§ Indicates significant difference on 9 months intervention between the 2 groups using repeated measures ANOVA ($P=0.026$)

attached stadiometer (SECA 245, Hamburg, Germany). BMI was calculated as weight in kg divided by height in m² (kg/m²). WC was measured at the midway point, between the inferior margin of the last rib and the iliac crest in the horizontal plane. BF and VF were measured using a digital body composition monitor (HBF-361, Omron Corporation, Kyoto, Japan), which applied the principle of bio-electric impedance analysis (BIA).

Fasting venous blood was taken for measurements of FPG, hs-CRP, adiponectin and fasting insulin. Serum hs-CRP and adiponectin levels were measured in duplicate using DRG[®] HS (C-Reactive Protein) commercial enzyme linked immunosorbent assay (ELISA) kits (DRG International, Inc., Springfield, NJ, USA) and Millipore[®] Human Adiponectin ELISA kits (EMD Millipore Corporation, Billerica, MA, USA), respectively. The intra-assay coefficient of variation for hs-CRP was 9.7%, and the intra-assay coefficient of variation for adiponectin was 3.74%. FPG was estimated using the glucose oxidase (GOD-PAD, Hitachi 912-2, Roche Diagnostic) method. Fasting serum insulin was measured using the chemiluminescence method with an IMMULITE[®] analyser (Diagnostic Product Corporation Euro/DPC Ltd., Caernarfon, Gwynedd, UK) at the Universiti Sains Malaysia's Endocrine Laboratory. Homeostasis model assessments (HOMA) for HOMA%S (insulin sensitivity) and HOMA%B (pancreatic B cell secretory capacity) were measured using HOMA software¹³. HOMA-IR (insulin resistance) parameters were calculated manually using the following formula: $HOMA-IR = (\text{fasting insulin in } \mu\text{IU/ml} \times \text{fasting glucose in mmol/L}) / 22.5^{14}$.

Follow-up visits were performed at the sixth and ninth months of intervention, wherein blood measurements and other study parameters were repeated. Drug compliance was determined by counting pills, and any side effects that occurred during treatment were investigated during patient visits.

Statistical Analysis

Statistical analyses were performed using the Statistical Package for Social Science (SPSS) Software version 12.0 (SPSS, Chicago, IL, USA). Data was presented as a mean (SD). Statistical significance was cited at $P<0.05$. Independent t-test was used to compare baseline values between orlistat- and sibutramine-treated groups. Repeated measures analysis of variance (ANOVA) was used to analyse within and between group changes in body weight and composition, metabolic profile and inflammatory marker after nine months orlistat and sibutramine treatment.

Results

Seventy-six obese subjects were randomly assigned to take either orlistat (n=39) or sibutramine (n=37). Throughout the nine month intervention, there were 15 dropouts in the orlistat-treated group and 13 dropouts in the sibutramine-treated group, resulting in a total of 24 subjects that completed the intervention in each group. Among the causes of dropouts were pregnancy, drug interaction, failure to attend follow-up examinations and non-compliance with the study's medication.

Table 1 shows the value of anthropometrics, body composition, FPG, HOMA%B and HOMA-IR at baseline

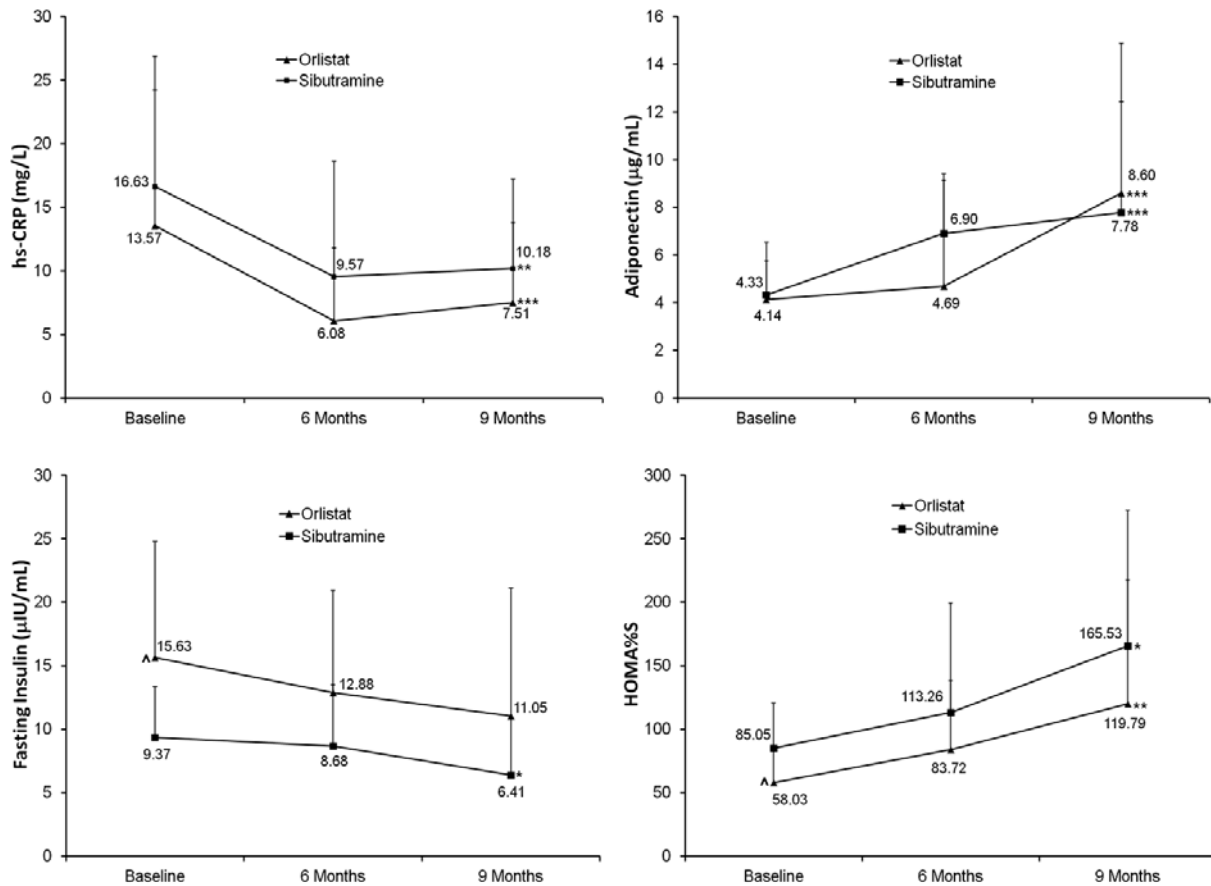


Fig. 1 hsCRP, adiponectin, fasting insulin and insulin sensitivity (HOMA%S) levels at baseline, 6 and 9 months of intervention with orlistat and sibutramine
 ^Indicates significant difference for baseline characteristics between the 2 groups using independent t-test (Fasting insulin, $P=0.013$; HOMA%S, $P=0.011$)
 * $P<0.05$, ** $P<0.01$, *** $P<0.001$: within group significant effects of time on 9 months intervention using repeated measures ANOVA
 Error bars represent standard deviations of the means

and during the six and nine month treatments of the orlistat- (n=24) and sibutramine-treated groups (n=24). There were no significant differences between the two groups in their baseline weight, BMI, WC, BF, VF, FPG and HOMA%B. However, HOMA%S was significantly higher in the sibutramine-treated group ($P=0.011$) (Fig. 1). HOMA-IR ($P=0.009$) (Table 1) and baseline fasting insulin ($P=0.013$) (Fig. 1) were significantly higher in orlistat-treated group.

After nine months treatment for both groups, weight, BMI, WC, BF and VF were significantly lower at the end of the nine month intervention. By contrast, FPG was significantly lower at the end of the nine month intervention for the orlistat-treated group. After the nine month intervention, the orlistat-treated group achieved an average weight loss of 5.58%, while the sibutramine-treated group achieved an average weight loss of 4.54% (Table

1). While hs-CRP was significantly lower at the end of the intervention period, adiponectin was significantly higher for both groups at the end of the intervention period (Fig. 1).

While HOMA-IR was significantly lower for both groups at the end of the nine months intervention (Table 1), HOMA%S was significantly higher for both groups at the end of the nine month intervention (Fig. 1). Serum fasting insulin and HOMA%B were significantly lower for the sibutramine-treated group (Table 1). In addition, except for FPG ($P=0.026$), there was no significant difference observed in the changes of weight, anthropometry, body composition, metabolic profile and hsCRP between both groups during the nine months treatment period (Table 1).

Discussion

After nine months of orlistat and sibutramine intervention, significant reductions in weight, BMI, WC, BF, and VF were seen in both the study's groups; there were no significant differences between both groups in these reductions. A significant reduction in hs-CRP levels and a significant increase in adiponectin levels were also observed in both groups with no significant differences between groups. Likewise, significant increases in HOMA%S and significant reductions (or improvements) in HOMA-IR were recorded in each group. Finally, while FPG significantly decreased in the orlistat-treated group, fasting insulin and HOMA%B significantly decreased in the sibutramine-treated group.

Anthropometrics and Body Composition

After nine months treatment, both the orlistat- and sibutramine-treated groups achieved significant reductions in their weight, BMI, WC, BF and VF. The orlistat-treated group achieved a 5.58% average weight loss, and the sibutramine-treated group achieved a 4.54% average weight loss. In the orlistat-treated group, 58.3% of the subjects reached a $\geq 5\%$ weight loss after nine months of therapy, and in the sibutramine-treated group, 50% of the subjects reached a $\geq 5\%$ weight loss after nine months of therapy. It was reported that a minimum weight loss of 5% is required to reduce visceral and subcutaneous fat in obese subjects and to improve their levels of glucose, insulin, adiponectin, leptin and hs-CRP¹⁵. Supporting our findings, previous studies showed significant improvement of body weight, BMI, BF, VF and WC after orlistat or sibutramine therapy^{16,17}. Furthermore, mean weight loss among our subjects was 4.62 kg and 3.84 kg respectively for orlistat and sibutramine treated groups. Similarly, in previous meta-analysis, weight loss with orlistat treatment has ranged between 2.5 and 3.2 kg, and for sibutramine-treated patients, between 3.6 and 4.7 kg¹⁸. Our study did not show significant differences in the reductions of weight, BMI, WC, BF and VF between the two groups; similar findings have been reported in an existing multicentre clinical trial¹⁹.

Metabolic Profile

Both treatments caused elevations in serum adiponectin levels after nine months but there was no significant difference in the changes of adiponectin levels between the two groups throughout the nine months treatment.

The results in our study corroborate with evidence that has been supported in previous studies. For instance, studies found that the orlistat- and sibutramine-treated

groups showed elevations of adiponectin levels and was associated with reduction in BMI and BF^{17,20}. In our study, the increase in adiponectin levels may have been due to weight loss. Adiponectin gene expression is increased by leanness and decreased by TNF- α and obesity²¹. There is a strong negative correlation between fat mass and concentration of plasma adiponectin²². Several experimental studies have shown that plasma adiponectin levels and adipose adiponectin mRNA expressions have each decreased in a majority of existing rodent models on obesity^{23,24}. These findings support evidence of changes in adiponectin levels due to weight loss in obese patients who received gastric partition surgery, and who found that weight loss enhanced their adiponectin blood levels²⁵.

Adiponectin is a multifunctional protein that regulates inflammation, energy homeostasis, insulin sensitivity and vascular reactivity²⁶. The association between adiponectin and insulin sensitivity has been studied before in human and animals. For example, in humans, adiponectin levels have correlated positively with insulin sensitivity as well as insulin-stimulated glucose disposal and have correlated negatively with serum insulin levels and resistance²⁷⁻²⁹. Meanwhile, several animal studies have revealed that adiponectin has been shown to improve whole-body insulin sensitivity in models of obese animals^{24,30} while animals with low levels of adiponectin develop high levels of TNF- α , severe insulin resistances, delayed clearance of plasma FFAs and low levels of the fatty-acid transport protein mRNA in muscle^{23,31}. This improvement in insulin sensitivity was due to the fact that adiponectin stimulates glucose uptake and fatty acid oxidation in both adipose tissue and skeletal muscle^{32,33}, besides its function in suppressing the output of hepatic glucose³⁰.

After nine months treatment, the orlistat- and sibutramine-treated groups showed an approximate 5% weight loss after nine months of intervention. This weight loss was associated with an increase in HOMA%S and a decrease in HOMA-IR. While FPG decreased significantly in the orlistat-treated group, no significant changes in FPG were recorded in the sibutramine-treated group. Fasting insulin and HOMA%B significantly decreased after the sibutramine treatment, and although some reduction was noted in the orlistat treatment, it did not reach statistical significance.

These findings concede with previous studies. For example, one study showed improvements of insulin sensitivity without significant changes in FPG after three

months of sibutramine therapy¹⁷. Another study showed that the orlistat-treated group had higher reductions in BMI and greater reductions in HOMA-IR when compared to its placebo group²⁰. Meanwhile, an existing meta-analysis has revealed that orlistat reduced FPG in four out of six of its studies, with no significant differences between FPG patients who were treated with sibutramine and FPG patients who were treated with a placebo³⁴.

In the current study, there is possible explanation for the differences that orlistat and sibutramine therapies have on FPG responses. It may be due to the differences in HOMA-IR that both groups had at baseline. At baseline, insulin resistance was significantly higher in the orlistat-treated group than it was for the sibutramine-treated group. Reduction in insulin resistance appears greater for the orlistat-treated group, although not significantly, which may have contributed to the group's more significant reduction in FPG. Findings in the current study are dissimilar to those in previous studies³⁵. Following a nine-month long intervention with a once daily 10 or 15 mg dosage of sibutramine, combined with a low-caloric diet for six months, sibutramine-treated patients experienced a mean weight loss of 4.54%. This weight loss was associated with a significant rise in serum adiponectin and significant improvements in FPG and insulin sensitivity. By contrast, no significant improvement in these parameters was observed in the orlistat-treated group. This discrepancy may be explained by the fact that weight loss in the orlistat-treated group was small (2.5%) and did not reach the minimum 5% from baseline. Minimum weight loss of 5% may be required to improve metabolic markers such as leptin, hs-CRP, adiponectin and glucose and insulin levels; it may also reduce visceral and subcutaneous fat in obese subjects¹⁵.

The anabolic actions of insulin on lipid, protein and glucose metabolism are essential for sustaining life. Insufficient insulin can lead to wasted protein, hyperlipidaemia and hyperglycaemia. Prompt response of the pancreatic β -cells to blood glucose changes via adjusting pancreas insulin release is critical in maintaining body blood glucose control. In a person with normal metabolism, pancreatic β -cells releases insulin after food consumption; the insulin released signals tissues responsive to insulin such as the liver, muscle and adipose tissue to utilise glucose from the blood thus lowering its concentration to normal values. However, in persons with insulin resistance, normal insulin levels failed to trigger adequate sig-

nal for glucose absorption. In these individuals, their pancreas compensates by producing more insulin so that their cells can be sufficiently triggered to absorb glucose. Therefore, the higher the HOMA%S, the lower the HOMA-IR and HOMA%B.

Hs-CRP

In this study, both orlistat and sibutramine caused significant decreases in serum hs-CRP. Conversely, there were no significant differences between each group's serum hs-CRP levels. The results in our study corroborate with evidence that has been supported in previous studies. Researchers have reported that orlistat and sibutramine treatment caused significant reduction in hs-CRP levels^{16,20,35} and this reduction was associated with reduction in BMI and BF¹⁸.

Hs-CRP is an independent risk factor for cardiovascular diseases such as stroke, coronary artery disease, myocardial infarction and peripheral artery disease while its presence in atherosclerotic lesions has been demonstrated previously^{36,37}. Increased hs-CRP levels as well as its positive correlation with obesity indices such as weight, BMI, WC, BF and VF have been previously reported in obese subjects^{8,29}. Hs-CRP levels were also reported to be strongly correlated with the severity of obesity and central obesity³⁸. This indicates that obesity is associated with a low-grade inflammatory state. Significant weight loss of 5.58% and 4.54% in the orlistat- and sibutramine-treated groups, respectively, could be a main contributor towards the reduction of hs-CRP levels. While weight reductions of 2.5% with orlistat were reported to cause no changes in CRP levels, CRP levels did fall after the 5.4% weight reduction in sibutramine-treated subjects³⁵. Even without pharmaceutical aid, significant decreases in CRP levels can be achieved as long as there are significant reductions in weight³⁹. These findings, which have been supported by evidence that hs-CRP is positively associated with obesity^{29,38}, suggest that hs-CRP levels are due in part to their production in adipose tissue. It can therefore be presumed that weight loss causes decreases in hs-CRP levels, as well.

During the study, some gastrointestinal side effects such as oily spotting, flatulence with discharge, fecal urgency, oily stool and increased defecation had been reported with orlistat-treated group. This is probably due to orlistat mechanism of action, where there is likely to be a higher presence of fat in the intestine as a result of reduction in fat absorption due to lipase enzyme inhibition. Nausea, insomnia, dry mouth, constipation, headache, altered taste had been reported by a few subjects in

sibutramine-treated group. However, these side effects were considered minor and tolerable by our subjects; advices on reducing and preventing these adverse effects were given to our subjects which helped in ameliorating most of these side effects. None of our study subjects requested to withdraw from this study due to these side effects. Among the advices given include, taking less fatty food in the orlistat-treated group. For sibutramine group, advices given include increasing intake of fibre and fluids to avoid constipation, as well as taking sibutramine early in the morning to minimize insomnia.

In our opinion, improvement in the parameters reported here namely visceral fat, adiponectin, hsCRP, fasting insulin level, sensitivity and resistance, were likely due to significant body weight reduction; however, this study cannot confirm this suggestion. Both drugs reduced weight significantly without significant difference between them, and similarly, both drugs improved the above parameters without significant difference between them. Orlistat and sibutramine may contribute in improving these parameters indirectly via their effect on reducing body weight. A few lifestyle modification studies without pharmaceutical interventional had also shown that improvement in certain metabolic and inflammatory profile among overweight and obese subjects can occur with significant weight loss. For example, a study by Ariffin et al.⁴⁰ had shown that nine months education on modified lifestyle intervention (by increasing physical activity and modifying diet) improved insulin sensitivity and resistance, reduced hs-CRP. Esposito et al.³⁹ reported that through low-energy diet and increased physical activity, there were reductions in body weight, BMI, waist circumference, CRP, fasting insulin and increment in adiponectin.

We conclude that nine months of orlistat- and sibutramine-based treatment significantly reduced weight that was associated with reductions in body and visceral fat, fasting insulin levels and resistance, hs-CRP and higher insulin sensitivity and levels of adiponectin. Improvements in anthropometric, body composition, adiponectin, insulin level and resistance and inflammatory were not significantly different between the orlistat- and sibutramine-treated groups. This suggests that, by reducing weight, both orlistat and sibutramine can effectively help manage obesity and reduce the metabolic and cardiovascular risks associated with obesity.

Conflict of Interest: The authors declare no conflict of interest.

Acknowledgements: We thank Universiti Sains Malaysia (USM) for providing Research University (RU) grant to conduct this study (1001/PPSP/812002) and USM fellowship to Dr. Belqes Al-Tahami.

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(Received, October 23, 2015)

(Accepted, February 14, 2017)