Metabolic Risk Markers in Leptin Resistant and Leptin Sensitive Obese Adult Subjects

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Leptin was initially believed to be an anti-obesity hormone, owing to its metabolic effects. However, obese individuals become resistant to satiety and weight-reducing effect of leptin. Leptin resistance refers to a condition in which some actions of leptin are impaired, even so its concentration is high. This study aimed to determine the metabolic risk markers in leptin resistant and leptin sensitive obese adult subjects. This study was conducted in 123 obese adult subjects (BMI≥30 kg/m^2) aged 20-60 years. To classify the leptin resistant and leptin sensitive obese groups, leptin-to-BMI ratio (1.55) was used as a cut-off point. Serum leptin level was determined by ELISA method. Fasting plasma glucose, serum triglyceride and high-density lipoprotein cholesterol levels were determined by enzymatic colorimetric methods. Metabolic syndrome was assessed by IDF criteria. Among the subjects, 39.8% (n=49) was leptin resistant and 60.2% (n=74) was leptin sensitive. Body mass index (BMI) of the leptin resistant and leptin sensitive obese subjects was 32.38±2.76 kg/m^2 and 31.90±2.92 kg/m^2 respectively. Although there was no significant difference in BMI between the two groups, serum leptin level of the leptin resistant obese subjects was significantly higher than that of leptin sensitive obese subjects (76.49±28.46 ng/ml *vs.* 29±13.86 ng/ml, respectively). Metabolic risk markers between the leptin resistant and leptin sensitive obese subjects showed non-significant difference except serum HDL cholesterol level which was higher in leptin resistant than leptin sensitive obese subjects. Eighty-nine out of 123 subjects (72.4%) had metabolic syndrome. The association between leptin sensitivity and metabolic syndrome among obese adult subjects was not found in this study. In conclusion, this study could not show any evidence of the role of leptin resistance on metabolic disorders in obese subjects.

Keywords: Leptin, Metabolic risk markers, Obese

INTRODUCTION

Obesity is a major risk factor for the development of cardiometabolic complications.[1] Individuals who had metabolic risk factors were more than eight-fold more likely to have coronary artery disease than individuals without these metabolic risk factors.[2]

Leptin was initially believed to be an anti-obesity hormone, owing to its metabolic effects. However, obese individuals become resistant to satiety and weight-reducing effect of leptin. Leptin resistance refers to a condition in which some actions of leptin are impaired, even so its concentration is high.[3]

Leptin resistance has been implicated in the pathogenesis of obesity related complications

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involving abnormalities of lipid metabolism.[4] Leptin acts as an insulin sensitizer when leptin levels are at low and normal levels whereas it may contribute to insulin resistance when leptin is chronically activated.[5] Furthermore, obese individuals retain leptin-mediated sympathetic activation to non-thermogenic tissues such as kidney, heart and adrenal glands. It may lead to sodium retention, sympathetic vaso-constriction and blood pressure elevation.[6]

Metabolic risk markers include abdominal obesity, high blood pressure, raised fasting plasma glucose, increased serum tri-glycerides, and decreased high-density lipoprotein cholesterol.[7] A cluster of these risk factors has become known as the metabolic syndrome.[8]

Evidence suggests that there was an association between serum leptin level and metabolic disorders, but other studies reported that there was no association between them. The role of leptin in metabolic disorders is still controversial.

In addition, Lee *et al.* in 2001 described the leptin resistance index by calculating 90th percentile of leptin-to-BMI ratio.[9] This index measures leptin level while controlling for the contribution of BMI. They stated that leptin resistance was strongly associated with extreme obesity (BMI ≥40 kg/m^2) and appeared to be a heritable trait.

In the study of Khin Mi Mi Lay in 2017, leptin resistance index of the obese adult subjects was higher than that of non-obese adult subjects.[10] Thin Thin Yu in 2016 reported that there was non-significant difference in leptin resistance index between persistent and current obese subjects.[11] There is limited information regarding the association between leptin resistance index (decreased leptin sensitivity) and metabolic disorders. Therefore, the present study was intended to find out whether there is an association between leptin sensitivity and metabolic syndrome among obese adult subjects.

MATERIALS AND METHODS

This study was a cross-sectional study conducted in 123 obese adult subjects (BMI ≥30 kg/m^2) aged 20-60 years from San-chaung, Dagon and Kamayut Townships, Yangon Region. Blood pressure and anthro-pometric measurements were done. Leptin-to -BMI ratio (1.55) was used as a cut-off point to classify the leptin resistant and leptin sensitive obese groups. Individuals with leptin-to-BMI ratio ≥1.55 are regarded as leptin resistant and <1.55 as leptin sensitive obese subjects. Serum leptin level was determined by ELISA method. Fasting plasma glucose, serum triglyceride and high-density lipoprotein cholesterol levels were determined by enzymatic colorimetric methods.

Individuals who do not have any components of metabolic syndrome according to IDF criteria (2006) are regarded as metabolically healthy obese subjects. Individuals who have at least one component of metabolic syndrome according to IDF criteria (2006) are regarded as metabolically unhealthy obese subjects.

Daily physical activity was assessed by Global Physical Activity Questionnaires developed by WHO (2016).[12] These ques-tionnaire were translated into Myanmar by Department of Medical Research. The information on physical activity participation was collected into three domains - activity at work, travel to and from places and recreational activities. Total physical activity MET-minutes per week was calculated as the sum of the total MET minutes of activity computed for each setting. Total physical activity <600 MET-minutes per week was considered as sedentary and ≥600 MET-minutes per week was considered as physically active.

Statistical analysis

Data collection was done by proforma. For categorical data, frequency and percentage were calculated. For the continuous data, mean (SD) was calculated. Skewed data

were presented as median and interquartile range. To compare the parameters between two groups, Student's 't' test and Mann-Whitney U test were used. To find the association between leptin sensitivity and metabolically healthy obesity, odds ratio with 95% CI was calculated. In this study, $p<0.05$ was regarded as statistically significant.

RESULTS

A total of 26 men and 97 women with a mean age of 43.68±9.79 years were participated. Median and interquartile range of serum leptin level of the obese adult subjects was 43.67 (26.71-65.55) ng/ml. Serum leptin levels of the male and female obese subjects were 14.81 (9.44-21.12) ng/ml and 52.25 (35.35-69.54) ng/ml, respectively. Metabolic risk markers of the obese adult subjects are shown in Table 1.

Table 1. Metabolic risk markers of the obese adult subjects (n=123)

Metabolic risk markers	Values
Waist circumference (cm)	98.65±8.19
Systolic blood pressure (mmHg)	121.66±11.99
Diastolic blood pressure mmHg)	81.77±9.69
Fasting plasma glucose mmol/L)	7.17±1.54
Serum triglyceride (mg/dL)	122.22 (94.44-178.89)
Serum HDL cholesterol (mg/dL)	42.75±10.20

Skewed data is presented as median & interquartile range.
All other values are presented as mean±SD.

The prevalence of the leptin resistant and leptin sensitive obese subjects were 39.8% (n=49) and 60.2% (n=74), respectively. Serum leptin levels of the leptin resistant and leptin sensitive obese subjects were 76.49±28.46 ng/ml and 29±13.86 ng/ml, respectively. Among the metabolic risk markers, a significant difference was found only in serum HDL cholesterol level between leptin resistant and leptin sensitive obese subjects ($p<0.05$) (Table 2).

Table 2. Comparison of metabolic risk markers

Metabolic risk markers	Leptin resistant n=49	Leptin sensitive n=74	P value
Waist circumference (cm)	97.08 ±6.90	99.68 ±8.83	0.085
Systolic blood pressure (mmHg)	121.35 ±13.04	121.86 ±11.33	0.816
Diastolic blood pressure (mmHg)	81.31 ±9.90	82.08 ±9.60	0.666
Fasting plasma glucose level (mmol/L)	7.16 ±1.48	7.18 ±1.59	0.94
Serum triglyceride level (mg/dL)	131.25 ±62.44	160.49 ±92.04	0.054
Serum HDL cholesterol level (mg/dL)	48.34 ±9.79	39.06 ±8.73	<0.001*

*Significant difference between two groups ($p<0.05$)

Eighty-nine out of 123 subjects (72.4%) had metabolic syndrome. There was no association between leptin sensitivity and metabolic syndrome among the obese adult subjects (OR: 0.48, 95% CI: 0.21-1.06).

DISCUSSION

In the present study, serum leptin level of the male obese subjects was lower than that of the female obese subjects. Variation in serum leptin level might be explained by difference in gender, fat percentage and other factors such as smoking, diet, genetics and physical activity.

Until now, there is no known cut-off point for leptin resistance and leptin sensitivity among obese subjects. Lee *et al.* in 2001 computed the ratio of leptin-to-BMI and proposed leptin-to-BMI ratio $\geq 90^{th}$ percentile as leptin resistance.[9] One previous study conducted on 44 obese (BMI >25 kg/m^2) and 42 non-obese (BMI <25 kg/m^2) between the age group 20-55 years and calculated leptin-to-BMI ratio. It was mentioned that the 90^{th} percentile of leptin-to-BMI ratio was 1.55.[10] Therefore, this value was used as a cut-off point for the present study to classify leptin resistant and leptin sensitive obese groups.

Body mass index (BMI) of the leptin resistant and leptin sensitive obese subjects was 32.38±2.76 kg/m^2 *vs*. 31.90±2.92 kg/m^2. Although there was no significant difference in BMI between the two groups, serum leptin level of the leptin resistant obese subjects was significantly higher than that of leptin sensitive obese subjects (76.49±28.46 ng/ml *vs*. 29±13.86 ng/ml, respectively).

In the present study, mean waist circumference of the study group (n=123) was 98.65±8.19 cm and those of the male (n=26) and the female subjects (n=97) were 105.52±7.97 cm and 96.80±7.24 cm, respectively. According to IDF criteria (2006), central obesity is defined as waist circumference of men ≥90 cm and women ≥80 cm in South-Asian population.[13] All the subjects involved in the present study were centrally obese subjects.

No significant difference was found in waist circumference between leptin resistant and leptin sensitive obese subjects (97.08±6.90 cm *vs*. 99.68±8.83 cm, respectively) in the present study. Leptin resistant and leptin sensitive are based on the serum leptin level; however, waist circumference indicates visceral adiposity across a wide age range.[14] Despres in 1998 reported that leptin is more closely related to peripheral fat mass (subcutaneous).[15] Minocci, *et al*. in 2000 reported that the contribution of visceral fat was not significantly associated with serum leptin level.[16] Therefore, it could explain the lack of significant difference in waist circumference between these two groups.

Although some studies had suggested that leptin as an independent predictor of insulin resistance and hypertension,[17, 18] there was no significant difference in fasting plasma glucose and blood pressure between leptin resistant and leptin sensitive obese subjects. According to the literature, it could be speculated that there would be impaired fat metabolism in the presence of leptin resistance, resulting in an increase in serum TG and a decrease in serum HDL.[4] In the present study, serum HDL cholesterol level was significantly higher in leptin resistant than leptin sensitive obese subjects. Regarding serum TG level, it was found to be lower in leptin resistant than leptin sensitive obese subjects.

One possibility is that there are some influencing factors such as dietary intake and physical activity on serum TG and HDL cholesterol concentrations. Dietary intake of total carbohydrate was associated with serum TG and HDL cholesterol levels.[19] Lowering of HDL concentration by a high CHO diet was also reported by Levy, *et al.* in 1966.[20] In the present study, history of dietary intake was not taken for both groups. So, it was unable to predict whether individuals take excess carbohydrate intake or not, and whether dietary intake of two study groups are different or not.

According to gender difference, serum leptin level of the female subjects is higher than male subjects. Regarding the characteristics of the study population, only females are involved in leptin resistant obese group whereas both males and females are involved in the leptin sensitive obese group. Generally, women have higher HDL cholesterol level than men.[21] Therefore, gender difference in study population could be one possible factor for higher serum HDL cholesterol level in leptin resistant obese group.

Monda, *et al*. in 2009 described that physical activity was associated with an increase in HDL and a decrease in TG.[22] In the present study, subjects were asked to fill out the questionnaire for physical activity (WHO, 2016), and the subjects were categorized into sedentary and active groups. Total physical activity <600 MET-minutes per week was considered as sedentary and ≥600 MET-minutes per week was considered as physically active. It was found that there was an association between physical activity and an increase in HDL (χ^2=16.96, p<0.05) and between physical activity and a decrease in TG (χ^2=5.36, p<0.05). However, there was no significant difference in proportion of sedentary and active subjects between the two groups (leptin resistant: 81.6% *vs.* 18.4%

and leptin sensitive: 73% *vs.* 27%). Thus, the higher TG and lower HDL in the leptin sensitive subjects could not be explained by the difference in physical activity. Therefore, the present findings suggest that dyslipidemia in obese subjects does not depend on leptin sensitivity and leptin resistance.

In the present study, although the leptin resistant obese group showed higher serum HDL cholesterol level than leptin sensitive obese group, 61.2% of leptin resistant obese subjects have decreased HDL cholesterol level and their mean values was lower than normal values. Individuals with low HDL cholesterol levels may have a greater risk for the incidence of cardiovascular disease.[23] Thus, the present study highlights the importance of controlling metabolic parameters and future risks associated with obesity.

In the present study, there was no association between leptin sensitivity and metabolic syndrome in obese adult subjects. The result was compatible with the finding of Park, *et al.* in 2004. [24] They reported that leptin did not appear to have a major role linking various components of metabolic syndrome, although it was strongly associated with obesity indices.[24] Hamidi, *et al* in 2006 also described that there was no significant association between leptin and metabolic syndrome status.[25]

Reaven in 1988 proposed that insulin resistance plays a role in metabolic syndrome.[26] Insulin and insulin resistance are involved in metabolic derangement in obese subjects. Thus, it could be assumed that metabolic disorders in obese subjects may not be solely due to leptin.

In the present study, serum insulin was not determined, and insulin resistance index was not able to calculate. Therefore, the relationship between leptin, insulin and metabolic syndrome could not be evaluated. In conclusion, the present study could not show any evidence of the role of leptin resistance on metabolic disorders in obese subjects.

Recommendation

Non-significant difference in metabolic risk markers between leptin resistant and leptin sensitive obese subjects might also be due to the fact that most of the subjects had BMI <40 kg/m^2. It has been reported that leptin resistance was more prevail in those with BMI ≥40 kg/m^2. Thus, further studies with inclusion of extremely obese subjects should be done. Serum insulin level should be measured as it might be a link between leptin and metabolic disorders in obesity. Moreover, metabolically healthy obese may change over to metabolically unhealthy obese. Since the present study was a cross-sectional study, longitudinal follow-up studies on metabolically healthy obese should be done and lifestyle intervention strategies are suggested to prevent and manage these important metabolic risk factors.

Competing interests

The authors declare that they have no competing interests.

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