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Relationship between Serum Leptin and Insulin Resistance in Persistent Obese and Current Obese People

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Adiposity and duration of obesity are important for development of type 2 diabetes. The present study, a cross-sectional one, aimed to investigate the relationship between serum leptin and insulin resistance in persistent overweight/obese subjects (n=46) and current overweight/obese people (n=48) (BMI ≥25, duration of obesity >15 and ≤15 years) from Sanchaung and Dagon townships, Yangon. Serum leptin and serum insulin levels were determined by ELISA method. Fasting plasma glucose level was determined by glucose oxidase, phenol, 4-aminophenazone method. Although serum leptin level was not statistically significant between two groups, serum insulin was significantly different between 2 groups (18.94±10.67 μIU/ml *vs.* 14.79±7.10 μIU/ml), respectively ($p<0.05$). Homeostasis model assessment of insulin resistance of the persistent overweight/obese group was significantly higher than that of the current group [median value (interquartile range) [4.46(3.00-5.44) *vs.* 3.40(2.66-4.57)]. Mean homeostasis model assessment (HOMA) of β-cell function in the persistent overweight/obese group was 179.28±84.54% and that of current overweight/obese group was 148.31±72.57%. A difference in mean HOMA β-cell function between two groups subjects was not significant ($p=0.06$). But, there was a significant association between duration of obesity and HOMA β-cell function impairment; current obesity having about 3 times (OR: 3.73, 95% CI=1.23-11.32) increased risk of β-cell function impairment. Correlation between serum leptin and HOMA-IR of all subjects was weak but statistically significant (Spearman's $\rho=0.240$, $n=94$, $p<0.05$). Therefore, the findings indicated that those with longer duration (i.e. persistence overweight/obese) might be more related to insulin resistance. However, those with lesser duration (i.e. current overweight/obese) were found to be more related with impairment of β-cell function. It seems that rapid rise in BMI within short duration is more likely to be associated with impairment of β-cell function.

Key words: Leptin, Insulin resistance, Persistent, Current

INTRODUCTION

Adiposity and duration of obesity are important for development of type 2 diabetes. Duration of obesity was defined as the time since body mass index (BMI) was first known to be at least 30 kg/m^2.[1] The number of years lived with obesity is directly associated with the risk of mortality. Longer exposure to obesity might be expected to lead to a longer exposure to endogenous production of reactive oxygen species and oxidative DNA damage, alterations in carcinogen-metabolizing enzymes, alteration in endogenous hormone metabolism and partial exhaustion of β-cells, with the resultant insulinopenia causing depressed glucose oxidation and impaired glucose tolerance.[1-3] The current obese people who had a medium number of years lived with obesity (5-14.9 years) have

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the risk of mortality more than doubled than normal weight people and the risk was almost tripled for those with the longest duration of obesity (≥15 years).[4]

Obesity enhances insulin resistance.[5] Insulin resistance (IR) is defined as resistance to the effects of insulin on glucose uptake, metabolism or storage. Insulin resistance in obesity is manifested by decreased insulin-stimulated glucose transport and metabolism in adipocytes and skeletal muscle, and by impaired suppression of hepatic glucose output.[6] Leptin, the satiety hormone, is a hormone produced by the fat cells in the body, which regulates the amount of fat stored in the body. Obesity promotes hyperleptinemia, which in turn self-promotes leptin resistance and further obesity, making leptin resistance both a consequence and cause of obesity.[7]

Leptin acts as an insulin sensitizer when leptin levels are at low and normal levels but it may contribute to insulin resistance when leptin is chronically activated.[8] Although insulin resistance and leptin resistance increase in parallel with the rise in adiposity, they differ in the timing of their development and their relationship to white adipose tissue mass.[9-11] The association between hyperinsulinemia, hyperleptinemia and insulin resistance is still controversial. Therefore, it was necessary to find out that serum leptin level can increase along with duration of obesity and hyperleptinemia can effect on insulin secretion and insulin resistance.

The aims of the present study were to determine and compare serum leptin, fasting blood glucose level, fasting insulin level and HOMA-IR in persistent and current overweight/obese people and to find out the relationship between serum leptin and HOMA-IR in persistent overweight/ obese and current overweight/obese people.

MATERIALS AND METHODS

A cross-sectional study carried out in persistent overweight/obese subjects (n=46) (BMI ≥25, duration of obesity >15 years) and current overweight/obese subjects (n=48) (BMI ≥25, duration of obesity ≤15 years) from Sanchaung and Dagon Township, Yangon. Plasma glucose level was determined by glucose oxidase, phenol, 4-aminophenazone (GOD-PAP) method. Serum insulin level was determined by ELISA method using DRG Insulin ELISA. Insulin resistance was calculated by formula.[12] Serum leptin concentration was determined by ELISA method using "Human Leptin ELISA Duoset".

$$\text{HOMA-IR} = \frac{\text{Insulin (}\mu\text{IU/ml)x Glucose (mmol/l)}}{22.5}$$

$$\text{HOMA } \beta\text{-cell function} = \frac{20 \text{x FPI (}\mu\text{IU/ml)}}{\text{FPG (mmol/l)-3.5}}$$

Data were presented as mean±SD. Skewed data were presented as median and interquartile range. Data analysis was done by using Statistical Package for Social Sciences (SPSS) software version 16. The difference between the mean of persistent overweight/ obese group and current overweight/ obese group was assessed by Student's t test and Mann-Whitney U test. Pearson's correlation and Spearman's correlation coefficient were computed to explore strength and significance of the relationships among variables. The statistical significance was set at $p<0.05$.

RESULTS

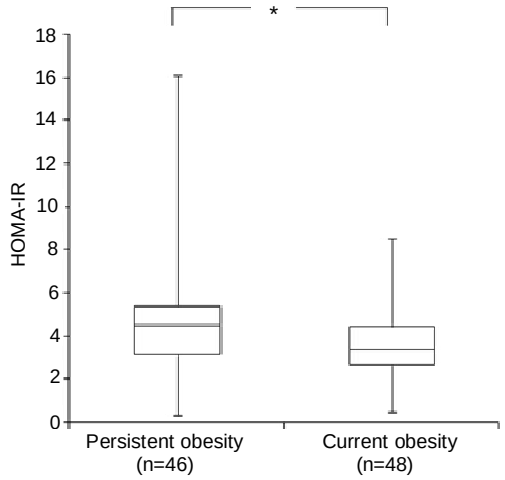
General characteristics of both study groups are shown in Table 1. Median value (interquartile range) of HOMA-IR was 4.46 (3.00-5.44) in the persistent overweight/ obese

Table 1. General characteristics of the study groups

	Overweight/obese groups		p
	Persistent	Current	value
Age (years)	44.57±7.57	48.90±6.90	<0.05
Height (m)	1.53±0.07	1.54±0.05	>0.05
Weight (kg)	69.50±8.39	68.06±8.72	>0.05
BMI (kg/m^2)	29.53±2.72	28.38±3.11	>0.05
Duration of obesity (years)	28.30±8.01	9.42±4.12	<0.01
Body fat percent (%)	44.91±4.89	43.01±5.98	>0.05
Serum leptin (ng/ml)	33.85±19.10	34.30±22.79	>0.05
Serum insulin (µIU/ml)	18.94±10.67	14.79±7.10	<0.05
Fasting plasma glucose (mmol/l)	5.59±0.55	5.58±0.56	>0.05

Data are shown in mean±SD

group and 3.40(2.66-4.57) in the current overweight/obese group. HOMA-IR of the persistent overweight/obese group was significantly higher (p=0.04) than that of the current overweight/obese group (Fig. 1). Mean HOMA β-cell function in the persistent overweight/obese group was 179.28± 84.54% and that of current overweight/obese group was 148.31±72.57%.



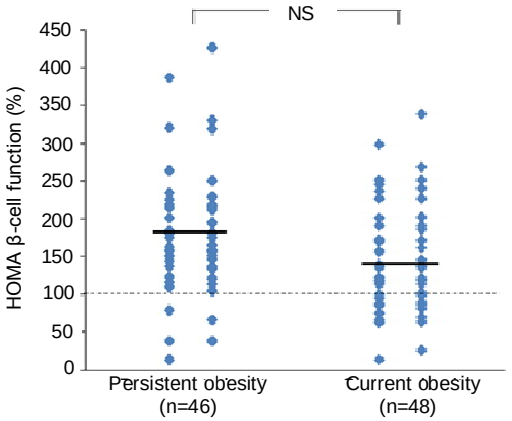
*****indicates significant difference between two groups (p<0.05)

Fig. 1. Comparison of HOMA-IR level of the study groups

A difference in HOMA β-cell function between persistent overweight/obese and current overweight/obese subjects was not significantly different (p=0.06) (Fig. 2). No correlation was found between serum leptin and serum insulin in all subjects and in two study groups. Correlation between serum leptin and HOMA-IR of all subjects in the present study was weak but statistically significant (Spearman's ρ=0.240, n=94, p<0.05) (Fig. 3). However, no correlation between serum leptin and HOMA-IR was found in the persistent overweight/obese group (Spearman's ρ=0.198, n=46, p>0.05) and the current overweight/obese group (Spearman's ρ=0.260, n=48, p>0.05).

Association of β-cell function between persistent and current overweight/obese groups

Five out of 46 persistent overweight/obese subjects (i.e. 10.87%) and 15 out of 48 current overweight/obese subjects (i.e.



NS indicates no significant difference between two groups (p>0.05).

Solid line (—) indicates mean value of different groups.
Dash line (- -) indicates normal HOMA β-cell function.

Fig. 2. Comparison of HOMA β-cell function of the study groups

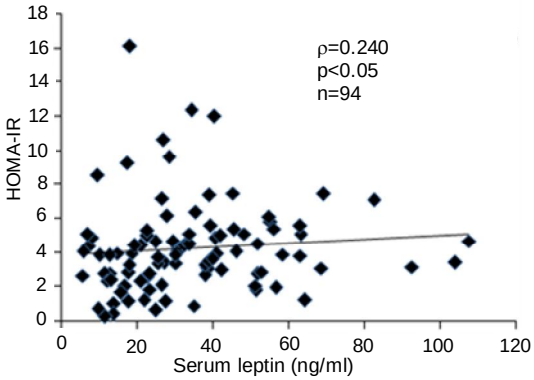


Fig. 3. Correlation between serum leptin and HOMA-IR in overweight/obese subjects

31.25%) had HOMA β-cell function values lower than 100% (i.e. normal HOMA β-cell function).[13] There was a significant association between duration of obesity and HOMA β-cell function, current obesity having about 3 times (OR: 3.73, 95% CI=1.23-11.32) increased risk of β-cell function impairment.

DISCUSSION

Some researchers have focused on the relationship between serum leptin and serum insulin, but the exact relationship between leptin and insulin is not clear and

is sometimes controversial. Chu, *et al.*[14] reported that the relationship between leptin and insulin level is complicated and may be bi-directional.

In the present study, serum leptin and fasting plasma glucose were not significantly different between persistent and current overweight/obese groups. The persistent overweight/obese group showed a significantly higher value in serum insulin and HOMA-IR than the current overweight/ obese group. No correlation was found between serum leptin and serum insulin in all subjects of two study groups. A weak positive correlation between serum leptin and HOMA-IR was found only in all subjects (Spearman's ρ=0.240, p=0.02, n=94) whereas no correlation between serum leptin and HOMA-IR was found in both groups.

Al-Sultan and Al-Elq (2006) also investigated in 89 non-diabetic healthy subjects with normal BMI between 20-25 kg/m^2 (n=43) and obese BMI >30 kg/m^2 (n=46) and their result was a significantly positive correlation (r=0.344, p=0.001, n=89) between leptin and HOMA-IR.[15] Although correlation was found between leptin and HOMA-IR in the present study, it was a weak correlation. In addition, the cross-sectional study design limits to evaluate causal relationships between leptin and insulin resistance. Therefore, the present study could not show any evidence regarding relationship between serum leptin, fasting serum insulin and insulin resistance in overweight/obese subjects with varying duration of obesity. However, the present findings pointed out that the relationship between serum leptin and insulin and the relationship between serum leptin and insulin resistance seems to be independent of duration of obesity.

The finding of the present study was inconsistent with the findings of Zimmet, *et al.*[16] and Mohamed, *et al.*[17] Zimmet, *et al.*[16] found that there was a significant positive correlation (r=0.63 in men and 0.64 in women, p<0.001 in both) between leptin and insulin concentration. They assumed that insulin may directly affect leptin concentration or that leptin reduces insulin values. In addition, Mohamed, *et al.*[17] showed that there was a significant positive correlation (r=0.5174, n=50, p<0.05) between leptin and insulin in obese and metabolic syndrome group.

In the present study, all participants were apparently healthy overweight/obese subjects with different duration of obesity, but these aforementioned two studies included those with normal BMI and those with metabolic syndrome. This difference in subjects' baseline characteristics could explain inconsistent findings between the present and their studies.

Evidence suggested that there is a close link between serum leptin and serum insulin level. However, there are many other independent factors relating to serum leptin and serum insulin level. Thus, the relationship between leptin and insulin resistance was not completely clear. In fact, both the degree of obesity and its central or peripheral fat mass distribution were important determinants of leptin levels; central (visceral) fat was associated with hyperinsulinemia and insulin resistance while peripheral (subcutaneous) fat was associated with hyperleptinemia, indicating that leptin and insulin resistance probably reflect two different metabolic compartments.[18]

In the present study, there was no significant difference in mean HOMA β-cell function between persistent and current overweight/ obese groups. However, a significant association was found between HOMA β-cell function impairment and duration of obesity in all subjects; current obesity having about 3 times increased risk of β-cell function impairment (OR: 3.73, 95% CI=1.23-1.32).

It was found that both persistent and current overweight/obese groups lead to a rise in obesity-related metabolic parameters such as fasting insulin level, HOMA-IR and HOMA-β cell function. The persistent overweight/obese group had higher degree of obesity, as well as obesity-related

metabolic parameters. There were some limitations in the present study: cross-sectional design of the study and participation of apparently healthy subjects with BMI between 25 and 29. In fact, longitudinal study is more appropriate to explore the effect of duration. Previous longitudinal studies found that the longer the duration of obesity, the lower the insulin secretory rate. Thus, the discrepancy in the findings might be explained by difference in study design.

Conclusion

The present findings indicated that those with longer duration (i.e. persistent overweight/obese) might be more related to insulin resistance, but they were found to probably be still in compensatory state. However, those with lesser duration (i.e. current overweight/obese) were found to be more related with impairment of β-cell function. It seems that rapid rise in BMI within short duration is more likely to be associated with impairment of β-cell function.

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