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ARTICLE

Relationship Between Serum Testosterone, Leptin, Interleukin-6 (il-6) Level and Insulin Sensitivity in Non-obese and Obese Male Subjects in Magway Region, Myanmar

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ABSTRACT

Objective: To determine the relationship between insulin resistance and related variables (serum testosterone, interleukin (IL-6) and leptin level) in obese and non-obese healthy subjects. Methods: Community-based cross-sectional, analytic study was undertaken in 60 subjects for each obese group (BMI ≥ 30.0 kg/m2) and non-obese group (BMI 18.5 to 24.9 kg/m2) (age;18-45 years) residing in Magway Township from December 2016 to December 2017. Serum insulin, testosterone, IL-6 and leptin levels were measured by enzyme linked immunoassay, and serum fasting glucose was measured by glucose oxidase method. Insulin sensitivity was calculated by HOMA formula (Homeostatic Model Assessment). Results: HOMA-IR, serum leptin and IL-6 level were significantly higher in obese group while serum testosterone level was significantly lower in obese group. There was a significantly correlation between HOMA-IR with leptin (r=0.306, p=0.001), IL-6 (r=0.237, p=0.009) and testosterone (r=-0.209, p=0.02). Moreover, serum leptin was significantly and positively correlated with IL-6 (r=0.391, p<0.001) while serum testosterone was significantly and negatively correlated with leptin (r=-0.408, p<0.001), and IL-6 (r=-0.34, p<0.001). Conclusions: Obese men are more likely to have low testosterone, high inflammatory markers leptin and Il-6, which were associated with decreased insulin sensitivity.

1. Introduction

The prevalence of obesity is rapidly worldwide. At least 2.8 million people die each year as a result of being overweight or obese [1]. Obesity is considered as chronic inflammatory disease. Leptin and IL-6 are known as low grade inflammatory markers which released from adipose tissue [2]. Most of studies have shown the significant association between these inflammatory cytokines (Leptin and IL-6) and obesity [3,4].

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Liu et al [5] reported that 41% of obese patients without diabetes have insulin resistance. It has been reported that serum IL-6 level was significantly and positively associated with insulin resistance [6,7] but few studies have found that IL-6 did not alter the effects of insulin on glucose homoeostasis [8]. Moreover, Senn et al [9] demonstrated that IL-6 induces cellular insulin resistance in hepatocyte. Considerable evidence from vitro study on rat adipocyte had shown that leptin impairs several metabolic actions of insulin [10]. A few studies indicated that serum leptin level was significantly and positively associated with insulin resistance in women with metabolic syndrome [11], post-menopausal women [12], non-obese adolescents (boys and girls) [13] and obese women [14]. However there is paucity of literature on the effect of leptin in obese male individuals on insulin resistance.

Significance of low testosterone levels was seen in obese men [15-17]. Xia et al [18] have reported recently that serum testosterone level was significantly and negatively associated with insulin resistance in elderly male type 2 diabetes mellitus (T2DM) patients with osteoporosis, whereas it has not been reported in inflammatory state of obesity. Moreover, there are convincing evidence demonstrated the important link between leptin, IL-6 and testosterone in vitro studies [19-21]. Thus serum leptin, IL-6 and testosterone level attract considerable attention in development of insulin resistance in inflammatory state of obesity. Thus the present study aims to investigate the relationship between serum testosterone, leptin and IL-6 levels and the relationship between each of these variables and insulin resistance in healthy adult male subjects.

2. Methodology

This cross-sectional analytical study was undertaken in apparently healthy non-obese and generally obese male adult subjects living in Magway Township, Myanmar from December 2016 to December 2017. Five quarters among total fifteen quarters in Magway Township were be selected by simple random sampling method. All the male subjects aged between 18-45 years residing in selected five quarters were selected. After that, they were thoroughly explained about the research. The participation in present study was absolutely voluntary and written informed consent was obtained.

All participants were undertaken by history taking and physical examination. Subjects who are fasting blood sugar > 7 mmol/L, subjects who are history of diabetes, cardiovascular diseases, bone diseases, endocrine diseases such as hyperthyroidism, hypo or hyperparathyroidism and Cushing syndrome and acute infection, subjects who are blood pressure more than 140/90 mmHg, subjects who are taking anti-oxidants e.g. vitamin C and anti-inflammatory drugs e.g. steroids, chronic smoker and chronic alcoholic were excluded from the study. Chronic alcoholic are those who drink distilled spirit (especially rum, whisky with 40 percent alcohol), an average of 140 ml/day for more than five years. Chronic smokers are those who had 25 or more pack-year of smoking history of any tobacco product such as cigarettes, cigars or rolled tobacco. The weight measurement was done by using a calibrated bathroom scale. Standing height was measured by using measuring tape. Body mass index was calculated. Waist circumference was measured by using a measuring tape. Then all the eligible subjects from each quarter were categorized into two groups; control group and obese group. Those with BMI 18.5-24.9 kg/m^2 were selected in the non-obese group and those with BMI $\geq$ 30.0 kg/m^2 were selected in the obese group. There were a total of 10 groups for five quarters. Twelve subjects from each group were recruited to the study by simple random sampling method. This was resulted in 60 subjects for each obese group and non-obese group. Age of the subjects was adjusted for each group.

All subjects were instructed to arrive at quarter's office at 8:00 am after fasting for 10 hours (from 10:00 pm to 8:00 am). On arrival, fasting blood sample (10 ml) taken by venipuncture was collected in two separate blood collecting tubes: one ml of blood was collected in tube containing10 mg of sodium fluoride for determination of blood sugar and 9 ml of blood in another tube for serum separation. Then all blood samples were transported to Common Research Laboratory, University of Medicine, Magway with effective cold chain system. On arrival, serum was separated and collected in 4 separate sample tubes and stored at (-20°C) until the blood sample analysis: one for determination of serum IL-6, one for determination of serum leptin, one for determination of serum insulin and one for determination of serum testosterone. Blood glucose level was determined on the same day of blood collection.

Data entry and analysis were done by SPSS software (version 22, SPSS Inc., Chicago, IL, USA). Independent "t" test was used to compare the normally distributed data and Mann-Whitney Test was used to compare the skewed data between non-obese and obese groups Correlation studies were done by Spearman's correlation. Differences were considered significant when $p < 0.05$.

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Table 1. Comparison of biochemical parameters of the study subjects (n =120)

variables	Non-obese group (n=60)	Obese group (n=60)	P value
	Mean ± SD or Median(IQR)		
Blood glucose level (mmol/L)	4.74±0.34	5.03±0.43	<0.001
Insulin (µIU/L)	10.31(8.03)	15.32(9.74)	<0.001*
HOMA-IR	2.18(1.55)	3.58(2.37)	<0.001*
Leptin (pg/ml)	3(2.48)	6(5.6)	<0.001*
IL-6 (pg/ml)	10(8)	38(37.5)	<0.001*
Testosterone (pg/ml)	5.55±2.43	4.07±1.34	<0.001

Note:
*Independent t test, *Mann-Whitney test*

3. Results

Table 1 indicated that comparison of biochemical parameters between non-obese and obese groups. There were significantly higher blood glucose level, serum insulin level, HOMA-IR, serum leptin level, serum IL 6 level and lower testosterone level in obese group compared with non-obese group.

Correlation of HOMA-IR and serum leptin, IL-6, testosterone levels in study population was illustrated in figure 1. HOMA-IR was significantly and weak positively correlated with serum leptin and IL-6 levels (Figure 1A, B). There was a significant weak negative correlation between HOMA-IR and testosterone level (Figure 1C).

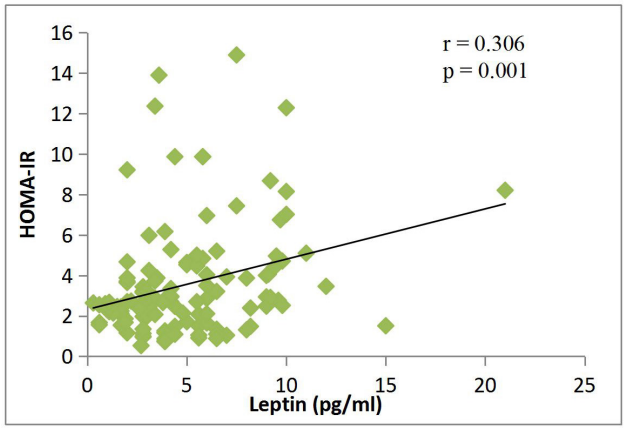

Figure 1A. Correlation between HOMA-IR and serum leptin level in study subjects

Notes:
r = spearman Correlation coefficient
n = total numbers of subjects
Statistical significant difference was set as p<0.05

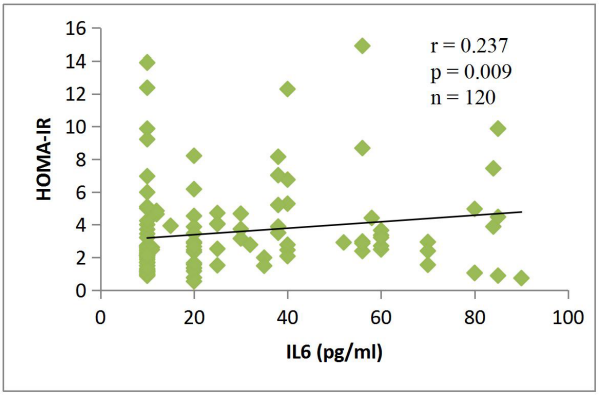

Figure 1B. Correlation between HOMA-IR and serum IL-6 level in study subjects

Notes:
r = spearman Correlation coefficient
n = total numbers of subjects
Statistical significant difference was set as p<0.05

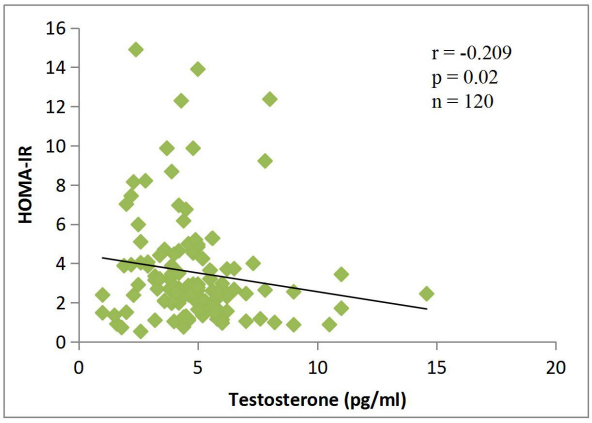

Figure 1C. Correlation between HOMA-IR and serum testosterone level in study subjects

Notes:
r = spearman Correlation coefficient
n = total numbers of subjects
Statistical significant difference was set as p<0.05

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As shown in figure 2, there was significant weak negative correlation between IL-6 and testosterone level (Figure 2A) and between leptin and testosterone levels (Figure 2B). Figure 2C showed that leptin was significantly and weak positively correlated with IL-6 level.

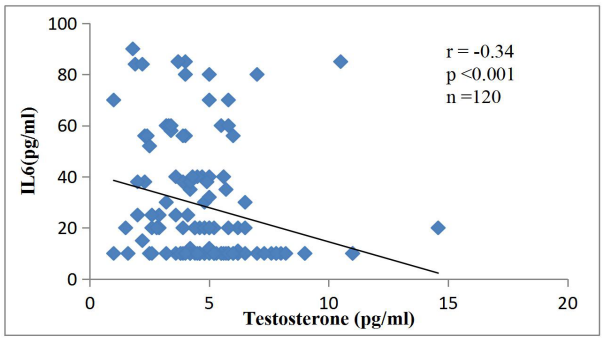

Figure 2A. Correlation between serum testosterone and serum IL-6 level in study subjects

Notes:
r = spearman Correlation coefficient
n = total numbers of subjects
Statistical significant difference was set as p<0.05

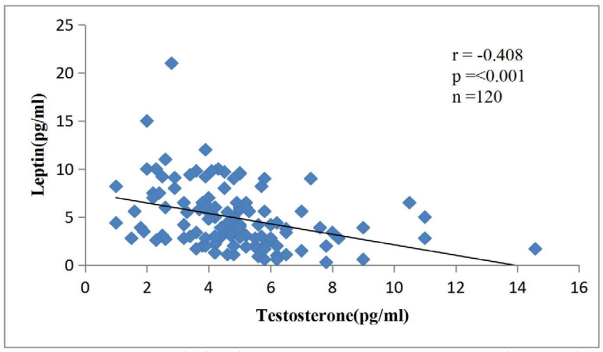

Figure 2B. Correlation between serum testosterone and serum leptin level in study subjects

Notes:
r = spearman Correlation coefficient
n = total numbers of subjects
Statistical significant difference was set as p<0.05

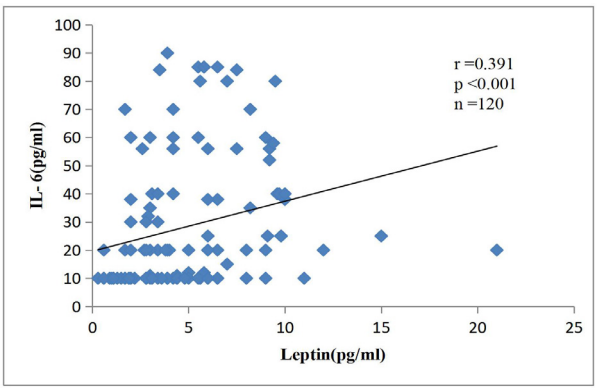

Figure 2C. Correlation between serum leptin and serum IL-6 level in study subjects

Notes:
r = spearman Correlation coefficient
n = total numbers of subjects
Statistical significant difference was set as p<0.05

4. Discussion

Obesity-associated insulin resistance is a major risk factor for T2DM and cardiovascular disease. Thus, a better understanding of the etiology of insulin resistance will be required to combat the epidemics of T2DM and cardiovascular disease. Many studies had shown that there is a significant strong epidemiological association between obesity and the development of insulin resistance [22-24] and even obese patients without diabetes have insulin resistance [5]. In present study, median (IQR) HOMA-IR of obese group was significantly higher than that of non-obese group (3.58(2.37) vs 2.18(1.55), p <0.001). Moreover, 75% of obese subjects were insulin resistance (HOMA-IR > 2.6) in present study. These findings agree with the reports of previous studies [5,23,24].

Previous studies revealed that pro-inflammatory cytokines and hormones released by adipose tissue and other factors have been proposed for the mechanisms by which obesity induced development of insulin resistance [2,6,10]. Ouchi et al [2] had reported that proinflammatory cytokines are over expressed in obesity. In our study, median (IQR) serum IL-6 level of obese group was significantly higher than that of non-obese group (38(37.5) vs 10(8) pg/ml, p <0.001). Possible mechanism of increased IL-6 level might be due to hyperplasia and hypertrophy of adipocytes in obese individual. Due to progressive enlargement of adipocyte, blood supply to adipocytes may be reduced and adipocytes are hypoxic which in turn lead to necrosis and macrophage infiltration into adipose tissue that cause overproduction of pro-inflammatory mediators [25,26]. The studies of Kern et al [6] and Senn et al [9] had been discovered that IL-6 contributes to insulin resistance in both humans and animals. IL-6 cause inhibition of action of insulin in primary hepatocytes, insulin-induced Akt activation and glycogen synthesis, reduction of glucose transporter-4 ($GLUT_4$) and insulin receptor substrate-1 expression, and suppression of insulin-induced lipogenesis [9]. Their findings supported our study since 1 pg/ml increased in serum IL-6 level was associated with 0.031units increased in HOMA-IR index on observed value of present study. It indicated that occurrence of insulin resistance was increased with high IL6 level. In present study, a significant weak positive correlation was found between HOMA-IR and serum IL-6 level in this study population (r=0.237, p=0.009, n=120). This finding was similar to previous studies [6,7,27].

The present study showed that median (IQR) serum leptin level of obese subjects (6(5.6) pg/ml) was significantly higher than that of non-obese subjects (3(2.48) pg/ml) (p < 0.001). The findings of present study agree with the studies of Stelzer et al [3], Al Maskari and Alnaqdy [4]

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and Osegbe et al [14]. Elevated serum leptin level in obesity is due to positive correlation between serum leptin and BMI, and more fat mass and more leptin synthesis in adipocytes of obesity [28]. In addition, serum leptin level is significantly and weak positively correlated with HOMA-IR in study population of present study (r=0.306, p= 0.001, n=120). This finding was similar to previous studies [12-14]. When adipocytes are exposed to glucose, insulin stimulates production of leptin to reduce food intake and increase energy expenditure whereas leptin decreases the secretion of insulin via a negative feedback and enhances tissue sensitivity to insulin (adipoinsular axis) [29]. In high serum leptin levels probably reflecting leptin resistance, deregulation of the adipocyte-insulin axis results in hyperinsulinemia associated with diabetes [30]. In present study, there was also a significant linear relationship between serum leptin level and HOMA-IR (B=0.229, p=0.018). Our study presented that serum leptin level is a significant predicting factor for insulin resistance.

Moreover, there was a significantly decreased in mean serum testosterone level of obese subjects when compared with non-obese subjects in present study (4.07±1.34 vs 5.55±2.43 pg/ml, p<0.001). Consistent with our study, Zumoff et al [15], Khaw and Barrett-Connor [16] and Gapstur et al [17] had reported that serum testosterone level is inversely correlated with body fat in men. Evidence from androgen receptor knockout mouse models demonstrates that deficiency of androgen action decreases lipolysis and is mainly responsible for the induction of obesity [31]. Additionally evidence is also accumulating that the reduced level of serum testosterone is an independent risk factor for diabetes and metabolic syndrome in men [18]. Holman et al [32] demonstrated that castration in male rats leads to the rapid development of insulin resistance, which is corrected by physiological testosterone replacement. The present study also showed that serum testosterone was significantly and weak negatively correlated to the HOMA-IR (r = -0.209; P =0.02, n=120) and negative linear relationship with HOMA-IR (B = -0.519, p<0.05). These findings agreed with previous studies [18,33].

Moreover, leptin and IL-6 had been found to have negative interaction with testosterone in in-vivo and in-vitro studies [19,20,34]. Both leptin and IL6 inhibit the stimulatory action of gonadotrophins on the Leydig cells of the testis to decrease testosterone production [20,35]. Administration of testosterone to men also suppressed serum leptin level [36] and IL-6 level [37]. Besides, leptin have closely related with inflammatory cytokines such as IL-6. Some studies reported that leptin may up-regulate IL-6 production via the activation of different intracellular signalling pathways [21] and another studies also reported that human IL6 enhanced central leptin action in mice [38]. The present study established significant negative correlation between testosterone level and IL-6 level (r= -0.34, p<0.001, n=120) and between testosterone level and leptin level (r=-0.408, p<0.001, n=120). Likewise, there was significant positive correlation between leptin and IL-6 levels in our study (r=0.391, p<0.001, n=120). These above-mentioned findings agreed with previous studies [3,34,39-41]. However, conclusions cannot be drawn about causality given the cross-sectional nature of the data.

5. Conclusion

Lower serum testosterone level, higher IL-6 level and leptin level are found in the obese group. Furthermore, HOMA-IR was weak negatively correlated with testosterone level and, also weak positively correlated with IL-6 as well as leptin. Therefore, obese men are more likely to have low testosterone, high inflammatory markers leptin and IL-6 which were associated with decreased insulin sensitivity suggest the need for an early metabolic assessment. This knowledge is fostering exploration of the molecular and genetic basis of the disease and new approaches to its treatment and prevention.

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