Original Article

Relationship between Respiratory Function and Serum Interleukin-6 Level in Nonobese and Obese Male Adult Subjects

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Abstract

Background and Aim: Proinflammatory cytokines may be the crucial factor in link between respiratory function decline and obesity. The aim of the present study is to investigate the relationship between respiratory function and serum interleukin-6 (IL-6) level in nonobese and obese male adult subjects. **Methods:** A community-based cross-sectional comparative study was carried out in 30 nonobese (body mass index [BMI] = 22.99 ± 1.08 Kg/m^2; waist circumference [WC] = 75.27 ± 4.08 cm), 34 generally obese (BMI = 30.88 ± 0.87 Kg/m^2; WC = 84.03 ± 3.02 cm), and 37 centrally obese subjects (BMI = 31.59 ± 2.11 Kg/m^2; WC = 96.08 ± 3.35 cm). Spirobank II spirometer was used to measure respiratory function (forced expiratory volume in 1 s [FEV_1], forced vital capacity [FVC], FEV_1/FVC, peak expiratory flow rate, and average forced expiratory flow between 25% and 75% of FVC). Serum IL-6 level was measured by enzyme-linked immunosorbent assay. For comparative studies, ANOVA test was used for normally distributed data and Kruskal–Wallis test was used for screwed data. Pearson's correlation and Spearman's rho test were used for correlation studies. **Results:** The percentage of predicted value of all respiratory function parameters of generally obese group as well as centrally obese group was significantly lower than that of nonobese group ($P < 0.05$). Median and interquartile range of serum IL-6 level of nonobese group, generally obese group, and centrally obese group were 10 (10–11) pg/mL, 32 (17.5–65) pg/mL, and 52 (25–65) pg/mL, respectively. There were significant differences between the groups ($P < 0.001$). There was a significant positive correlation between serum IL-6 levels and BMI ($r = 0.519$, $n = 101$, $P < 0.001$) as well as WC ($r = 0.547$, $n = 101$, $P < 0.001$). All respiratory function parameters were significantly and negatively correlated with anthropometric measurements (BMI and WC) as well as serum IL-6 level. Respiratory functions were more significantly and strongly correlated with anthropometric parameters than serum IL-6. **Conclusion:** It was concluded that reduced respiratory function in obesity might be due to mechanical effect of obesity and systemic low-grade inflammatory effect of obesity is partly contributed.

Keywords: Body mass index, Interleukin-6, respiratory function, waist circumference

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Introduction

The prevalence of obesity has increased dramatically in the recent decades. Previously, it was thought that obesity is a problem of developed countries; nowadays, it becomes pandemic. In Myanmar as a developing country, the prevalence of obesity increased from 15% to approximately 17.6% in adult population between 2010 and 2014.[1] The hazards of obesity include dyslipidemia, diabetes mellitus, hypertension, and cardiovascular accidents.[2] Many evidence has been reported that obesity is associated with respiratory dysfunction such as chronic obstructive pulmonary disease (COPD) and asthma.[3-5]

Many studies have reported an inverse relation between respiratory function and anthropometric parameters such as body mass index (BMI), waist circumference (WC), percentage of fat mass, and skinfold thickness.[6-10] Relation between obesity and respiratory function observed in most of previous studies was simply explained by BMI as the measure of overall obesity, but it cannot indicate the fat distribution.

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A major limitation of these measures is that they do not distinguish between fat mass and muscle (lean) mass, which have opposite effect on respiratory function. Increasing fat mass impairs respiratory function and muscle (lean) mass improves respiratory function.[11,12] Moreover, Asians have increased tendency to abdominal adiposity and gender difference in fat distribution, "apple vs pear shaped", may also have differential effects on pulmonary functions.[13-16] Some previous studies used the subjects in both sexes and had small sample size. It has been reported that abdominal or central adiposity is a better indicator of visceral fat (the metabolically active fat depot) which has been implicated in various metabolic syndromes.[17,18]

Although many studies have reported that obesity is associated with reduced respiratory function, the underlying mechanisms have not been clearly understood. Apart from mechanical effect of obesity on respiratory function, systemic inflammation may also be a link in this association because obesity itself is a chronic low-grade systemic inflammatory disease.[5,19] There is many evidence reporting the overexpression of proinflammatory cytokines in obesity.[4,8,20,21] Adipose tissue mainly secretes the proinflammatory mediators such as interleukin-6 (IL-6), tumor necrosis factor-α, and leptin.[22,23] Among them, IL-6 is a keystone proinflammatory mediator which is associated with respiratory function impairment.[24]

Therefore, the present study measured and compared the respiratory function and serum IL-6 level in nonobese and obese male adult subjects. Moreover, to explore the effect of systemic inflammation on respiratory function in obesity, the present study investigated the relationship of respiratory function and serum IL-6 level in nonobese and obese male adult subjects.

Materials and Methods

Subject selection

A community-based cross-sectional comparative study was carried out in male adult subjects of age 18–45 years who lived in Magway Township using multistage sampling method. At the first stage, five quarters among total 15 quarters in Magway Township were selected by simple random sampling method. At the second stage, all the male subjects aged between 18 and 45 years residing in the selected five quarters were assessed for their eligibility to the study by inclusion and exclusion criteria. Subjects were selected from the apparently healthy population and exclusion criteria were acute or chronic infections, being under any medication such as drugs affecting respiratory function and antioxidants, current smoker, current alcoholic, and presence of known respiratory diseases, chest wall or spinal deformity, and any intra-abdominal abnormalities. The detailed procedure was explained and written informed consent was taken. To exclude, the diseases, history-taking and physical examination were carried out according to pro forma. The weight measurement was done using a weighing machine. Standing height was measured using a measuring tape. BMI was calculated. WC was measured using a measuring tape. Then, all the eligible subjects from each quarter were categorized into three groups; nonobese group, generally obese group, and centrally obese group according to their anthropometric data. This resulted in five nonobese groups, five generally obese groups, and five centrally obese groups. At the third stage, eight subjects from each five nonobese groups, five generally obese groups, and five centrally obese groups were recruited to this study by simple random sampling method. Therefore, a total of 120 subjects (40 subjects for each group of nonobese, generally obese, and centrally obese male adult subjects) were recruited to participate in this study. This study was approved by the Ethics and Research Committee of the University of Medicine, Magway.

Data collection method

Subjects were instructed to fast overnight (both solid and liquid) from 10:00 pm to 8:00 am. On the day of experiment, subjects were instructed for arriving at the Ward Administrator Office at 8:00 am. On arrival, 5 min was allowed to take rest. After 5 min rest, forced vital capacity (FVC) maneuver was done using Spirobank II spirometer. Then, 3 mL of venous blood sample was collected from antecubital vein under aseptic condition using a disposable syringe and needle for each subject. The blood was kept in plain tube and allowed to clot for 30 min at room temperature before centrifugation. The blood sample was taken to the Common Research Laboratory, University of Medicine, Magway, in a cold box. Then, the blood was centrifuged for 15 min at 3000 rpm. Serum was separated and kept in a separate screw-tight bottle which was stored at −20°C until analysis in the Common Research Laboratory, University of Medicine, Magway.

Respiratory function test

Respiratory function parameters were measured using Spirobank II spirometer (910575, Medical International Research, Italy). To make a correct spirometry test, the subject was instructed to fit the nose clip to ensure no air escape, to insert the mouthpiece beyond the teeth, to make testing in standing position, and to lean forward during expiration. The subject was instructed to start the test by breathing quietly for a few moments. When ready to start, the subject inspired slowly as much air as possible and then made a complete expiration as fast as possible. The subject was instructed to continue expiration for 6 s. The test would be repeated several times by repeating the cycle without taking the mouthpiece out of the mouth. The Spirobank II spirometer recognized the best test among several trials and showed the results of the best test on the screen.

Measurement of serum interleukin-6 level

Serum IL-6 levels were determined by enzyme-linked immunosorbent assay (IL-6 immunoassay, DRG Instruments, Germany).

Statistical analysis of data

Data entry and analysis were done by SPSS software version 20 (IBM, Armonk, New York, United States of

America). Respiratory function test values were described as mean ± standard deviation. Respiratory function test values were compared using ANOVA test and *post hoc* analysis. Serum IL-6 levels were expressed as median and interquartile range and compared using Kruskal–Wallis test. Pearson's correlation was used to correlate between respiratory function and anthropometric data. Correlation between serum IL-6 level and respiratory function test values as well as anthropometric data was done by nonparametric (Spearman's rho) test. Significant level was set at $P \leq 0.05$.

Results

Table 1 shows the general characteristics of the subjects participated in this study. The percentage of predicted value of respiratory function parameters of nonobese group was significantly higher than that of generally and centrally obese group [Table 2]. Median and interquartile range of serum IL-6 level were significantly different between nonobese group (10 [10–11] pg/mL), generally obese group (32 [17.5–65] pg/mL), and centrally obese group (52 [25–65] pg/mL) as shown in Figure 1. The significant positive correlations between serum IL-6 level and BMI as well as WC are shown in Figure 2a and b. Respiratory function was significantly and negatively correlated with anthropometric parameters [Table 3] and serum IL-6 level [Table 4].

Table 1: Weight, height, body mass index and waist circumference parameters of the subjects expressed in mean±standard deviation

Variable	Nonobese group (*n*=30)	Generally obese group (*n*=34)	Centrally obese group (*n*=37)
Weight (kg)	60.33±4.15	83.38±5.15	86.35±8.93
Height (m)	1.62±0.51	1.64±0.06	1.65±0.06
BMI (kg/m^2)	22.99±1.08	30.88±0.87	31.59±2.11
WC (cm)	75.27±4.08	84.03±3.02	96.08±3.35

BMI: Body mass index, WC: Waist circumference

Table 2: Comparison of respiratory function parameters (forced expiratory volume in first second, forced vital capacity, ratio of forced expiratory volume in first second and forced vital capacity, peak expiratory flow, average forced expiratory flow between 25% and 75% of forced vital capacity) between groups expressed in mean±standard deviation

Variable	Non-obese group (*n*=30)	Generally obese group (*n*=34)	Centrally obese group (*n*=37)
Respiratory function parameters (Pred %)			
FEV_1	76.57±3.70	74.21±5.43[a]	72.56±5.15[b]
FVC	70.60±3.43	68.38±4.83[a]	65.28±5.85[b*,c]
FEV_1/FVC	115.13±4.44	111.68±2.32	114.31±4.21[b*,c]
PEF	81.40±3.83	76.76±5.55[a]	74.31±11.02[b*]
$FEF_{25\%-75\%}$	93.80±11.04	92.26±10.26	89.09±8.67[b*]

Statistical analysis was done by ANOVA test and *post-hoc* analysis. [a]Indicates significant difference at $P<0.05$ between nonobese group and generally obese group. [b]Indicates significant difference at $P<0.05$; [b*]Indicates significant difference at $P<0.01$ between nonobese group and centrally obese group. [c]Indicates significant difference at $P<0.05$ between generally obese group and centrally obese group. $P<0.05$ was considered significant. FEV_1: Forced expiratory volume in first second, FVC: Forced vital capacity, FEV_1/FVC: Ratio of forced expiratory volume in first second and forced vital capacity, PEF: Peak expiratory flow, $FEF_{25\%-75\%}$: Average forced expiratory flow between 25% and 75% of FVC, Pred%: Percentage of predicted value, SD: Standard deviation

Discussion

A total of 120 subjects (40 subjects for each group of nonobese, generally obese, and centrally obese male adult subjects) were recruited to participate in this study by multistage sampling method. Among them, five nonobese subjects, four generally obese subjects, and two centrally obese subjects who did not follow the instructions were excluded from the study. One nonobese subject with hypotension was also excluded from this study. Four nonobese subjects and two generally obese subjects were dropped out for error in spirometry testing. For matching the BMI between generally obese and centrally obese subjects, one centrally obese subject was excluded from the study because of higher BMI. Thus, 101 subjects (30 nonobese, 34 generally obese, and 37 centrally obese subjects) remained in this study. Mean age and weight were compared among three groups. Mean body weight and BMI were not significantly different between generally obese and centrally obese groups.

When comparisons in the respiratory function parameters were made between the three groups of participants, observed values were converted to the percentage of the predicted values so as to avoid the confounding effects of age, height, and ethnic group. The reference equations specific to Myanmar population were not available. However, the winspiroPRO 2.5 software

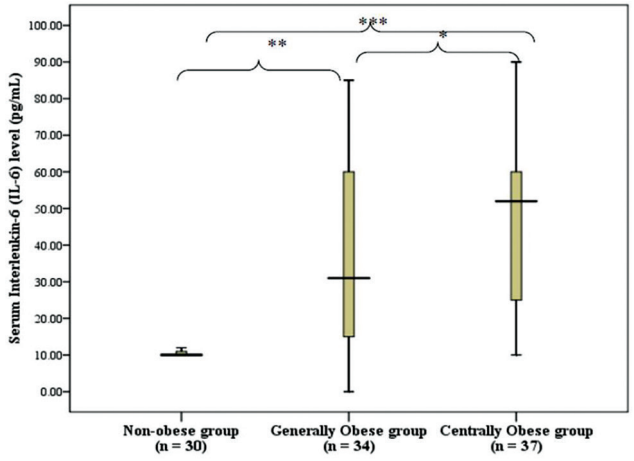

Figure 1: Comparison of serum interleukin-6 level in nonobese group (n = 30), generally obese group (n = 34), and centrally obese group (n = 37). Solid line represents medium value of serum interleukin-6 level. *** indicates significant difference at $P < 0.001$. ** indicates significant difference at $P < 0.01$. * indicates significant difference at $P < 0.05$. Comparison was done by Kruskal–Wallis test

(Medical International Research, Roma, Italy) provided with the spirometer presents a number of sets of reference equations with ethnic correction factors. Among them, the present study used the ECSC/ERS equations as a reference to the ethnic group being set up at Oriental.[25]

Table 3: Correlation between body mass index and waist circumference with percentage of predicted value of respiratory function parameters

Parameters	*r*	*P*
Correlation with BMI		
FEV_1	−0.27	<0.05
FVC	−0.32	<0.001
FEV_1/FVC	−0.48	<0.001
PEF	−0.27	<0.05
$FEF_{25\%-75\%}$	−0.26	<0.05
Correlation with WC		
FEV_1	−0.29	<0.05
FVC	−0.41	<0.001
FEV_1/FVC	−0.43	<0.001
PEF	−0.32	<0.05
$FEF_{25\%-75\%}$	−0.24	<0.05

BMI: Body mass index, WC: Waist circumference, FEV_1: Forced expiratory volume in first second, FVC: Forced vital capacity, FEV_1/FVC: Ratio of forced expiratory volume in first second and forced vital capacity, PEF: Peak expiratory flow, $FEF_{25\%-75\%}$: Average forced expiratory flow between 25% and 75% of FVC, *r*: Pearson's correlation coefficient

Table 4: Correlation between serum interleukin-6 level and percentage of predicted value of respiratory function parameters

Parameters	ρ	*P*
Correlation with serum IL-6 levels		
FEV_1	−0.232	<0.05
FVC	−0.309	<0.05
FEV_1/FVC	−0.266	<0.05
PEF	−0.234	<0.05
$FEF_{25\%-75\%}$	−0.222	<0.05

ρ: Spearman's rho correlation coefficient. IL-6: Interleukin-6, FEV_1: Forced expiratory volume in first second, FVC: Forced vital capacity, FEV_1/FVC: Ratio of forced expiratory volume in first second and forced vital capacity, PEF: Peak expiratory flow, $FEF_{25\%-75\%}$: Average forced expiratory flow between 25% and 75% of FVC

In the present study, although there was a decrease in respiratory function of obese subjects compared to nonobese subjects, the percentage of predicted values of respiratory function parameters of nonobese and obese subjects were normal according to Global Initiative for Chronic Obstructive Lung Disease (2017) classification. To determine the effect of abdominal obesity on respiratory function, subject selection was done on the same BMI group for generally obese and centrally obese groups. It was noted that FVC was significantly decreased from generally obese (n = 34) to centrally obese group (n = 37) ($P < 0.05$) while forced expiratory volume in 1 s (FEV_1) was not different between these two groups. Consequently, FEV_1/FVC of centrally obese group was significantly higher than that of generally obese group ($P < 0.05$).

The result of the present study is in accordance with previous study done by Sugerman *et al*., which reported that abdominal or central obesity may restrict the descent of the diaphragm and increase thoracic pressure, leading to limited lung expansion, compared to general obesity which may compress mainly on the chest wall.[26] Similarly, Durgesh *et al*. also reported that increased abdominal fat mass may impede the descent of the diaphragm and increase thoracic pressure.[27] Furthermore, abdominal or central obesity is likely to reduce expiratory reserve volume via compressing the lungs and diaphragm.[28,29]

Average forced expiratory flow between 25% and 75% of FVC ($FEF_{25\%-75\%}$), the predictor of small airway function, was significantly decreased in centrally obese group compared with nonobese group, whereas there was no significant difference between generally obese group and nonobese group. Reduction in percentage of predicted value in $FEF_{25\%-75\%}$ indicates small airway narrowing.

In the present study, there was a significant negative correlation between BMI and respiratory functions as shown in Table 3. These findings agree the results of previous studies.[30-33] It was

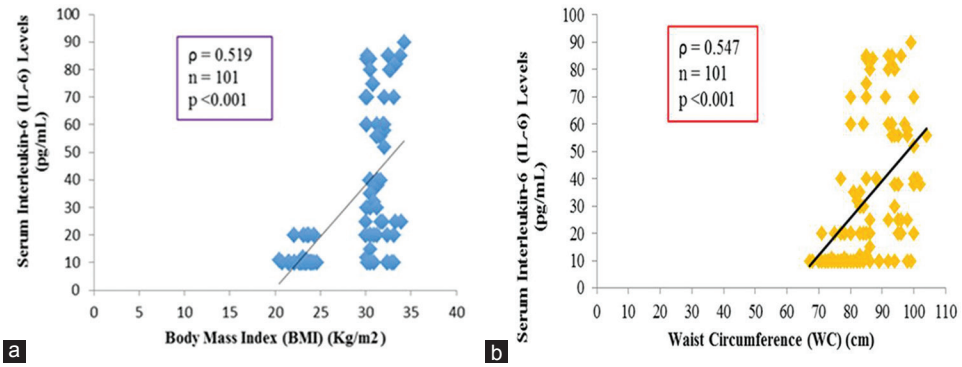

Figure 2: (a) Correlation between serum IL-6 level and BMI. ρ: Spearman's rho correlation coefficient, *n*: Total number of subjects, IL-6: Interleukin-6, BMI: Body mass index. NB: Correlation was done using nonparametric test (Spearman's rho test). (b): Correlation between serum IL-6 level and WC. ρ: Spearman's rho correlation coefficient, *n*: Total number of subjects, IL-6: Interleukin-6, WC: Waist circumference. NB: Correlation was done using non-parametric test (Spearman's rho test)

also shown that WC was significantly and negatively correlated with respiratory functions and it was in line with previous studies.[15,30-33] Among the respiratory function parameters, FEV_1/FVC had strongest correlation with BMI ($r = -0.48$, $n = 101$, $P < 0.001$) as well as with WC ($r = -0.43$, $n = 101$, $P < 0.001$). It was also noted that 1 cm increase in WC was associated with a 10 mL reduction in FVC and 4 mL reduction in FEV_1 on observed value of the present study.

Shaheen *et al*. reported that 1 cm increase in WC was associated with 4.4 mL reduction in FVC and 4.3 mL reduction in FEV_1 in nonobese and obese female subjects.[31] Chen *et al*. also reported similar results but with greater value as 1 cm increase in WC was associated with 13 mL reduction in FVC and 11 mL reduction in FEV_1 in normal, overweight, and obese subjects in both sexes.[15] In COPD patients, average 1 cm increase in WC was associated with 20 mL reduction in FVC and 13 mL reduction in FEV_1.[34] From all these studies including the present study taking together, it was noteworthy that increased WC exerted adverse effect on respiratory function.

The present study also showed that serum IL-6 level was significantly higher in the centrally obese group than generally obese group ($P < 0.05$) as well as nonobese group ($P < 0.001$). It was also significantly higher in generally obese group than nonobese group ($P < 0.01$) [Figure 1]. The circulating proinflammatory cytokine IL-6 was three times increase in generally obese group and five times increase in centrally obese group than that of nonobese group in the present study. Systemic low-grade inflammation is defined as two to four times elevation in circulating levels of proinflammatory cytokines.[35] Accordingly, systemic low-grade inflammation presents in generally obese group and centrally obese group and is more marked in centrally obese group compared with generally obese group.

According to the study done by Kim *et al*., enlarged WC in centrally obese subject results from deep visceral adipose tissue (VAT) mass which pushes the abdominal muscle outward. It can be assumed that centrally obese subjects in the present study have increase mass of VAT.[36] There is some evidence of *in vitro* studies that reported that VAT secreted two to three times higher IL-6 level than subcutaneous adipose tissue (SAT). In these studies, VAT and SAT are extracted from cell cultures of adipocytes originating from obese individuals.[37,38] In animal models of obesity, surgical removal of visceral fat led to a decrease in IL-6 level to near control level.[36]

Accordingly, the present study also showed that WC ($\rho = 0.547$, $n = 101$, $P < 0.001$) had more powerful relationship with serum IL-6 level than BMI ($\rho = 0.519$, $n = 101$, $P < 0.001$). This result is similar to that observed by previous studies.[6-8] All these findings taking together, it could be concluded that higher circulating concentration of IL-6 in centrally obese subjects might be due to increased amount of VAT mass and central obesity partly contributes to the formation of low-grade chronic inflammatory state.

In the present study, there were significant negative correlations between percentage of predicted value of respiratory functions and serum IL-6 level in the study population ($n = 101$) as shown in Table 4. Similarly, Al-Jiffri *et al*. conducted a study on 40 obese children and found out the significant negative relationship between serum IL-6 and respiratory function (FEV_1 and FVC).[39] Another study done by Lessard *et al*. reported a significant negative correlation between serum IL-6 and respiratory function (FEV_1 and FVC) in 282 middle-aged obese men.[5] Zedan *et al*. also found that there is a significant negative correlation between FEV_1/FVC ratio and serum IL-6 levels in 80 obese Egyptian adolescents.[40] IL-6 increases the hepatic production of C-reactive protein, which causes lung parenchymal damage and pulmonary fibrosis, leading to structural changes.[41,42] This structural change narrows the airway and limits the air flow. Peak expiratory flow (PEF) and $FEF_{25\%–75\%}$ are useful way for the predictor of small airway function and the present study demonstrating the significant negative correlation between serum IL-6 and PEF ($\rho = -0.234$, $n = 101$, $P < 0.05$) as well as $FEF_{25\%–75\%}$ ($\rho = -0.222$, $n = 101$, $P < 0.05$). All these findings are accountable for possible role of IL-6 in respiratory function decline.

Conclusion

In the present study, there was a significant positive correlation between serum IL-6 level and BMI ($\rho = 0.519$, $n = 101$, $P < 0.001$) as well as WC ($\rho = 0.547$, $n = 101$, $P < 0.001$). Moreover, there was also a significant negative correlation between serum IL-6 level and respiratory function. Therefore, it can be concluded that obesity is a disease associated with systemic inflammation and an increase in inflammatory mediators which may result in airway hyperactivity, leading to respiratory function decline.

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Conflicts of interest

There are no conflicts of interest.

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