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Research Article

Relationship of Serum Interleukin-6, Malondialdehyde and Cholesteryl Ester Transfer Protein in Patients with Metabolic Syndrome

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Abstract

Metabolic Syndrome (MetS) is a major health burden throughout the world because of its high prevalence and risk of atherosclerosis and cardiovascular disease (CVD). The present study was aimed to find out the relationship of serum Cholesteryl Ester Transfer Protein (CETP), with interleukin-6 (IL-6) and malondialdehyde (MDA) as the contributory factors to dyslipidemia in patients with Metabolic Syndrome (MetS). The cross-sectional comparative study was conducted at the Outpatient Department (OPD) of medical units in Mandalay General Hospital. The clinically diagnosed cases of metabolic syndrome (n = 40) who attended to OPD of medical unit in Mandalay General Hospital were categorized as patients with metabolic syndrome according to National Cholesterol Education Program (Adult Treatment Panel [ATP] III) (2001). An apparently healthy volunteers (n = 40) who were staffs of University of Medicine Mandalay participated as controls in this study. Serum IL-6 and serum CETP levels were determined by sandwich enzyme linked immunosorbent assay (ELISA). Serum MDA level was determined by colorimetric method based on a thiobarbituric acid reacting substances (TBARS) assay.

The mean level of serum IL-6 (30.25 ± 21.58 pg/mL) and MDA levels (10.99 ± 9.54 μmol/L) were significantly higher in MetS patients than that of controls, $p < 0.0001$. The serum IL-6 level was positively associated with MDA level in MetS patients ($r = 0.86$), $p < 0.0001$ and in controls ($r = 0.44$) $p < 0.0001$, respectively.

The mean serum CETP level was significantly higher in MetS patients (4.86 ± 0.83 μg/mL) compared to controls (1.47 ± 1.13 μg/mL), $p < 0.0001$. There was a strong positive correlation between IL-6 and CETP level in both controls ($r = 0.73$) $p < 0.0001$ and MetS patients ($r = 0.62$) ($p < 0.0001$).

The present study indicated that serum IL-6, MDA and CETP levels were found to be higher in patients with MetS than in controls. The inflammatory cytokine especially IL-6 and oxidative stress marker, MDA was positively associated with serum CETP considered as a marker for dyslipidemia in MetS as the high CETP level may reflect reduced HDL-C and reduced LDL particle.

In conclusion, present data indicated that the release of inflammatory cytokine especially IL-6 and oxidative stress marker, MDA were found to be associated with serum CETP contributing to dyslipidemia as one of the components of MetS. However, these markers could not be considered as contributory factor to metabolic syndrome (MetS).

Keywords: *Cardiovascular Disease (CVD); Cholesteryl Ester Transfer Protein (CETP); Interleukin-6 (IL-6); Malondialdehyde (MDA); Outpatient Department (OPD); Adult Treatment Panel (ATP); Enzyme Linked Immunosorbent Assay (ELISA); Thiobarbituric Acid Reacting Substances (TBARS); Metabolic Syndrome (MetS)*

Introduction

The metabolic syndrome is one of the major challenges in public health in the world due to urbanization, obesity and sedentary lifestyle. According to The International Diabetes Federation (IDF) report, the metabolic syndrome (MetS) has been encountered in one-quarter of the world's adult population.

In US, the prevalence of the metabolic syndrome in the adult with age of 20 years and above was ranging from 34% to 40% [1].

In 2004, the prevalence of the metabolic syndrome was 10.5% in the healthy adult population in Yangon [2]. It accounts for five-fold increase in the risk of type 2 diabetes mellitus and two-folds the risk of cardiovascular disease within five to ten years [3]. In 2002, Lakka and colleagues reported that patients with the metabolic syndrome had a significantly increased mortality from coronary arterial diseases. Moreover, the risk for coronary heart disease and stroke was increased three-folds in patients with the metabolic syndrome and cardiovascular mortality was increased six-folds [4].

Various researchers reported that oxidative stress was found to be associated with MetS. Oxidative stress plays a pivotal role in the pathogenesis of diabetes mellitus, hypertension and atherosclerosis [5]. It has been reported that oxidative stress was found to be associated with MetS as the higher MDA level was observed in subjects with metabolic syndrome [6].

Obesity was found to be associated with oxidative stress according to previous findings. Furukawa., *et al*. (2004) proved that there was relationship between fat accumulation and increased oxidative stress in human and mice. The interleukin-6 and other adipokines were found to be increased in oxidative stress [5]. Inflammatory markers such as fibrinogen, prothrombin activation inhibitor-1, cytokine such as tumor necrotic factor α, transforming growth factor β, IL-6, IL-1 and IL-18 were found to be increased in patients with MetS [7]. IL-6 production in abdominal adipose tissue was three times higher than that in subcutaneous adipose tissue, regarded as potentially contributory factor to Insulin resistance [8].

The metabolic syndrome might be prothrombotic and proinflammatory state [9]. IL-6 could be considered as one of the components of metabolic syndrome such as hypertension, insulin resistance, obesity and dyslipidaemia [10].

One possible mechanism for elevated inflammatory markers is obesity as high in adipose tissue considered as major source of inflammatory cytokines, interleukin-6 (IL-6), interleukin-1 (IL-1), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-12 (IL-12) and tumor necrotic factor α (TNF-α). The level of pro-inflammatory cytokine, IL-6 was increased in T2DM with obesity and hypertension [11].

Sandhofer and colleagues (2006) reported that CETP level was increased in men with the metabolic syndrome but not in female counterpart [12]. It was indicated that an increase CETP level might reflect the reduced HDL-cholesterol and reduced LDL particle diameter contributed to dyslipidemia as one of the components of the metabolic syndrome. CETP, as a key component in reverse cholesterol transport, mediates the transfer of cholesteryl ester from cholesterol-rich lipoproteins to triglyceride rich lipoproteins in exchange for TGs [13].

Angelica, Gabriel and Claudia (2013) demonstrated the relationship of inflammation and obesity as a result of deregulated signal transduction of insulin that induce the release of inflammatory substances, leading to the dyslipidaemia in metabolic syndrome [14].

There was no exact data about the relationship of inflammatory cytokine and oxidative stress marker (MDA) with CETP level in the metabolic syndrome. This study will explore the mechanism that underly development of dyslipidemia, one of the components of MetS by determining serum IL-6, MDA and CETP level in MetS.

Materials and Methods

Subjects

The cross-sectional comparative study was conducted at the Outpatient Department (OPD) of medical units in Mandalay General Hospital. The fourty MetS patients with age range of 40 - 60 years and fourty healthy volunteers who were staffs of University of Medicine Mandalay with age and sex matched with MetS patients participated as controls in this study. The clinically diagnosed cases of metabolic syndrome who attended to OPD of medical unit in Mandalay General Hospital were categorized as patients with metabolic syndrome.

According to National Cholesterol Education Program (Adult Treatment Panel [ATP] III) (2001) [15], metabolic syndrome is diagnosed as those who have 3 out of 5 criteria, having Waist circumference – men 90 cm, women 80 cm (for South Asia) [16] and/or Blood pressure: 130 / 85 mmHg and/or Fasting blood glucose 110 mg/dl and/or Triglycerides ≥ 150 mg/dl and/or HDL cholesterol for Men < 40 mg/dl and for women < 50 mg/dl.

After taking informed consent, history taking, and physical examination were done in all subjects and data were recorded in proforma. Blood pressure and waist circumference and fasting blood glucose level were determined in all subjects.

Waist circumference was measured at midway between the lowest portion of the rib cage and iliac crest laterally; midway between the xiphoid process of the sternum and the umbilicus anteriorly; to the nearest centimeter (cm) according to ATP III (2001) [15]. Blood pressure is measured according to ESH/ESC, 2013 [17]. At least two BP measurements was taken in the sitting position, spaced 1–2 min apart, and additional measurements if the first two are quite different. The average BP was taken, and data were recorded in proforma.

The five milliliters of venous blood were taken after overnight fasting from all subjects under aseptic condition. Two milliliters of blood were collected with tube containing anti-coagulant Sodium fluoride for analysis of plasma glucose and another three milliliter of blood was collected with plain tube for analysis of serum CETP and IL-6 and MDA level. Serum was separated by centrifugation for 15 min at 3000 rpm. Then the aliquot of serum were placed into separate tubes and stored at -20ºC until analysis. The fasting blood glucose was determined by enzymatic photometric method (Glucose oxidase). The serum malondialdehyde (MDA) level was determined by colorimetric method by using lipid peroxidation (MDA) assay kit (Sigma Aldrich). Thiobarbituric acid (TBA) 99% pure was purchased from BDH (BDH, England); malondialdehyde tetrabutylammonium salt (MDA salt) 96% pure and methanol 99.8% pure were from Sigma-Aldrich. All other chemicals and reagents were of an analytical standard with high purity.

Serum IL-6 and serum CETP level were determined by ELISA by using Human IL-6 ELISA kits and Human CETP ELISA kits purchased from Abebio Company, China.

Biochemical methods

The serum malondialdehyde (MDA) level was determined by colorimetric methods based on the reaction of MDA with thiobarbituric acid (TBA) to generate with heating a colored product called thiobarbituric acid reactive substance (TBARS) [18].

In this reaction principle, lipid peroxides in serum reacts with thiobarbituric acid (TBA) and give a pink colored pigment. The maximum formation of reaction product is attained around pH 7.5. In the reaction, one molecule of MDA reacts with two molecules of TBA with the production of pink pigment having an absorption maximum at 532 - 535 nm.

Serum IL-6 and serum CETP level were determined by ELISA according to manufacturer's instruction.

This study was approved by the Academic Board of Study of Master of Medical Science (Biochemistry), University of Medicine, Mandalay, Myanmar.

Statistical analysis

Unpaired "t" test was used to analyze the comparison of biochemical parameters between MetS patients and controls. Coefficient of correlation (r) was calculated to assess the relationship between biochemical parameters in MetS patients and controls. *p* value < 0.05 was considered to be statistically significant.

Results

In the present study, the serum levels of IL-6, MDA and CETP were determined in controls and patients with MetS. There were 40 patients with MetS and 40 apparently healthy subjects as controls. The mean age of controls was 52.0 ± 4.0 year and MetS patients was 52.5 ± 4.14 years. Table 1 showed the general characteristics of study population.

General characteristics	Controls (n = 40)	Patients with MetS (n = 40)
Sex (male/female)	10/30	4/36
Age (yrs)	52 ± 4.0	52.5 ± 4.14
Waist Circumference (cm)	71.03 ± 4.75	112.93 ± 14.01
Systolic BP (mmHg)	107.75 ± 8.32	149.75 ± 8.32
Diastolic BP (mmHg)	69.25 ± 6.94	91.88 ± 3.87
FBS (mg/dL)	77.76 ± 7.92	120.24 ± 4.86

Table 1: *General characteristics of the study population.*

In present study, mean waist circumference of controls and MetS patients were 71.03 ± 4.75 cm 112.93 ± 14.01cm, respectively. The mean systolic and diastolic blood pressure of patients with MetS and controls were (SBP 149.73 ± 8.31 Vs 107.75 ± 8.32 mmHg and DBP 91.88 ± 3.87 Vs 69.25 ± 6.94 mmHg). The fasting blood sugar of controls and that of MetS patients were 77.76 ± 7.92 mg/dL and 120.24 ± 4.86 mg/dL, respectively. Comparisons of serum levels of IL-6, MDA and CETP in controls and patients with MetS was shown in the table 2.

Biochemical Parameters	Controls (n = 40)	Patients with MetS (n = 40)	p
IL-6 (pg/mL)	11.93 ± 6.76	30.25 ± 21.58	p < 0.0001
MDA (µmol/L)	2.33 ± 1.93	10.99 ± 9.54	p < 0.0001
CETP (µg/mL)	1.47 ± 1.13	4.86 ± 0.83	p < 0.0001

Table 2: *Comparisons of serum levels of IL-6, MDA and CETP in controls and patients with MetS.*

In this study, the mean serum IL-6 level of MetS patient was 30.25 ± 21.58 pg/mL and that of control was 11.93 ± 6.76 pg/mL. The difference was statistically significant, p < 0.0001. Serum MDA level of the patients with MetS (10.99 ± 9.54 µmol/L) was significantly higher than that of controls (2.33 ± 1.93 µmol/L), p < 0.0001. Serum CETP level of the MetS patients was 4.86 ± 0.83 µg/mL and that of controls was 1.47 ± 1.13 µg/mL. It was statistically significant, p < 0.0001.

There was significant positive correlation between serum IL-6 and MDA levels in both controls (r = 0.448) p < 0.0001 and in patients with MetS, (r = 0.86) (p < 0.0001), shown in figure 1a and 1b.

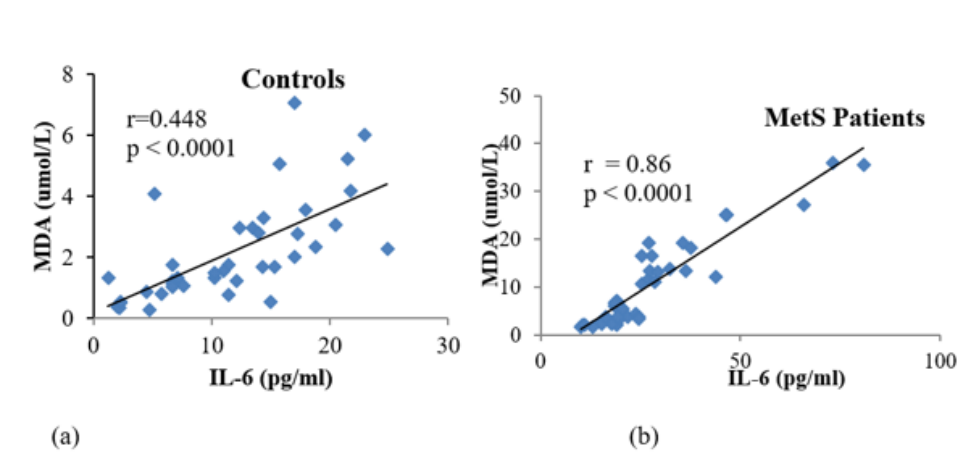

Figure 1: *Correlation between serum IL-6 (pg/ml) and MDA levels (µmol/L) in (a) Controls (b) MetS patients.*

The serum IL-6 level was positively associated with CETP level in both controls (r = 0.73,p < 0.0001) and MetS patients, r = 0.62, p < 0.0001 (Figure 2a and 2b).

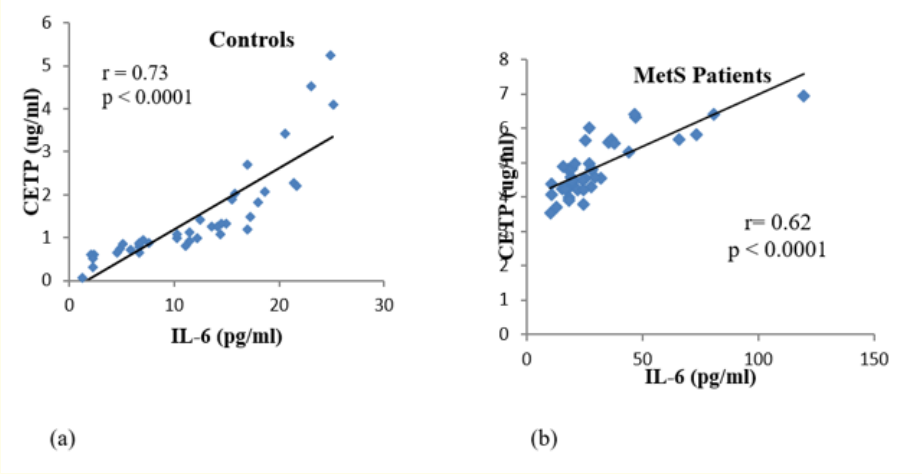

Figure 2: *Correlation between serum IL-6 and CETP levels in (a) controls (b) MetS patients.*

Discussion

In present study, serum IL-6, MDA and CETP levels were determined to assess the relationship of serum Cholesteryl Ester Transfer Protein (CETP) with interleukin-6 (IL-6) as a marker of low-grade inflammation and malondialdehyde (MDA) as marker of oxidative stress contributing to dyslipidemia in patients with MetS.

In present study, the mean serum IL-6 level of controls was 11.93 ± 6.76 pg/mL and that of patients with MetS was 30.25 ± 21.58 pg/mL. The IL-6 level of patients with MetS was significantly higher than that of controls, p < 0.0001. The mean serum MDA level of patients

with MetS (10.99 ± 9.353 µmol/L) was significantly higher than that of controls (2.33 ± 1.93 µmol/L), $p < 0.0001$. The mean serum CETP level was significantly higher in patients with MetS (4.86 ± 0.83 µg/mL) in comparison with controls (1.47 ± 1.13 µg/ml), $p < 0.0001$.

The mean serum IL-6 concentration of healthy subjects reported by Mohammadi., *et al*. 2017 [19] and Korita., *et al*. 2016 [20] were 4.6 ± 0.2 pg/mL and 6.65 ± 5.2 pg/mL, respectively. The serum IL-6 levels of healthy subjects in above studies were lower than that of the present study.

The correlation between IL-6 and TNF-α serum levels with MetS and its components have been studied in 125 healthy controls and 125 MetS patients [19]. According to finding of Mohammadi., *et al*. 2017, the serum IL-6 levels in MetS patients were 98.14 ± 17.94 (pg/mL), whereas in the healthy controls were 4.6 ± 0.2 (pg/mL). Serum IL-6 was significantly higher in the MetS patients than in the controls ($P < 0.001$). However, no correlation was observed between MetS components and IL-6 or TNF-α serum levels in above study [19].

Therefore, present data agreed with that of above studies. The wide range of the mean IL-6 level was observed among different studies. This might reflect the variation in methodology, genetic background, lifestyle, sex and age distribution of participants.

In 2016, Laishram., *et al*. studied the serum IL-6 concentration in healthy subjects and obese subjects with MetS [11]. The mean IL-6 level was significantly increased in obese subjects with MetS (14.34 ± 4.98 pg/mL) as compared to those of healthy subject (mean IL-6 level 7.41 ± 0.54 pg/mL), $p < 0.0001$. The above study pointed out that low-grade inflammation might be the key contributory factor related to obesity in development of metabolic syndrome.

The significant association between CRP levels and BMI, waist circumference was observed in the healthy control subjects, but there was weak association between obesity and TNF-αR2, IL-6, and endothelial markers were somewhat weaker [21].

IL-6 is produced from several different cells including adipocyte and macrophages found in the adipose tissue [22]. IL-6 production in abdominal adipose tissue is at least three times higher than that in subcutaneous adipose tissue, thereby potentially contributing to insulin resistance [8].

It has been indicated that the high number of adipose tissue macrophages, which are responsible for increase in plasma concentration of proinflammatory cytokines, especially IL-6 and TNF α expression [11]. These proinflammatory cytokines are capable of increasing insulin resistance directly in adipocyte, muscle and hepatic cells leading to augmentation of systemic insulin resistance.

In present study, the mean serum MDA concentration was 2.33 ± 1.93 µmol/L in controls and 10.99 ± 9.53 µmol/L in patients with MetS. The mean serum MDA concentration was significantly higher in patients with MetS than that of controls, $p < 0.0001$.

In Myanmar, MDA levels of healthy subjects with different age range have been studied by various researchers. It has been reported that the mean plasma MDA level of healthy subjects with age range of 25 - 35 years were 4.63 ± 0.82 µmol/L [23], those with age range of 30 - 55 years were 3.04 ± 0.51 µmol/L [24], those with age range of 65 - 75 years were 1.96 ± 0.66 µmol/L [25] and those with age range of 20 - 45 years were 2.44 ± 2.03 µmol/L [26]. The range of mean value in different age group lies between 1.96 - 4.63 µmol/L.

The serum MDA level has been studied as an oxidative stress marker in a variety of cases. The discrepancy of findings of the mean MDA level in healthy subjects reported by various researchers might be due to confounding factors for oxidative stress such as aging, smoking, alcohol drinking and intake of naturally occurring antioxidant nutrients of the individuals.

Gopal., *et al*. 2012 and Yesilbursa., *et al*. 2004 reported that the mean MDA level of healthy subjects were 1.58 1.6 µmol/L and 0.63 0.14 µmol/L, respectively [27,28]. The ages of subject in above studies were between 20 - 40 years and 40 - 48 years. The mean plasma MDA level of healthy subjects in the present study was within the range of the above studies but there was wide range of age distributions in previous studies.

In the study conducted by Kiran., *et al*. 2016, serum MDA levels was significantly higher in MetS patients (5.73 ± 0.98 µmol/L) than in healthy subjects (0.07 ± 0.01 µmol/L), $p < 0.001$ [29].

Bitla., *et al*. 2012 had studied serum MDA level in patients with MetS and healthy subjects. The serum MDA levels were significantly higher in subjects with MetS (mean 3.44 ± 0.47 µmol/L) than that of the healthy subjects (mean 0.67 ± 0.062 µmol/L) [30].

MDA considered as oxidative stress marker has been implicated to oxidative modification of LDL molecules and modification of other cells, mainly, macrophage. Oxidized LDL induces transformation of macrophages into foam cells that occur in the intima of the artery wall thus giving rise to other cardiovascular diseases such as atherosclerosis which is one of the risk factors in MetS [31].

In 2004, Furukawa and colleagues also reported that obesity induced oxidative stress impairs glucose uptake in muscle and fat, and decreased insulin secretion from pancreatic β cells. Increased oxidative stress also underlies the pathophysiology of hypertension, atherosclerosis, and development of metabolic syndrome [5].

Hamma., *et al*. 2015 reported that obesity, the main component of MetS was found to be associated with oxidative stress, and, in turn, oxidative stress might be associated with an excess production of adipokines, which contributed to the development of metabolic syndrome [32]. Obesity is one of the independent risk factors for type 2 DM, cardiovascular diseases, various cancer and other health problems, which can lead to high morbidity and mortality.

In the present study, the mean serum CETP level of patients with MetS was significantly higher than that of controls (4.86 ± 0.83 µg/mL Vs 1.47 ± 1.13 µg/mL) $p < 0.0001$.

Win-Kyaw-Thu (2015) had studied the CETP level in 28 normolipidemic subjects and 28 hyperlipidemic subjects. The mean serum CETP concentration of the normolipidemic subjects was 1.86 ± 0.44 µg/mL [33]. The mean serum CETP concentration of the present study was within the range of the above study.

Metabolic syndrome is characterized by three or more metabolic abnormalities, including obesity, insulin resistance, hypertension, hyperglycemia, and dyslipidemia. Obesity is associated with dyslipidemia, which is influenced by body fat distribution. CETP is an important determinant of lipoprotein composition because of its capacity to mediate the transfer of cholesteryl esters (CEs) from CE-rich lipoproteins to TG-rich lipoproteins in exchange for TGs. CETP levels and activity were increased in obese subjects [34].

Sandhofer., *et al*. 2006 reported that the mean CETP level of MetS patients (1.87 ± 0.78 µg/mL) was higher than that of healthy subjects (1.40 ± 0.66 µg/mL), $p < 0.001$ [12]. The above study indicated that high CETP level might reflect reduced HDL-C and reduced LDL particle diameter as a marker for dyslipidemia in MetS.

Arai., *et al*. 1994 has studied serum CETP level in 30 obese subjects. The mean serum CETP levels of the obese subjects (2.73 ± 0.61 µg/mL) was significantly higher than that of healthy subjects (2.14 ± 0.63µg/mL) $p < 0.0001$ [35]. In above study, the high activity of CETP could be explained by the accumulation of fat tissues, which synthesize more CETP mass than other organ. This finding proved that there was the positive association between CETP activity and mass in obese subjects. So, subcutaneous fat may play a crucial role in regulation of plasma CETP level.

The serum CETP level of healthy subjects in the present study was comparable with those of above studies. The discrepancy of mean CETP concentration in MetS patients between various research might be due to differences in genetic or ethnic background of the subjects.

The CETP mediate the transfer of cholesterol esters from cholesterol rich lipoproteins to TG-rich lipoprotein in exchange for TGs. This lipid exchange promotes the generation of smaller HDL and LDL particle [12]. Small dense-LDLs are prone to modification, have a lower

affinity for the LDL-receptor and, thus, are considered to be more atherogenic than normally-sized LDL particles [35]. The occurrence of small dense-LDLs and low HDL- cholesterol have been linked to CVD.

It has been stated that atherosclerosis is not only a lipid disorder, but rather a process of dynamic interactions between endothelial dysfunction, subendothelial inflammation and the wound healing response of the vascular smooth muscle cells [19].

In the present study, the mean serum CETP level of MetS patients with central obesity, waist circumference (M ± SD), 112.93 ± 14.01 (cm) was significantly higher than that of controls having waist circumference, 71.03 ± 4.75 (cm).

In 2004, Goff., *et al*. reported that CETP concentration may increase up to two to threefold in obese subjects [36].

The serum IL-6 and MDA levels were determined to find out the association between inflammation and oxidative stress. In the present study there was positive correlation between serum IL-6 and MDA levels in controls ($r = 0.44$) ($p < 0.0001$and in patients with MetS, ($r = 0.86$) ($p < 0.0001$).

It has also been reported that there was a positive correlation between serum IL-6 and MDA, $r = 0.56$, $p < 0.05$ [37].

So, finding of present study was consistent with that of above study. It has been shown that there was an association between systemic inflammation and oxidative stress in metabolic syndrome. Additionally, the systemic inflammation and oxidative stress have been shown to have primary predictive value for coronary heart disease.

In present study, the serum IL-6 and CETP levels were determined to assess the association between inflammation and dyslipidemia in MetS. The present data showed that the mean serum IL-6 level was positively associated with CETP in controls ($r = 0.73$) ($p < 0.0001$) and patients with MetS ($r = 0.62$) ($p < 0.0001$). The significant positive correlation ($r = +0.44$, $p < 0.0001$) was observed between IL-6 and the number of MS components according to ATP III [6].

Guedes., *et al*. 2016 reported that there was a positive correlation between and the inflammatory cytokine, IL-6 and dyslipidemia, ($p < 0.05$) [38]. So, these studies explored a link between the oxidative stress and inflammatory status in subjects with MetS.

The present study indicated that serum IL-6, MDA and CETP levels were found to be higher in patients with MetS than in controls. The inflammatory cytokine especially IL-6 and oxidative stress marker, MDA was positively associated with serum CETP considered as a marker for dyslipidemia in MetS as the high CETP level may reflect reduced HDL-C and reduced LDL particle.

Conclusion

In present study, serum IL-6, MDA and CETP levels were significantly higher in MetS patients than in controls. The serum IL-6 level and MDA were positively associated with CETP levels in healthy subjects as well as in patients with MetS.

The present data indicated that the release of inflammatory cytokine especially IL-6 and oxidative stress marker, MDA was found to be associated with serum CETP contributing to dyslipidemia as one of the components of MetS. However, these markers could not be considered as contributory factor to metabolic syndrome (MetS).

Moreover, present data supported previous finding that there was an association of inflammatory cytokines, IL-6 and MDA with CETP as a contributory factor of dyslipidemia. Present data might be helpful to clinician for therapeutic intervention of lipid-lowering agents with CETP inhibitor in MetS patients with dyslipidemia by reduction of release of inflammatory cytokines and MDA.

Conflict of Interest

The authors declare that there is no conflicts of interest in publication of this research.

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