Serum Tumor Necrosis Factor-α Levels and Components of the Metabolic Syndrome in Obese Adolescents

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Tumor necrosis factor-α (TNF-α) seems to be increased in obese subjects, suggesting its role as a proinflammatory cytokine to insulin resistance and metabolic abnormalities in obesity. The aim of this study was to evaluate the relationship between serum TNF-α, soluble TNF-α receptor 1 (sTNF-R1), TNF-α receptor 2 (sTNF-R2), and metabolic syndrome (MS) components and anthropometric indices in obese and non-obese adolescents. A cross-sectional study was performed on obese and non-obese adolescents. We studied 71 adolescents (age, 15 to 16 years old); 39 were obese (obese group; 14 males and 25 females) and 32 were non-obese adolescents (non-obese lean group; 12 males and 20 females). The body mass index (BMI), waist circumference (WC), waist-to-hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure (DBP) were determined in each subject. The serum TNF-α, sTNF-R1, sTNF-R2, fasting plasma glucose (FPG), and lipid profile were also measured. The mean serum TNF-α, sTNF-R1, and sTNF-R2 were significantly higher in the obese than the non-obese group (TNF-α, 18.15 *v* 5.88 pg/mL, $P < .001$; sTNF-R1, 2.01 *v* 1.40 ng/mL, $P < .001$; sTNF-R2, 6.06 *v* 3.70 pg/mL, $P < .001$). The serum TNF-α concentrations were positively correlated with the BMI (TNF-α, $r = 0.346$, $P < .05$; sTNF-R1, $r = 0.624$, $P < .001$; sTNF-R2, $r = 0.482$, $P < .001$, respectively) and WC (TNF-α, $r = 0.525$, $P < .05$; sTNF-R1, $r = 0.700$, $P < .001$; sTNF-R2, $r = 0.669$, $P < .001$, respectively). The serum TNF-α was positively correlated with triglyceride (TG) and DBP, and negatively with high-density lipoprotein-cholesterol (HDLC). The sTNF-R1 and sTNF-R2 were correlated with TG and DBP, and TG, respectively. Obese compared with non-obese adolescents exhibited higher concentrations of TNF-α and its soluble receptors, and the higher TNF-α concentrations were associated with several components of MS in obese adolescents.

OBESITY IS A health risk frequently associated with complications, such as type 2 diabetes, dyslipidemia, high blood pressure, and cardiovascular disease.[1-4] The underlying mechanisms of obesity-related chronic complications are proposed to be related to many hormones and cytokines, such as insulin, tumor necrosis factor-α (TNF-α), leptin, and sex steroids.[5-7]

Obese patients with the metabolic syndrome (MS) generally have a visceral fat distribution and are at increased risk of cardiovascular disease. It appears that increased visceral fat is associated with biochemical abnormalities, which lead to insulin resistance, and MS and insulin resistance are associated with visceral adipose tissue products, such as free fatty acids, as well as cytokines, such as TNF-α.[8]

TNF-α is a well-known proinflammatory cytokine, with important metabolic and/or weight-regulating effects on lipid metabolism.[9-12] A relationship between serum TNF-α, insulin resistance, and obesity has recently been demonstrated in various studies.[13-16] As previous studies suggested, TNF-α could interfere with early steps of the insulin signaling pathway, causing blunted insulin sensitivity or insulin resistance and be partially responsible for the disturbances of glucose and lipid metabolism associated with obesity and the MS.[17-20] The plasma concentrations of TNF-α were elevated in obese adults,[21,22] and those of the TNF-α receptors, TNF-α receptor 1 (sTNF-R1) and TNF-α receptor 2 (sTNF-R2) were also found to be elevated in obese adults.[23,24]

There have been no studies reporting serum TNF-α levels in obese adolescents. One study demonstrated higher TNF-α levels in childhood obesity and described a positive correlation between the relative body mass index (BMI) and the serum TNF-α,[25] however, the TNF-α receptors were not examined in that study.

The aims of this study were to compare the anthropometric index and the serum levels of TNF-α and its receptors in obese adolescents and to also analyze the variables involved in their increase in adolescent obesity. The influences of TNF-α, and its 2 soluble receptors, were assessed on the various components of the MS.

SUBJECTS AND METHODS

Subjects

This study included a total of 71 adolescents (age, 15 to 16 years; 39 obese and 32 non-obese). Adolescents with any history of coronary heart disease, primary hyperlipidemia, hypertension, diabetes or glucose intolerance, and secondary obesity were excluded from the study. Subjects with any acute conditions, such as flu, were also excluded. Of the 71 adolescents recruited, there were 14 and 25 obese males and females, respectively, with a BMI more than 25kg/m^2 according to Asia-Pacific criteria of obesity and 12 male and 20 female age-matched non-obese adolescents, with a BMI less than 23. None of the subjects were on medications that affected their glucose homeostasis or sympathetic nervous system activity or on anti-inflammatory medications.

Anthropometric and Blood Pressure Measurements

A trained nurse using standard techniques made all measurements. The standing height was measured to the nearest 0.1 cm using a fixed standiometer and the body weight to the nearest 0.1 kg. The BMI was calculated by dividing weight (kg) by the square of the height (m^2).

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Table 1. Anthropometric Parameters of the Study Group

	Obese (n = 39)	Non-obese (n = 32)	*P*
Male/female	14/25	12/20	
Age (yr)	15.31 ± 0.47	15.41 ± 0.50	.394
Weight (kg)	78.04 ± 12.11	54.95 ± 4.26	<.001
Height (cm)	163.15 ± 8.52	165.61 ± 6.04	.174
BMI (kg/m^2)	29.44 ± 2.92	20.06 ± 0.89	<.001
WC (cm)	93.83 ± 5.55	74.83 ± 3.96	<.001
WHR	0.91 ± 0.05	0.77 ± 0.02	<.001
Fat (kg)	28.03 ± 5.96	10.87 ± 2.89	<.001
Fat percent (%)	35.87 ± 6.37	19.99 ± 5.96	<.001

Abbreviations: BMI, body mass index; WC, waist circumference; WHR, waist-to-hip ratio.

The waist circumference (WC) was measured midway between the lowest rib margin and the iliac crest at the end of gentle expiration. The fat mass and percentage body fat were measured by bioimpedence analysis using a bioimpedence analyzer (InBody 3.0, Seoul, Korea).

The sitting systolic blood pressure (SDP) (Korotkoff phase I) and diastolic blood pressure (DBP) (Korotkoff phase V) were determined using a mercury sphygmomanometer, after a 10-minute rest in the sitting position.

Metabolic Evaluation

Blood samples were obtained from the subjects after a 12-hour overnight fast. The serum was separated by centrifugation of the freshly drawn blood and stored at −80°C until required for analysis.

The serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein-cholesterol (HDLC), and fasting plasma glucose (FPG) were measured using a Hitachi 747 Autoanalyzer (Hitachi, Tokyo, Japan). All of the coefficients of variation (CV) were <3% on duplicate measures. The low-density lipoprotein-cholesterol (LDLC) was calculated using the Friedewald equation.

The serum TNF-α was measured using a commercially available highly sensitive enzyme-linked immunosorbent assay (ELISA) kit (BioSource, San Jose, CA). Assays were performed exactly as recommended by the manufactures. The minimum detectable concentration of TNF-α enzyme-amplified sensitivity assay (EASIA) was estimated to be 3 pg/mL, which was taken as the average TNF-α concentration of 20 replicates of the zero standard + 2 SD (standard deviation). The intra-assay and interassay of CVs were <7% and <9%, respectively.

The soluble TNF-α (sTNF)-R1 EASIA and sTNF-R2 EASIA (BioSource) are immunoenzymometric assays performed on a microtiter plate (soluble p55 and p75 TNF-α receptors, respectively). The minimum detectable concentrations were estimated as 50 and 0.1 ng/mL, respectively, and were defined as the sTNF-R1 or sTNF-R2 concentration corresponding to the average of 20 replicates of the zero standard + 2SD. The intra-assay and interassay CVs were <7% and <9%, respectively. The sTNF-R1 EASIA does not cross react with the sTNF-R2, and the TNF-α does not interfere with the assay.

Statistical Analysis

The statistical assessment was conducted using the SPSS statistical package for windows (version 9.0, Chicago, IL), and the results were expressed as the mean ± SD. The mean values of the groups were compared using Student's unpaired *t* tests. Statistical significance was set at the 95% level ($P < .05$).

The correlation between variables was evaluated using Spearman's correlation coefficients and regression analyses. Multivariate regression analyses were performed using the Stepwise method. For each variable, the potential confounding factors were evaluated by analyses of the raw and adjusted regression coefficients.

RESULTS

Table 1 shows the anthropometric data of both groups. The body weight, BMI, WC, and WHR were significantly different between the 2 groups. With the obese subjects, the males had higher body weights (81.71 ± 11.48 *v* 75.99 ± 12.19 kg, $P < .05$) and WC (96.23 ± 5.62 *v* 92.48 ± 5.13 cm, $P < .05$) than the females, but in the non-obese group, there were no significant differences in the body weights and WCs. Table 2 shows the selected parameters related to MS, and TG was significantly higher in the obese group (128.00 ± 50.14 *v* 62.13 ± 14.58 mg/dL, $P < .001$).

Serum TNF-α Levels

The mean serum TNF-α was significantly higher in the obese than the non-obese group (18.15 ± 6.73 *v* 5.88 ± 1.97 pg/mL, $P < .001$) (Fig 1). The mean serum TNF-α R1 and R2 were also significantly higher in the obese than the non-obese group (R1, 2.01 ± 0.55 *v* 6.06 ± 2.30 ng/mL, $P < .001$; R2, 1.40 ± 0.14 *v* 3.70 ± 0.59 pg/mL, $P < .001$, respectively). In the obese group, sex-related differences in the serum TNF-α and its receptor R1 and R2 levels were noted, with the males showing higher levels than the females (TNF-α, 35.37 ± 14.37 *v* 11.14 ± 6.04 pg/mL, $P < .001$; sTNF-R1, 2.36 ± 0.57 *v* 1.88 ± 0.43 ng/mL, $P < .01$; sTNF-R2, 8.51 ± 1.70 *v* 4.69 ± 1.16 pg/mL, $P < .001$).

Serum TNF-α and WC

In the single linear correlation for the obese group, the serum TNF-α concentration was positively correlated with both the BMI ($r = 0.346$; $P < .005$) and WC ($r = 0.525$; $P < .001$), and both the sTNF- R1 and sTNF-R2 were positively correlated with the BMI ($r = 0.624$, $P < .001$ and $r = 0.482$, $P < .001$, respectively) and WC ($r = 0.700$, $P < .001$ and $r = 0.669$, $P < .001$, respectively). Figure 2 shows the single linear correlation of the serum TNF-α, sTNF-R1, and sTNF-R2 with the WC and BMI for the obese and non-obese adolescents.

Serum TNF-α and the Metabolic Syndrome

With regard to the MS components, the univariate correlation analysis is summarized in Table 3. In the combined group

Table 2. Selected Parameters Related to Metabolic Syndrome

	Obese (n = 39)	Non-obese (n = 32)	*P*
TC (mg/dL)	173.87 ± 32.19	165.00 ± 15.44	.158
TG (mg/dL)	128.00 ± 50.14	62.13 ± 14.58	<.001
HDLC (mg/dL)	48.21 ± 11.70	50.34 ± 8.71	.394
LDLC (mg/dL)	104.93 ± 28.69	100.60 ± 14.21	.439
FPG (mg/dL)	84.56 ± 6.39	86.69 ± 8.54	.235
SBP (mm Hg)	118.38 ± 10.92	120.84 ± 9.81	.327
DBP (mm Hg)	72.10 ± 9.03	70.53 ± 8.41	.454

Abbreviations: TC, total cholesterol; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; LDLC, low-density lipoprotein cholesterol; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure.

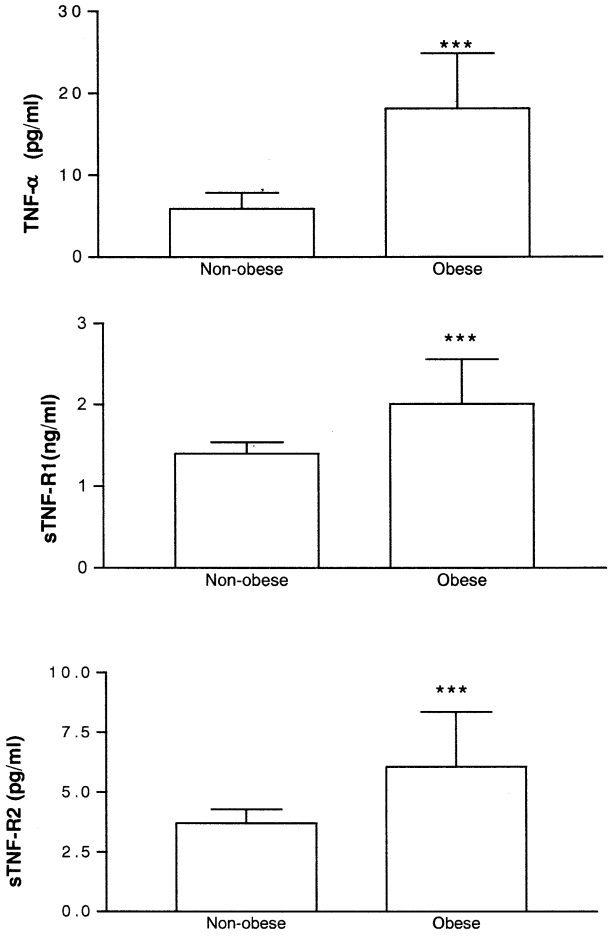

Fig 1. Serum concentrations of (A) TNF-α, (B) sTNF-R1, and (C) sTNF-R2 levels in the obese and non-obese groups; ***$P < .001$; TNF-α, tumor necrosis factor-α; sTNF-R1, soluble tumor necrosis factor-α receptor 1; sTNF-R2, soluble tumor necrosis factor-α receptor 2.

(obese and non-obese together), the serum TNF-α correlated positively with the TG and DBP, and negatively with the HDLC. The TNF-α R1 and R2 were correlated with the TG and DBP and the TG, respectively. The multiple variate regression analysis showed that TG was positively associated with serum TNF-α, and this characteristic slightly attenuated when corrected for BMI and WC.

In the obese group, the serum TNF-α concentration correlated positively with the TG and SBP. The TC, HDLC, FPG, and DBP were not correlated with the TNF-α, but the sTNF-R1 was correlated with the TG, SBP, and DBP and the sTNF-R2 with the TG in the obese group.

DISCUSSION

This study has shown that the serum TNF-α, sTNF-R1, and sTNF-R2 levels were elevated in the obese compared with the non-obese group in both the male and female adolescents. The serum TNF-α concentration was positively correlated with the BMI and WC and some components of MS, including the TG, SBP, and DBP in adolescents.

Many studies have demonstrated elevated TNF-α, and its receptor, levels in obese compared with control adults[21,23,24,26] and also in children.[25] In one study with obese children (mean age, 9.75 years), the serum TNF-α level was highly elevated compared with those in malnourished and control children.[25] In this study, the serum TNF-α levels were elevated 3-fold in the obese compared with the non-obese adolescents. The serum sTNF-R1 and sTNF-R2 were also elevated 1.44-fold and 1.64-fold in the obese group, respectively. Increased circulating TNF-α and its receptors may comprise one component of obese adolescents.

There have been a few studies comparing the TNF-α levels between the sexes.[23,27,28] In children (mean age, 13.6 years; range, 12 to 16 years), boys had heavier body weights (55.2 ± 12.6 *v* 50.5 ± 9.6 kg, $P < .001$) and higher TNF-α R1 levels (1.77 ± 0.46 *v* 1.49 ± 0.37 ng/mL, $P < .001$) than girls.[28] In this study, the male obese adolescents showed higher TNF-α, and its receptor, levels. This finding could be explained by the fact that the males had heavier weights and larger waists than the females.

The relationship between obesity and serum TNF-α levels has recently been demonstrated in various studies.[15,26] It has been suggested that TNF-α secretion in vitro is increased in the adipose tissue from obese subjects, which causes metabolic disturbances.[29] In one study, the serum TNF-α showed a significant positive linear correlation with BMI in the obese adults.[30] In another study, the circulating TNF-α was correlated with WHR, but not with BMI, in obese adults.[21] There have been several studies demonstrating that WC is also a useful measure of fat distribution for children and adolescents.[31,32] In this study, the serum TNF-α, and its 2 receptors, were positively correlated with BMI, a marker of the total adiposity, and also with WC in the obese adolescents. However, the correlation coefficients were higher with WC, a good, albeit indirect, marker of the visceral fat mass, than the BMI. This might suggest that the serum TNF-α is more closely related to abdominal obesity, or visceral fatness, which is the major component of MS, than the total adiposity.

It is well known that obesity is related to cardiovascular morbidity and mortality. Obesity is also thought to be associated with accelerated coronary atherosclerosis in young adult men, adolescents, and even children.[7,33] In the present study, some components of MS were compared between the obese and non-obese adolescents. TG was significantly higher in the obese adolescents than the non-obese. This might suggest that MS could begin in earlier life if excess fat is present.

It has been proposed that proinflammatory cytokines, such TNF-α, have deleterious effects on glucose homeostasis and can disrupt insulin signaling pathways in both pancreatic β cells, liver, and adipose tissue.[34] TNF-α and interleukin (IL)-6 are related to lipid metabolism of adipose tissues, possibly causing further metabolic disturbances.[29] It has been demonstrated that the serum TNF-α concentration is associated with the degree of early atherosclerosis and correlated with metabolic perturbations.[35] Overweight children had higher BP, plasma insulin and leptin levels, as well as adverse insulin-resistance status than normal-weight children,[27] and hyperinsulinemic obese children (aged 6 to 9 years) showed greater impairment in the parameters considered as constituents of MS.[36] As one study with obese patients who had undergone

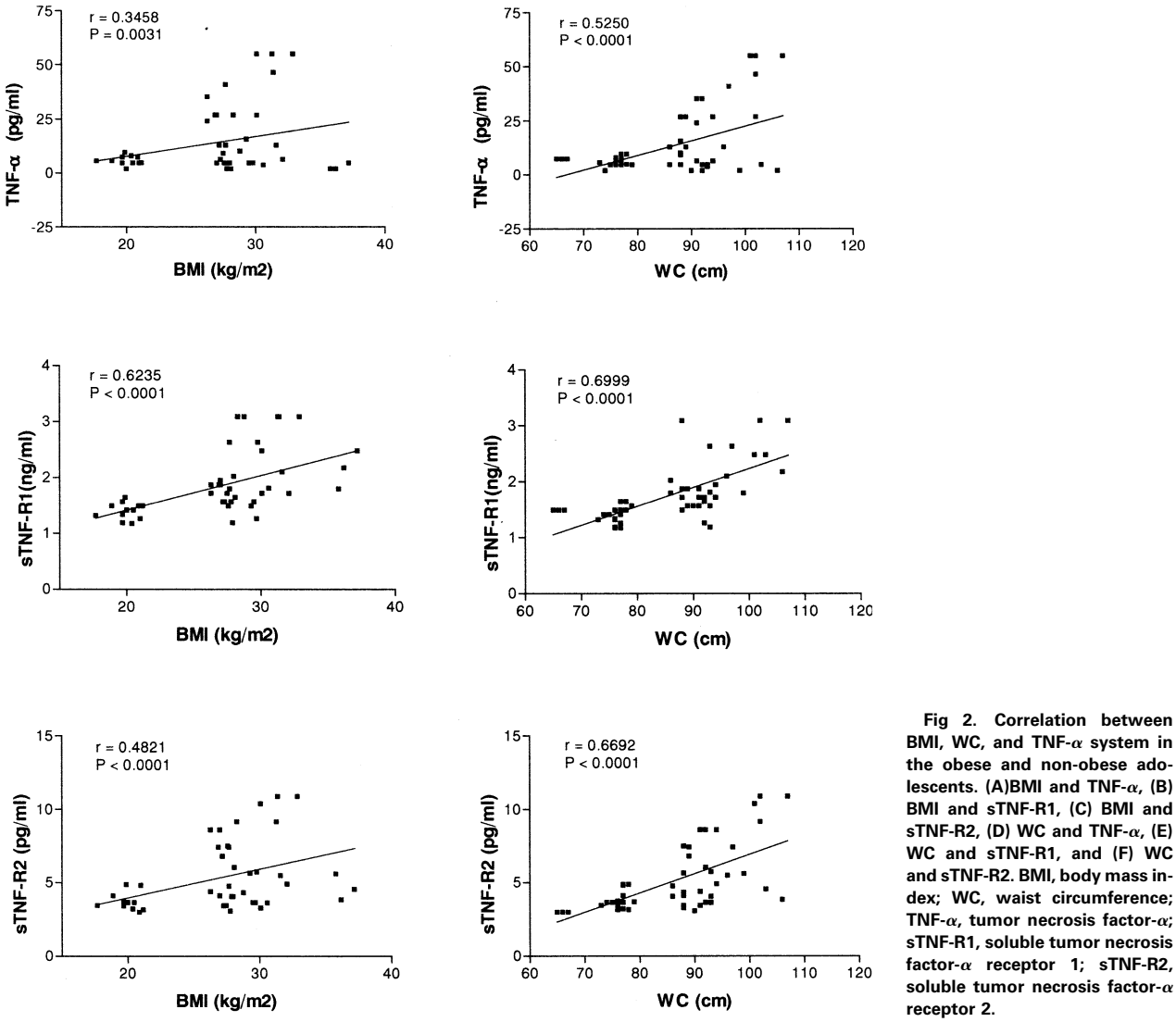

Fig 2. Correlation between BMI, WC, and TNF-α system in the obese and non-obese adolescents. (A)BMI and TNF-α, (B) BMI and sTNF-R1, (C) BMI and sTNF-R2, (D) WC and TNF-α, (E) WC and sTNF-R1, and (F) WC and sTNF-R2. BMI, body mass index; WC, waist circumference; TNF-α, tumor necrosis factor-α; sTNF-R1, soluble tumor necrosis factor-α receptor 1; sTNF-R2, soluble tumor necrosis factor-α receptor 2.

Table 3. Coefficients of the Simple Correlation (*r*) Between Different Variables in the Subjects (obese and non-obese group)

	TNF-α	sTNF-R1	sTNF-R2	BMI	WC
TC (mg/dL)	NS	NS	NS	NS	NS
TG (mg/dL)	0.414*	0.497*	0.486*	0.608*	0691*
HDLC (mg/dL)	−0.259†	NS	NS	NS	NS
FPG (mg/dL)	NS	NS	NS	NS	NS
SBP (mm Hg)	NS	NS	NS	NS	NS
DBP (mm Hg)	0.331†	0.376*	NS	NS	0.265†

Abbreviations: TNF-α, tumor necrosis factor-alpha; sTNF-R1, tumor necrosis factor-alpha receptor 1; sTNF-R2, tumor necrosis factor-alpha receptor 2; BMI, body mass index; WC, waist circumference; TC, total cholesterol; TG, triglycerides; HDLC, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; SBP, systolic blood pressure; DBP, diastolic blood pressure; NS, not significant.

*$P < .001$; †$P < .05$.

abdominal surgery suggested that abdominal obesity and serum TNF-α seem to be the best correlates of the lipoprotein disturbance characteristic of the MS,[37] this study showed correlation between TNF-α and TG. The single linear correlation analysis found correlation between the serum TNF-α with different MS variables (TG and DBP), and TNF-α was positively associated with TG with borderline significance, and this characteristic was attenuated when adjusting for BMI and WC. This correlation would be more prominent if visceral fat was measured in the subjects. The risk of developing obesity-related diseases may be, in part, a function of the increased TNF-α among susceptible persons early in life.

There were some limitations with this study; the small number of subjects, especially male adolescents. A larger study might be helpful to characterize the relationship between obesity and its related cytokines and hormones in this age group. To evaluate and clarify the underlying mechanism relating the

TNF-α and components of MS, the serum fasting insulin level will need to be measured in the future.

To summarize, for this age group, higher serum TNF-α levels were noted in the obese adolescents compared with non-obese, and high serum TNF-α concentrations correlated with both BMI and WC levels. Increased circulating TNF-α, and its receptors, and their association with some components of MS, may be one of the characteristics of obese adolescents.

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