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Evaluation of Pro-Inflammatory Markers Adiponectin and Tumor Necrosis Factor Alpha (TNF-A) and Their Correlation with Metabolic Syndrome and Its Components.

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Abstract

Background: Several components of metabolic syndrome (MS) facilitate its diagnosis, including abdominal obesity, hyperlipidemia, high blood pressure, and insulin resistance. The production of adiponectin and tumor necrosis factor-alpha (TNF-α) seems to be associated with MS. This study aimed to assess the levels of adiponectin and TNF-α in patients with metabolic syndrome and correlation with MS components.

Methodology: This prospective case-control study investigated 60 subjects, comprising 20 control and 40 MS patients.Serum adiponectin and TNF-α levels were measured using the enzyme-linked immunosorbent assay (ELISA).

Results: Serum concentration of TNF-α was significantly higher in MS patients than in control(16.31 ± 5.61 vs 8.45±1.52pg/ml, p < 0.001)and significant hypoadiponectinemia was found in MS patients compared to control(3.14±1.45 vs 8.24±5.12 ug/ml, p-value < 0.001).Serum TNF – α level was significantly higher in diabetic than non-diabetic patients with metabolic syndrome. There was a positive correlation of TNF-α with BMI and fasting blood sugar and triglyceride level. Serum adiponectin level was negatively correlated with fasting blood glucose, serum triglyceride level, and BMI.

Conclusions: Patients with Metabolic Syndrome had significantly higher serum TNF-α levels than controls. Serum adiponectin level was found significantly lower in metabolic syndrome patients than controls. Measuring the serum concentration of adiponectinand TNF-αmay be useful for the management of the metabolic syndrome.

Keywords: TNF-α, Adiponectin, Metabolic syndrome, Metabolic syndrome components.

Introduction

Metabolic syndrome is a clinical syndrome characterized by the constellation of various components namely, obesity, hyperglycemia, hypertension, low high-density lipoprotein(HDL) level, and high triglycerides[1]. There are several definitions for metabolic syndrome, leading to some difficulty in comparing data from studies using different criteria. The National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) is the most widely used[2,3]. Abdominal obesity is not a prerequisite for diagnosis; the presence of any three of the five criteria listed constitutes a diagnosis of metabolic syndrome.

Metabolic syndrome is defined by the Adult treatment panel III (ATPIII) as the presence of any **three** of the following five traits:Abdominal obesity, defined as a waist circumference ≥102 cm (40 in) in men and ≥88 cm (35 in) in women. [waist circumference ≥90 cm in males and ≥80 cm in females in India. Serum triglycerides ≥150 mg/dL (1.7 mmol/L) or drug treatment for elevated triglycerides. Serum high-density lipoprotein (HDL) cholesterol <40 mg/dL (1 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women or drug treatment for low HDL cholesterol. Blood pressure ≥130/85 mmHg or drug treatment for elevated blood pressure. Fasting plasma glucose (FPG) ≥100 mg/dL (5.6 mmol/L) or drug treatment for elevated blood glucose.

Adipose tissue secreted several bioactive proteins, or adipokines, that regulate hepatic and peripheral glucose and lipid metabolism and play a key role in energy homeostasis and inflammation. These adipokines include leptin, adiponectin, resistin, and tumor necrosis factor-alpha (TNF-α).

Adipokines have many actions on insulin resistance and inflammation; they might have important roles in the pathogenesis of metabolic syndrome[4].Adiponectin is a hormone secreted exclusively by adipose tissue that produces beneficial effects on lipid metabolism, enhancing both lipid clearance from plasma and beta-oxidation of fatty acids in muscle[5]. Low circulating levels of adiponectin are associated with several components of metabolic syndrome including visceral adiposity, hypertriglyceridemia, and insulin resistance. It also has direct anti-inflammatory effects, suppressing tumor necrosis factor-alpha production in the liver [5].

In contrast to adiponectin,TNF-α is a proinflammatory adipokine that is secreted from infiltrated monocytes and macrophages into adipose tissue and has a central role in inflammation and autoimmune diseases[6]. TNF-α correlates with obesity and it has been shown to directly impair both insulin signaling in insulin-sensitive tissues and insulin secretion[7,8,9,10]. The current study aimed to measurethe serum level of adiponectin and TNF-α in both metabolic syndrome patients and healthy control and to analyze the correlation with metabolic syndrome variables.

Material and Methods

This study was carried out prospectively from June 2018 toMay 2020, at Index medical college and hospital, Indore, M.P. We included a total of 60 adults (> 18 yrs) subjects in our study. Patients were selected from those attending the outpatient clinics of the medicine department. Out of those, 40 were Metabolic Syndrome patients (case), and 20 were healthy volunteers (control). Healthy volunteers were selected from the patients attending medical OPD for a routine checkup. They were age and sex-matched. None of the controls had liver disease, inflammatory disease, or metabolic syndrome. Informed written consent was obtained from all participants and the study was approved by the local ethics committee.

All patients underwent a detailed history, anthropometric measurement, clinical examination, and biochemical tests. Diagnosis of metabolic syndrome was presumptive, based upon the ATP Panel III guideline.

Anthropometric Measurements

Anthropometric measurement was performed in all participants.Weight, height, and waist circumference were measured with the standard method and BMI was calculated by dividing weight (kg) by square of height (m^2). The waist circumference (WC) was measured midway between the lowest rib margin and the iliac crest at the end of gentle expiration measured using a non-stretchable fiber measuring tape. The sitting systolic blood pressure (SBP) (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.

Serum Adipokine Levels Fasting serum TNF-α and adiponectin levels were measured in all patients and the control group.After clotting, the samples were centrifuged at approximately 3000 rpm for 10 minutes and the serum was separated. Serum samples for TNF-α and adiponectin were aliquoted (250-500 µl) to avoid repeated freeze-thaw cycles and stored frozen at -20 °C. The serum TNF-α was measured using a commercially available highly sensitive human enzyme-linked immunosorbent assay (ELISA) kit (Diaclone SAS, France) (Cat No: 950.090.096, batch no: 1100-125)Assay was performed as recommended by the manufacturer.The normal reference value according to the manufacturer was below 8pg/ml[11]. The serum adiponectin level was measured by using the Human Adiponectin Enzyme-Linked Immunosorbent Assay (ELISA) kit manufactured by Diagnostic Biochem Canada Inc.

Reference values for adiponectin[12]

Group	N	Mean (µg/ml)	95% confidence range (µg/ml)
BMI < 25	50	9.7	3.4 – 19.5
BMI 25-30	50	7.1	2.6 – 13.7
BMI > 30	50	4.5	1.8 -9.4

Biochemical Parameters

Overnight fasting venous blood samples ofall participants were taken. The serum total cholesterol (CHOD-PAP enzymatic method), triglycerides (GPO-PAP enzymatic method), high-density lipoprotein-cholesterol (PEG-CHOD-PAP enzymatic method), and fasting plasma glucose (GOD-POD enzymatic method) were measured using Autoanalyzer. The low-density lipoprotein-cholesterol (LDLC) was calculated using the Friedewald equation.

Statistical Analysis

The statistical analysis was performed with R studio (open source analytical tool V 1.2.335) and Microsoft excel sheet. Results were expressed as the mean and standard deviation. In the present study, for comparing the means between the two groups, the Students paired 't' test was used. For finding out the association between independent and dependent variables, Pearson's Chi-square test was applied, for finding out the statistical significance between the means of more than two groups, one-way ANOVA was used and for finding out the correlation between two parametric variables Pearson's Coefficient of Correlation 'r' was used. A p-value of < 0.05 was taken as statistically significant.

Results

Demographics and biochemical characteristics of all subjects are shown in table no 1 and table no 2.

Table 1: Baseline characteristic of metabolic syndrome patients and control group

Characteristic	MS (n= 40) Mean ± SD	Control (n=20) Mean ± SD	p-value	Result
Age	57.05±12.07	61.15±7.41	0.170	Non Sig
BMI	28.18±3.81	23.11±2.54	0.000	**Sig**
Waist Circumference	98.45±8.23	86.05±4.56	0.000	**Sig**
Systolic BP	131.83±12.95	117.60±9.51	0.000	**Sig**
Diastolic BP	89.35±13.40	82.90±5.49	0.044	**Sig**
FBS (mg/dl)	117.95±30.19	95.25±8.23	0.002	**Sig**
Triglyceride (mg/dl)	188.75±95.09	130.70±31.06	0.010	**Sig**
HDL(mg/dl)	40.15±8.86	41.15±5.25	0.474	Non Sig
TNF α (pg/ml)	16.32±5.61	8.45±1.52	0.001	**Sig**
Adiponectin (µg/dl)	3.14±1.45	8.24±5.12	0.001	**Sig**

As shown in table no.1 the mean age of patients was 57.05±12.07 years and control was 61.15± 7.41 years. Metabolic syndrome patients were obese compared to control. MS patients had significantly higher BMI and waist circumference than control (p-value< 0.000). Metabolic syndrome patients also had significantly higher fasting blood sugar, serum triglyceride level, and systolic and diastolic blood pressure than control. Serum TNF-α was significantly higher in MS patients than healthy controls group (16.32±5.61 vs 8.45±1.52 pg/ml, p < 0.001). Mean serum adiponectin level was significantly low in MS patients compared to the healthy control group (3.14 ± 1.45 vs 8.24 ± 5.12 µg/ml, p-value <0.001).

Table 2: Age and Anthropometric characteristic of metabolic syndrome patients and control group

Variables	Sex	Case			Control			T-Test	p-value
		N	Mean	Std. Deviation	N	Mean	Std. Deviation		
Age	Male	28	55.57	12.40	16	60.69	8.16	-1.474	0.148
	Female	12	60.50	10.99	4	63.00	2.94	0.440	0.667
WAIST	Male	28	98.57	8.79	16	85.13	4.53	5.669	0.000
	Female	12	98.27	7.12	4	89.15	2.50	2.293	0.038
BMI	Male	28	27.82	3.35	16	22.51	2.43	5.551	0.000
	Female	12	29.02	4.80	4	25.50	1.29	1.419	0.178

As shown in table no 2out of 40 patients, 12 patients (30%) were female and 28 patients (70%) were male. The mean ages of male and female patients were 55.57±12.40 and 60.50±10.99 years respectively.Metabolic syndrome patients had significantly higher BMI and waist circumference in males (p value<0.000)compared to control, but it was not significant in female patients when compared to control.

Table 3: Diabetes and Grade of NAFLD in case and control group.

Variable	Case (n-40)	Control (n=20)
DM	27 (67.5%)	0
Non DM	13 (32.5%)	20 (100%)
NAFLD	30 (75%)	0
Grade I	13 (32.5%)	
Grade II	13 (32.5%)	
Grade III	04 (10%)	

Out of 40 metabolic syndrome patients, thirty patients (75%) patients also had NAFLD and 27 patients (67.5%) were diabetic. Twenty healthy subjects (control) had normal liver function tests and other blood investigation and ultrasound scans.

Table 4: Value of serum TNF-α and Adiponectin according to gender.

Variable	Case					Control				
	Sex	N	Mean	Std. Deviation	p-value	Sex	N	Mean	Std. Deviation	p-value
TNF-α	Male	28	16.44	5.59	0.842	Male	16	8.24	1.57	0.230
	Female	12	16.04	5.91		Female	4	9.28	1.02	
Adiponectin	Male	28	3.22	1.41	0.571	Male	16	8.44	5.09	0.726
	Female	12	2.93	1.58		Female	4	7.40	5.92	

There was no statistically significant difference found between male and female serum TNF-α level (16.44±5.59 vs 16.04±5.91 pg/ml, p-value= 0.8) in metabolic syndrome patients.Similarly to TNF-α, there was no statistically significant difference found, when compared serum adiponectin level between male and female metabolic syndrome patients (3.22±1.41 vs 2.93±1.58 µg/ml, p-value = 0.57)

Table 5 : Serum TNF-α and Adiponectin level relation with BMI

Variable	BMI <25 kg/m^2(n=7)	BMI 25-30 kg/m^2 (n=21)	BMI > 30 kg/m^2 (n=12)	Control (n=20)	p-value
TNF-α	12.81±4.20	16.64±5.89	17.79±5.34	8.45±1.52	<0.05
Adiponectin	4.44±1.35	3.28±1.01	2.10±1.18	8.24±5.12	<0.05

As shown in table no 5 MS patients had a significantly higher level of TNF-α according to BMI grade (p-value <0.05) when compared to control with ANOVA test. Similarly adiponectin level was significantly low in higher BMI patients when compared to control with ANOVA test.

When serum TNF-α, and adiponectin level was correlated with fasting blood glucose, triglyceride level, BMI and systolic BP using the students (t) test and Pearson Correlation. We observed that TNF-α showed positive correlation and serum adiponectin level was negatively correlated with fasting blood glucose, serum triglyceride level, and BMI.

Establishment of cutoff values of TNF –α and Adiponectin in metabolic syndrome patients and healthy control group.

Receiver operating curve for serum TNF-α and adiponectin level was built to predict metabolic syndrome. The best cut-off value of TNF-α obtained by ROC curve was 11.2 pg/ml for predicting metabolic syndrome. (AUROC 0.98, p-value<0.0001, with 82.5%Sensitivity, 98.0% Specificity, and 92.01% accuracy). The best cut-off value for adiponectin obtained by ROC curve was < 4.2 µg/ml for predicting metabolic syndrome. (AUROC 0.88, p-value<0.0001, with 85% Sensitivity, 85%Specificity, and 80% accuracy).

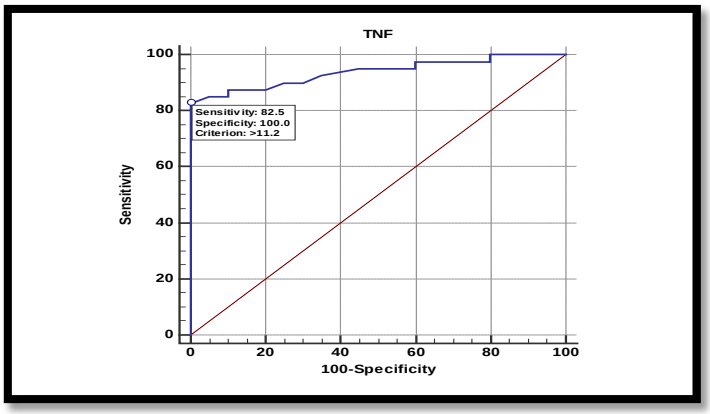

Figure 1: ROC curve of Serum TNF- α for predicting the metabolic syndrome.

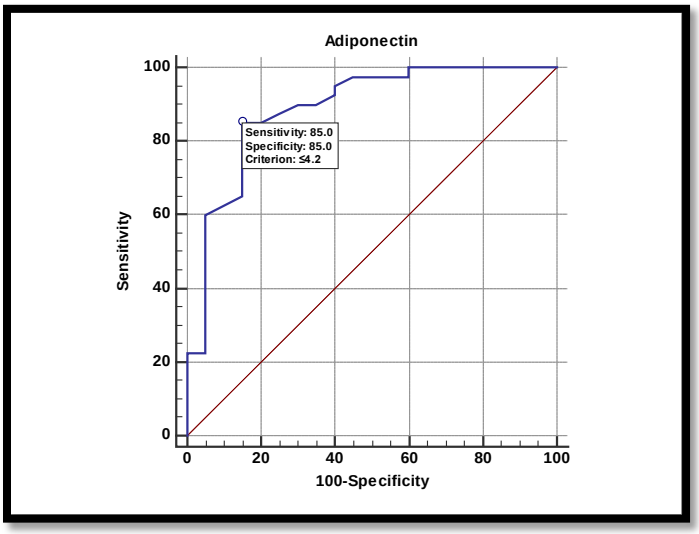

Figure 2: ROC curve of serum level of Adiponectin for predicting the metabolic syndrome

Discussion

The production of adiponectin and tumor necrosis factor alpha (TNF-α) seem to be associated with MS components. Adiponectin is an adipose-derived protein with multivalent function including anti-atherogenic, insulin-sensitizing, lipid oxidation enhancing, and vasodilatory activities[13-22]. Therefore, decreased plasma concentration of adiponectin may play a significant role in the development of metabolic syndrome, In contrast, TNF-α is a well-known pro-inflammatory marker with important metabolic and weight-regulating effect on lipid metabolism.A relationship between serum TNF-α and metabolic components(hyperglycemia, hypertriglyceridemia, hypertension, abdominal obesity) has recently been demonstrated in various studies[23-26]. We have found significantly higher serum level of TNF-α in patients with metabolic syndrome than in healthy control. Similarly, a study was done by Mohammadi M et al,[27] suggested that Metabolic Syndrome patient had significantly greater serum interleukin 6 (IL-6)and TNF-α levels than control, supporting the evidence that inflammation plays an important role in the pathogenesis of the disease. Additionally, IL-6 and TNF-α serum levels may predict metabolic syndrome.In 2004, Moon et al,[28] showed that serum level of TNF-α in obese adolescent MS patients correlated positively with BMI, waist circumference, triglyceride level, and diastolic blood pressure and negatively with HDL cholesterol. Indulekha K. et al,[29]found levels of inflammatory marker TNF-α was higher in subjects with MS than those without MS. This observation alsosupported by PfKeiffer A et al[30], Hotamisligil GS et al[31], Hauner H et al[32], Winkler G et al[33] studies which have demonstrated elevated TNF-α level in obese compared with control adult and also in children.Nilsson et al,[34]observed increased serum TNF-α concentration in elderly diabetic men, which significantly correlated with higher BMI, fasting plasma glucose, triglyceride level, and negatively correlated with serum HDL-cholesterol.HoweverFew other studies done by Mohamad-Ali et al[35], Considine RV et al[36], Vidal H et al[37] showed no difference in TNF-α level between controls and patients with metabolic syndrome.

Our study demonstrated that patients with metabolic syndrome had a significantly lower level of serum adiponectin compared to the control group and a similar result was found in other studies Ryo M et al[38], Weyer C et al[39], Arita Y et al.[40]JiEun Yun et al[41] study investigated type 2 diabetes patients and found that significant negative correlation with metabolic syndrome components and serum adiponectin level. One prospective Korean study was done by Choi KM et al[42] also showed a similar result. Matsuzawa Y et al[43]demonstrated that adiponectin may play a key role in the prevention of metabolic syndrome. In obesity, especially with visceral fat accumulation significant hypoadiponectinemia was observed[43].Hypoadiponectinemia is significantly associated with the clinical phenotype of the metabolic syndrome and quantification of serum level of adiponectin

may be helpful for early diagnosis and management of metabolic syndrome by Ryo M. et al[44].

Another study done by Anize Delfino von Frankenberg evaluated that circulating levels of adiponectin are reduced in the presence of MS, cardiovascular disease, and DM2, and also further decreases as the number of MS components increases. A lower level of adiponectin was associated with high visceral fat in metabolic syndrome and also related to HDL cholesterol and higher triglyceride level [45].

Conclusions

Our study suggests that the TNF-α level was significantly higherin metabolic syndrome patients. Serum adiponectin level was found significantly low in metabolic syndrome patients.We have found a new cut-off value for TNF-α was 11.2pg/ml and adiponectin was 4.2µg/ml. These adipokines could represent markers to evaluate metabolic syndrome pathogenesis and to predict the risk of progression.

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