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Evaluation of the Plasma Adiponectin Level in Individuals Suffering from Metabolic Syndrome

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KEYWORDS

Adiponectin, metabolic syndrome, type 2 diabetes, BMI, Blood pressure and Inflammation.

ABSTRACT:

Introduction: Adiponectin is one of the adipocytokines and has a physiological role in glucose and lipid, as well as

cardiovascular regulation. Adiponectin is interestingly different from other adipocytokines being negatively correlated with increased body fat.

Aims and Objectives: A study of correlation of Adiponectin levels in metabolic syndromes. Correspondence of adiponectin levels and various components of metabolic syndrome such as Blood pressure, Lipid profile, BMI (Basal metabolic index), Waist circumference, Blood sugar levels (fasting and post prandial).

Methods and Materials: This observational cross-sectional hospital-based study was performed in Department of Biochemistry, Index Medical College, Hospital and Research Centre Indore MP, India. Study population: 300 patients attending in Department of Biochemistry, Index Medical College, Hospital and Research Centre Indore MP, India with metabolic syndrome during the study period.

Result: We observed that statistically significant lower adiponectin levels were associated with most features.

Conclusion: Adiponectin level was significantly decreased as the number of metabolic yndrome components increases.

Introduction

Adiponectin is one of the adipocytokines and has a physiological role in glucose and lipid, as well as cardiovascular regulation. Adiponectin is interestingly different from other adipocytokines being negatively correlated with increased body fat. Despite the fact that adipose tissue is the unique source of adiponectin, its levels seen with lower levels in obese subjects, higher levels seen associated with decreased body weight, could be explained by negative feedback in obesity.[1]

It is believed that adiponectin affects the cardiometabolic syndrome pathogenesis through its negative effect on blood glucose and free fatty acids levels.[2] The link between adiponectin secretion and insulin resistance seems to be bidirectional. Adiponectin improves the sensitivity of insulin

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www.jchr.org
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receptors in peripheral tissues; affect food intake and metabolic rate.[3] On the other side, increased insulin levels related to decreased bioactive adiponectin levels, which lead to further insulin resistance. Inflammation and oxidative stress associated with insulin resistance decrease adiponectin levels.[4]

Adiponectin, the most abundant anti-atherogenic and anti-inflammatory adipocytokine found in circulation has direct effects on glucose and lipid metabolism, improves insulin sensitivity and central fat distribution.[5] Adiponectin levels are inversely correlated with visceral adiposity.[6] A lower level of adiponectin is associated with insulin resistance, obesity, MetS and CVD.[7] Low level of circulating adiponectin may be used as a possible biomarker for MetS.[8] On the other hand, Leptin as an anti-obesity adi-pocytokine plays critical roles in regulating food intake, maintaining energy expenditure and body weight. Serum leptin levels in patients with MetS are higher than those in healthy controls.[9] Increased leptin level predicts metabolic syndrome development independent of obesity. In fact, adiponectin and leptin levels show an inverse correlation with each other.[10]

Material and Method

Population/Patients: This observational cross-sectional hospital-based study was performed in Department of Biochemistry, Index Medical College, Hospital and Research Centre Indore MP, India.

Study population: 300 patients attending in Department of Biochemistry, Index Medical College, Hospital and Research Centre Indore MP, India with metabolic syndrome during the study period.

Study Design: Cross-sectional study

Study Location: Department of Biochemistry, Index Medical College, Hospital and Research Centre Indore MP, India.

Sample Size: 300 patients (Medicine Department IPD/OPD)

Inclusion criteria

- Both the sexes consulting in OPD or IPD Index Medical College, Hospital and Research Centre Indore MP, India.
- Study will be conducted on -150 Metabolic syndrome patients (75 female and 75 male) their ages ranged between (44-60 years) from General medicine department in Index Medical College, Hospital and Research Centre Indore MP, India.
- 150 healthy persons (75 female and 75 male) their ages ranged between (40-60 years).
- Visceral obesity, defined as waist circumference ≥ 102 cm in men and ≥ 88 cm in women.
- Fasting plasma glucose (≥100 mg/dl), or patient on hypoglycemic treatment.
- Systolic blood pressure (SBP) ≥130 mmhg and/or diastolic blood pressure (DBP) ≥85 mmhg, or patient on antihypertensive treatment.
- Serum triglycerides ≥ 150 mg/dl or patient on lipid lowering treatment and HDL cholesterol < 40 mg/dl in men, and < 50 mg/dl in women

Exclusion Criteria

- Chronic liver disease
- Chronic renal failure
- Patients on corticosteroid therapy
- Autoimmune disease
- Malignancy
- Pregnancy

Study tool

- Case reporting form
- Consent form

Procedure methodology

After written informed consent form had been obtained, detailed history of the presenting symptoms and their onset was recorded. Detailed histories of all the patients were obtained (like demographic details, age of patient, clinical details), blood pressure, heart rate, Lipid profile BMI, Blood sugar level (fasting and

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(06), 2501-2509 | ISSN:2251-6727

prandial) was noted on patient's proforma.

Five ml of fasting (12-16 hours) venous blood samples were taken from all subjects participating in the study and divided into 2 parts: the 1st part put in plain tube and left to clot and the blood centrifuged at 3000xg for 15 minutes. Fasting blood glucose was determined immediately, then the rest of the serum stored at - 20°c for determination of lipid profile.

Fasting blood glucose (FBG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) were measured enzymatically by auto-analyzers. HDL-C was determined after dextran sulfate-magnesium chloride precipitation of non-HDL-C. According to the Friedewald equation, low-density lipoprotein cholesterol l (LDL-C) was calculated in serum samples with TG ≤400 mg/dl. For the current sub-study, adiponectin was measured with the enzyme- linked immunosorbent assay (ELISA) kit in 180 randomly selected sera. Intra and inter-assay CVs were 10 and 12 % for adiponectin, respectively.

The 2nd part was put in a tube containing EDTA and the plasma separated by centrifugation at 3000xg for 15 minutes and stored at -20°c for determination of adiponectin and the kit was supplied from Immuno concept pharmaceuticals.

Total Cholesterol

Cholesterol is measured enzymatically in serum or plasma in a series of coupled reactions that hydrolyze cholesteryl esters and oxidize the 3-OH group of cholesterol. One of the reaction byproducts, H2O2 is measured quantitatively in a peroxidase catalyzed reaction that produces a color. Absorbance is measured at 500 nm. The color intensity is proportional to cholesterol concentration. Elevated levels of cholesterol increase the risk for coronary heart disease (CHD). Cholesterol is measured to help assess the patient's risk status and to follow the progress of patient's treatment to lower serum cholesterol concentrations. Desirable cholesterol levels are considered to be those below 200 mg/dL in adults and below 170 mg/dL in children.

Triglycerides

Triglycerides are measured enzymatically in serum or plasma using a series of coupled reactions in which triglycerides are hydrolyzed to produce glycerol. Glycerol is then oxidized using glycerol oxidase, and H2O2, one of the reaction products, is measured as described above for cholesterol. Absorbance is measured at 500 nm.

High density lipoprotein (HDL) cholesterol

Low serum concentrations of HDL-cholesterol are associated with increased risk for CHD. Coronary risk increases markedly as the HDL concentration decreases from 40- to 30 mg/dL. A low HDL-cholesterol concentration is considered to be a value below 35 mg/dL, and high HDL, >60 mg/dL. HDL-cholesterol values are also used in the calculation of LDL-cholesterol (see LDL section below).

Direct HDL method. HDL is measured directly in serum. The basic principle of the method is as follows. The apo B containing lipoproteins in the specimen are reacted with a blocking reagent that renders them non-reactive with the enzymatic cholesterol reagent under conditions of the assay. The apoB containing lipoproteins are thus effectively excluded from the assay and only HDL-chol is detected under the assay conditions.

The reagents are purchased from Roche/Boehringer-Mannheim Diagnostics. The method uses sulfated alpha-cyclodextrin in the presence of Mg+2, which forms complexes with apoB containing lipoproteins, and polyethylene glycol-coupled cholesteryl esterase and cholesterol oxidase for the HDL-cholesterol measurement.

Assay of Adiponectin: We used the Quantikine ELISA kits (R&D Systems, Bio-techne, Minneapolis, MN, USA) described below. The "Quantikine Human Total Adiponectin/Acrp30 Immunoassay" is a solid-phase ELISA designed to measure total (low, middle and high molecular weight) human Adiponectin. The lower limit of quantitation (LLOQ) is 3.9 ng/mL, the upper limit of quantitation (ULOQ) is 250 ng/mL and the limit of detection (LOD) is 0.891 ng/mL. The assay time is 4.5 h.

Statistical Analysis: Microsoft Excel was used in creating the database and producing graphs, while the data were analyzed using the Statistical Package for the

Journal of Chemical Health Risks
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JCHR (2023) 13(06), 2501-2509 | ISSN:2251-6727

Social Sciences (SPSS) version 23.0 for Windows. Categorical variables are reported as frequencies and percentages and continuous variables as the mean ± SD. Categorical variables were compared using Chi Square/Fisher's exact test. Continuous variables were compared using independent samples *t*-test. All variables were tested to check the normal distribution of the data. The Pearson / Spearman correlation coefficients were employed for parametric and nonparametric variables to investigate the possible associations between case-control and other biochemical parameters. Receiver Operating Curve (ROC) analysis was done to find the adiponectin level which was used as cut off to predict the occurrence of metabolic syndrome and their sensitivity & specificity. P values less than 0.05 ($p<0.05$) was considered statistically significant.

Result

Table no. 1: Adiponectin levels as means (S.D.) in subjects positive to individual component of metabolic syndrome (MS) according to International Diabetes Federation (IDF) criteria and in subjects not having the component of MS

			Frequency (n=300)	Adiponectin (µg/ml) (Mean±SD)	P value
BMI (kg/m^2)	**≤25**		99 (33.0)	14.51±2.90	**0.001**
	>25		201 (67.0)	12.37±3.53	
SBP (mmHg)	**≤ 130**		194 (64.7)	14.65±3.55	**0.001**
	>130		106 (35.3)	11.12±3.57	
DBP (mmHg)	**≤ 85**		225 (75.0)	14.18±3.69	**<0.001**
	>85		75 (25.0)	11.30±2.24	
FBS (mg/dl)	**≤100**		135 (45.0)	14.51±3.06	**<0.001**
	>100		165 (55.0)	12.64±3.09	
Triglyceride (mg/dl)	**≤ 150**		98 (32.7)	15.25±3.69	**0.001**
	>150		202 (67.3)	12.54±2.87	
HDL-C (mg/dl)	**Male**	**≤40**	35 (11.7)	12.45±3.72	0.038
		>40	115 (38.3)	13.80±3.22	
	Female	**≤50**	78 (26.0)	12.76±3.92	0.021
		>50	72 (24.0)	14.27±4.02	
Waist circumferences	**Male**	**<90**	93 (31.0)	14.06±3.34	**0.003**
		≥90	57 (19.0)	12.65±2.38	

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(06), 2501-2509 | ISSN:2251-6727

(cm)	**Female**	**<80**	66 (22.0)	13.98±3.73	0.094
		≥80	84 (28.0)	12.93±3.83	

Independent samples t test used; *Significant (P<0.05)

Discussion

Adiponectin is an adipokine secreted specifically from the adipose tissue. The inverse relationship between body fat and serum adiponectin levels has been demonstrated, and weight reduction can increase adiponectin levels.[11] Adiponectin modulates glucose metabolism by having insulin-sensitising effects. Adiponectin also decreases circulating free fatty acid concentrations and muscle triglyceride content by stimulating fatty acid oxidation in muscle via AMP-activated protein kinase (AMPK). Thus, adiponectin is a hormone that links adipose tissue and whole-body glucose metabolism. Low adiponectin levels have been associated with type 2 diabetes and insulin resistance.[12] Adiponectin has been found to have vaso-protective and anti-inflammatory effects and therefore could be viewed as a potential link between MS and its cardiovascular consequences. The current study we tried to find the correlation of Adiponectin levels in metabolic syndrome and also with various components of metabolic syndrome. A special interest was to explore how adiponectin levels relate to the new worldwide definitions of MS proposed by the International Diabetes Federation (IDF).

The present study design was a cross sectional study that has been carried out over a period of one year. It was used to estimate the correlation of Adiponectin levels in metabolic syndrome and also with various components of metabolic syndrome. **Shashank R. Tiwari et al[13], Nur Firdaus Isa et al[14], Ming-Chun Chen et al[15], Agathi Ntzouvani et al[16]** and **Y. Premchandra singh et al[17]** also enrolled the similar methodology in their respective studies.

Helma Karimi et al[18], Shraddha Madanagobalane et al[19] and **Amita Yadav et al[20]** did case-control studies of the adiponectin levels and its association with metabolic syndrome or with individual components of metabolic syndrome. The case and control study were not adopted by us because it was very difficult to convince healthy and mentally fit patients to take part in the study and to go through several tests and screening.

Correspondence of adiponectin levels and various components of metabolic syndrome such as Blood pressure, Lipid profile, BMI (Basal metabolic index), Waist circumference and Blood sugar levels (fasting and post prandial)

Development of a method for suitable estimate of metabolic syndrome in regular clinical practice offerings a main challenge for physicians and public health policy makers. The present study provided suggestion of the effectiveness for assessment of serum adiponectin level as an appropriate and sensitive biomarker for the estimation of metabolic syndrome particularly in our study area.

Diagnosis of Metabolic Syndrome was based on International Diabetes Federation (IDF) criteria for diagnosis of metabolic syndrome, which includes any three or more of the following abnormalities:

- Visceral obesity, defined as waist circumference ≥ 102 cm in men and ≥ 88 cm in women.
- Fasting plasma glucose (≥100 mg/dl), or patient on hypoglycemic treatment.
- Systolic blood pressure (SBP) ≥130 mmHg and/or diastolic blood pressure (DBP) ≥85 mmHg, or patient on antihypertensivetreatment.
- Serum triglycerides ≥ 150 mg/dl or patient on lipid lowering treatment and
- HDL-cholesterol < 40 mg/dl in men, and < 50 mg/dl in women

After written informed consent form had been obtained, detailed history of the presenting symptoms and their onset was recorded. Detailed histories of all the patients were obtained (like demographic details, age of patient, clinical details), blood pressure, heart rate, Lipid profile BMI, Blood sugar level (fasting and prandial) was noted on patient's proforma.

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(06), 2501-2509 | ISSN:2251-6727

The following risk factors and criteria were used: central obesity (waist circumference; men ≥ 90 cm, women ≥ 80 cm) plus any two of the following: (1) raised triglycerides (> 1.7 mmol/L (150 mg/dL) or specific treatment for this lipid abnormality); (2) reduced HDL- cholesterol (men <1.03 mmol/L (40 mg/dL) or women <1.29 mmol/L (50 mg/dL) or specific treatment for this lipid abnormality); (3) raised blood pressure (≥ 130/85 mm Hg or treatment of previously diagnosed hypertension); (4) raised fasting plasma glucose (≥ 5.6 mmol/L (100 mg/dL) or previously diagnosed type 2 diabetes).

Shashank R. Tiwari et al[21], **Nur Firdaus Isa et al**[22], **Ming-Chun Chen et al**[23], and **Y. Premchandra singh et al**[24] also used the similar procedures in their perspective study. On average, subjects without Metabolic Syndrome (MetS) were younger, had a smaller body mass index and waist circumference than those with MetS patients. They also had a lower BP, pulse rate, and fasting plasma glucose than the subjects with MetS, as well as significant differences in lipid profile in with MetS patients. The mean serum adiponectin concentration was higher in people without MetS 15.79±2.90 mg/ml than those with MetS 11.02±2.63 mg/ml (P<0.001).

We observed that statistically significant lower adiponectin levels were associated with most features of metabolic syndrome. Adiponectin level was also significantly decreased as the number of metabolic syndrome components increases. According to our multivariate analysis results, the serum adiponectin concentration was significantly negative correlated with the SBP (r= -0.262; p<0.05), BMI (r= -0.288; p<0.05), Total Cholesterol (r= -0.515; P<0.001), and LDL (r= -0.305; p<0.05) respectively.

In present study the mean level of adiponectin with corresponding BMI in the normal subjects of this ethnic population is (11.02±2.63 vs 15.79±2.90 µg/ml) other published reports of adiponectin level in European (9.85 ± 2.33 vs 10.89 ±0.86 µg/ml) or even from the mainland India (9.85 ± 2.33 Vs 16.7 ±7.6 µg/ml).[25] However the mean value of adiponectin and mean BMI is almost similar with those reported from Chinese (9.85 ± 2.33 vs 8.52±0.57 µg/ml) and South Asian population (9.85 ± 2.33 vs 8.26 ±0.45 µg/ml).[26]

The present was found the mean baseline adiponectin level was lower in the diabetic subjects than in the non-diabetic subjects (11.19±3.09 vs. 15.21±3.06 µg/ml; P <0.001). **Snehalatha C et al**[27] also reported the adiponectin level was lower in the diabetic subjects than in the non- diabetic subjects (11.3 ±5.5 vs. 16.7 ±7.6 µg/ml; P = 0.0017). **Y. Premchandra singh et al**[24] reported the adiponectin level was lower in the diabetic subjects than in the non-diabetic subjects (6.07 ± 1.02 vs. 7.48 ± 1.91 µg/ml; P = 0.003). The present study agrees previous findings that type II diabetes and metabolic syndrome were associated with low serum adiponectin concentrations. Low adiponectin level was a strong predictor of future development of diabetes, also showed a positive predictive association. **Nur Firdaus Isa et al**[22] reported the no significant difference of the adiponectin level between hyperglycemic and non-hyperglycemic in their studied subjects. Increasing the sample size and expanding their cross-sectional study to a cohort study with longer follow-up may fill in the gaps.

The adiponectin concentration found in our study patients with hypertension was (12.12±3.57 µg/ml) lower than those without hypertension was (14.09±3.55 µg/ml) and association was statically significant. **Masato Furuhashi et al**[28] reported the adiponectin concentrations were reduced in insulin-resistant essential hypertensives but not normotensives or non–insulin-resistant hypertensives, suggesting that hypoadiponectinemia in essential hypertensives is associated with insulin resistance. **Renaldi O et al**[29] stated the hypoadiponectinemia and insulin resistance represent independent risk factors for metabolic syndrome development.

In this study, the relationship of adiponectin with waist circumference was in male (<90 cm-13.74±3.34 µg/ml vs ≥90cm-11.18±2.38 µg/ml; P=0.034) and association was significant but in female (<80 cm-12.96±3.73 µg/ml vs ≥80cm-15.37±3.83 µg/ml; P=0.094) and association was insignificant. While **Y. Premchandra singh et al**[24] reported the relationship of adiponectin with waist circumference appeared to be stronger than other obesity indices or BMI, indicating that central fat distribution (visceral obesity) is a better determinant of circulating adiponectin than total fat mass. Waist circumference in female was (>80 cm-5.98±1.18 µg/ml vs 9.9±2.7 µg/ml; P<0.001) and Waist

Journal of Chemical Health Risks
www.jchr.org
JCHR (2023) 13(06), 2501-2509 | ISSN:2251-6727

circumference in male was (> 90 cm 5.81±4.10 µg/ml vs 7.90±0.05 µg/ml; P<0.001).

In our study the serum adiponectin concentration was significantly negative correlated with the SBP (r= -0.262; p<0.05), BMI (r= -0.288; p<0.05), Total Cholesterol (r= -0.515; P<0.001), and LDL (r= -0.305; p<0.05) respectively. **Blaslov K et al**[30] reported the patients with higher adiponectin level (n = 39) had significantly lower waist circumference (P< 0.002), fasting venous glucose levels (P< 0.001), higher HDL3-cholesterol (P = 0.011), and eGDR (P = 0.003) in comparison to the group with lower adiponectin who showed higher prevalence of MS (P = 0.045). eGDR increased for 1.09mg/kg−1 min−1 by each increase of 1 μg/mL total fasting plasma adiponectin (P = 0.003). In the logistic regression model, adiponectin was inversely associated with the presence of MS (P = 0.014). **Taniguchi A et al**[30] reported the serum adiponectin level was negatively correlated to BMI (r = −0.308, P = .002), diastolic blood pressure (r = −0.269, P = .012), and triglycerides (r = −0.338, P< .001), and positively correlated to high-density lipoprotein cholesterol (r = 0.300, P = .003) in their patients. **Chen MC et al**[23] reported the serum Adiponectin was inversely associated with Metabolic Syndrome

Conclusion

The present results suggest that circulating levels of adiponectin are reduced in the presence of the metabolic syndrome and also decrease as the number of metabolic syndrome components increases. The association of adiponectin with HDL cholesterol, triglycerides, Fasting Blood Sugar, BMI, and waist circumference may partly explain the lower levels of adiponectin found in individuals with metabolic syndrome. Further prospective studies are needed to confirm the mechanisms underlying this association.

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