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Original Research Article

Correlation of Adiponectin in Metabolic Syndrome among Newly Diagnosed Patients of T2DM in a Tertiary Care Center of Kumaon Region of Uttrakhand

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Abstract

Introduction: The prevalence of metabolic syndrome (MS)and type 2 diabetes mellitus(T2DM) has reached epidemic levels. Thus there is a need to study novel biomarkers involved in their etiopathogenesis and associated cardiovascular complications. Adiponectin, an adipokine has been implicated in insulin resistance, inflammation, obesity, and atherosclerosis associated with metabolic syndrome. In the Kumaon region, studies regarding adiponectin and its relationship in T2DM and MS patients are lacking, with this the present study was planned.

Material and Methods: Eighty seven newly diagnosed T2DM patients, enrolled in this study were divided into 2 groups. Group I comprised 48 cases of MS and rest 39 patients without MS were included in group II. All of the study subjects were assessed for anthropometric, clinical, and biochemical parameters.

Results: Lower levels of adiponectin were found in group I than in group II($p<0.001$). A significant and inverse correlation of adiponectin was observed with BMI, WC, HOMA -IR, hs-CRP, and triglyceride levels while a significantly positive correlation was seen with HDL-C in both the study groups. However, a stronger and better correlation was observed in the MS group than without the group.

Conclusions: Adiponectin was found to be decreased and significantly correlated with raised BMI, insulin resistance, hs-CRP, and dyslipidemias in the study subjects.

Keywords: Adiponectin, Metabolic Syndrome (MS), Type 2 Diabetes Mellitus (T2DM), Homeostatic Model Assessment-Insulin Resistance (HOMA-IR).

Introduction

Metabolic syndrome, previously called multiple risk syndrome, syndrome X or deadly Quarlet is characterized by the clustering of various metabolic and circulatory disorders which predisposes an individual to atherosclerotic diseases as well as type 2 diabetes mellitus [1,2]. Various clinical and epidemiological studies have suggested the key role of visceral fat as compared to subcutaneous in the development of multiple risk factors including hypertriglyceridemia,

hypertension, and insulin resistance associated with the etiopathogenesis of metabolic syndrome [3-5].

Adipose tissue earlier known as energy storing organ, is now classified as an endocrine system for its function to secrete bioactive substances collectively called adipokines or adipocytokines including interleukins (1 and 6), tumor necrosis factor (TNF-α), leptin, adiponectin [3,4]. These adipocytokines act through autocrine, paracrine, and endocrine mechanisms to have effects on various metabolic processes like fatty acid oxidation, lipogenesis, gluconeogenesis, glucose uptake, insulin signaling, and energy homeostasis in skeletal muscle, liver, and others [6,7].

Adiponectin (adipoQ,apM1, ACRp30, GBP28), is the most abundant protein synthesized predominantly by white adipose tissue. is encoded by the APM1 gene located on chromosome 3q27 [8]. Under physiological conditions, it possesses anti-inflammatory, anti-atherogenic, and insulin-sensitizing properties [9]. Adiponectin mediates its biological actions by binding to its receptors, adipoR1, adipoR2and T chain expressed predominantly in the liver and skeletal muscles. On binding adipoR1 and adipoR2, adiponectin activates the AMP kinase pathway, peroxisome proliferator-activated receptor (PPAR-α and PPAR γ) respectively, resulting in enhanced glucose uptake by muscles, inhibition of gluconeogenesis, reduction of the synthesis of fatty acids, and stimulation of their oxidation [10,11]. Furthermore, adiponectin enhances insulin sensitivity, ensuring effective protection against the development of metabolic syndrome and T2DM [12]. Studies have demonstrated that obesity causes the downregulation of adiponectin receptors, and

reduces levels of adiponectin leading to an increase in insulin resistance, subclinical inflammation, and endothelial dysfunction, proposed as contributing factors to the development of metabolic syndrome, diabetes mellitus, and cardiovascular complications [13,14]. Various clinical and experimental studies have provided insight into the importance of hypoadiponectinemia as an independent marker of IR, associated with MS, and significantly related to T2DM development [13-15].

Asian Indians have an obesity phenotype characterized by lean BMI, central obesity, and high body fat percentage which is associated with insulin resistance, high risk of diabetes, and development of its associated complications [16]. Currently, the prevalence of type 2 diabetes in India and globally has reached epidemic proportions [2]. It has been documented from metabolic studies that in humans various adipokines including adiponectin have been implicated in the development of insulin resistance and type 2 diabetes mellitus [2,17].

With this background, the purpose of the present study was 1) to determine the concentrations of adiponectin in newly diagnosed patients of T2DM with and without metabolic syndrome defined according to International Diabetes Federation (IDF) criteria 2) to evaluate the correlation of serum adiponectin levels with insulin resistance, HbA1c,fasting glucose, high sensitivity C –reactive protein (a marker of inflammation) and other parameters associated with the MS including body mass index (BMI), waist circumference, lipid profile, blood pressure in the study subject

Material and Methods

After permission from the medical research unit of Government Medical College Haldwani, the present study was conducted in the Department of biochemistry in collaboration with the medical department. The study population comprised a total of 87 newly diagnosed patients with type 2

diabetes patients according to IDF criteria. These were classified into two groups. Group 1 was forty-eight cases of newly diagnosed T2 DM patients defined as metabolic syndrome (MS). All of these were having high waist circumferences (>80cm in females and >90 cm in males) along with any of the following four parameters: triglycerides>150mg/dl, HDLc<50 mg/dl, SBP>130 mmHg, DBP>85 mmHg, raised fasting plasma glucose >126 mg/dl. Group II was the rest of the thirty-nine newly diagnosed diabetes patients not meeting the criteria of MS.

The patients already on anti-diabetic therapy and lipid-lowering drugs or drugs that interfere with glucose and lipid estimation were excluded from the study. patients with a history of chronic illness, cancer, kidney or cardiovascular diseases as well as females with gestational diabetes were not enrolled in the study.

After written and informed consent, all the study subjects were assessed for detailed clinical and physical examination. Taking all the aseptic precautions about 5 ml of blood was collected from the peripheral vein after an overnight fast of 8-10 hours. The blood was divided into two aliquots, one 3ml was divided into a fluoride vial(for FBG), EDTA vial (for HbA1c), and plain vial for estimation of hs-CRP, lipid profile, creatinine, uric acid, and the rest 2 ml was collected in a plain vial for quantitative analysis of insulin and adiponectin. This was processed according to standard protocol and separated serum was stored at -800C for further analysis.

Anthropometric assessment:

weight and height of all the patients were measured according to standard protocol. Body weight in Kg was measured in light clothing without shoes and was recorded to the nearest Kg. Height was measured in a fully erect standing position after removing the shoes and was taken to the nearest centimetres. BMI was calculated by software with the formula: BMI (kg/m2) = Weight (kg)/ Height (m2).

Waist circumference was measured midway between the costal margin and the iliac crest. Hip circumference was taken as the largest circumference at the posterior extension of the buttocks.

Waist-to-hip ratio (WHR) was also calculated as waist circumference divided by hip circumference.

Systolic and diastolic blood pressure was measured on the right arm using a sphygmomanometer by the auscultatory method.

Biochemical analysis:

Samples collected from study groups were processed and analyzed on Roche / Hitachi Cobas 501c fully automated biochemistry analyzer in the Biochemistry central laboratory.

Lab investigations done were those of fasting blood glucose, glycosylated hemoglobin (HbA1c), lipid profile including total cholesterol (TC), triglycerides (TG),high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C). All estimations were performed on the closed system using the manufacturer's kit. The normal range of measured parameters was as follows: fasting blood glucose =70- 100 mg/dL; HbA1c < 6.5%; total cholesterol < 200 mg/dL; TG < 170 mg/dL; LDL-C = 90-130 mg/dL; HDL-C ≥ 40 mg/dL in Males and ≥ 50 mg/dL in Females, creatinine =0.8-1.4mg/dl, uric acid=3.5-7.0 mg/dl, hsCRP< 3 mg/L

Fasting serum insulin levels (µIU/mL) were measured in a fully automatic immunoassay analyzer, E 411 of ROCHE based on the principle chemiluminescent immunoassay (CLIA) technique. Samples were quantitatively analyzed within a few hours of sample collection following the package-insert instructions. Insulin levels

of 2-25 µIU/mL were considered to be normal.

Homeostatic model assessment-insulin resistance (HOMA-IR) was used to evaluate insulin resistance(IR). It was calculated by software using the formula :

HOMA IR= Fasting serum insulin (IU/mL) X Fasting plasma glucose (mg/dL)/405

For the classification of IR, the HOMA score was used as a reference: 0.5-1 optimal, suggesting insulin sensitivity,1-1.9 for early IR, 1.9 - 2.9 for low IR, and> 2.9 for significant IR(18).

Serum Adiponectin levels were estimated by sandwich ELISA using DBC Diagnostics Biochem, Canada Inc. kits, with a sensitivity of 0.06 ng/ml.

Statistical analysis

Data were analyzed using a statistical package for social sciences software package version (SPSS)20. The data were expressed as mean ± SD for continuous variables. Nominal variables were expressed with numbers and percentages. Student t-test detected the difference in two variables of measured parameters. The Pearson's and Spearman correlation coefficient determined the correlation between serum adiponectin and demographic and biochemical parameters.

The results were considered nonsignificant if *the P value was* > 0.05, significant if $P < 0.05$ or less, and highly significant if $P \leq 0.01$.

Results

Table 1: Shows baseline characteristics of the study population

Parameters	Group1 (with MS) n=48	Group II (without MS) n=39	P value
Age (years)	48.56 ± 6.24	46.98 ±5.76	NS
Gender			
Females (n=49)	28(32.18%)	21(24.12%)	NS
Males (n=38)	20(22.28%)	18(20.68%)	NS
BP (mmHg)			
SBP	138.46±3.06	127.12±1.34	<0.01
DBP	87.56±1.32	78.49±0.98	<0.01
BMI (kg/m2)	28.84 ± 2.51	22.72 ± 4.56	
18-24	1(2%)	24 (61.55%)	<0.001
25-29	18 (37.51%)	13(33.33%)	<0.001
>30	29 (60.41%)	2(5%)	<0.001
WC (centimeters)	97.64±6.67	85.68±6.18	<0.001
Females	92.40±1.08	78.72±0.92	<0.001
Males	102.92±12.21	92.64±11.52	<0.001
WHR			
Females>0.85	27(96.42%)	5(23.80%)	<0.001
Males>0.90	18(90%)	7(38.88%)	<0.001

BMI: body Mass Index, WC: waist Circumference, WHR: waist Hip Ratio, BP: Blood pressure, DBP: diastolic blood pressure, SBP: Systolic Blood pressure.

Table I shows the baseline characters of the study groups. The mean age of presentation in the two groups was 48.56 ± 6.24 and 46.98 ±5.76 years respectively with no significant difference. Out of the total of eighty-seven study subjects,49(56.32%) were females, and the rest 38(43.67%) were males. The mean ± SD value of SBP and

DBP in group I (138.46±3.06 and 87.56±1.32 mm Hg) was significantly higher (p<0.001) than in the subjects of group II (127.12±1.34 and 78.49±0.98).The BMI of MS subjects (group I)than those without MS(28.84 ± 2.51 vs 22.72 ± 4.56 ;p<0.001). The majority (60.41%) of MS patients were obese with BMI >30 kg/m2 while in group II,61.55 % we're having a BMI range of 25-29 kg/m2.The waist circumference in centimeters of group I was also significantly higher than group II(97.64±6.67 vs 85.68±6.18 ; p<0.001).In addition, most of (27 out of 28) females in the MS group were with WHR > 0.85 while 14 out of 20 males in the MS group were having WHR > 0.90. In group II five females and seven males had higher WHR.

Table 2: Shows the biochemical parameters estimated in study groups

Parameters	Group1 (with MS) n=48	Group II (without MS) n=39	P Value
FBS(mg/dl)	162. 68 ± 22.82	168.52±24.87	0.182
HbA1c(%)	9.32±1.21	8.42±0.52	<0.05
Total Cholestrol (mg/dl)	168.69±28.86	159.74± 41.82	0.081
Triglycerides(mg/dl)	268.72± 32.92	186.52± 12.62	<0.001
LDLc(mg/dl)	121.62 ±6.02	110.72±7.78	0.059
HDLc(mg/dl)	38.15± 2.24	40.16± 1.21	0.041
TG/HDLc	4.34± 1.08	3.22 ±0.76	<0.01
Creatinine (mg/dl)	0.87±0.09	0.92±0.16	0.156
Uric acid (mg/dl)	4.95±0.18	4.62±0.21	0.072
hs-CRP(mg/L)	7.32±2.04	6.36±1.94	<0.01
Insulin (µIU/L)	7.94±1.86	6.01±0.62	<0.01
HOMA-IR	1.32±1.04	1.09±0.79	<0.01
Adiponectin(µg/ml)	6.52±2.58	11.93±3.62	<0.001
Females	6.89 ±1.92	12.76± 2.24	<0.001
Males	5.17 ±2.14	9.16 ±2.78	<0.001

FBS: fasting blood sugar, HbA1c: glycated haemoglobin, LDLc: low density lipoprotein cholesterol, HDLc: high density lipoprotein cholesterol, hs-CRP: high sensitive c reactive protein, HOMA-IR: Homeostatic model assessment-insulin resistance, P >0.05: non-significant, P<0.05: significant, P<0.01: highly significant

Table 2; depicts the mean ± SD levels of biochemical parameters of the study subjects. No significant difference (p=0.182) was seen in FBS levels of both the groups while the HbA1c values in group I was statistically raised (p< 0.01) than group II. In the present study the significantly higher value (p<0.001) of TG and lower levels of HDL-c were observed in group I (268.72 ± 32.92 and 38.15 ± 2.24) as compared to group II (186.52 ± 12.62 and 40.16 ± 1.21). However, no significant difference was observed in the values of TC (p =0.082)and LDL-c (p=0.059) among the study groups. The mean values of hs-CRP and fasting insulin were found to be significantly raised (p<0.01) in the MS group than without MS type 2DM subjects. The HOMA-IR levels in group I was also significantly higher than group II (1.32 ± 1.04 vs 1.09 ± 0.79 ;p<0.001). Our results showed a significantly lower (p<0.001) serum adiponectin concentration in MS patients

(6.52±2.58 µg/ml) as compared to those without MS (11.93±3.62 µg/ml)

Table 3: Depicts the correlation of adiponectin levels with anthropometric, clinical and biochemical parameters in study groups.

Parameters studied	Group1 (with MS) r value	P value	Group II (without MS) r value	P value
BMI	- 0 .476	<0.001	-0.362	<0.001
WC	-0.617	<0.001	-0.318	<0.001
WHR	-0.482	<0.001	-0.149	<0.001
HbA1c	-0.189	0.048	-0.078	0.042
SBP	-0.239	0.131	-0.124	0.056
DBP	-0.256	0.042	-0.131	0.047
TC	-0.246	0.112	-0.068	0.124
TG	-0.510	<0.001	-0.348	<0.001
LDLc	-0.121	0.067	-0.076	0.072
HDLc	0.641	<0.01	0.487	<0.01
TG/HDLc	-0.562	<0.001	-0.412	<0.001
HOMA-IR	-0.645	<0.01	-0.484	<0.001
hs-CRP	-0.641	<0.001	-0.524	<0.001

As shown in table 3, adiponectin levels were significantly inversely correlated with obesity indices (BMI, WC, and WHR), HbA1c, DBP, TG, TG/HDLc, HOMA-IR, and hs-CRP.In addition, a statistically significant positive correlation was observed between adiponectin and HDL-c levels.

Table 4 : Illustrates the concentration of adiponectin ,HOMA-IR and hs-CRP in study subjects, grouped as per grades of BMI

Parameters	Normal BMI, n=25 (<25 kg/m2)	Overweight, n=31 (25-30 kg/m2)	Obese, n=31 (<30 kg/m2)
Adiponectin(µg/ml)	13.52 ± 4.58	10.89 ± 3.10	5.15 ± 2.26
HOMA-IR	0.49 ± 0.15	1.07 ± 0.74	1.46 ± 1.02
hs-CRP (mg/L)	4.89 ± 1.79	6.19 ± 2.46	8.02 ± 2.94

Table 4; illustrates that the levels of adiponectin were reduced with increasing BMI. However, levels of HOMA-IR and hs-CRP were observed to be raising with higher BMI.

Discussion

Metabolic Syndrome, characterized by the congregation of multiple risk factors including obesity, hypertension, elevated triglycerides, reduced HDL-c along with impaired fasting blood glucose has been associated with the increased risk of T2DM and macrovascular complications [19,20].

Adiponectin increases insulin sensitivity and contributes to protection against the development of T2DM and MS [20,21]. In the present study, we have observed lower levels of adiponectin in both MS and without MS T2DM groups. However, the levels were significantly lower in MS patients than in those without MS. This

finding is in agreement with various studies [22-24] including by Fisman et al reporting low levels of adiponectin in T2DM and CAD and an inverse relation of serum adiponectin to body fat mass and the degree of insulin resistance. They concluded hypoadiponectinemia is a strong risk marker for the development of MS [13].

Furthermore, adiponectin concentration was higher in females of both study groups than the male counterpart. This finding is as per previous experimental and clinical studies suggesting that sex hormones such as estrogen and testosterone regulate the production of adiponectin. In addition, the fact that females are more sensitive to insulin action may have also contributed to higher adiponectin levels in females than males [25,26].

In this study, we have observed the inverse and significant correlation of adiponectin concentrations with obesity indices including BMI, WC, WHR, and hs-CRP, an inflammatory marker. As consistent with various studies, we have also observed a progressive decrease in adiponectin levels with increasing obesity indicated by raised BMI [27,28]. Cho SA et al also reported that, unlike the other adipokines, serum adiponectin levels were reduced in obese individuals and negatively correlated with chronic subclinical inflammation markers [29]. In addition, Choi HM et al have documented that high visceral fat accumulation is associated with less secretion of adiponectin and suggested the inhibitory effect of inflammatory cytokine including TNF-α on adiponectin synthesis as well as its secretion [30]. Furthermore, Balagopal et al have shown that an increase in adiponectin levels after weight reduction in obese subjects is correlated with a decrease in proinflammatory cytokines like leptin, IL6, and hs- CRP [31]. In contrast, Yeli Wang et al have reported that independent of BMI or CT-assessed abdominal fat people with T2DM have lower plasma adiponectin concentrations suggesting hypoadiponectinemia as a marker independent of obesity in T2DM and associated cardiovascular diseases [32].

We have found increasing HOMA-IR and decreased adiponectin with increasing BMI. In addition, a negative correlation between HOMA –IR and adiponectin levels in both with and without MS T2DM groups. Earlier studies had documented that physiologically hormone insulin mediates the secretion of adiponectin from adipose tissue and adiponectin in turn acts as a signaling protein in various metabolic pathways and has involvement in the regulation of insulin synthesis and provokes its sensitivity [1,4,33]. Recently Nabila et al reported that even after adjustment for various risk factors there is an association of low adiponectin with incident T2DM and concluded that adiponectin could be a useful screening marker for the early diagnosis of T2DM in a population [34]. In addition, evidences suggest that insulin resistance associated with obesity may be attributed to the reduced synthesis of circulating adiponectin levels. With the increase of adiponectin levels by therapeutic agents or weight reduction, beneficial effects on insulin sensitivity, and lipoprotein metabolism may be there, to protect from these risk factors for MS and T2DM development [28,35,36]. In the existing literature, the association between T2DM and dyslipidemia has been well documented [37-40].

Adiponectin plays an important role in lipid metabolism as it enhances fatty acid oxidation and inhibits lipogenesis in the liver [1,3]. In the current study raised the level of triglyceride was inversely correlated and HDL-C concentration was positive with decreased adiponectin levels in both the study groups. Consistent with previous studies [38-40], recently Zocchi et

al have documented that low-grade chronic inflammation associated with obesity, reciprocally regulates serum levels as well as activities of adiponectin and HDLc

predisposing to endothelial dysfunctions evident in pathological states including T2DM and MS [41,42].

Limitations:

It was a hospital-based study, so the findings cannot be generalized to the community level. A large sample size, community-based prospective study has to be conducted to determine the exact relationship between adiponectin and metabolic syndrome parameters in this region.

Conclusions:

The results show that serum adiponectin levels in MS patients were significantly lower than without MS newly diagnosed T2DM subjects in the Kumaon region of Uttarakhand. Serum adiponectin levels were found to be inversely associated with the glycemic indices, obesity markers, HOMA-IR, and inflammatory marker(hs-CRP) more strongly in the MS syndrome group than without the MS group. Thus weight reduction, lifestyle modifications, and therapeutic interventions, to increase adiponectin levels may be valuable in the management of various risk factors associated with metabolic syndrome and T2DM development and their progression to various

complications. In the future epidemiological studies are required to establish the role of adiponectin as a biomarker as well as a therapeutic agent in type 2 diabetes mellitus.

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