MÆDICA - a Journal of Clinical Medicine

ORIGINAL PAPER

MAEDICA – a Journal of Clinical Medicine
2024; 19(3): 494-501
https://doi.org/10.26574/maedica.2024.19.3.494

Association of Adipokines and CIMT in Metabolic Syndrome in Western Uttar Pradesh Population: a Cross-Sectional Study

Ravi Pratap SINGH[a], Kalpana CHAUHAN[b], Alok TRIPATHI[c], Rekha CHOUDHARY[d]

[a]Associate Professor, Department of Biochemistry, Subharti Medical College, Meerut (UP) 250005, India

[b]Professor, Department of Microbiology, Subharti Medical College Meerut (UP) 250005, India

[c]Associate Professor, Department of Anatomy, Mahatma Vidur Autonomous State Medical College, Bijnor (UP) 246701, India

[d]Associate Professor, Department of Biochemistry, Mahatma Vidur Autonomous State Medical College, Bijnor (UP) 246701, India

ABSTRACT

Background: *A cluster of metabolic indicators responsible to elevate the risk of high blood sugar, heart diseases along with stroke is called metabolic syndrome (MetS). Adipokines play critical roles in the formation and progression of these clusters of diseases. Adiponectin enhances fatty acid oxidation, prevents foam cell formation and improves lipid metabolism. In contrast, plasminogen activator inhibitor-1 (PAI-1) possesses pro-atherogenic properties. Carotid intima-media thickness (CIMT) is directly associated with an increased risk of myocardial infarction and stroke. Complete information about the association related to adipokines and CIMT in MetS of Indian population is lacking.*

Objective: *To evaluate the association of adipokine levels and PAI-1 with CIMT in MetS patients, including its components.*

Materials and methods: *We performed a cross-sectional study and IDF criteria were used for the screening of MetS. A total of 164 subjects with MetS (88 males and 76 females) and 100 controls (54 males and 46 females) were enrolled. Serum levels of adiponectin and PAI-1 were measured using ELISA. A CIMT measurement of carotid arteries was also done. The relationship between various parameters was assessed by the Pearson correlation coefficient test.*

Results: *The levels of adiponectin were lower ($p < 0.001$), while those of PAI-1 and CIMT were higher ($p < 0.001$) when we compared patients with controls. When the number of metabolic abnormalities*

Address for correspondence:
Dr. Rekha Choudhary, Associate Professor
Department of Biochemistry, Mahatma Vidur Autonomous State Medical College, Bijnor (UP) 246701, India
Tel.: 8319006619, 8889642561; email: cdr.rekha76@gmail.com

Article received on the 8th of August 2024 and accepted for publication on the 24th of September 2024

increased, the levels of adiponectin decreased and those of PAI-1 increased. There was a strong negative association between PAI-1 levels and those of adiponectin (p <0.001).

Conclusion: *Our findings indicate that elevated PAI-1 levels are associated with a higher probability of having MetS and negatively impact MetS-related components.*

Keywords: metabolic syndrome (MetS), adipokine, adiponectin, plasminogen activator inhibitor-1 (PAI-1), insulin resistance, atherosclerosis.

INTRODUCTION

The clustering of cardiovascular risk factors, including central adiposity, hypertension, hyperglycemia, high triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C), is referred to as metabolic syndrome (MetS). This syndrome is a strong predictor of the long-term risk of high blood sugar and diseases of the heart and circulation (cardiovascular disease – CVD) (1-4). The primary driving force behind MetS is related to obesity (5) Adipose tissue products, such as adiponectin, leptin, plasminogen activator inhibitor-1 (PAI-1), resistin, inflammatory cytokines and angiotensinogen, are known to affect the systemic metabolism (6). Adiponectin plays a crucial role in regulating insulin sensitivity and the development of insulin resistance (7). Adiponectin activates adenosine monophosphate-activated protein kinase and peroxisome proliferator-activated receptor-γ in the skeletal muscles and liver. This activation plays a role in stimulation of the phosphorylation of acetyl-CoA carboxylase and fatty acid oxidation, thereby reducing tissue triglyceride content related to muscles along with the liver. These changes enhance insulin sensitivity *in vivo* (6, 7). Studies show that plasma levels of adiponectin are significantly reduced in obese individuals (8) and they are also decreased in those with type 2 diabetes mellitus (T2DM), CVD, hypertension, along with MetS (9-11). Decreased levels of plasma adiponectin are related to an increased body mass index (BMI), decreased insulin sensitivity, less favourable plasma lipid profiles and elevated levels of inflammatory markers, all of which contributing to a heightened risk for developing CVD. Consequently, adiponectin levels are promising indicators for clinical use; they are also helpful as strong markers of underlying medical complications related to metabolism (12, 13).

The fully grown adipocyte is a potential source of circulating PAI-1 in humans. Plasma PAI-1 levels are very high in people with obesity and insulin resistance, and they are positively correlated with features of MetS. These high levels also predict future risks for T2DM and CVD, suggesting that PAI-1 may contribute to the complication of obesity along with insulin resistance, potentially acting as a causal link between obesity and CVD (13-15).

Carotid intima-media thickness is a non-invasive, cost-effective, rapid and reproducible measurement. Increased CIMT, a proxy for carotid atherosclerosis, is a significant determinant of CVD and stroke risks (13-15). Furthermore, it is well known that MetS is significantly associated with stroke. Adiponectin, PAI-1 and CIMT are interconnected in the context of cardiovascular health and MetS. Low adiponectin levels are associated with high PAI-1 levels, which in turn are associated with increased CIMT; there are few studies that have evaluated the association of adipokines and CIMT in Indian population (16-19). However, the association between adipokines in MetS population is currently unclear, especially in India.

MATERIAL AND METHODS

In this cross-sectional study, subjects aged 18 to 60 years (to exclude post-menopausal women) were screened for the presence of MetS according to the standard set by the International Diabetes Federation (IDF). The criteria included central obesity, defined as a waist circumference of ≥90 cm for males and ≥80 cm for females, plus any two of the following conditions: elevated triglycerides (>150 mg/dL), reduced HDL-C (<40 mg/dL in men and <50 mg/dL in women), raised blood pressure (systolic ≥130 mm Hg or diastolic ≥ 85 mm Hg), and elevated fasting glucose (≥100 mg/dL). A total of 164 subjects with

MetS (88 males and 76 females) and 100 control subjects (54 males and 46 females) were enrolled from the Metabolic Outpatient Department (OPD) of Chhatrapati Shivaji Subharti Hospital, Subharti Medical College (SMC), Swami Vivekanand Subharti University (SVSU), Meerut, India. Age- and sex-matched healthy subjects without MetS were screened and selected as controls. All participants underwent a clinical examination. Subjects with type 1 diabetes, hepatitis, renal disease, pregnancy, alcoholism, infectious diseases, or those on any medication were excluded from the study on the basis of patients' personal medical history.

Physical examination

Routine examination including height, weight, pulse, blood pressure and waist circumference (WC) were recorded. General and systemic examination was done and findings were noted.

A designated research physician measured participants' anthropometric and body composition parameters. The BMI was calculated as each subject's weight in kilograms divided by the square of their height in meters. Waist circumference was measured using a measuring tape along the horizontal plane of the iliac crest after the subject exhaled (20).

Blood pressure levels were measured using a mercury sphygmomanometer on the right arm of participants in a relaxed sitting position. Blood pressure levels were reported as the mean of four replicate readings.

Laboratory analysis

Fasting blood samples were drawn under all aseptic precautions. Estimation of glucose, HbA_{1c}, lipid profile, insulin and highly sensitive C-reactive protein (hsCRP) were done on Abbott architect ci4100 integrated Chemistry & Immunology System, in the Central Lab of CSSH. The laboratory is accredited by National Accreditation Board for Testing and Calibration Laboratories (NABL), New Delhi, India.

One aliquot of the sample was frozen at −80°C for the measurement of plasma adiponectin and PAI-1. Quantitative estimation of adiponectin and PAI-1 levels were performed using commercially available enzyme-linked immunosorbent assay kits (Invitrogen™ Human Kits). Serum insulin resistance was estimated by the homeostasis model assessment (HOMA-IR) and calculated as fasting insulin (μIU/mL) x fasting glucose (mg/dL)/405 (20).

Carotid intima-media thickness was measured in the Department of Radiodiagnosis & Imaging, SMC on Samsung HS70 ultrasound unit with high resolution linear probe of 5-10 MHz frequency. Participants were examined in the supine position with their head slightly extended and turned in the opposite direction of the carotid artery. CIMT measurements were done at the proximal, middle and distal levels of both common carotid arteries. The mean of the maximum readings of three right and three left far walls were used to estimate CIMT (21). The current study was approved by the ethical committee of SMC (ethical clearance letter no. 503/259 dated 15.02.2023), Meerut, India, and written informed consent was obtained from all subjects.

Statistical analysis was performed using EPI INFO 3.5.3 (CDC; Atlanta; USA). Data were presented as mean±SD or number (%) unless otherwise specified. Parametric data were analysed using Student's t-test. If Bartlett's chi-square test for equality of population variances yielded a p-value of less than 0.05, the Kruskal-Wallis test was used. Chi-square test was used for the analysis of non-parametric data. To find out the association between various parameters, univariate regression analysis was conducted. A p-value which was considered statistically significant was less than 0.05.

RESULTS

Our study included 264 subjects (164 patients with MetS and 100 healthy controls), with an equal sex ratio in both groups. The mean ages of cases and controls were comparable. When BMI values were compared between MetS and control groups, the BMI was higher in MetS subjects than controls. Among cases, 98 (60%) had T2DM and 39 (24%) impaired glucose tolerance. Hypertension was present in 74 cases (45%). Triglycerides (TG), total cholesterol (TC), low-density lipoprotein (LDL) and very low-density lipoprotein (VLDL) levels were significantly higher, while high-density lipoprotein (HDL) levels were significantly lower in the MetS group compared to controls. Notably, 32 controls (32%) also had low HDL levels. Most cases (96/164, or 58.54%) had four features of MetS, followed by 41 cases (25%) with three features

TABLE 1. Anthropometric, biochemical, metabolic and carotid intima-media thickness (CIMT) values in cases and controls

Parameters	Cases (n=164) (%)	Controls (n=100) (%)	P value
Age	43.4 ± 5.3	41.9 ± 4.0	0.21
WHR (male)	1.18 ±0.1	0.84 ± 0.04	<0.0001
WHR (female)	1.21 ± 0.11	0.74 ± 0.03	<0.0001
BMI (kg/m^2)	32.4 ± 4.2	25.3 ± 3.7	<0.0001
Systolic BP (mm Hg)	134.0 ± 14.2	122.2 ± 9.0	0.001
Diastolic BP (mm Hg)	84.0 ± 9.7	76.3 ± 8.2	0.004
Glycemic status			
FPG (mg/dL)	141 ± 37	91 ± 8	<0.0001
PPG (mg/dL)	214 ± 51	124 ± 19	<0.0001
HbA_{1c} (%)	7.9 ± 0.9	5.0 ± 0.4	<0.0001
Insulin (µIU/mL)	10.7 ± 10.2	5.2 ± 2.38	<0.0001
HOMA-IR	3.85 ± 4.14	1.82 ± 0.47	0.029
Lipid profile			
Triglycerides (mg/dL)	212 ± 58	110 ± 32	<0.0001
HDL (mg/dL)	34 ± 7	46 ± 12	<0.0001
TC (mg/dL)	234 ± 42	171 ± 31	<0.0001
LDL (mg/dL)	139 ± 39	111 ± 222	<0.0001
VLDL (mg/dL)	40 ± 12	19 ± 15	<0.0001
Metabolic features	-		
None	-	43 (43)	
One	-	57 (57)	
Two	-	-	
Three	41 (25)	-	
Four	96 (58.54)	-	
Five	27 (16.46)	-	
Inflammatory markers			
hsCRP (mg/dL)	4.07 ± 1.72	2.09 ± 0.98	0.0006
Adipokines			
Adiponectin (ng/mL)	10.26 ±3.78	26.5 ± 7.6	<0.0001
PAl-1 (ng/mL)	58.19 ± 16.24	21.5 ± 6.14	<0.0001
CIMT (mm)	0.78 ± 0.17	0.45 ± 0.09	<0.0001

WHR=waist hip ratio; BMI=body mass index; BP=blood pressure;
FPG=fasting plasma glucose; PPG=postprandial plasma glucose;
HbA_{1c}=glycated haemoglobin;
HOMA-IR=homeostatic model assessment of insulin resistance;
HDL=high density lipoprotein; TC=total cholesterol;
LDL=low density lipoprotein;
VLDL=very low density lipoprotein;
hsCRP=highly sensitive C-reactive protein;
PA-1=plasminogen activator inhibitor-1;
CIMT=carotid intima-media thickness.

and 27 cases (16.46%) with all features. Subjects with MetS had significantly lower adiponectin levels (10.26±3.78 ng/mL *vs.* 26.5±7.6 ng/mL; $p < 0.001$) and significantly higher PAI-1 levels (58.19±16.24 ng/mL *vs.* 21.5±6.14 ng/mL; $p < 0.001$) compared to controls (Table 1).

Adiponectin levels decreased and PAI-1 levels increased with increasing number of metabolic abnormalities (Table 2, Figure 1).

There was no significant difference in adiponectin levels between sexes. Univariate regression analysis revealed that adiponectin was negatively associated with BMI. Among various parameters of MetS, the correlation of adiponectin was negative with most parameters, excepting a positive association for HDL-C. Adiponectin was strongly negatively associated with inflammatory markers (hsCRP) and the procoagulant marker PAI-1. Additionally, adiponectin was negatively correlated with insulin resistance as measured by HOMA-IR (Table 3). In univariate regression analysis, PAI-1 was positively associated with BMI and negatively associated with HDL. Plasminogen activator inhibitor-1 had a positive association with all parameters of MetS, except for one negative association with HDL. Also, PAI-1 had a strong positive association with hsCRP, insulin resistance (fasting plasma insulin and HOMA-IR), total cholesterol and LDL-cholesterol, but a strong negative association with adiponectin (Table 3).

Table 4 shows participants' general characteristics categorized by serum PAI-1 quartiles (Q1-Q4). Adiponectin levels decreased as PAI-1 levels increased ($p < 0.05$). Conversely, higher PAI-1 levels were associated with increases in age, FBG, HbA1c%, total cholesterol, LDL and TG ($p < 0.05$). The highest prevalence of MetS was observed in the Q3 quartile of serum PAI-1 (Table 4).

TABLE 2. Division of study groups based on the number of metabolic syndrome components

Group	No. of MetS components present in subjects		Adiponectin	PAI-1	CIMT (mm)
1	Zero (no component)		28.7	17.86	0.39
2	1 (WC)		25.3	24.27	0.47
3	1+1 (WC + 1 components)		18.4	27.11	0.48
4	**1+2 (WC + 2 components)**	**Metabolic syndrome***	12.3	34.86	0.56
5	**1+3 (WC + 3 components)**		10.7	49.54	0.69
6	**1+4 (WC + 4 components)**		8.5	51.84	0.77
7	**1+5 (WC + 5 components)**		7.6	63.15	0.92

**As per* the International Diabetes Federation 2005

MetS=metabolic syndrome; PA-1=plasminogen activator inhibitor-1; CIMT=carotid intima-media thickness.

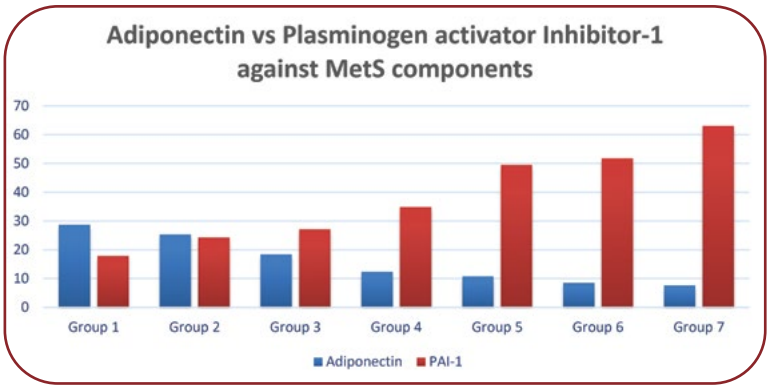

FIGURE 1. Comparative bar-graph of adiponectin and plasminogen activator inhibitor-1 (PAI-1) against metabolic syndrome (MetS) components

The study population was grouped as 1–7, depending on the presence of several components of MetS (0, 1, 1+1, 1+2...). It was observed that the appearance of the number of components of MetS was increasing; PAI-1 were found to be more significantly increased, excepting adiponectin, which was found to be more affected (Table 2).

Adiponectin, PAI-1 and CIMT are interconnected in the context of cardiovascular health and MetS. Low adiponectin levels are associated with high PAI-1 levels, which in turn are associated with increased CIMT, and CIMT is posi-

TABLE 3. Association between various parameters of the study

Parameters	Adiponectin		PAI-1	
	Beta coefficient	p value	Beta coefficient	p value
Age	-0.205 (0.05)	0.054	0.105 (0.01)	0.382
Sex	0.845 (0.02)	0.591	-0.593 (0.02)	0.648
BMI	-0.785 (0.46)	<0.00001	0.638 (0.43)	<0.00001
Metabolic syndrome				
WHR	-18.598 (0.45)	<0.00001	15.324 (0.41)	<0.00001
FPG	-0.74 (0.31)	<0.00001	0.098 (0.28)	<0.00001
Hypertension	-6.173 (0.20)	0.00003	4.741 (0.18)	0.0009
Triglycerides	-0.051 (0.35)	<0.00001	0.048 (0.39)	<0.00001
HDL	0.281 (0.09)	0.024	-0.149 (0.12)	0.012
Other parameters				
Total cholesterol	-0.038 (0.16)	0.002	0.053 (0.18)	0.006
LDL	-0.035 (0.04)	0.231	0.028 (0.05)	0.032
hSCRP	-1.540 (0.21)	0.00001	1.489 (0.34)	<0.00001
Fasting plasma insulin	-0.251 (0.06)	0.22	0.145 (0.09)	0.052
HOMA-IR	-0.840 (0.14)	0.007	0.734 (0.22)	0.001
PAI-1	-0.871 (0.60)	<0.00001	-	-
Adiponectin	-	-	-0.686 (0.60)	<0.00001

BMI=body mass index; WHR=waist hip ratio; FPG=fasting plasma glucose;
HDL=high density lipoprotein; LDL=low density lipoprotein;
hsCRP=highly sensitive C-reactive protein;
HOMA-IR=homeostatic model assessment of insulin resistance;
PA-1=plasminogen activator inhibitor-1.

TABLE 4. Subjects grouped by estimated plasminogen activator inhibitor-1 (PAI-1) quartiles (Q1-Q4)

Group	All	Q 1	Q2	Q3	Q4	P value
N	264	66	66	66	66	
Age (years)	46.3±5.9	45.2±8.5	48.2±7.4	52.4±4.8	54.2±6.2	0.001
BMI (kg/m^2)	34.7±7.4	30.8±5.8	32.1±6.3	33.3±4.2	32.4±6.2	0.260
Systolic BP (mm Hg)	130.4±15.2	134.8±16.58	131.0±18.5	133.6±12.8	130.6±16.2	0.328
Diastolic BP (mmHg)	78.2±10.8	79.9±12.6	80.1±8.2	83.6±8.0	80.1±10.6	0.204
FPG (mg/dL)	128.9±41.2	115.8±47.6	139.8±31.3	154.4±23.5	167.4±12.1	0.001
TG (mg/dL)	170.2±88.4	154.2±48.5	182.8±64.2	185.5±89.9	192.0±68.4	0.013
HDL (mg/dL)	41.8±16.2	45.9 ± 12.6	40.1± 10.4	42.0±15.8	41.6±10.7	0.548
HbA$_{1c}$ (%)	6.8±1.4	5.4±1.6	6.3± 1.3	6.9±0.9	7.8±0.7	0.001
TC (mg/dL)	191.2±67.6	158.3±48.7	168.8±39.9	192.3±41.1	208.6±36.5	0.001
LDL (mg/dL)	132.8±58.5	112.5±42.8	126.1±35.2	132.6±47.8	149.7±43.2	0.001
Insulin (µIU/mL)	8.28±11.82	9.46±9.58	11.25±4.34	13.52±5.6	17.36±6.7	0.017
Adiponectin (ng/mL)	13.1±13.68	18.62±7.94	13.67±8.54	9.92±7.46	7.55±6.83	0.001
PAI-1 ng/mL	38.8±19.5	17.68±-3.96	25.38±6.13	39.38±9.37	57.64±14.53	0.001
MetS	164 (62.12)	36 (21.95)	41 (25)	47 (28.66)	40 (24.39)	0.125

BMI=body mass index; BP=blood pressure; FPG=fasting plasma glucose; TG=triglyceride;
HbA$_{1c}$=glycated haemoglobin; HDL=high density lipoprotein; TC=total cholesterol; LDL=low density lipoprotein;
PA-1=plasminogen activator inhibitor-1; MetS=metabolic syndrome.

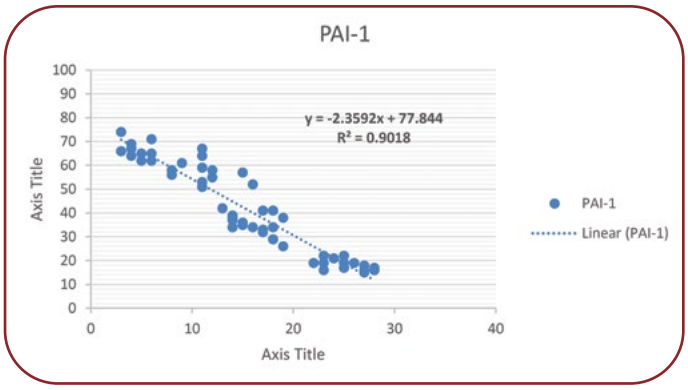

FIGURE 2. Plasminogen activator inhibitor-1 (PAI-1) levels showing a strong negative association with adiponectin

tively associated with PAI-1 and negatively associated with adiponectin.

DISCUSSION

Metabolic syndrome is indeed becoming more prevalent both in the United States and globally, with significant implications for CVD in Asia (22-31). In the present study, the fact that all cases had significantly higher values of the WHR and BMI than controls in both sexes aligns with what is known as the "Asian Indian obesity phenotype" (23). Our findings reveal that CIMT is positively associated with PAI-1 and negatively associated with adiponectin, which is similar to the study conducted by Sepulveda *et al* (31).

Also, when comparing the adiponectin levels between the two groups, we found that MetS subjects had significantly lower adiponectin levels than controls, which is consistent with the majority of studies on MetS across various ethnicities and genders as well as age groups. The mechanism involved in the association of adiponectin and PAI-1 with MetS involves insulin resistance. The anti-inflammatory properties of adiponectin counteract the pro-inflammatory effects of PAI-1. The latter impairs the endothelial dysfunction, while adiponectin improves it (31). However, there are exceptions. Thus, Sepulveda *et al* reported higher adiponectin levels in MetS patients (31), and another study found low adiponectin levels that were not statistically significant (36). No sex differences in adiponectin levels were observed in the present study, although other studies (34) have reported higher adiponectin levels in female subjects. Additionally, adiponectin levels were negatively correlated with age, BMI, FPG, hypertension, TGs, TC, high-sensitivity C-reactive hsCRP, HOMA-IR and PAI-1. Conversely, adiponectin levels were positively correlated with basal BMR and HDL, which is in accordance with the existing literature (35-39). However, some discrepancies between our study and others were noted. For instance, we found no correlation with fasting insulin, as also observed by a study from South India (20), which contrasts with studies reporting a negative correlation (30, 35, 40). Additionally, we found a negative correlation between adiponectin and cholesterol, similarly to the study performed by Bilgili *et al* (29), while some studies (20, 34, 40) found no such relationship.

According to the present study, the association of adiponectin and PAI-1 levels was a strong negative one, even after adjusting for factors like HOMA-IR and CRP. This finding aligns with the study conducted by Bilgili *et al* (29), who have also reported an inverse relationship between plasma adiponectin and PAI-1 ($r = -0.653$, $P < 0.001$). Subjects with MetS had higher PAI-1 levels than controls, which was consistent with many studies in the literature (15, 29, 41-43). However, in our study, PAI-1 levels were higher than those reported in other ethnic populations. The increased PAI-1 levels observed in the Indian population when compared with African population can be related to the increased prevalence of PAI-1 4G allele (44).

The level of PAI-1 increased with the number of metabolic abnormalities, and a similar trend was reported by other studies (30, 41). Among the various MetS parameters, PAI-1 was positively associated with all, except for HDL-cholesterol, with which it showed a negative association. In our study, PAI-1 was shown to have a positive association with inflammatory markers (hsCRP), insulin resistance (fasting plasma insulin, HOMA-IR), total and LDL-cholesterol, and a strong negative association when compared with adiponectin. These findings are consistent with other studies that have reported significant correlations between PAI-1 and obesity and dyslipidemia variables (45).

Study limitations

Data from our small clinical samples and the limited number of subjects may not be represen-

tative for general populations. Also, CIMT may be influenced by other risk factors that have not been tested in our study. Sex specific association between adipokine profile and PAI-1 has not been done. Age wise distribution in male and female subjects along-with its association with biochemical parameters needs to be further added.

CONCLUSION

Our findings indicate that elevated levels of PAI-1 are associated with an increased risk of MetS and its adverse effects. Additionally, lower levels of adiponectin are negatively correlated with the risk of MetS and its components. These results suggest a potential link between PAI-1 and the prevalence of MetS; however, this association requires clarification through prospective studies. In summary, the association between adiponectin, PAI-1 and CIMT highlights the complex interplay between adipose tissue, inflammation and cardiovascular health. ❑

Conflicts of interest: none declared.
Financial support: none declared.

References

1. **Kim D, et al.** Sex-specific associations between adipokine profiles and carotid-intima media thickness in the Cameron County Hispanic cohort (CCCHC). *Cardiovasc Diabetol* 2023;22:231.
2. **Roy PKr, Islam J, Lalhlenmawia H.** Prospects of potential adipokines as therapeutic agents in obesity-linked atherogenic dyslipidemia and insulin resistance. *Egypt Heart J* 2023;75:24.
3. **Babaei P, Hoseini R.** Exercise training modulates adipokine dysregulations in metabolic syndrome. *Sports Med Health* Sci 2022;4:18-28.
4. **Misra A, Misra R, Wijesuriya M, Banerjee D.** The metabolic syndrome in South Asians: Continuing escalation and possible solutions. *Indian J Med Res* 2007;125:345-54.
5. **Chen G, Liu C, Yao J, et al.** Overweight, obesity, and their associations with insulin resistance and -cell function among Chinese: A cross-sectional study in China. *Metabolism* 2010;59:1823-1832.
6. **Scherer PE.** Adipose tissue: From lipid storage compartment to endocrine organ. *Diabetes* 2006;55:1537-1545.
7. **Kadowaki T, Yamauchi T.** Adiponectin and Adiponectin Receptors. *Endocr Rev* 2005;26:439-451.
8. **Arita Y, Kihara S, Ouchi N, et al.** Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. Biochem *Biophys Res Commun* 1999;257:79-83.
9. **Hotta K, Funahashi T, Arita Y, et al.** Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;20:1595-1599.
10. **Kumada M, Kihara S, Sumitsuji S, et al (Osaka CAD Study Group).** Association of hypoadiponectinemia with coronary artery disease in men. *Arterioscler Thromb Vasc Biol* 2003;23:85-89.
11. **Ouchi N, Ohishi M, Kihara S, et al.** Association of hypoadiponectinemia with impaired vasoreactivity. *Hypertension* 2003;42:231-234.
12. **Trujillo ME, Scherer PE.** Adiponectin: Journey from an adipocyte secretory protein to biomarker of the metabolic syndrome. *J Intern Med* 2005;257:167-175.
13. **Alessi MC, Juhan-Vague I.** PAI-1 and the metabolic syndrome: links, causes, and consequences. *Arterioscler Thromb Vasc Biol* 2006;26;2200-7.
14. **De Maat MP, Bladbjerg EM, Drivsholm T, et al.** Inflammation, thrombosis and atherosclerosis: Results of the Glostrup study. *J Thromb Haemost* 2003;1:950-957.
15. **Vague P, Juhan-Vague I, Aillaud MF, et al.** Correlation between blood fibrinolytic activity, plasminogen activator inhibitor level, plasma insulin level, and relative bodyweight in normal and obese subjects. *Metabolism* 1986;35:250-253.
16. **Mahadik SR, Deo SS, Mehtalia SD.** Association of adiposity, inflammation and atherosclerosis: The role of adipocytokines and CRPin Asian Indian subjects. *Metab Syndr Relat Disord* 2008;6:121-128.
17. **Mohan V, Deepa R, Pradeepa R, et al.** Association of low adiponectin levels with the metabolic syndrome – The Chennai Urban Rural Epidemiology Study (CURES-4). *Metabolism* 2005;54:476-481.
18. **Snehalatha C, Yamuna A, Ramachandran A.** Plasma adiponectin does not correlate with insulin resistance and cardiometabolic variables in nondiabetic Asian Indian teenagers. *Diabetes Care* 2008;31:2374-2379.
19. **Vikram NK, Misra A, Pandey RM, et al.** Adiponectin, insulin resistance, and C-reactive protein in post pubertal Asian Indian adolescents. *Metabolism* 2004;53:1336-1341.
20. **Matthews DR, Hosker JP, Rudenski AS, et al.** Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412-419.
21. **Amato M, Montorsi P, Ravani A.** Carotid intima-media thickness by B-mode ultrasound as surrogate of coronary atherosclerosis: correlation with quantitative coronary angiography and coronary intravascular ultrasound findings. *Eur Heart J* 2007;28:2094-2101.
22. **Grundy SM, Cleeman JI, Daniels SR, et al.** Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation* 2005;112:2735-2752. https://doi.org/10.1161/CIRCULATIONAHA.105.169404.
23. **Bhatnagar D, Anand IS, Durrington PN, et al.** Coronary risk factors in people from theIndian Subcontinent living in west London and their siblings in India. *Lancet* 1995;345:405-409.
24. **Banerji MA, Faridi N, Atluri R, et al.** Body composition, visceral fat, leptin, and insulin resistance in Asian Indian men. *J Clin Endocrinol Metab* 1999;84:137-144.
25. **Tajtáková M, Petrásova D, Petrovicová J,**

et al. Adiponectin as a biomarker of clinical manifestation of metabolic syndrome.
Endocr Regul 2006;40:15-19.

26. **Santaniemi M, Kesäniemi YA, Ukkola O.** Low plasma adiponectin concentration is an indicator of the metabolic syndrome.
EurJ Endocrinol 2006;155:745-750.
27. **Choi KM, Ryu OH, Lee KW, et al.** Serum adiponectin, interleukin-10 levels and inflammatory markers in the metabolic syndrome.
Diabetes Res Clin Pract 2007;75:235-240.
28. **Restituto P, Colina I, Varo JJ, Varo N.** Adiponectin diminishes platelet aggregation and sCD40L release. Potential role in the metabolic syndrome.
Am J Physiol Endocrinol Metab 2010;298:E1072-E1077.
29. **Bilgili S, Celebiler AC, Dogan A, Karaca B.** Inverse relationship between adiponectin and plasminogen activator inhibitor-1 in metabolic syndrome patients.
Endocr Regul 2008;42:63-68.
30. **You T, Nicklas BJ, Ding J, et al.** The metabolic syndrome is associated with circulating adipokines in older adults across a wide range of adiposity.
J GerontolA Biol Sci Med Sci 2008;63:414-419.
31. **Sepulveda KK, Huffman FG, Mclean M, Zarini GG.** Increase dadiponectin among Cuban American type 2 diabetics with metabolic syndrome.
FASEB J 2009;23:547-548.
32. **Mori Y, Hoshino K, Yokota K, et al.** Role of hypoadiponectinemia in the metabolic syndrome and its association with post-glucose challenge hyper-free fatty acidemia: A study in prediabetic Japanese males.
Endocrine 2006;29:357-361.
33. **Patel DA, Srinivasan SR, Xu JH, et al.** Adiponectin and its correlates of cardiovascular risk in young adults: The Bogalusa Heart Study.
Metabolism 2006;55:1551-1557.
34. **Yang WS, Lee WJ, Funahashi T, et al.** Plasma adiponectin levels in overweight and obese Asians.
Obes Res 2002;10:1104-1110.
35. **Seino Y, Hirose H, Saito I, Itoh H.** High molecular weight multimer form of adiponectin as a useful marker to evaluate insulin resistance and metabolic syndrome in Japanese men.
Metabolism 2007;56:1493-1499.
36. **Hung J, McQuillan BM, Thompson PL, Beilby JP.** Circulating adiponectin levels associate with inflammatory markers, insulin resistance and metabolic syndrome independent of obesity.
Int J Obes (Lond) 2008;32:772-779.
37. **Tanianskiĭ DA, Firova EM, Shatilina LV, Denisenko AD.** Adiponectin: Lowering in metabolic syndrome and independent relation to hypertriglyceridemia.
Kardiologiia 2008;48:20-25.
38. **Ryu HK, Yu SY, Park JS, et al.** Hypoadiponectinemia is strongly associated with metabolic syndrome in Korean type 2 diabetes patients.
J Am Coll Nutr 2010;29:171-178.
39. **Ku BJ, Kim SY, Lee TY, Park KS.** Serum ferritin is inversely correlated with serum adiponectin level: Population-based cross-sectional study.
Dis Markers 2009;27:303-310.
40. **Lewandowski KC, Szosland K, O'Callaghan C, et al.** Adiponectin and resistin serum levels in women with polycystic ovary syndrome during oral glucose tolerance test: A significant reciprocal correlation between adiponectin and resistin independent of insulin resistance indices.
Mol Genet Metab 2005;85:61-69.
41. **Mertens I, Verrijken A, Michiels JJ, et al.** Among inflammation and coagulation markers, PAI-1 is a true component of the metabolic syndrome.
Int J Obes (Lond) 2006;30:1308-1314.
42. **Greyling A, Pieters M, Hoekstra T, et al.** Differences in the association of PAI-1 activity with the metabolic syndrome between African and Caucasian women.
Nutr Metab Cardiovasc Dis 2007;17:499-507.
43. **Ajjan R, Carter AM, Somani R, et al.** Ethnic differences in cardiovascular risk factors in healthy Caucasian and South Asian individuals with the metabolic syndrome.
J Thromb Haemost 2007;5:754-760.
44. **Naran NH, Chetty N, Crowther NJ.** The influence of metabolic syndrome components on plasma PAI-1 concentrations is modified by the PAI-1 4G/5G genotype and ethnicity.
Atherosclerosis 2008;196:155-163.
45. **Kraja AT, Province MA, Arnett D, et al.** Do inflammation and procoagulation biomarkers contribute to the metabolic syndrome cluster?
NutrMetab (Lond) 2007;4:28.