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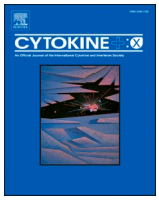

Plasminogen activator inhibitor-1 mediate downregulation of adiponectin in type 2 diabetes patients with metabolic syndrome

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ABSTRACT

Introduction: Metabolic syndrome (MetS) is a multifactorial disease characterized by metabolic abnormalities. Plasminogen activator inhibitor-1(PAI-1) is a key factor of the fibrinolysis its expression is elevated in insulin resistance, obesity, and MetS. In addition, an adiponectin produced by adipocytes is also key factor in MetS. This study aimed to investigate the relationship between PAI-1, adiponectin levels in MetS.

Patients and Methods: A total of 379 subjects were analyse in this cross-sectional study. MetS was defined by NCEP ATP-III criteria. Anthropometric, fasting blood glucose, HbA1c, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, PAI-1, and adiponectin were measured.

Results: PAI-1 levels were higher in MetS compared with non-MetS. In addition, adiponectin levels were significantly lower in MetS compared to non-MetS. Furthermore, increased level of PAI-1 corresponds with increase in prevalence of MetS. PAI-1 levels were significantly associated with MetS (OR = 2.51, CI = 1.23 – 5.14; p = 0.039).

Conclusion: PAI-1 increases the risk of MetS. PAI-1 and adiponectin regulation is useful in assesing the presence and severity of MetS. Further pharmacological targeting of PAI-1 studies are necessary for MetS management.

1. Introduction

Metabolic syndrome (MetS) is characterized by the clustering of metabolic abnormalities that co-occur more often than by chance in an individual. These metabolic abnormalities include abdominal obesity, elevated blood pressure, hyperglycemia and dyslipidemia [1]. Apart from these health disparities and metabolic diseases, MetS is also associated with elevated levels of coagulation factors (fibrinogen and PAI-1) in prothrombotic state, elevated markers of inflammation, accumulation of excessive fat in nonalcoholic fatty liver disease (NAFLD) and reproductive tract disorders [1].

The prevalence and etiology of MetS varies widely by ethnicity and by the criteria used in its definition. A comparative MetS prevalence according to International Diabetes Federation (IDF), World Health Organization (WHO), harmonized, and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria among type 2 diabetes mellitus (T2DM) patients is reported to be 59.9%, 31.2%, 65.6%, and 70.1%, respectively in Ethiopian population. The difference in MetS criteria led to difference in MetS within same population [2]. The MetS prevalence is very high in T2DM patients suggesting that diabetes patients are at increased risk of subsequent morbidities. Thus, it is essential that key factor that causes MetS need to be elucidated.

Previous study has demonstrated that serum PAI-1 has been known to play an important role in inflammation, obesity, diabetes, atherosclerosis, sarcopenia, and MetS [3]. Increased PAI-1 level is considered a true components of the MetS [4]. PAI-1 is a 50 KDa single chain glycoprotein, acts as a physiological inhibitor of tissue-type plasminogen activator and urokinase-type plasminogen activator. Both tissue-type and urokinase-type plasminogen activator convert inactive plasminogen into its fibrin degrading form, plasmin [5]. Previous study has also reported that decreased adiponectin level is known to play a central role in the obesity, insulin resistance, and cardiovascular disease [6]. A study by Santaneimi et al., in Finnish subjects reported that low adiponectin levels correlated with number MetS components [7]. Adiponectin an adipocytokine produced by adipocytes present in very high concentration in blood circulation. The role of adiponectin as a key physiological regulator of glucose metabolism, lipid metabolism and insulin sensitivity had consistently demonstrated in human and rodent model [6]. Role of adiponectin as a biomarker for MetS has been emphasized in different population [8].

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There have been relatively few studies on the role of PAI-1 and adiponectin in patients with MetS despite active research [9,10,11]. Current evidence demonstrates that adiponectin and PAI-1 are associated with the MetS. To our knowledge, no large study has addressed the role of PAI-1 and adiponectin in T2DM patients with MetS, making it important to study these key factors simultaneously in community for the first time with high diabetes prevalence.

2. Patients and methods

2.1. Patients

In this Cross-sectional study, 379 adult Saudi T2DM subjects (183 men and 197 women) aged from 30 to 79 years were enrolled from University Diabetes Center, King Saud University Medical City (KSUMC), King Saud University, Riyadh. Subjects with type 1 diabetes, gestational diabetes, hepatitis, dialysis, myocardial infarction and or stroke, cancer were excluded on recruitment.

The current study was approved by the Institutional Review Board of College of Medicine, King Saud University, Riyadh [IRB approval number: E10-124]. All participant provided written informed consent for participation. We used STROBE (Strengthening the reporting of observational studies in epidemiology) recommendation for data collection and reporting [12].

2.2. Assessment of MetS

All the participants were group into metabolic syndrome (MetS) and non-metabolic syndrome (non-MetS) according to (NCEP-ATP III) diagnostic criteria, it defines the presence of MetS as currently having 3 or more of the following 5 metabolic risk factors 1. Central obesity (waist circumference > =102 cm for men and > = 88 cm for women), 2. Elevated triglycerides (> =150 mg/dl) or specific medication for hypertriglyceridemia, 3. Low high-density lipoprotein (< = 40 mg/dl for men and < = 50 mg//dl for women) or specific medication for low HDL, 4. Fasting blood glucose (> = 100 mg/dl), 5. High blood pressure (> = 130/85 mmHg) or drug treatment for hypertension [13].

2.3. Data measurement

Anthropometric and body composition of the subjects were measured by a designated research physician. Body mass index (BMI) was calculated as each subject weight in kilograms divided by height in meters, and waist circumference (WC) was measured using a measuring tape along the horizontal plane of the iliac crest after exhaling [14].

2.4. Laboratory analysis

From each participant fasting blood samples were collected. These blood samples were centrifuge and processed for serum and store at −80 °C freezer. Fasting blood glucose (FBG), HbA1c %, total cholesterol (TC), High-density lipoprotein (HDL), Low-density lipoprotein (LDL), Triglycerides (TG), urea, creatinine was measured by enzymatic methods by Randox Daytona clinical chemistry analyzer (Randox, UK).

Determination of serum adiponectin, c-peptide, insulin, plasminogen activator inhibitor-1(PAI-1) was measured using Randox Evidence Biochip analyzer using customized chemiluminescent assays (Randox Laboratories Ltd., Crumlin, UK). MetS array I (insulin, C-peptide, PAI-1) Randox evidence, Catalog No. EV3754, MetS array II (adiponectin) Randox evidence, Catalog No. EV3758. The sensitivity of the Evidence insulin was determined to be 2.32 μIU/ml, 0.21 ng/ml for C-peptide, 2.34 ng/ml for PAI-1, and 167 ng/ml for adiponectin respectively. While the detectable range of each assay was 0.001–300 μIU/ml for insulin, 0.001–60 ng/ml for C-peptide, 0.001–200 ng/ml for PAI-1, and 0.001–40,000 ng/ml was for adiponectin.

2.5. Statistical analysis

The clinical data is expressed as mean ± standard deviation for continuous and normally distributed variables and median (inter-quartile range) for skewed variables. The Student's *t*-test and chi-square (χ^2) test was used to compare MetS and non-MetS subjects. Subjects were group into (Q1-Q4) quartiles groups, according to serum PAI-1 and adiponectin levels. One-way ANOVA was used to analyses the study participants in PAI-1 quartile groups (Q1-Q4). We measure the odd ratio (OR) and 95% confidence interval (CI) with a multiple logistic regression analysis model to assess the relationship of PAI-1 and adiponectin for MetS and its components after controlling for variables age, gender, diabetes duration and BMI. All the statistical analysis was performed using SPSS version 21.0. A $P < 0.05$ considered as significant.

3. Results

Baseline and clinical characteristics of the subjects are presented in Table 1. The 77.6% of the subjects were met with MetS criteria. The mean age in MetS group was 57.6 ± 8.3 years, while the mean age of subjects in non-MetS group was 58.9 ± 10.6 years there was no statistical significance among the group. The percentage of male subjects (43.5%) in MetS group was lower compared with non-Mets group (63.5%) ($p < 0.01$). Additionally, subjects with MetS showed higher BMI, wait circumference, Systolic blood pressure, HbA1c%, triglycerides, and insulin relative to non-MetS subjects ($p < 0.01$). Conversely, subjects with MetS had lower HDL levels than non-MetS subjects ($p < 0.01$). PAI-1, levels were significantly higher in MetS subjects (26.34 (16.17–40.44) (ng/ml)), compared with non-MetS subjects (22.35 (11.71–32.09) (ng/ml) ($p < 0.01$)). Conversely, subjects with MetS had lower adiponectin levels (2696.0 (1739.0–4788.0) (ng/ml)), compare with non-MetS subjects (3978.0 (1965.5–7084.5) (ng/ml) ($p < 0.01$)).

Table 2 shows the general characteristic of study subjects' group by

Table 1
Baseline characteristics of Non-MetS and MetS subjects.

Variables	Non-MetS subject n = 85	MetS Subject n = 294	P value
Age (years)	58.9 ± 10.6	57.6 ± 8.3	0.224
Male Gender, n (%)	54 (63.5%)	128 (43.5%)	0.001
Diabetes duration (years)	19.4 ± 6.7	19.0 ± 6.4	0.666
BMI (kg/m^2)	28.2 ± 5.0	33.1 ± 6.1	0.001
Waist (cm)	97.5 ± 12.0	107.3 ± 11.1	0.001
Systolic BP (mmHg)	123.4 ± 15.0	136.0 ± 16.6	0.001
Diastolic BP (mmHg)	70.3 ± 9.5	72.4 ± 9.7	0.080
HbA1c (%)	9.0 ± 1.8	9.7 ± 1.7	0.003
FBG (mg/dl)	164.7 ± 73.9	175.5 ± 65.5	0.211
Total Cholesterol (mg/dl)	164.9 ± 38.7	171.6 ± 40.0	0.171
LDL (mg/dl)	104.7 ± 48.8	113.6 ± 45.4	0.120
HDL (mg/dl)	48.5 ± 15.4	42.7 ± 11.3	0.001
TG (mg/dl)	110.0 ± 46.0	164.4 ± 73.4	0.001
Urea (mg/dl)	25.9 ± 16.0	25.0 ± 13.9	0.616
Creatinine (mg/dl)	0.91 (0.73–1.08)	0.90 (0.74–1.09)	0.052
ACR (mg/g)	7.29 (4.03–15.85)	8.62 (5.05–16.29)	0.536
C-peptide (ng/ml)	0.46 (0.24–1.13)	0.54 (0.27–1.09)	0.379
Insulin (μIU/ml)	13.01 (7.13–22.72)	19.82 (10.44–32.88)	0.009
PAI-1 (ng/ml)	22.35 (11.71–32.09)	26.34 (16.17–40.44)	0.013
Adiponectin (ng/ml)	3978.0 (1965.5–7084.5)	2696.0 (1739.0–4788.0)	0.001

Data are presented as mean ± standard deviation for normally distributed variables and median (Inter quartile range (25th- 75th)) for non-normally distributed variables. Categorical data are presented as frequencies and percentage. *p* Values of ≤ 0.05 was considered significant. BMI: Body mass index, BP: blood pressure, FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ACR: Albumin-to-creatinine ratio, PAI-1: Plasminogen activator inhibitor-1, TG:Triglycerides

Table 2
Shows the general characteristic of study subjects grouped by estimated serum PAI-1 quartiles (Q1-Q4).

PAI-1 ng/ml	All 24.9, (15.36–38.21)	Q1 10.77, (6.15–12.73)	Q2 19.53, (17.11–22.76)	Q3 30.34, (27.89–33.46)	Q4 52.87, (44.68–66.75)	P value
N	379	95	95	95	94	
Age (years)	57.9 ± 8.9	58.5 ± 9.7	60.4 ± 9.9	57.4 ± 7.7	55.2 ± 8.9	0.001
Male Gender, n (%)	182 (48.0%)	54 (56.8%)	50 (52.6%)	43 (45.3%)	35 (37.2%)	0.038
Diabetes duration (years)	19.1 ± 6.4	20.9 ± 7.5	19.7 ± 6.5	18.5 ± 5.8	17.4 ± 5.2	0.001
BMI (kg/m^2)	32.0 ± 6.2	31.3 ± 6.0	31.5 ± 6.6	33.3 ± 5.8	31.9 ± 6.6	0.130
Waist (cm)	105.2 ± 12.0	103.8 ± 12.5	104.9 ± 12.55	107.7 ± 11.2	104.3 ± 11.5	0.121
Systolic BP (mmHg)	133.1 ± 17.0	136.0 ± 20.22	132.8 ± 16.2	133.9 ± 15.6	129.9 ± 15.4	0.102
Diastolic BP (mmHg)	71.9 ± 9.7	72.1 ± 10.2	72.7 ± 9.7	72.2 ± 9.4	70.8 ± 9.6	0.547
HbA1c (%)	9.5 ± 1.7	9.2 ± 1.8	9.1 ± 1.7	10.0 ± 1.7	9.7 ± 1.5	0.001
FBG (mg/dl)	173.1 ± 67.4	161.4 ± 58.6	172.5 ± 61.7	191.0 ± 76.8	167.4 ± 68.2	0.020
Total Cholesterol (mg/dl)	170.0 ± 39.7	161.9 ± 39.7	159.6 ± 34.7	177.6 ± 41.9	181.0 ± 38.5	0.001
LDL (mg/dl)	111.6 ± 46.3	97.5 ± 42.8	97.3 ± 38.9	122.0 ± 50.2	129.7 ± 43.7	0.001
HDL (mg/dl)	44.0 ± 15.5	43.9 ± 13.6	42.8 ± 11.8	44.0 ± 13.6	45.2 ± 10.8	0.623
TG (mg/dl)	152.01 ± 71.9	134.0 ± 65.9	144.9 ± 79.7	161.8 ± 62.8	167.8 ± 73.9	0.004
Urea (mg/dl)	25.2 ± 14.4	23.8 ± 16.6	25.2 ± 18.0	25.3 ± 11.3	26.7 ± 10.01	0.607
Creatinine (mg/dl)	0.90 (0.74–1.09)	0.86(0.67–1.10)	0.91 (0.77–1.06)	0.92 (0.80–1.09)	0.89 (0.74–1.06)	0.484
ACR (mg/g)	8.30 (4.61–16.01)	8.31 (4.38–14.99)	8.30 (4.42–18.50)	8.63(5.94–15.97)	7.879 (4.56–16.00)	0.805
C-peptide (ng/ml)	0.50 (0.27–1.09)	0.43(0.24–1.05)	0.65(0.21–1.25)	0.63 (0.31–1.31)	0.50 (0.31–1.09)	0.677
Insulin (μIU/ml)	16.73 (9.25–30.41)	14.96 (7.46–27.02)	14.17 (8.0–27.34)	22.55 (13.20–32.0)	47.71 (16.09–95.71)	0.333
PAI-1 (ng/ml)	24.94 (15.36–38.21)	10.77 (6.15–12.73)	19.53 (17.11–22.76)	30.34(27.89–33.46)	52.87 (44.68–66.75)	0.001
Adiponectin (ng/ml)	2938.0(1762.0–5186.0)	3990.0 (2412.0–7540.5)	3655.0 (1848.0–5942.0)	2492.00 (1691–4365.0)	2153.0 (1522.0–3871.50)	0.001
MetS n (%)	294 (77.6)	66 (22.4)	70 (23.8)	78 (26.5)	80 (27.2)	0.035

Data are presented as mean ± standard deviation for normally distributed variables and median (Inter quartile range (25th- 75th)) for non-normally distributed variables. Categorical data are presented as frequencies and percentage. *p* Values of ≤ 0.05 was considered significant. BMI: Body mass index, BP blood pressure, FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, ACR: Albumin-to-creatinine ratio, PAI-1: Plasminogen activator inhibitor-1.

estimated serum PAI-1 quartiles (Q1-Q4). Increased level of PAI-1 corresponds with decrease in age and male gender, diabetes duration, adiponectin ($p < 0.05$). Conversely, increased level of PAI-1 corresponds with increase in HbA1c%, FBG, total cholesterol, LDL, Triglyceride and ($p < 0.05$). In all quartiles, groups (Q1-Q4) the highest prevalence of MetS occurred in the highest quartiles of serum PAI-1 (Table 2.)

Figure 1.

For all the four groups, greater the number of MetS components number present, the greater the serum PAI-1 level (Fig. 1.).

Legend: Mean serum PAI-1 levels and MetS components numbers. Geometric mean values of serum PAI-1 are shown for subjects who met MetS criteria. Error bars represent upper 95 %CI. The trend of mean PAI-1 values across categories of MetS components was significant of all the four groups.

Figure 2.

For all the four groups, the greater the number of MetS components present, the lower the serum adiponectin level (Fig. 2.).

Legend: Mean adiponectin levels by the number of MetS components. Geometric mean values of adiponectin are shown for subjects who met MetS criteria. Error bars represent upper 95 %CI. The trend of mean adiponectin values across categories of MetS components was significant of all the four groups.

Table 3a shows the odd ratio and confident interval by multiple logistic regression analysis models for MetS components in relation to serum PAI-1. In unadjusted models, higher serum PAI-1 levels were significantly associated with higher odds of having MetS. The unadjusted ORs (95% CI) for MetS in relation to quartiles of PAI-1 levels were (OR = 2.51, CI = 1.23 – 5.14). In comparison, with lowest quartiles subjects of PAI-1 levels, subjects in the highest quartiles of PAI-1 levels were more likely to have central obesity (OR = 1.92, 95% CI = 0.97 – 3.82), and elevated TG (OR = 2.99, CI = 1.63–5.46). After adjustment for age, gender, duration of diabetes and BMI. The adjusted odd ratio for MetS in relation to quartiles of PAI-1 levels was (OR = 2.66, CI = 1.22–5.82), for central obesity (OR = 2.35, CI = 0.90 – 6.19), for TG (OR = 2.88, CI = 1.56–5.32) respectively. There was a significant linear increase of ORs for MetS, Central obesity, elevated TG ($p < 0.05$) with increase in PAI-1.

Table 3b shows the odd ratio and confident interval by multiple

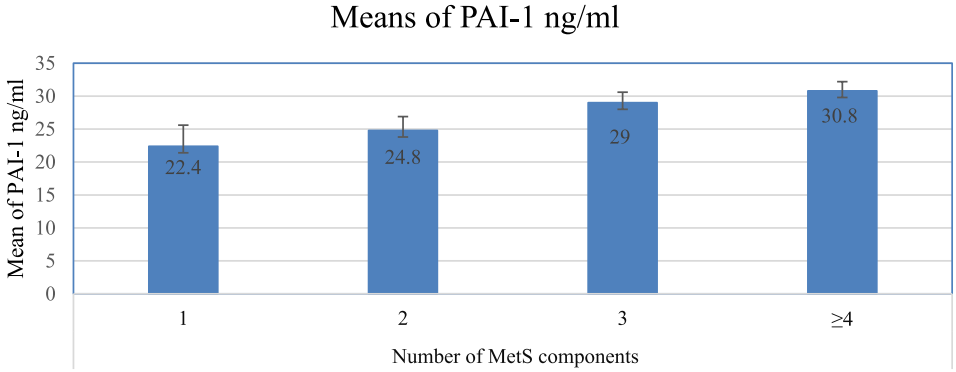

Fig. 1. Means of PAI-1 levels by number of MetS components (P < 0.04).

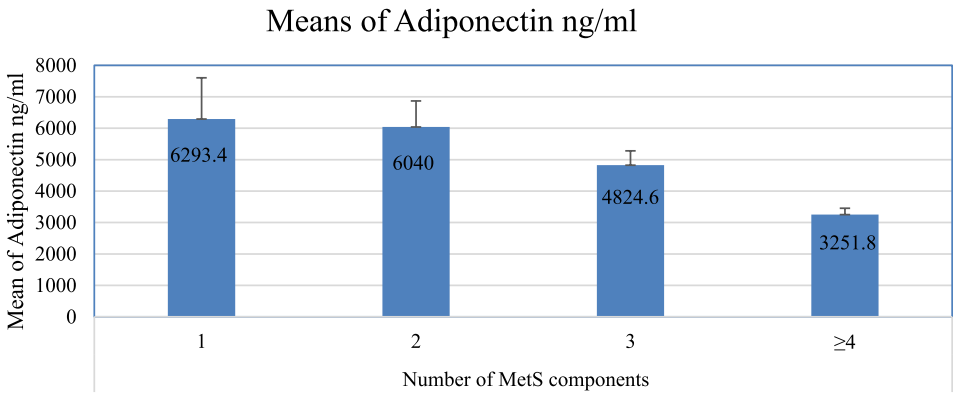

Fig. 2. Means of Adiponectin levels by number of MetS components ($p < 0.001$).

Table 3a
OR (95 %CI) by multiple Logistic Regression Models for Metabolic syndrome components in relation to biomarker (PAI-1).

	PAI-1 (n=379)									
	Q1	Q2			Q3			Q4			P for Trend
	n = 95	n = 95			n = 95			n = 95			
		OR	95% CI		OR	95% CI		OR	95% CI		
			Lower	Upper		Lower	Upper		Lower	Upper	
MetS, n	66/95	70/95			78/95			80/94			
Model 1	1.00	1.23	0.65	2.31	2.02	1.02	3.99	2.51	1.23	5.14	0.039
Model 2	1.00	1.21	0.64	2.31	1.87	0.94	3.74	2.17	1.05	4.52	0.120
Model 3	1.00	1.30	0.66	2.57	1.64	0.79	3.41	2.66	1.22	5.82	0.093
WC, [b] n	66/94	70/95			82/95			77/94			
Model 1	1	1.24	0.65	2.35	2.90	1.37	6.14	1.92	0.97	3.82	0.026
Model 2	1	1.20	0.59	2.46	2.62	1.16	5.92	1.25	0.58	2.73	0.126
Model 3	1	1.53	0.64	3.66	1.93	0.73	5.14	2.35	0.90	6.19	0.329
BP, [c] n	62/95	58/95			58/95			47/94			
Model 1	1	0.83	0.46	1.51	0.83	0.46	1.51	0.53	0.30	0.96	0.175
Model 2	1	0.75	0.40	1.38	0.87	0.48	1.61	0.63	0.34	1.15	0.457
Model 3	1	0.87	0.48	1.59	0.85	0.46	1.55	0.58	0.32	1.05	0.307
TG, [d] n	27/95	29/94			49/95			51/94			
Model 1	1	1.12	0.60	2.10	2.68	1.47	4.89	2.99	1.63	5.46	<0.001
Model 2	1	1.20	0.64	2.25	2.75	1.49	5.05	2.95	1.59	5.46	<0.001
Model 3	1	1.10	0.59	2.05	2.62	1.42	4.82	2.88	1.56	5.32	<0.001
HDL, [e] n	48/91	46/90			51/92			57/94			
Model 1	1	0.94	0.52	1.68	1.11	0.62	1.99	1.38	0.77	2.47	0.584
Model 2	1	0.95	0.52	1.71	1.05	0.58	1.89	1.23	0.68	2.24	0.843
Model 3	1	0.89	0.49	1.60	0.98	0.54	1.79	1.24	0.68	2.26	0.731

Model 1 is unadjusted. Model 2 is adjusted for age, gender. Model 3 is adjusted for diabetes duration and BMI.
b WC ≥ 102 cm for male and ≥ 88 cm for female.
c Systemic hypertension (BP ≥ 130/85 mm Hg).
d Elevated TG (≥150 mg/dL).
e Low HDL-cholesterol (male, ≤40 mg/dL; female, ≤50 mg/dL).

logistic regression models for MetS components in relation to adiponectin. In unadjusted logistic regression models, higher adiponectin levels were significantly associated lower odds of having MetS (Table 3b). In comparison with subjects in the quartile 1 of adiponectin level, subject in the Quartile 4 of adiponectin level were less likely to have MetS (OR = 0.47, 95% CI = 0.24–0.92), central obesity (OR = 0.52, CI = 0.26–1.01), triglyceride (OR = 0.25, 95 % CI = 0.13–0.47), HDL (OR = 0.39, CI = 0.21–0.73) respectively. There was a significant linear decrease of OR with increasing quartiles of adiponectin levels. After adjustment of age, gender, diabetes duration and BMI the adjusted ORs (95 % CIs) for MetS or components of MetS in relation to adiponectin quartiles levels were MetS (OR = 0.51, CI = 0.25–1.07), Central obesity (OR = 0.64, CI = 0.25–1.69), elevated triglyceride (OR = 0.25, CI = 0.13–0.49), HDL (OR = 0.43, CI = 0.22–0.81) respectively.

4. Discussion

The present study demonstrates that circulating PAI-1 level were significantly higher, while adiponectin levels were significantly lower in MetS subjects. Increased PAI-1 level was independently associated with the higher odds of having MetS. An additional novel findings is that PAI-1 is positively associated with MetS component triglyceride. This study also demonstrated well known negative association of adiponectin and MetS components. The estimated prevalence of MetS reported from the present study was found to be 78%, which is similar to Kashmir type 2 diabetes patients [15]. In addition to the above study, another study also reported higher 80.3% of Mets prevalence in Nepalese type 2 diabetes [16]. Collectively, MetS is estimated to be present in 75–80% of T2D patients and it is varying in different ethnicity [17].

PAI-1 is a member of serine-protease inhibitor. PAI-1 is secreted in blood circulation by platelets, adipocytes, endothelial cells, vascular smooth muscle, and hepatocytes [18]. In the present study, we found

Table 3b
OR (955 %CI) by multiple Logistic Regression Models for Metabolic syndrome components in relation to biomarker adiponectin.

	Adiponectin (n=355)										
	Q1	Q2			Q3			Q4			P for Trend
	n=89	n=89			n=89			n=88			
		OR	95% CI		OR	95% CI		OR	95% CI		
			Lower	Upper		Lower	Upper		Lower	Upper	
MetS, n	**71/89**	**76/89**			**73/89**			**57/88**			
Model 1	1	1.48	0.68	3.24	1.16	0.55	2.45	0.47	0.24	0.92	0.006
Model 2	1	1.31	0.59	2.90	1.01	0.47	2.18	0.44	0.22	0.91	0.018
Model 3	1	1.59	0.69	3.63	1.17	0.53	2.57	0.51	0.25	1.07	0.026
WC, [b] n	70/89	76/88			74/88			57/87			
Model 1	1	1.72	0.78	3.80	1.43	0.67	3.08	0.52	0.26	1.01	0.005
Model 2	1	1.30	0.55	3.04	1.06	0.46	2.44	0.42	0.19	0.92	0.030
Model 3	1	2.83	0.99	8.10	2.06	0.74	5.72	0.65	0.25	1.69	0.021
BP, [c] n	48/89	46/89			52/89			62/88			
Model 1	1	0.91	0.51	1.65	1.20	0.66	2.17	2.04	1.10	3.78	0.057
Model 2	1	0.87	0.48	1.60	1.08	0.59	2.00	1.56	0.82	2.97	0.344
Model 3	1	0.90	0.50	1.63	1.15	0.63	2.10	1.97	1.04	3.74	0.081
TG, [d] n	50/89	47/89			31/89			21/87			
Model 1	1	0.87	0.48	1.58	0.42	0.23	0.76	0.25	0.13	0.47	<0.001
Model 2	1	0.91	0.50	1.66	0.45	0.24	0.82	0.28	0.15	0.54	<0.001
Model 3	1	0.88	0.48	1.58	0.42	0.23	0.77	0.25	0.13	0.49	<0.001
HDL, [e] n	56/88	59/89			49/85			33/81			
Model 1	1	1.12	0.61	2.08	0.78	0.42	1.43	0.39	0.21	0.73	0.004
Model 2	1	1.05	0.56	1.97	0.73	0.39	1.36	0.39	0.20	0.74	0.010
Model 3	1	1.14	0.61	2.12	0.79	0.43	1.46	0.43	0.22	0.81	0.013

Model 1 is unadjusted. Model 2 is adjusted for age, gender. Model 3 is adjusted for diabetes duration and BMI.
b WC ≥ 102 cm for male and ≥ 88 cm for female.
c Systemic hypertension (BP ≥ 130/85 mm Hg).
d Elevated TG (≥150 mg/dL).
e Low HDL-cholesterol (male, ≤40 mg/dL; female, ≤50 mg/dL).

that PAI-1 level for MetS group were higher than non-MetS group 26.34 (16.17–40.44) ng/ml vs 22.35 (11.71–32.09) ng/ml). Our findings are consistent with previous studies [9,10,11]. Increased in PAI-1 levels are reported when adipocytes are stimulated by TNF-α, transforming growth factor-β, angiotensin II, glucocorticoids, insulin, hypoxia, and ROS suggesting that PAI-1 might play a role in inflammatory mechanisms while also affecting vasculature, adiposity, insulin resistance and MetS [18,19,20].

Accumulating data demonstrated that there is well-established link between PAI-1 and Mets [21]. As the number of MetS risk factors increases the level of PAI-1 increases [Fig. 1]. Consistent with our results, similar observations have been reported in other studies were MetS has higher PAI-1 levels than non-MetS [22]. Suggesting strong relationship exists between the mean PAI-1 level and the number of metabolic components. Furthermore, clinical studies in mice demonstrated that low PAI-1 levels decrease weight gain, increases body expenditure, and improves insulin resistance in high fat diet (HFD) fed mice [23]. Furthermore, it revealed that obese adolescents with and without MetS who underwent weight loss therapy at baseline shown higher PAI-1 levels than non-Mets subjects. After one year of weight loss therapy, anthropometrics, biochemical, inflammatory, and neuroendocrine variables were significantly improved. PAI-1 were significantly decreased, reaching similar to the non-MetS group at the end of the therapy [24]. Furthermore, pharmacological targeting of PAI-1, inhibits metabolic dysfunction and producing beneficial metabolic effects such as attenuation of obesity, adipose tissue inflammation, hyperglycemia and steatohepatosis in murine model of MetS [25].

Notably, in the current study multiple logistic regression analysis results demonstrate PAI-1 and triglyceride level are independent predictors of MetS. Increased in WC and TG were found to be independent variables associated with an increased PAI-1 level in multiple logistic regression model [26]. However, it is hypothesized that PAI-1 induced metabolic dysfunction in adipose tissue by macrophage mediated inflammation in high fat diet obese murine model. Collectively, pharmacological inhibition of PAI-1 improved the metabolic status in high fat fed mice by decreasing macrophage infiltration in adipose tissue [27]. The pathophysiological mechanisms by which PAI-1 persuade the development of MetS need to be elucidated in detail and more evidence are needed to explain the inflammatory mechanism modulated by PAI-1 in metabolic disorder.

Adiponectin is produced and secreted predominantly by adipocytes in adipose tissue. It exerts pleiotropic effects on liver, kidney, pancreatic beta cells, blood vessels, brain, bone, and immune cells [28]. Human and rodent models have consistently demonstrated the role of adiponectin as an important physiological regulator of insulin sensitivity, glucose, and lipid metabolism [6]. Previous studies have also implicated that serum adiponectin level decreased in metabolic disorders such as obesity, type 2 diabetes, inflammatory state, and insulin resistance [28,8]. Role of adiponectin as a biomarker for MetS has been emphasized in different population [8].

In the present study, MetS subjects had significantly lower adiponectin levels than non-MetS (2696.0 (1739.0–4788.0) ng/ml vs 3978.0 (1965.5–7084.5) ng/ml. Previous studies have reported low adiponectin levels outcome differences by various age groups, gender, and different ethnicity [9,10,11]. Cross-sectional studies have also evaluated the association between the different MetS components and adiponectin levels in population with different metabolic profiles [29,30]. The results of a cross-sectional study conducted in the elderly U.S. Rancho Bernardo cohort also demonstrated that individuals with MetS had lower circulating levels of adiponectin compared to individuals without MetS [31]. Furthermore, the presence of each of the MetS components was associated with lower level of adiponectin [9,10,11]. As the number of MetS risk factors increases the level of adiponectin decreases [Fig. 2] similarly, reported in other studies [10]. Santaneimi et al., studied a Finnish subject and found that low adiponectin level as an indicator of the MetS and low adiponectin levels correlated with an increasing number of MetS components [7]. Previously, the ARIRANG study investigated the association of serum adiponectin with the regression of MetS in

population based longitudinal study. During, follow-up for an average 2.6-year Mets disappear in 29.8% of men and 32.1% women. It also demonstrated that increased serum adiponectin levels paly a protective role and are the predictors for regression of MetS [32]. Notably, our multiple logistic regression analysis demonstrate that PAI-1 and adiponectin were independent predictors of the MetS, suggesting that higher level of PAI-1and lower level of adiponectin might increase the risk for developing MetS. Furthermore, our findings demonstrate that lower adiponectin and elevated PAI-1 levels were associated with MetS and its components, inverse relation was observed between adiponectin and PAI-1 levels in MetS. Similar observations have been reported by other study [9]. Although, there is an evidence of ethnic variations in the PAI-1 level and limited data on the association of PAI-1 with MetS in Indian [11,9].

Importantly, during the 10-year follow-up from a community-based cohort, higher PAI-1 and lower adiponectin level were also found to associated with the risk of developing prediabetes and type 2 diabetes [33]. Recently, it was demonstrated that PAI-1 is associated with hyperlipidemia and is directly involved in lipid metabolism. Additionally, pharmacological inhibition of PAI-1 prevents hepatic steatosis, dyslipidemia and reduces total cholesterol levels through mechanisms that involves reduced proprotein convertase subtilisin/kexin type 9 (PCSK9) synthesis [34]. Our data will provide novel insights into the nature of this association among community with high diabetes prevalence. Furthermore, our results suggest that PAI-1 may play a possible role in lipid metabolism. Our results recommend assessing and modulating the serum adiponectin and PAI-1 concentrations may be useful for the management of the MetS as observed by other studies [9].

The strength of the current study is that this is the first study among Arab community with high diabetes prevalence that demonstrate the relationship between PAI-1 and MetS. Furthermore, we provided a detailed logistic regression analysis including MetS components and regression models adjusted for anthropometric variables such as age, gender, BMI, and duration of diabetes. The clinical data presented in the current study demonstrate consistency for anthropometric measurement and assays used for measuring PAI-1, and adiponectin providing internal validity to the current study. Moreover, we restricted our analysis in treatment naïve subjects for diabetes, hypertension, and dyslipidemia.

Limitation of the current study is that we did not consider medication history of oral glycemic agents for diabetes, hypertension, and lipid lowering agents for dyslipidemia. Future, studies with large sample size and examining PAI-1 in different ethnic population will be needed. To eliminate laboratory sources bias, researcher and laboratory persons who are not aware of the underlying research hypothesis ran and validated specific assays under laboratory code.

In Conclusion our findings suggested that increased PAI-1 level is associated with increase odd of having MetS risk and adverse effects for MetS related components. Moreover, lower adiponectin level was associated negatively with MetS risk and its components. Our results suggest a potential link between PAI-1 and the prevalence of MetS, these association need to be clarified by prospective studies.

Authors contributions

Conception or design: K.S, S.S.N. Acquisition, analysis, or interpretation of data: S.S.N. Drafting the work or revising: K.S., S.S.N. Final approval of the manuscript: K.S., S.S.N.

Disclosure Statement

Disclosure of interest

The authors report no conflict of interest.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M.A. Cornier, D. Dabelea, T.L. Hernandez, R.C. Lindstrom, A.J. Steig, N.R. Stob, R. E. Van Pelt, H. Wang, R.H. Eckel, The metabolic syndrome, Endocr. Rev. 29 (2008) 777–822, https://doi.org/10.1210/er.2008-0024.

[2] T. Bizuayehu Wube, M. Mohammed Nuru, A. Tesfaye Anbese, A Comparative Prevalence Of Metabolic Syndrome Among Type 2 Diabetes Mellitus Patients In Hawassa University Comprehensive Specialized Hospital Using Four Different Diagnostic Criteria, Diabetes Metab. Syndr. Obes. 12 (2019) 1877–1887, https://doi.org/10.2147/DMSO.S221429.

[3] M. Cesari, M. Pahor, R.A. Incalzi, Plasminogen Activator Inhibitor-1 (Pai-1): A Key Factor Linking Fibrinolysis And Age-Related Subclinical And Clinical Conditions, Cardiovasc. Ther. 28 (2010) e72–e91, https://doi.org/10.1111/j.1755-5922.2010.00171.x.

[4] I. Mertens, A. Verrijken, J.J. Michiels, M. Van der Planken, J.B. Ruige, L.F. Van Gaal, Among inflammation and coagulation markers, PAI-1 is a true component of the metabolic syndrome, Int. J. Obesity 30 (8) (2006) 1308–1314.

[5] H. Ha, E.Y. Oh, H.B. Lee, The role of plasminogen activator inhibitor 1 in renal and cardiovascular diseases, Nat. Rev. Nephrol. 5 (4) (2009) 203–211, https://doi.org/10.1038/nrneph.2009.15.

[6] A. Achari, S. Jain, Adiponectin, a Therapeutic Target for Obesity, Diabetes, and Endothelial Dysfunction, Int. J. Mol. Sci. 18 (6) (2017) 1321, https://doi.org/10.3390/ijms18061321.

[7] M. Santaniemi, Y.A. Kesäniemi, O. Ukkola, Low plasma adiponectin concentration is an indicator of the metabolic syndrome, Eur. J. Endocrinol. 155 (5) (2006) 745–750, https://doi.org/10.1530/eje.1.02287.

[8] M. Ryo, T. Nakamura, S. Kihara, M. Kumada, S. Shibazaki, M. Takahashi, M. Nagai, Y. Matsuzawa, T. Funahashi, Adiponectin as a biomarker of the metabolic syndrome, Circ. J. 68 (11) (2004) 975–981, https://doi.org/10.1253/circj.68.975.

[9] S. Bilgili, A.C. Celebiler, A. Dogan, B. Karaca, Inverse relationship between adiponectin and plasminogen activator inhibitor-1 in metabolic syndrome patients, Endocr. Regul. 42 (2008) 63–68.

[10] M.K. Garg, M.K. Dutta, N. Mahalle, Adipokines (adiponectin and plasminogen activator inhhibitor-1) in metabolic syndrome, Indian, J. Endocrinol. Metab. 16 (2012) 116–123, https://doi.org/10.4103/2230-8210.91206.

[11] A.K. Ahirwar, A. Jain, B. Goswami, M.K. Bhatnagar, J. Bhatacharjee, Imbalance between protective (adiponectin) and prothrombotic (Plasminogen Activator Inhibitor-1) adipokines in metabolic syndrome, Diabetes Metab. Syndr. 8 (3) (2014) 152–155, https://doi.org/10.1016/j.dsx.2014.04.035.

[12] E. von Elm, D.G. Altman, M. Egger, S.J. Pocock, P.C. Gøtzsche, J. P. Vandenbroucke, The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies*, Bull. World Health Organ. 85 (11) (2007) 867–872, https://doi.org/10.2471/BLT.07.045120.

[13] P.L. Huang, A comprehensive definition for metabolic syndrome, Dis. Model Mech. 2 (2009) 231–237, https://doi.org/10.1242/dmm.001180.

[14] S.M. Grundy, J.I. Cleeman, S.R. Daniels, K.A. Donato, R.H. Eckel, B.A. Franklin, D. J. Gordon, R.M. Krauss, P.J. Savage, S.C. Smith, J.A. Spertus, F. Costa, American Heart Association, National Heart, Lung, and Blood Institute, Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement, Circulation 112 (17) (2005) 2735–2752, https://doi.org/10.1161/CIRCULATIONAHA.105.169404.

[15] S. Lone, K. Lone, S. Khan, R.A. Pampori, Assessment of metabolic syndrome in Kashmiri population with type 2 diabetes employing the standard criteria's given by WHO, NCEPATP III and IDF, J. Epidemiol. Glob. Health. 7 (2017) 235–239, https://doi.org/10.1016/j.jegh.2017.07.004.

[16] D.R. Pokharel, D. Khadka, M. Sigdel, N.K. Yadav, S. Acharya, R.C. Kafle, P. S. Shukla, Prevalence of metabolic syndrome in Nepalese type 2 diabetic patients according to WHO, NCEP ATP III, IDF and Harmonized criteria, J. Diabet. Metab. Disord. 13 (1) (2014), https://doi.org/10.1186/s40200-014-0104-3.

[17] C.M. Alexander, P.B. Landsman, S.M. Teutsch, S.M. Haffner, Third National Health and Nutrition Examination Survey (NHANES III), National Cholesterol Education Program (NCEP), NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older, Diabetes 52 (2003) 1210–1214, https://doi.org/10.2337/diabetes.52.5.1210.

[18] K. Srikanthan, A. Feyh, H. Visweshwar, J.I. Shapiro, K. Sodhi, Systematic Review of Metabolic Syndrome Biomarkers: A Panel for Early Detection, Management, and Risk Stratification in the West Virginian Population, Int. J. Med. Sci. 13 (1) (2016) 25–38, https://doi.org/10.7150/ijms.13800.

[19] A.T. Kraja, M.A. Province, D. Arnett, L. Wagenknecht, W. Tang, P.N. Hopkins, L. Djoussé, I.B. Borecki, Do inflammation and procoagulation biomarkers contribute to the metabolic syndrome cluster? Nutr. Metab. (Lond.) 4 (1) (2007) 28, https://doi.org/10.1186/1743-7075-4-28.
[20] A.A. Bremer, S. Devaraj, A. Afify, I. Jialal, Adipose tissue dysregulation in patients with metabolic syndrome, J. Clin. Endocrinol. Metab. 96 (11) (2011) E1782–E1788, https://doi.org/10.1210/jc.2011-1577.
[21] M.-C. Alessi, Irène Juhan-Vague, PAI-1 and the metabolic syndrome: links, causes, and consequences, Arterioscler. Thromb. Vasc. Biol. 26 (10) (2006) 2200–2207, https://doi.org/10.1161/01.ATV.0000242905.41404.68.
[22] N. Kodaman, M.C. Aldrich, R. Sobota, F.W. Asselbergs, N.J. Brown, J.H. Moore, S. M. Williams, Plasminogen Activator Inhibitor-1 and Diagnosis of the Metabolic Syndrome in a West African Population, J. Am. Heart Assoc. 5 (10) (2016), https://doi.org/10.1161/JAHA.116.003867.
[23] U.J. Jung, M.-S. Choi, Obesity and Its Metabolic Complications: The Role of Adipokines and the Relationship between Obesity, Inflammation, Insulin Resistance, Dyslipidemia and Nonalcoholic Fatty Liver Disease, Int. J. Mol. Sci. 15 (2014) 6184–6223, https://doi.org/10.3390/ijms15046184.
[24] F.C. Corgosinho, A. de Piano, P.L. Sanches, R.M. Campos, P.L. Silva, J. Carnier, L. M. Oyama, L. Tock, S. Tufik, M.T. de Mello, A.R. Dâmaso, The role of PAI-1 and adiponectin on the inflammatory state and energy balance in obese adolescents with metabolic syndrome, Inflammation 35 (3) (2012) 944–951, https://doi.org/10.1007/s10753-011-9397-2.
[25] H.B. Khoukaz, Y. Ji, D.J. Braet, M. Vadali, A.A. Abdelhamid, C.D. Emal, D. A. Lawrence, W.P. Fay, Drug Targeting of Plasminogen Activator Inhibitor-1 Inhibits Metabolic Dysfunction and Atherosclerosis in a Murine Model of Metabolic Syndrome, Arterioscler. Thromb. Vasc. Biol. 40 (6) (2020) 1479–1490, https://doi.org/10.1161/ATVBAHA.119.313775.
[26] K. Iida, S. Tani, W. Atsumi, T. Yagi, K. Kawauchi, N. Matsumoto, A. Hirayama, Association of plasminogen activator inhibitor-1 and low-density lipoprotein heterogeneity as a risk factor of atherosclerotic cardiovascular disease with triglyceride metabolic disorder: a pilot cross-sectional study, Coron. Artery Dis. 28 (2017) 577–587, https://doi.org/10.1097/MCA.0000000000000521.
[27] L. Wang, L. Chen, Z. Liu, Y. Liu, M. Luo, N. Chen, X. Deng, Y. Luo, J. He, L. Zhang, M.A. Hill, R. Li, J. Wu, PAI-1 Exacerbates White Adipose Tissue Dysfunction and Metabolic Dysregulation in High Fat Diet-Induced Obesity, Front. Pharmacol. 9 (2018) 1087, https://doi.org/10.3389/fphar.2018.01087.
[28] L.G. Straub, P.E. Scherer, Metabolic Messengers: Adiponectin, Nat. Metab. 1 (3) (2019) 334–339, https://doi.org/10.1038/s42255-019-0041-z.
[29] S.-B. Koh, J. Yoon, J.-Y. Kim, B.-S. Yoo, S.-H. Lee, J.-K. Park, K.-H. Choe, Relationships between Serum Adiponectin with Metabolic Syndrome and Components of Metabolic Syndrome in Non-Diabetic Koreans: ARIRANG Study, Yonsei Med. J. 52 (2011) 234–241, https://doi.org/10.3349/ymj.2011.52.2.234.
[30] A.D. von Frankenberg, A.F. Reis, F. Gerchman, A.D. von Frankenberg, A.F. Reis, F. Gerchman, Relationships between adiponectin levels, the metabolic syndrome, and type 2 diabetes: a literature review, Arch. Endocrinol. Metabol. 61 (2017) 614–622, https://doi.org/10.1590/2359-3997000000316.
[31] G.A. Laughlin, E. Barrett-Connor, S. May, C. Langenberg, Association of adiponectin with coronary heart disease and mortality: the Rancho Bernardo study, Am. J. Epidemiol. 165 (2007) 164–174, https://doi.org/10.1093/aje/kwk001.
[32] J.-Y. Kim, D. Yadav, S.V. Ahn, S.-B. Koh, A prospective study of serum adiponectin and regression of metabolic syndrome: The ARIRANG study, Biochem. Biophys. Res. Commun. 466 (2) (2015) 201–205, https://doi.org/10.1016/j.bbrc.2015.09.007.
[33] N.H. Cho, E.J. Ku, K.Y. Jung, T.J. Oh, S.H. Kwak, J.H. Moon, K.S. Park, H.C. Jang, Y.J. Kim, S.H. Choi, Estimated association between cytokines and the progression to diabetes: 10-year follow-up from a community-based cohort, J. Clin. Endocrinol. Metabol. 105 (2020) e381–e389. https://doi:10.1210/clinem/dgz171.
[34] J.A. Levine, C. Oleaga, M. Eren, A.P. Amaral, M. Shang, E. Lux, S.S. Khan, S. J. Shah, Y. Omura, N. Pamir, J. Hay, G. Barish, T. Miyata, H. Tavori, S. Fazio, D. E. Vaughan, Role of PAI-1 in hepatic steatosis and dyslipidemia, Sci. Rep. 11 (1) (2021), https://doi.org/10.1038/s41598-020-79948-x.