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Original Article

Proportional correlates of adipolin and cathepsin S in metabolic syndrome patients with and without prediabetes

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ABSTRACT

Background: Adipolin and cathepsin S are intricately involved in pathophysiology of metabolic syndrome (MetS) and prediabetes (PreDM).
Aims & methods: This cross-sectional study aimed to compare and correlate between these metabolic biomarkers as well as between them and adiposity, atherogenicity and hematological indices in MetS patients. Our cross-sectional study involved recruiting 29 normoglycemic MetS, 30 newly diagnosed drug naïve PreDM-MetS patients versus 29 lean, healthy and normoglycemic controls.
Results: Adipolin and cathepsin S plasma levels were significantly higher in both MetS (normoglycemic and PreDM) groups vs. healthy controls. Evidently proportional adipolin-cathepsin S association was markedly signified in 59 MetS participants (normoglycemic and PreDM). Distinctively unlike adipolin, inverse cathepsin S-diastolic blood pressure (DBP) but direct cathepsin S-monocyte count and its monocyte -to- lymphocyte ratio cross-correlated were marked. Notably unlike cathepsin S, adipolin was positively associated with each of FPG, A1C and TG, visceral adiposity index, lipid accumulation product and atherogenic index of plsama in the MetS pool of participants (N = 59).
Conclusions: Given the intergroup discrepancies in adiposity, atherogenicity indices and their correlations (as well as hematological indices) with biomarkers; this cross-sectional study cannot rule out either biomarker as an associative predictor or as a surrogate indicator and putative prognostic tool for the prediction/prevention and treatment of metabolism dysregularities.

1. Introduction

Adipolin (CTRP12) is a novel adipokine, with essential role as insulin sensitizer and anti-inflammatory agent, available in abundance in adipose tissue [1] with enhancing glycemic control [2]. Full form not cleaved isoforms of adipolin enhances insulin sensitivity and stimulates glucose uptake. As obesity found to facilitate the cleavage of adipolin [3], it is found to be lessened in diabetes, inflammation, and overweight individuals. Adipolin and other novel therapeutic options that boost adipolin concentrations can be new effective therapies for diabetic and insulin resistant patients [1,3–5], Adipolin, in contrast to most other adipokines, are associated with insulin sensitivity rather than insulin resistance and obesity [6,7].

One of the leading adipose-derived adipokines is cathepsin S which is a proteolytic enzyme, from the cysteine proteinase family, that helps in the breaking down process of damaged or unwanted proteins in the endo-lysosomal pathway [8,9]. Moreover, cathepsin S plays a major role in the degradation of the invariant chain; it collaborates in MHC class II antigen presentation [10]. Unlike other cathepsin group adipokines, cathepsin S solely is restrictedly expressed in tissues and is more stable at a neutral pH, which endorses its important role in localized disease microenvironments [10]. Cathepsin S levels appeared to increase significantly in obese patients compared to healthy lean subjects As expected, increased cathepsin S brings about its secretion as extracellular molecules which begin a variety of disorders including arthritis, cancer, diabetes and cardiovascular diseases [11]. Many studies found that higher cathepsin S levels accompanied with increased insulin resistance and, therefore, a higher chance for getting diabetes, because cathepsin S is involved in the early blood sugar imbalance pathway [12].

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This study aimed to investigate the plasma levels of adipolin and cathepsin S and their correlations with a set of clinical parameters such as MetS related adiposity, hematologic and atherogenic indices in normoglycemic and hyperglycemic patients with MetS in Jordan.

2. Material and methods

2.1. Patients

A cross sectional study was conducted to examine the comparison and relation between plasma level of adipolin and cathepsin S in three groups of Jordanian population as follows:

1 MetS-normoglycemic group included 29 normoglycemicpatients who were overweight or obese with 3 or more of MetS criteria [13].
2 MetS-PreDM group included 30 PreDM patients [14], who were overweight or obese with 3 or more of MetS criteria[13], but necessarily drug naïve/newly diagnosed.
3 Control group included 29 healthy participants who were normoglycemic (A1C<5.7%, FPG<100 mg/dL) and lean (BMI<25 kg/m^2) mainly considered for comparison purposes.

Exclusion criteria were as follows:

1. Non-fasting subjects
2. Pregnant or breast feeding/lactating women.
3. Any prior use of anti-diabetic agent such as (sulfonylureas, meglitinides, biguanides, thiazolidinediones, alpha-glucosidase inhibitors, or insulin) either for diabetes itself or for any other condition.
4. Any prior use of lipid lowering agents.
5. Clinical evidence of autoimmune, life-threatening diseases, alcohol, drug abuse, and recently diagnosed and untreated endocrine disorder.
6 Individuals with known inflammatory diseases such as the inflammatory bowel disease.

2.2. Methods

The appropriate participants were approached randomly while they were in the waiting room in the Family Medicine Clinic or in the nursing room to measure blood pressure, weight, height, anthropometric and demographic data. Then the participants were carefully interviewed for obtaining other clinical information such as risk factors of CVD, DM, polycystic ovary syndrome (PCOS), hypertension (HTN), high-density lipoprotein cholesterol (HDL-C)< 50 mg/dL, smoking, alcohol consumption, physical inactivity, triglycerides (TG) > 250 mg/dL, also history of surgery. Sandwich enzyme linked immunosorbent assay (ELISA) was used for determining plasma level of both Adipolin (Bio-Tek Instrument, USA) and Cathepsin S (Abcam, USA). Participants were categorized into three groups: 29 non-diabetic MetS patients, 30 preDM/MetS patients and 29 healthy controls (Fig. 1). Supplementary Table 1 briefs

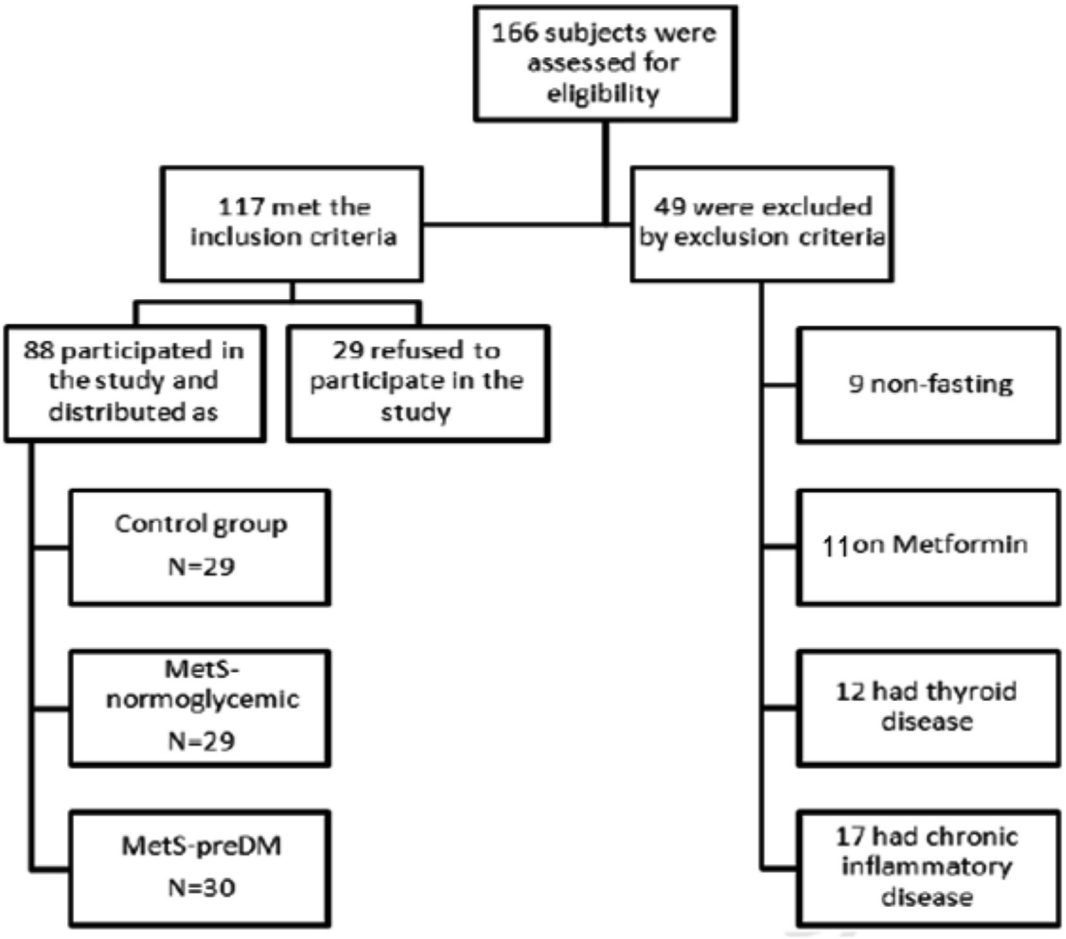

Fig. 1. The recruitment process flow chart.

all study indices calculations (Suppl. Table 1).

2.3. Statistical analysis

All study subjects were coded according to the study arm they belong to. Data were entered and analyzed via IBM SPSS© statistics 22 (SPSS, Inc., USA). Gender differences among the groups were tested using Chi-square test. One-way Analysis of Variance (ANOVA) test was used for comparing continuous independent variables between the study groups. Spearman correlation was

Table 1
Comparison of study clinical and anthropometric parameters, adiposity, atherogenicity and hematological indices as well as metabolic risk biomarkers.

Gender							
Gender		Total Sample Number (%) N = 88	Control Group Number (%)N = 29	MetS Group Number (%) N = 29	MetS/PreDM Group Number (%) N = 30		*P-value
Female, N (%)		67 (76.1%)	21 (72.4%)	22 (75.8%)	24 (80%)		0.334
Male, N (%)		21 (23.9%)	8 (27.6%)	7 (24.2%)	6 (20%)		
Total		88 (100%)	29 (100%)	29 (100%)	30 (100%)		
Age							
	Total Sample Mean ± SD N = 88	Control Group Mean ± SD# N = 29	MetS Group Mean ± SD# N = 29	MetS/PreDM Group Mean ± SD# N = 30		*P-value	
Age (years)	49.72 ± 1.17	44.39 ± 2.05	49.07 ± 2.00	55.68 ± 1.51		<0.001	
Clinical characteristics							
	Control, group N = 29 Mean ± SD#	MetS group, N = 29 Mean ± SD#	MetS/PreDM, group.N = 30 Mean ± SD#	P#-value	P^1-value	P^2-value	P^3-value
SBP (mmHg)	117.1 ± 2.23	138.17 ± 1.64	137.42 ± 3.06	**<0.001**	**<0.001**	**<0.001**	1
DBP (mmHg)	73.03 ± 1.86	86.47 ± 1.56	85.42 ± 2.26	**<0.001**	**<0.001**	**<0.001**	1
FPG (mg/dL)	85.31 ± 1.40	88.53 ± 1.72	112.57 ± 3.45	**<0.001**	1	**<0.001**	**<0.001**
A1C%	5.08 ± 0.07	5.28 ± 0.06	6.22 ± 0.13	**<0.001**	0.408	**<0.001**	**<0.001**
TG (mg/dL)	92.82 ± 5.49	201.68 ± 16.89	210.93 ± 25.64	**<0.001**	**<0.001**	**<0.001**	1
LDL-C (mg/dL)	129.65 ± 6.07	143.87 ± 6.12	142.21 ± 7.23	0.244	0.380	0.519	1
HDL-C (mg/dL)	59.33 ± 2.26	44.00 ± 2.05	47.19 ± 3.07	**<0.001**	**<0.001**	**0.003**	1
TC (mg/dL)	195.80 ± 6.26	208.60 ± 7.32	218.03 ± 8.40	0.105	0.673	0.105	1
Non-HDL-C (mg/dL)	136.46 ± 6.96	164.59 ± 6.35	170.84 ± 7.86	**0.002**	**0.019**	**0.003**	1
Adiposity indices							
WC (cm)	87.23 ± 1.81	107.1 ± 1.96	107.66 ± 2.30	**<0.001**	**<0.001**	**<0.001**	1
HC (cm)	99.13 ± 1.53	116.73 ± 2.00	115.19 ± 2.29	**<0.001**	**<0.001**	**<0.001**	1
BMI (Kg/m^2)	23.20 ± 0.34	33.85 ± 1.04	33.10 ± 1.23	**<0.001**	**<0.001**	**<0.001**	1
WHR	0.88 ± 0.01	0.92 ± 0.01	0.94 ± 0.01	**0.004**	0.083	**0.004**	0.847
WHtR	0.54 ± 0.01	0.67 ± 0.01	0.67 ± 0.02	**<0.001**	**<0.001**	**<0.001**	1
C-index	1.30 ± 0.02	1.34 ± 0.01	1.36 ± 0.02	0.059	0.424	0.057	1
BAI	29.92 ± 0.78	39.66 ± 1.24	38.77 ± 1.71	**<0.001**	**<0.001**	**<0.001**	1
LAP	29.09 ± 3.09	108.99 ± 10.79	102.91 ± 11.90	**<0.001**	**<0.001**	**<0.001**	1
VAI	1.33 ± 0.12	3.95 ± 0.45	5.38 ± 1.76	**0.026**	0.252	**0.024**	1
Atherogenicity indices							
AIP	0.19 ± 0.04	0.63 ± 0.05	0.62 ± 0.07	**<0.001**	**<0.001**	**<0.001**	1
TC/HDL-C	3.47 ± 0.20	4.90 ± 0.20	6.12 ± 1.32	0.063	0.617	0.058	0.835
LDL-C/HDL-C	2.40 ± 0.17	3.37 ± 0.15	3.59 ± 0.43	**0.008**	0.053	**0.01**	1
Non-HDL-C/HDL-C	2.48 ± 0.20	3.90 ± 0.20	5.16 ± 1.32	0.057	0.621	0.051	0.773
Hematology related indices							
RDW-CV% (%)	14.4 ± 0.23	14.45 ± 0.18	14.62 ± 0.25	0.766	1	1	1
PLT count ($\times 10^9$/L)	273.03 ± 12.36	274.50 ± 11.42	271.23 ± 8.92	0.978	1	1	1
Monocytes%	5.63 ± 0.28	5.31 ± 0.24	5.40 ± 0.24	0.653	1	1	1
Neutrophiles%	57.39 ± 1.12	57.39 ± 1.59	59.82 ± 1.72	0.418	1	0.755	0.769
Lymphocytes%	33.49 ± 1.17	33.14 ± 1.27	30.20 ± 1.46	0.152	1	0.23	0.348
MLR	0.17 ± 0.01	0.17 ± 0.01	0.21 ± 0.03	0.191	1	0.432	0.288
NLR	1.81 ± 0.10	1.87 ± 0.13	2.53 ± 0.43	0.11	1	0.174	0.253
PLR	8.46 ± 0.49	8.79 ± 0.57	10.33 ± 1.08	0.186	1	0.257	0.479
Metabolic risk biomarkers							
Adipolin (ng/ml)	**0.33 ± 0.192**	**1.08 ± 0.96**	**1.41 ± 0.77**	**<0.001**	**<0.001**	**<0.001**	**0.235**
Cathepsin S (pg/ml)	**40562.1 ± 9902.54**	**53062.5 ± 23869.30**	**58330.4 ± 16448.44**	**0.001**	**0.029**	**0.001**	**0.938**

Pairwise comparisons were done through Bonfferoni adjustment.
adjusted mean and P-value obtained by ANOVA test.
P-value <0.05 was highlighted bold.
P^1 MetS group versus control, P^2 MetS/PreDM versus control, P^3 MetS/PreDM versus MetS.
AIP: atherogenicity index of plasma, BAI: body adiposity index, C-index: conicity index, DBP: diastolic blood pressure, FPG: fasting plasma glucose, A1C%: percent glycosylated-hemoglobin, HC: hip circumference, HDL-C: high density lipoprotein-cholesterol, LAP: lipid accumulation product, LDL-C/HDL-C: low density lipoprotein cholesterol -to- high density lipoprotein cholesterol ratio, LDL-C: low density lipoprotein-cholesterol, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, non-HDL-C/HDL: non high density lipoprotein -to- high density lipoprotein ratio, Non-HDL-C: non-high density lipoprotein cholesterol, PLR: platelet-to-lymphocyte ratio. PLT: platelet, RDW: red cell width, SBP: systolic blood pressure, TC/HDL-C: total cholesterol -to- high density lipoprotein cholesterol ratio, TC: total cholesterol, TG: triglyceride, WC: waist circumference, WHR: waist -to- hip ratio, WHtR: waist -to- height ratio.

used for continuous variables that were not normally distributed (as assessed by Shapiro Wilk test for assessment of normality assumption) to evaluate the relationship between them in the pooled sample of MetS patients (normoglycemic MetS alone plus MetS-PreDM patients).

3. Results

3.1. Demographic and clinical characteristics

Outstandingly systolic blood pressure (SBP), diastolic blood pressure (DBP), non-high density lipoprotein (non HDL-C), and triglycerides (TG) were markedly higher in both MetS groups (non- and pre-diabetic) vs. controls ($P^{1 \text{ and } 2}<0.05$). Conversely HDL-C was markedly lower in both MetS groups (non- and pre-diabetic) vs. controls ($P^{1 \text{ and } 2}<0.05$). In contrast to the rest of clinical characteristics; fasting plasma glucose (FPG) and glycosylated hemoglobin (A1C) had significant differences between the normoglycemic MetS and the MetS/PreDM groups ($P^3 < 0.001$). In both MetS groups (normoglycemic and prediabetic) the adiposity indices [waist circumference (WC), hip circumference (HC), body mass index (BMI), waist to height ratio (WHtR), body adiposity index (BAI) (but not conicity index (CI)] were significantly higher in comparison to controls' ($P^{\#, 1 \text{ and } 2}<0.05$). Exceptionally waist to hip ratio (WHR) and visceral adiposity index (VAI) were significantly higher in the MetS-PreDM group (but not normoglycemic MetS) vs. control ($P^2 < 0.05$).

3.2. Adipolin and cathepsin S levels

Adipolin plasma level (ng/mL) was significantly higher in both MetS (normoglycemic and PreDM) groups vs. healthy controls ($P^{1 \text{ and } 2}<0.001$). Similarly, circulating level of cathepsin S (pg/mL) in both MetS groups (normoglycemic and PreDM) was substantially higher vs. controls ($P^{1 \text{ and } 2}<0.05$) (Table 1 and Figs. 2 and 3). Neither molecular cardiometabolic biomarker had intergroup variation between MetS study arms ($P^3 > 0.05$).

3.3. Adipolin and cathepsin S correlations

As shown in Table 2, in the MetS pool of normoglycemic and PreDM participants (N = 59). Evidently proportional cathepsin S-adipolin association was markedly signified. Distinctively inverse cathepsin S-DBP but direct cathepsin S- monocyte count and Monocyte-to-lymphocyte ratio (MLR) cross correlated was marked. Notably, unlike cathepsin S, adipolin was positively associated with each of FPG, A1C and TG, adiposity indices VAI and Lipid accumulation product (LAP) and atherogenicity index of plasma (AIP). Neither biomarker had substantial relations with Red cell distribution width (RDW-CV %), neutrophils, lymphocytes, neutrophil to lymphocytes ratio (NLR), Plateletto lymphocyte ratio (PLR) or platelet counts. The two biomarkers plasma levels correlate significantly and directly to each other in the pooled MetS group (both normoglycemic and PreDM participants) correlation (Fig. 4).

4. Discussion

Consistent with our study, where adipolin correlated significantly with A1C, a study[2]found that adipolin levels decreased significantly in Q10 group following supplementation, ($P < 0.01$) concomitantly with A1C decrease ($P < 0.001$). A study showed results consistent with our study regarding TGs, SBP, and DBP which was significantly higher, whereas HDL-cholesterol was significantly lower in subjects with metabolic disturbances [15].While, in contrast to our study, serum adipolin concentrations were significantly lower in MetS [15]. On one hand serum adipolin significantly and negatively correlated with BMI, WHR and glucose [15]· on the other hand in our study we found a positive correlation between adipolin and glucosebut failed to find a significant correlation with either BMI or WHR. In consistency with our study; previous studies [16,17] on cathepsin S showed higher cathepsin S levels in association with diabetes. However a study [17], showed in contrast to our study, that cathepsin S significantly and directly correlated only with TG and VLDL ($P < 0.05$).

5. Study conclusion and limitations

Among the limitations in our study were it was not possible to establish causality with a cross-sectional study design of a single time point sampling. Further prospective studies are needed for validation. Considering the financial limitations, recruiting larger sample size was not a considered feasibility. Besides in each study arm, 65% were females versus 35% males, there was no equal gender distribution in any of the study arms.

In conclusion, both adipolin and cathepsin S plasma levels were significantly higher in normoglycemic-MetS and PreDM-MetS

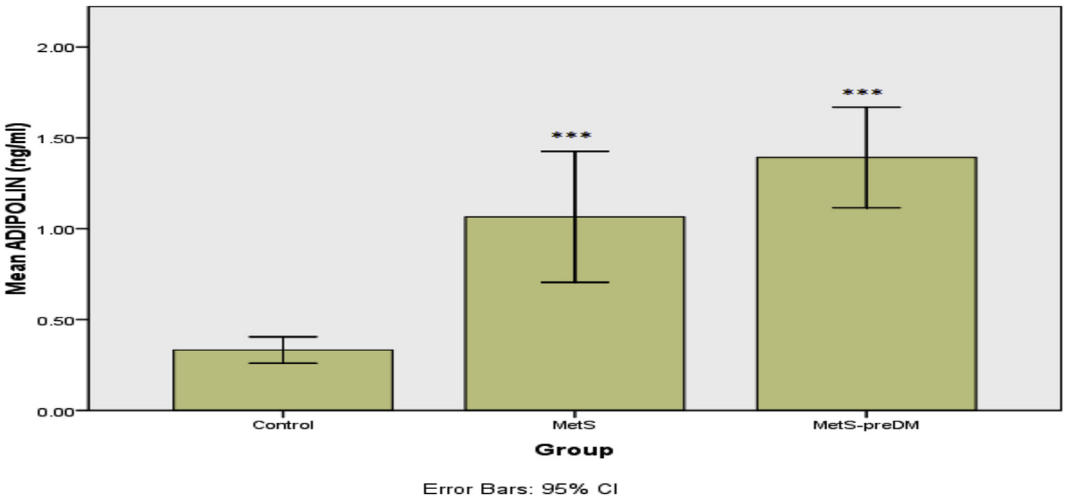

Fig. 2. Bar chart presentation of adipolin plasma level in each study group (results are mean ± SD). P-value<0.05, **P-value<0.01, ***P-value<0.001 vs. controls*.

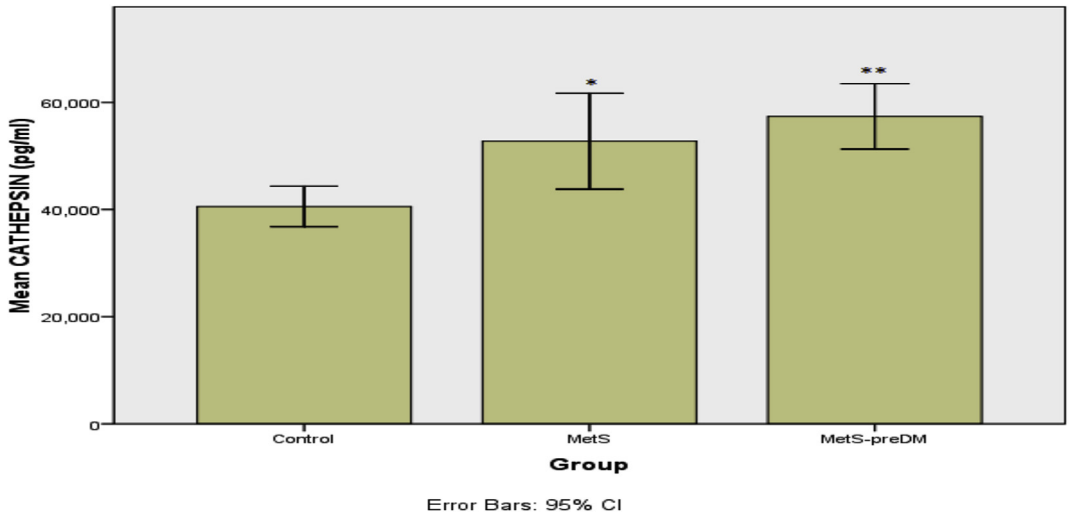

Fig. 3. Bar chart presentation of cathepsin S plasma level in each study group (results are mean ± SD). P-value<0.05, **P-value<0.01, ***P-value<0.001 vs. controls.

Table 2
Cathepsin S and adipolinCorrelations in pooled MetS (both normoglycemic and pre-diabetics) participants (N = 59).

Clinical parameters										
		SBP (mm Hg)	DBP (mm Hg)	FPG (mg/dL)	A1C%	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TC (mg/dL)	Non-HDL-C (mg/dL)
Adipolin (ng/mL)	R	0.050	−0.071	0.387**	0.337**	0.357**	0.072	−0.028	0.097	0.126
	P-value	0.709	0.594	0.002	0.003	0.006	0.586	0.835	0.464	0.343
Cathepsin S (pg/mL)	R	−0.150	−0.288*	0.221	0.062	0.097	0.120	−0.047	0.153	0.178
	P-value	0.257	0.027	0.093	0.641	0.464	0.366	0.721	0.249	0.178
Adiposity indices										
		WC (cm)	HC (cm)	C-index	BMI (Kg/m2)	BAI	WHR	WHtR	LAP	VAI
Adipolin (ng/mL)	R	0.164	0.148	0.035	0.145	0.160	−0.044	0.171	0.343**	0.291*
	P-value	0.214	0.264	0.790	0.274	0.226	0.743	0.196	0.008	0.026
Cathepsin S (pg/mL)	R	0.183	0.135	0.081	0.169	0.206	−0.020	0.203	0.131	0.085
	P-value	0.165	0.307	0.541	0.200	0.117	0.882	0.122	0.322	0.524
Atherogenicity indices										
		Adipolin (ng/mL)	Cathepsin S (pg/mL)	Non-HDL-C/HDL-C ratio		TC/HDL-C ratio		LDL-C/HDL-C ratio		AIP
Adipolin (ng/mL)	R	1.000	0.398**	0.231		0.233		0.222		0.275*
	P-value	–	0.002	0.078		0.076		0.090		0.035
Cathepsin S (pg/mL)	R	0.398**	1.000	0.149		0.149		0.132		0.086
	P-value	0.002	–	0.259		0.261		0.318		0.519
Hematology related indices										
		RDW-CV%	PLT count (x 10^3/μL)	Monocytes %	Neutrophils %	Lymphocytes %	MLR	NLR	PLR	
Adipolin (ng/mL)	R	0.119	−0.029	0.112	0.167	−0.206	0.172	0.208	0.159	
	P-value	0.369	0.826	0.398	0.205	0.118	0.194	0.114	0.228	
Cathepsin S (pg/mL)	R	0.040	0.061	0.267*	0.060	−0.171	0.285*	0.136	0.142	
	P-value	0.765	0.648	0.041	0.650	0.196	0.029	0.304	0.283	

AIP: Atherogenicity index of plasma, BAI: body adiposity index, C-index: conicity index, DBP: diastolic blood pressure, FPG: fasting plasma glucose, A1C%: percent glycosylated-hemoglobin, HC: hip circumference, HDL-C: high density lipoprotein-cholesterol, LAP: lipid accumulation product, LDL-C: low density lipoprotein-cholesterol, LDL-C/HDL-C: low density lipoprotein cholesterol-to-high density lipoprotein cholesterol ratio, MLR: monocyte-to-lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, non-HDL-C: non-high density lipoprotein cholesterol, non-HDL-c/HDL: non-high density lipoprotein-to-high density lipoprotein ratio, PLR: platelet-to-lymphocyte ratio, PLT: platelet, RDW-CV%: red cell distribution width, SBP: systolic blood pressure, TC: total cholesterol TC/HDL-C: total cholesterol-to -high-density lipoprotein cholesterol ratio, TG: triglyceride, WC: waist circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio. ***. Correlation is significant at the 0.05 level (2-tailed). ****. Correlation is significant at the 0.01 level (2-tailed).** We used a Spearman correlation coefficient rs, rs = 0.1–0.29 means small relationship, rs = 0.3–0.49 means moderate relationship, and rs > 0.5 means high relationship.

groups compared to the control group.The two biomarkers plasma levels correlate significantly and directly to each other in the pooled MetS group (both normoglycemic and PreDM participants). Adipolin plasma level correlates proportionally with each of FPG, A1C, TG, LAP, AIP and VAI. Furthermore cathepsin S plasma level correlated directly with monocytes' count and MLR, but inversely with DBP. These data cannot rule both biomarkers out of any possible molecular interplay or crosstalk with the pathophysiology of MetS and preDM; or as surrogate biomarkers and putative prognostic/diagnostic tools for the prediction/prevention and potential treatment targets for metabolism dysregularities.

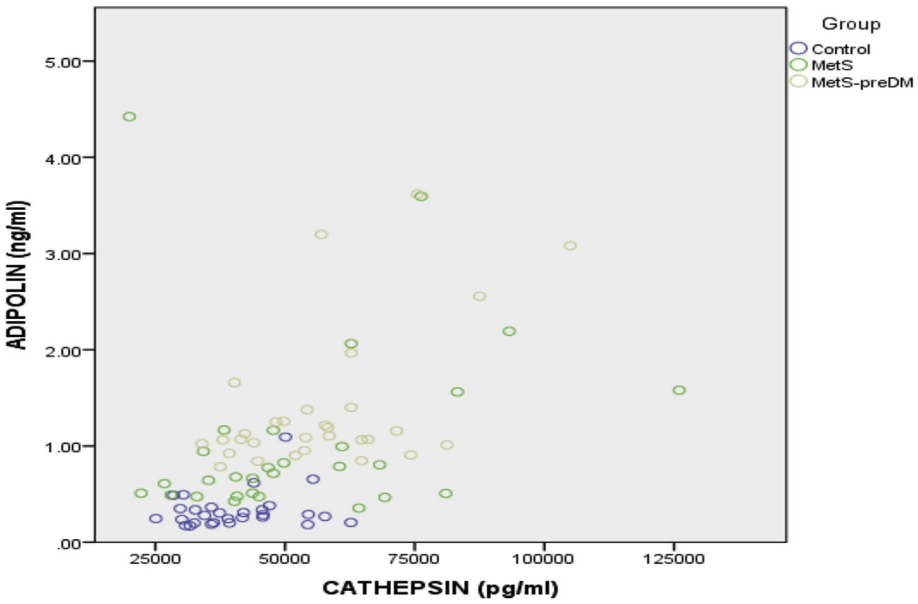

Fig. 4. Scatter plot of adipolin and cathepsin S correlation.

Conflicts of interest

The authors declare none.

Statement

This article does not contain any studies with animals performed by any of the authors.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.06.010.

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