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Original Article

Increased malondialdehyde vs. reduced sirtuin 1 in relation with adiposity, atherogenicity and hematological indices in metabolic syndrome patients with and without prediabetes

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ABSTRACT

Background: Sirtuin 1 (SIRT 1) and malondialdehyde (MDA) were implicated in metabolic syndrome (MetS) and type 2 diabetes mellitus (T2DM) pathophysiology.
Aims and methods: This cross-sectional study aimed to investigate both SIRT 1 and MDA in 30 lean healthy control, 31 normoglycemic MetS subjects and 30 MetS-Pre/T2DM drug naïve. C orrelation studies were established for both biomarkers with adiposity indices [conicity index (CI), waist circumference (WC), weight-to-height (WHtR) ratio, weight-to-hip (WHR) ratio, hip circumference (HC), and body adiposity index (BAI)], hematological indices [red cell distribution width (RDW), mean platelet volume (MPV), platelet-to-lymphcyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR)] and atherogenicity indices (atherogenicity index of plasma (AIP = $\log_{10}$TG/HDL-C ratio), TC/HDL-C and LDL-C/HDL-C ratios].
Results: SIRT1 levels (ng/mL) were markedly lower in both MetS groups (2.12 ± 0.06 and 2.32 ± 0.19, respectively, vs. controls 4.73 ± 0.15; $P < 0.05$). Conversely, a gradual increase in MDA levels (μM) was attained (MetS 72 ± 3.3 and MetS pre-T2DM 81 ± 6.1 vs. controls 62 ± 3.5; $P > 0.05$). A significant inverse MDA-SIRT1 relationship was observed ($P = 0.006$). SIRT1 correlated inversely with all the studied adiposity (WC: $P < 0.001$, HC: $P < 0.001$, WHR: $P < 0.001$, C-index: $P < 0.001$, BAI: $P < 0.001$) and atherogenicity indices (AIP: $P < 0.001$, TC/HDL-C: $P < 0.001$, LDL-C/HDL-C: $P < 0.001$) as well as MPV ($P < 0.01$). Whereas MDA directly with WHtR, CI and BAI (WC: $P < 0.01$, HC: $P < 0.05$, BMI: $P < 001$, WHtR: $P < 0.001$, C-index: $P < 0.005$, BAI: $P < 0.01$).
Conclusion: The substantial variations and correlations emphasize a potential molecular role of SIRT1 and MDA in the pathophysiology of MetS and pre/T2DM.

1. Introduction

Sirtuin 1 (SIRT1) is a NAD+-dependent deacetylase for many nuclear histones and transcription factors. Hence, it acts as an energy sensor through NAD levels fluctuation [1]. SIRT1 plays a crucial role in the overall net metabolic picture of the body. It promotes cholesterol catabolism [2], suppresses both of fat storage and anabolism [3], facilitates insulin secretion [4] and signaling [5], enhances adiponectin expression and inhibits genetic translation of several inflammatory mediators [5–6]. A significant decline in SIRT1 levels was linked to metabolic syndrome (MetS) components with a marked higher declining in components grouping [7]. More importantly, SIRT1 levels reduction was found to be associated with subclinical atherosclerosis in MetS patients [7]. However, malondialdehyde (MDA) is produced in the body from arachidonic acid either enzymatically along with thromboxane A2 or non-enzymatically by peroxidation. MDA has a strong electrophilic character consequently, it binds to protein changing its conformation, and hence, disrupting its biological function [8]. In addition, MDA acts as a signal messenger regulating gene expression of glucose-stimulated insulin secretion key regulators. This could explain how lipid peroxidation can produce hyperinsulinemia [9]. Moreover, MDA elevates directly with type 2 diabetes mellitus (T2DM) duration [10]. Lipid ratios are appealing and practical metabolic parameters with an acceptable sensitivity and specificity. Obviously, these ratios were associated with cardiovascular risk in T2DM [11]. Visceral obesity can be simply and non-invasively estimated using waist circumference (WC), hip circumference (HC), waist-to-hip ratio (WHR), waist-to-height ratio (WHtR). Conicity index

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Table 1
Diagnostic criteria of MetS (IDF [20]).

Criteria	Diagnosis
Central obesity	Waist circumference ≥ 94 cm in men or ≥ 80 cm in women*.
Elevated triglycerides	≥ 150 mg/dl, or specific treatment for this lipid abnormality
Low HDL-C	< 40 mg/dl in men or < 50 mg/dl in women or specific treatment for this lipid abnormality
Elevated blood pressure	Systolic ≥ 130 mm Hg and/or Diastolic ≥ 85 mm Hg. Or treatment of previously diagnosed hypertension.
Elevated fasting plasma glucose	≥100 mg/dl or previously diagnosed T2DM

* for Eastern Mediterranean and Middle East (Arab) populations IDF uses European data until more specific data are available. *if body mass index (BMI) is above 30, central obesity can be assumed.

(CI) is introduced as a novel visceral obesity marker that enables direct comparison between individuals and even populations [12]. Body adiposity index (BAI) was recently proposed as a unified total body fat percent estimator irrespective to gender and ethnicity [13]. Therefore, CI, BAI, WHR and WHtR are considered as good predictors of cardiovascular risk. However, their discrimination varies among populations [14–18].

Mean platelet volume (MPV), red cell distribution width (RDW), platelet-to-lymphocyte ratio (PLR), monocyte-to-lymphocyte ratio (MLR), and neutrophil-to-lymphocyte ratio (NLR) introduced as non-expensive hematological indices indicate systemic inflammation.

The study aimed to compare both MDA and SIRT1 plasma levels in normoglycemic MetS and pre-diabetic or newly diagnosed

Table 2
Comparison of clinical characteristics, adiposity, atherogenicity and hematological indices between study groups.

	Control group, N = 30 Mean ± S.E	MetS group, N = 31 Mean ± S.E	MetS pre/T2DM, N = 30 Mean ± S.E	P-value	P[1]	P[2]	P[3]
			Gender				
Female, N (%)	17(56.7%)	15(48.4%)	16(53.3%)	0.808			
Male, N (%)	13(43.2%)	16(51.6%)	14(46.7%)				
Age, years	31.1 ± 1.7	44.5 ± 2.0	51.8 ± 2.0	<**0.001**			
			Clinical parameters and molecular metabolic biomarkers				
MDA, μM	62 ± 3.5 N=28	72 ± 3.3 N = 30	81 ± 6.1 N = 30	0.085	0.211	0.218	0.4
SIRT1, ng/mL	4.73 ± 0.15 N=29	2.12 ± 0.06 N=29	2.32 ± 0.19 N = 30	<**0.00001**	<**0.001**	<**0.001**	0.318
SBP, mmHg	112 ± 3.2	132 ± 2.6	131.3 ± 2.9	<**0.001**	<**0.001**	<**0.001**	1
DBP, mmHg	70 ± 2.1	80 ± 1.7	81 ± 2	**0.001**	**0.002**	**0.003**	1
FBG, mg/dL	85.7 ± 5	91.3 ± 4.1	122 ± 4.6	<**0.001**	1	<**0.001**	<**0.001**
HbA1C %	5.12 ± 0.1	5.2 ± 0.1	6.4 ± 0.1	<**0.001**	1	<**0.001**	<**0.001**
TG, mg/dL	63.9 ± 19.4	186.8 ± 15.9	211 ± 18	<**0.001**	<**0.001**	<**0.001**	0.889
LDL-C, mg/dL	97.6 ± 7.3	121.8 ± 6	134 ± 6.8	0.007	**0.048**	**0.005**	0.483
HDL-C, mg/dL	47.6 ± 2.9	42.6 ± 2.4	39.5 ± 2.7	0.194	0.608	0.214	1
TC, mg/dL	159 ± 8.2	201 ± 6.7	215.6 ± 7.7	<**0.001**	**0.001**	<**0.001**	0.477
			Adiposity indices				
WC, cm	78.4 ± 1.9	103 ± 1.55	105.5 ± 1.76	<**0.001**	<**0.001**	<**0.001**	0.971
HC, cm	93.65 ± 2.2	115.8 ± 1.7	119 ± 1.97	<**0.001**	<**0.001**	<**0.001**	0.451
BMI, kg/m^2	21.4 ± 0.97	33.5 ± 0.79	34.5 ± 0.9	<**0.001**	<**0.001**	<**0.001**	1
WHR	0.84 ± 0.015	0.89 ± 0.012	0.89 ± 0.014	**0.028**	**0.024**	0.138	1
WHtR	0.48 ± 0.011	0.62 ± 0.009	0.63 ± 0.01	<**0.001**	<**0.001**	<**0.001**	1
C-index	1.21 ± 0.014	1.27 ± 0.011	1.28 ± 0.013	**0.004**	**0.008**	**0.007**	1
BAI	26.3 ± 1.34	35.4 ± 1.1	36.8 ± 1.24	<**0.001**	<**0.001**	<**0.001**	1
			Atherogenicity indices				
AIP	0.2 ± 0.5	0.6 ± 0.04	0.7 ± 0.05	<**0.001**	<**0.001**	<**0.001**	1
TC/HDL-C	3.4 ± 0.8	5 ± 0.7	6.6 ± 0.7	**0.041**	0.427	**0.037**	0.320
LDL-C/HDL-C	2.1 ± 0.68	3 ± 0.6	4.3 ± 0.6	0.11	1	0.128	0.366
			Hematological indices				
RDW	13.5 ± 0.2	13.5 ± 0.2	13.8 ± 0.2	0.436	1	0.904	0.689
MPV, fL	7 ± 0.4	9.1 ± 0.3	8.7 ± 0.4	**0.001**	**0.001**	**0.025**	1
MLR	0.3 ± 0.04	0.3 ± 0.03	0.2±.04	0.515	1	0.844	1
NLR	2.36 ± 0.4	1.9 ± 0.3	2 ± 0.4	0.662	1	1	1
PLR	104 ± 9.1	121.6 ± 7.4	97 ± 8.5	0.59	0.47	1	**0.026**

[a]Covariate appearing in the model is evaluated at the following value: age = 42.73.
Pairwise comparisons were done through Bonferroni adjustment.
Adjusted mean and P-value obtained by ANCOVA test.
Age analysis by ANOVA test, Levene,s test P-value = 0.305.
Gender analysis by Chi square.
P[1] MetsS group versus control, P[2]MetS pre/T2DM versus control, P[3] MetS pre/T2DM versus MetsS.
DPB: diastolic blood pressure, FBG: fasting blood glucose, HbA1C%: percent glycosylated- hemoglobin, HDL-C: high density lipoprotein-cholesterol, LDL-C: low density lipoprotein-cholesterol, MDA: malondialdehyde, SBP: systolic blood pressure, SIRT1: sirtuin1, TG: triglycerides, TC: total cholesterol,WC: waist circumference, HC: hip circumference, WHR: waist-to-hip ratio, WHtR: waist-to-height ratio, C-index: conicity index, BAI: body adiposity index, RDW: red cell width, MPV: mean platelet volume, PLT: platelet, MLR: monocyte-to- lymphocyte ratio, NLR: neutrophil-to-lymphocyte ratio, PLR: platelet-to-lymphocyte ratio.

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