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Plasma GSH as Independent Antioxidant Factor of Metabolic Syndrome Lowering by a Lifestyle Modification Program

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ABSTRACT

Introduction: *Metabolic syndrome (MetS) is accompanied by pro-oxidative processes that might be reversed or attenuated by the physical exercise.*

Objective: *To investigate the impact of a lifestyle modification program (LiSM) on antioxidant status and redox processes in MetS.*

Methodology: *It was analyzed data from participants of the ongoing dynamic coort-study "Move for Health" during the period of 2009-2012. Fifty-seven subjects full filed the inclusion criteria of attending the 20wk-LiSM with nutritional counseling and supervised aerobic exercises. Assessment at baseline and end of LiSM were undetaken for anthropometric, clinical, dietary, cardiorespiratory fitness (CRF) and plasma-biochemistry data. Plasma hydrophilic total antioxidant performance (TAP) along with malondialdehyde (MDA) and total and oxidized (GSSG) glutathione were measured and reduced (GSH) glutathione was estimated. MetS was defined by NCEP(2005) criteria. Statistical significance was set at p <0,05.*

Findings: *Primary outcomes after LiSM were the decreasing of BMI, WC and body fat and the increasing of HEI, CRF, HDL-c, GSH and plasma TAP. These changes were similar in both groups, MetS and non-MetS. MetS decreased by 16.4%. In the MetS group, the TAP variation during 20wk-LiSM correlated significantly with WC (r=-0.47), fasting blood glucose (r=-0.48) and MDA (r=-0.45) and, in non-MetS group TAP correlated with HDL-c (r=0.38) and GSH (r=0.45). After LiSM, the TAP-responsive (≥3% increased) subjects differed from the non-TAP-responsive (≤3%) by presenting increased values of CRF, HDL-c, uric acid and GSH, and decreased SBP, GSSG and GSSG/GSH ratio. The multiple-adjusted regression analysis pointed out the increased GSH as the only independent risk factor for TAP changes, during LiSM, either in presence or absence of MetS.*

Conclusion: *Thus, this 20-wk LiSM changed the pro-antioxidant balance by modifying GSH redox status irrespective to the presence or absence of MetS.*

Keywords
Glutathione redox, Metabolic syndrome, Plasma antioxidants.

Introduction

Metabolic syndrome (MetS) is characterized by the clustering of several metabolic abnormalities present in the same individual, which increases prothrombotic and proinflammatory markers [1]. In MetS pathophysiological process, inflammatory and oxidative stresses are considered as triggers of atherosclerosis and recurrent diseases such as type-2 diabetes and cardiovascular diseases (CVD) [2].

Several factors can influence oxidative imbalance in the body. Malondialdehyde (MDA) is a very sensitive biomarker for lipoxidation reflecting the magnitude of the oxidative imbalance present in the organism [3]. As shown previously, subjects with higher plasma MDA showed higher prevalence of MetS. Multiadjusted logistic regression analysis identified as determinants of higher plasma MDA the altered values of waist circumference (WC) and γ-glutamyltransferase (γ-GT) followed by hypertriglyceridemia, hyperglycemia, insulin resistance (IR), higher dietary sugar-intake, and presence of MetS [4].

The imbalance between antioxidant defense and free radicals' production facilitates oxidation of lipids, proteins and nucleic structures determining cell dysfunction with generalized responses [5]. One is assumed that in these cases an oxidative stress is occurring due to incapacity of antioxidant protection and nucleophilic substances for quenching excess of electrophilic substances. One of these most important endogenous nucleophilic substances is the tripeptide γ-glutamyl-cysteinyl-glycine, also called glutathione (GSH) [6]. Into the cell, the GSH redox system is important for quenching the excess of hydroperoxide from mitochondrial metabolic processes and, as well as in the plasma, also shows detoxification actions by extinction of toxic lipid peroxidation bioproducts such as reactive aldehydes [7]. Increasing evidence indicates that MetS is affected by genetic [8,9] and lifestyle factors, such as alcohol consumption, soft drink intake, coffee consumption and sedentary behaviours [10-13]. Higher adherence to the Healthy Lifestyle Score was associated with a lower risk of developing metabolic syndrome [14].

Lifestyle modification (LiSM), with nutritional counseling and physical activity, as primary care for MetS prevention and treatment has been previously established [15]. Physical exercise accomplishes both, anti-inflammatory and antioxidant effects [16], as previously described in older women on resistance training [17,18].

As the two important determinants of body weight, diet and physical activity can influence obesity and most of the MetS components directly [19,20]. Antioxidants and anti-inflammatory components from fruits and vegetables are hypothesized to play an important role in MetS [21,22]. A meta-analysis indicates that fruit or/and vegetable consumption may be inversely associated with risk of MetS. It suggests that people should consume more fruits and vegetables to decrease the risk of MetS [23].

Overall, the impact of LiSM programs on antioxidant status and redox processes are poorly described. The present study shows the effects of a LiSM program on plasma antioxidant status and the influence of the MetS presence on this process.

Material and Methods

Study Population and Design

Subjects enrolled in the Brazilian "Move for Health Program" were studied. This program promotes healthy lifestyle by nutritional counseling and physical exercise as primary care for chronic non-communicable diseases. One hundred twelve adults spontaneously sought the program to change their habits. This longitudinal study offered 20 weeks of intervention with LiSM. Inclusion criteria were ≥40 years old and subjects were required to submit clinical readiness for physical activity (PAR-Q). In addition, they must have at least one MetS component and should not have complications from hepatic, renal, autoimmune, inflammatory and cardiovascular diseases. We excluded individuals using vitamin supplements, anti-inflammatory medications and chronic alcoholics. Of those 112 subjects, 57 (72% women) completed the 20- week LiSM protocol and performed all assessments. The studied population was essentially composed by adults (55 ± 8yrs), overweight (35%) or obese (65%), non-smokers (67%) and in use of hypoglycemiant, hypolipidemic, antihypertensive or antidepressant drugs (59%). According to the presence or not of MetS (before protocol), subjects were divided in two groups: without MetS (n=30) and with MetS (n=27). Subjects were aware of the study and signed a consent form based on the "experiments involving humans" of the Brazilian "National Council of Health, Ministry of Health" and the declaration of Helsinki. Both the design and consent form were submitted and approved by the Research Ethics Committee (Letter 262/2010) of the Botucatu Medical School, São Paulo State University (UNESP).

Lifestyle Modification Protocol

Protocol consisted by supervised exercise sessions, Monday to Friday. Alternately, subjects were submitted to walking and stretching at Mondays, Wednesdays and Fridays and resistance training at Tuesdays and Thursdays. They should attend three or more sessions during the week, otherwise would be excluded from activities. Nutritional counseling was applied weekly through lectures in groups with relevant nutritional context in which subjects were comprised. Clinical, cardiorespiratory fitness, body composition, anthropometric, dietary and laboratory assessments were performed before and after 20-week LiSM intervention. This protocol is validated and is in accordance with the American College of Sports Medicine's guidelines for exercise prescription and treatment for chronic non-communicable diseases [24].

Clinical, Nutritional and Lism Compliance Evaluations

During clinical evaluation, subject's history for diseases and PAR-Q were assessed [25]. At the same time, systolic and diastolic

blood pressures were measured and cardiorespiratory fitness (CRF) was performed in a maximal treadmill test (Balke protocol) to estimate maximal oxygen consumption, VO_{2max} (mL/kg/min) [26]. Heart rate, blood pressures and electrocardiogram were monitored throughout the test.

Body mass index (BMI) and waist circumference WC were measured according to World Health Organization (WHO) recommendations [27]. Body fat percentage and lean mass were estimated by equations considering electric resistance and reactance of the body provided by a bioelectric impedance device (Biodynamics®, model 450, USA).

Subjects' nutritional histories were recorded by 24-hour recall. Dietary data were obtained in household measures and converted to grams and milliliter enabling chemical analysis of food consumption. Then data were processed by a nutritional analysis program (NutWin®, Support Program for Nutrition, version 1.5, UNIFESP, 2002). We used the adapted Healthy Eating Index (HEI) [28], compiled from the American HEI [29], to assess dietary quality. MetS diagnosis used the criteria described by the American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement [19].

Laboratory Assessments

Blood samples were drawn by vacuum venipuncture after overnight fasting. Lipid parameters (total and HDL-cholesterol, and triglycerides), fasting blood glucose (FBG), uric acid and γ-GT were measured within 4 hours after blood collection by dry chemistry method (Vitros® 5600, Johnson & Johnson Company, USA). The LDL-cholesterol concentrations were estimated by Friedewald's formula [30]. Serum insulin concentrations were measured by chemiluminescent method (Immulite 2000®, Siemens Healthcare Diagnostics, Germany). The HOMA-IR index was used for estimating insulin resistance [31,32]. Serum CRP was measured by a high-sensitivity immuno-nephelometric assay (Siemens Healthcare Diagnostics, Germany). Plasma MDA levels were measured by high performance liquid chromatography with fluorimetric detection (HPLC; system LC10A®, Shimadzu, Japan) as previously described [33]. GSH and GSSG plasma levels were also measured by HPLC as previously described [34] using n-ethyl-maleimide (NEM) as preservative during blood collection. Samples were analyzed as total glutathione and as oxidized glutathione (GSSG). Reduced glutathione (GSH) values were obtained by subtracting GSSG values from total glutathione values of each subject. The antioxidant glutathione redox ratio was calculated (GSSG/GSH) [35].

Plasma total antioxidant performance (TAP) was measured based on the method described by Beretta *et al.* [36]. Briefly, it was assayed the plasma capacity for protecting the fluorescent probe BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-s-indacene) from oxidation performed by the AAPH (2,2`Azobis 2-amidino-propano-dihidroclorado). The assay reaction occurred in black 96-well plate, in triplicates, and fluorescence was monitored at specific reader (Wallac Vitor 2X®, Perkin-Elmer, Boston, MA, USA). TAP was expressed in percentage in comparison to the phosphatidylcholine standard matrix.

Statistical Analysis

The statistical analysis was performed by Statistical Analysis Software (SAS version 9.1.3, SAS Institute, USA). Data were tested for normality using the Kolmogorov-Smirnov test. Data description is presented as mean ± standard deviation (parametric variables) or median and quartile range between 25 and 75 pecentiles (nonparametric variables). LiSM effects on analyzed variables were assessed by paired-t test for parametric variables and "signed-rank" test for non-parametric variables. Multiple regression analysis was used to assess the relationship among changes (delta) of analyzed variables and markers. A backward stepwise to determine influence (R^2) among variables was settled. This later test excludes variables with less influence from the model, leaving the one(s) with greater significant influence on dependent variables. The α significance in all analyzes was set at 5% ($p < 0,05$).

Results

Both groups, with and without MetS, responded similar to LiSM by increasing HEI and CRF and decreasing WC, keeping similar plasma levels of CRP and MDA (Table 1). MetS was 47% at baseline and 31% after 20wk-LiSM (16% reduction), decreased WC was the major outcome to LiSM. However, patients with MetS showed higher WC, body fat, HOMA-IR and plasma triacylglycerol, and lower HDL-C not only at baseline, but also at the end of LiSM, as compared to subjects without MetS.

Regarding the plasma-antioxidant biomarkers, subjects without MetS responded better to LiSM by presenting an increased TAP and GSH and a decreased GSSG/GSH ratio, than the patients with MetS (Table 1).

In non-MetS subjects, changes in plasma TAP were directly and significantly correlated with changes in GSH (r=0.45) and HDL-c (r=0.38). LiSM increased HDL-C only in subjects without MetS (Figure 1). On the other hand, changes in plasma TAP of those with MetS were inversely and significantly correlated with changes in fasting blood glucose (r=-0.48), WC (r=-0.47), and MDA (r=-0.45) (Figure 2).

In comparison to the TAP-non responsive (≤3% decreasing) subjects, the TAP-responsive (≥3% decreasing) to LiSM showed higher values of CRF, HDL-c, uric acid and GSH, along with lower GSSG and GSSG/GSH ratio. Overall TAP responsiveness to LiSM was linked to higher CRF (Table 2). Thus, regarding plasma TAP levels, the GSH (increasing) and GSSG (decreasing) changes were the influencing factors for subjects without MetS, while only GSH (increasing) levels influenced plasma TAP of subjects with MetS. Table 3 shows that GSH (increase) was the independent factor for LiSM response irrespective to MetS, whereas TAP (increase) and GSSG (decrease) response to LiSM

Table 1: Primary LiSM outcomes in subjects without and with MetS.

	Without MetS (n=30)		With MetS(n=27)	
	Baseline	after LiSM	Baseline	after LiSM
MetS [n(%)]	0 (0%)[a]	0 (0%)[a]	27 (100%)[a]	18 (67%)[b]
BMI (kg/m^2)	29.0 ± 5.7[a]	28.7 ± 5.6[a]	32.9 ± 6.9[a]	32.4 ± 6.3[b]
WC (cm)	92.0 ± 15.2[a]	89.6 ± 12.6[b]	102.2 ± 14.8[a]*	99.6 ± 14.7[b]*
Body fat (%)	31.7 (29.3-42.9)[a]	31.3 (28.3-35.4)[a]	45.3 (31.5-47.4)[a]*	42.8 (31.2-45.7)[b]*
HEI (points)	77.3 ± 12.3[a]	82.2 ± 14.4[b]	79.9 ± 12.6[a]	84.0 ± 10.6[b]
SBP (mm/Hg)	127 ± 23[a]	123 ± 11[a]	137 ± 17[a]	130 ± 15[a]
DBP (mm/Hg)	81 ± 11[a]	76 ± 9[a]	83 ± 10[a]	81 ± 9[a]
CRF (mL/kg/min)	30.4 ± 5.7[a]	33.1 ± 5.8[b]	29.5 ± 4.7[a]	32.8 ± 4.4[b]
FBG (mg/dL)	91.7 ± 20.5[a]	92.6 ± 26.5[a]	120.0 ± 40.2[a]	113.8 ± 36.3[a]
HOMA-IR	1.80 (1.34-2.87)[a]	1.69 (1.34-2.90)[a]	4.81 (1.76-6.26)[a]*	3.94 (2.28-5.08)[a]*
TAG (mg/dL)	116 (85-143)[a]	108 (85-146)[a]	159 (139-240)[a]*	160 (109-279)[a]*
Total-C (mg/dL)	190.7 ± 40.0[a]	201.3 ± 34.0[a]	208.3 ± 35.4[a]	209.2 ± 32.9[a]
LDL-C (mg/dL)	115.5 ± 35.3[a]	122.2 ± 32.7[a]	129.4 ± 33.9[a]	130.0 ± 27.1[a]
HDL-C (mg/dL)	51.5 ± 12.7[a]	54.5 ± 12.3[b]	41.1 ± 7.2[a]	42.3 ± 8.5[a]*
Uric acid (mg/dL)	4.4 (3.6-5.2)[a]	4.5 (3.4-4.9)[a]	4.5 (3.8-5.5)[a]	4.8 (3.6-5.6)[a]
Gamma-GT (U/L)	21.5 (16.0-36.0)[a]	21.5 (17.0-25.0)[a]	34.0 (20.0-50.0)[a]	28.0 (19.0-43.0)[a]
CRP (mg/L)	2.39 (1.27-6.63)[a]	2.82 (1.12-6.07)[a]	4.08 (1.92-8.06)[a]	3.85 (1.53-6.86)[a]
Plasma TAP (%)	48.4 ± 7.4[a]	53.7 ± 8.1[b]	46.5 ± 7.9[a]	47.1 ± 7.5[a]*
GSH (µmol/L)	5.37 ± 1.86[a]	6.44 ± 2.07[b]	5.13 ± 1.90[a]	5.24 ± 1.73[a]*
GSSG (µmol/L)	0.52 (0.44-0.77)[a]	0.52 (0.47-0.65)[a]	0.73 (0.49-0.82)[a]	0.74 (0.52-0.84)[a]
GSSG/GSH	0.14 ± 0.06[a]	0.11 ± 0.06[b]	0.15 ± 0.12[a]	0.14 ± 0.09[a]
MDA (µmol/L)	0.39 (0.27-086)[a]	0.31 (0.23-0.91)[a]	0.45 (0.28-0.96)[a]	0.34 (0.27-0.87)[a]

MetS: metabolic syndrome; BMI: body mass index; WC: waist circumference; HEI: healthy eating index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRF: cardiorespiratory fitness; FBG: fasting blood glucose; TAG: triacylglycerol; CRP: C-reactive protein; Plasma TAP: plasma total antioxidant performance; GSH: reduced glutathione; GSSG: oxidized glutathione; MDA: malondialdehyde. Different letters mean statistical significance for LiSM effects ($p<0.05$). *means statistical significance difference between groups at the same time point ($p<0.05$).

Table 2: Plasma TAP responsiveness after LiSM*.

	Plasma TAP response after LiSM	
Δ	Positive (≥3%, n=24)	Negative (≤3%, n=13)
BMI (kg/m^2)	-0.34 ± 1.22[a]	-0.26 ± 0.74[a]
WC (cm)	-1.25 (-3.25- -0.50)[a]	-0.80 (-3.88- 0.50)[a]
Body fat (%)	-0.65 (-1.43- 0.49)[a]	-0.38 (-0.73- 0.01)[a]
HEI (points)	4.79 (3.09-13.4)[a]	4.23 (-3.48- 15.7)[a]
SBP (mm/Hg)	-5.0 (-16.3- 5.5)[a]	0.0 (-5.0- 10.0)[b]
DBP (mm/Hg)	-2.0 (-10.0- 2.5)[a]	0.0 (-10- 0.0)[a]
CRF (mL/kg/min)	3.60 (1.05-5.95)[a]	1.80 (1.35-3.62)[b]
FBG (mg/dL)	-2.0 (-6.8- 1.25)[a]	-0.5 (-2.5- 3.5)[a]
HOMA-IR	-0.7 (-1.0- 1.3)[a]	0.3 (-0.9- 6.3)[a]
TAG (mg/dL)	-1.5 (-33.5- 11.0)[a]	8.0 (-23.8- 29.0)[a]
Total-C (mg/dL)	7.0 (-9.3- 22.3)[a]	4.0 (-14.0- 17.5) [a]
LDL-C (mg/dL)	4.2 (-12.8- 20.2)[a]	4.1 (-7.9- 20.7)[a]
HDL-C (mg/dL)	3.2 ± 8.4[a]	-0.2 ± 6.4[b]
Uric acid (mg/dL)	0.3 (-1.6- 0.7)[a]	-0.3 (-0.6- 0.2)[b]
Gamma-GT(U/L)	-1.0 (-8.0- 2.3)[a]	-2.0 (-3.0- 0.5)[a]
CRP (mg/L)	-0.56 (-2.82- 2.05)[a]	0.50 (-2.55- 1.24)[a]
GSH (µmol/L)	1.61 ± 1.48[a]	0.12 ± 1.45[b]
GSSG (µmol/L)	-0.08 (-0.14-0.03)[a]	0.07 (0.02-0.09)[b]
GSSG/GSH	-0.05 ± 0.04[a]	0.02 ± 0.02[b]
MDA (µmol/L)	-0.09 ± 0.25[a]	0.02 ± 0.23[a]

BMI: body mass index; WC: waist circumference; HEI: healthy eating index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CRF: cardiorespiratory fitness; FBG: fasting blood glucose; TAG: triacylglycerol; CRP: C-reactive protein; GSH: reduced glutathione; GSSG: oxidized glutathione; MDA: malondialdehyde. Different letters mean statistical significance ($p<0.05$).

Table 3: Adjusted* multiple regression analyses between changes in plasma TAP and primary correlated markers and MetS components in subjects without or with MetS after LiSM.

	Without MetS				With MetS		
	Δ	Plasma TAP			Δ	Plasma TAP	
	β	SE	*p*		β	SE	*p*
GSH	0.83	0.30	0.02	GSH	0.72	0.24	0.03
HDL cholesterol	0.39	0.23	0.13	Malondialdehyde	-0.51	0.31	0.16
Diastolic BP	0.28	0.25	0.29	HDL cholesterol	0.18	0.25	0.50
Malondialdehyde	-0.07	0.49	0.89	GSSG	0.11	0.19	0.59
Fasting blood glucose	-0,33	0.47	0.45	Fasting blood glucose	0.09	0.26	0.74
GSSG	-0,65	0.24	0.03	Waist circumference	-0.31	0.16	0.11
				Systolic Blood Pressure	-0.34	0.23	0.20
*Adjusted for age, sex, smoking, remedy use, BMI, healthy eating index and cardiorespiratory fitness.							

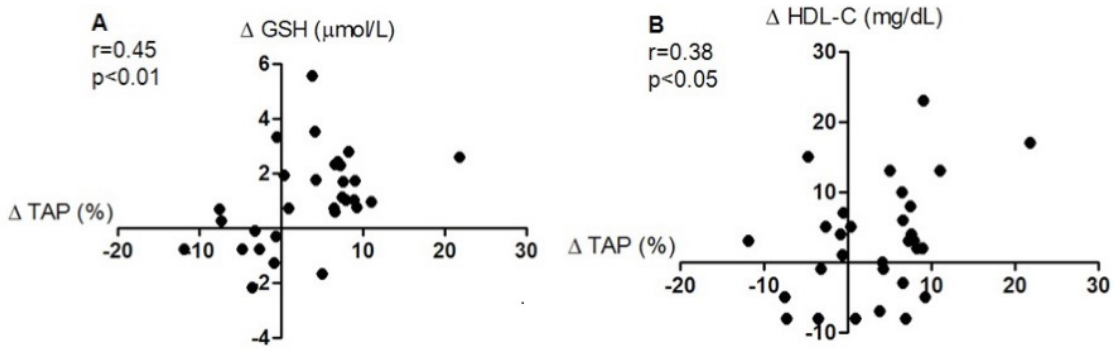

Figure 1: Direct significant correlations between changes in plasma total antioxidant performance (TAP) and plasma GSH (A) or HDL cholesterol (A) in subjects without MetS after 20-wk LiSM.

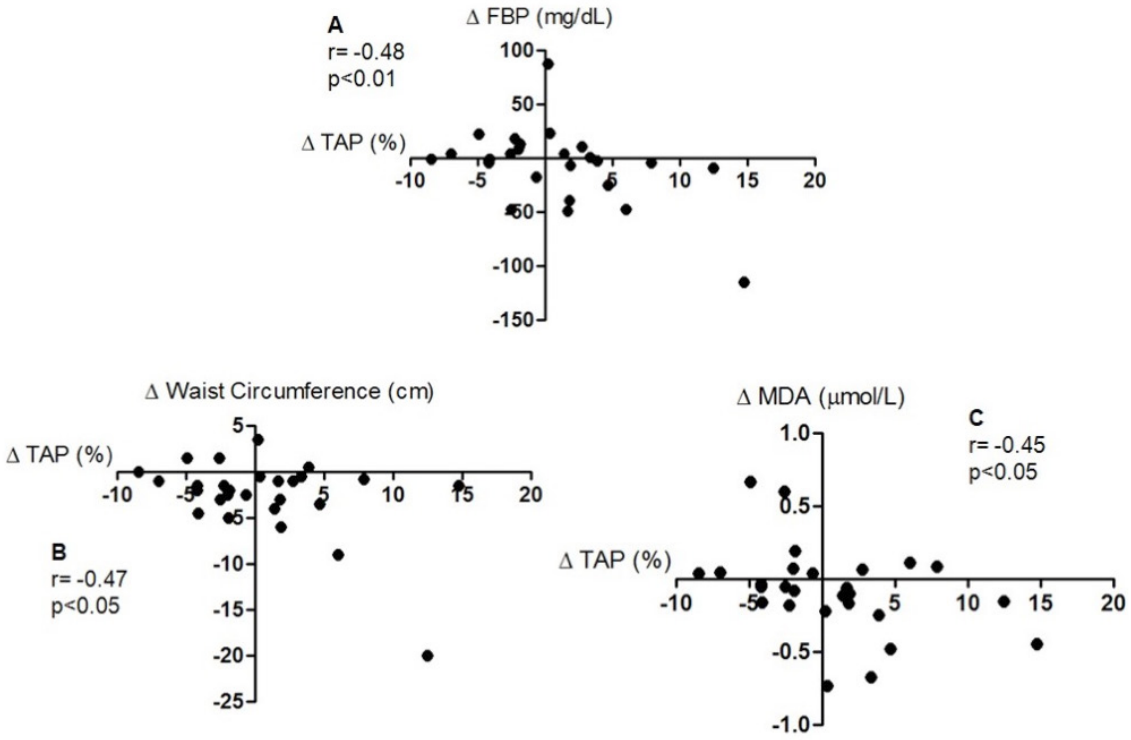

Figure 2: Inverse significant correlations between changes in plasma total antioxidant performance (TAP) and changes in plasma fasting blood glucose (FBG) (A), waist circumference (B) and plasma malondialdehyde (MDA) (C) in subjects with MetS after 20-wk LisM.

depended upon MetS absence. Overall TAP responsiveness to LiSM was linked to higher CRF and HEI, along with higher HDL-C, uric acid and GSH, associated to lower GSSG and GSSG/GSH ratio.

Discussion

MetS was 47% at baseline. Our cross-sectional studies described that MetS prevalence varied from 28% to 51% and, its decreasing in response to LiSM varied from 12.4% to 16.9% depending on length of 10 to 24 weeks protocols [37] and, 12.7% to 25.4% under mixed(walking-strength) or hydrogymnastics exercises [38]. Additional dietary interventions accentuated the reduction of MetS by 20-wk LiSM, showing 29% decreasing with omega-3 polyunsaturated fatty acid [39] and 24% decreasing with fiber 25g/d (in 10wks) [40].

Presently, with 20-wk LiSM with supervised mixed(walking-strength) exercises without specific dietary intervention, the MetS reduction was 16%, having an increased HEI and CRF along with decreased WC as the major outcomes. We used MDA and GSSG as representative products of oxidized lipids and proteins, whereas uric acid was taken as the major hydro soluble anti-oxidant agent (50%) out the cell [41] and GSH as the major intracellular hydro soluble antioxidant [42,43]. For the oxidative biomarkers, subjects without MetS responded better to LiSM than the patients with MetS.

By its definition MetS has abnormal values for WC and TG(TAG), as presented here. Such phenotype of MetS is characterized as hypertriglyceridemic waist [44] and, it is reported to be related to mitochondrial dysfunction in tissues such as liver, skeletal muscle and adipose tissue [45]. Dysfunctional mitochondrion is characterized by abnormally elevated amounts of reactive oxygen species to a less extent ATP production [46]. In liver and skeletal muscle, mitochondrial dysfunction is associated with ectopic fat deposition (fatty liver and myosteatosis) which also impact ROS and electrophilic substances production able to induce systemic or organ-specific pathological processes [47]. Additionally, the low availability of intracellular ATP impacts some energy dependent biochemical reactions such as GSH synthesis [48].

Plasma GSH reflects intracellular GSH [49], which is primarily synthesized in liver and kidney and exported to plasma by the gamma-glutamyl-transpeptidase activity in plasma membrane. Cysteine is the rate limiting amino acid for GSH synthesis and, along with the enzyme gamma-glutamylcysteine synthetase (γGCS) are ATP-dependent. Therefore, low-abundance of ATP from mitochondrial dysfunction would impact on activity of this enzyme [48]. Our LiSM influenced reductions of total body fat percentage and waist circumference in subjects with MetS, however, without major changes on dyslipidemia (hypertriglyceridemia and diminished HDL-C) and insulin resistance.

The results also showed TAP responsiveness to LiSM linked to higher CRF and HEI now, along with higher levels of HDL-C, uric acid and GSH, associated to lower GSSG and GSSG/GSH ratio. The fact that TAP responsiveness to LiSM was linked to higher CRF might be due to the effective antioxidant therapy of exercise training [50,51]. However, the reductive effect of LiSM was seen only in GSSG and not in MDA.

In the presence of MetS, the TAP response to LiSM was indirectly correlated to WC, blood glucose and MDA. MetS patients showed higher values of HOMA-IR, CRP-hs and MDA than the non-MetS subjects and, the LiSM effect in reducing these parameters was insignificant. In previous work, LiSM reduced MDA of MetS, but the MDA concentrations responded better to changes on glucose homeostasis suggesting a MetS phenotype with higher hyperglycemia impact on MDA formation [4,52]. Therefore, the pro-oxidant state of MetS can be attenuated after lifestyle modification if glucose metabolism homeostasis were recovered and if liver inflammation were reduced, respectively [52].

In healthy conditions, moderate exercise induces an up-regulation of SOD and, consequently, decreases oxidative stress [53,54]. Exercise has the most potent effect on endothelium-dependent vasodilatation and the endothelium derived nitric oxide is thought to be necessary to maintain an adequate vascular response to increased blood-flow demands during exercise. Shear stress ensures substrate availability, as the rate-limiting step of eNOS, which generates ROS in the absence of L-arginine [55]. Though, shear stress is an important component of exercise, and it affects vascular NO concentration, and increases the velocity of the endothelial high-affinity/low-capacity transport system for L-arginine [56]. By doing that, physical activity increases endothelial nitric oxide synthase (eNOS) expression and/or eNOS Ser^{1177} phosphorylation (mediated by an increase in Akt expression and/or phosphorylation) [57]. Muscular contraction dependent [Ca++] also modulates eNOS activity but shear stress lead to eNOS phosphorylation on serine residues independent from increases in $[Ca^{2+}]$ [58].

Clinical and experimental studies have reported beneficial effects of regular physical activity in increasing nitric oxide (NO) bioavailability and reducing oxidative stress. How could exercising training, which increases total oxygen uptake and in turn the expression of extracellular superoxide dismutase (ecSOD) with consequent production of ROS, can improve endothelial derived NO? [59,60] As answer it was demonstrated that exercise training increases both eNOS and ecSOD expression thus alternating the premature breakdown of NO by ROS [55].

Thus, overall exercise training may correct endothelium-dependent vasodilatation by a variety of mechanisms. First, shear stress augments the expression of nitric oxide synthase in endothelial cells. Second, shear stress induces up-regulation of the cytosolic copper-and-zinc containing superoxide dismutase, a free-radical scavenger. The inactivation of nitric oxide by a vascular superoxide or other reactive oxygen species may thereby be attenuated. Third, shear-stress-mediated suppression of angiotensin-converting enzyme may influence endothelium dependent relaxation by affecting local concentration of bradykinin

by keeping it active [61,62]. Thus, regular physical exercises increase antioxidant SOD (superoxide dismutase) expression, and decreases in NADPH oxidase activity and expression of its subunits (gp91^{phox}, p22^{phox} and nox4), leading to reduced ROS generation [63]. These complex mechanisms allow physical exercises to normalize high blood pressure irrespective to body weight changes [61].

Conclusion

The present results indicated that plasma antioxidant status responded to a lifestyle modification program with nutritional counseling and regular exercise and, therefore, plasma biomarkers of antioxidant and redox balance can be considered good marker for healthy related-reliability after anti-sedentary programs. However, the presence of MetS entangled the effects of LiSM on TAP, particularly on MDA behavior. In spite of that, the changes of TAP presented a direct relationship to both GSH and HDL-C, leading GSH (increase) as the only independent factor for LiSM response irrespective to MetS, while TAP (increase) and GSSG (decrease) response were dependent upon the absence of MetS.

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