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Biomarkers of Oxidative Stress in Syndrome Metabolic Patients, a Case Control Study

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Abstract

Background: Owing to the proposal of the increase of oxidative stress (OxS) as an early event in the development of the metabolic syndrome (MetS), the aim of the present study was to evaluate certain OxS biomarkers in patients with MetS compared to healthy people age-matched and younger to assess the relevance of aging in OxS and MetS.

Methods: A total of 72 patients, 32 who fulfilled the Adult Treatment Panel III criteria for the MetS and 40 individuals without MetS, 20 age-matched to the MetS patients (Control I) and 20 younger subjects (Control II) were studied. We measured several anthropometric and serum parameters and two kinds of molecules related to OxS: modified molecules by reactive oxygen species (ROS) such as oxidized LDL (oxLDLc), and consumed or inducted molecules (enzymes or antioxidants such as Glutathione reductase GR,) associated with ROS metabolism. The statistical analysis was performed using SPSS v18.0.

Results: Only significant differences were observed in the values of GR between the MetS patients and Control I (50.31 ± 8.15 U/L vs 59.50 ± 9.98 U/L). We found significantly higher levels in the MetS patients compared to Control II of oxLDLc (96.77 ± 23.05 U/L vs 60.17 ± 16.28 U/L), F_2-isoprostanes (3.17 ± 1.78 µg/g creatinine vs 2.04 ± 0.80 µg/g creatinine) and protein cabonils (PC) (0.56 ± 0.26 nmol/mg vs 0.29 ± 0.13 nmol/mg).

Conclusions: Results have shown that MetS patients don't present a superior OxS in comparison to age-related healthy individuals. Finally, aging is more relevant to OxS than MetS *per se*.

Keywords: Metabolic syndrome; Oxidative stress biomarkers; Aging; Oxidized low density lipoprotein; Reactive oxygen species; Antioxidant enzymes

Introduction

During the last years, metabolic syndrome (MetS) has consistently increased worldwide. It is becoming a public health concern and a clinical condition highly related to increasing obesity incidence, sedentary lifestyle, and excessive caloric intake. The National Cholesterol Education Program's Adult Treatment Panel III report (ATP III) identified the MetS as a multiplex risk factor for cardiovascular disease (CVD). The componets of MetS are: impaired glucose tolerance, hypertriglyceridemia, low high-density lipoprotein (HDL) levels, raised blood pressure, and obesity (particularly visceral adiposity) [1]. A lifestyle summarized as a lack of physical activity and moderate-to-high intake of calories seems to be one of the most important causes of rapidly increasing prevalence of the MetS [2].

Oxidative stress is defined as an imbalance between oxidants (ROS) and the antioxidant defense in the organism in favor of oxidants. These oxidants can interact with proteins, phospholipidis or nucleic acids. During oxidation, diferent compounds are formed so may serve as biomarkers of oxidative stress (OxS) process in humans [3]. Increased OxS has been suggested as an early event in the development of the MetS and might contribute to disease progression [4,5]. Therefore, OxS occurs predominatly in people with MetS than among those without it, although not all authors have found this [6,7].

The association between the MetS and a high prevalence of ox-LDL was reported the first time for Paul Holvoet [8,9]. They supported the predictive value of the MetS for coronary heart disease (CHD) and suggested that baseline levels of oxLDL add prognostic information concerning future risk for myocardial infarction (MI) [10]. These findings, along with previous research into the association of LDL oxidation with atherosclerosis and CHD, provide evidence that LDL oxidation is a common basis for the MetS and CHD or, more particularly, for inducing atherothrombotic coronary disease [11,12]. Tsimikas et al. [13] also demonstrated the temporal increases of circulating oxLDL in association with acute coronary syndromes. In aggregate, these data supported the hypothesis that an increase in oxLDL reflects plaque instability although the oxidation of LDL takes place in the arterial wall and not in the circulation [14].

Aging is a biological state related with progressive decline of organ functions and the development of age-related diseases. The causes of aging remain unknown, probably being related to a multifactorial process. To date, the free radical and mitochondrial theories seem to be the two most noticeable theories on aging [15]. They related OxS and mitochondria, so damaged mitochondria can produce an increso of ROS, leading to progressive increase of the potential damage in the organism. Aging is a gradual and adaptive process characterized by a diminished homeostatic response resulting from accumulated physiologic, biochemical; psychological and social wear on an organism

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[16,17]. Even being considered as normal physiological process, it can be boost in presence of high levels of OxS or by chronic inflammatory processes (CIP) [18].

Owing to the increase of OxS derived by aging, the aim of this study was to evaluate certain OxS biomarkers in patients with MetS compared to healthy people of similar age and younger, in order to determine whether the OxS is modified in MetS patients owing to its relationship with aging.

Materials and Methods

Study population

The study included a total of 72 patients, 32 who fulfilled the Adult Treatment Panel III criteria for the MetS: obesity (waist circumference ≥ 102 cm in men or ≥ 88 cm in women), blood pressure of 130/85 mmHg or higher, fasting glucose of 110 mg/dL or more, TG of 150 mg/dL or more and HDLc below 40 mg/dL for men or 50 mg/dL for women. The MetS was defined as present when subjects had ≥ 3 of the risk factors.

We also studied 40 individuals without MetS, 20 age-related to the MetS patients (Control Group I) and 20 younger subjects (Control Group II). Both patients groups with MetS (n=32) and the Control Group I (n=20) were recruited at the cardiovascular risk unit in Primary Care of Murcia. The Control Group II was composed by younger healthy volunteers.

The inclusion criteria of all the patients were: no vitamin supplements consumption; alcohol consumption ≤ 30 g/day. No renal, hepathic or gastrointestinal diseases, cancer or allergies; no abnormal dietary habits; nonsmokers.

The study was carried out in accordance with the Helsinki Declaration and the Ethical Committee of the Universitary Hospital Virgen de la Arrixaca, Murcia, and Spain. Involvement was voluntary and all participants gave their informed consent to join the study.

Anthropometric measurements

After recording the clinical history and conducting the physical examination, we obtained the following anthropometric parameters measurements: weight, height, body mass index (BMI). Weight was measured while the subject was wearing underwear and was in a fasted state (after evacuation). A scale calibrated before each measurement, was used. Height was obtained with a cursor stadiometer graduated in millimeters. The subject was barefoot with the back and hands in contact with stadiometer in the Frankfurt horizontal plane. BMI was calculated by dividing weight (Kg) by height squared (m^2). Waist circumference (cm) was measured to the nearest 0.5 cm with a tape measure at the umbilical scar level.

Blood sampling

Blood samples were obtained from the median cubital vein and placed in EDTA-containing vials. Blood was centrifuged to obtain serum at 3.000 × g during 10 minutes at room temperature within 1 hour of collection and stored at 80ºC until assays were performed.

Serum lipids

The concentrations of glucose, cholesterol total, LDLc, HDLc and TG were assayed using automated systems (Cobas 711, Roche Diagnostics).

Homocysteine

Homocysteine levels were measured by quantitative determination by using an in t ensifying immunonephelometric particle test in a BN ProSpec® an a lyser (according to the protocol supplied in the kit for Siemen s N Latex HCY OPAX 03). The reference interval for homocysteine concentration with the use of this method is from 4.9-14 µm/L.

Antioxidant enzymes

The determination of SOD and GPx was analyzed in total blood by a commercial kit (Randox Laboratories Ltd, UK). The concentration of GR was determined in serum by a commercial kit (Randox Laboratories Ltd, UK). These assays were carried out on a Hitachi 912 analyser (Roche Diagnostics Systems®). Values for SOD and GPx were normalized per gram of hemoglobin (Hb).

Oxidative stress biomarkers

• oxLDL (U/L): A competitive enzyme-linked immune-absorbent assay (ELISA; Mercodia, Uppsala, Sweden; with an intra-assay and interassay variation's coefficient of 4.8 and 4.5 respectively, for 82 U/L) was used to determine oxLDLc concentration in serum.

• F_2-isoprostanes (µg/g creatinine): (The urinary levels of 15-F_2-isoprostane were determined using a competitive enzyme-linked immunosorbent assay (Oxford Biomedical Research, Inc. Oxford, Michigan, USA). The results were normalized per milligram of creatinine measured in urine.

• 8-OHdG (ng/mL): The 8-hydroxiguanosine was measured with an ELISA kit (Japan Institute for the Control of Aging, Fukuroi, Shizuoka, Japan).

• PC (nmol/mg): The carbonylated proteins were measured by an ELISA kit (Biocell Corporation Ltd., New Zealand).

Statistical analysis

We performed a descriptive study in which we calculated the mean, standard deviation, minimum and maximum values for the quantitative measurements performed. The completion of this analyze was made with the entire sample and differentiated by study groups. We included the calculation of confidence intervals of 95%.

For the comparison of means with a dichotomous variable, we used the statistic test t-Student.

In cases where the qualitative variable had more than 2 categories, we used analysis of variance of one way (ANOVA) performing a posteriori the Tukey test with the correspondent corrections. All results were considered significant at a level of $p<0.05$. The analyses were performed using SPSS v18.0.

Results

Table 1 shows the anthropometric parameters and lipid profile of Control Group I compared to Control Group II; MetS patients compared to Control Group I and MetS patients compared to Control Group II (age, weight, BMI, glucose, total cholesterol, TG, LDLc, homocisteíne, HDLc, Apo A-I, Apo B, cholesterol/HDLc and TG/HDLc). The results are expressed as mean ± standard deviation.

According to lipid profile results, Control Group I presents levels (mean values) significantly higher ($p<0.05$) than those in Control Group II of total cholesterol (219.90 ± 40.46 mg/dL *vs* 172.25 ± 30.92 mg/dL) and LDLc (133.40 ± 29.99 mg/dL *vs* 92.60 ± 27.89 mg/dL).

The MetS patients compared to Control Group I presented significantly higher levels ($p<0.05$) of glucose (131.44 ± 26.05 mg/dL

Variable	Controls I: Adult Mean ± SD (n= 20)	Controls II: Young Mean ± SD (n= 20)	*p*-value (1)	MetS Patients Mean ± SD (n=32)	Controls I: Adult Mean ± SD (n= 20)	*p*-value (2)	MetS Patients Mean ± SD (n=32)	Controls II: Young Mean ± SD (n= 20)	*p*-value (3)
Age (years)	56.35 ± 4.58	24.70 ± 2.34	0.000*	58.03 ± 4.48	56.35 ± 4.58	0.261	58.03 ± 4.48	24.70 ± 2.34	0.000*
Weight (Kg)	73.36 ± 12.09	-	-	84.44 ± 16.08	73.36 ± 12.09	0.007*	84.44 ± 16.08	-	-
BMI (Kg/m^2)	27.43 ± 5.12	-	-	32.02 ± 4.98	27.43 ± 5.12	0.002*	32.02 ± 4.98	-	-
Glucose (mg/dL)	95.55 ± 13.45	89.95 ± 6.36	0.258	131.44 ± 26.05	95.55 ± 13.45	0.000*	131.44 ± 26.05	89.95 ± 6.36	0.000*
Total cholesterol (mg/dL)	219.90 ± 40.46	172.25 ± 30.92	0.001*	223.13 ± 41.72	219.90 ± 40.46	0.954	223.13 ± 41.72	172.25 ± 30.92	0.000*
TG (mg/dL)	108.70 ± 44.31	88.0 ± 51.79	0.450	155.69 ± 60.32	108.70 ± 44.31	0.009*	155.69 ± 60.32	88.0 ± 51.79	0.000*
LDLc (mg/dL)	133.40 ± 29.99	92.60 ± 27.89	0.000*	135.94 ± 32.72	133.40 ± 29.99	0.955	135.94 ± 32.72	92.60 ± 27.89	0.000*
Homocysteine (µmol/L)	11.575 ± 2.9088	11.511 ± 7.8024	0.999	11.672 ± 2.5840	11.575 ± 2.9088	0.997	11.672 ± 2.5840	11.511 ± 7.8024	0.992
HDLc (mg/dL)	62.55 ± 17.88	62.10 ± 13.75	0.996	53.72 ± 17.67	62.55 ± 17.88	0.161	53.72 ± 17.67	62.10 ± 13.75	0.192
Apo A-I (mg/dL)	175.0 ± 30.22	-	-	157.53 ± 31.22	175.0 ± 30.22	0.052	157.53 ± 31.22	-	-
Apo B (mg/dL)	99.10 ± 20.10	-	-	110.09 ± 18.31	99.10 ± 20.10	0.048*	110.09 ± 18.31	-	-
Cholesterol/HDLc	3.66 ± 0.80	2.91 ± 0.86	0.153	4.53 ± 1.66	3.66 ± 0.80	0.052	4.53 ± 1.66	2.91 ± 0.86	0.000*
TG/HDLc	19.2 ± 0.99	1.62 ± 1.40	0.787	3.31 ± 1.70	1.92 ± 0.99	0.003*	3.31 ± 1.70	1.62 ± 1.40	0.000*

SD: standard deviation, BMI: Body mass index, TG: Triglycerides, LDL-c: dense-low density lipoprotein, HDL-c: high-density lipoprotein. p-value (1): significance between Control I and Control II, p-value (2): significance between Control I and MetS patients, p-value (3): significance between Control II and MetS patients. Notes: Data are mean ± SD. * Statistically significant differences.

Table 1: Anthropometric parameters and Lipid profile by MetS status and age (n = 72).

Variable	Controls I: Adult Mean ± SD (n= 20)	Controls II: Young Mean ± SD (n= 20)	*p*-value (1)	MetS Patients Mean ± SD (n=32)	Controls I: Adult Mean ± SD (n= 20)	*p*-value (2)	MetS Patients Mean ± SD (n=32)	Controls II: Young Mean ± SD (n= 20)	*p*-value (3)
SOD (U/g Hb)	947.85 ± 272.04	904.55 ± 247.14	0.885	875.53 ± 323.03	947.85 ± 272.04	0.658	875.53 ± 323.03	904.55 ± 247.14	0.934
GPx (U/g Hb)	25.58 ± 15.91	29.12 ± 9.71	0.684	25.76 ± 13.14	25.58 ± 15.91	0.999	25.76 ± 13.14	29.12 ± 9.71	0.657
GR (U/L)	59.50 ± 9.98	51.19 ± 12.35	0.027*	50.31 ± 8.15	59.50 ± 9.98	0.005*	50.31 ± 8.15	51.19 ± 12.35	0.949
oxLDL (U/L)	86.25 ± 17.36	60.17 ± 16.28	0.000*	96.77 ± 23.05	86.25 ± 17.36	0.159	96.77 ± 23.05	60.17 ± 16.28	0.000*
8-OHdG (ng/mL)	18.76 ± 5.41	22.90 ± 7.55	0.310	21.41 ± 10.82	18.76 ± 5.41	0.552	21.41 ± 10.82	22.90 ± 7.55	0.823
F_2 Isoprostanes (µg/g creatinine)	2.42 ± 1.14	2.04 ± 0.80	0.672	3.17 ± 1.78	2.42 ± 1.14	0.156	3.17 ± 1.78	2.04 ± 0.80	0.017*
PC (nmol/mg)	0.63 ± 0.19	0.29 ± 0.13	0.000*	0.56 ± 0.26	0.63 ± 0.19	0.425	0.56 ± 0.26	0.29 ± 0.13	0.000*

SOD: superoxide dismutase, GPx: glutathione peroxidase, GR: glutathione reductase, oxLDL: oxidized LDL; 8-0HdG: 8-hydroxy-2'-deoxyguanosine; PC: carbonyl protein. p-value (1): significance between Control I and Control II, p-value (2): significance between Control I and MetS patients, p-value (3): significance between Control II and MetS patients. Notes: Data are mean ± SD. * Statistically significant differences.

Table 2: Antioxidant status: enzymes and oxidative stress biomarkers by MetS status and age (N = 72).

vs 95.55 ± 13.45 mg/dL), TG (155.69 ± 60.32 mg/dL *vs* 108.70 ± 44.31 mg/dL), Apo B (110.09 ± 18.31 mg/dL *vs* 99.10 ± 20.10 mg/dL) and TG/HDLc (3.31 ± 1.70 *vs* 1.92 ± 0.99).

Moreover, the levels of glucose (131.44 ± 26.05 mg/dL *vs* 89.95 ± 6.36 mg/dL), total cholesterol (223.13 ± 41.72 mg/dL *vs* 172.25 ± 30.92 mg/dL), TG (155.69 ± 60.32 mg/dL *vs* 88.0 ± 51.79 mg/dL), LDLc (135.94 ± 32.72 mg/dL *vs* 92.60 ± 27.89 mg/dL), cholesterol/HDLc (4.53 ± 1.66 *vs* 2.91 ± 0.86) and TG/HDLc (3.31 ± 1.70 *vs* 1.62 ± 1.40) were significantly higher ($p<0.05$) in the MetS patients compared to Control Group II.

Table 2 presents the antioxidant status marked by: enzymes (SOD, GPx, GR) and certain biomarkers of oxidative damage as oxLDLc (endothelial damage), F_2-isoprostanes (lipid peroxidation) 8-OHdG (DNA damage), and PC (protein damage). We established the normal reference values for oxidative damage biomarkers in a previous article, as follows: SOD 931.97 ± 271.09 U/g Hb; GPx 27.58±6.89 U/g Hb; GR 46.56 ± 11.68 U/L; oxLDLc 63.23 ± 16.23 U/L; 8-OHdG 23.27 ± 10.58 ng/mL; F_2-isoprostanes 2.26 ± 0.9 µg/g creatinine; and PC 0.34 ± 0.15 nmol/mg.

Regarding the antioxidant status, we have observed statistically significant higher ($p<0.05$) levels in the Control Group I compared to Control Group II of GR (59.50 ± 9.98 U/L *vs* 51.19 ± 12.35 U/L), oxLDLc (86.25 ± 17.36 U/L *vs* 60.17 ± 16.28 U/L) and PC (0.63 ± 0.19 nmol/mg *vs* 0.29 ± 0.13 nmol/mg). In addition, only significant lower differences were observed in the values of GR between the MetS patients and Control Group I (50.31 ± 8.15 U/L *vs* 59.50 ± 9.98 U/L).

We found significantly higher levels in the MetS patients compared to Control Group II of oxLDL (96.77 ± 23.05 U/L *vs* 60.17 ± 16.28 U/L), F_2-isoprostanes (3.17 ± 1.78 µg/g creatinine *vs* 2.04 ± 0.80 µg/g creatinine) and PC (0.56 ± 0.26 nmol/mg *vs* 0.29 ± 0.13 nmol/mg) (Table 2).

Discussion

It was found significantly higher levels of glucose, TG and Apo B in the subjects with MetS compared with Control Group I according with our observational study recently published [19]. Several authors have also refered the elevation of TG values and glucose levels in MetS with respect to healthy population age-matched [20,21]. HDLc, LDLc and plasma cholesterol levels were not significantly higher in MetS patients with respect to Control Group I, previously reported fact [22]. This could be related to the inter-individual variability and also related to the age of the control Group I, so also could explain the lack of differences between the OxS biomarkers.

The Control Group I presented significantly higher ($p<0.05$) mean values than Control Group II of total cholesterol and LDLc, which could be related to the age difference between these groups (Table 1). Moreover, the levels of glucose, total cholesterol, TG and LDLc were significantly higher in the MetS patients compared to Control Group II.

Regarding the antioxidant status and its comparison between the two Control Groups, it was observed statistically significant higher ($p<0.05$) levels in the Control Group I compared to Control Group II of GR, oxLDLc and PC. These results suggest a superior OxS (endothelial and protein damage in the older subjects) due to aging, and a possible endogenous adaptation to an increase on the oxidative status of the organism (marked as the increase on GR). In addition, only significant differences were observed in the values of GR between Control Group I and the MetS patients, which may be due to a superior antioxidant capacity of the healthy individuals against those with MetS. However, Vávrová et al. [23] found higher activities of GR ($p<0.001$) for those subjects with MetS but altogether they found increased oxidative stress in MetS and a decreased antioxidative defense correlated with some laboratory (triglycerides, high-density lipoprotein cholesterol (HDL-C)) and clinical (waist circumference, blood pressure) components of MetS.

Significantly higher levels in MetS patients were also found compared to Control Group II of oxLDLc, F_2-isoprostanes and PC. These results indicate that the MetS patients have a superior endothelial, lipidic and protein damage than the younger controls. Furthermore, considering that MetS patients presented higher levels of oxLDLc compared to Control Group I and thath it had also shown significantly higher levels of oxLDLc than the Control Group II, it can be suggested that these results are probably due to aging. There were neither significant differences in the other antioxidant biomarkers nor the other enzymes between the MetS patients and the Control Groups.

Aging is a multifactorial complex process and its molecular mechanism remains unclear. It is now well established that biological aging correlates with the accumulation of oxidized biomolecules in most tissues [24]. In the present study of age-related increases in concentrations of oxidized biomolecules, disparities have been observed between intracellular and extracellular proteins. OxS induced peroxidation of membrane lipids is powerfull dangerous so it leads to a disfunction on the biological capacity of the cell membrane (such as the degree of fluidity). Moreover, it could lead to the inactivation of membrane-bound receptors or enzymes, which in turn may impair normal cellular function and increase tissue permeability. Moreover, lipid peroxidation may contribute to and strengthen cellular damage resulting from generation of oxidized products, some of which are chemically reactive and covalently modify critical macromolecules.

MetS is one of the major public health concerns as its prevalence increases worldwide with a subsequent predisposition to type II diabetes and CV disease [21]. Previous evidence supports the important role that OxS plays in MetS-related manifestations. The evidence for increased OxS is still a matter of debate. Fujita et al. [22] reported that systemic OxS increased in subjects with MetS, being closely related to the increase of visceral fat.

Moreover, Galle et al. [25] found that OxS promotes the formation of oxLDLc, which is involved in the initiation and progression of atherosclerosis [26]. Additionally, OxS has been suggested to be involved in the etiology of a host of chronic diseases and aging in general [23]. But there is controversy on the occurrence of OxS in patients with MetS. Some studies showed higher levels of markers of oxidative damage (circulating oxidized LDL and plasma F_2-isoprostanes) between MetS patients and healthy individuals [27]. Meanwhile, others authors did not found found significant changes on the levels of these biomarkers [28,20,7]. In the present study OxS biomarkers and endogenous antioxidant enzymes (excepting GR) were found not to shown significant changes, comparing MetS patients and age-matched healthy individuals (Control Group I); according to Sjogren [28] Seet [20] and Shrestha [7]. That fact could be due to the similar plasmatic cholesterol level of MetS and Control I (223.13 ± 41.72 and 219.90 ± 40.46 mg/dL), col-LDL (135.94 ± 32.77 and 133.40 ± 29.99mg/dL) and BMI (32.02 ± 4.98 and 27.43 ± 5.12). Colas et al. [27] suggested an association between an excess of visceral fat and biochemical parameters associated with OxS in LDL. Obesity is quite associated with MetS, and may represent a major factor in the OxS evidenced in LDL from obese MetS patients. Sigurdardottir [21] established that circulating ox-LDL is associated with risk factors of MetS, but oxidation of LDL occurs in the arterial wall and not in the circulation. Comprehensive understanding of the molecular mechanism, underlying inflammation and OxS with implications for metabolic stress must be achieved to attenuate the impacts of obesity-induced insulin resistance and ensuing MetS.

Taking together, the present results do not show an increase on the OxS owing to the development of MetS disease. In fact, MetS patients compared to healthy younger subjects shown a superior endothelial, lipidic and protein oxidative damage (marked as oxLDL, 8-OHdG F_2-isoprostanes and PC).

Conclusion

The results of the study have shown that MetS patients don't present a superior OxS in comparison to age-related healthy individuals. Therefore, differences between MetS patients and Group I (same age) are quite minor that differences between MetS and Group II (younger). Consequently, aging is more relevant to OxS than the MetS *per se*. However; more research is needed to understand OxS induced damage and its relationship with the development of MetS and aging.

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