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Increased oxidative stress according to number of risk factors in metabolic syndrome patients

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Introduction

- The prevalence of the MetS is increasing rapidly throughout the world, in parallel with the increasing prevalence of diabetes and obesity; thus, it is now considered as a major public health problem

King H, Aubert RE, Herman WH. Diabetes Care 1998;21:1414-31.

- Existing evidence suggests that the incidence of MetS is rising in developed countries and in developing countries such as Brazil

Grundy SM. Arterioscler Thromb Vasc Biol 2008;28:629–636.

- Metabolic syndrome (MetS):
  - Insulin resistance, arterial hypertension, visceral adiposity and dyslipidemia;

Reaven GM. Diabetes, 1988;37:1595–607.

NCEP ATP III: Clinical Identification of the Metabolic Syndrome (≥ 3 of 5 criteria)

D-R-O-P	Risk Factor	Defining Level
D = ***Dyslipidemia***	Triglycerides	≥ 150 mg/dL
	HDL cholesterol	Men: < 40 mg/dL Women: < 50 mg/dL
R = ***Insulin resistance***	Fasting glucose	≥ 100 mg/dL
O = ***Obesity***	Abdominal Obesity (Waist Circumference)	Men: > 102 cm (> 40") Women: > 88 cm (> 35")
P = ***Blood pressure***	Blood pressure	≥ 130/85 mm Hg

Medscape

NCEP ATP III Circulation 2005;112(17):2735-2752

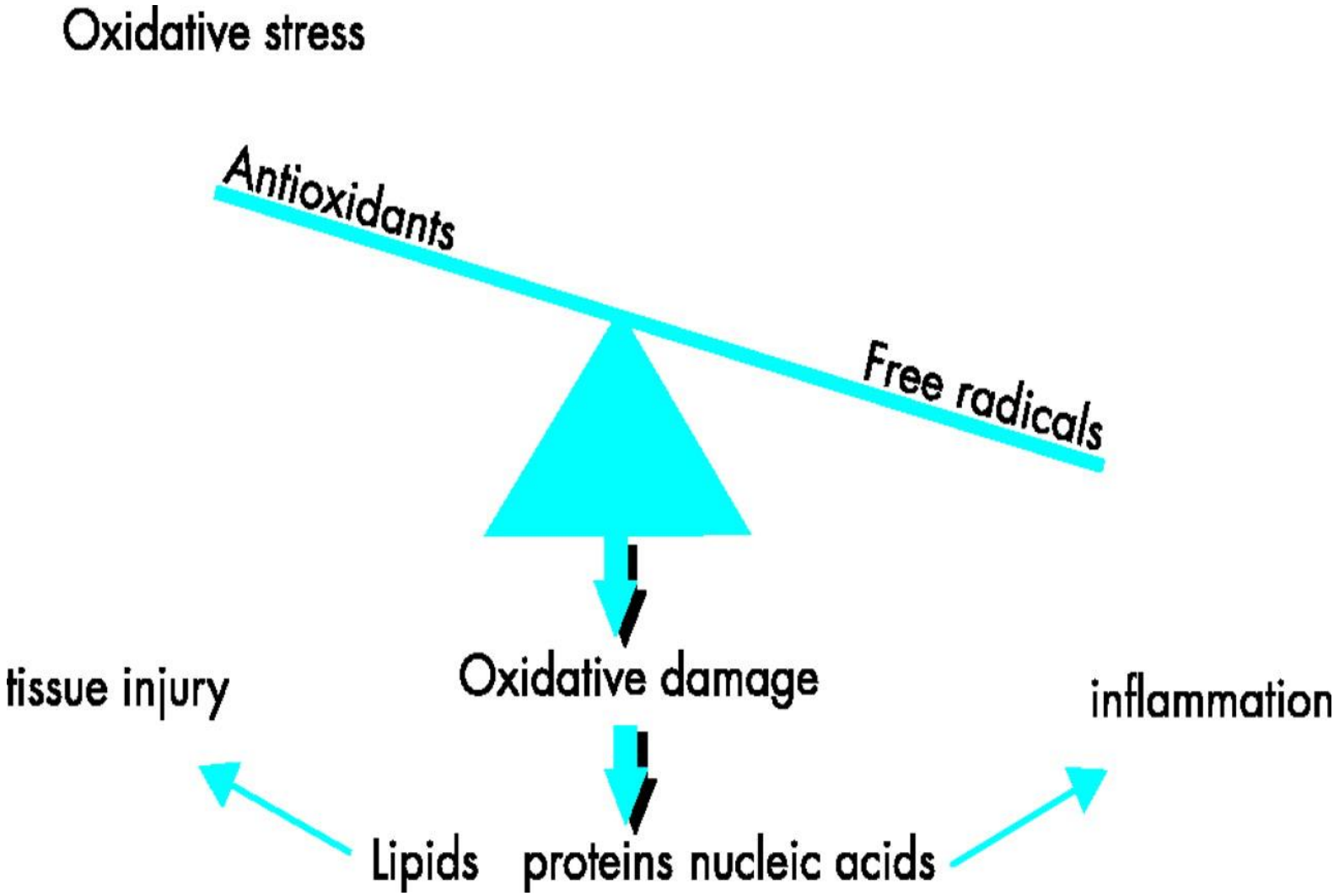
Introduction

- The harmful effects of free radicals, mainly reactive oxygen species (ROS) and/or reactive nitrogen species, have been implicated in the physiopathology of obesity, hypertension, endothelial dysfunction, and MetS

Ohmori K, *et al*. *Ann Epidemiol* 2005;15:80–84.
Urakawa H, *et al*. *J Clin Endocrinol Metab* 2003;88:4673–4676.
Abdilla N, *et al*. *J Hum Hypertens* 2007;21:68–75.

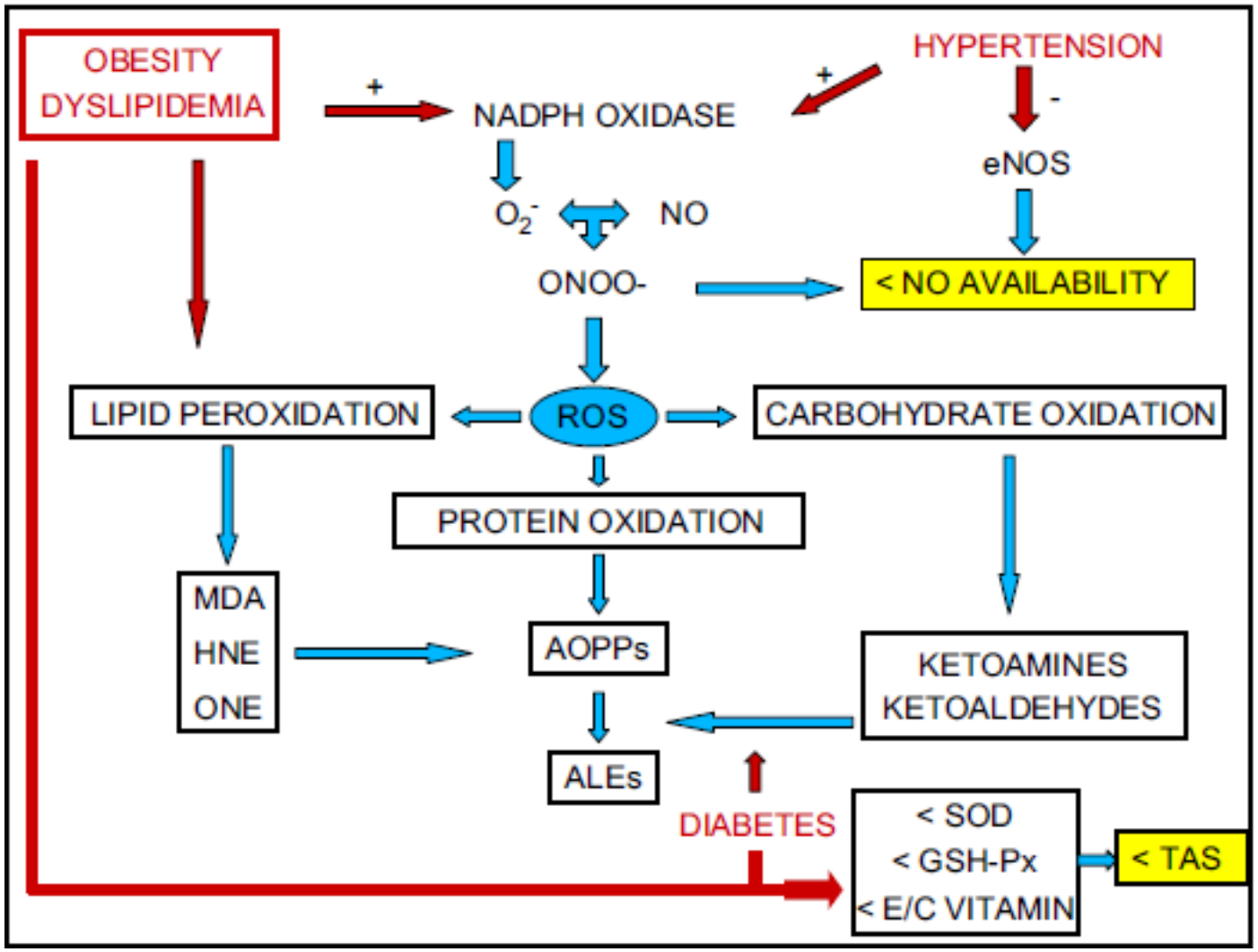
- Some reports have suggesting that oxidative stress may be the underlying mechanism of dysfunctional metabolism in obese subjects

Ceriello A, Motz E. Arterioscler Thromb Vasc Biol 2004;24:816–823.
Lee, K-U. Diabetes Res Clin Pract 2001;54 (Suppl 2):29–33.



Occup Environ Med 2003;**60:**612-616

Introduction



Hopps E et al. Nutrition, Metabolism & Cardiovascular Diseases (2010) 20, 72-77

Introduction

- The imbalance between pro-oxidant and antioxidant mechanisms has been considered one of the most important pathophysiological mechanisms of chronic diseases;

- There are consistent evidences in the literature to support the hypothesis that oxidative stress could be considered an early event in MetS pathophysiology rather than merely a consequence

Yubero-Serrano EM, et al. Exp Mol Med 2013;45:e28-34.

Furukawa, et al. *J. Clin. Investig.* ***2004, 114, 1752–1761.***

Introduction

- Advanced oxidation protein products (AOPPs) are an oxidatively modified form of proteins (mainly albumin) created as the result of excessive generation of ROS and reactive chlorine species (mainly chloramine produced by myeloperoxidase in activated neutrophils).

Piwowar A. Pol Merkur Lekarski 2010;28:166–169

  - AOPPs have been reported as the most appropriate parameter for determination of oxidative stress (OS)

Venturini D. et al Nutrition Research, 2015;35:759-765

- AOPPs have been studied in several metabolic conditions, such as
  - Overweight subjects (Krzystek-Korpacka et al 2008, Venturini et al, 2012),
  - Patients with obesity (Atabek et al, 2006, Koçak et al, 2007, Krzystek-Korpacka et al 2008),
  - Type 1 diabetes mellitus (Kalousová et al., 2002, Martin-Gallán et al 2003),
  - Type 2 diabetes mellitus (Kalousová et al., 2002, Catakay 2005, Piwowar et al 2007),
  - Metabolic syndrome (Korkmaz et al 2013, Zurawska-Plaksej et al, 2014, Venturini et al 2015).

- Alterations in the total antioxidant capacity also appear to play a significant role in the MetS

Venturini D, Simão AN, Scripes NA, et al. Obesity (Silver Spring) 2012;20:2361–6.
Bahadoran Z, Golzarand M, Mirmiran P, et al. Nutr Metab (Lond) 2012;9:70.
Faienza MF, Francavilla R, Goffredo R, et al. Horm Res Paediatr 2012:158–64.

Introduction

- The use of the total antioxidant capacity (TRAP) has been proposed to explore plasma antioxidant capacity due to known and unknown antioxidants present in the sample as well as their cooperation.

Skalicky J,. Et al. Clin Chem Lab Med 2008;46:499–505.

Introduction

- The measurement of TRAP in conditions associated with hyperuricemia, as in subjects with MetS, may be inaccurate because uric acid concentration is responsible for 60% of total plasma antioxidant capacity.
- Some reports have verified an unexpected increase in TRAP in MetS subjects.
- Thus, a correction of TRAP based on uric acid concentration is needed.

Skalicky J, *et al*. *Clin Chem Lab Med* 2008;46:499–505.
Simão AN, et al. Nutrition 2008;24:675–681.

Aim

- The objective of the present study was to correlated two biomarkers of OS with metabolic features in MetS patients

Materials and Methods

- This study evaluated 48 women, aged 32-58 years recruited from University Hospital of Londrina, Paraná, Brazil.
- The groups were divided according to MetS components in 3 groups
  - G1 (with 3 components)
  - G2 (with 4 components)
  - G3 (with 5 components)
- Adult Treatment Panel III (ATP III) criteria.

NCEP ATP III Circulation 2005;112(17):2735-2752

- After fasting for 12 h, the subjects underwent the following laboratory blood analysis: glucose, total cholesterol (TC), high density lipoprotein cholesterol (HDLc), low density lipoprotein cholesterol (LDLc), triacylglycerol (TG), uric acid and C reactive protein (CRP) which were evaluated by a biochemical auto-analyzer (Dimension Dade AR, Dade Behring, Deerfield, IL, USA), using Dade Behring kits.

- AOPP, as markers of protein damage, and total antioxidant capacity (TRAP) as antioxidant were evaluated by the semiautomated method described by Witko-Sarsat et al and chemiluminescence, respectively.
- Pro-oxidant-antioxidant imbalance (PAI) was calculated divided AOPP/TRAP.

Statistical analysis

- Data are expressed as medians and inter quartile range (25%-75%). Wilcoxon test with post hoc Dunn was performed. The results were considered significant when $p < 0.05$. A statistical analysis program (Graph Pad Instat; Graph Pad Software, Inc, California, CA, USA) was used for evaluations.

Results

Table 1: Anthropometric, biochemical and oxidative stress parameters according the number of metabolic syndrome components

Parameters	G1 (n = 17)	G2 (n = 16)	G3 (n = 15)
Age (years)	50 (37-55)	53 (32-55)	51 (32-58)
BMI (Kg/m^2)	30,30 (22,67-38,77)	33,05 (26,62-43,43)	38,74 (27,82-52,10)a
WC (cm)	98 (75-112)	100 (91-128)	121 (93-140) a
SBP (mmHg)	130 (110-140)	120 (110-160)	136 (100-170)
DBP (mmHg)	80 (70-100)	80 (60-110)	80 (50-145)
Glucose (mg/dL)	101 (81-114)	109 (93-353)	143 (108-372)b,c
TC (mg/dL)	194 (152-289)	212 (155-298)	206 (122-244)
HDL-C (mg/dL)	44 (31-85)	39 (31-53)	41 (28-47)
LDL-C (mg/dL)	127 (83-197)	139 (82-228)	109 (47-171)
Triacylglycerol (mg/dL)	133 (39-426)	175 (89-253)	215 (131-587)a
Uric acid (mg/dL)	4,13 (3,39-5,68)	4,59 (3,10-6,90)	5,65 (3,15-8,24) a,e
hsCRP (mg/dL)	2,70 (1,10-6,90)	6,15 (2,10-18,80)	13,50 (2,23-23,00) b,f
AOPPs (umol/L)	73,01 (40,87-127,93)	77,77 (49,75-239,39)	241,65 (77,53-545,55) b,c
TRAP (uM of Trolox / UA mg/dl)	243,24 (187,46-283,35)	219,75 (146,43-263,12)	141,45 (103,93-245,64) b,c
PAI	0,30 (0,14-0,57)	0,37 (0,21-0,91)	2,13 (0,37-3,89) b,c

a: p<0.05 (G3 vs G1) **b**: p<0.0001 (G3 vs G1) **c**: p<0.0001 (G3 vs G2)
d: p<0.05 (G3 vs G2) **e**: p<0.05 (G2 vs G1) **f**: p<0.0001 (G3 vs G2)

Discussion

- In a recent study conducted by me and colleagues, protein oxidation was more related to MetS components than lipid peroxidation

  - In this study, AOPPs showed a positive correlation with WC ($r = 0.318$, $P < 0.01$), fasting glucose ($r = 0.250$, $P < 0.05$), HOMA-IR ($r = 0.043$, $P < 0.01$), TG ($r = 0.713$, $P < 0.0001$), hsCRP ($r = 0.275$, $P < 0.05$), and uric acid ($r = 0.356$, $P < 0.01$),whereas there was an inverse correlation with HDL-c ($r = -0.399$, $P < 0.001$).

Venturini D. et al. Nutrition Research, 2015; 759-765.

Discussion

Table 4 – Spearman correlation between oxidative stress markers and MetS components

	Hydroperoxides	FOX	AOPPs	TRAP	PAI
BMI	0.081	0.217	0.215	0.025	0.239
WC	0.155	0.217	0.318 *	–0.242 **	0.386 *
SBP	0.164	–0.024	0.061	0.022	0.083
DBP	0.017	–0.063	0.110	–0.062	0.089
Fasting glucose	0.331 *	0.022	0.250 **	–0.322 *	0.388 *
Fasting insulin	0.098	0.226	0.267	–0.356 *	0.344 **
HOMA-IR	0.1799	0.115	0.043 *	–0.463 ***	0.519 ***
HDL-C	–0.055	–0.001	–0.399 ***	0.246 **	–0.480 *
TG	–0.231	0.109	0.713 †	–0.153	0.687 †
CRP	–0.1634	0.110	0.275 **	–0.039	0.278 **
Uric acid	–0.060	0.015	0.356 *	–	0.557 †

* $P < .01$.
** $P < .05$.
*** $P < .001$.
† $P < .0001$.

Discussion

- Our findings are consistent with other investigations regarding protein oxidation in patients with metabolic syndrome.

  Hopps E, Caimi G. Clin Invest Med 2013;36:E1–E8

- Caimi et al. observed higher concentration of carbonyl groups in these patients

  Caimi G, Hopps E, Noto D et al. Diabetes Metab Syndr 2013;7:38–41

- Korkmaz et al. found increased AOPP levels and pro-oxidant/antioxidant balance (PAB) values.

  Korkmaz GG, Altınoglu E, Civelek S et al. Metabolism 2013;62:828–835

Discussion

- Fujita *et al*. (2006) demonstrated that oxidative stress values increased with the number of MetS components.

Fujita K, et al. *Circ J* 2006;70:1437–1442.

- More recently, some studies have also shown that AOPP levels increased progressively with the number of MetS components

Yubero-Serrano EM, et al. Exp Mol Med 2013;45:e28–34.
Zurawska-Plaksej E, et al. J Endocrinol Invest 2014. http://dx.doi.org/10.1007/s40618-014-0111-8 [Published on line June, 24th].

Discussion

- Piwowar et al evaluated the components of the oxidative/antioxidative status in 94 patients with type 2 diabetes and demonstrated that AOPPs enhanced progressively with increasing BMI.

Piwowar A, Kordecka MK, Warwas M. Diabetes Res Clin Pract 2007;77:188–92.

Discussion

- Corroborating to this study, in a short communication, we demonstrated that serum levels of AOPP were elevated with increasing BMI in obese women.

Venturini D. et al., Diabetes and Obesity International Journal , 2016

Evaluation of Oxidative Stress in Overweight Subjects With or Without Metabolic Syndrome

Danielle Venturini[1], Andréa N.C. Simão[1], Nicole A. Scripes[1], Larissa D. Bahls[1], Petrônio A.S. Melo[2], Francine M. Belinetti[2], Marcell A.B. Lozovoy[3] and Isaias Dichi[2]

Obesity (2012) **20**, 2361–2366. doi:10.1038/oby.2012.130

The objective of this study was to verify the influence of metabolic syndrome (MetS) on oxidative stress and antioxidant defense in overweight subjects.

Discussion

Table 2: Oxidative stress evaluation in control (C) and overweight subjects without (O) or with metabolic syndrome (OMS).

	C (n=30)	O (n=44)	OMS (n=39)	C x O	C x OMS	O x OMS
Hydroperoxides (cpm)	14195 (3239-29363)	14648 (14260-36956)	18386 (8688-65580)	NS	< 0.05	NS
AOPP (umol/L)	136,75 (70,41-240,5)	133,95 (68,42-243,8)	395,87 (97,2-737,86)	NS	< 0.001	< 0.001
FOX (mM)	1,38 (0,32-1,90)	1,14 (0,59-2,53)	1,85 (0,27-3,82)	NS	NS	< 0.001
TRAP (uM of Trolox)	683.5 (407.6-994.5)	643.9 (429.8-1054.0)	796.1 (509.5-1091.0)	NS	NS	NS

Kruskal-Wallis test with post hoc Dunn test. Data are median (min – max). NS, non significant; C, control subjects; O, overweight subjects without metabolic syndrome; OMS, overweight subjects with metabolic syndrome; AOPP: Advanced oxidation protein products; FOX, Ferrous Oxidation-Xylenol Orange Assay; TRAP: Total radical-trapping antioxidant parameter.

Discussion

Uric acid is involved in cardiovascular disease risk and is also responsible for ~60% of plasma TRAP; therefore, TRAP status may be overestimated in subjects with hyperuricemia.

Simão AN, et al. *Nutrition* 2008;24:675–681.

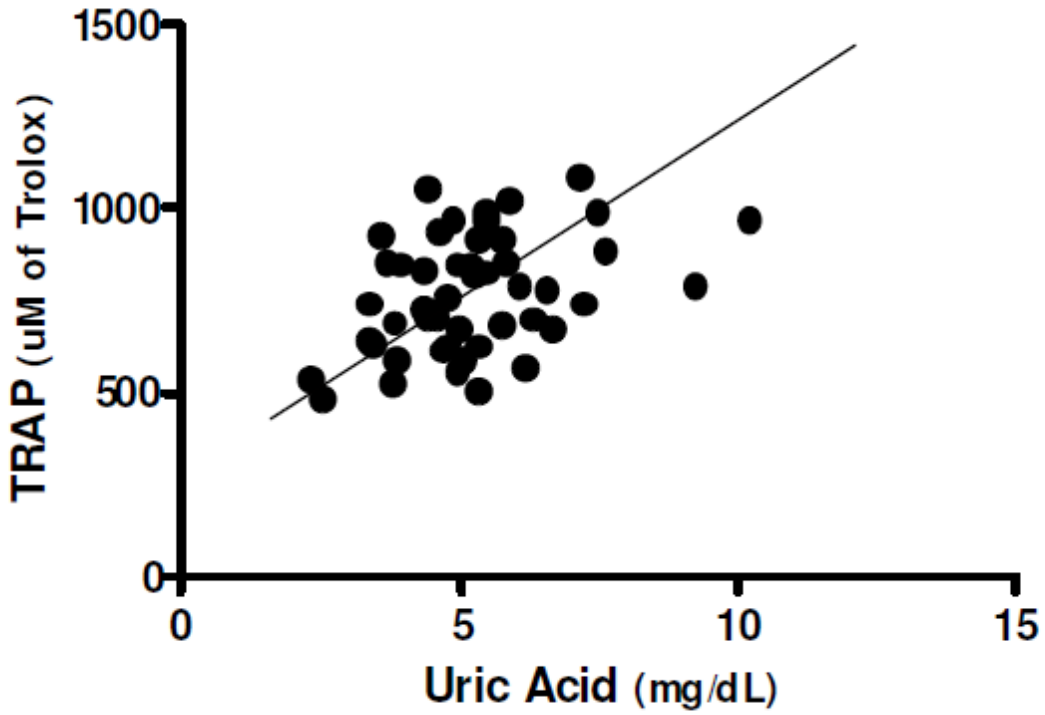


Figure 1: Spearman's correlation between total radical-trapping antioxidant parameter (TRAP) and uric acid concentrations in overweight subjects (O + OMS) (r=0.3400, p=0.0181). O, overweight subjects without metabolic syndrome; OMS, overweight subjects with metabolic syndrome.

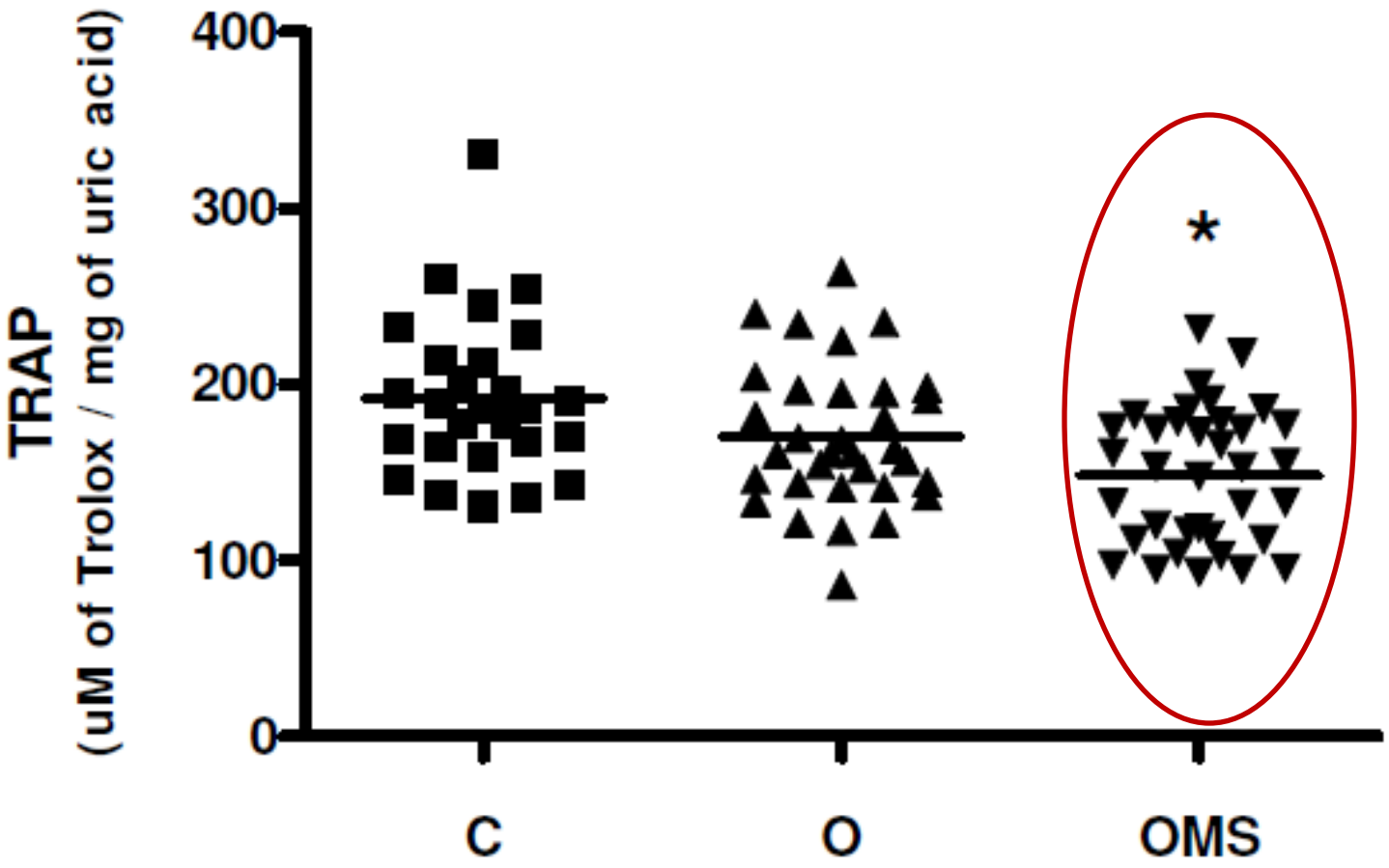


Figure 2: Total radical-trapping antioxidant parameter (TRAP) / uric acid rate in control (C) and overweight subjects without (O) or with metabolic syndrome (OMS). * C vs. OMS ($p < 0.001$).

Limitations

- The current study has some limitations to be considered.
  - First is the small number of participants;
  - Second, this cross sectional study is unable to determine causality between metabolic abnormalities and oxidative stress.

Conclusion

- This study showed that the metabolic disorders were determinant for the redox imbalance, characterized by increased plasma oxidation and reduced antioxidant capacity.

Thank you!