Oxidative homeostasis dysregulation may promote pathogenesis of cardio-metabolic complications in childhood obesity

Corica Domenico[1], Aversa Tommaso[1], Ruggeri Rosaria Maddalena[2], Cristani Mariateresa[3], Panasiti Ilenia[1], De Luca Filippo[1], Wasniewska Malgorzata[1]

[1] Department of Human Pathology of Adulthood and Childhood, Unit of Pediatrics, University of Messina- Italy
[2] Department of Clinical and Experimental medicine, Unit of Endocrinology, University of Messina- Italy
[3] Department of Chemical, Biological and Pharmaceutical Science, University of Messina – Italy

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Introduction

Advanced glycation end-products (AGEs) are heterogeneous groups of irreversible adducts resulting from non-enzymatic glycation and glyoxidation of proteins, lipids, and nucleic acid[1]. AGEs and its cell receptor RAGE have been involved in the pathophysiology of cardiovascular and metabolic diseases. Interaction of AGEs with RAGE results in an increased generation of oxygen radicals and increased expressions of pro-inflammatory cytokines. Circulating soluble AGE receptor (sRAGE) competes with RAGE for AGEs, to counterbalance the negative effects of their interaction[1]. AGE/sRAGE-ratio have been suggested to be expression of the oxidative state[1], as well as advanced oxidation protein products (AOPPs)[2].

Objectives

To investigate the changes in oxidative balance and to define factors influencing AGEs, sRAGE, AGEs/sRAGE-ratio and AOPPs levels in a cohort of obese children compared to controls.

Material and methods

Forty-one overweight and obese children and adolescents (group A; range 5–16 years) and thirty-six healthy, lean, age and sex-matched controls (group B) were recruited. **Inclusion criteria:** BMI SD > 1 corrected for age and sex, born as healthy full-term infant. **Exclusion criteria were:** genetic and endocrine causes of obesity, arterial hypertension, chronic diseases and therapies, smoking. Lipid and glucose profiles, liver, renal and thyroid function tests, uric acid, C-reactive protein (CRP), AGEs, sRAGE and AOPPs serum concentrations, were evaluated in both groups.

Results

HOMA-IR, triglycerides, total cholesterol/HDL-ratio, Atherogenic-index of plasma (AIP), CRP, uric acid were significantly ($p<0.005$) higher, whereas HDL was significantly lower in overweight/obese patients compared to controls. Significant differences of AGEs/sRAGE-ratio, AOPPs and sRAGE levels between groups are represented in Figure 1. Correlation between BMI SD and AGE/sRAGE-ratio, AOPPs, AGEs and sRAGE are reported in Figure 2. Furthermore, AGE/sRAGE-ratio and AOPPs positively correlate with total cholesterol/HDL-ratio (p= 0.000), AIP (p= 0.02 and p= 0.000, respectively), CRP (p= 0.000), and negatively correlate with HDL (p= 0.004 and p= 0.000, respectively). AOPPs positively correlate with HOMA (p= 0.002) and AGEs (p= 0.003), and negatively with sRAGE (p= 0.003).
BMI SD was a significant predictor of AGEs/sRAGE-ratio (B=0.06; p=0.000), AOPPs (B=0.202; p=0.000) and sRAGE (B= -67.1; p= 0.000). **CRP was a significant predictor of** AGEs/sRAGE-ratio (B=0.21; p = 0.000), AOPPs (B=0.55; p= 0.01) and AGEs (B= 34.1; p= 0.04). **Total cholesterol/HDL-ratio was a significant predictor of** AGEs/sRAGE-ratio (B= 0.06; p= 0.008), AOPPs (B=0.23; p= 0.000), AGEs (B=14.1; p=0.02), and sRAGE (B= -56.3; p= 0.01). HOMA was a significant predictor of AOPPs (B=0.12; p=0.03). **A significant influence of BMI SD on oxidative stress markers levels was confirmed by stepwise multivariate regression analysis.**

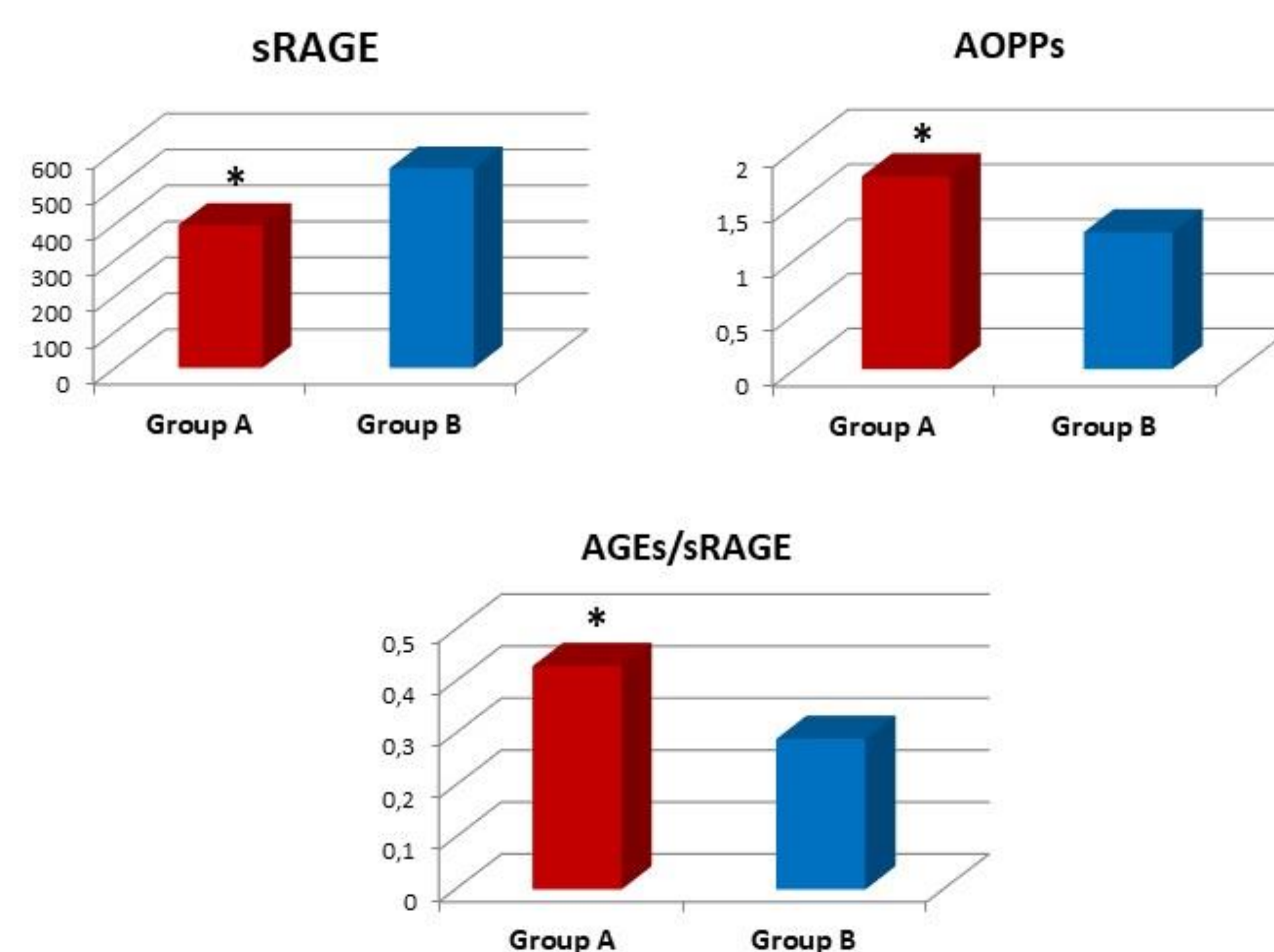Figure 1 – Significant differences of oxidative stress markers between group A and group B.

Figure 2 – Correlation between BMI SD and oxidative stress markers

Conclusions

Our findings demonstrate a relative shift in stressors from anti-stressors in overweight/obese children, suggesting the presence of oxidative homeostasis dysregulation and an enhanced susceptibility to oxidative/inflammatory tissues damage, that may contribute to the pathogenesis of long-term cardiovascular and metabolic complications. Moreover, we confirmed the role of AGEs/sRAGE-ratio as biomarkers for oxidative state.

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2- Liu SX, Hou FF, Guo ZJ, et al. Advanced oxidation protein products accelerate atherosclerosis through promoting oxidative stress and inflammation. Arterioscler Thromb Vasc Biol 2006;26:1156e62

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