Nutrition, Metabolism & Cardiovascular Diseases (2012) 22, 237–243

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/nmcd

Nutrition, Metabolism & Cardiovascular Diseases

Elevated advanced oxidation protein products (AOPPs) indicate metabolic risk in severely obese children

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Received 21 January 2010; received in revised form 25 April 2010; accepted 3 June 2010

KEYWORDS
Advanced oxidation protein products;
Childhood obesity;
Insulin resistance;
Metabolic risk factors;
Oxidative stress

Abstract *Background and aims:* The assessment of oxidative stress may aid in the identification of subsequent metabolic risk in obese children. The objective of this study was to determine whether the plasma level of advanced oxidation protein products, analyzed with a recently proposed modified assay that involves a delipidation step (mAOPPs), was related to metabolic risk factors (MRFs) in severely obese children.
Methods and results: The plasma levels of mAOPPs were determined by spectrophotometry in 54 severely obese and 44 healthy children. We also measured lipid peroxidation biomarkers (thiobarbituric acid-reactive substances, malondialdehyde, and 8-isoprotane $F_{2\alpha}$) and sulfhydryl groups, a marker of antioxidant defense. Protein oxidation and lipid peroxidation markers were higher and sulfhydryl levels were lower in obese children compared with controls. Taking metabolic risk into account, obese children were subdivided according to the cutoff point (53.2 μmol/L) obtained for their mAOPPs values from the ROC curve. Anthropometric measures and the existence of hypertension did not differ between groups. The presence of dyslipidemia and insulin resistance was significantly higher in the group with higher mAOPPs levels. The highest levels of mAOPPs were found in the children with ≥3 MRFs. The level of mAOPPs was positively correlated with triglycerides and negatively correlated with high-density lipoprotein cholesterol. There was no correlation of this marker of protein oxidation with biomarkers of lipid peroxidation.

Abbreviations: AOPPs, advanced oxidation protein products; mAOPPs, modified advanced oxidation protein products; BMI, body mass index; BP, blood pressure; FGIR, fasting glucose-to-insulin ratio; HDL-C, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment index; MRFs, metabolic risk factors; -SH groups, sulfhydryl groups; TG, triglycerides; WC, waist circumference.

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0939-4753/$ - see front matter
doi:10.1016/j.numecd.2010.06.002

Conclusion: The determination of mAOPPs in delipidated plasma is an easy way to evaluate protein oxidation. It may be useful in severely obese children for better cardiovascular risk assessment.

Introduction

Obese children have elevated oxidative stress levels that may contribute to the pathogenesis of long-term complications such as cardiovascular disorders and type 2 diabetes [1]. Thus, determination of oxidative stress markers, in addition to clinical and laboratory indices, has been proposed for evaluation of obese children [2]. The most frequently used approach is the measurement of lipid peroxidation. In addition to lipids, proteins are also recognized as important targets for oxidants. The oxidative structural and functional modification of proteins could be an important event leading to endothelial dysfunction [3]. Until recently, however, protein oxidation has not been extensively studied in clinical settings because of a lack of easily accessible methods for detection of protein damage. Advanced oxidation protein products (AOPPs) are a relatively novel oxidative stress marker. They have mainly been related with impaired carbohydrate metabolism in subjects with type 1 or 2 diabetes [4,5]. Atabeck et al. [6] found that this marker was increased in obese children and adolescents. A recent study showed that juvenile overweight/obesity and obesity-related disorders were associated with increased AOPPs levels [7]. Nevertheless, there is currently insufficient data linking protein oxidative stress determined by AOPPs levels to metabolic risk factors (MRFs) in children. Paradoxically, despite higher AOPPs, obese children display lower plasma advanced glycation products (involved in the pathogenesis of diabetic complications) in comparison with their lean counterparts [8]. In addition, current methods might be overestimating AOPPs values because of interferences caused by lipid levels (principally triglycerides) [9]. For these reasons, the aim of this study was to investigate the value of AOPPs, using a modified assay that includes a delipidation step (mAOPPs), as a marker of protein oxidation in obese children to assess their clinical utility to identify obese children who are at risk for complications. We also investigated the relationship of this marker with others biomarkers of lipid oxidation in childhood obesity.

Methods

Study population

A total of 98 children aged 7—14 years were enrolled in this study. Fifty-four of these children were referred to the outpatient clinic at Dr. Peset University Hospital (Valencia, Spain) for investigation and treatment of obesity. All these children were affected by severe essential obesity with a body mass index (BMI) higher than 2.5 standard deviations from the mean for their age and gender [10]. The other 44 children constituted the control group. The children were recruited by primary care physicians during routine clinical check-ups and gave their consent to participate in the study. All subjects were Caucasian and of Spanish descent. Exclusion criteria were the presence of concomitant diseases, genetic syndromes, endocrine disorders, and chronic allergies. No children had an infectious and/or inflammatory illness, which was confirmed by medical histories and physical examinations. Pubertal stage was assessed by inspection and palpation in each patient by the same pediatrician according to the criteria of Marshall and Tanner. All of the subjects were $\leq$ stage 3, and female subjects had not yet begun menstruation. Nutritional habits were similar in all children; there were no vegetarians, and no patients were taking supplemental vitamins. Informed written consent was obtained from all parents, and oral consent was obtained from all children. The Ethical Committee of the hospital approved the research.

Measurements

On the day of entry to the study, all children underwent a complete clinical history and examination. Weight and height measurements were taken with the child lightly dressed and barefoot, according to standardized methods. Waist circumference (WC) was obtained over the unclothed abdomen at the narrowest point between the rib cage and the superior border of the iliac crest. Hip circumference was measured over light clothing at the level of the widest diameter around the buttocks using non-elastic flexible tape, and measurements were recorded to the nearest 0.1 cm. We used the BMI z-score for age and gender as a fatness index. The fat mass percentage was obtained via bioelectrical impedance using the BC-418MA Tanita Segmental Body Composition Analyzer (Tanita Europe BV, Hoofddorp, The Netherlands) and converted to normalized parameters using comparison to the 50th standard percentile for age and gender for the fat mass percentage (relative fat mass) [11]. The distribution of fat mass was evaluated by relating the WC to the 50th percentile for age and gender [12] as well as the WC/hip circumference and WC/height indices.

Blood pressure (BP) was measured using an automated sphygmomanometer (Dinamp 200; GE medical Systems Information Technologies, Inc., Milwaukee, Wisconsin, USA). Elevated BP ($\geq$95th percentile for height) was determined using tables provided by the Task Force Report [13].

Laboratory procedures

After overnight fasting, blood samples were taken from the antecubital vein. Routine biochemical blood tests included serum glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol,