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Original article

Oxidative stress and metabolic syndrome: Effects of a natural antioxidants enriched diet on insulin resistance

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SUMMARY

Background & aims: Oxidative stress (OS) could play a role in metabolic syndrome-related manifestations contributing to insulin resistance (IR). The aim of the present study was to gain insight the relationships between OS, IR and other hormones involved in caloric balance, explaining the effects of a natural antioxidant-enriched diet in patients affected by metabolic syndrome.

Methods: We investigated the effects of dietary antioxidants on IR, studying 53 obese (20 males and 33 females, 18–66 years old, BMI 36.3 ± 5.5 kg/m^2), with IR evaluated by Homeostasis Model Assessment (HOMA)-index, comparing 4 treatments: hypocaloric diet alone (group A) or plus metformin 1000 mg/daily (group B), natural antioxidants-enriched hypocaloric diet alone (group C) or plus metformin (group D). A personalized program, with calculated antioxidant intake of 800–1000 mg/daily, from fruit and vegetables, was administered to group C and D. The glycemic and insulinemic response to oral glucose load, and concentrations of total-, LDL- and HDL-cholesterol, triglycerides, uric acid, C reactive protein, fT3, fT4, TSH, insulin-like growth factor 1 were evaluated before and after 3-months. Plasma Total antioxidant capacity was determined by H_2O_2-metmyoglobin system, which interacting with the chromogen ABTS generates a radical with latency time (LAG) proportional to antioxidant content.

Results: Despite a similar BMI decrease, we found a significant decrease of HOMA and insulin peak only in group B and D. Insulin response (AUC) showed the greatest decrease in group D (25.60 ± 8.96%) and was significantly lower in group D vs B. No differences were observed in glucose response, lipid metabolism and TAC (expressed as LAG values). TSH values were significantly suppressed in group D vs B.

Conclusions: These data suggest that dietary antioxidants ameliorate insulin-sensitivity in obese subjects with IR by enhancing the effect of insulin-sensitizing drugs albeit with molecular mechanisms which remain yet to be elucidated.

1. Introduction

Oxidative stress (OS) is defined as an imbalance between prooxidant and antioxidant factors, in favour of the first ones, causing oxidative damage to lipids, proteins and nucleic acids in different biological systems and therefore functional and structural impairment of different molecules. Main factors are reactive oxygen species (ROS), highly reactive short-lived derived of oxygen metabolism produced in all tissues [1].

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OS could play an important role in metabolic syndrome (MS)-related manifestations (atherosclerosis, hypertension, type 2 diabetes, contributing to insulin resistance (IR) [2]. Patients with MS have elevated oxidative damage, since decreased antioxidant protection, depressed vitamin C and α-tocopherol concentrations, decreased superoxide dismutase activity have been demonstrated, together with increased lipid peroxidation, malondialdehyde levels, protein carbonyls and xanthine oxidase activity [3,4]. γ- and α-tocopherol supplementation decreased plasma malondialdehyde and 4-hydroxynonenale (HNE), lipid peroxides and urinary nitrotyrosine [5]. Moreover, total body fat and waist circumference have been shown to be related to OS-mediated endothelial dysfunction and endothelial catalase levels [6].

However, the reciprocal influences between OS and IR are not clear. OS, together with chronic inflammation and lipid oversupply have been claimed to be involved in development and exacerbation of IR [7]. Experimental data suggest that OS is one of the factors contributing to diabetic complications [8].

Previous works of our group have shown a reduction in antioxidant defence in patients with severe obesity after bariatric surgery, especially the lipophilic antioxidant Coenzyme Q10 [9]. Very recently, it has been shown in severely obese patients with type 2 diabetes that bariatric surgery could result in better glucose control than medical therapy; surgery was also proposed considering side effects of metformin [10]. However, the rate of complications after surgery should induce to search for less invasive approaches.

To gain insight into the relationships between OS, IR and other hormones involved in caloric balance (GH-IGF-1 axis, thyroid hormones), we studied patients affected by MS, treating them with different pharmaco-dietary schedules, to investigate the effects of dietary antioxidants on IR.

2. Materials and methods

Fifty-three obese subjects, 20 males and 33 females, were enrolled in the study. Age (mean ± SD) was 44.2 ± 12.7 (range 18–66); BMI was 36.3 ± 5.5 kg/m^2 (range 25.8–45.5). All subjects presented Insulin Resistance, evaluated by homeostasis model of insulin resistance (HOMA-IR) = {[fasting insulin (U/ml)] * [fasting glucose (mmol/l)]}/22.5 [11]. Basal evaluation was performed when the patients were at their own normal diet. Exclusion criteria were liver and renal failure, drugs except anti-hypertensive treatment, drugs affecting lipid metabolism, pituitary disorders (including "empty sella" syndrome). Written informed consent was obtained, according to Helsinki declaration. The protocol study was approved by Institutional department councils of our respective affiliations.

3. Treatments

Four different three-months treatments were compared: hypocaloric diet alone (**group A**, n = 16) or plus metformin 1000 mg/daily (**group B**, n = 16), diet enriched with natural antioxidants alone (**group C**, n = 11) or plus metformin (**group D**, n = 10). Patients were randomly assigned to one of these treatment. A personalized program, with mean caloric intake of 1500 Kcal, 25% proteins, low glycemic index CHO and a calculated antioxidant intake of 800–1000 mg daily, derived by fruit and vegetables, was administered to groups C and D (Table 1).

Patients received individualized dietetic nutritional counseling by a dietitian during regular interviews in accordance to a predetermined nutrition protocol as already described [12]. This protocol included general guidelines referring to the time and frequency of dietitian consultations, data to be collected during the nutrition assessment, although it did permit individualization of the diet to meet the specific needs of the patients.

3.1. Dietary intake assessment

Dietary intake was recorded for 3 days by means of 3-day diet diaries. Each patient was instructed by a dietitian on how to fill the diary. Dietary records (weighted food) were analyzed by means of a computerized software (Progeo, Ascoli Piceno, Italy) implemented with country specific food composition tables from the Italian National Institute of Research on Food and Nutrition [13]. In addition, antioxidant composition, regarding flavonoids, was calculated following USDA 2007 [14]. In addition mean daily ORAC (Oxygen Radical Absorbance Capacity) was calculated (see Appendix 1) [15].

3.2. Body weight and composition

At baseline (i.e. a few days before the treatment started), at 4 and 8 weeks and at the end of treatment (the day when the treatment finished), the following parameters were measured: weight, body mass index (BMI, kg/m^2), mid arm circumference, fat free mass (FFM) by bioelectrical impedance, energy and protein intakes. The measurements were taken by the same individual. The adherence to the diet and the declared intake of nutrients were investigated at each visit. People outside ±15% of the recommended intakes were invited to continue the diet but were dropped from the study. We excluded similarly patients with food intolerances, allergies or other kinds of unsatisfaction.

Body weight was measured in light clothes with an electronic scale (Seca 910; Seca, Hamburg, Germany) to the nearest 0.1 kg and height was measured with a stadiometer (Seca 220 telescopic measured rod; Seca) to the nearest 0.1 cm. Mid upper arm circumference of the nondominant arm was measured to the nearest 0.1 cm with a non-elastic tape measure. FFM was determined by bioelectric impedance analysis (BIA) with the use of BIA 101-body Impedance Analyzer (AKERN, Florence, Italy) periodically calibrated to ensure the accuracy of measurements. Patients were measured in the morning, after an overnight fast, in the supine position with arms 30° from the body and legs not touching one another on the examination table, with source and sensor electrodes placed on the dorsum of both hand and foot. FFM was calculated by using a multiple regression BIA equation, as also validated in patients [16].

3.3. Biological sample collection and analysis

In all patients, a blood sample was collected at 08.00 am. After centrifugation at 2000 g for 10 min, plasma aliquots were

Table 1
Main features of the two diets (see Appendix 1 for detailed composition).

Hypocaloric mediterranean diet (groups A and B)		
Kcal 1500; protein, g 80–90; lipid, g 40–50; carbohydrate, g 196–216. Total antioxidants: mg 400		
Carotenoid	Beta-carotene	mg 0.3
	Lutein-zeaxanthin	mg 0.2
	Lycopene	mg 0.7
Total flavonoids	(Anthocyanidins/flavan-3-ols/flavones/flavonols)	mg 90
Vitamins	Vit C	mg 300
	Vit E	mg 6.7
Minerals	Selenium	μg 15
Hypocaloric antioxidant-enriched mediterranean diet (groups C and D)		
Kcal 1500; protein, g 80–90; lipid, g 40–50; carbohydrate, g 196–216. Total antioxidants: mg 900		
Carotenoids	Beta-carotene	mg 0.5
	Lutein-zeaxanthin	mg 0.4
	Lycopene	mg 0.7
Total flavonoids	(Anthocyanidins/flavan-3-ols/flavones/flavonols)	mg 500
Vitamins	Vit C	mg 400
	Vit E	mg 7.3
Minerals	Selenium	μg 15

Seasonally adjusted daily intakes, Ref: USDA [20].