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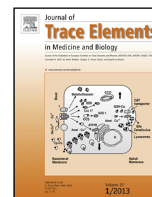

Clinical Studies

The beneficial effects of rosuvastatin are independent of zinc supplementation in patients with atherosclerosis☆

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ABSTRACT

Background: Statins have multiple antiatherosclerotic effects, but can reduce blood plasma concentrations of minerals, including zinc. As zinc possesses antiinflammatory and antioxidant effects, low zinc status can promote injuries or inadequate tissue repair in endothelial cells. Metallothionein (MT) expression might modulate responses induced by statins in patients with atherosclerosis. However, research regarding mineral status and the use of statins is scarce. This study evaluated the effects of zinc supplementation on zinc status and expression of the zinc-dependent *MT1F* and *MT2A* genes in patients with atherosclerosis treated with rosuvastatin.
Methods: A double-blind, randomized clinical trial was performed with 54 participants treated with 10 mg rosuvastatin for 4 months with or without zinc supplementation (30 mg/day). Diet, lipid profile, high-sensitivity reactive protein C (hs-CRP), plasma and erythrocyte zinc concentrations, erythrocyte superoxide dismutase (SOD) activity, and *MT1F* and *MT2A* genes expression were analyzed before and after intervention.
Results: Rosuvastatin therapy was effective in reducing low- and non-high-density lipoprotein, total cholesterol, triglycerides, and hs-CRP levels, independent of zinc supplementation. Additionally, zinc treatment had no effect on SOD enzyme activity ($P = 0.201$), plasma ($P > 0.671$) and erythrocyte ($P > 0.123$) zinc concentrations, or the pattern of *MT1F* and *MT2A* genes expression ($P = 0.088$ and $P = 0.229$, respectively).
Conclusions: The effectiveness of rosuvastatin treatment is independent of the effects of zinc supplementation. Moreover, rosuvastatin treatment did not have a significant impact on zinc status or *MT1F* and *MT2A* genes expression in patients with atherosclerosis.

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Introduction

Studies investigating zinc's biological properties have enhanced our knowledge regarding its involvement in atherogenic mechanisms [1]. Since zinc possesses antiinflammatory and antioxidant effects, low zinc status can promote injuries or inadequate tissue repair in endothelial cells [2,3].

Metallothioneins (MT) regulate intracellular zinc absorption, cellular redistribution, and excretion [4,5]. MT binds to zinc under different physiological and pathological conditions. MT expression elevates in response to oxidative stress and inflammatory agents [6] resulting in increased cellular zinc uptake and its removal from blood plasma [7]. Hence, zinc concentrations may be reduced in cardiovascular disease patients due to these metabolic alterations and increased nutritional requirements [8–10]. Conversely, reduced plasma mineral concentrations in atherosclerosis patients have been attributed to medications, especially statin derivatives [11,12]. Statins have antiatherosclerotic effects, which positively

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correlate with reduced LDL cholesterol levels. Further, they can exert beneficial pleiotropic effects including improved endothelial function and decreases in inflammation and oxidative stress [13]. Conversely, high MT expression may concomitantly increase statin-induced antiinflammatory and antioxidative stress responses in atherosclerosis patients undergoing statin treatment because zinc regulates statin-induced gene expression in vascular endothelial cells [14].

There is shortage of data regarding zinc concentrations in atherosclerotic patients undergoing rosuvastatin treatment. Mainly, no information is available regarding whether concomitant treatment with rosuvastatin and zinc supplements improves antioxidant capacity or alters zinc biomarkers. This is important since patients are often recommended to take non-toxic, supplementary doses of zinc to maintain adequate zinc status [15].

Thus, to understand the association between zinc status and the effect of statins and to direct supplementation strategies in atherosclerotic patients, we evaluated the effects of zinc supplementation on zinc status, high-sensitivity C-reactive protein (hs-CRP) levels, lipid profile, SOD activity and MT gene (*MT1F* and *MT2A*) expression in rosuvastatin-treated atherosclerotic patients.

Materials and methods

Subjects

Fifty-four patients were selected for this study (Clinicaltrials.gov I.D NCT01547377) conducted in Natal city, Northeast Brazil, between January 2008 and April 2009. All participants had atherosclerosis and had previously undergone percutaneous coronary angioplasty. Inclusion criterion was stable angina along with either of the following: (1) the diagnosis of atherosclerosis via angiography, revealing >70% stenosis in the lumen in at least 1 segment of a major epicardial artery, or (2) >50% left main coronary artery stenosis. Exclusion criteria included (1) serious cardiac complications and postoperative diseases such as thyroid, hematological, congenital, and autoimmune abnormalities, as well as liver disease, kidney failure, neoplasia, and osteoporosis; (2) use of antacids, antibiotics, and/or vitamin-mineral supplements; and (3) and alcoholism or smoking.

Patients were randomly assigned to the zinc supplemented ($n = 27$; 17 men, 10 women) or placebo groups ($n = 27$; 16 men, 11 women). This study was approved by the Research Ethics Committee at the Onofre Lopes University Hospital (HUOL) of the Federal University of Rio Grande do Norte (UFRN), protocol no 487/10. All participants provided written informed consent.

Study procedures

This double-blind, randomized clinical trial compared the effect of combined oral zinc supplementation (30 mg Zn/day) and a placebo (inactive pills identical in appearance to zinc supplement), both taken in association with 10 mg/day of rosuvastatin (Crestor®; AstraZeneca, London, UK) over a 4-month period. Zinc supplement was prepared using Zinc Chelazome® (zinc bis-glycine chelate; catalog number 3506, lot 262761), which was kindly provided by Albion Laboratories, Inc. (Clearfield, UT).

Randomization was performed by a pharmacist of the Companhia da Fórmula (Natal, Brazil), where the capsules were produced. Bottles of both supplement and placebo pills were given unique codes and then delivered to the investigators in batches of 10, with a 1:1 supplement-to-placebo ratio. All information about this process was retained solely by the pharmacist; therefore, both study participants and investigators were blind to the treatment. Participants were assigned bottles randomly, and the code number was recorded so that researchers could later investigate the impacts of each treatment on participants' biochemical analytes.

Participants attended a preliminary appointment (baseline) during which we performed a clinical evaluation and conducted an interview in order to obtain general information. During this baseline visit, we used a 216-cm handheld stadiometer with a platform (WSC; Cardiomed, Curitiba, Brazil) to measure the height, and an MEA-03140 solar digital balance (Tanita, Arlington Heights, IL, USA) to measure the weight of the participants; these values were used to calculate body mass index (BMI). We also measured abdominal circumference and collected blood in order to perform biochemical analysis. Four return visits were scheduled at 1-month intervals; totally, 5 visits were scheduled per participant. During each monthly visit to the outpatient clinic, participants received both statin medication and a bottle of zinc supplement or placebo. A clinical assessment was also performed at this time, and each participant was recalled 24 h after each visit for assessment of their dietary intake. During the post-treatment period, after the 4-month study period was complete, each participant's anthropometric data were again assessed, and a second blood sample was collected for biochemical analyses.

Biochemical analysis

All glassware and plastic containers used during blood collection and mineral analyses were carefully demineralized in nitric acid bath to 30% for at least 12 h, and rinsed using ultra-pure (Milli-Q®) water 10 times to minimize minerals contamination.

Blood samples (30 mL) were obtained after a 12-h fast for biochemical analysis. The blood was distributed in tubes, with or without anticoagulants, as following: (1) no anticoagulant (10 mL) for lipid profile, glucose, aspartate aminotransferase, alanine aminotransferase, and CRP analysis; (2) EDTA (5 mL) for erythrocyte superoxide dismutase (SOD) analysis; (3) 30% sodium citrate (10 mL) for plasma zinc and erythrocyte analysis; and (4) EDTA (5 mL) for RNA extraction. Serum and plasma were separated by centrifugation for 15 min at 3500 rpm at 4 °C. The erythrocyte mass obtained was washed three times with 5 mL of 0.9% saline, slowly homogenized by inversion and centrifuged again at $10{,}000 \times g$ for 10 min (SIGMA® 2K15 centrifuge, Germany) at 4 °C, after which the supernatant was discarded. Following the final centrifugation, the saline solution was aspirated and the erythrocyte mass was carefully extracted using a micropipette, transferred into demineralized Eppendorf tubes and stored for later analysis of zinc and hemoglobin. For assays that were not performed on the day of blood collection, aliquots were stored at −80 °C.

An AU400 chemical analyzer (Olympus, Tokyo, Japan) and Olympus laboratory kits were used to measure total cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL-c), glucose, aspartate aminotransferase, and alanine aminotransferase levels. Quality control was performed in accordance with the standards of the National Quality Control Program of the Brazilian Society of Clinical Analyses (SBAC). The low-density lipoprotein (LDL-c) cholesterol level was determined using the Friedewald formula (LDL = total cholesterol − HDL-c + [triglycerides/5]) when the triglyceride concentrations were <400 mg/dL. We measured the non-HDL cholesterol level (total cholesterol − HDL-c), which represents the sum of LDL-c and very-low-density lipoprotein cholesterol, using the formula provided by the National Cholesterol Education Program (NCEP) III (2002) [16].

Plasma and erythrocyte zinc determinations were performed by atomic absorption spectrophotometry, using the Varian Spectra AA – 240 device (Varian Medical Systems, Inc., Milpitas, CA), calibrated with the following working conditions: length wave 231.9 nm, slit 1.0 nm, 5.0 mA amperage, expansion factor 1.0, and sample flow 5 mL/min. A standard zinc solution (Tritisol®, Merck, Germany)

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