Nutrition, Metabolism & Cardiovascular Diseases (2014) **24**, 1213–1220

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

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

Effects of magnesium supplements on blood pressure, endothelial function and metabolic parameters in healthy young men with a family history of metabolic syndrome

E. Cosaro [a,1], S. Bonafini [a,1], M. Montagnana [b], E. Danese [b], M.S. Trettene [a], P. Minuz [a], P. Delva [a], C. Fava [a,*]

[a] Department of Medicine, Azienda Ospedaliera Universitaria Integrata of Verona, University of Verona, Italy
[b] Department of Life and Reproduction Sciences, Azienda Ospedaliera Universitaria Integrata of Verona, University of Verona, Italy

Received 13 December 2013; received in revised form 13 May 2014; accepted 19 May 2014
Available online 28 May 2014

KEYWORDS
Magnesium;
Metabolic syndrome;
Diabetes;
Positive family history;
Blood pressure;
Flow mediated dilatation;
Arterial stiffness

Abstract *Background and aims:* Magnesium plays an important role in the modulation of vascular tone and endothelial function and can regulate glucose and lipid metabolism. Patients with hypertension, metabolic syndrome (MetS) and diabetes mellitus (T2DM) have low body magnesium content; indeed, magnesium supplementation has been shown to have a positive effect on blood pressure (BP) and gluco-metabolic parameters. The aim of our study was to evaluate the effect of magnesium supplements on hemodynamic and metabolic parameters in healthy men with a positive family history of MetS or T2DM.

Methods and results: In a randomized, double-blind, placebo-controlled 8-week crossover trial with a 4 week wash-out period, oral supplements of 8.1 mmol of magnesium-pidolate or placebo were administered twice a day to 14 healthy normomagnesemic participants, aged 23–33 years. The primary endpoint was office BP, measured with a semiautomatic oscillometric device. Secondary endpoints included characteristics of the MetS, namely endothelial function, arterial stiffness and inflammation. Plasma and urinary magnesium were measured in all participants while free intracellular magnesium was measured only in a subsample.

There was no significant difference in either systolic and diastolic BP in participants post-magnesium supplementation and post-placebo treatment when compared to baseline BP measurements. Further, the metabolic, inflammatory and hemodynamic parameters did not vary significantly during the study.

Conclusions: Our study showed no beneficial effect of magnesium supplements on BP, vascular function and glycolipid profile in young men with a family history of MetS/T2DM (trial registration at clinicaltrial.gov ID: NCT01181830; 12th of Aug 2010).

Introduction

Metabolic syndrome (MetS), the clustering of central obesity with other features of insulin resistance, such as elevated glucose level or overt diabetes, dyslipidemia, and elevated BP, has been regarded as a worldwide pandemic [1]. Nevertheless, the precise pathogenesis of the syndrome is controversial, and the search for a unifying factor

* Corresponding author. Department of Medicine, Division of Internal Medicine C, Piazzale LA Scuro 10, 37134 Verona, Italy. Tel.: +39 45 8124414; fax: +39 45 8027465.
E-mail address: cristiano.fava@med.lu.se (C. Fava).
[1] These authors contributed equally to the manuscript.

http://dx.doi.org/10.1016/j.numecd.2014.05.010
0939-4753/

has been essentially fruitless. It has been proposed that several micro- and macro-nutrients play a role in the development of the metabolic and hemodynamic alterations in MetS.

Many studies have focused on magnesium, which is involved in glucose and lipid metabolism, modulates vascular resistance and plays a fundamental role in many vital cellular pathways [2–5]. Magnesium is the second most abundant intracellular cation and the fourth most abundant cation in the body [6]. Most of the total storage of magnesium is in tissues (99%) with only 1% located extracellularly. Thus, the assessment of serum magnesium cannot adequately detect the presence of ion depletion, and a deficiency of ion stores can exist even in the presence of normal serum values [6]. Magnesium is mainly consumed through the diet, and it has been estimated that daily magnesium intake in a normal Western diet (approximately 300–360 mg/day) is often inadequate for the body's needs [6].

Intracellular magnesium is involved in essential functions for cell survival. It acts as a cofactor in more than 300 chemical reactions, including glycolysis, the process of phosphorylation, the response to growth factors, cell proliferation and mitochondrial energy production and promotes cell glucose uptake to optimize the action of insulin [6]. Magnesium acts also as a calcium antagonist by competing with calcium ions for many cation binding sites in membranes and proteins. Furthermore, magnesium is involved in the regulation of myocardial cell contractility, vascular tone and the basic response to pressor agents towards vasodilatation [2–4,6]. Numerous clinical studies have linked several components of the MetS with a low magnesium dietary intake [7,8]. This association has become increasingly important in Western countries where the burden of MetS and its long-term consequences is rising and constitutes a public health emergency [1]. It has been proposed that serum magnesium deficiency is an independent risk factor for all of the individual components of MetS [7,9]. Hypomagnesemia has been documented in patients diagnosed with impaired glucose tolerance, type 2 diabetes mellitus (T2DM) and MetS [10,11].

Some clinical trials in targeted populations, such as diabetics and obese or hypertensive participants, have reported a positive effect of magnesium supplementation on BP and glycometabolic parameters [12–14]. It has also been postulated that the effect of magnesium along with other nutrients and vitamins could be enhanced if the intake precedes the clinical onset of the disease [15].

Finally, because the offspring of patients with diabetes or MetS are at an increased risk of developing these metabolic disorders due to genetic and environmental factors, they represent a target population in whom preventive intervention could be addressed.

Thus, we conducted a cross-over double blind placebo-controlled trial in young, healthy normomagnesemic men with a positive family history of MetS and/or T2DM to assess the effect of magnesium supplementation for 8 weeks on several components of MetS and vascular hemodynamics.

Methods

Sixteen male patients, aged between 23 and 33 years, were recruited between offspring of patients who were followed in the "Hypertension outpatient clinic" in Verona University Hospital. Inclusion criteria were: good health and a positive family history of MetS and/or diabetes mellitus type 2 in at least one first-degree relative (AHA/NHLBI criteria) [1]. The exclusion criteria were: a clinical diagnosis of hypertension (BP $>$ 140/90 mmHg on several occasions and/or the use of antihypertensive treatment), diabetes mellitus (ADA criteria) or obesity (BMI $>$ 30 kg/m^2), use of lipid-lowering drugs or continuous therapy with nonsteroidal inflammatory drugs, use of vitamins or micro-nutrients supplements; hypermagnesemia at randomization; previous cardiovascular events and/or cerebrovascular disease; chronic renal insufficiency, chronic inflammatory liver disease, kidney disease, malignancies, gastrointestinal dysfunction with hypo-mobility; smoking more than 5 cigarettes per day. Eligibility criteria were verified by the physicians involved in the study.

Study design

The study was conducted according to a double-blind placebo controlled cross-over design lasting 8 weeks (see Fig. 3). Between the first and the second phase of the study, at least 4 weeks of wash-out was instituted. The primary endpoint of the study was the effect of magnesium supplementation on "office" blood pressure. Secondary endpoints were significant changes in the other parameters associated with MetS according to the AHA/NHLBI criteria and the HOMA index, endothelial function, arterial stiffness and high sensitivity C reactive protein (HS-CRP). The study was approved by the Ethical Committee of the University Hospital of Verona, and written informed consent was obtained from each participant. The trial was registered in the *ClinicalTrials.gov* database with the identification code NCTO1181830 (12th of Aug 2010).

Randomization and magnesium allocation

The randomization sequence was generated by a computer-generated random-number list without blocks. A pharmacist who was not otherwise involved in the study kept the randomization list until the trial was completed. The randomization numbers and the assigned treatment were contained in serially numbered envelopes and kept by staff who were not involved in the outcome assessment.

Plastic bags containing 8.1 mmol of Magnesium pidolate powder or placebo (lactose) were provided by the Hospital Pharmacy and taken by the participants twice a day, in the morning and evening before meals (16.2 mmol of Magnesium pidolate per day equivalent to 368 mg of elementary Mg) for 8 weeks. Both drugs were prepared by the pharmacy in indistinguishable packs so that it was impossible for either the patients or the physician to know which medication was being assigned to each participant.