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NUTRITION

Association of plasma manganese levels with chronic renal failure

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ABSTRACT

Manganese (Mn) is an essential trace element involved in the formation of bone and in amino acid, lipid and carbohydrate metabolism. Mn excess may be neurotoxic to humans, affecting specific areas of the central nervous system. However, relatively little is known about its physiological and/or toxicological effects, and very few data are available concerning the role of Mn in chronic renal failure (CRF). This paper describes a 12-month study of the evolution of plasma Mn levels in predialysis patients with CRF and the relationship with energy and macronutrient intake. The participants in this trial were 64 patients with CRF in predialysis and 62 healthy controls. Plasma levels of creatinine, urea, uric acid, total protein and Mn were measured. The glomerular filtration rate (GFR) was calculated using the Cockcroft-Gault index. The CRF patients had higher plasma levels of creatinine, urea, uric acid and Mn and a lower GFR than the controls. Plasma Mn was positively correlated with creatinine, plasma urea and plasma uric acid and was negatively correlated with the GFR and the intake of energy and macronutrients. In conclusion, CRF in predialysis patients is associated with increases in circulating levels of Mn.

Introduction

Alterations in trace element metabolism in renal insufficiency are common. Nevertheless, the mechanisms responsible for these changes are still not fully understood [1,2].

Manganese (Mn) is an essential trace element involved in the formation of bone and in amino acid, lipid and carbohydrate metabolism. However, Mn excess may be neurotoxic to humans, affecting specific areas of the central nervous system [3,4].

Little information exists regarding the behaviour of Mn in renal disease and what has been reported is contradictory and mainly focused on haemodialysis patients. Some authors have observed significant increases in Mn content in the hair of patients [5]. Ohtake et al. [6] reported a case of Mn-induced Parkinsonism in a patient on maintenance haemodialysis therapy. According to another study, the occurrence of bilateral pallidal hyperintensity on T1-weighted images in all patients undergoing haemodialysis is associated with high serum Mn levels [7]. However, other authors have described the opposite effect. Some authors have measured a decrease in Mn levels in haemodialysis patients [8–10]. Koh et al. [11] observed an association between low Mn values in blood and the risk of renal disease, and suggested that this situation may favour disease progression. This element is a cofactor for SOD, so Mn deficiency may contribute to excess oxidative stress in uraemia [12–14].

Given the limited information available on the role of Mn in chronic renal failure (CRF), the aim of this study is to investigate changes in plasma levels of Mn in predialysis patients with CRF and their relation to the biochemical parameters used in monitoring these patients and to the intake of energy and macronutrients.

Materials and methods

Patients

The participants in this cross-sectional trial were patients with CRF in predialysis who attended the nephrology outpatient clinic of the Virgen de las Nieves University Hospital, Granada (Spain). The following inclusion criteria were applied: plasma creatinine concentration >2.5 mg/dL, plasma creatinine clearance between 10 and 45 mL/min, stable clinical condition (stable blood pressure; no special diet; no digestive system or systemic disease, neoplasias or treatment with corticosteroids or immunosuppressors), normalised metabolic acidosis and lipid alterations, age between 18

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and 70 years. This study was carried out in accordance with the World Medical Association Code of Ethics (Declaration of Helsinki) and all procedures were approved by the Hospital's Ethics Committee.

The study group comprised 64 patients (27 women, 37 men) aged 18–70 years with a mean age of 54 ± 16 years (mean ± SD). Control samples were obtained at random from adults aged 18–70 years living in Granada (Spain). Control participants were asked whether they had any acute or chronic illness and were included if they were (or appeared to be) in good health; pregnant and lactating subjects were excluded. The controls included 62 healthy people (33 men and 29 women) with a mean age of 46 ± 10 years. All participants provided their consent by signing an informed consent form.

On day 0, all participants, and at the end of the study, only patients received a physical examination and clinical as well as nutritional data were recorded. The experimental phase of our study lasted 12 months, during which period the patients consumed the low-protein diets recommended by the hospital. Patients aged younger than 60 years and non-obese patients consumed a diet that provided 35 kcal/kg b.wt./day. Patients with obesity and/or older than 60 years were advised to consume a diet that provided 30 kcal/kg b.wt./day. To adjust the energy content of the low-protein diet, we considered obesity to exist when the participant weighed more than 125% of ideal weight [15]. After 12 months, the participation rate was 76.5%. The reasons for dropout or withdrawal included scheduled dialysis, death, laboratory error or loss of samples.

The pharmacological treatment was similar for all patients and was adjusted depending on the individual's clinical status. Medications included calcium-chelated phosphate, calcitriol, oral sodium bicarbonate, ferrous sulphate, antihypertensives (mainly angiotensin-converting enzyme inhibitors), furosemide and subcutaneous erythropoietin.

At the beginning of the study and after 12 months, food consumption was assessed by a 24-h recall method that was repeated over 3 days (including a weekend or holiday) [16]. Data were obtained by a dietician with the aid of an open questionnaire and photographs as a reference for portion size. The pictures displayed fresh foods or foods prepared according to standard recipes for dishes that are widely consumed in the study area. Food intake was converted to energy and nutrients using the Spanish Food Composition Table [17]. The food composition database utilised AYS44 diet analysis software obtained from ASDE, SA (Valencia, Spain).

Body weight was measured with a portable digital scale (Tefal, Sensitive Computer 9202 series 2/0, France) with a precision of 0.1 kg, and height was measured with a portable stadiometer (Holtain Portable, London, UK) with a precision of 0.1 cm. All measurements were obtained following the techniques and recommendations of the International Biological Programme by personnel suitably trained for this task.

Analytical methods

In the morning, blood was collected (10 mL) during fasting conditions in tubes that contained lithium heparin as an anticoagulant (Venoject, Terumo Corporation, Leuven, Belgium). The samples were centrifuged at 1200 × *g* for 15 min at 20 °C to separate the plasma and were stored at −80 °C until analysis. Excreted urine over a 24-h period was collected, following standard guidelines. Diuresis was measured and an aliquot stored at −80 °C until analysis.

Creatinine in plasma and 24-h urine, as well as the urea, uric acid and total protein concentrations in plasma were measured with enzymatic colorimetric tests in a Hitachi Modular P autoanalyser (Roche Diagnostics, Grenzach, Germany). The glomerular filtration rate (GFR) was estimated in patients by creatinine clearance and by the determination of diuresis and plasma and urinary creatinine at 24 h. The GFR was also measured in the patients and controls using the Cockcroft-Gault index = (140 − age/72 × plasma creatinine) × weight (×0.85 for women) [18].

Plasma Mn was determined using an inductively coupled plasma mass spectrometer (ICP-MS) model 7500 supplied by Agilent Technologies (Agilent, Tokyo, Japan), using a carrier gas flow of 1.03 L/min, collision gas (He) flow of 4.3 mL/min, RF power of 1550 W and energy discrimination of 3 V. All lenses were optimised daily. All materials used in the analysis were previously cleaned with supra-pure nitric acid and ultra-pure water (18.2 Ω) obtained using a Milli Q system. Samples and the certified reference material (Seronorm Trace Elements Serum L-1, Ref 201405. Billingstad, Norway) were prepared by attack with nitric acid and hydrogen peroxide (supra-pure quality, Merck) in a microwave digester (Milestone, Sorisole, Italy). When the samples had been digested, the extracts were collected and made up to a final volume of 10 mL with-ultra pure water for subsequent analysis.

The calibration curve was prepared following the Ga addition technique (adding 0.04 mg/L) as an internal standard, using stock solutions of 1000 mg/L of Mn (Merck).

The accuracy of the method was evaluated by analysis of the certified reference material, obtaining the value of 8.2 ± 0.2 μg/L (certified value 7.8–8.8 μg/L), and by recovery studies in samples of organs enriched with Mn standards, obtaining a recovery of 93%. The mean of five separate determinations was used.

Statistical analysis

All variables and indexes were analysed by descriptive statistics. Results are reported as means and standard deviations. When the data were distributed normally according to the Kolmogorov–Smirnov test, parametric tests (Student's *t*-test for independent or related samples) were used. For variables that required nonparametric testing, the Mann–Whitney test for unrelated samples was used. Linear regression analysis was used to obtain bivariate correlations. Pearson's correlation coefficient was calculated for the 95% confidence levels. All analyses were conducted with version 15.0 of the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Differences were considered significant at the 5% probability level.

Results

This paper examines the 12-month evolution of plasma Mn levels in predialysis patients with CRF and the relationship with energy and macronutrient intake.

Table 1 lists the following characteristics of the participants, showing mean values and SD for controls and patients at day 0 and for patients after 12 months: age, anthropometric variables (weight, height, body mass index [BMI]), plasma parameters indicative of renal function (plasma creatinine, Cockcroft-Gault index, plasma urea, plasma uric acid and plasma total proteins), plasma Mn and energy and macronutrient intake. All these parameters, except total plasma proteins, worsened significantly in the patients compared to controls during the study period, which is indicative of progressive renal dysfunction. Interestingly, patients with CRF had higher plasma Mn levels than the controls at the beginning of the study and these concentrations had increased significantly by the end of the study.

In this study, we also evaluated the relationship between plasma levels of Mn and macronutrient consumption. This relationship had not been studied previously due to the unreliability of the food composition tables, as the number of foods in which Mn is present is very low. In our study, the female patients had a lower consumption