Magnesium and zinc status in patients with chronic renal failure: influence of a nutritional intervention

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Abstract. Chronic renal failure (CRF) alters the metabolism for a number of elements, and can lead to deficiency of these nutrients. Among the causes of these alterations are reduced food intake and the low element content of some low-protein diets recommended in CRF. This study aimed to determine whether nutritional status for magnesium and zinc were changed by a nutritional intervention providing patients with CRF with enough information to prepare a low protein diet that met their needs. The effects of the intervention were compared in 40 adult participants divided into two groups. The control group consumed their usual prescribed diet, and the nutritionally instructed group received dietary training to teach them how to choose foods that met their nutritional needs. The study period lasted 12 months. Food consumption was assessed by 24-h recall. Magnesium and zinc were measured in plasma at the start and at the end of the study. Participants in the nutritionally instructed group decreased their protein intake and increased that of carbohydrates, magnesium and zinc. Plasma zinc correlated with glomerular filtration rate, measured as creatinine clearance, \((r = 0.37)\) plasma protein \((r = 0.39)\) and zinc intake \((r = 0.63)\). At the start of the study 1 participant in the control group and no participants in the instructed group had hypomagnesaemia (< 1.8 mg/dL) whereas 2 participants in the control group and 5 in the instructed group had hypozincemia \((Zn < 70 \, \mu g/dL)\). After the intervention we observed no changes in the number of participants with hypomagnesaemia in either group, whereas hypozincemia was found in only 1 participant in the control group and 1 in the instructed group (changes in the instructed group were significant; \(p < 0.05\)). Nutritional intervention benefited our participants by improving their ability to choose foods that provided magnesium and zinc while reducing their protein intake. The results of this study indicate that the dietary intervention enabled participants to better control their protein intake and zinc status without detriment to magnesium status.

Key words: chronic renal failure, magnesium, zinc, nutritional status, nutritional intervention

Chronic renal failure (CRF) provokes imbalances of elemental status in physiological fluids and tissues [1], and can lead to deficiency in or raised levels of these nutrients, but the mechanisms responsible for these changes are poorly understood, and the contribution of toxicity or deficiency in some elements to the symptoms of CRF is uncertain. Among the causes of these alterations are reduced food intake and the low element content of some low-protein diets recommended in CRF to delay the progression of kidney damage [2, 3].
Because renal excretion is the major route of elimination of magnesium from the body, hypermagnesaemia may be more likely in patients with CRF. However, CRF is accompanied by a decrease in tubular resorption of magnesium ions, lower magnesium intake and diminished intestinal absorption of this element [4], all of which help maintain magnesaemia within the normal range. It is only in advanced CRF when increases in fractional magnesium excretion may be inadequate and magnesium balance may become positive. The imbalance may be aggravated if the patient is taking magnesium-containing medications. When the increase surpasses 4.8 mg/dL, diminished reflexes, respiratory paralysis and heart failure can ensue [5].

Low circulating zinc concentrations have been described in CRF. The cause of the decrease is unclear but may be a consequence of the low-protein diets recommended for these patients [3]. Zinc deficiency in CRF may also be partly due to impaired intestinal absorption [6], alterations in tubular transport or loss of ion-transporting plasma proteins [3].

Nutritional intervention for CRF is complicated. A complex diet, combined with sickness and reduced food intake, puts the patient at risk of malnutrition. The goals for nutritional intervention are to maintain or improve nutritional status and prevent malnutrition, to implement an appropriate diet and nutritional prescriptions based on nutritional status, and to facilitate compliance with the nutritional intervention through education and monitoring. The diet and nutritional prescriptions should be individualized to make it easy for the patient to follow. The prescription is based on the nutritional requirements and the patient’s food preferences and clinical conditions [7].

The present study was designed to determine whether nutritional status for magnesium and zinc were changed by a nutritional intervention providing patients with CRF with enough information to prepare a low protein diet based on their food preferences adjusted to their individual needs and to facilitate compliance with the nutritional intervention.

**Materials and methods**

**Patients**

The participants in this longitudinal, prospective, experimental nutritional trial were patients with CRF on predialysis. The inclusion criteria were: serum creatinine concentration > 25 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, neoplasia, or treatment with corticosteroids or immunosuppressors), corrected metabolic acidosis and lipid alterations, age between 18 and 70 years, and knowing how to read and write. The study was authorized by the Ethics Committee of the Hospital Universitario Virgen de las Nieves in Granada, Spain. All patients provided their consent by signing an Informed Consent form.

The sample was consecutive and nonprobabilistic, since all patients who met the inclusion criteria and were seen at the nephrology outpatient clinic of the Hospital Universitario Virgen de las Nieves between November 1999 and June 2006 were included.

The sample of patients initially invited to participate consisted of 64 men and women aged 18 to 70 years. The final sample consisted of 40 persons (24 men, 16 women) with a mean age of 54 (SD 13) years. The final participation rate was 62.5%, and the reasons for dropout or withdrawal by the investigators were scheduled dialysis (20.0%), nonadherence to the diet (45.0%), death (10.0%), or laboratory error or loss of samples (30%).

The patients were divided randomly into two groups. The control group (20 participants chosen at random) consisted of patients who remained on the same prescribed low-protein diet as before the study. The nutritionally instructed group (20 participants chosen at random) consisted of patients who were instructed by a trained dietitian to consume a conventional low-protein diet that was adjusted to their individual needs, based on foods they usually consumed. The diet supplied 0.6 g protein (50% high biological value)/kg weight per day [8, 9] and 35 kcal/kg weight per day [8] and was low in sodium, potassium, phosphates, saturated fat and refined sugar. This educational intervention took each participant’s eating habits into account along with the nutritional recommendations for patients with CRF [2] and the recommended daily allowances (RDA) for the adult population in Spain [10] for nutrients not included in the recommendations for patients with CRF. This phase lasted for 1 week. The educational session was personalized to take into account the participants’ eating habits.

Participants with obesity (50%) and participants older than 60 years (47.3%) were advised to consume a diet that provided 30 kcal/kg b.wt per day. To adjust the energy content of the low-protein diet we considered obesity to exist when the participant...
weighed more than 125% of his or her ideal weight. [11]. The other 50% of the patients comprised the control group, whose usual low-protein diet was not changed.

On day 0 of the study all participants received a physical examination, and clinical and nutritional data were recorded. The second (experimental) phase of the study lasted 12 months, during which participants in the nutritionally instructed group consumed the low-protein diets they designed themselves during the initial dietary intervention to ensure adherence, while participants in the control group continued to consume the low-protein diet recommended by the hospital. This diet was based on a weekly low-sodium menu that supplied a mean of 46.3 g protein/day, 54.6 g fat/day and 240 g carbohydrates/day.

Pharmacological treatment was similar in all participants and was adjusted depending on individual clinical status. Medications included calcium-chelated phosphate, calcitriol, oral sodium bicarbonate, ferrous sulfate, antihypertensives (mainly angiotensin-converting enzyme inhibitors), furosemide and subcutaneous erythropoietin.

At the start of the study and after 12 months, food consumption was assessed with a 24-h recall method which was repeated over 3 days (including a weekend or holiday) [12]. The data were obtained by a dietitian with the aid of an open questionnaire and photographs as a reference for portion size. The pictures showed fresh foods or foods prepared according to usual recipes for dishes that are widely consumed in the study area. Food intakes were converted to energy and nutrients with the help of the Spanish Food Composition Table [13]. The food composition database was used under AYS44 Diet Analysis software from ASDE, SA (Valencia, Spain).

Analytical methods

In the morning after the participants had abstained from eating or drinking overnight, blood was collected (10 mL) in tubes that contained lithium heparin as an anticoagulant (Venoject, Terumo Corporation, Leuven, Belgium). The samples were centrifuged at 3,000 g for 15 min at 20°C to separate plasma, and were stored at –80°C until analysis.

Creatinine, urea, uric acid, albumin and total protein concentrations were measured with enzymatic colorimetric tests in a Hitachi Modular P autoanalyzer (Roche Diagnostics, Grenzach, Germany). The glomerular filtration rate (GFR) was estimated by creatinine clearance, by the determination of diuresis and serum and urinary creatinine at 24 hours. Plasma magnesium and zinc were measured by atomic absorption spectroscopy (Perkin Elmer Analyst 300 spectrometer, Norwalk, CT, USA). Seronorm Trace Elements assays (ref 201405) (SERO AS, Billingstad, Norway) were used as quality control measures for element concentrations. The value obtained for magnesium was 1.97 (SD 0.43) mg/dL (certified 95% CI, 1.86-2.05 mg/dL) and that for zinc was 1.38 mg/L (certified 95% CI, 1.23-1.43 mg/L). For each element we used the mean of five separate determinations.

Hypomagnesaemia was defined as plasma concentration of magnesium of < 1.8 mg/dL, and hypozincæmia was defined as plasma concentration of zinc of < 70 μg/dL [14].

Statistical analysis

All variables and indexes were analyzed with descriptive statistics, and the results are reported as the mean and standard deviation. When the data were distributed normally according to the Kolmogorov-Smirnov test, we used parametric tests, i.e. Student’s t test for independent or related samples. For variables that required nonparametric testing we used the Wilcoxon test for related samples and the Mann-Whitney test for unrelated samples. Z test was used to find differences between the participants with low plasma levels of magnesium or zinc.

Linear regression analysis was used to find bivariate correlations; Pearson’s correlation coefficient was calculated for 95% confidence levels. Multiple logistic regression analysis was used to estimate the degree of association between intake or plasma values (dependent variable) and gender, age, group (control and experimental) and experimental period (day 0 and 12 month) The model was adjusted for all variables. Analysis of variance (ANOVA) was used to look for interactions in analytical values between sexes, age groups and experimental period. All analyses were carried out with version 14.0 of the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL). Differences were considered significant at the 5% probability level.

Results

At the start of the study (day 0) there were no differences between the control and the nutritionally instructed group in any of the biochemical indicators of renal function. At 12 months, there were still no differences between the two groups. Neither were there any significant differences between the
control patients at day 0 and at 12 months, or between the instructed patients at day 0 and at 12 months, as regards the biochemical parameters indicative of renal function. The urea/creatinine ratio in both groups remained below the cut-off value for excess protein intake (> 40 mg/dL) [15] (table 1).

Energy intakes were below the RDA at time 0 in both groups (control and instructed) and although it increased during the study period, energy intake did not reach the recommended value of 35 kcal/kg b. wt per day in either group by the end of the experimental period. This situation might reflect the reduced intake and poor adherence to dietary recommendations often seen in patients with CRF [16, 17]. Despite the low energy intakes, we found no significant changes in BMI (table 1).

Protein intake increased in the control group and decreased in the instructed group during the nutritional intervention period. Magnesium intake increased in both groups (control and nutritionally instructed) during the experimental period, but these changes were only significant in the nutritionally instructed group. Zinc intake increased signifi-

Table 1. Biochemical indicators of renal function, anthropometric variables, energy, macronutrients, magnesium and zinc intakes, plasma concentrations of magnesium and zinc and number of patients with low plasma magnesium or zinc concentrations at the start (day 0) and at the end of the experimental period (12 months), in control and nutritionally instructed patients with chronic renal failure

<table>
<thead>
<tr>
<th>Biochemical indicators of renal function</th>
<th>Day 0</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (mg/dL)</td>
<td>3.43 ± 1.18</td>
<td>3.20 ± 0.77</td>
</tr>
<tr>
<td>Glomerular filtration rate (GFR) (mL/min)</td>
<td>26.19 ± 7.82</td>
<td>27.17 ± 9.12</td>
</tr>
<tr>
<td>Plasma urea (mg/dL)</td>
<td>111.50 ± 21.60</td>
<td>113.50 ± 19.37</td>
</tr>
<tr>
<td>Urea/creatinine ratio</td>
<td>33.21 ± 6.10</td>
<td>35.27 ± 7.39</td>
</tr>
<tr>
<td>Plasma uric acid (mg/dL)</td>
<td>6.76 ± 1.75</td>
<td>7.10 ± 0.80</td>
</tr>
<tr>
<td>Plasma total protein (g/dL)</td>
<td>6.91 ± 0.74</td>
<td>7.12 ± 0.57</td>
</tr>
</tbody>
</table>

Anthropometric variables

| Body weight (kg) | 76.72 ± 18.80 | 76.40 ± 11.13 | 76.84 ± 16.20 | 74.85 ± 12.40 |
| BMI (kg/m²)      | 28.20 ± 7.06 | 27.38 ± 5.40 | 28.25 ± 6.50 | 26.83 ± 5.52 |

Intake

| Energy (kcal/d)       | 1815 ± 420 | 1790 ± 437 | 2075 ± 659 | 1995 ± 223 |
| Energy (kcal/kg weight/day) | 23.65 ± 7.73 | 23.42 ± 9.50 | 27.00 ± 10.50 | 26.86 ± 6.17 |
| Protein (g/day)       | 71.10 ± 23.98 | 74.67 ± 16.10 | 114.06 ± 66.19 | 49.14 ± 17.64 |
| Protein/kg weight/day | 0.93 ± 0.39 | 0.98 ± 0.34 | 1.48 ± 0.56 | 0.66 ± 0.27 |
| Carbohydrates (g/day) | 203.39 ± 66.90 | 200.78 ± 44.96 | 212.17 ± 49.99 | 266.14 ± 22.94 |
| Total fat (g/day)     | 79.49 ± 14.79 | 73.92 ± 37.37 | 84.62 ± 21.69 | 80.20 ± 25.77 |
| Fiber (g/day)         | 17.95 ± 8.57 | 16.93 ± 3.77 | 19.44 ± 7.63 | 19.90 ± 3.63 |
| Mg (mg/day)           | 242.36 ± 75.45 | 218.65 ± 56.68 | 270.13 ± 57.67 | 260.21 ± 51.83 |
| Mg (%RDA)             | 72.34 ± 22.51 | 66.87 ± 17.33 | 80.86 ± 17.47 | 77.67 ± 15.60 |
| Zn (μg/day)           | 6.09 ± 2.57 | 6.14 ± 2.33 | 9.85 ± 5.56 | 8.01 ± 1.59 |
| Zn (%RDA)             | 40.60 ± 17.13 | 43.60 ± 10.53 | 65.66 ± 17.06 | 53.40 ± 10.60 |

Plasma concentrations

| Mg (mg/dL)           | 2.28 ± 0.30 | 2.21 ± 0.24 | 2.10 ± 0.38 | 2.29 ± 0.29 |
| Zn (μg/dL)           | 74.00 ± 8.85 | 75.10 ± 11.02 | 82.22 ± 10.29 | 78.71 ± 6.40 |

Number of patients with low plasma magnesium or zinc concentrations

| Plasma Mg (< 1.8 mg/dL) | 1 | 0 | 1 | 0 |
| Plasma Zn (< 70 μg/dL)   | 2 | 5 | 1 | 1 |

Data are expressed as the mean ± standard deviation. a Control day 0 vs Control 12 months; b Control vs Nutritionally instructed at day 0 or at 12 months; c Nutritionally instructed at day 0 vs Nutritionally instructed at 12 months. p < 0.05 in all cases.% RDA: Percent recommended daily allowance covered.
cantly in both groups over the experimental period. In neither of the two groups was plasma magnesium found to change by the end of the study period with respect to its initial values. Plasma zinc concentrations had increased in both groups (control and instructed) by the end of the study, and this increase was significant in the control group (table 1).

At the start of the study, 1 participant in the control group and no participants in the nutritionally instructed group had plasma magnesium values < 1.8 mg/dL. After the intervention we observed no changes in the number of participants with hypomagnesaemia in either group. At the start of the study (day 0), 2 participants in the control group and 5 in the nutritionally instructed group had low plasma zinc concentrations (plasma Zn < 0.70 mg/dL), whereas at the end of the study period (12 months), deficient zinc concentrations were found in only 1 participant in the control group and 1 in the experimental group. Changes in the instructed group were significant (p < 0.05) (table 1).

Linear regression analysis between nutrient intakes and biochemical variables shows that protein intake correlated with magnesium and zinc intake (r = 0.73, p < 0.01; r = 0.74, p < 0.01, respectively) (figure 1). Moreover, plasma zinc correlated with glomerular filtration rate (GFR) (r = 0.37, p < 0.05), plasma total protein (r = 0.39, p < 0.05) and zinc intake (r = 0.63, p < 0.01) (figure 2). Logistic regression analysis did not disclose significant associations between intake or plasma values (dependent variable) and gender, age, group (control or experimental) or experimental period (day 0 or 12 months). Analysis of variance to search for interactions between plasma concentrations and gender, age, group or experimental period revealed a significant interaction between age and plasma magnesium concentration (p = 0.012).

Discussion

Although there is no consensus as to the optimal protein intake in patients with CRF, low-protein diets have traditionally been recommended for these patients to delay disease progression [18]. Our findings show that at the beginning of the study, protein intakes were similar in both groups, and were higher than the recommended intakes. High protein intakes are common in the adult population in southern Spain [19]. After 12 months, adherence to the diet in the nutritionally instructed group was better than in the control group. In the former group, protein intake decreased by 33.8%, whereas in the control group it increased by 59.1% (table 1). Although our participants did not attain exactly the prescribed value of 0.6 g protein/kg b. wt/day, the educational intervention was an important factor in controlling protein intake. In the instructed group the nutritional intervention helped participants attain values lower than 0.8 g protein/kg/day, the target value recommended by the British Renal Association [20]. In this group plasma urea showed a tendency to decrease (table 1), probably because of the lower protein intake [21]. Intakes of magnesium at the start and at the end of the study period were below the recommended values in both groups (table 1). Intakes of this element were also lower than the values documented for the adult population in our setting [22].

The nutritional recommendations made to instructed group led to them reducing protein consumption by 25 g/day and increasing that of carbohydrates by 66 g/day, approximately. In our study area, carbohydrate-rich foods constitute the most important source of magnesium (provides 18.3%) [22]. As a result of following the recommendations, the patients in this group had increased their intake of this element at the end of the study (table 1).

Renal excretion is the major route of elimination of magnesium from the body, so CRF may contribute to hypermagnesaemia. However, a compensatory decrease in tubular resorption maintains appropriate levels of urinary magnesium excretion, so that magnesium balance remains normal or slightly negative in patients with uremia. Slightly negative balances usually appear as a result of a combination of low intake and the impaired intestinal absorption of magnesium that characterizes CRF [4]. In the present study, the mean plasma concentration of magnesium in both groups was within normal limits. Despite the fact that magnesium intake was below the RDA [10], we observed only 1 case of hypomagnesaemia in the control group (table 1). It is important that patients remain within normal limits, because it has recently been suggested that hypomagnesaemia is a risk factor for sub-clinical inflammation in pre-dialysis patients [23], and a significant predictor of higher mortality in hemodialysis patients [24]. In advanced CRF (with a GFR < 15 mL/min), fractional magnesium excretion may not increase enough, and a positive ion balance may result [5]. In our study none of the participants had hypermagnesaemia (> 3.04 kcal/kg weight/day) [14], probably because of the low magnesium intake together with a GFR which, although reduced,
remained above the values reported to cause hyper-
magnesaemia (table 1) [5].
Zinc intakes at the start and conclusion of the
study period were below the recommended values
in both groups (table 1). Intakes of this element
were also lower than the values documented for
the adult population in our setting [25]. In both
groups, the zinc intake at the start of the study
period approached the value found in patients
with CRF [3].
Low-protein diets consumed by patients with
CRF can lead to low zinc intake, since in southern
Spain 40.9% of the zinc is supplied mostly by meat
[25]. The linear correlation between protein intake
and magnesium and zinc intake (figure 1) supports
the hypothesis that low-protein diets can lead to
deficient magnesium and zinc intakes.
It is currently accepted that plasma zinc concentra-
tion is a valid indicator of whole-body zinc status in
the absence of confounding factors such as infection
or stress [26]. Low circulating zinc concentrations
have been reported in CRF [2]. The cause of this
decrease is unclear, although it may be a consequence
of the low-protein diet as noted above, or a result of
reduced intake, which is often seen in the course of
CRF [11]. Zinc deficiency in CRF can also be attrib-
uted, in part, to impaired intestinal absorption,
although the cause of this impairment remains

Figure 1. Protein intake correlation with (A) Mg intake; (B) Zn intake in all patients.
Figure 2. Plasma Zn correlations with (A) Glomerular Filtration Rate (GFR); (B) Plasma protein; (C) Zn intake in all patients.
unknown [6]. The direct correlation of GFR with plasma zinc concentration suggests that as the disease progressed and GFR became increasingly impaired, plasma levels of this ion decreased (figure 2).

A high percentage of our participants had lowered plasma zinc concentrations at the start of the study period. Twelve months later the percentage of participants with zinc deficiency was reduced by half in the control group and by 80% in the nutritionally instructed group (table 1). In general, the percentage of participants with zinc deficiency at the end of the study (5%) was lower than in the healthy adult population in our geographical area (17.8%) [23]. The reduction in the proportion of control group participants with zinc deficiency was unsurprising in light of the significant increase in protein intake in this group. However, the reduction in the proportion of participants in with zinc deficiency was even greater in the instructed group, despite the fact that protein intake decreased in these participants (table 1). These results arise from the fact that during the experimental period, in the control group, 1 of the patients increased his intake of zinc, as a consequence of increased protein consumption, while the other patient’s nutritional pattern remained unchanged. In the case of the patients selected for nutritional intervention, the 5 participants considered to be zinc-deficient at the start of the study period were only mildly so (their plasma zinc levels ranged from 62-68 μg/dL). The nutritional recommendations made to this group led to them reducing protein consumption and increasing that of carbohydrates (see above) (table 1). In our study area, carbohydrate-rich foods constitute the most important source of zinc after proteins [25]. As a result of following the recommendations, the patients in this group presented a more homogeneous nutritional pattern, together with moderate increases in zinc intake (table 1). This circumstance led to the fact that by the end of the study period, four of the five patients who had presented deficiencies now had acceptable levels of plasma zinc.

The results show that the nutritional intervention benefited our participants by improving their ability to choose foods that reduced their protein intake. Moreover, our findings emphasize the importance of diet in controlling zinc intake and maintaining zinc balance during CRF without resorting to dietary supplementation. The results of this study also indicate that the dietary intervention enabled participants to better control their protein intake and zinc status without detriment to their magnesium status.

Acknowledgments

This research was supported by Plan Nacional I+D project 1FD 1997-0642.

References


