DOI: 10.1590/S0004-28032015000200004

ARQGA/1770

COPPER AND MAGNESIUM DEFICIENCIES IN PATIENTS WITH SHORT BOWEL SYNDROME RECEIVING PARENTERAL NUTRITION OR ORAL FEEDING

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ABSTRACT - ***Background*** - Patients with short bowel syndrome have significant fluid and electrolytes loss. ***Objective*** - Evaluate the mineral and electrolyte status in short bowel syndrome patients receiving intermittent parenteral nutrition or oral feeding. ***Methods*** - Twenty two adults with short bowel syndrome, of whom 11 were parenteral nutrition dependent (PN group), and the 11 remaining had been weaned off parenteral nutrition for at least 1 year and received all nutrients by oral feeding (OF group). The study also included 14 healthy volunteers paired by age and gender (control group). Food ingestion, anthropometry, serum or plasma levels of sodium, potassium, phosphorus, magnesium, calcium, zinc, iron and copper were evaluated. PN group subjects were evaluated before starting a new parenteral nutrition cycle. ***Results*** - The levels of sodium, potassium, phosphorus, calcium and zinc were similar between the groups. The magnesium value was lower in the PN group (1.0 ± 0.4 mEq /L) than other groups. Furthermore, this electrolyte was lower in the OF group (1.4 ± 0.3 mEq /L) when compared to the Control group (1.8 ± 0.1 mEq/L). Lower values of copper (69±24 vs 73±26 vs 109±16 µg/dL) were documented, respectively, for the PN and OF groups when compared to the control group. ***Conclusion*** - Hypomagnesemia and hypocupremia are electrolyte disturbances commonly observed in short bowel syndrome. Patients with massive intestinal resection require monitoring and supplementation in order to prevent magnesium and copper deficiencies.

HEADINGS - Mineral deficiency. Electrolytes. Parenteral nutrition. Short bowel syndrome.

INTRODUCTION

Short bowel syndrome (SBS) occurs when the functional mass of the small intestine is insufficient for adequate digestion of food and absorption of nutrients and fluids[21]. In the initial phase of SBS, parenteral nutrition (PN) is usually necessary and there is not an absolute criterion for weaning off PN. In the intermediate phase, the efforts are primarily devoted to intestinal adaptation to oral feeding[29]. The inability to maintain an adequate nutrition makes the patient dependent on PN therapy[34, 45]. In this situation, the therapy is focused on nutrient replacement, patient rehabilitation and the return to social activities, providing an improved quality of life[44]. Since home PN is not a therapeutic option provided by the Brazilian public health system, patients with severe malabsorptive states receive intermittent PN in our service at the Clinical Hospital of Ribeirão Preto of the University of São Paulo[7, 32]. These patients are hospitalized every 10-40 days to receive PN cycles (3-8 days), depending on symptoms such as diarrhea, dehydration, and poor nutritional status[7].

Patients with SBS have significant fluid loss, which is a difficult and common problem, especially in those with a minimal residual intestine. The majority of minerals are absorbed in the proximal small intestine, whereas most of fluids and electrolytes are absorbed in the distal small intestine and colon[21]. There is little knowledge on the bioavailability of dietary mineral and electrolytes in SBS patients. The severity of malabsorption is related to the extent of the residual intestine, the concentration of biliary salts in the intestinal lumen and the transit time[25]. Therefore, the aim of this study was to compare the serum levels of iron (Fe), copper (Cu), zinc (Zn), sodium (Na), potassium (K), magnesium (Mg), phosphorus (P) and calcium (Ca) in intermittent PN-dependent SBS patients, in subjects who had been weaned off PN and healthy volunteers.

Declared conflict of interest of all authors: none
Source of Funding: Fundacão de Amparo à Pesquisa do Estado de São Paulo (FAPESP), Brazil (Grant # 2007/52058-1).
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METHODS

This study was conducted in a university hospital from December 2007 to November 2008. The research was approved by the Institutional Ethics Committee, and all volunteers signed an informed consent. Twenty-two SBS patients were divided into two groups. The first group (PN group, n=11) consisted of PN-dependent subjects, and the second (OF group, n=11) included patients who were under oral feeding. Hemodynamically unstable subjects and those with intestinal inflammatory diseases, neoplasia, hepatic failure, and diagnoses of active infectious diseases were excluded.

The PN group consisted of SBS patients who were under intermittent PN, five women and six men, aged 50±12 years, with a median length of remaining small intestine of 25 (10-100) cm and an intestinal transit time up to 15 minutes. Intestinal resection had been performed 15 (6-88) months before, and the colon was present in six patients. For each hospitalization period, the PN group subjects received PN infused by using a totally implantable central venous catheter according to the current recommendations[1]. PN provided 1386±272 kcal (31±6 kcal/kg) daily of energy, and 51±5 g amino acids (1.1±0.2 g/kg), 222±38 g glucose (4.5±1.7g/kg) and 29±18 g lipids (0.8±0.3 g/kg) daily. A mixture of multiple trace elements containing 2.5 mg of Zn, 0.8 mg of Cu, 0.4 mg of manganese and 10 µg of chromium (Ad-element®, Darrow, Rio de Janeiro, Brazil) was added to the PN formulations. The electrolytes were calculated according to individual requirements which take into account body weight and serum levels (Na: 1.4±0.1 mEq/kg/day; K: 1.7±0.2 mEq/kg/day; Mg: 20±3 mEq/day; P: 38±2 mmol/day; Ca: 8.8±0.9 mEq/day).

Eight women and three men, aged 56±12 years, were included in the OF group. They had median length of remaining small intestine of 110 (40-210) cm, and the colon was present in nine patients. These patients had undergone intestinal resection 72 (18-180) months before, and received PN during 2 to 6 months after the intestinal resection. PN was discontinued when patients presented satisfactory evolution, at least one year prior to the study.

All SBS patients (PN and OF groups) were followed-up by a specialized outpatient service, which advised them to follow an oral diet at home and to take vitamin and mineral tablets (Centrum®, Wyeth, Richmond, VA, USA) on a daily basis. Each tablet contained 162 mg of Ca, 2 mg of Cu, 18 mg of Fe, 125 mg of P, 100 mg of Mg, 40 mg of K, 15 mg of Zn, and others.

This study also included healthy volunteers (control group, n=14), composed of five men and nine women, aged 51±8 years, who worked in the institution.

Food questionnaire and anthropometry

Composition of the habitual oral diet was assessed by a Semi-Quantitative Food Frequency Questionnaire[46]. In determining the amount of Na intake, additional table salt was not counted. Weight and height measurements were obtained by using standardized techniques, and the body mass index (BMI, kg/m^2) was determined.

Laboratorial analysis

Blood samples were collected from all volunteers after a 12-hour fasting period. PN-dependent patient arrived at the hospital after an overnight fast, and anthropometric data and blood samples were collected prior to the start of PN infusion. Serum levels of Na[2], K[2], P[16], Fe[38], Zn[38] and Cu[3] were analyzed by atomic absorption flame spectrophotometry. Mg[5] and total Ca[41] serum levels were determined by colorimetry.

Statistical analysis

Data are reported as mean ±SD or median and range, according to the distribution of the variables. The differences between groups were determined by ANOVA-F and the Tukey test for variables with normal distribution and by the Kruskal-Wallis and Dunn tests for non-parametric variables. Fisher test was used to compare categorical variables (presence or absence of deficiency). Statistical significance was set at P<0.05. Data analyses were performed with Statistica® software (version 8.0, StatSoft Inc, Tulsa, Oklahoma).

RESULTS

Despite similar macronutrient intake between the all groups (Table 1), PN-dependent SBS subjects presented lower body weight (46±6 kg in PN and 66±13 kg in OF) (P<0.01) and lower BMI (18±22 kg/m^2 in PN and 25±4 vs 29±5 kg/m^2 in OF, P<0.01), as compared to controls (76±15 kg and BMI 25±4 kg/m^2).

The PN group showed lower values of hemoglobin, mean corpuscular volume (MCV), plasma values of total protein, transferrin and total cholesterol (Table 2). No volunteer presented increased levels C-reactive protein (CRP). On the other hand, ferritin plasma levels were increased in four patients in the PN group and in three patients in the OF group. In addition, all participants presenting plasma ferritin levels above reference values also presented low plasma transferrin levels. Alpha-1-acid glycoprotein (α1-AGP) was increased in three individuals (151, 162 e 184 mg/dL) of the PN group, who did not present increased ferritin or CRP, resulting in greater mean values of α1-AGP in the PN group as compared to OF and control groups.

There was no statistical difference in the serum levels of Na, K, P, Ca and Zn between the groups (Table 3). However, Mg and Cu levels were lower in the PN group when compared to the others.

TABLE 1. Daily oral nutritional intake of patients with short bowel syndrome on intermittent parenteral nutrition (PN group), receiving oral feeding (OF group) and healthy volunteers (Control group)

	PN group (n=11)	OF group (n=11)	Control group (n=14)	RDA/AI
Energy (kcal)	2269±846	2164±885	2297±774	
Energy (kcal/kg)[a,b]	50±18	34±14	31±11	
Protein (g)	82±23	98±51	89±34	M:56/F:4
Protein (g/kg)[b]	1.8±0.3	1.5±0.7	1.2±0.5	0.8-1.2
Carbohydrate (g)	316±124	273±99	292±118	130
Lipid (g)	65±26	86±36	82±35	20-35
Sodium (mg)	1324 (467-3049)	1280 (724-3740)	1638 (624-3438)	1300
Potassium (mg)	3235 (1706-3631)	3128 (1835-4312)	3264 (1556-4795)	4700
Phosphorus (mg)	1099±444	1477±703	1308±466	700
Magnesium (mg)	313±92	375±171	400±31	M:420/F:320
Calcium (mg)[a]	562± 267	1149±470	849±407	1000
Iron (mg)	14±5	17±8	17±7	8
Zinc (mg)	10±3	11±4	11±4	M:11/F:8
Copper (mg)	1.4±0.5	1.5±0.9	1.4±0.6	0.9

a: *P*< 0.05 between PN group and OF group; b: *P*< 0.05 between PN group and Control group; RDA: recommended dietary allowances; AI: adequate intakes; M: male; F: female

TABLE 2. Clinical and nutritional laboratory data of patients with short bowel syndrome on intermittent parenteral nutrition (PN group), receiving oral feeding (OF group) and healthy volunteers (Control group)

	PN group (n=11)	OF group (n=11)	Control group (n=14)	Reference range
Blood glucose (mg/dL)	73±16	80±11	90±10	70-100
Urea (mg/dL)	22±10	32±17	29±4	15-40
Creatinine (mg/dL)	1.0±0.5	0.7±0.2	0.9±0.2	0.7-1.5
Hemoglobin (g/dL)[a,b]	11.5±1.6	13.2±1.5	14±1.4	M:13.5-17.5/ F:12-15.5
MCV (fL)[c]	94±4	96±5	90±4	82-98
Leukocytes ($10^3/mm^3$)	6.0±1.2	5.8±1.6	6.7±2.0	4-11
Lymphocytes ($10^3/mm^3$)	1.7±0.6	1.8±0.6	1.8±0.5	>1000
Total Proteins (g/dL)[a,b]	6.1±0.5	6.7±0.5	6.8±0.3	6.4-8.2
Albumin (g/dL)	3.9±0.7	4.2±0.4	4.3±0.1	3.5-5.0
Transferrin (mg/dL)[a,b]	140±61	202±98	202±29	250-310
Total bilirubin (mg/dL)	0.6±0.3	0.6±0.3	0.7±0.2	0.2-1.2
AST (U/L)	25 (17-327)	25 (7-35)	23 (18-44)	15-37
ALT (U/L)	30 (20-145)	29 (14-50)	23 (12-88)	30-65
CRP (mg/dL)	0.3±0.3	0.3±0.3	0.2±0.04	≤0.5
Ferritin (ng/mL)	326 (17-1475)	96 (32-861)	106 (5-495)	M:28-397/F:6-159
α1-AGP (mg/dL)[a,b]	121±43	73±21	79±18	50-120
Cholesterol (mg/dL)[a,b,c]	87±21	151±45	208±25	< 200
Triglycerides (mg/dL)	113±49	100±41	129±73	<150

a: *P*< 0.05 between PN group and OF group; b: *P*< 0.05 between PN group and Control group; c: *P*< 0.05 between OF group and Control group. MCV: mean corpuscular volume; AST: aspartate aminotransferase; ALT: alanine aminotransferase; CRP: C-reactive protein; α1-AGP: alpha1-acid glycoprotein; M: male; F: female.

TABLE 3. Serum concentration of minerals and electrolytes in patients with short bowel syndrome on intermittent parenteral nutrition (PN group), receiving oral feeding (OF group) and healthy volunteers (Control group)

	PN group (n=11)	OF group (n=11)	Control group (n=14)	Reference range
Sodium (µmol/L)	140±3	141±3	139±2	135-145
Potassium (µmol/L)	3.7±0.6	4.2±0.6	4.1±0.5	3.5-5.0
Phosphorus (mg/dL)	3.4±1	3.6±1.1	3.6±0.4	2.5-4.9
Magnesium (mEq/L)[a,b,c]	1.0±0.4	1.4±0.3	1.8±0.1	1.5-2.3
Calcium total (mg/dL)	8.8±1.0	9.2±0.9	9.4±0.3	8.5-10.1
Iron (mg/dL)	102±37	83±27	88±24	35-140
Zinc (µg/dL)	68±25	84±37	90±9	50-120
Copper (µg/dL)[b,c]	69±24	72±26	109±16	70-140

a: *P*<0.05 between PN group and OF group; b: *P*<0.05 between PN group and control group; c: *P*<0.05 between OF group and Control group.

Hyponatremia and hypoferremia were not observed in SBS patients. Figure 1 shows the number of patients with serum levels of K, P, Mg, Ca, Zn and Cu below reference values. Hypomagnesaemia (P=0.03, Fisher's exact test) was more frequent in the PN group when compared to the OF group. No abnormalities in the electrolyte and mineral levels in the control group volunteers were observed, except for a slight hypokalemia in one individual who was using diuretics for the treatment of arterial hypertension.

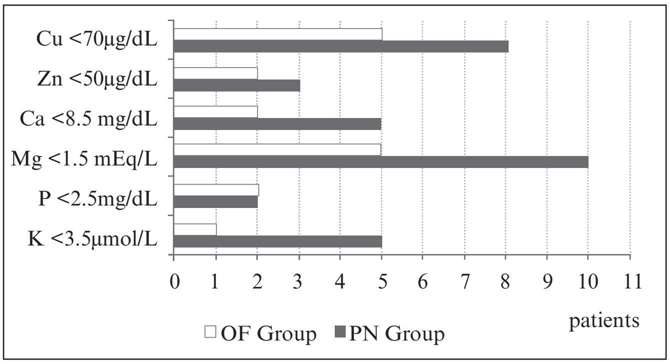

FIGURE 1. Amount of patients with short bowel syndrome who presented serum levels of electrolytes and minerals below the reference values in the PN group (n=11) and OF group (n=11).

DISCUSSION

In the present study, low Cu and Mg serum levels were observed in patients with intestinal resection as compared to healthy volunteers, especially in those under intermittent PN. There were no differences in the serum levels of Na, K, P, Ca, Fe and Zn between the groups, and apart from Na and Fe within normal range, all mineral values were lower than reference values.

In this study, hypomagnesaemia was highly prevalent in both PN-dependent patients and in those under oral feeding. Mg deficiency is often present in hospitalized patients[10] and is common in SBS[37], regardless of the short intestine's absorptive capacity and the length of the residual jejunum[31]. In a retrospective study of 15 patients with severe intestinal resection, 66% presented hypomagnesaemia[30]. In normal conditions, 25% to 60% of dietary Mg is absorbed in the gastrointestinal tract[36]. In patients with severe SBS, net Mg absorption is very low or slightly negative[25], and a positive balance is only obtained with parenteral Mg supply[25, 30]. Fatty acids, derived from the digestion of fat or bacterial carbohydrate fermentation, bind to Mg and result in insufficient absorption[31]. In normal conditions, the kidneys are responsible for regulating the total body content of Mg[39]. This regulation depends on glomerular filtration, volume status and various metabolic states[36], including the acid load in the body[40]. Lactic acidosis is a consequence of SBS[6, 48], but there are no available studies describing the influence of the acid-base status on renal Mg excretion in SBS patients.

In the present study, the PN-dependent individuals presented lower hemoglobin values with no evidence of macrocytosis, microcytosis or reduced serum Fe levels. In patients under home PN, 73% presented normochromic anemia[8], and 55% had evidence of iron-deficiency anemia, ascribed to mild Fe loss from the gastrointestinal tract[23]. However, Fe serum levels were normal in tissue samples obtained from the autopsy of SBS patients who were under home PN[17]. Our patients did not receive intravenous Fe and all of them were advised to take Fe sulfate tablets, which may contribute to the maintenance of serum Fe levels within normal range in SBS individuals[15].

PN-dependent patients presented high plasma ferritin levels and low plasma transferrin, indicating an iron overload due to excessive supplementation via Fe sulfate tablets. In this context, the mechanism of anemia observed in these patients may be more related to low protein status rather than Fe status.

In our study, the patients who had been weaned off PN presented higher MCV, which may in its turn be caused by Cu deficiency[14, 43]. Cu deficiency was common in our SBS patients, especially among those who depend on PN. Such results can't be explained by an insufficient IV Cu replacement, since the pharmaceutical form routinely used in SBS exceeded the recommended amount[1]. The intermittent PN infusion scheme and diminished Cu absorption capacity may explain the mechanism underlying Cu deficiency in SBS patients. In addition, the possibility of an increased Cu depletion due to the activity of cuproenzymes such as the antioxidant superoxide dismutase, cannot be ruled out[19].

Different from our findings, 67% of children with intestinal failure presented Zn deficiencies as they transitioned from PN to enteral nutrition[47]. On the other hand, a modest elevation in Zn levels was observed in tissue samples from autopsied PN-dependent SBS patients[28]. Plasma or serum Zn concentrations are most widely used to measure Zn status, however, these values may be negatively affected by factors other than those related to Zn losses[27, 28].

Ca consumption in the PN group was lower than in the OF group, probably due to nutritional instructions for limiting milk and dairy products' intake, or insufficient supplementation[13]. Also, similarly to our results, approximately one third of home PN patients present hypocalcemia[8]. Its main mechanism is ascribed to Ca precipitation with unabsorbed fatty acids[35], which result in a less effective absorption[12] and consequent calcium loss in stools[25]. Also, a large supply of parenteral amino acid may induce excessive calcium loss by urine[4]. On the other hand, a preserved colon may play an important role in calcium absorption in patients with extensive small bowel resection[18]. Accordingly to our results, phosphorus deficiency was uncommon in SBS patients under long-term PN, because of adequate oral intake and phosphorus absorption[25].

Similarly to our findings, Na deficiency has not been reported in patients receiving long-term PN due to SBS[24, 26]. Fecal Na loss is excessive when the colon is absent and results in extremely low Na excretion in the urine[24]. Although mean values of K serum levels were similar between the SBS patient groups (PN and OF), a greater number of individuals with K deficiency was found in the PN group. Subjects with remaining jejunum length ranging from 50 cm to 150 cm absorb around 60% of dietary K[24]. Besides, malnourished adults present lower K serum levels than those with a normal nutritional status[11]. We can't reject the hypothesis that the K serum levels in PN group may be a reflection of renal insufficiency at some extent.

Deficiencies of electrolytes and minerals observed in this study can't be explained by an inadequate intake, even though eating stimulates enteric losses rich in these elements[15]. An intestinal biopsy was not performed, which could indicate adaptive changes in the mucosa. After proximal small bowel resections, the ileum is capable of adapting to the loss of absorptive surface area by increased villous height and crypt depth[9]. This adaptive mechanism effectively increases the absorption of water, electrolytes, and nutrients to maintain adequate hydration and nutrition[20]. Furthermore, patients with SBS with severe malabsorption present adaptive colonic changes that include an increased absorptive surface with an unchanged proliferative/apoptotic ratio and well-preserved absorptive protein transporters[22].

The assessment of mineral and electrolyte levels in PN-dependent patients is difficult to perform because of many confounding factors. We performed blood collection before the start of PN infusion, since blood mineral and electrolyte levels may be influenced by the infusion and consequently not reflect tissue concentrations. Even by taking these precautions, serum levels may not be as reliable as careful balance studies[15]. Decreased mineral and electrolyte serum levels may be indicative of real deficiencies or redistribution-related deficiencies. Although the acute inflammatory response does not affect erythrocyte concentrations of Cu[33]**,** acute phase reactions related to infectious or inflammatory conditions may cause a redistribution of minerals[42]. In this context, Mg and Cu deficiencies in SBS patients under PN may be a result of an inflammatory process, since some of these patients also presented increased g1-AGP, which is an acute-phase marker. Even in the absence of clinical signs of infection, the increase in g1-AGP levels may be associated with the presence of totally implantable venous catheters and PN infusion. This interpretation is corroborated by the fact that patients in the OF group also presented decreased Cu and Mg but 1-AGP levels within normal range. Besides, changes in serum levels of minerals may be more related to changes in the trace-element-binding proteins' concentration rather than a reflection of deficiencies. Also, alterations in the acid-base balance may influence the urinary excretion of cations, leading to mineral deficiencies.

In conclusion, hypomagnesaemia and hypocupremia were highly prevalent in PN-dependent patients, and K, Ca and Zn deficiencies were also common. SBS patients who had been weaned off PN for a long time are still at risk of Cu and Mg deficiencies. These patients need a long-term follow-up and an intensive nutritional care in order to prevent electrolyte and mineral deficiencies. The treatment of patients with SBS requires a multidisciplinary approach and any potential complicating factor must be identified, closely monitored and treated early.

Authors' contributions

All authors have contributed significantly to the design, execution, analysis and writing of the final submitted version, and share responsibility for the contents of the paper.

Braga CBM, Ferreira IML, Marchini JS, Cunha SFC. Deficiência de cobre e magnésio em pacientes com Síndrome do Intestino Curto sob nutrição parenteral ou alimentação por via oral. Arq Gastroenterol. 2015,52(2):94-9.

RESUMO - ***Contexto*** - Ressecções intestinais extensas resultam em perda de fluídos e eletrólitos. ***Objetivo*** - Avaliar os níveis séricos de minerais e eletrólitos em pacientes com síndrome do intestino curto, dependentes ou não de nutrição parenteral. ***Métodos*** - O estudo incluiu 22 adultos com síndrome de intestino curto, sendo 11 dependentes de nutrição parenteral (Grupo NP) e 11 sujeitos que recebiam todo aporte nutricional por via oral (Grupo VO). Foram incluídos 14 voluntários saudáveis, pareados para a idade e o gênero (Grupo Controle). A avaliação da ingestão alimentar, antropometria, níveis sanguíneos de sódio, potássio, fósforo, magnésio, cálcio, zinco, ferro e cobre foram documentados em todos os voluntários. ***Resultados*** - Os níveis sanguíneos de sódio, potássio, fósforo, cálcio e zinco foram similares entre os grupos de estudo. Os níveis séricos de magnésio foram menores no Grupo NP (1,0±0,4 mEq/L) em relação aos demais grupos. Além disso, a concentração desse eletrólito foi menor no Grupo VO (1,4±0,3 mEq/L) em relação ao Grupo Controle (1,8±0,1 mEq/L). Foram documentados menores valores cobre (69±24 vs 73±26 vs 109±16 µg/dL) nos grupos NP e VO quando comparados com o Grupo Controle, respectivamente. ***Conclusão*** - Hipomagnesemia e hipocupremia são distúrbios eletrolíticos comumente observados na síndrome de intestino curto. Os pacientes com ressecção intestinal extensa requerem monitorização e suplementação de magnésio e cobre a fim de prevenir deficiências.

DESCRITORES - Deficiência de minerais. Eletrólitos. Nutrição parenteral. Síndrome do intestino curto.

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Received 18/9/2014
Accepted 28/11/2014