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Serum copper evolution in patients that underwent endoscopic gastrostomy for long term enteral feeding

Evolución del cobre sérico en pacientes sometidos a gastrostomía endoscópica para nutrición enteral a largo plazo

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Abstract

Background and aims: Copper (Cu) is a well studied trace element but little is known about Cu evolution in long term endoscopic gastrostomy (PEG) feeding. We aimed to evaluate the evolution serum Cu since the gastrostomy until 12 weeks after the procedure in PEG patients fed with homemade meals.

Methods: A prospective observational study was performed evaluating serum copper, albumin, transferrin and body mass index (BMI) at the time of the gastrostomy, 4 weeks and 12 weeks after. Data also included age, gender, NRS 2002 and nature of the underlying disease causing dysphagia: head and neck cancer (HNC) or neurological dysphagia (ND). After gastrostomy, patients were fed with homemade PEG meals.

Results: One hundred and forty-six patients enrolled, 89 men, aged 21-95 years, 90 with neurologic dysphagia (ND), and 56 with head and neck cancer (HNC). 78 (53%) showed low BMI. Initially, Cu ranged 42-160 µg/dl (normal: 70-140 µg/dl); 130 patients (89%) presented normal Cu, 16 (11%) presented hypocupremia, 53% low albumin (n = 77), and 94 (65%) low transferrin. After 4 weeks, 93% presented normal Cu, 7% presented hypocupremia, low albumin was present in 34%, and low transferrin in 52%. After 12 weeks, 95% presented normal Cu, 5% presented hypocupremia, low albumin was present in 25%, and low transferrin in 32%. Comparing age, gender, underlying disease, BMI, albumin and transferrin, there were no significant differences on serum Cu.

Key words:

Copper. Gastrostomy. PEG. Enteral feeding.

Conclusions: Most patients present normal serum Cu when gastrostomy is performed. For patients presenting hypocupremia before gastrostomy, homemade meals are effective for normalizing serum Cu.

Resumen

Introducción y objetivos: el cobre (Cu) es un oligoelemento muy estudiado, pero poco se sabe de su evolución en los pacientes alimentados por gastrostomía endoscópica (GEP). Pretendemos evaluar la evolución del Cu sérico desde la gastrostomía hasta 12 semanas después de la intervención en estos pacientes alimentados con preparaciones domésticas.

Métodos: realizamos un estudio observacional prospectivo para evaluar el Cu sérico, la albúmina, la transferrina y el índice de masa corporal (IMC) en el momento de la GEP, tras 4 semanas y 12 semanas después de la intervención. Los datos incluyen edad, género, NRS 2002 y enfermedad subyacente: cánceres de cabeza y cuello (CCC) y disfagia neurológica (DN). Después de la intervención, estos pacientes fueron alimentados con preparaciones domésticas.

Resultados: 146 enfermos (89 hombres), entre 21-95 años: CCC-56, DN-90. Valores de Cu entre 42-160 µg/dl (normal: 70-140 µg/dl); normales 89% (n = 130); bajos 11% (n = 16), albúmina baja: 53% (n = 77), transferrina baja: 65% (n = 94), IMC bajo: 53% (n = 78). Después de 4 semanas: valores normales de Cu en 93% y bajos en 7%, albúmina baja en 34%, transferrina baja en 52%. Tras 12 semanas: valores normales de Cu en 95% y bajos en 5%, albúmina baja en 25%, transferrina baja en 32%. No encontramos diferencias significativas en el Cu sérico cuando se compara edad, género, enfermedad subyacente, IMC, albúmina y transferrina.

Palabras clave:

Cobre. Gastrostomía. GEP. Nutrición enteral.

Conclusiones: la mayoría de los enfermos presentan Cu sérico normal en el momento de la gastrostomía. Para los enfermos con Cu sérico bajo antes del procedimiento, la alimentación con preparaciones domésticas parece suficiente para su normalización progresiva.

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INTRODUCTION

Trace elements (TE) are inorganic elements that are required in small quantities for normal metabolic functions. Frequently, TEs are cofactors of enzymes or part of them. Copper (Cu) is one of the most studied trace elements and the third most abundant transition metal in the human body, just after Iron (Fe) and Zinc (Zn). It can present four different oxidation states (Cu^0, Cu^{+1}, Cu^{+2} e Cu^{+3}), with a predominance of Cu^{+2} (1,2). It is the cofactor of several fundamental enzymes: cytochrome-c oxidase, lysyl oxidase, CuZn superoxide dismutase, methane monooxigenase, tyrosinase and ceruloplasmin (3,4). Several Cu dependent mechanisms have been studied in the angiogenesis process, as growth promoting agents and as other cancer relevant signaling agents. Cu is present in a wide variety of foods. The richest categories are vegetables, sea food (oysters), liver and kidneys, muscle meat, chocolate, nuts, cereal grains, vegetables and dried fruits.

Cu deficiency is associated to neurological features, mostly polyneuropathy and myelopathy (5). Vascular changes associated to Cu deficiency are due to a lack of a cross-link in collagen and elastin leading to aneurism and arterial dissections (6). Cu deficiency is also associated with normocytic anemia, leukopenia e neutropenia (7). Given its metabolic importance, subclinical deficiencies need to be accounted for, particularly in patients and groups of risk. Health care teams should be ready to provide an early intervention, through dietary changes or supplementation, in order to correct Cu deficiency.

The indications for enteral feeding include all the situations when oral intake is not sufficient or safe, including neurological or mechanical dysphagia, esophagus narrowing for benign or malign condition, and critically ill patients (8-12). The selection of the delivery route of enteral nutrition is dependent on the time foreseen for this feeding option. Percutaneous endoscopic gastrostomy (PEG) is the gold standard for long term (> 3 weeks) enteral feeding.

Little is known about serum Cu evolution in long term PEG feeding. We aimed to evaluate serum Cu in home PEG feeding patients fed with homemade meals, assessing serum Cu when PEG is performed and in the follow-up period after 4 and 12 weeks. Also, we aimed to evaluate serum Cu variations with age, gender, underlying disease, body mass index and serum proteins.

SUBJECTS AND METHODS

This prospective observational study was conducted in the Artificial Feeding outpatient's consultation of our hospital, from October 2011 to October 2013. According to the underlying disease causing dysphagia, patients were included in one of two groups: a) head and neck cancer (HNC) including oral cavity, pharynx, larynx and esophageal proximal cancer; and b) neurological dysphagia (ND) including acute and chronic disorders.

The inclusion criteria included:

1. Indication for endoscopic gastrostomy with dysphagia longer than 3-4 weeks.
2. Previous intake 50% under their caloric needs.
3. After gastrostomy, patients should be fed with homemade diets through PEG.
4. Complete medical records should be available.
5. Patients had to be clinically stable.

All patients were evaluated by the Enteral Feeding Team at the time of the PEG procedure, and after 4 weeks and 12 weeks, using always the same protocol. The assessment of previous intake before PEG was performed with a retrospective dietary recall. After the gastrostomy procedure patients were fed with homemade meals because in Portugal enteral feeding products are not refunded, which makes them too expensive for most patients. Homemade meals were prescribed according to each patient nutritional need. In each case the patient and/or a family member or caregiver was trained in home tube feeding, including diet administration and monitoring complications. Collected data included:

1. Age and gender.
2. Underlying disease causing dysphagia (classified as HNC or ND).
3. Nutritional Risk Screening 2002 (NRS 2002).
4. Body mass index (BMI).
5. Serum albumin, transferrin and Cu concentrations.

NUTRITIONAL RISK IDENTIFICATION

For nutritional screening we used the tool recommended by ESPEN, the Nutritional Risk Screening - NRS 2002 (13).

GLOBAL NUTRITIONAL ASSESSMENT

Most patients presented speech impairments that were caused by the same underlying disorders causing dysphagia. For these patients, global nutritional assessment relied mostly in objective data, anthropometry and serum data, including albumin and transferrin. Body mass index (BMI) was obtained as body weight/height squared in most patients. If patients were bedridden and could not stand up, BMI was estimated using the mid upper arm circumference and regression equations described by Powell-Tuck/Hennessy, which had been previously used by our group (14,15). Malnutrition was defined as a BMI < 18.5 kg/m^2 for adult patients younger than 65 years and < 22 kg/m^2 for patients with 65 years or older (16). Although serum proteins may be influenced by a wide range of non-nutritional factors, albumin < 3.5 g/l and transferrin < 200 mg/dl were considered as suggestive of malnutrition.

BLOOD SAMPLES ASSAYS

A blood sample was obtained minutes before the gastrostomy procedure, between 8:00 and 10:00 AM following at least 12 hours of fasting. Part of the blood sample was used for the standard PEG patient evaluation, including serum proteins. Other part of the blood sample was split into specifically designed metal-free tubes for Cu assessment. Serum Cu samples were assayed using ICP-AES

– inductively coupled plasma-atomic emission spectroscopy (washing solution 5% HNO3 in water, Fluka® patterns 1,000 mg/L). We considered 70-140 µg/dl as normal reference values for Cu (17,18).

Statistical analysis

The influence of gender and the underlying disease in Cu values in the three stages of evaluation was performed with a mixed ANOVA for repeated measurements. The applicability of assumptions, including data normality and sphericity of the variance-covariance matrix, were evaluated, respectively, by the Shapiro-Wilk test (p's > 0.05) and the Box M test (p's > 0.05). To study the Cu relation with age and proteins, we used Pearson correlation coefficient. All the results are considered to be significant for a 5% significance level.

ETHICAL CONSIDERATIONS

This study was approved by the Hospital Ethics Committee. All subjects and/or their families were informed of the purpose and procedures of the study and gave their informed consent.

RESULTS

CHARACTERISTICS OF THE STUDY POPULATION

A total of 146 dysphagic patients performed PEG and were enrolled in the study, 89 men and 57 women, aging from 21 to 95 with a mean age of 68.2 years (SD = 14.2) and a median age of 68 years. Of these patients, 90 were 65 or older (Table I).

Dysphagia from neurologic disease (ND) was the most common diagnosis (90 patients), comprising strokes (29 patients), dementias (20), neurosurgical injuries (24), amyotrophic lateral sclerosis (6) and other neurological diseases (11). The second cause of dysphagia was head and neck cancer (HNC), with 56 patients. This group comprises cancers that were located in the oral cavity (10), larynx (15), pharynx (20), and proximal esophagus (11).

Before the PEG procedure, all patients had dysphagia for at least one month. All of them had prior intake under 50% of daily caloric needs. Nutritional risk screening (NRS-2002) presented a ≥ 3 score in all patients, signaling nutritional risk. All patients were clinically stable at the moment of PEG and sample collection (unstable patients were postponed).

INITIAL EVALUATION (TABLE II)

Copper serum concentrations

A total of 146 patients were evaluated, Cu ranging 42-160 µg/dl (normal range: 70-140 µg/dl), with a mean of 97.23 ± 25.6 µg/dl

Table I. Characteristics of the study population (n = 146)

Characteristics n = 146	
Age	*Years*
Max.	95
Min.	21
Mean (SD)	68.2 (14.2)
Median	68
≥ 65 years	90
< 65 years	56
Gender	
Female	57
Male	89
Group diagnosis:	
Head neck cancer (HNC)	56
Oral cavity	10
Pharynx	20
Larynx	15
Proximal esophagus	11
Neurological dysphagia (ND)	90
Stroke	29
Dementia	20
Neurosurgical injury	24
Amyotrophic lateral sclerosis	6
Other disorders	11

Table II. Evolution of copper, albumin, transferrin and BMI

	T0	T1	T3
Copper (µg/dl) Mean ± SD	n = 146 97.23 ± 25.6	n = 89 96.96 ± 17.1	n = 40 98.5 ± 19.4
< 70 µg/dl ≥ 70 µg/dl	11% (16) 89% (130)	7% (6) 93% (83)	5% (2) 95% (38)
Albumin (g/dl) Mean ± SD	n = 144 3.4 ± 0.35	n = 89 3.66 ± 0.07	n = 40 3.82 ± 0.09
< 3.5 g/dl ≥ 3.5 g/dl	53% (77) 47% (67)	34% (30) 66% (59)	25% (10) 75% (30)
Transferrin (mg/dl) Mean ± SD	n = 144 184 ± 0.6	n = 89 197 ± 6.5	n = 40 208 ± 8.1
< 200 mg/dl ≥ 200 mg/dl	65% (94) 35% (50)	52% (46) 48% (43)	32% (13) 68% (27)
BMI (Kg/m^2) Low BMI Normal BMI	n = 146 53% (78) 47% (68)	n = 89 54% (48) 46% (41)	n = 40 48% (19) 52% (21)

and a median of 92 µg/dl. Most patients, 130 (89%), were within the normal range. Only 16 (11%) presented hypocupremia, 13 from the ND group and 3 from the HNC group. No statistically significant differences were detected between both groups (HNC and ND) ($t_{144} = 0.059$, $p = 0.953$). The elderly patients group presented 13% of low values, a higher percentage than the one presented by the younger group (6%).

Albumin and transferrin serum concentrations

Albumin and transferrin were evaluated in 144 patients. Regarding albumin, we obtained a mean of 3.4 g/dl ± 0.35 and a median of 3.4 g/dl, ranging from 1.4 to 5.2 g/dl (normal range 3.5-5 g/dl). More than half of the patients (53%, n = 77) presented low albumin. Regarding transferrin, we obtained a mean of 184.0 mg/dl and a median of 183 mg/dl, ranging from 74 to 331 mg/dl (normal range 200-300 mg/dl). Two thirds, 94 patients (65%), presented low transferrin. Almost half, 66 patients (46%), presented low levels of both proteins.

Body mass index

Most of the patients had the BMI calculated from Quetelet's equation kg/m^2. Only in 62 (42.5%) cases (53 ND, 9 HNC) BMI was estimated using the mid upper arm circumference and regression equations described by Powell-Tuck/Hennessy. Among the 146 patients, 78 (53%) showed low BMI (< 18.5 kg/m^2 for patients younger than 65 and < 22 kg/m^2 for patients of 65 years of age or older). When we divided the study population according to the cause of dysphagia, 47 patients from the ND group presented a low BMI (52%) while in HNC group 31 patients also presented a low BMI (55%). In the group of older patients, 58 (64%) presented low BMI, while in the younger group only 20 (36%) presented low BMI.

FOLLOW-UP

After 4 weeks of PEG procedure, 89 patients were followed up (56 men, 33 women). Twenty five patients died and 29 were lost to follow-up. Three patients were not compliant with PEG feeding and their tube was removed. From these 89 patients, 83 (93%) had Cu into normal range and 6 (7%) had low values.

Cu: Among the initial 16 patients with low Cu, 3 patients maintained their low values, 3 improved their values, 3 were lost to follow-up, and 7 died. From the initial 130 patients with normal Cu, 80 maintained their values and 3 decreased their values. Looking at the two main study groups we found a similar mean for Cu, 98.5 µg/dl in HNC and 96 µg/dl in ND.

Albumin: Regarding the 89 patients, 30 (34%) had values under normal, and 59 (66%) patients had normal values. From the previous evaluation (T0) 39 patients maintained their normal values, 25 maintained low values, 4 decreased values and 21 increased their values from low to the normal range. Looking at the two main study groups we found a similar mean for albumin, with 3.9 g/l from HNC and 3.53 g/l from ND.

Transferrin: Among these 89 patients, 46 (52%) had values under normal, and 43 (48%) patients presented normal values. From the previous evaluation (T0) 25 patient maintained their normal values, 38 maintained low values, 6 decreased values and 20 increased their values from low to normal range. Looking at the two main study groups (HNC and ND) we found a similar mean, with 205.37 mg/dl for HNC and 187.72 mg/dl for ND.

BMI: In relation to the youngest group we found a BMI mean of 19.88 kg/m^2, and among the older group we found a mean of 20.98 Kg/m^2. Looking into the two main study groups we found a mean of 19.88 kg/m^2 for HNC and 20.82 kg/m^2 for ND. According to age and the underlying disease, we found a mean of 19.86 kg/m^2 for HNC and 20.43 kg/m^2 for ND in the youngest group, and 19.91 kg/m^2 and 21.20 kg/m^2 for HNC and ND, respectively, in the older one. No significant differences were found.

After 12 weeks of PEG feeding, 40 patients were followed up. Ten patients died between the 4th and the 12th week after gastrostomy. Thirty seven were lost to follow-up and two patients had their PEG removed.

Cu: Thirty eight patients (95%) had serum Cu concentration into normal range and 2 (5%) under normal range.

From the previous evaluation with 83 patients with normal Cu, 34 were lost to follow-up, 36 maintained their values, 9 died and PEG was removed from two. Among the patients with low values, 3 died, 2 improved their values and 2 were lost. Looking at the two main study groups we found a similar mean for Cu, 93.81 µg/dl in HNC patients and 101.7 µg/dl in ND.

Albumin: Thirty (75%) patients had normal values, while 10 (25%) had values under normal range. From the previous evaluation of these 40 patients (T1), 28 maintained normal values, 8 maintained low values, 3 increased their values from low to normal range and 1 decreased to low range. Looking at the two main study groups we found a similar mean for albumin, with 4.06 g/l in HNC and 3.57 g/l in ND.

Transferrin: Among these 40 patients, 27 (68%) had normal values while 13 (32%) were under normal range. From the previous evaluation of these 40 patients (T1), 21 maintained values into normal range, 7 improved their values into normal range, 11 maintained their values low and 1 decreased to low values. Looking at the two main study groups we found a similar mean for transferrin, with 226.12 mg/dl from HNC and 211.61 mg/dl from ND.

BMI: Regarding the youngest group, we found a mean of BMI of 20.22 kg/m^2, and a mean of 21.51 kg/m^2 regarding the oldest group. Looking at the two main study groups we found a mean of 20.46 kg/m^2 for HNC and 20.48 kg/m^2 for ND. According to age and the underlying disease, we found a mean of 20.78 kg/m^2 from HNC and 18.99 kg/m^2 from ND in the youngest group, and 20.14 kg/m^2 and 21.96 kg/m^2 from HNC and ND, respectively, in the oldest group. No significant differences were found.

EVOLUTION OF CU CONCENTRATION AFTER FOUR AND TWELVE WEEKS AND ITS RELATIONSHIP WITH PROTEINS AND UNDERLYING DISEASES (TABLE III)

It was not detected simultaneous significant influence the etiology and time the Cu values (statistics with sphericity, F_{2s} = s0.235, p = 0.790, non-centrality parameter = 0.472, observed power = 0.086). Considering only the three evaluation moments, no significant changes were detected (statistics with sphericity, F_2 = 1.215, p = 0.302, non-centrality parameter = 2.430, observed power = 0.258). Considering now only etiology, there were no statistically significant differences detected (statistics with sphericity, F_1 = 1.651, p = 0.207, non-centrality parameter = 1.651, observed power = 0.240) (Fig. 1). Although no differences are detected, the analysis of figure 1 shows that the group with ND has higher Cu values in any of the evaluation moments.

With regard to gender, the analysis had to be performed separately for men and women, since there were no females presenting head and neck cancer. In relation to male gender, results were similar to those obtained previously (Fig. 2, gender: male). Although no differences are detected, it can be deduced from the analysis of figure 2 (gender: male), that the group with ND has higher Cu values in any of the evaluation moments it is the identical behavior to the general.

As for the females, and only for ND etiology, no statistically significant differences between the three evaluation moments were detected, as shown in figure 2 (gender: female). Analyzing the graph of figure 2 (gender: female), it is found that Cu values increased over time, and their different behavior in males with ND can be observed.

No significant correlations were detected between Cu values and age, albumin, transferrin, hemoglobin and Zn in any of the evaluation moments (Table III).

DISCUSSION

Cu plays a role as a cofactor for various enzymes in the human body and it is essential for the structure and functioning of the nervous system (19). Cu deficiency is associated with increased osteoporosis, poor immune response, impairment of hematopoiesis and neurologic disorders (20,21). The main causes of non-inherited Cu deficiency are deficient income and malabsorption (22). Hypocupremia had been associated with age, gender and smoking habits.

In the literature Cu deficiency is rarely identified in enteral feeding (23). Our results also suggest that Cu deficiency in dysphagic patients that underwent enteral feeding is unusual. When patients were proposed to PEG feeding, hypocupremia was identified only in 16 (11%) patients. Even with a prior low caloric intake of less

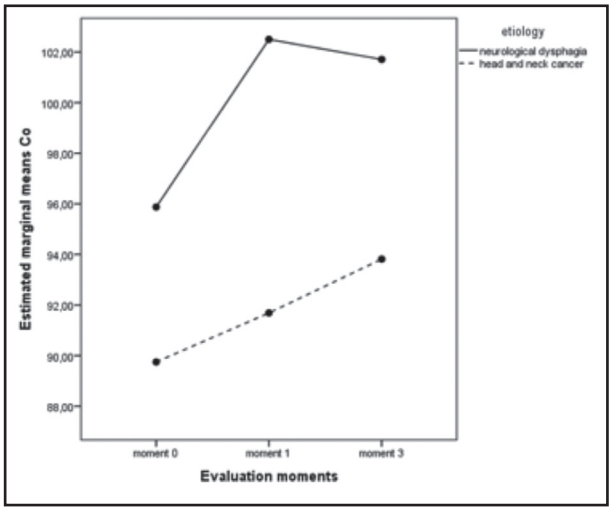

Figure 1.
Estimated marginal means to copper.

Table III. Pearson correlation coefficients to study the relationship between Cu and age and proteins (albumin, transferrin)

	Cu 1	Cu 3	Age	Albumin 0	Albumin 1	Albumin 3	Transferrin 0	Transferrin 1	Transferrin 3
Cu 0	0.531**	0.581**	- 0.032	0.099	0.019	0.126	0.011	- 0.028	- 0.067
Cu 1		0.638**	- 0.133	- 0.025	- 0.018	- 0.211	- 0.036	0.021	0.105
Cu 3			0.133	- 0.096	0.027	0.070	0.063	0.030	0.215
Age				- 0.337**	- 0.263**	- 0.238	- 0.094	- 0.131	- 0.151
Albumin 0					0.615**	0.658**	0.690**	0.559**	0.316*
Albumin 1						0.797**	0.386**	0.599**	0.315*
Albumin 3							0.317*	0.394**	0.342*
Transferrin 0								0.607**	0.495**
Transferrin 1									0.345*
Transferrin 3									

**Correlation is significant at the 0.05 level (2-tailed). **Correlation is significant at the 0.01 level (2-tailed).*

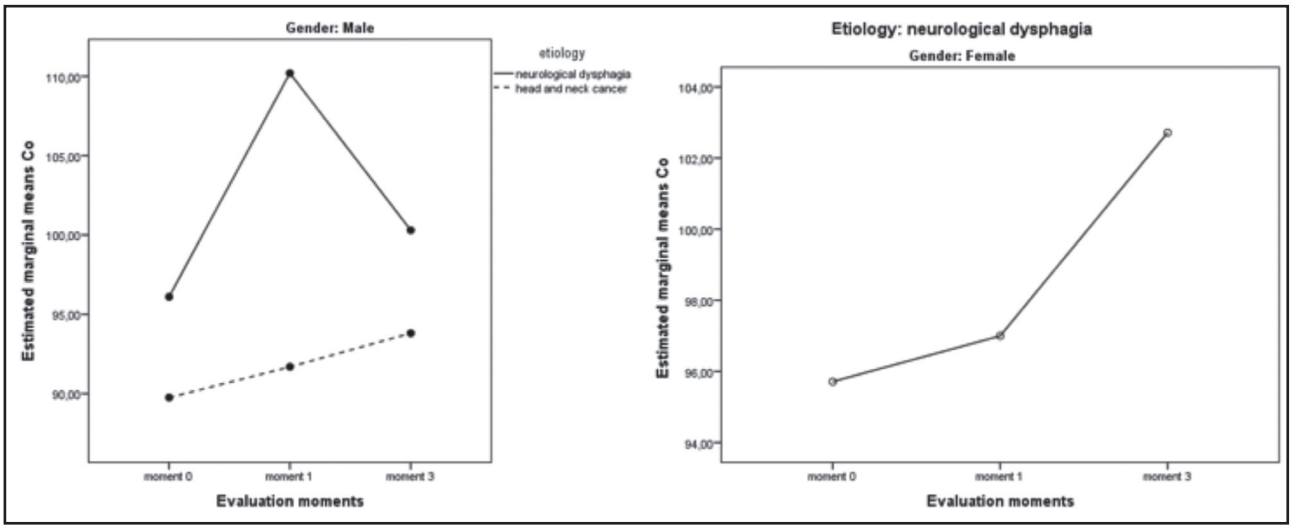

Figure 2.

Estimated marginal means to copper, for male and female.

than 50% of daily caloric needs, most patients maintained acceptable Cu values.

Analyzing the behavior of Cu in relation to other factors that had been usually associated with hypocupremia such as age, gender and smoking habits we found results which suggest that there is no relationship with any of them. We did not find any significant influence of gender or age in Cu values in the three stages of evaluation. Also, no correlation between Cu and serum proteins, albumin, and transferrin was found.

From the Cu deficiency group we found a high number of patients with ND (13 from ND and 3 from the HNC group), but we did not find significance of the influence of the underlying disease (ND or HNC) in Cu values in the three stages of evaluation. Finally, although we did not record smoking habits, it is known that virtually all HNC patients present heavy smoking habits. and there was no significant difference regarding ND patients. This suggests that smoking may not be of major importance, concerning serum Cu of PEG patients.

Home enteral feeding is the good choice for enteral feeding, because it presents low cost when compared with hospital stay, low infections rated, and it allows the patients to stay at home in a comfortable environment. Most of our patients went home after PEG was performed. All of our patients are fed with enteral homemade meals, because industrialized formulas are expensive and they are not reimbursed in our country, so their continued use is impractical for low-income families (24). The most common gastrostomy homemade meals are soups with mixed meat and fish, fruit juice, daily products with mixed cereals, and milky flour. Sometimes it is difficult to reach the desired caloric intake with homemade diet because manipulated foods are diluted due to the tube gauge and, also, the capacity for tolerating bolus is sometimes diminished (25). Nevertheless, hypocupremia was identified only in a few patients, 11% before PEG, 7% after 4 weeks PEG feeding and 5% after 12 weeks. Long term dysphagia seems to induce hypocupremia only in a very small fraction of PEG patients and homemade PEG meals seem to be effective for normalizing serum Cu. This could be explained in part because Cu is widely distributed in food and the major contributors of Cu include organ meats (liver and kidneys), muscle meat, seafood, seeds, vegetables and cereal grains.

CONCLUSIONS

Despite the low previous intake, most dysphagic PEG patients present normal serum Cu when gastrostomy is performed. In the few patients with low initial serum Cu, this seems to be unrelated with age, gender, nature of the underlying disorders and normal or low BMI, serum albumin or transferrin. For the minority of patients presenting hypocupremia before gastrostomy, our results also suggest that homemade PEG meals seem to be effective for normalizing serum Cu.

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