Original Article

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

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Background and Objectives: Patients undergoing endoscopic gastrostomy (PEG) present with protein-energy malnutrition (PEM) but little is known about zinc status. Our aim was to evaluate serum zinc, its relationship with serum proteins and with the nature of the underlying disorder, during the first 3 months of PEG feeding. **Methods and Study Design:** Prospective observational study during a 3-month period after gastrostomy. Data was collected at initial PEG procedure (T0), after 4 (T1) and 12 weeks (T3). Initial evaluation included: age, gender, disorder causing dysphagia, Neurological Dysphagia (ND) or Head and Neck Cancer (HNC), NRS-2002, BMI, albumin, transferrin, zinc. At T1 and T3, a blood sample was collected for zinc, albumin, transferrin. Serum zinc evaluation was performed with ICP-AES – Inductively Coupled Plasma-Atomic Emission Spectroscopy. Patients were fed with homemade meals. **Results:** A total of 146 patients (89 males), 21-95 years were studied: HNC-56, ND-90 and low BMI in 78. Initial low zinc in 122; low albumin in 77, low transferrin in 94; low values for both proteins in 66. Regarding the serum protein evolution, their levels increase T0-T3, most patients reaching normal values. zinc has a slower evolution, most patients still displaying low zinc at T3. Significant differences between the 3 moments for zinc (p=0.011), albumin (p<0.0001) and transferrin (p=0.014). **Conclusion:** PEG patients are prone to PEM and zinc deficiency. Most patients present decreased zinc, suggesting that zinc deficiency is common in PEG candidates and is not corrected during 3 months of enteral feeding. Zinc deficiency should be expected and teams taking care of PEG patients should use zinc supplementation.

Key Words: dysphagia, serum zinc, endoscopic gastrostomy, malnutrition

INTRODUCTION

Zinc (Zn) is one of the most important trace elements and is involved in three major types of metabolic functions: catalytic, regulatory and structural.[1-3] Zn may be involved in macular degeneration in the elderly, common flu, prevention and treatment of diarrhea in children and treatment of Wilson's disease.[4,5] Zn deficient patients may develop immune dysfunction, increased oxidative stress, increased generation of inflammatory cytokines and growth retardation. The most severe deficiency is displayed by patients with the rare Acrodermatites Enteropathica.[6] The World Health Organization highlighted Zn deficiency as one the 10 major factors contributing to disease in developing countries, potentially affecting nearly one third of world population.[4,7] The risk of developing Zn deficiency is higher in vulnerable groups such as elderly, children, alcoholics and patients with chronic diseases.[1,2,8-10] It can also be associated with short bowel syndrome, excessive GI losses (diarrhea, emesis and high output fistulas) and long term parenteral nutrition.[11]

Zn deficiency is frequently caused by deficient ingestion.[12] This can result from dysphagia caused by a neurological disorder or from an obstructive disease. Regardless of the underlying disease, dysphagia reduces the oral intake by decreasing deglutition efficiency and safety, leading to nutrient depletion.[13-15] If dysphagia causes insufficient oral intake and there is no other disturbance of digestive tract, tube feeding is the obvious option.[13] Percutaneous endoscopic gastrostomy (PEG) is a simple and

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safe method for providing enteral nutrition to patients with dysphagia in cases where tube feeding is required for longer than 3 weeks.[16-18] Frequently, long-term dysphagic patients that underwent PEG have reduced oral intake weeks before the procedure and often present weight loss and protein energy malnutrition (PEM) when gastrostomy is performed. Serum proteins, such as albumin and transferrin, are classic markers for PEM and have been considered a major feature of malnutrition. Nevertheless, these proteins are also markers of inflammatory activity and should be used with other nutritional markers.

Patients that underwent gastrostomy frequently present PEM but, as far as we know, there are no systematic studies on Zn or other trace elements in PEG patients except the ones from our team.[19,20] The aims of present study were: (I) Evaluation of serum Zn concentration in dysphagic patients undergoing gastrostomy for enteral feeding and comparison of the two main groups of underlying disorders: head or neck cancer (HNC) and neurological dysphagia (ND); (II) Comparison of serum Zn concentration in three moments: at the time of the PEG procedure (T0), and after 4 (T1) and 12 (T3) weeks of PEG feeding, and (III) Assessing the relationship between serum Zn and serum albumin and transferrin concentrations and its evolution in dysphagic patients that underwent gastrostomy for enteral feeding.

MATERIALS AND METHODS

Subjects

All the adult (≥18 years) patients with long term dysphagia, submitted to endoscopic gastrostomy in order to improve nutritional care were invited to participate in this study. Exclusion criteria were refusal to participate in the present study and gastrostomy performed in other clinical settings different from HNC or ND. According to the underlying cause of dysphagia, two study groups were evaluated: (I) HNC, including esophageal proximal cancer and (II) ND, including acute and chronic neurologic disorders.

After the PEG procedure, all patients were discharged from our hospital and lived either in nursing homes or in their own homes, being followed by the Enteral Feeding Team (the dietitian, the gastroenterologist and the nurse) at the Artificial Nutrition Outpatient Consultation. Patients were mostly fed with home-made meals since the Portuguese Health System does not reimburse enteral feeding products, rendering them too expensive for patients and their families. Only when these meals could not account for the patients' nutritional needs (less than 10% of the cases) are the patients were provided with enteral feeding products, albeit for short periods and never exceeding one third of the total energy intake.

Initial evaluation

Nutritional assessment

Body mass index (BMI) was obtained in most patients using the equation Weight/Height^2. Weight was measured using a calibrated digital scale. Height was measured using a stadiometer. If patients were bedridden and could not stand up for weight and height evaluation, BMI was estimated using the Mid Upper Arm Circumference and regression equations described by Powell-Tuck/Hennessy, which have previously been proved to provide a reliable BMI estimation in PEGpatients.[21] BMI cut-off point for malnutrition was defined for values below 18.5 kg/m^2 for adult patients younger than 65 years old and below 22 kg/m^2 for patients with 65 years or older.

Energy intake was calculated using a 3-day dietary diary. Nutritional Risk Screening (NRS-2002) was used to assess nutritional risk but, as many of these patients have major speech difficulties due to neurological disorders or head and neck cancer, tools that depend on oral communication were generally unreliable.

Biochemical evaluation

We evaluated Zn concentration at the time of PEG procedure (T0) and also during the follow-up after four (T1, nearly one month) and twelve weeks (T3, nearly three months). Simultaneously, we evaluated albumin and transferrin concentration, serum markers of malnutrition and/or inflammation.

A blood sample was obtained from these patients before the procedure to add to the nutritional evaluation. Blood samples were obtained between 8:00 and 10:00 AM following at least 12 hours of fasting. Part of each blood sample was used for the standard PEG-patient evaluation, which includes serum proteins assessment. The remainder of the sample was collected into metal-free tubes for Zn assessment. The samples were centrifuged and serum was stored at -80ºC. Serum Zn was evaluated using ICP-AES – Inductively Coupled Plasma-Atomic Emission Spectroscopy.

We considered normal values: 70-120 µg/dL for Zn, ≥35 g/L for albumin, and ≥2 g/L for transferrin.

Follow-up

Patients were evaluated by Enteral Feeding Team at 4 and 12 weeks after PEG procedure, being the laboratory assessment similar to the initial. BMI at 4 and 12 weeks was not included in the present study. No nutritional risk was evaluated at T1 or T3.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0. Results were considered significant at a 5% level. To test the normality of the data, we used the Kolmogorov-Smirnov test fitting, performing the analysis for the whole sample and for each group individually (ND and HNC). To compare the three moments (the moment of the PEG procedure, and both four and twelve weeks post-procedure) we employed ANOVA test for repeated measures, since the assumption of normality was verified (p>0.05 for every test) and the Sphericity was verified using the Mauchly's Test of Sphericity. To compare the two study groups (ND and HNC) we used the t-test for two independent samples. To study the relationship between albumin, transferrin and Zn we used the Pearson correlation coefficient.

Ethical considerations

This study was approved by the Hospital Ethics Committee (n 016/2011). All subjects were informed of the purpose and procedures of the study and gave their informed consent.

RESULTS

Evaluation in the day of gastrostomy (T0)–Table 1

This study included 146 dysphagic patients who were admitted for PEG: 89 men and 57 women, with ages ranging between 21-95 years (91 patients ≥65 years old) and a mean age of 68.2 years (SD=14.2). Patients were divided in two groups according to the underlying disease: head and neck cancer (HNC: 56 patients) and neurological dysphagia (ND: 90 patients). HNC were located in the oral cavity (n=10), larynx (n=15), pharynx (n=20), and proximal esophagus (n=11). ND group included strokes (n=29), dementias (n=20), neurosurgical injuries (n=24), amyotrophic lateral sclerosis (n=6) and other neurological diseases (n=11).

Before gastrostomy, all patients had dysphagia for at least one month after the diagnosis of the underlying disease. All of them presented low oral ingestion, less than 50% of their caloric needs. They were clinically stable at the moment of gastrostomy, with unstable patients being excluded or postponed. Nutritional Risk Screening (NRS-2002) presented a score ≥3 in all patients, signaling the nutritional risk.

Table 1. Characteristics of the study population (n=146)

Characteristics	n or mean (SD)
Age (years)	
Max	95
Min	21
Mean (SD)	68.2 (14.2)
≥65 years	90
<65 years	56
Gender	
Women	57
Men	89
Group diagnosis	
Head neck cancer (HNC)	56
Oral cavity	1
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

BMI

According to age, patients were split into two groups for nutritional status classification according to BMI: below 65 years old and 65 and older. In the former group (n=55), BMI ranged between 13 and 38.5 kg/m^2, with a mean value of 21 kg/m^2. For the latter group (n=91), BMI ranged between 13.8 kg/m^2 and 34.1 kg/m^2, with a mean value of 21.25 kg/m^2. From low BMI patients, 47 (52%) were from the ND group and 31 (55.3%) were from the HNC group. Low BMI was found in 56 patients (61.5%) from the older group and in 22 patients (40%) from the younger group.

Zn

Zn concentration was evaluated in 146 patients, ranging 31-114 µg/dL (normal range: 70-120 µg/dL). The mean value was 53.9±16.2 µg/dL, with a median of 51 µg/dL. Zn was low in 122 patients (84%), while 24 patients (16%) had normal values, although close to the lower limit. From these 24 patients, 17 were from the neurosurgery ward, presenting sudden conditions and acute brain lesions from trauma or surgery; from the remaining 7, 4 had HNC and 3 suffered from progressive neurological disorders. From the 122 patients with low Zn, 52 presented HNC, (93% of the HNC group) and 70 were from the ND group (78% of the ND group).

Albumin

From 144 patients, we found a mean albumin of 34±0.4g/L, with values ranging from 14 to 52 g/L. More than half of the patients (n=77, 53%) presented low albumin, from which 24 belonged to the HNC group and 53 to ND group.

Transferrin

From 144 patients, we found a mean transferrin of 1.84 g/L, with values ranging from 0.74 to 3.31 g/L. Nearly two-thirds of the patients (n=94, 65%) presented with low transferrin. Looking at two main groups (HNC and ND), the mean transferrin values were 1.86 g/L and 1.87 g/L, respectively. There were no major differences between the two main groups of underlying diseases (63% of HNC and 50% of ND) neither between elderly or patients under 65 years old. Nearly half of the patients (n=66, 46%) presented low serum levels of both proteins.

Follow-up 4 weeks (T1) – Table 2

After 4 weeks of PEG procedure (T1), 89 patients were followed up (56 men, 33women). Twenty-five patients died and 29 were lost to follow-up. Three patients were not compliant with PEG feeding and their tubes were removed

Zn

From the initial 122 patients with low Zn, 72 maintained their low values and 3 improved their values, 22 were lost to follow-up, 23 died and 2 had the tubes removed. From the initial 24 patients with normal Zn, 6 patients maintained their values, 8 decreased their values, 7 were lost to follow-up, 2 died and 1 had the tube removed. From the remaining 89 patients, 9 had Zn in the normal range while 80 patients had low values.

Albumin

From the initial 144 patients with albumin assessed 88 were followed-up. From the initial 67 patients with normal albumin, 39 maintained their values, 4 decreased their values, 16 were lost to follow-up, 5 died and 3 had the tubes removed. From the initial 77 patients with low albumin, 25 patients maintained their low values, 20 improved their values, 12 were lost to follow-up and 20 died.

Transferrin

From the initial 144 patients with albumin assessed 88 were followed-up. From the initial 50 patients with normal transferrin, 24 maintained their values, 8 decreased their values, 10 were lost to follow-up, 5 died and 3 had

Table 2. Evolution of zinc, Albumin and Transferrin concentrations

	T0	T1	T3	*p* value
Zinc (µg/dL), n	146	89	40	
Mean±SD	53.94±16.20	54.9±1.71	55.2±1.94	0.011*
<70, n (%)	122 (84)	80 (89)	32 (80)	
≥70, n (%)	24 (16)	9 (11)	8 (20)	
Albumin (g/L), n	144	88	40	
Mean±SD	34 g/l±3.5	3.66±0.07	3.82±0.09	<0.0001*
<35L, n (%)	77 (53)	29 (33)	10 (25)	
≥35, n (%)	67 (47)	59 (67)	30 (75)	
Transferrin (g/L), n	144	88	40	
Mean±SD	1.84±0.6	1.97±0.65	2.08±0.81	0.014*
<2, n (%)	94 (65)	46 (52)	13 (32)	
≥2, n (%)	50 (35)	42 (48)	27 (68)	

*Statistically signify cant differences were found between the 3 moments.

the tubes removed. From the initial 94 patients with low transferrin, 38 patients maintained their low values 18 improved their values, 18 were lost to follow-up and 20 died.

From the 9 patients who showed normal Zn levels, 3 had normal albumin and 2 had normal transferrin levels.

Follow-up 12 weeks (T3) – Table 2

After 12 weeks of PEG procedure (T3), 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 the PEG tube removed.

Zn

From these 40 patients, 8 (20%) had serum Zn concentration into normal range and 32 (80%) under normal range. From the previous evaluation (T1), 2 maintained normal values, 32 maintained low values and 6 improved their values.

Albumin

From these 40 patients, 30 (75%) patients had normal values, while 10 (25%) had values under normal range. From the previous evaluation (T1), 27 patients maintained normal values, 8 maintained low values, 3 increased their values from low to the normal range and 2 decreases to low range.

Transferrin

From these 40 patients, 27 (68%) had normal values while 13 (33%) were under normal range. From the previous evaluation (T1), 20 maintained values into normal range, 7 improved their values into the normal range, 12 maintained their values low and 1 decreased for low values.

Evolution of Zn concentration after four weeks and twelve weeks, and its relationship with proteins and underlying diseases (Table 2)

For Zn concentration, statistically significant differences were found between at least one of the three moments (by Huynh-Feldt statistics, since there was no sphericity, $F_{1.681}$=5.181, p=0.011), verifying the paired multiple comparisons stating that T0 and T1 (p=0.041), T0 and T3 (p=0.011), and rejecting the hypothesis that T1 and T3 (p=0.122). Analyzing the graph of Figure 1, it was found

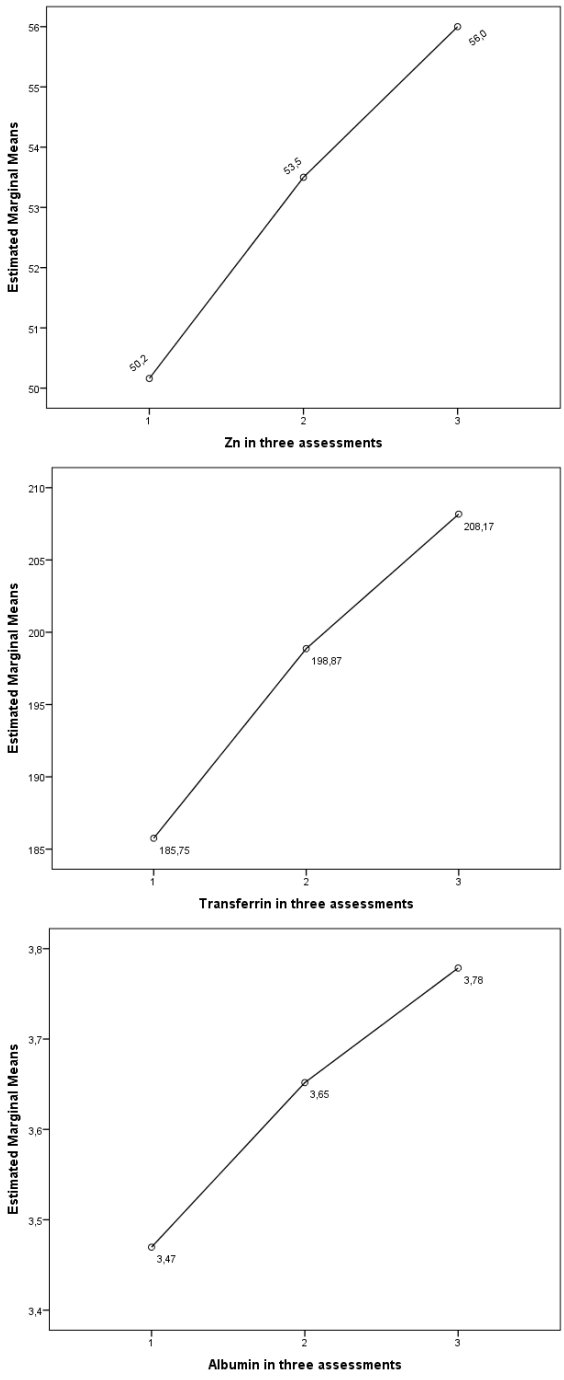

Figure 1. Evaluation of the Zn, albumin and transferrin concentration in dysphagic patients at each moment (g/L)

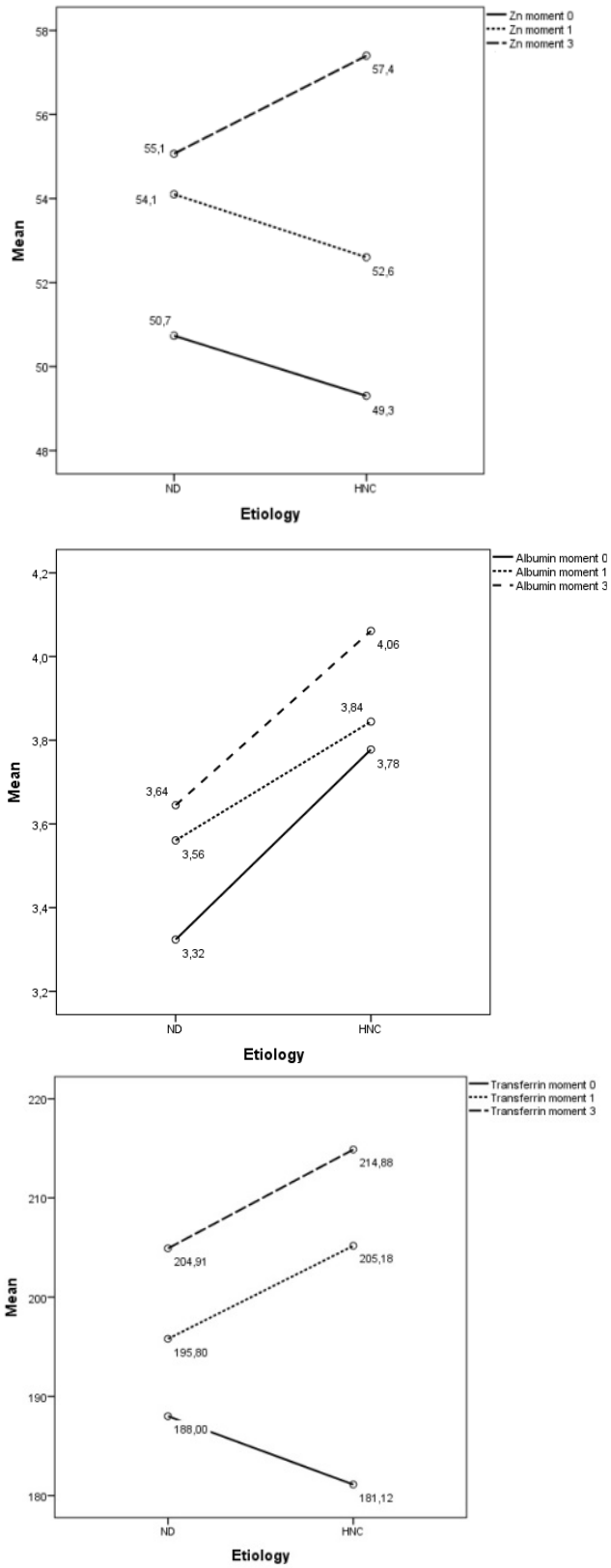

Figure 2. Mean of Zn, albumin and transferrin concentration in ND and HNC groups at each moment.

that there is a statistically significant tendency to increase Zn concentration over time. Nevertheless, most patients present low serum Zn at T1 and T3, despite the slow serum Zn increase over time.

Looking at albumin concentration, statistically significant differences were found comparing the 3 moments (by Huynh-Feldt statistics, since there was no sphericity, $F_{1.859}$=13.988, p<0.0001), verifying the paired multiple comparisons that T0 andT1 (p=0.002), T0 and T3 (p<0.0001) and T1 and T3 (p=0.017) (Figure 1).

Concerning transferrin, statistically significant differences were also detected between at least one of the three moments (by F statistics, since there was sphericity, F_2=4.478, p=0.014). By the paired multiple comparisons test, we conclude that T0 and T1 (p=0.048), T0 and T3 (p=0.004), and reject the hypothesis that T1 and T3 (p=0.281). Like the case of Zn, the concentration of transferrin has a tendency for increasing, even though the increase from the second to the third moment was not statistically significant (Figure 1).

Comparing Zn, albumin and transferrin concentrations in both groups (ND and HNC), statistically significant differences were found in: (1) Zn concentration at T0 ($t_{138.295}$=2.321, p=0.022); (2) albumin concentration at T0 ($t_{97.174}$=-3.156, p=0.002), at T1 (t_{94}=-2.077, p=0.041) and at T3 (t_{56}=-2.485, p=0.016) of evaluation (Figure 2).

Table 3 contains the correlations between Zn, albumin and transferrin concentration at all evaluation moments. The Zn concentration in T3 was positively, albeit weakly, correlated with the concentration of albumin at T1 (r=0.399, p=0.02) and T3 (r=0.471, p=0.002), and with transferrin concentration at T1 (r=0.343, p=0.021) and T3 (r=0.368, p=0.020). The concentration of albumin and transferrin were significantly positively correlated (p<0.05 or p<0.01) and with intensities ranging between weak (r=0.315) and moderate to strong (r=0.797) at all evaluation moments.

DISCUSSION

Patients suffering from long standing dysphagia present a very high risk of developing malnutrition due to the reduced oral intake and the wasting effects of the underlying diseases.[22,23] This malnutrition may include both protein deficiency and trace element deficiency. Serum Zn concentration is the easiest and most commonly used marker of Zn status and correlates reasonably well with oral intake.[1,24] In two previous studies, we identified low serum Zn concentrations in most patients that who had undergone endoscopic gastrostomy.[19,20] These patients also exhibited deficiency in intracellular Zn, a harder to assess and less used measurement.[19]

In our study we identified a large percentage of patients with Zn deficiency, probably as a result of dysphagia-related insufficient oral intake prior to gastrostomy, similar to the results found in the literature in some cases of tube feeding and other clinical settings.[25-28] Our findings are similar with other reports that suggested Zn deficiency in humans was a frequent dietary problem accompanying many chronic diseases, since lack of Zn storage has an important role in health status.[29,30] Additionally, the literature mentions some risk conditions for Zn deficiency, like smoking and excessive alcohol intake, and these conditions are typically fulfilled by most patients of the HNC group.[8,31] Comparing Zn concentration between the two groups of long term dysphagic patients (HNC and ND), we identified similar Zn deficiency in both groups. Only 4 patients with HNC had normal Zn, compared with 20 patients from the ND group. Seventeen out of the 20 ND patients suffered traumatic brain injury, with an adequate

Table 3. Pearson correlations between Zn, albumin and transferrin in all evaluation moments

	Zn moment 1	Zn moment 3	Albumin moment 0	Albumin moment 1	Albumin moment 3	Transferrin moment 0	Transferrin moment 1	Transferrin moment 3
Zn moment 0	0.574**	0.385**	0.146	0.168	0.155	0.114	0.068	-0.136
Zn moment 1		0.628**	0.104	0.198	0.175	0.073	0.109	0.162
Zn moment 3			0.187	0.339*	0.471**	0.239	0.343*	0.368*
Albumin moment 0				0.615**	0.658**	0.690**	0.559**	0.316*
Albumin moment 1					0.797**	0.386**	0.599**	0.315*
Albumin moment 3						0.317*	0.394**	0.342*
Transferrin moment 0							0.607**	0.495**
Transferrin moment 1								0.345*

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

oral intake prior to the accident. These 17 patients did not suffer along period of low intake as the others, since the trauma until the gastrostomy, and Zn deficiency had less time to develop. This suggests that, despite the excessive alcohol intake and smoking being very frequent in HNC patients, the development of Zn deficiency before the PEG procedure was mostly related with progressive low intake caused by dysphagia and less related with the nature of the underlying disorder.

Another aim of our study was to evaluate the relationship between Zn concentration and serum markers of malnutrition and/or inflammation (albumin and transferrin). Theoretically, Zn concentration levels may be positively related to the protein concentration, as a direct consequence of starvation. Most of our patients displayed low serum proteins reflecting the reduced dietary intake and the activity of the underlying diseases. Roughly, half of the patients presented low BMI (n=78), which suggests a low prior intake and PEM. We identified a large number of patients with low Zn and low albumin and transferrin. More than half (53%) of the patients presented low albumin and nearly two-thirds (65%) presented with low transferrin. Almost half of the patients (46%) presented with low serum levels of both proteins. These low serum levels reflect previous low intake as well as the inflammatory activity of the underlying disorders.

Looking at T1 and T3 (4 weeks and 12 weeks after PEG procedure, respectively), we found similar results. Zn deficiency was constant in the majority of patients, but serum proteins were slowly increased over time suggesting that enteral feeding by gastrostomy with homemade meals was not sufficient to compensate lower levels of Zn, but the macronutrients intake could be sufficient to increase serum proteins. We did not find an important relationship in the evolution of Zn and albumin and transferrin.

Our study suggests that Zn deficiency in PEG patients, before and after the gastrostomy, is mostly related with long term low Zn intake and unrelated with the nature of the underlying disease. Zn deficiencies may be subclinical and unapparent. Zn assessment should be included in the evaluation of dysphagic patients and, probably, in the evaluation of all malnourished patients regardless of the cause. As an alternative, Zn supplementation could be systematically considered in long term dysphagic patients.

Limitations of the study

The follow up of these PEG patients is very difficult, creating a limitation to our study. We had a large percentage of dropouts and a small percentage of PEG feeding incompliance and tube removal. Our team uses routinely the predictive model that foretells high mortality risk in PEG patients during the first 3 weeks after the procedure, as previously described and high risk patients are selected to nasogastric tube feeding.[32] Nevertheless, some patients may die in the first few weeks. Also, some patients were either sent away to distant institutions, or lack sufficient social support. These limitations may explain the small number of published studies focusing on long term follow-up of PEG patients.

Conclusion

Dysphagic PEG patients that underwent endoscopic gastrostomy were prone to present protein and energy malnutrition and Zn depletion. In our experience, serum Zn concentrations were severely decreased in the majority of patients, suggesting that low Zn is common in PEG candidates that undergo endoscopic gastrostomy. Our results also suggested that enteral nutrition, using home prepared meals, was not satisfactory to correct Zn deficiency but seemed to be sufficient to increase serum proteins. In the future, if serum Zn evaluation is not available for PEG candidates or PEG patients, Zn deficiency should be assumed as very likely and supplementation should be provided.

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AUTHOR DISCLOSURES

The authors have no potential conflicts of interest.

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