Nutrición Hospitalaria

Nutr Hosp. 2015;32(6):2725-2733
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Original/*Nutrición enteral*

Selenium in dysphagic patients who underwent endoscopic gastrostomy for long term enteral feeding

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Abstract

Background and aims: **endoscopic gastrostomy (PEG) patients usually present protein-energy malnutrition, but little is known about selenium deficiency. We aimed to assess serum selenium evolution when patients underwent PEG, after 4 and 12 weeks. We also evaluated the evolution of albumin, transferrin and Body Mass Index and the influence of the nature of the underlying disease.**

Methods: **a blood sample was obtained before PEG (T0), after 4 (T1) and 12 (T3) weeks. Selenium was assayed using GFAAS (Furnace Atomic Absorption Spectroscopy). The PEG patients were fed through homemade meals. Patients were studied as a whole and divided into two groups: head and neck cancer (HNC) and neurological dysphagia (ND).**

Results: **we assessed 146 patients (89 males), between 21-95 years old: HNC-56; ND-90. Normal values of selenium in 79% (n=115); low albumin in 77, low transferrin in 94, low values for both serum proteins in 66. Low BMI in 78. Selenium has slow evolution, with most patients still displaying normal Selenium at T3 (82%). Serum protein levels increase from T0 to T3, most patients reaching normal values. The nature of the underlying disease is associated with serum proteins but not with selenium.**

Conclusions: **low serum selenium is uncommon when PEG is performed, after 4 and 12 weeks of enteral feeding and cannot be related with serum proteins levels or dysphagia cause. Enteral nutrition using customized**

SELENIO SÉRICO EN PACIENTES CON DISFAGIA SOMETIDOS A GASTROSTOMÍA ENDOSCÓPICA PERCUTÁNEA PARA NUTRICIÓN ENTERAL PROLONGADA

Resumen

Introducción y objetivos: **los pacientes con gastrostomía endoscópica (GEP) presentan malnutrición calórica-proteica, pero poco se conoce sobre la deficiencia de selenio. Estudiamos la evolución del selenio sérico en el momento de la GEP y después 4 y 12 semanas. Además, evaluamos la evolución de albúmina, transferrina, índice de masa corporal (IMC) y la influencia de la enfermedad subyacente.**

Métodos: **obtenemos una muestra de sangre antes de la gastrostomía (T0), y después de 4 (T1) y 12 (T3) semanas. El selenio fue valorado mediante GFAAS (Furnace Atomic Absorption Spectroscopy). Los enfermos consumieron alimentos de preparación doméstica. Los pacientes fueron estudiados como un grupo y después separados en dos grupos: cánceres de cabeza y cuello (CCC) y disfagia neurológica (DN).**

Resultados: **146 enfermos (89 hombres), entre 21-95 años: CCC-56, DN-90. Valores normales de selenio en 79% (n=115), albúmina baja: 77 enfermos, transferrina baja: 94, las dos proteínas bajas: 66, IMC bajo: 78. El selenio ha demostrado una evolución lenta en el 82% de los enfermos presentando selenio normal en T3. Las proteínas séricas incrementaron sus valores en T0-T3, la mayoría de los enfermos alcanzó niveles normales. La enfermedad subyacente, CCC o DN, se relacionó con las proteínas, pero no con el selenio.**

Conclusiones: **el selenio sérico bajo es poco común antes de la gastrostomía; después de 4 y 12 semanas de nutrición enteral no tiene relación con las proteínas séricas ni con la enfermedad que causa la disfagia. La nutrición**

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Recibido: 11-VIII-2015.
Aceptado: 6-IX-2015.

homemade kitchen meals is satisfactory to prevent or correct Selenium deficiency in the majority of PEG patients.

(*Nutr Hosp*. 2015;32:2725-2733)

DOI:10.3305/nh.2015.32.6.9756

Key words: *Selenium. Gastrostomy. PEG. Enteral feeding*

con alimentación de preparación doméstica es suficiente para prevenir o corregir la deficiencia de selenio de la mayoría de los enfermos.

(*Nutr Hosp*. 2015;32:2725-2733)

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Palabras clave: *Selenio. Gastrostomía. GEP. Nutrición enteral.*

Introduction

Selenium (Se) is an essential non-metallic trace element, required in small amounts for normal metabolism[1,2]. Se compounds occur in organic forms like selenomethionine and selenocysteine amino acids[3-5]. These forms are metabolized and utilized in the synthesis of selenoproteins with antioxidant, anti-inflammatory, antitumorigenic, antiangiogenic, antiatherogenic and immunomodulatory effects[6,7]. Twenty five selenoproteins with essential functions have been identified and grouped into three classes: Glutathione peroxidases, thioredoxin reductases and iodothyronine deiodinases[8-11]. Se deficiencies occur due to inappropriate ingestion, increase needs and losses. This can affect various biochemical pathways resulting in severe repercussions, including organ dysfunction, poor wound healing and alteration of immune system[12-15].

Dysphagia may occur in the setting of neurological disorders or as consequence of obstructive disease. Whatever the underlying disease, dysphagia reduces the oral intake by decreasing swallow efficacy and safety, leading to depletion of nutrients[16]. If oral intake from food and/or nutritional supplements is insufficient or the patient can't eat/drink safely, and there is no other disturbance of digestive tract, tube feeding is the obvious option to deliver nutrients when proximal obstructions or oropharyngeal dysphagia occurs[17]. Percutaneous endoscopic gastrostomy (PEG) is a simple and safe method of providing long term enteral access for patients with dysphagia if tube feeding is required for longer than 3 weeks[18,19]. Frequently, long term dysphagic patients with neurological disease or head or neck cancer, referred for PEG, have reduced oral intake during weeks before procedure. Very often, dysphagic patients 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 but these proteins are also markers of inflammatory activity and should be used with other nutritional markers. If the occurrence of PEM in patients referred to gastrostomy is well known, to the best of our knowledge in the literature there are no systematic studies evaluating Se or other trace elements in outpatients that underwent endoscopic gastrostomy, except the studies from our team[20, 21].

The aims of the present study were:

1. Assess the evolution of serum Se in dysphagic patients that underwent endoscopic gastrostomy for long term enteral nutrition in three moments: when PEG is performed and after 4 and 12 weeks post-procedure. Also assess the evolution of albumin and transferrin concentration and Body Mass Index (BMI) in the same three moments.
2. Explore the influence of the nature of the disease, neurological dysphagia (ND) or head and neck cancer (HNC) in Se, albumin, transferrin and BMI in these three moments.

Material and methods

The present study was a prospective, observational study that evaluated serum Se concentration in adult dysphagic patients referred to endoscopic gastrostomy for long term enteral nutrition. Serum Se concentration was evaluated: when PEG is performed (T0), after 4 (T1) and 12 weeks (T3) post-procedure and compared to references range. Also we intended evaluate the evolution of albumin, transferrin and BMI in the same period. Furthermore, the study explored the relationship between etiology of the disease with Se, albumin, transferrin and BMI in these three moments of evaluation.

We included adult (≥ 18 years) patients with long term dysphagia that underwent endoscopic gastrostomy. All adult PEG patients were invited to participate. The exclusion criteria were age <18 years and refusal to be included in the study.

After the gastrostomy procedure patients were fed with homemade meals because in Portugal enteral feeding products are not refund, which makes them too expensive for most of our patients. Only when these meals could not account for the patients' nutritional needs were enteral feeding products provided for short periods, not more than 10% of the patients, with supplements with 200 Kcal, albeit never exceeding one third of the energy intake.

According to the underlying disease causing dysphagia, two study groups were considered: (1) head and neck cancer (HNC), including oesophageal proximal cancer, and (2) neurological dysphagia (ND) including acute and chronic disorders.

Collected data included patient's age, gender, etiology (nature of the underlying disease causing dysphagia), Nutritional Risk Screening, BMI, and serum albumin, transferrin and Se concentration. All of the usual procedures of our nutritional evaluation of PEG patients were performed. Anthropometric measures and biochemical evaluation these patients were performed at T0, T1 and T3.

Initial evaluation (T0)

Nutritional risk assessment

For nutritional screening we used the tool recommended by E.S.P.E.N., the Nutritional Risk Screening - NRS 2002[22]. A dietary recall from the previous weeks before gastrostomy was obtained from patients, family or caregivers.

Anthropometric evaluation

BMI was obtained in most patients and expressed as body weight/height squared (kg/m^2). 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 was previously been used by our group[23,24]. Malnutrition was defined as a BMI < 18,5kg/m^2 for adult patients younger than 65 years and < 22 kg/m^2 for patients with 65 years or older[25]. BMI was evaluated at T0, T1 and T3.

Sampling and Blood Samples Assays

From patients that underwent endoscopic gastrostomy, a blood sample was obtained some minutes before the gastrostomy procedure. Samples were obtained between 8:00 and 10:00 AM following at least 12 hours of fasting. Part of the blood sample of each patient 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 Se assessment. After centrifugation serum samples were kept frozen (-80ºC) until the analysis. Serum samples were analyzed and reported from the laboratory (REQUIMTE - Rede de Química e Tecnologia Departamento de Química/Faculdade de Ciências e Tecnologia da Universidade Nova de Lisboa). Serum Se was assayed using GFAAS – Furnace Atomic Absorption Spectroscopy (5%HNO3 in water with diluting solution 0.1%HNO3 (v/v) 0.1%Triton X 100, Fluka® patterns 1000mg/L). We considered reference values for Se: 8-27,2μg/dl[27]. The cut-offs for albumin <3,5 g/l and transferrin <200 mg/dl were considered suggestive of malnutrition.

Follow-up

Patients were evaluated by Enteral Feeding Team (dietitian, gastroenterologist and nurse) at 4 weeks and 12 weeks after PEG procedure, being the assessment similar to the initial. BMI was registered at 4 and 12 weeks, and a blood sample was obtained for laboratory assessment. No nutritional risk was evaluated.

Statistical analysis

It was used the Statistical Package for Social Sciences (IBM SPSS Statistics), version 22.0. The results are considered significant for a 5% significance level.

The significance of the influence of etiology (neurological dysphagia group and head and neck cancer group) in Se values, albumin, transferrin and BMI in the three stages of evaluation was performed with a mixed ANOVA for repeated measurements. The applicability of assumptions, including the 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).

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 study population at the moment of PEG procedure - T0 evaluation (Table I)

This study included 146 dysphagic patients who were admitted for endoscopic gastrostomy, 89 men and 57 women, ranging in age from 21 to 95 years with a mean age of 68.2 ±14.2 years. From these, 91 (62%) were aged ≥ 65 years old. All patients had at least one month with dysphagia after the diagnosis of the underlying disease before the PEG procedure and prior intake under 50% of caloric needs. NRS 2002 presented a score ≥ 3 in all patients. At the moment of sample collection, and gastrostomy procedure all patients were clinically stable, unstable patients are excluded or postponed.

Two main groups were studied according the underlying disease: first group with head and neck cancer (HNC) with 56 patients and the second group with neurological dysphagia (ND) with 90 patients. The ND group comprises strokes (n=29), dementias (n=20), neurosurgical injuries (n=24), amyotrophic lateral sclerosis (n=6) and other neurological diseases (n=11) causing dysphagia; HNC cancers were, mostly, located

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

Characteristics	*Absolute number*
Age	**Years**
Máx	95
Min	21
Mean (SD)	68.2 (14.2)
≥ 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

in the oral cavity (n=10), larynges (n=15), pharynges (n=20), and proximal oesophagus (n=11).

Selenium concentration

Selenium: From 146 patients the mean of serum Se was 10.22 ± 3.67 mg/dl ranging from 0.2-26.1 mg/dl (normal range: 8-27.2 mg/dl). From these patients, 115 (79%) had normal Se; 31(21%) had low values between 0.2 and 7.9 mg/dl. From these 20 (64.5%) were from the ND group and 11 (35.5%) were from the HNC group. Elderly patients group presented 14% of low values similar to the younger group.

Albumin and transferrin concentration

Albumin: From 144 patients the mean of serum concentration was 3.4g/dl±0.35 ranging from 1.4 to 5.2 g/dl. More than half of the patients 53% (n=77) presented low albumin but only 21% of these (n=16) were the same who presented low serum Se. Looking at the two main study groups (HNC and ND) the mean of albumin was 3.62 g/dl and 3.27 g/dl respectively.

Transferrin: From 144 patients with the mean of serum concentration was 184.60 mg/dl ranging from 74 to 331 mg/dl. Nearly two-thirds (n=94, 65%) of the patients presented low transferrin but only 2014% (n=20) of these patients were the same who presented low serum Se values. Sixty six patients (46%), presented low levels of both proteins. Looking at the two main study groups (HNC and ND) the mean of transferrin was 186.28 mg/dl and 187.72 mg/dl respectively. There were no major differences between the two main groups of underlying disease (63% of HNC and 50% for ND) neither between elderly or patients under 65 years old.

Anthropometric evaluation: BMI

From 146 patients most of them had the BMI calculated from Quetelet's equation kg/m2. 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. From 146 patients, 78 (53%) showed low BMI (<18,5 kg/m2 for patients younger than 65 years and <22 kg/m2 for patients with 65 years 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%). Older patients group presented more malnutrition (n=58; 64%) compared to younger (n=20; 36%).

Follow-up 4 weeks

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

Selenium concentration

Selenium: From the initial 115 patients with normal Se, 64 maintained their values, 12 decreased their values, 15 were lost to follow-up, 22 died and 2 removed the tube. From the initial 31 patients with low Se, 3 patients maintained their low values, 10 improved their values, 14 were lost to follow-up, 3 died and 1 removed his tube. From remain 89 patients, 74 (82%) had Se into normal range while 15 (18%) had low values.

Albumin and transferrin concentration

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 removed his tube. 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 removed his tube. 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.

Anthropometric evaluation

BMI: For the youngest group we found a mean of BMI of 19.88 Kg/m^2. For the oldest group we found a mean of 20.98 Kg/m^2. According age and underlying disease we found a mean of 19.86 Kg/m^2 from HNC and 20.43 Kg/m^2 from ND in patients under 65 years old and, 19.91 Kg/m^2 and 21.20 Kg/m^2 from HNC and ND in the patients older than 65 years old.

Follow-up 12 weeks

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 PEG was removed.

Selenium concentration

Selenium: Thirty three patients (82%) had serum Se concentration into normal range and 7 (18%) under normal range. Six of these 7 patients went from normal values at T1 to low serum Se at T3. One of them presented with low Se from T1.

Albumin and transferrin concentration

Albumin: 30 (75%) patients had normal values, while 10 (25%) had values under normal range. From the previous evaluation (T1), 27 patient 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 normal range, 12 maintained their values low and 1 decreased for low values.

Anthropometric evaluation

BMI: For the patients under 65 years old we found a mean of BMI of 20.22 Kg/m^2 and a mean of 21.51 Kg/m^2 for the older patients. 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 age and underlying disease we found a mean of 20.78 Kg/m^2 from HNC and 18.99 Kg/m^2 from ND in the patients under 65 years old and, 20.14 Kg/m^2 and 21.96 Kg/m^2 from HNC and ND in the older patients, respectively.

Influence of etiology in serum Se, Albumin and Transferrin concentration and BMI in the three evaluation moments

Selenium and etiology (Fig. 1)

Looking at figure 1 the behaviour of Se in the three evaluation moments is different depending on the etiology of the disease. The ND group has a tendency to decrease Se values, while the HNC group increases over time but no statistically significant difference was found (Greenhouse-Geisser statistic, $F_{1,644} = 1.698$, $p = 0.196$, observed power = 0.313). Considering the three evaluation moments, no statistically significant differences were found between the three distinct periods (Greenhouse-Geisser statistic, $F_{1,644} = 1.741$, $p = 0.456$, observed power = 0.159).

Albumin and etiology (Fig. 2)

From the analysis of figure 2, there has been a favourable evolution until the week 12. The HNC group shows significantly higher values in the three moments. They were significant changes over the three evaluation moments (Greenhouse-Geisser statistic, $F_{1,644} = 11.557$, $p < 0{,}0001$, observed power = 0.987). The paired multiple comparisons were detected statistically significant differences between all three evaluation moments ($p<0.05$). They were also detected statistically significant differences between the two groups ($p=0.008$).

Transferrin and etiology (Fig. 3)

From the analysis of figure 3 It seems that on the moment 0 has lowest values of transferrin, a gradual increase occurring over the evaluation moments. It was not detected simultaneous influence of underlying disease and time in the transferrin values (F statistic for sphericity verified, $F_2 = 0.706$, $p = 0.496$, observed power = 0.166). Considering each evaluation moment, statistically significant differences were found between them (F statistic for sphericity verified, $F_2 = 5{,}066$, $p = 0.008$, observed power = 0.808). Multiple pairwise comparisons, it is concluded that the moment 0 differs significantly from the moment 1 ($p = 0.025$) and from moment 3 ($p = 0.002$).

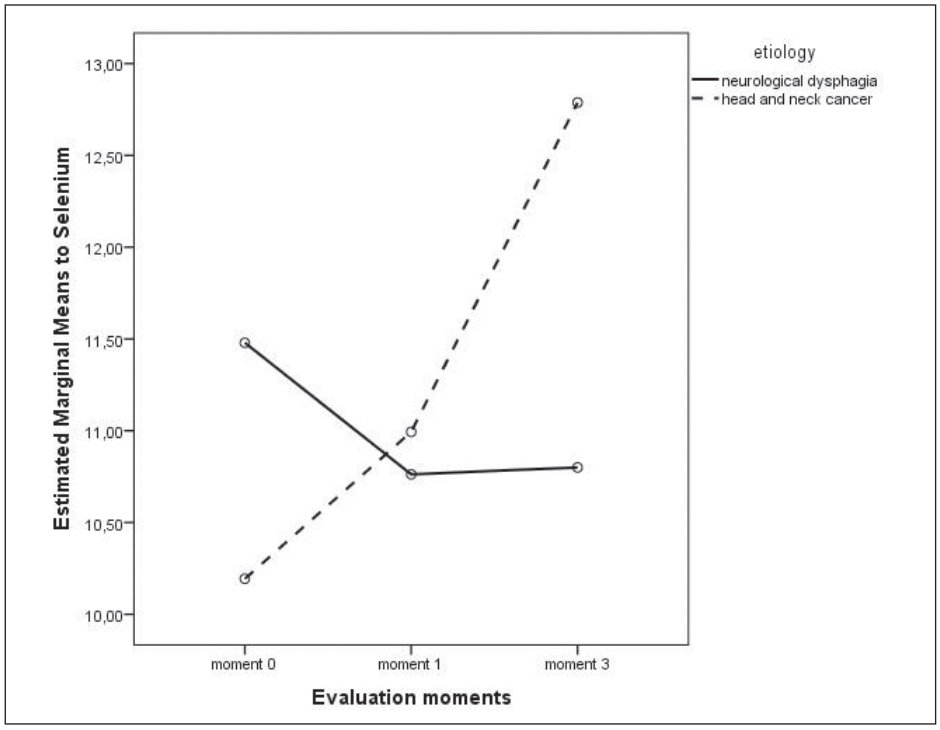

Fig. 1.

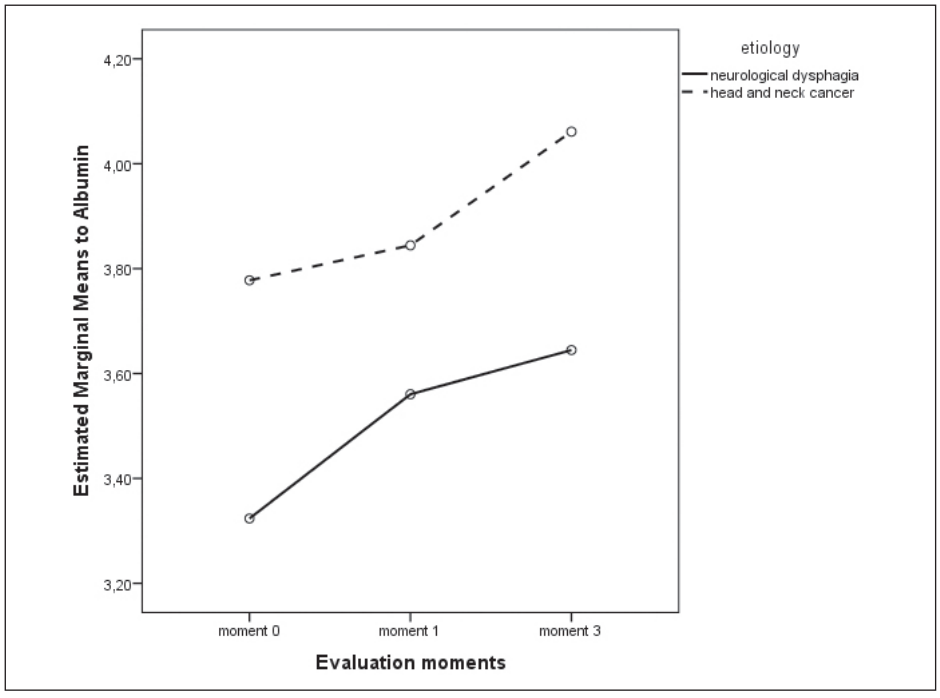

Fig. 2.

BMI and etiology (Fig. 4)

Regarding the BMI, it was not detected simultaneously influence of time and the etiology of the disease in BMI (Greenhouse-Geisser statistic, $F_{1,499}$ = 0. 258, p = 0.708, observed power = 0.085); considering only the three evaluation moments, it was not detected significant changes (Greenhouse-Geisser statistic, $F_{1,499}$ = 0.215, p = 0.742, observed power = 0.079) and considering only the two main groups of the disease, there were not detected statistically significant differences between them too (p = 0.216). Figure 4 illustrates the small changes of BMI over the evaluation moments and between the two groups of the disease. However, it is noted that the group ND presented, at any moment of the evaluation, higher values.

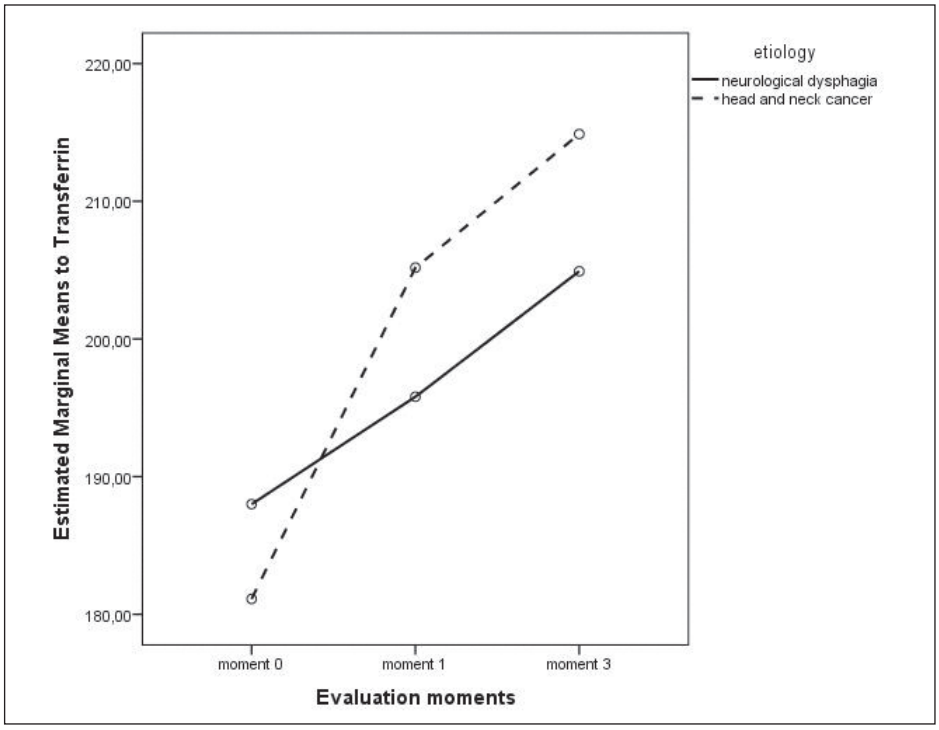

Fig. 3.

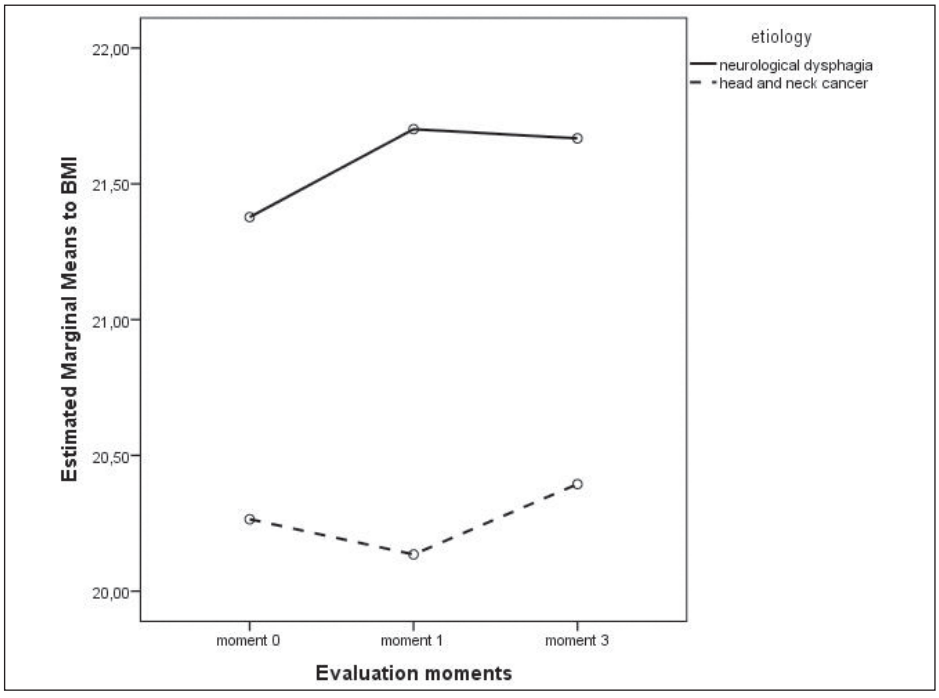

Fig. 4.

Discussion

Due the large biological functions of Se, we aimed evaluate its evolution in dysphagic patients when they are referred to PEG, 4 and 12 weeks after the procedure. These biological functions include defense against oxidative stress, that have a protective effect at various stages of cancer and may prevent degenerative neurological diseases[6,7,26-29]. Subclinical deficiencies of Se, without signs and symptoms but with biochemical or physiological consequences, may be frequent and have important adverse effects on health of these undernourished patients[30,31]. Most of patients with dysphagia show PEM as a direct consequence of starvation but Se remain stable until its main enzyme glutathione peroxidase, decrease[32]. We found that, at

the moment of the procedure most patients presented normal Se and only a small group presented low values. This little percentage of patients under normal values could suggest that biological storage of Se has not been exhausted, and even a small amount of food intake is sufficient to maintain normal concentration since the major forms of Se in the diet are highly bioavailable and this absorption is very efficient.

At the follow-up after 4 and 12 weeks, we found an increase, although not significant, in the percentage of patients with normal Se. After the gastrostomy, the majority of the food intake of these patients is muscle meat mixed and dairy products. It seems enough to preserve and increase Se concentration. Also, the age does not seem to interfere in Se concentration. Only 14% of the older group presented low Se, similar to the younger group. Our results confirm that enteral feeding by gastrostomy is effective for maintaining Se levels with some increase in HNC group.

Regarding serum proteins when patients are referred to PEG, most of them displayed low levels of these proteins that can be attributable to reduced dietary intake and/or the activity of the underlying diseases[33,34]. Our patients had lower protein-energy intake due to dysphagia, lower than 50% of their needs, which can in part, explain these findings. It is know that malnutrition in these patients includes deficiency in some serum proteins like albumin and/or transferrin and trace elements (TE) as it does with Zn in a previous study done by our team[20,21]. Regarding the behaviour of these proteins during the period of the study, globally, although with some variations, their values increase over time. This suggests a positive nutritional evolution and/or a decrease of inflammation in both groups, HNC and ND. A low BMI may be due to several causes such as insufficient protein-energy intake, tobacco smoking and excessive alcohol intake, are typically fulfilled by most of our patients with HNC and by some ND patients.

Another aim of our study was to explore, the influence of the etiology of the underlying disease in the concentration of serum Se, albumin, transferrin and BMI. Regarding the behaviour of Se when we look at both groups (HNC and ND) we have found similar levels in normal range in most of the patients (79% and 80.4.% respectively).

Looking at the evolution of albumin, we found statistically significant differences between the two groups in the three evaluation moments. HNC shows higher values than ND in the three moments and significant influences of the etiology of disease in this evolution were identified. Looking at the evolution of transferrin, we found statistically significant differences between the two groups in each evaluation moment. Finally when we look to the influence of etiology in the variation of BMI, and did not found statistically significant differences between the two groups.

Our study has an important limitation but is with no doubt the reality of the daily clinical practice. Follow up of these PEG patients is difficult due to frequent dropouts. Many patients died because of the progression of the underlying diseases. Our team uses routinely the equation that predicts high risk of PEG patients for dying during the first 3 weeks after the gastrostomy procedure, as previous described[35]. Even so there are patients who die in the first weeks. A little percentage, had PEG removed recovering oral feeding. A number of our initial patients was sent to institutions far away from our hospital and followed by other teams.

Follow up of PEG patients is always difficult and subject to a large number of dropouts. This may be one of the reasons that lead to the small number of published studies focusing long term follow up of these patients.

Conclusion

Dysphagic patients when are referred to PEG are prone to present PEM and micronutrient depletion regardless of underlying disease. Our results suggest that low Se is uncommon in patients that underwent to endoscopic gastrostomy and cannot be related with age, gender, BMI, serum proteins levels or the dysphagia cause. The etiology of the disease causing dysphagia seems to influence albumin and transferrin during enteral nutrition but did not influence serum Se. We believe that enteral nutrition using customized homemade kitchen meals is satisfactory to prevent Se deficiency in most PEG patients.

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