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Serum Zn levels in dysphagic patients who underwent endoscopic gastrostomy for long term enteral nutrition

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Abstract

Background and aims: **Dysphagic patients who underwent endoscopic gastrostomy (PEG) usually present protein-energy malnutrition, but little is known about micronutrient malnutrition. The aim of the present study was the evaluation of serum zinc in patients who underwent endoscopic gastrostomy and its relationship with serum proteins, whole blood zinc, and the nature of underlying disorder.**

Methods: **From patients that underwent gastrostomy a blood sample was obtained minutes before the procedure. Serum and whole blood zinc was evaluated using Wavelength Dispersive X-ray Fluorescence Spectroscopy. Serum albumin and transferrin were evaluated. Patients were studied as a whole and divided into two groups: head and neck cancer (HNC) and neurological dysphagia (ND).**

Results: **The study involved 32 patients (22 males), aged 43-88 years: HNC = 15, ND = 17. Most (30/32) had low serum zinc, 17/32 presented normal values of whole blood zinc. Only two, with traumatic brain injury, presented normal serum zinc. Serum zinc levels showed no differences between HNC and ND patients. There was no association between serum zinc and serum albumin or transferrin. There was no association between serum and whole blood zinc.**

Conclusions: **Patients had low serum zinc when gastrostomy was performed, similar in HNC and ND, being related with prolonged fasting and unrelated with the underlying disease. Decrease serum zinc was unrelated with low serum proteins. Serum zinc was more sensitive than whole blood zinc for identifying reduced zinc intake. Teams taking care of PEG-patients should include zinc evaluation as part of the nutritional assessment, or include systematic dietary zinc supply.**

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Key words: *Zinc. Gastrostomy. PEG. Dysphagia. Malnutrition.*

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

Resumen

Objetivos: **Pacientes con disfagia sometidos a Gastrostomía Endoscópica (PEG) presentan malnutrición calórico-proteica, mas poco se conoce acerca da malnutrición en micronutrientes. El objetivo del presente trabajo fue el estudio del zinc sérico en pacientes portadores de PEG y su relación con proteínas séricas, zinc de sangre total y enfermedades de base.**

Métodos: **De los pacientes portadores de PEG se ha obtenido antes del procedimiento. La determinación del zinc del suero y total se ha obtenido por lo método Wavelength Dispersive X-ray Fluorescence Spectroscopy. Fueron consideradas la albumina y la transferrina. Se estudiaron pacientes como un todo y se dividieron en: cáncer de cabeza y cuello (CCC) y enfermedad neurológica (EN).**

Resultados: **32 pacientes (22 hombres), 43-88 años: CCC = 15, EN = 17. La mayoría (30/32) presento lo zinc en suero bajo. Solo dos, con lesión cerebral traumática, tenían valores normales de zinc. En la sangre total, 17/32 estaban dentro del rango normal. Sin diferencias entre los grupos CCC-EN. Sin asociación entre lo zinc sérico y la albumina o transferrina. Sin asociación entre lo zinc en suero y total.**

Conclusiones: **los enfermos presentaran zinc sérico bajo no momento de la PEG, relacionado con el ayuno prolongado y no con la enfermedad subyacente. La reducción del zinc sérico no está relacionada con las proteínas. Lo zinc sérico fue más sensible para la identificación de reducción de la ingesta. Los grupos que se ocupan de enfermos con PEG deben incluir la determinación del zinc en la evaluación o incluir el suministro de zinc.**

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Palabras clave: *Zinc. Gastrostomía. PEG. Disfagia. Malnutrición.*

Introduction

Trace elements are required in small amounts for normal metabolism. Zinc (Zn) is one of the most important and is involved in three major types of functions, catalytic, regulatory and structural[1-3]. The World Health Organization highlighted Zn deficiency as one the 10 major factors contributing to disease in developing countries[4]. Usually, it is caused by deficient ingestion or inherited Zn deficiency[5] but, even in developed countries, the risk of developing Zn deficiency is high in vulnerable groups such as the elderly[2,6], alcoholics[1] and patients with chronic diseases.[7] Zn deficiency can also be associated with short bowel syndrome, excessive GI losses (diarrhea, emesis, and high output fistulas) and long term parenteral nutrition[8]. The most widely used marker of Zn status is serum concentration witch correlates reasonably well with intake[1]. Serum Zn levels are a marker of therapeutic and prognostic response[9,10]. As Zn is mainly transported in plasma bound the albumin and other proteins, the interpretation of plasma Zn must be taken together with changes in those proteins.

Dysphagia is a discomfort during swallowing, or during the progression of the alimentary bolus[11]. It may occur in the setting of a neurological disorder or an obstructive disease, most frequently a head or neck cancer. Whatever the underlying disease, dysphagia reduces the oral intake by decreasing swallow efficacy and safety, leading to depletion of macronutrients and micronutrients. Dysphagic patients need nutritional support. When oral intake is insufficient, and there is no other disturbance of digestive tract, tube feeding is the obvious option. Percutaneous endoscopic gastrostomy (PEG) is the gold standard if tube feeding is required for longer than 3 weeks, being associated with less treatment failures and achieving better nutritional support then long-term nasogastric feeding tubes.[12] Long term dysphagic patients with neurological disease or head or neck cancer, referred for endoscopic gastrostomy, frequently present with protein-calorie malnutrition. To the best of our knowledge, there are no systematic studies evaluating Zn or other trace elements in patients that underwent endoscopic gastrostomy, although Zn is essential in vital functions[13] including the immune response[14,15] which is important for these patients with burden diseases. Our hypothesis were that: (i) dysphagic patients that underwent endoscopic gastrostomy had low serum Zn concentrations, resulting from a large period of low ingestion, unrelated with the dysphagia cause, (ii) these variations were independent of serum proteins variations, and (iii) serum Zn would be more strikingly lower than whole blood Zn reflecting the slower changes of intracellular Zn that occur in the blood cells, a major component of whole blood Zn. In or to evaluate these hypothesis four aims were established for the present study.

Aims

The aims of our study were:

1. Evaluation of serum Zn concentration in dysphagic patients referred to gastrostomy for long term enteral nutrition.
2. Comparison of the serum concentration of Zn between two groups of long term dysphagic patients that underwent endoscopic gastrostomy: patients with head and neck cancer or with neurological dysphagia.
3. Evaluation of the association between serum concentration of Zn and serum albumin and transferrin, serum markers of malnutrition and/or inflammation.
4. Evaluation of the association between serum Zn and whole blood Zn.

Patients and methods

We studied consecutive adult patients that were referred and underwent endoscopic gastrostomy in order to have nutritional support for long term dysphagia. All adult patients were invited to participate. The only exclusion criteria were age < 18 years and refusal to be included in the study. All other patients were included. Two main study groups were examined: head and neck cancer (HNC) and neurological dysphagia (ND). HNC patients included oesophageal proximal cancer. The group of neurologic patients included acute and chronic disorders. Nutritional Risk Screening –NRS 2002– presented a score ≥ 3 in every patient, signalling the nutritional risk, but, as most of these patients have important speech difficulties due to neurological disorders or head and neck cancer, nutritional assessment tools depend on oral communication were unreliable. Global nutritional assessment relied mostly in objective evaluation, using anthropometry and serum data, including albumin and transferrin. Albumin < 35 g/l and transferrin < 2,0 g/l were considered suggestive of malnutrition. Body Mass Index (BMI) was obtained in most patients using the equation Weight/Height^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 and proved to provide a reliable BMI estimation in PEG-patients.[16] BMI was considered normal if ≥ 18,5 and low if < 18,5.

From these patients that underwent endoscopic gastrostomy a blood sample was obtained minutes before the procedure, in order to contribute to nutritional evaluation. Blood 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 two glasses of metal-free tubes for Zn evaluation, as follow: 1) venous blood samples were collected into heparin trace elements tube for determination of Zn in whole blood (3,5 ml of blood) and 2) a tube for centrifugation for serum Zn determination (7,5 ml of blood). After centrifugation samples were kept frozen (-80ºC) until the analysis. After unfreezing all samples were submitted to analysis. The Zn composition of the serum and Zn of whole blood was detected using Wavelength Dispersive X-ray Fluorescence Spectroscopy (WDXRF). Serum Zn was considered normal in the range 70-120 µg/dl; Whole blood Zn was considered normal in the range 440 a 860 µg/dl[17,18]. Albumin ≥ 35 g/l and transferrin ≥ 2,0 g/l were considered normal concentration.

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

Statistical analysis

The statistical analysis was done with the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL), version 19.0. All statistical tests were performed at the 5% level of significance. Independent Samples t-test was used to assess the difference between the group of patients with low zinc concentration and normal albumin/transferrin concentration and the groupof patients with low zinc concentration and low albumin/transferrin concentration. Cut-off points were established according with the normal values defined above. For equality of variances, the Levene's Test was used. Association between serum zinc and whole blood zinc, serum albumin and serum transferrin has been assessed using the Spearman correlation coefficient.

Results

This cross sectional analytical study involved 32 dysphagic patients (22 males and 10 females with age range 43-88 years) who were admitted for gastrostomy. Two main study groups were examined: the first one group with head and neck cancer (HNC: 15 patients) and the second with neurological dysphagia (17 patients). HNC patients were mostly, laryngeal (n = 6), pharyngeal (n = 3), and proximal oesophageal cancer (n = 4). The group of neurologic patients comprises mainly stroke, traumatic brain injury and dementia. Table I shows the characteristics of the study population including the demographic data (age and gender), and the distribution of underlying diseases causing dysphagia.

Table I
Characteristics of the study population

Value obtained *Clinical Characteristics*	*n*	*%*
Age	***Years***	
Max	88	
Min	43	
Mean	67,25	
Gender		
Female	10	
Male	22	
Diagnosis		
Dementia	3	
Stroke	6	
Traumatic Brain Injury	2	
Other neurological diseases	6	
Oesophageal cancer	4	
Laryngeal cancer	6	
Pharyngeal cancer	3	
Mouth cancer	1	
Cervical cancer mass	1	

All patients had at least one month with dysphagia after the diagnosis of the underlying disease before the PEG procedure. All of them had oral ingestion under 50% of caloric needs. All patients were clinically stable at the moment of sample collection, as gastrostomy is performed only in patients with stable conditions and unstable patients are excluded or postponed.

Only 10 patients presented low Body Mass Index, and 23 had normal BMI. Conversely, only 8 patients displayed normal serum albumin and transferrin and all of them had also normal BMI. The other 24 patients exhibited low albumin and/or transferrin values suggestive of malnutrition. Table II shows low values in absolute values and percentage for serum Zn, whole

Table II
Values in absolute values and percentage

Parameters	*Patients*					
	Neurological		*Head and neck cancer*		*All group*	
Low parameters	*n*	*(%)*	*n*	*(%)*	*n*	*(%)*
Serum Zn (<70 µg/dl)	15	88%	15	100%	30	94%
Zn whole blood(<440 µgZn/gHb)	7	41%	8	53%	15	47%
Albumin (<3.5 g/dl)	10	59%	6	40%	16	50%
Transferrin (< 2.0 g/l)	11	65%	10	66%	21	66%

blood Zn, albumin and transferrin of the two groups of dysphagic patients. Most patients, 30/32 (94%), had low serum Zn concentrations. Only two patients presented normal serum concentration for Zn, albumin and transferrin. These were neurosurgical patients with traumatic brain injury. They both suffered an acute trauma, having presented an adequate intake prior to the accident. More than half, 17/32, (53%) of the patients, present normal values of whole blood Zn.

When we divided into two groups the group of neurological dysphagia show 88% (15) of patients had low serum Zn concentration. All HNC patients (100%) presented low serum Zn status. For albumin, 50% of patients presented a low serum albumin, 40% of head and neck cancer and 59% of neurological group. Transferrin presented values under normal in 66% of patients, 66% for HNC and 65% for ND. No differences were found between patients with head and neck cancer and patients with neurological dysphagia for their serum zinc levels, as shown by the t test ($p = 0.688$). Therefore the origin of dysphagia does not seem to relate with serum Zn levels.

No association between serum zinc and serum albumin ($p = 0.307$) and serum transferrin ($p = 0.340$) has been detected, as assessed by the Spearman correlation coefficient. Similarly, no association seems to exist between serum and whole blood zinc association ($p = 0.162$).

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 disease. Long standing dysphagia may occur in the sequence of a neurological disorder or a head or neck cancer. The prevalence of swallowing disorders is very high in patients with acute or chronic neurological disease[19], so these patients are always at nutritional risk including Zn deficiency. Head and neck cancer patients, including oral, pharyngeal, laryngeal and proximal oesophageal cancer, also suffer from dysphagia, caused by obstruction due to cancer growth. These patients frequently developed severe malnutrition and caquexia[20], induced by direct cancer effects, cancer anorexia, personal characteristics and treatment. Although malnutrition is usual feature, nutritional assessment of these dysphagic patients is difficult because the same disorders that induce dysphagia also cause impaired speech capacities. Nutritional assessment tools that need dialog with the patients are frequently useless. Enteral feeding teams frequently depend on objective evaluations, as anthropometry[21,22] or laboratory data for nutritional evaluation. Our patients had variable BMI values but most of them displayed low serum albumin and/or transferrin. To the best of our knowledge, this reflects an on-going malnutrition progression, serum proteins dropping first, BMI being affected when the malnutrition advances.

Trace elements requirements in critically ill patients are unknown[23]. Requirements in several diseases, like cancer, progressive neurological disease, stroke, and brain injury patients are, probably, greater than in healthy individuals. The increase requirements due to increased metabolic states, pre-existing deficiencies or increased body losses can lead to deficiency of one or more elements. These deficiencies can be clinically evident or may develop as subclinical deficiency states[1]. Classical syndromes with typical signs and symptoms of deficiencies are well identified and increase the risk of poor outcomes and increased costs for health services. However, subclinical deficiencies of trace elements, with biochemical or physiological consequences, may be more frequent and those subclinical deficiencies may have important adverse health effects in undernourished patients.

Serum Zn concentration is the easiest and most commonly used marker of Zn status[24]. Unlike other micronutrients there is no storage form of Zn in body, but serum Zn correlates reasonably well with intake[1]. In our study values were compared with the literature[16,17]. Low serum Zn levels was found in 30 from 32 dysphagic patients (94%) and serum Zn concentrations were severely decreased (mean: 46 μg/dl)[17,18,25].

One of the aims of our study was to compare serum concentration of Zn in the two major groups of long term dysphagic patients. Serum Zn was decreased in most of the patients of both HNC and ND groups. We found similar results for each one. For HNC and ND we found low values in serum Zn concentration (respectively 100%-88%), whole blood Zn concentration (respectively 53%-41%), serum albumin (respectively 40%-59%) and serum transferrin (respectively 66%-65%). All patients demonstrate a high prevalence of low serum concentration of nutritional markers. There was no significant difference in the two groups of patients. Only two patients presented with normal values (> 70 μg/dl). They were neurosurgical patients with traumatic brain injury. They both suffered an acute trauma, with an adequate oral intake prior to the accident. Acute traumatic brain injury patients displayed a normal serum Zn, not because of the nature of the underlying lesion, but because they were hospitalized since the beginning of the disorder causing dysphagia, and beneficiated from adequate nutritional support. So, the significant fall in serum Zn concentration of our patients seems related to the prolonged starvation induced by dysphagia and unrelated with the nature of the underlying disease. Acute traumatic brain injury patients had normal

Another aim of our study was to evaluate the relationship of serum concentration of Zn with total serum proteins, albumin and transferrin, serum markers of malnutrition and/or inflammation. Low serum Zn may be related with serum proteins through two mechanisms: (i) serum proteins and Zn may decrease in parallel, as a direct consequence of starvation; (ii) approximately 70% Zn in serum binds to serum

albumin[26] and serum Zn may decrease when albumin concentration falls. In our study, decreased serum Zn was found both in patients with normal and low albumin and with normal and low transferrin. Globally, decreased serum Zn cannot be ascribed to reduce albumin biding capacity. In the other hand, we identified a large number of patients with low serum Zn and normal albumin and transferrin. Most likely because the lack of major Zn reserves, serum Zn level seems to be more sensitive to shorter starvation periods then albumin or transferrin.

Serum Zn and whole blood Zn were compared with reference value. More than half, 53% of the patients, present normal values in Zn whole blood concentration, but, almost patients present low serum Zn, only two patient's present normal serum Zn. Whole blood Zn represents intracellular and extracellular Zn. Although serum Zn reflects reasonably daily intake, intracellular Zn has a much slower turnover and is less sensitive to progressive starvation. In order to identify patients that require Zn supplementation, serum Zn seems to be more sensitive and more useful than whole blood Zn. The data provided by the present study suggests that measuring whole blood Zn or even, as a possible alternative, measuring blood cell Zn, would not provide useful information for nutritional support of these patients.

This study supports the notion that patients with prolonged dysphagia are at risk of development of Zn deficiency. Zn deficiencies may develop subclinically and serum Zn evaluation should be included in the evaluation of dysphagic patients and, probably, in the evaluation of all malnourished patients, whatever the cause. Nevertheless, evaluating Zn serum concentrations is far from being easily available in many hospitals and health facilities. In our experience almost all patients presented serum Zn concentrations severely decreased. In dysphagic patients, serum Zn deficiency seem to be more frequent and earlier then dropping of serum proteins or BMI lowering. In dysphagic patients, if laboratory evaluation of Zn serum concentrations is not available, Zn deficiency should be assumed as very probable and supplementation should be provided, even without previous laboratory data.

Conclusions

In our experience most dysphagic patients had low Zn concentration when gastrostomy was performed and intensive nutritional support begun. This significant decrease in serum Zn concentration was found in patients with head and neck cancer as well as in neurological patients and seems to be related with prolonged fasting and unrelated with the nature of the underlying disease. Decrease in serum Zn concentration is unrelated with low serum proteins and a normal albumin level does not exclude Zn deficiency. Serum Zn is more sensitive than whole blood Zn for identifying Zn reduced intake.

As Zn is not routinely evaluated, the authors suggest that teams taking care of PEG-feed patients should include serum Zn concentration as part of the nutritional assessment, or include systematic dietary Zn supply in the nutritional therapy protocol.

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