OLIGOELEMENTOS EM DOENTES SUBMETIDOS A GASTROSTOMIA ENDOSCÓPICA PERCUTÂNEA PARA NUTRIÇÃO ENTÉRICA DE LONGA DURAÇAO

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Tese para obtenção do grau de Doutor em Ciências da Vida
na Especialidade de Investigação Clínica
na Faculdade de Ciências Médicas da Universidade Nova de Lisboa

dezembro, 2015

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Esta Dissertação integra-se no percurso do Grupo de Estudo de Nutrição Entérica (GENE) do Hospital Garcia de Orta.

O GENE dedica-se à implementação da Nutrição Artificial de longa duração em doentes ambulatórios (nutrição entérica na sua maioria) e apoia também doentes internados.

Em 1999 com o início das gastrostomias endoscópicas o grupo sentiu a necessidade de apoiar estes doentes de forma específica e multidisciplinar. Desde então desenvolveu atividade em 3 vertentes: assistencial, formativa e científica. Assistiu mais de 1000 doentes ambulatórios incluindo 800 gastrostomizados/jejunostomizados. Aceitou dezenas de estagiários pré e pós graduados numa época em que acompanhar estes doentes de forma integrada era ainda excecional. Desenvolveu múltiplos cursos de formação e de pós-graduação em Nutrição Artificial e esteve presente contribuindo com a sua experiência noutros cursos de várias instituições académicas e científicas. Desde o início desenvolveu investigação científica nesta área com dezenas de apresentações, de publicações, teses de mestrado e a atual dissertação.

If I have seen further, it is by standing on the shoulders of giants

Sir Isaac Newton, 1676

à minha filha Carla

aos meus Pais

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LISTA DE ABREVIATURAS

AVC	Acidente Vascular Cerebral
CCF	Cancro Cervicofacial
Cr	Crómio
Cu	Cobre
CuZn	Cobre/zinco superóxido dismutase
DiOs	Tetraiodotironina 5 desiodases
DN	Doenças Neurológicas
DRI	Dietary Reference Intakes (Ingestão Dietética Recomendada)
ELA	Esclerose Lateral Amiotrófica
Fe	Ferro
FTG	Fator de tolerância à glucose
GPxs	Glutationa-peroxidases
IA	Ingestão adequada
Kcal	Kilocalorias
mg	Miligramas
NE	Nutrição entérica
OMS	Organização Mundial de Saúde
PEG	Gastrostomia Endoscópica Percutânea
PEJ	Jejunostomia Endoscópica Percutânea
PEG-J	Gastrostomia Endoscópica Percutânea com extensão jejunal
PJ	Jejunostomias Percutâneas
PSJ	Jejunostomias Percutâneas Cirúrgicas
RDA	Recommended Dietary Allowance (Recomendação Dietética de Referência)
Se	Selénio
Sec	Selenocisteína
SeMet	Selenometionina
SNE	Sonda nasoentérica
SNG	Sonda nasogástrica
SNJ	Sonda nasojejunal
SNO	Suplementos nutricionais orais

TCE	Traumatismo Cranioencefálico
TRXRs	Tioredoxina redutases
UL	Limite Superior Tolerável de Ingestão
Zn	Zinco
µg	Microgramas

RESUMO

Os oligoelementos (ou elementos-traço) são elementos inorgânicos necessários em pequenas quantidades como componentes essenciais de estruturas biológicas. São fornecidos pelos alimentos e encontram-se amplamente difundidos nestes. Uma alimentação saudável deverá fornecer todos estes oligoelementos em doses suficientes para não surgir carência. A sua concentração é regulada através do processo de absorção pelo tubo digestivo e da sua excreção. Alguns podem ser armazenados em locais inativos ou numa forma não-reativa evitando tanto a sua deficiência como o seu excesso. No entanto, em situações de carência alimentar prolongada e/ou ingestão alimentar monótona podem surgir carências em um ou mais oligoelementos podendo resultar em compromisso do metabolismo e danos para o doente.

Doentes com disfagia prolongada apresentam carência em macronutrientes pela reduzida e quase sempre monótona, ingestão alimentar. A intervenção nutricional com alimentação entérica por gastrostomia pode ocorrer tardiamente, quando os doentes já apresentam carências energéticas e proteicas. Em Portugal, na alimentação por gastrostomia utilizam-se habitualmente alimentos comuns que podem fornecer as necessidades em macronutrientes mas poderão não compensar as necessidades em oligoelementos. Estes quadros carenciais podem ter sinais evidentes, mas é de salientar que no caso das carências subclínicas prolongadas, podem existir consequências biológicas e clínicas relevantes, que passam desapercebidas. A identificação de carências específicas em doentes com disfagia e sob nutrição entérica poderá constituir um avanço no suporte nutricional e permitir uma intervenção mais efetiva.

Os cinco artigos que compõem esta tese pretendem explorar e responder a esta problemática. Nos doentes com patologia neurológica ou carcinoma cervicofacial com disfagia prolongada e que foram submetidos a gastrostomia endoscópica, foi nosso objetivo identificar o padrão sérico de 5 oligoelementos: zinco (Zn), selénio (Se), cobre (Cu), crómio (Cr) e ferro (Fe) durante os primeiros meses de nutrição entérica por gastrostomia. Foi também nosso objetivo avaliar a evolução das proteínas séricas nestes doentes e ainda perceber como a concentração sérica dos oligoelementos é influenciada por idade, género e pela patologia de base conducente à disfagia. A avaliação foi feita em

três momentos: no momento da gastrostomia endoscópica (T0), 4 (T1) e 12 (T3) semanas depois.

No momento T0 verificou-se que o Zn foi o oligoelemento que surgiu com mais baixa concentração sérica na maioria dos doentes. Identificou-se igualmente uma baixa concentração de Zn no sangue total que reflete o Zn intracelular. Contrariamente, os outros oligoelementos apresentavam valores dentro dos limites da normalidade na maioria dos doentes. Não foi encontrada qualquer associação entre a concentração sérica de oligoelementos e a doença subjacente, as proteínas séricas e o Índice de Massa Corporal.

Na avaliação da concentração sérica dos mesmos oligoelementos durante 4 a 12 semanas de uso da gastrostomia endoscópica, verificámos que os oligoelementos se comportaram de forma diversa. Assim, relativamente ao Zn, verificou-se manutenção de valores séricos baixos na maioria dos doentes. Os restantes oligoelementos responderam favoravelmente à alimentação por PEG com alimentos correntes, mesmo estando inicialmente abaixo dos valores normais. Quanto às proteínas séricas, aumentaram os seus valores. Destes resultados podemos destacar: 1) a importância da monitorização de oligoelementos em doentes com disfagia prolongada e sob nutrição entérica através de gastrostomia, 2) a necessidade de uma intervenção precoce e monitorização de resultados 3) a necessidade de suplementação precoce com Zn.

Palavras-chave: oligoelementos, desnutrição, nutrição entérica, gastrostomia, disfagia.

ABSTRACT

Trace elements are inorganic elements present in small amounts as essential components of biologic structures. They are widely distributed in the food, hence a healthy diet should be able to provide sufficient amount of trace elements to prevent deficiencies. Trace elements concentration is regulated through the digestive track absorption and excretion processes. Some elements may be stored in inactive locations or in a non-reactive state, preventing both deficiency and excess. However, in situations of prolonged malnutrition and/or monotonous feeding, deficiencies in one or more trace elements may arise, resulting in impaired metabolic pathways and patient damage.

Patients with prolonged dysphagia may present macronutrient deficiency due to the reduced and almost always monotonous dietary intake. Nutritional intervention through gastrostomy may be delayed to a point where patients already present both calorie and protein deficiencies. In Portugal, common homemade food is usually used in gastrostomy feeding but, while it can meet the patient's macronutrient needs, it may fail to supply trace element needs. These deficiency frameworks may have evident signs, but it should be noted that there be relevant biological and clinical consequences in cases of prolonged subclinical deficiencies without clinical signs. Identifying specific deficiencies in dysphagia patients undergoing enteral feeding may become an advance in nutritional support and make way for a more effective intervention.

The five articles that compose this thesis intend to explore and provide an answer to this issue. In neurologic or head and neck cancer patients, with prolonged dysphagia undergoing endoscopic gastrostomy, our goal was to identify the serum pattern of five trace elements during the first months after the procedure: zinc (Zn), selenium (Se), copper (Cu), chromium (Cr) and iron (Fe). As an additional goal, we evaluated evolution of serum protein concentration in these patients and attempted to understand how serum trace elements concentration is influence by age, gender and underlying dysphagia-inducing disease.

Evaluation was conducted in three moments in time: at the time of gastrostomy (T0), and four weeks (T1) and twelve weeks (T3) following the procedure.

At T0, we verified that Zn was the trace element with the lowest serum concentration in the majority of our patient sample. We identified also a low all blood Zn concentration which

reflects intracellular Zn. Conversely, the remaining trace elements present normal values in the majority of the sample. No relationship was found between trace elements serum concentration and underlying disease, serum proteins and Body Mass Index.

In serum concentration of the same trace elements at four and twelve weeks following the gastrostomy procedure, it was verified that trace elements present distinctive behaviors. Zn concentration remains low in the majority of patients, while the remaining trace elements responded positively to PEG feeding with homemade meals, even in cases where initial serum concentration was low. Moreover, serum protein concentration also improved. From these results, we can highlight the importance of monitoring trace element concentration in patients with prolonged dysphagia undergoing PEG feeding and the need for an early Zn supplementation.

Key words: trace elements, malnutrition, enteral feeding, gastrostomy, dysphagia.

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PUBLICAÇÕES:

1. **Carla Adriana Santos**, Jorge Fonseca, José Brito, Tânia Fernandes, Luísa Gonçalves, António Sousa Guerreiro. “Serum Zn levels in dysphagic patients who underwent endoscopic gastrostomy for long term enteral nutrition”.
   Nutr Hosp. 2014;29(2):359-364.

2. **Carla Adriana Santos**, Jorge Fonseca, Elisabete Carolino, António Sousa Guerreiro“. Serum trace elements in dysphagic gastrostomy candidates before endoscopic gastrostomy for long term enteral feeding”.
   Clin Nutr. 2015. DOI: 10.1016/j.clnu.201505.006.

3. **Carla Adriana Santos**, Jorge Fonseca, Teresa Lopes, Elisabete Carolino, António Sousa Guerreiro. "Selenium in dysphagic patients that underwent endoscopic gastrostomy for long term enteral feeding".
   Nutr Hosp. 2015;32(6):2725-33.

4. **Carla Adriana Santos**, Jorge Fonseca, Teresa Lopes, Elisabete Carolino, António Sousa Guerreiro. "Serum zinc evolution in dysphagic patients that underwent endoscopy gastrostomy for long term enteral feeding".
   Asia Pac J Clin Nutr. 2015 [In press].

5. **Carla Adriana Santos**, Jorge Fonseca, Teresa Lopes, Elisabete Carolino, António Sousa Guerreiro. "Serum Copper evolution in patients that underwent endoscopic gastrostomy for long term enteral feeding".
   Nutr Hosp. 2015 Under review.

COMUNICAÇÕES:

Carla Santos, José Brito, Tânia Fernandes, Jorge Fonseca. Zinco Sérico em Doentes Disfágicos Submetidos a Gastrostomia Endoscópica para Nutrição Entérica Prolongada" **–** Comunicação oral
Semana Digestiva/XXXIII Congresso Nacional de Gastrenterologia e Endoscopia Digestiva, Vilamoura 2013

6. **Santos CA,** Fonseca J, Fernandes T, Brito J. Serum Zn levels in dysphagic patients who underwent endoscopic gastrostomy for long term enteral feeding - Poster
   35th ESPEN Congress", Leipzig – Germany, Set 2013

7. **Carla Adriana Santos,** Jorge Fonseca. Trace elements status in patients referred to gastrostomy for prolonged enteral nutrition - Poster
   36th ESPEN Congress", Gèneve - Switzeland, Set 2014

8. **Carla Adriana Santos**, Jorge Fonseca, Elisabete Carolino, António Sousa Guerreiro". Serum trace elements in dysphagic gastrostomy candidates before endoscopic gastrostomy for long term enteral feeding" – Comunicação oral
   37th ESPEN Congress", Lisboa - Portugal, Set 2015

CAPITULO 1

INTRODUÇÃO

Este estudo surge na sequência de um trabalho continuado de vários anos em Nutrição Artificial no Grupo de Estudo de Nutrição Entérica (GENE) do Hospital Garcia de Orta onde têm sido seguidas muitas centenas de doentes sob nutrição entérica e também sob nutrição parentérica. Pretendeu responder a uma das muitas questões que o acompanhamento clínico destes doentes repetidamente nos põe.

Os doentes que requerem nutrição artificial habitualmente estão em risco de desnutrição ou desnutridos, com carências em macronutrientes e micronutrientes. A carência em macronutrientes dos nossos doentes foi estudada na minha dissertação de mestrado a qual demonstrou que estes doentes quando referenciados para gastrostomia já apresentavam desnutrição grave, traduzida tanto nos parâmetros antropométricos como nos laboratoriais. Estes resultados foram apresentados de forma a demonstrar a necessidade de uma intervenção nutricional mais precoce permitindo uma atuação efectiva e tentando melhorar o prognóstico. Em continuidade com o trabalho anterior, este estudo tem como objetivo identificar a carência em micronutrientes, nomeadamente oligoelementos, no momento da gastrostomia e a sua relação com a deficiência energética e proteica causada pela disfagia. A carência de oligoelementos pode ocorrer por suporte nutricional inadequado e/ou por aumento das necessidades ou das perdas. A sua gravidade depende do estado nutricional anterior, da duração e gravidade da patologia subjacente, das perdas de nutrientes acrescidas e/ou do hipermetabolismo. É espectável que doentes disfágicos possam desenvolver carências em oligoelementos e que posteriormente, após a gastrostomia sob nutrição entérica prolongada, possam manter ou agravar estas carências em oligoelementos, pelas doenças consumptivas e pela reduzida e monótona ingestão alimentar durante um longo período. Acresce que em Portugal o Serviço Nacional de Saúde não tem um mecanismo formal e genérico de comparticipação para aquisição de produtos para nutrição entérica. Com algumas exceções pontuais e muito minoritárias as formulações definidas pela União Europeia como “alimentos dietéticos para fins medicinais específicos”, têm de ser custeados pelos doentes e cuidadores. A larga maioria dos nossos doentes sob nutrição entérica prolongada recorre a alimentação de preparação doméstica, que é a única fonte de oligoelementos. Assim,

mesmo após a gastrostomia e durante a nutrição entérica regular, a evolução das concentrações séricas dos oligoelementos tem sido desconhecida.

Pretendeu-se com este estudo avaliar os doentes com disfagia, no que diz respeito às concentrações em oligoelementos no momento da gastrostomia e determinar como a alimentação com alimentos correntes poderá influenciar a evolução daquelas concentrações. Os resultados poderão fundamentar uma intervenção efetiva e precoce, melhorando o apoio clínico e nutricional a estes doentes.

I) FUNDAMENTAÇÃO TEÓRICA

1. Oligoelementos

1.1. Características Gerais

Os oligoelementos (ou elementos-traço) são elementos inorgânicos necessários em pequenas quantidades como componentes essenciais do metabolismo humano.[1-3] Surgem como iões carregados ou como co-fatores de enzimas ou parte delas (p. ex. metaloenzimas). [4,5] Devem ser fornecidos pela alimentação e a sua necessidade varia de miligramas a microgramas por dia. A sua concentração é regulada entre o processo de absorção pelo tubo digestivo e a sua excreção. Alguns podem ser armazenados em locais inactivos ou numa forma não-reactiva evitando tanto a sua deficiência como o seu excesso.

Todos os oligoelementos apresentam potencial para provocar toxicidade mas, apenas relativamente a alguns a comunidade científica identificou sinais e sintomas de deficiência como no caso da deficiência em ferro, mundialmente difundida. Por outro lado outros oligoelementos, como o selénio, apenas geram carência em alguns grupos populacionais ou em contextos específicos. [6-8] Algumas deficiências são difíceis de detetar pois os efeitos ocorrem ao nível celular e subcelular sem manifestações clínicas evidentes.[9] A prazo, as deficiências subclínicas prolongadas sem sinais evidentes, podem trazer graves consequências. É aqui que deve incidir a nossa atenção. [10,11]

Existe uma crescente preocupação relativamente a deficiências nutricionais no desenvolvimento de doenças degenerativas relacionadas com o envelhecimento, como o cancro e as doenças neurodegenerativas. [12-14] As grandes dificuldades na definição do papel dos oligoelementos no contexto destas doenças incluem as dificuldades na sua avaliação em seres humanos, definição de necessidades e ainda a sua interação com outros minerais com compostos orgânicos e com medicamentos.

Identificamos os elementos considerados essenciais ao organismo humano, para os quais existem DRI's (Dietary References Intake) definidas, incluindo Ferro, Zinco, Cobre, Selénio, Iodo, Manganésio, Molibdeno, Flúor, Crómio. Outros elementos presentes na Tabela Periódica, podem ser identificados como essenciais como é o caso do Alumínio,

Arsénio, Boro, Cádmio, Germânio, Chumbo, Lítio, Níquel, Rubídio, Sílica e Vanádio embora não estejam bem definidas as suas funções biológicas e a sua importância metabólica, nem estejam determinados estados carênciais específicos. [15-18] A maioria dos estudos tem sido efetuada em animais e não têm DRI's estabelecidas.[19] Serão explorados, nesta dissertação, os cinco oligoelementos Ferro (Fe), Zinco (Zn), Cobre (Cu), Selénio (Se) e Crómio (Cr) por terem quadros clínicos e manifestações biológicas de carência bem estudadas. Optámos por não incluir outros elementos com carências bem estudadas mas relacionadas com órgãos específicos, como o Iodo por ser maioritariamente ligado à patologia tiroideia e o Flúor por estar sobretudo relacionado com a fisiopatologia dentária.

1.2. Zinco

1.2.1. Bioquímica e papel biológico do zinco

O Zinco (Zn) é um dos mais importantes oligoelementos e está envolvido em três funções maiores, catalítica, reguladora e estrutural.[20,21] Foi descrito pela primeira vez, em 1869, por Raulin, que revelou o seu papel no crescimento do fungo, *Aspergillus Níger*.[22] Os primeiros contributos decisivos para a compreensão da importância biológica do Zn surgiram em 1940 com a identificação da primeira metaloenzima dependente de Zn, a anidrase carbónica, importante na homeostase ácido-base e, mais tarde em 1985, com a descoberta dos domínios dedo de zinco (zinc finger domain).[23]

Está envolvido na atividade de mais de 300 enzimas, pode atuar como co-fator catalítico ou co-catalítico e na atividade catalítica, nomeadamente enzimas proteicas e síntese de ácidos nucleicos ou como componente integrante estabilizando a estrutura terciária em proteínas, como na formação de dedos de zinco. Pode estar associado a um maior número de proteínas formando os domínios de ligação como os dedos de Zn, domínios dedos RING e domínios LIM por ligação aos resíduos de cisteína e histidina (Cys4 ou Cys2His2) [24,25] que se encontram em posições conservadas dentro da sequência polipeptídica, com um papel alargado no controle da transcrição e expressão de genes [23,25,26] e na síntese de DNA e RNA.[27-29] Pela ligação à metalotioneina protege contra o stress oxidativo [28,30] inibindo a propagação de radicais livres ao ligar-se seletivamente a iões metálicos pro-oxidantes.[31-36]

O marcador mais utilizado na avaliação do Zn no organismo é a sua concentração sérica que se relaciona bem com a ingestão.[37,38] A concentração sérica normal é de aproximadamente 70-100µg/dl e o plasma é a fonte primária deste elemento para todas as células, apresentando uma dinâmica rápida e sob um controlo homeostático preciso. Os níveis séricos de Zn são um marcador de prognóstico e de resposta terapêutica.[39,40] Como o Zn é maioritariamente transportado no plasma ligado à albumina (±70%) e a outras proteínas como a 2-macroglobulina, a transferrina e a imunoglobulina, a interpretação do Zn sérico deve ser feita em conjunto com as alterações na albumina, transferrina e outras proteínas.[41] Os valores de Zn no sangue total refletem modificações lentas e são fortemente influenciado pelo Zn eritrocitário.

1.2.2. Recomendações nutricionais

Em 1974 foram estabelecidas as RDA, pela *Food and Nutrition Board of the National Research Council da USA National Academy of Sciences*. Em substituição das RDA foram emitidas DRI's pela OMS em 2001. As DRI para o Zn, são de 11 mg/dia para homens e 8 mg/dia para mulheres.[42] O nível de Zn considerado seguro para adultos é baseado na redução na atividade da Cu/Zn superóxido-dismutase eritrocitária.

O Zn está amplamente distribuído nos alimentos. [43,44] Fontes ricas em Zn incluem a carne, peixe, marisco, nozes, sementes, legumes, grãos de cereais e alguns cereais de pequeno-almoço enriquecidos neste elemento. Sendo o Zn encontrado maioritariamente no gérmen e no farelo dos cereais, cerca de 80% do total é perdido durante a moagem, razão pela qual os grãos integrais tendem a ser mais ricos em Zn do que os grãos refinados não fortificados. [45-48] Contudo, fontes vegetais são consideradas menos biodisponíveis pela presença de ácido fítico que se liga ao Zn formando complexos insolúveis, inibindo a sua absorção. As dietas vegetarianas, sem adequada supervisão, são um fator de risco para o desenvolvimento da deficiência neste elemento.

DRI's para o Zinco

Food and Nutrition Board, Institute of Medicine, National Academies

Infants		Children		Man		Woman		Pregnancy	
0-6 mo	2 mg/d	1-3 y	3 mg/d	9-13 y	8 mg/d	9-13 y	8 mg/d	≤ 18 y	12 mg/d
7-12 mo	3 mg/d	4-8 y	5 mg/d	14-18 y	11 mg/d	14-18 y	9 mg/d	19-30 y	11 mg/d
				19-30 y	11 mg/d	19-30 y	8 mg/d	31-50 y	11 mg/d
				31-50 y	11 mg/d	31-50 y	8 mg/d	Lactation	
				51-70 y	11 mg/d	51-70 y	8 mg/d	≤ 18 y	13 mg/d
				>70 y	11 mg/d	>70 y	8 mg/d	19-30 y	12 mg/d
								31-50 y	12 mg/d

FONTE: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed via www.nap.edu.

1.2.3. Síndromes clínicas de deficiência e estados de deficiência subclínicos

A deficiência em Zn é comum, mesmo nos países desenvolvidos e a maior causa de morbilidade neste contexto.[49,50] Estima-se a sua carência mundial possa atingir os 2 mil milhões de indivíduos.[51,52] Em 1960 no Irão e no Egipto, foi encontrada e descrita pela primeira vez a sua deficiência clínica em adolescentes masculinos que apresentavam baixa estatura e hipogonadismo. Cavdar *et al* conduziram um estudo da carência de Zn na geofagia e demonstraram que com a sua suplementação, estes adolescentes apresentaram aumentos significativos na estatura, peso, desenvolvimento ósseo e maturação sexual secundária. [53]

A deficiência deste oligoelemento pode ser adquirida ou hereditária, como na Acrodermatite Enteropática (Doença de Danbolt-Closs), uma doença autossómica recessiva.[54,55] A deficiência adquirida em Zn deve-se habitualmente à ingestão dietética deficiente, independentemente do motivo. Habitualmente está associada a alguns grupos vulneráveis tais como idosos, alcoólicos, nutrição parentérica prolongada sem suplementação adequada (deste oligoelemento), tratamento com penicilamina (usada no tratamento da doença de Wilson), doentes portadores de doenças crónicas (diabetes, insuficiência renal, síndrome do intestino curto, entre outras) e a perdas digestivas excessivas (diarreia, vómitos e fistulas de alto débito.[56,57], motivo pelo qual a organização Mundial de Saúde (OMS) alertou para a sua ocorrência nos países desenvolvidos.[26]

A deficiência em Zn diminui a expressão da metalotioneina aumentando a suscetibilidade para transformações induzidas pelo Cr (VI) promovendo a carcinogénese.[58] Pode desenvolver alterações fisiopatológicas que incluem disfunção no sistema imune, aumento do stresse oxidativo, aumento na geração de citoquinas inflamatórias, aumento da incidência de doenças neurodegenerativas como a doença de Alzheimer e a doença de Parkinson.[59-61] As manifestações clínicas desta deficiência em humanos incluem atraso de crescimento e desenvolvimento, erupções cutâneas, dificuldades de cicatrização, dermatite bolhosa, imaturidade sexual, alopecia, diarreia, perda de peso e morte. As deficiências subclínicas podem estar associadas ao aumento da morbilidade, envolvendo alterações no sistema imunitário e atraso na cicatrização. [62,63] São estas deficiências,

sem sinais clínicos, que exigem antecipação de suspeitas e atuação precoce, antes do quadro clínico ser evidente.

Não existe reserva funcional de Zn no organismo, pelo que uma adequada ingestão dietética com alimentos ricos neste oligoelemento é necessária numa base regular. É fundamental a ingestão de alimentos de origem animal tais com carne vermelha, aves, peixe, fontes ricas e rapidamente disponíveis em Zn dietético atribuídas à libertação de L-aminoácidos e cisteína. A exceção é o leite de vaca que não apresenta este efeito provavelmente devido ao seu conteúdo em caseína e ao elevado teor em cálcio. A baixa ingestão dos alimentos ricos em Zn é o principal motivo da sua deficiência. Outros fatores dietéticos como o conteúdo em fitatos da dieta, podem influenciar a biodisponibilidade do Zn, causando formação de complexos insolúveis no tubo digestivo. O conteúdo em fitatos foi identificado como um problema em países onde os menus são baixos em alimentos de origem animal e ricos em grãos abundantes em fitatos, cereais e legumes.[64,65] Dietas com elevado valor energético parecem promover a deficiência funcional em Zn pois a relação ideal para a sua utilização é de 2µg Zn/Kcal.

Comparativamente com outros iões metálicos com propriedades químicas semelhantes, o Zn é relativamente inofensivo.[66] Apenas em doses muito elevadas, entre 100-300 mg/dia, doses suprafisiológicas, podem ter efeito tóxico o que faz com que estas intoxicações agudas sejam raras.[67]

Grupo de risco para desenvolver carência de zinco

1. Idosos
2. Amamentação exclusiva com leite materno > 6 meses
3. Vegetarianos
4. Alcoólicos
5. Doenças crónicas: Diabetes
Insuficiência renal crónica
Insuficiência hepática
Insuficiência pancreática
Síndromes de má absorção
Infecção
Sepsis
Dermatites extensas

1.3. Selénio

1.3.1. Bioquímica e papel biológico do Selénio

O Selénio (Se) é um elemento essencial, sendo necessário muito pequenas quantidades para o metabolismo humano.[68,69] Considerado originalmente como um elemento tóxico, é hoje classificado como um oligoelemento fundamental na saúde humana. Foi inicialmente isolado e identificado pelo químico suíço Jöns Jakob Berzelius em 1817 que o batizou em homenagem a deusa da Lua, *Selene*, em Grego.[70] É um elemento não-metálico apresentando como formas predominantes, o selenato de sódio, o selenido (H_2Se), o selenito (SeO_3^{2-}) e os aminoácidos selenometionina (SeMet) e selenocisteína (Sec), sendo estas formas metabolizadas e utilizadas na síntese de selenoproteínas.[70-72] O selenato inorgânico e a selenite estão predominantemente na água enquanto os compostos orgânicos de Se (SeMet e Sec) encontram-se nas proteínas dos alimentos constituindo a principal fonte de Se nos mamíferos. As selenoproteínas apresentam funções anti-oxidantes, anti-inflamatórias, anti-tumorogenicas, anti-angiogenicas, anti-aterogenicas e imunomoduladoras. [73,74] Há três classes de selenoproteinas com funções essenciais: GPXs (Glutationa-peroxidases), TRXRs (Tioredoxina redutases) e as DIOs (Tetraiodotironina 5 desiodases).[75-78]

Existem duas reservas maiores de Se no organismo humano. A primeira é a selenometionina e a segunda é a GPX do fígado. O conteúdo em Se nos tecidos selénio-dependentes como o fígado, rins e músculo e a expressão das GPXs é controlado pelo Se dietético.[79] A sua absorção ocorre no intestino delgado, maioritariamente no duodeno.[80] As formas orgânicas de Se são melhor absorvidas e têm maior biodisponibilidade do que as inorgânicas (como o selenito e o selenato).[81]

Selenoproteínas humanas

Selenoproteínas	Funções
Tireorredoxina redutase (TrxR1, TrxR2, TrxR3)	Redução da tireoxina envolvida em processos biológicos tais como replicação de ADN, regulação da transcrição do fator de atividade e apoptose. Redução de outros substratos como a selenite, peróxidos de lípidos, vitamina C e GPx.
Iodotironina deiodinase (DIO1, DIO2, DIO3)	Síntese da forma activa da hormona tiroideia T3 (DIO1 e DIO2) e a sua inactivação (DIO3)
Glutationa peroxidases (GPx):	
. GPX Citosolico (GPx 1)	Redução H_2O_2 e hidroperoxidases orgânicas
. GPx especifica gastrointestinal (GPx 2)	Redução H_2O_2 e hidroperoxidases orgânicas
. GPx do plasma (GPx 3)	Redução H_2O_2 e hidroperoxidases orgânicas
. GPx hidroperoxidade fosfolipidica (GPx 4)	Redução direta das hidroperoxidases dos fosfolipidos e colesterol
. GPx olfactivo (GPx 6)	Pode ter papel antioxidante: encontrado apenas nos embriões e epitélio olfactivo do adulto
Selenofosfatase sintetase 2 (SPS2)	Biosíntese da monoselenofosfato, dador activo de selénio necessário à formação de selenocisteína durante a síntese de selenoproteínas
Selenoproteínas P (Sel P)	A maior selenoproteínas do plasma sanguíneo, com funções como anti-oxidantes e responsável pelo transporte de selénio do fígado para outros tecidos
Selenoproteínas M (Sel M) e selenoproteínas 15 (Sep15)	Possivelmente envolvidas na dobragem das proteínas no reticulo endoplasmático
Selenoproteínas N (Sel N)	Pode ser requisitada para a formação primaria dos músculos; mutação no gene Sel N pode associar-se a distúrbios musculares
Selenoproteínas R (Sel R, MsrB1)	Redução dos resíduos de metionina oxidada nas proteínas
Selenoproteínas S (Sel S)	Pode ter papel antioxidante. Possivelmente envolvida na remoção de proteínas deformadas do reticulo endoplasmático para degradação no citosol
Selenoproteínas W (Sel W)	Parece ter papel antioxidante. Encontrada maioritariamente no músculo e cérebro
Sel H, Sel I, Sel K, Sel O, Sel T, Sel V	Pouco definidas ou sem função conhecida

Adaptado de (Gromadzinska et al. 2008; Lu and Holmgren 2009; Moghadaszadeh and Beggs 2006; Reeves and Hoffman 2009)

1.3.2. Recomendações nutricionais

As recomendações de Se estão baseadas na quantidade deste elemento necessária para otimizar a atividade da GPX. A RDA é idêntica para homens e mulheres e são de 55 µg/dia.[82]

O Se está presente nos alimentos predominantemente na forma de SeMet (o principal composto de Se encontrado inicialmente em animais que receberam este selenoaminoácido mas que é posteriormente convertido em Sec), Sec (o selenoaminoácido predominante nos tecidos quando é dado Se inorgânico aos animais), selénio-metilselenocisteina (o maior composto de Se encontrado em plantas ricas em Se como o alho, cebola e brócolos) e selenato (o maior composto inorgânico abundante nos tecidos animais e vegetais).[83,84]

Está presente na carne, peixe e outros produtos do mar, leite e lacticínios, pão, cereais, nozes, fruta, vegetais e a maioria apresenta alta biodisponibilidade. Contudo, a quantidade e o tipo de Se nos alimentos varia grandemente e depende da quantidade de Se no solo e da sua composição.[85]

Dietary Reference Intakes (DRIs): Selenium
Food and Nutrition Board, Institute of Medicine, National Academies

Infants		Children		Man/ Woman		Pregnancy	
0-6 mo	15 µg/d	1-3 y	20 µg/d	9-13 y	40 µg/d	≤ 18 y	60 µg/d
7-12 mo	20 µg/d	4-8 y	30 µg/d	14-18 y	50 µg/d	19-30 y	60 µg/d
				19-30 y	50 µg/d	31-50 y	60 µg/d
				31-50 y	50 µg/d	Lactation	
				51-70 y	50 µg/d	≤ 18 y	70 µg/d
				>70 y	50 µg/d	19-30 y	70 µg/d
						31-50 y	70 µg/d

FONTES: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed via www.nap.edu.

1.3.3. Síndromes clínicas de deficiência e estados de deficiência subclínica

A deficiência em Se está associada a duas doenças endémicas da China, dependentes do baixo conteúdo deste elemento no solo, a doença de Keshan e a síndrome de Kashin-Beck.[86,87] As deficiências podem também ocorrer por ingestão inadequada, aumento das necessidades, aumento das perdas, afetando vários processos bioquímicos, estando associadas a um aumento da incidência de cancro, infertilidade, má cicatrização, diminuição da função imune e aumento da mortalidade.[88-94] Também a nutrição

parentérica prolongada foi identificada como uma causa de deficiência grave em Se associada a alterações no músculo-esquelético.[95]

A suplementação para a população em geral não está recomendada, mas indivíduos com risco de desenvolver carência devem ser suplementados. Populações de zonas endémicas com solos de baixa concentração de Se, vegetarianos, portadores de doenças que comprometam a ingestão e/ou absorção, a nutrição parentérica de longa duração, estão em risco de deficiência e devem ser suplementados. Doentes desnutridos, com risco de deficiência de Se merecem atenção especial, bem como aqueles submetidos a qualquer forma de nutrição artificial por períodos prolongados.

O UL é baseado nos efeitos adversos da selenose (toxicidade). Para os EUA está estabelecido nos 400 µg/dia e para o Reino Unido 300 µg/dia.

1.4. Cobre

1.4.1. Bioquímica e papel biológico do Cobre

O Cobre (Cu) é o 3.º metal de transição mais abundante no corpo humano, depois do Ferro (Fe) e do Zn. Surge em quatro estados de oxidação (Cu^0, Cu^{+1}, Cu^{+2} e Cu^{+3}) predominando nos sistemas biológicos como Cu^{+2}. É um cofator de diversas enzimas fundamentais: a citocromo-*c* oxidase, a lisil oxidase, a CuZn superóxido dismutase, a metano monooxigenase, a tirosinase e a ceruloplasmina. Vários mecanismos dependentes do Cu têm sido propostos na angiogénese, fatores de crescimento e outros agentes de sinalização relevantes para o crescimento de tumores.

O Cu é absorvido na parte proximal do tubo digestivo, estômago e duodeno, mas o local de absorção máxima continua por identificar. A sua absorção varia entre <20% com uma ingestão>5mg/dia até >50% com uma ingestão <1 mg/dia.[42] A absorção e disponibilidade podem ser influenciadas por fatores independentes das concentrações de Cu no organismo. O ácido clorídrico facilita a disponibilidade de Cu no intestino delgado. A absorção também é influenciada pela competição de vários iões, incluindo o Zn, o Fe, o molibdénio, o chumbo e o cádmio. O Zn e o cádmio parecem ser os inibidores mais potentes da absorção, possivelmente pela competição com o Cu para o transporte e/ou pelo aumento das concentrações intestinais de metalotioneínas. Os polímeros de glicose aumentam o co-transporte de Cu e água para as células intestinais, no entanto, a frutose e outros hidratos de carbono, as fibras vegetais, os fitatos e a diminuição de sódio no lúmen intestinal inibem a absorção intestinal. [96] Grandes concentrações de aminoácidos e péptidos podem ligar-se ao Cu e reduzir a sua absorção. Contudo, em concentrações moderadas estes ligandos podem reduzir a formação de hidróxido de Cu e aumentar a absorção deste elemento. [97] Ácidos orgânicos como os citratos, lactatos e o glutamato aumentam a solubilidade e a absorção de Cu. O fígado é o órgão central na homeostase do Cu, envolvido nos mecanismos de transporte, absorção, armazenamento e excreção.

Dada a sua importância nutricional, as deficiências subclínicas devem ser consideradas, particularmente nos grupos de risco. A intervenção deve ser precoce através de alterações dietéticas ou de suplementação.

1.4.2. Recomendações nutricionais

As RDAs estabelecidas para o Cu são entre 700 a 900 µg/dia (0,9mg) para adolescentes e adultos de ambos os géneros, entre 340 e 440 µg/dia para crianças e para lactentes entre 200 e 220 µg/dia.(98)

O nível máximo de Cu considerado seguro (UL) para adultos é de 10000 µg/dia. Nas crianças o UL varia com a idade: 1-3 anos/1000 µg/dia; 4-8 anos/3000 µg/dia; 9-13 anos/5000 µg/dia; 14-18 anos/8000 µg/dia. O UL para crianças com idade inferior a 1 anos não está estabelecido.(99)

Encontra-se numa grande variedade de alimentos, à exceção do leite de vaca que contém apenas valores entre 150 µg/L a 180 µg/L. A ingestão diária aponta estar entre 600 e 2000µg/dia. Os alimentos mais ricos em Cu, são os mariscos (ostras), vísceras (fígado e rim), carnes (músculo), legumes, chocolates, nozes, grãos de cereais, leguminosas e frutas secas. O Cu fornecido pelas bebidas não tem expressão.

Dietary Reference Intakes (DRIs): Copper
Food and Nutrition Board, Institute of Medicine, National Academies

Infants		Children		Man/ Woman		Pregnancy	
0-6 mo	200 µg/d	1-3 y	340 µg/d	9-13 y	700 µg/d	≤ 18 y	1000 µg/d
7-12 mo	220 µg/d	4-8 y	440 µg/d	14-18 y	890 µg/d	19-30 y	1000 µg/d
				19-30 y	900 µg/d	31-50 y	1000 µg/d
				31-50 y	900 µg/d	Lactation	
				51-70 y	900 µg/d	≤ 18 y	1300 µg/d
				>70 y	900 µg/d	19-30 y	1300 µg/d
						31-50 y	1300 µg/d

FONTES: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). www.nap.edu.

1.4.3. Síndromes clínicas de deficiência e estados de deficiência subclínica

Instabilidades na homeostase do Cu provocam alterações na homeostase do Fe. A deficiência em Cu está associada a alterações neurológicas, principalmente polineuropatia desmielinizante e mielopatia.[100] Observam-se também alterações vasculares, por falha nas ligações cruzadas do colagénio e da elastina com repercussão na força e elasticidade dos tecidos, surgindo aneurismas e disseções arteriais. A deficiência de Cu está igualmente associada à anemia normocítica e hipocrómica, leucopenia e neutropenia.[101] São frequentes alterações esqueléticas por desmineralização observando-se fraturas ósseas e osteoporose.[102]

A deficiência em Cu é rara nos países desenvolvidos, embora já tenham sido relatados alguns casos. Na década de 1960 foi identificada deficiência de Cu em lactentes peruanos com nutrição precária.[103] Os fatores predisponentes para a carência em Cu são a prematuridade, baixo peso à nascença, desnutrição especialmente combinada com alimentação de lactentes com leite de vaca e alimentação parentérica prolongada.[104] No entanto, em países em desenvolvimento as dietas são pobres em Cu, podendo-se enriquecer estas dietas, nomeadamente Cu, para que as gestações sejam mais bem sucedidas.[105]

Uma ingestão elevada em Zn e baixa em proteínas assim como dietas ricas em fibra diminuem a absorção de Cu. A deficiência em Cu nas crianças, pode ser consequência de baixas reservas à nascença, ingestão inadequada, deficiente absorção, aumento das necessidades em períodos de crescimento rápido ou aumento das perdas.

A suplementação com Cu tem efeito imediato, sendo que as concentrações de ceruloplasmina podem aumentar dentro de 24 a 48 horas. Normalmente, as concentrações de Cu retornam aos valores normais antes das concentrações de ceruloplasmina. Pode ser uma possível explicação o facto de que a repleção de ceruloplasmina não seja de importância primordial na correcção da deficiência de Cu. Uma concentração plasmática de Cu inferior a 900 µg/L apoia o diagnóstico de deficiência de Cu (particularmente se for inferior a 450 µg/L), assim como concentrações baixas ou

ausentes de ceruloplasmina.[34] Na maioria dos doentes, quando o Cu é inferior a 450 µg/L, a concentração de ceruloplasmina é inferior a 200 µg/L.

1.5. Crómio

1.5.1. Bioquímica e papel biológico do Crómio

O Crómio (Cr) é considerado um elemento com funções metabólicas essenciais nomeadamente no metabolismo de carbohidratos, proteínas e lípidos.[29,106,107]

A sua função no metabolismo dos carbohidratos relaciona-se sobretudo com a diminuição da resistência à insulina e ao estímulo da captação de glicose pelas células dos tecidos alvo.[108,109] A sua carência poderá propiciar o aparecimento de Diabetes Tipo 2.[27] O Cr age sob a forma de um complexo orgânico de baixo peso molecular denominado "fator de tolerância a glicose" (FTG). Isolado inicialmente em 1929 em leveduras e em 1957 em humanos promoveu assim a sua pesquisa no metabolismo glucídico. Este complexo é formado por Cr^{3+}, ácido nicotínico, glicina, cisteína e ácido glutâmico.[110,111]

É encontrado nos alimentos nas formas trivalentes (Cr^{3+}) que é a forma mais estável sob condições de redução. A forma hexavalente ou Cr VI, é encontrada no ambiente produzida por processos industriais, principalmente, no fabrico de ligas metálicas sendo considerado carcinogéneo quando inalado. O óxido de Cr VI tem caráter ácido e dele deriva o ácido crómico originando ácidos policrómicos.

O Cr dietético é absorvido na mucosa intestinal, duodeno e jejuno, em sítios específicos e não por difusão simples. A absorção do Cr da dieta é muito baixa, entre 0.5% e 2% é absorvido na forma trivalente, enquanto o excesso é excretado pelas fezes e pela urina.[112,113] Diferentes estudos apontam para uma absorção inversa à ingestão. Uma ingestão de cerca de 20µg apresenta uma absorção na ordem dos 2% enquanto uma ingestão de 40µg apresenta uma absorção entre 0.4 e 0.5%.[114] Alguns estudos sugerem que o exercício físico pode aumentar a absorção de Cr, mas tal ainda está por confirmar.

O Cr é armazenado no fígado, baço, outros tecidos moles e osso. A maioria do Cr absorvido é excretada rapidamente na urina enquanto que o Cr não absorvido é eliminado nas fezes.[115]

1.5.2. Recomendações nutricionais

As DRI's para o Cr encontram-se entre 20-35 mg/dia para homens e mulheres.[116] A ingestão adequada (IA) está ainda a ser debatida. A IA é baseada na ingestão estimada de Cr resultantes da quantidade média de Cr/ 1000 kcal de dietas equilibradas e do consumo médio de energia.

A absorção do Cr trivalente pode ser afetada pela ingestão de amido, ácido ascórbico, minerais, oxalatos, fitatos e aminoácidos.[117]

As fontes dietéticas incluem alguns grãos integrais e os cereais integrais são mais ricos que os cereais refinados. Carne, aves e peixe fornecem cerca de 1-2mg por porção, mas a carne processada geralmente é mais rica em Cr e poderá ser enriquecida por fontes externas. A quantidade de Cr em frutas e vegetais é extremamente variável mas apresenta maior concentração em vegetais verdes como os brócolos. Também se encontram quantidades apreciáveis nas nozes, na gema de ovo, na levedura de cerveja e em algumas cervejas e vinhos, nomeadamente os tintos de origem francesa.[115,118]

Dietary Reference Intakes (DRIs): Chromium
Food and Nutrition Board, Institute of Medicine, National Academies

Infants		Children		Man		Woman		Pregnancy	
0-6 mo	0.2 mg/d	1-3 y	11 mg/d	9-13 y	25 mg/d	9-13 y	21 mg/d	≤ 18 y	29 mg/d
7-12 mo	5.5 mg/d	4-8 y	15 mg/d	14-18 y	35 mg/d	14-18 y	24 mg/d	19-30 y	30 mg/d
				19-30 y	35 mg/d	19-30 y	25 mg/d	31-50 y	30 mg/d
				31-50 y	35 mg/d	31-50 y	25 mg/d	Lactation	
				51-70 y	30 mg/d	51-70 y	20 mg/d	≤ 18 y	44 mg/d
				>70 y	30 mg/d	>70 y	20 mg/d	19-30 y	45 mg/d
								31-50 y	45 mg/d

FONTES: Dietary Reference Intakes for Calcium, Phosphorous, Magnesium, Vitamin D, and Fluoride (1997); Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline (1998); Dietary Reference Intakes for Vitamin C, Vitamin E, Selenium, and Carotenoids (2000); Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, and Zinc (2001); Dietary Reference Intakes for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (2002/2005); and Dietary Reference Intakes for Calcium and Vitamin D (2011). These reports may be accessed via www.nap.edu.

1.5.3. Síndromes clínicas de deficiência e estados de deficiência subclínica

A deficiência em Cr está associada a nutrição parentérica prolongada sem suplementação. Os sinais e sintomas clínicos incluem perda de peso inexplicável, neuropatia periférica, diminuição da tolerância à glicose, aumento das necessidades de insulina, aumento dos ácidos gordos livres no plasma e baixo quociente respiratório. Esta deficiência é apontcada como um dos fatores contribuintes para a Diabetes Mellitus.[29,119,120]

O Cr alimentar não apresenta toxicidade, o que é parcialmente explicado pela sua fraca absorção.[115]

1.6. Ferro

1.6.1. Bioquímica e papel biológico do Ferro

O Fe tem várias funções vitais no metabolismo humano. É parte integrante de importantes sistemas enzimáticos para além de servir de transportador de oxigénio para os tecidos, serve como transportador de electrões entre células e atua como centro catalítico num largo espectro de funções metabólicas.[121,122]

O Fe pode surgir com carga entre -2 e +6. Nos sistemas biológicos esses estados de oxidação ocorrem predominantemente na forma ferrosa (Fe^{2+}) ou férrica (Fe^{3+}) sendo intermutáveis.

A maioria do Fe do organismo está presente nos eritrócitos como hemoglobina. Esta molécula contém 4 subunidades, cada uma com um grupo heme contendo um átomo de Fe e uma cadeia proteica. O Fe é armazenado de uma forma reversível no fígado como ferritina e hemosiderina enquanto o seu transporte é assegurado pela transferrina.

A absorção do Fe varia com a sua concentração no organismo e a fonte dietética de Fe, podendo variar entre 40% num estado de deficiência e 10% durante a repleção.[123] Existem duas formas: Fe heme (ou hémico) e Fe não-heme. A maior fonte de Fe heme é a hemoglobina e mioglobina presente na carne, aves e peixe. As fontes de Fe não-heme são os vegetais, frutos e cereais.

A ferropénia, carência de Fe no organismo, apresenta impacto negativo em diversas funções orgânicas.[124] A manifestação da ferropénia mais conhecida é a anemia ferropénica. Contudo a ferropénia tem um impacto metabólico mais alargado. Esta deficiência tem efeitos negativos no metabolismo oxidativo: nos músculos aumenta a formação de ácido láctico, no cérebro em desenvolvimento afeta várias estruturas na fase precoce do seu desenvolvimento, de uma forma irreversível, reduz a capacidade de trabalho físico e influencia negativamente o funcionamento do sistema imunológico.

1.6.2. Recomendações nutricionais

O Fe alimentar existe sob duas formas: a forma heme da hemoglobina, mioglobina e algumas enzimas e a forma não-heme encontrada nos alimentos de origem vegetal. As RDA's para homens e mulheres pós-menopáusicas são de 8 mg/dia, para mulheres em idade fértil é de 18 mg/dia e para os adolescentes de 11 mg/dia.

RDA	
Infants and young children	7-11 mg/day, according age
Children and adolescent	8-15 mg/day, according age
Adults	8-18 mg/day, according age
Pregnant woman	27 mg/day, according age
Infants	9-10 mg/day, according age

Adaptedo de: U.S. Department of Agriculture, Agricultural research service: Nutrient Database for Standard Reference, Release 18, retrieved 2005, Data Laboratory home page: http//www.nal.usda.gov/fnic/foodcomp/Data/SR18/sr18.html.

Fontes de Fe heme incluem a carne, peixe e aves. Fornecem habitualmente cerca de metade do Fe com elevada biodisponibilidade. O restante está na forma não-heme que apresenta uma absorção menor pelo organismo. Os alimentos vegetais como os legumes, frutos, pães integrais e cereais integrais contêm entre 0.1 – 1.4 mg de Fe não-heme por cada porção. Produtos alimentares fortificados com Fe, que incluem pão, cereais e barras energéticas podem contribuir para o total de Fe não-hémico da dieta.

1.6.3. Síndromes clínicas de deficiência e estados de deficiência subclínica

A deficiência em Fe apresenta uma elevada prevalência em bebés, crianças, adolescentes e mulheres em idade fértil, especialmente grávidas, particularmente em países pouco desenvolvidos.[125,126] Este fato ocorre por devido às necessidades em Fe serem muito elevadas nestes grupos.

O Fe é fundamental para o desenvolvimento de diversos tecidos nomeadamente do cérebro e fígado. Ferropénia e anemia ferropénica são frequentemente usados como sinónimos mas não se pode confundir deficiência em Fe com anemia por deficiência de Fe. Deficiência de Fe significa diminuição das reservas de Fe. A anemia por deficiência de Fe ganha importância quando está comprometido o fornecimento de oxigénio aos tecidos.

A progressão para uma anemia por carência de Fe desenvolve-se em três fases: a primeira consiste numa diminuição das reservas de Fe acompanhado por uma diminuição da ferritina sérica, que reflecte as reservas do fígado, da medula óssea e do baço. A segunda fase consiste na diminuição no transporte de Fe que se reflete num aumento na capacidade de ligação do Fe. A transferrina apresenta mais sítios de ligação do Fe por diminuição do Fe disponível. A terceira fase ocorre quando não há hemoglobina suficiente para novos eritrócitos. Outras consequências deletérias da deficiência em Fe surgem em conjunto com a anemia.

Não se verificam excessos com o Fe alimentar pois a sua absorção é controlada de acordo com as necessidades. Contudo, devemos estar alerta para os alimentos fortificados e suplementos alimentares que podem trazer riscos de sobrecarga.

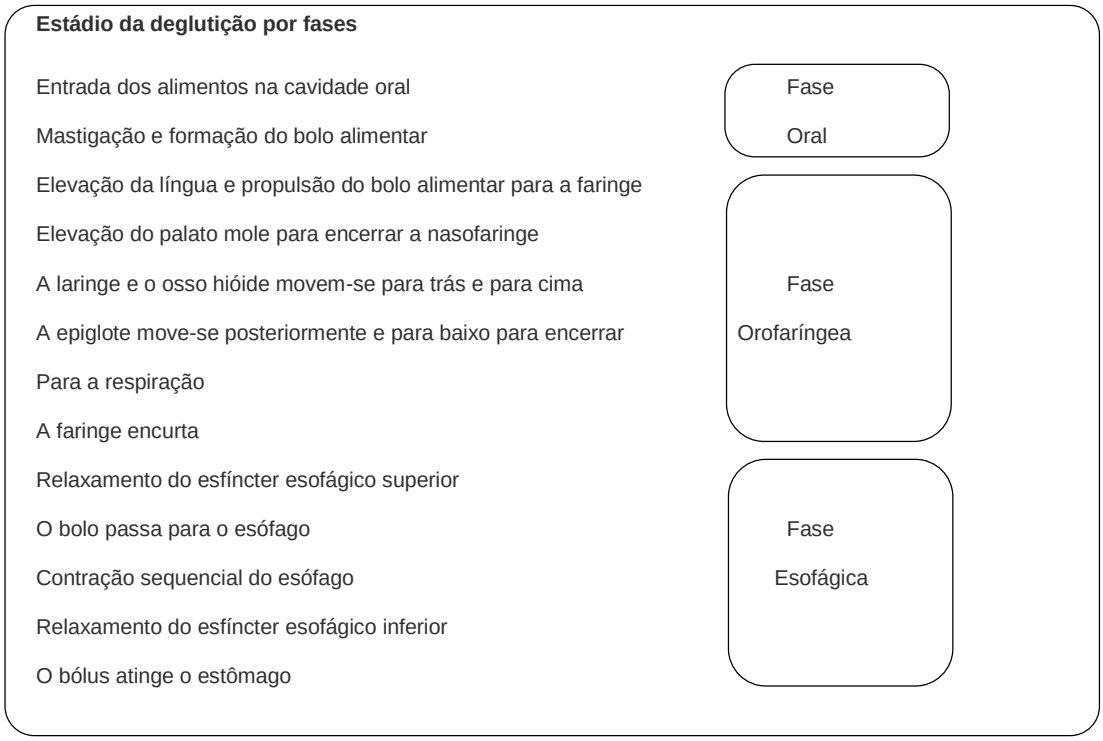
2. Disfagia

2.1. Definição e classificação

Disfagia é uma palavra de origem grega que significa dificuldade ou desconforto na deglutição (disfagia orofaríngea), ou durante a progressão do bolo alimentar, com a sensação de atraso na progressão dos alimentos entre a boca e o estômago (disfagia esofágica). (127)

A deglutição é um processo complexo que requer controlo e regulação pelo sistema nervoso. Este processo é regulado pelo centro de deglutição, através de vários pares de nervos craneanos e, no esófago médio e distal, por um alargado reflexo peristáltico autónomo coordenado pelo sistema nervoso entérico.(128) Alterações nestes processos, como uma descoordenação ou fraqueza nos biomecanismos desta função, caracterizam a disfagia.

Estádios da deglutição



Adaptado de: WGO Practice Guidelines

2.1.1. Disfagia orofaríngea

A disfagia orofaríngea, também denominada como disfagia "alta" pela sua localização, manifesta-se pela dificuldade em iniciar o processo de deglutição. Deve-se a uma descoordenação das ações neuromusculares que decorre desde o encerramento dos lábios até à abertura do esfíncter esofágico superior na sequencia de uma complicação mecânica e/ou obstrutiva ou alterações na motilidade neuromuscular.[129] O diagnóstico está associado a sinais e sintomas como a dificuldade em iniciar a deglutição, regurgitação nasal, tosse ou redução do reflexo da tosse e engasgamento. A aspiração para a laríngе e vias aéreas distais podem ocorrer sem tosse levando a complicações pulmonares, infeção, desnutrição, desidratação e morte.[127,130,131] As causas mecânicas incluem as doenças malignas tais como as neoplasias cervicofaciais, a redução da função muscular, o divertículo de Zenker, as linfadenopatias, algumas infeções com abcessos e, mais raramente, a osteofitose cervical. As doenças neuromusculares incluem dois grandes grupos: doenças com compromisso predominante das funções nervosas superiores e doenças com compromisso predominante da motilidade. O primeiro grupo de doenças inclui as demências e o acidente vascular cerebral (AVC). O segundo grupo inclui a doença de Parkinson, as alterações nos nervos cranianos, a paralisia bulbar, a esclerose lateral amiotrófica, a miastenia gravis e a distrofia muscular oculofaríngea.

2.1.2. Disfagia esofágica

A disfagia esofágica pode resultar de alterações da motilidade ou da presença de um obstáculo em qualquer ponto do trajeto esofágico, desde o esófago cervical até ao abdominal. Envolve doenças da mucosa, neuromusculares e do mediastino. É um sintoma comum a um grande número de alterações, incluindo neoplasias do esófago, acalásia, espasmo esofágico difuso, estenose péptica, esofagite eosinofílica, anéis de Schatzki e esclerodermia.[128]

2.2. **Consequências da disfagia no estado nutricional**

A disfagia pode ocorrer na sequência de uma doença neurológica ou por uma obstrução mecânica. De todas as doenças neurológicas o AVC é a situação clínica que mais frequentemente gera disfagia. Vários estudos demonstraram uma incidência significativa de disfagia orofaríngea após um AVC, variando entre 23% a 50%.[132] Das alterações mecânicas de origem maligna o carcinoma cérvico-facial (CCF) é a que mais contribui para a disfagia com uma prevalência entre os 50% a 60% e com uma incidência entre 10000 e 20000 novos casos por ano.[133] A disfagia grave, que pode ser agravada pela radioterapia associada à xerostomia e mucosite, apresenta um enorme impacto na ingestão alimentar destes doentes.[134]

Independentemente da doença subjacente à disfagia, esta pode levar à diminuição da ingestão oral por diminuição da eficácia e da segurança da deglutição, podendo por isso induzir desnutrição, com diminuição de macro e micronutrientes. A identificação precoce do risco de aspiração e o manejo das complicações são a chave de uma abordagem bem-sucedida. Se o risco de aspiração estiver presente e/ou a ingestão alimentar oral não for suficiente para garantir uma ingestão segura e um bom estado nutricional e não existir outra alteração do tubo digestivo, a alimentação entérica por tubo é a opção óbvia para garantir um adequado aporte proteico-energético. Para providenciar um aporte nutricional adequado por tubo, temos à disposição sondas nasogástricas (SNG) ou acessos percutâneos. A sua escolha depende do tempo que se prevê para esta forma de alimentação e da doença de base.

3. Nutrição Entérica

3.1. Conceito de Nutrição Entérica

O termo Nutrição Entérica (NE) engloba todas as formas de suporte nutricional que implicam o uso de "alimentos dietéticos para fins medicinais específicos" definido na regulação legal europeia da Comissão Diretiva de 1999/21/EC de 25 março independentemente da via de alimentação. Esta definição inclui suplementos nutricionais orais (SNO) e alimentação por sonda (tube feeding) por via nasal ou percutânea.[135]

3.2. Indicações para NE

As indicações para NE englobam todas as situações em que a alimentação oral é insuficiente ou perigosa. Estas incluem anorexia, disfagia e outras limitações físicas, psicológicas ou comportamentais assim como aumento das necessidades nutricionais.[136-141] O principal objetivo da NE é fornecer nutrientes de forma suficiente e adequada para preservar a massa magra, evitar a perda de peso e a desnutrição e, corrigir deficiências nutricionais em macro e micronutrientes.

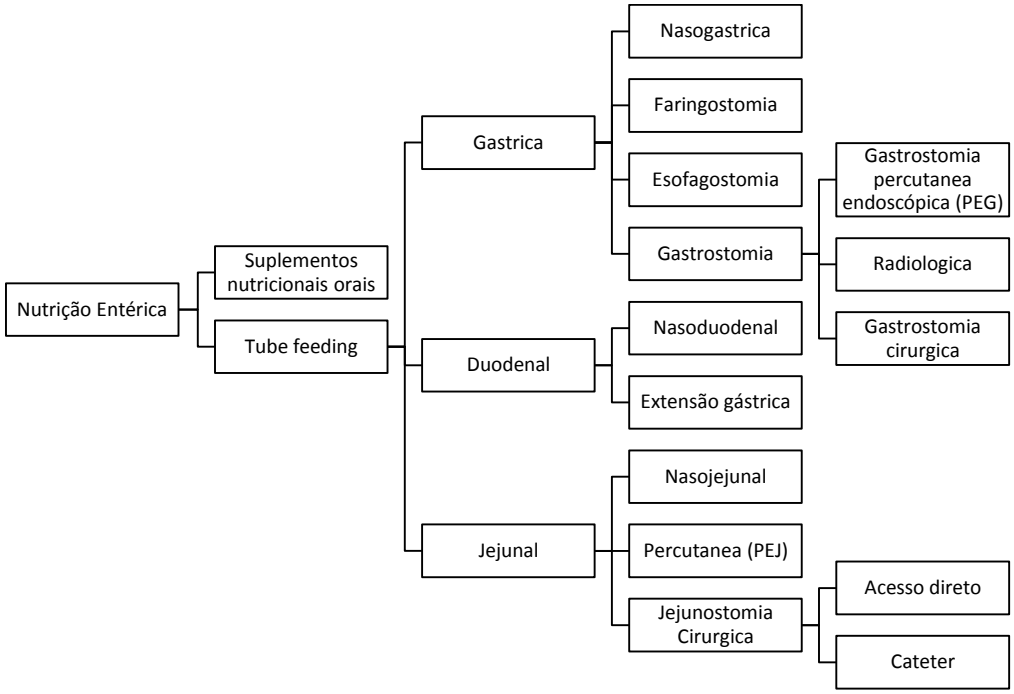
3.3. Acessos para NE

A alimentação utilizada para NE pode ser administrada por via oral (SNO) ou por sonda. Esta última é feita através de sondas que podem ser transnasais ou transcutâneas. As sondas transorais são usadas raramente porque são mal toleradas pelos doentes. Os acessos transcutâneos são feitos diretamente na parede abdominal até ao estômago, diretamente para o jejuno ou ainda através do estômago até ao duodeno ou jejuno.

Nasal ou transcutâneo, o acesso gástrico é o mais frequente, mais simples e adapta-se bem à maioria das indicações para NE por sonda. Contudo, o acesso jejunal é uma alternativa para ser usada em doentes selecionados, ou seja, incapazes de tolerar a alimentação gástrica por obstrução, gastroparésia e/ou para evitar o refluxo gastroesofágico e o risco de pneumonia de aspiração.

Está disponível uma grande variedade de sondas para NE, incluindo sondas para colocação nasogástrica (SNG), sondas nasojejunais (SNJ), tubo gástricos por introdução

percutânea que podem ser colocados endoscopicamente (PEG) ou cirurgicamente (Gastrostomias cirúrgicas). Há também tubos de jejunostomia percutânea (PJ) que podem ser colocados cirurgicamente (PSJ) ou endoscopicamente (PEJ) e ainda através da gastrostomia percutânea com extensão jejunal (PEG-J).



Acessos para NE. Adaptado de: Howard P; Jonkers-Schuitem, C; Furnis, L, et al (2006) [142]

3.3.1. Sondas nasais

As sondas nasais são colocadas em doentes incapazes de deglutir ou com uma deglutição pouco eficaz e/ou segura. São designadas como sondas nasogástricas (SNG) se forem colocados com a ponta distal do tubo no estômago e sondas nasoentéricas (SNE) se forem colocadas no duodeno ou jejuno, quando é necessária alimentação intestinal. As mais comuns são as SNG. Apenas se recorre às segundas quando é impossível ou desaconselhada a administração de alimentação no estômago. Após a sua inserção e antes de administrar a alimentação, é necessário confirmar a posição, normalmente por RX ou aspiração de fluido gástrico. A tolerância dos doentes às SNG é

baixa, considerando que é desconfortável quer no que respeita à inserção quer no que respeita à permanência. Por este motivo, frequentemente estas sondas são retiradas interrompendo a administração não só da alimentação como da medicação. Apesar da utilização de sondas ser o método mais utilizado para NE e por ser, de um modo geral o mais rápido, se for utilizado por um período longo pode trazer algumas complicações. Dentro destas complicações destacam-se lesões da asa do nariz, sinusites crónicas, estenoses esofágicas, fistulas esófago-traqueais e pneumonias de aspiração.

3.3.2. Sondas Percutâneas

Para NE de longa duração, por um período superior a 3-4 semanas, o acesso percutâneo é o recomendado quando estão reunidas as indicações para a sua utilização.

3.3.2.1. Sondas Gástricas

A utilização de um acesso transcutâneo para o estômago – gastrostomia – com colocação de sonda gástrica pode ser feito com suporte endoscópico, radiológico ou cirúrgico. O acesso endoscópico é a primeira opção e a mais comummente usada. Atualmente o acesso cirúrgico é usado apenas quando o acesso endoscópico não é possível.

3.3.2.2. Sondas Intestinais

O acesso transcutâneo para o intestino delgado – jejunostomia ou gastrojejunostomia – com colocação de sondas intestinais é pouco frequente. As sondas intestinais são usadas apenas quando não é possível ou seguro o uso de sondas gástricas. São exemplos a presença de uma gastrectomia prévia, o refluxo gastroesofágico grave, um tumor gástrico, entre outras situações que não permitem a alimentação gástrica.

3.3.3. Acesso endoscópico: Gastrostomia endoscópica percutânea

Descrita inicialmente em 1980 por Michael Gauderer, a gastrostomia endoscópica percutânea (PEG) tornou-se o método mais utilizado para acesso entérico quando é necessária alimentação por sonda por um período longo, superior a 3-4 semanas.

Consiste na introdução de uma sonda no estômago por via percutânea auxiliado por endoscopia. Está associado a menos falhas no tratamento e permite melhor suporte nutricional comparativamente com as SNG, para nutrição entérica de longa duração. [143-147]

Esta técnica pode utilizar vários métodos em que o mais difundido é o método "Pull" (Ponsky-Gauderer). Existem outros métodos como o "push" (Sachs-Vine), "introducer" (Russel) e Versa (T-fastener).[148,149] Recentemente foram comercializados entre nós dispositivos (Pexact®) que permitem associar uma gastropexia à gastrostomia endoscópica, tornando o procedimento mais seguro.

Existem vários sistemas comerciais de sondas para PEG. A escolha do diâmetro depende da idade do doente e do ponto anatómico para a sua colocação distal (estômago ou jejuno). As sondas de gastrostomia podem ser utilizadas com intenção profilática ou terapêutica, estando indicadas para suplementação/nutrição prolongada quando a ingestão oral não é nutricionalmente suficiente na sequência de uma disfagia prolongada, independentemente da etiologia.[150] A PEG é um procedimento minimamente invasivo realizado sob sedação, com baixa probabilidade de falha.[151,152] Quando comparada com a gastrostomia cirúrgica tradicional apresenta menor morbilidade, menores custos e a sua realização é mais rápida e segura.

Indicações para acesso nutricional gástrico ou intestinal

Indicação para acesso nutricional gástrico ou intestinal
Indicações Gerais para Nutrição Entérica
Deglutição comprometida
Obstrução na área cervicofacial ou tubo digestivo proximal
Fistulas na área cervicofacial ou tubo digestivo proximal
Indicações para acesso jejunal
Refluxo gastro-esofágico grave
Gastroparesia
Pancreatite aguda grave
Anatomia alterada (ex.: gastrectomia prévia)
Gastric outlet syndrome/obstrução duodenal
Fistula gástrica ou duodenal

Adaptado de: Toussaint, Van Gossum, Ballarin, Arvanitakis, 2015

Adaptado de: Toussaint, Van Gossum, Ballarin, Arvanitakis, 2015

Contra-Indicações para acesso nutricional gástrico ou intestinal

Contra-Indicações para acesso nutricional gástrico ou intestinal
Contra-indicações absolutas
Tubo digestivo não funcionante (oclusão, pseudoclusão, ileus)
Peritonite/Isquémia da mesentérica
Defeito na parede abdominal
Coagulopatia grave
Antagonistas da Vitamina K
Contra-indicações relativas
Ascite
Úlcera Gástrica
Shunt Ventrículo-peritoneal
Fraturas faciais instáveis
Presença de ostomias, tubos de drenagem e escaras cirurgicas

Adaptado de: Toussaint, Van Gossum, Ballarin, Arvanitakis, 2015

3.3.4. Escolha da dieta para NE

A NE engloba suplementos nutricionais orais (SNO) e alimentação por sonda (tube feeding) por via nasal, nasoentérica ou percutânea.[135]

3.3.4.1. Suplementos nutricionais orais

Existe uma gama alargada de SNO, de diferentes consistências (líquida, pudins) e formulações (lácteos, frutos). Fazem parte do conceito alargado de fórmulas comerciais para NE que engloba fórmulas para NE por sonda e SNO como ”alimentos dietéticos para fins medicinais específicos“ estando definidos na regulação legal europeia da comissão diretiva de 1999/21/EC de 25 Março de 1999.

Existem nas seguintes apresentações comerciais: enriquecidos em proteínas e calorias, em gordura, em imunonutrientes, restritos em gordura e em proteínas e ainda SNO isentos de gordura. Estão recomendados como suplementação nutricional após identificação de risco nutricional. São a primeira linha na terapia nutricional coadjuvante na desnutrição com inadequada ingestão oral. A sua utilização está indicada no doente oncológico antes

de uma cirurgia major ou durante a quimio/radioterapia, assim como terapia concomitante noutras doenças que possam desenvolver desnutrição favorecendo o aumento da ingestão calórico-proteica. O uso de SNO está, também, associado à diminuição das úlceras de pressão.(146)

3.3.4.2. Dietas para NE por sonda

A escolha da fórmula nutricional a administrar depende da posição distal do tubo, e do seu calibre, das necessidades nutricionais e, não menos importante, da capacidade financeira do doente e dos familiares/cuidadores, para suportar todos os custos. Para as fórmulas industriais "ready-to-use" o preço é variável de acordo com os nutrientes específicos utilizados.

3.3.4.2.1. Dietas de preparação doméstica

Dietas de preparação doméstica são preparadas com alimentos correntes mas cozinhados, triturados e homogeneizados para administração por sonda. Normalmente, as preparações mais comuns são sopas onde lhe é adicionada carne (vaca ou aves), peixe, sumos de fruta, produtos lácteos, nomeadamente leite, iogurtes, papas lácteas e cereais. As necessidades nutricionais são calculadas individualmente de acordo com as necessidades de cada doente, determinando a composição da dieta. As necessidades nutricionais são calculadas para as proteínas, gorduras, glícidos, micronutrientes e electrólitos. Por vezes, há dificuldade em atingir as necessidades nutricionais na dieta, por um lado porque estas são muitas vezes hiperdiluídas de acordo com o diâmetro do tubo e existe uma capacidade diminuída por parte do doente para receber o bólus de alimentação.(152) Existe alguma variação na escolha do diâmetro do tubo a utilizar para infusão dos alimentos. A escolha da via de administração e do tipo de alimentação a utilizar depende da instituição de saúde onde é realizado o procedimento, do tempo estimado para utilização desta via de alimentação e do local anatómico onde fica a ponta distal do tubo.(153-154)

O uso de alimentos correntes para administrar por sonda pode ocorrer tanto no internamento hospitalar como no ambulatório. Neste ultimo não é invulgar a opção por alimentos correntes porque a alimentação pretende ser semelhante aquela que é utilizada por os outros membros da família, permitindo maior integração familiar e social e também, porque as formulações industriais "ready-to-use" são mais dispendiosas por não serem comparticipadas em Portugal.[155,156]

3.3.4.2.2. Fórmulas comerciais para NE por sonda

São fórmulas pré-preparadas, "ready-to-use" que se englobam na designação mais ampla para NE como "dietary food for medical purpose" de acordo com a diretiva da União Europeia de 1999. Existe uma gama alargada de fórmulas para NE disponíveis, estéreis e prontas a usar. De acordo com a composição podem ser completas ou incompletas, standards ou específicas, obedecendo a regras de rotulagem onde estão identificados todos os constituintes, origem e natureza das proteínas assim como ~~e~~ outros dados considerados relevantes. Quanto ao teor em micronutrientes devem constar no rótulo os valores mínimos e máximos por 100 ml. Cada 1500Kcal das fórmulas nutricionalmente completas, deve conter todas as RDA's destes elementos.

Quanto à hidrólise dos macronutrientes as fórmulas industriais podem ser poliméricas, oligoméricas e elementares. As fórmulas poliméricas apresentam todos os constituintes na forma não digerida e têm indicação para a maioria das situações clínicas. Apenas num número reduzido de situações clínicas onde não é aconselhado o uso de dietas poliméricas estão indicadas as oligoméricas que, por apresentarem os seus constituintes mais hidrolisados, apresentam também maior osmolaridade, nem sempre sendo bem toleradas.

4. Patologias em estudo

4.1. Doenças Neurológicas

O espectro de doenças neurológicas é vasto e requer diferentes abordagens nutricionais. A disfagia de origem neurológica é a principal indicação para alimentação entérica por sonda. A doença neurológica causadora de disfagia compreende doenças cerebrovasculares (acidente vascular cerebral - AVC), doenças do neurónio motor/esclerose lateral amiotrófica, demências, tumores e cirurgia encefálica, traumatismo craneo-encefálico, atraso do desenvolvimento psicomotor em crianças e outras doenças neurológicas.[157]

4.1.1. Doenças cerebrovasculares/acidente vascular cerebral

A disfagia é comum após AVC com uma incidência aproximadamente de 45%. Os doentes não apresentam uma deglutição segura e eficaz, podendo ocorrer aspiração para a via aérea. É frequente a ocorrência de pneumonia, abcesso pulmonar e insuficiência respiratória. A NE por sonda é recomendada em todos os doentes após AVC que não estejam capazes de uma ingestão alimentar adequada por via oral. Nalguns casos os doentes apresentam uma recuperação na deglutição em poucos dias pós AVC. Após este episódio, mesmo que a recuperação ocorra dentro de alguns dias a algumas semanas, o suporte nutricional não deve ser adiado até à recuperação total da eficácia e segurança da deglutição, devendo ser iniciado de imediato. A NE é segura, eficaz e fácil de manejar e está associada com uma redução do risco de morte e de mau prognóstico quando iniciada precocemente, dentro de 7 dias após o início do AVC.[141]

4.1.2. Doenças do neurónio motor/esclerose lateral amiotrófica

Os doentes com esclerose lateral amiotrófica (ELA) apresentam disfagia com compromisso da ingestão alimentar, levando à deterioração do estado nutricional. A ELA é caracterizada por compromisso progressivo dos neurónios motores e da força muscular. Gradualmente os doentes perdem a segurança e eficácia da deglutição e torna-se imperativo fornecer um suporte nutricional e hídrico adequado dado que a desnutrição e a

desidratação podem acelerar a progressão da doença.[158] Nestes doentes o suporte nutricional não pode ser

adiado e a alimentação por PEG é o método comummente utilizado para o fornecimento de uma nutrição adequada às necessidades nutricionais aumentadas verificadas atavés de alimentação hipercalórica.[159-161] Numa fase inicial, após PEG o peso estabiliza mas a perda de peso é inevitável com a progressão da doença.[158] A importância de fornecer uma alimentação adequada às necessidades nutricionais é inquestionável, contudo a importância da intervenção nutricional na evolução da doença contínua em discussão.[161,162]

4.1.3. Demência

Demência é o termo genérico para definir um declínio grave e progressivo das funções nervosas superiores de tal forma que interfere com as atividades de vida diárias. A forma mais comum de demência é a doença de Alzheimer contribuindo entre 60 a 80% dos casos. O segundo tipo mais comum de demência é do tipo vascular. Doentes com demência em estado avançado apresentam compromisso da memória, especialmente recente, do pensamento e do comportamento assim como alterações na capacidade de se auto-alimentar. A instalação da disfagia é progressiva e a decisão para PEG nem sempre é simples.

4.1.4. Doenças neurocirúrgicas

O traumatismo crânio-encefálico (TCE) é a causa mais comum de morte e incapacidade em pessoas entre os 15 e os 30 anos.[163] O TCE combina alterações sistémicas (hipoxia, hipotensão e hipercapnia) e locais, que em conjunto cursam para uma alteração patológica secundária [164] associada ao desenvolvimento de um estado hipermetabólico, com aumento do gasto calórico, hipercatabolismo e diminuição da ingestão nutricional induzida pela disfagia neurológica.[165-167] O suporte nutricional efetivo e precoce é fundamental na recuperação destes doentes.[168]

4.1.5. Atraso psicomotor

O atraso do desenvolvimento psicomotor pode incluir todas as situações adquiridas na infância (paralisia cerebral, TCE), síndromes genéticas (síndrome de Down, síndrome de Rett) e patologias degenerativas (distrofia miotónica).[157]

Estes doentes exibem habitualmente problemas nutricionais sendo na maioria dos casos por deficiente ingestão. Podem apresentar dificuldades na deglutição, vómitos e distúrbios da motilidade do tubo digestivo. Para além do risco nutricional apresentam um risco igualmente grave, a pneumonia de aspiração. O uso de PEG pode providenciar uma adequada NE de longa duração e melhorar o estado nutricional em doentes com deficiência grave e atraso mental.[169] Na larga maioria dos casos, estes doentes são gastrostomizados na infância. Ocasionalmente, um doente com este tipo de alterações desde a infância é referenciado para gastrostomia em idade adulta. Nenhum doente deste grupo foi incluído no presente estudo.

4.1.6. PEG nas doenças neurológicas

A disfagia de origem neurológica é a indicação mais frequente para realização de PEG, onde o AVC contribui com mais de 45% dos doentes.[170] Contudo, a decisão deve ser tomada considerando o tempo previsto de disfagia que deve ser superior a 3-4 semanas e também a esperança de vida. Esperança de vida muito curta mesmo que superior a 1mês é habitualmente considerada como desaconselhando o procedimento. No período inicial do AVC a evolução é, frequentemente, muito difícil de prever. Habitualmente a PEG é adiada por 3 a 4 semanas até ser possível uma boa avaliação da deglutição e ser clara a persistência da disfagia.

4.2. Cancro cervicofacial

O cancro cervicofacial (CCF) engloba um grupo complexo de cancros com diferentes localizações anatómicas. Inclui a cavidade oral (lábios, gengivas, linha entre as bochechas e os lábios, pavimento da boca, língua, palato duro e pequena área da gengiva); a faringe

(nasofaringe, orofaringe e hipofaringe); a laringe (cordas vocais, epiglote); os seios perinasais e a cavidade nasal; as glândulas salivares e esófago proximal.

Doentes com CCF desenvolvem frequentemente uma desnutrição grave e caquexia, sendo a sua prevalência estimada entre 40 a 80%.[171-173] Existem diversos fatores que contribuem para a desnutrição: os efeitos diretos do tumor, a anorexia oncológica, características pessoais e tipo de tratamento (cirurgia, radioterapia e/ou quimioterapia). Os efeitos diretos do tumor incluem a sua localização anatómica que pode provocar uma dificuldade na mastigação e na deglutição, trismos, odinofagia e aspiração. O tratamento cirúrgico pode alterar a anatomia e diminuir a ingestão oral. A radioterapia e a quimioterapia apresentam efeitos colaterais como dor, náuseas e vómitos, mucosite, fibrose das glândulas salivares, disgeusia, xerostomia, necrose dos tecidos moles, problemas dentários, infeções e trismos. O baixo estrato socioeconómico associado ao uso abusivo de álcool e tabaco também contribuem para uma redução na ingestão oral. Uma redução da ingestão alimentar associada a um metabolismo anormal com graves alterações metabólicas, características da malignidade, podem explicar a incapacidade de reversão total da desnutrição pelo suporte nutricional.

4.2.1. PEG em CCF

O risco destes doentes desenvolverem uma desnutrição grave exige uma intervenção nutricional imediata. A indicação para PEG está presente na maioria dos casos podendo ser realizada profilacticamente ou terapeuticamente no contexto da redução da ingestão oral e/ou aumento das necessidades nutricionais. Vários estudos apoiam o uso profilático de PEG prévio ao início do tratamento pois está associado a menos complicações e menor perda de peso no decurso da doença, quando comparado com o seu uso terapêutico.[174,175]

Adicionalmente, o uso profilático da PEG em doentes com CCF parece prevenir uma perda de peso futura, fenómeno comum nestes doentes.[151] Está igualmente associado com a redução da morbilidade e mortalidade.[176-178] O suporte nutricional através da PEG apresenta-se como uma via segura para diminuir o risco de aspiração acidental podendo ainda ser utilizada para a administração de fármacos.

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CAPITULO 2

OBJETIVOS

Esta dissertação pretendeu estudar a evolução das concentrações séricas de oligoelementos em doentes com disfagia alimentados através de uma gastrostomia endoscópica. Para tal, foi avaliada esta concentração imediatamente antes do procedimento de gastrostomia e após 4 e 12 semanas sob nutrição artificial utilizando alimentação de preparação doméstica.

Objetivos do estudo:

1. Determinar a concentração sérica de oligoelementos em doentes com disfagia referenciados e submetidos a gastrostomia endoscópica percutânea para nutrição entérica de longo prazo.
2. Determinar se, no caso de não apresentarem carência em oligoelementos no momento da gastrostomia, poderemos manter concentrações normais através de alimentação de preparação doméstica.

3. Determinar se, no caso de apresentarem carência sérica em oligoelementos no momento da gastrostomia, poderemos normalizar estas concentrações através de alimentação de preparação doméstica.

Para alcançar estes objetivos foram desenvolvidos 5 estudos. Dois destes estudos foram desenvolvidos no momento da realização da gastrostomia endoscópica percutânea para avaliar a concentração de cada oligoelemento e, os restantes 3 estudos pretenderam avaliar a evolução às 4 e 12 semanas. Foram escolhidos 3 dos 5 oligoelementos iniciais. Para perceber a variação na concentração sérica foi escolhido um dos elementos com concentração baixa inicial e os outros com concentração sérica normal. Foi escolhido o Zinco por se encontrar numa concentração baixa na maioria dos doentes e o Selénio e Cobre que apresentavam valores normais na maioria dos doentes aquando da referenciação. Nesta evolução pretende-se avaliar o papel dos alimentos de preparação doméstica na concentração destes oligoelementos por esta ser a forma mais comum praticada em ambulatório.

Para avaliação da concentração sérica no momento da gastrostomia endoscópica percutânea:

Estudo1

1) "**Serum Zn levels in dysphagic patients who underwent endoscopic gastrostomy for long term enteral nutrition**". Estudo preliminar que envolveu os primeiros 32 doentes em estudo. Teve como objetivos:

- Avaliação da concentração sérica de Zinco em doentes com disfagia referenciados para gastrostomia para nutrição entérica de longa duração.
- Comparação da concentração sérica de Zinco entre dois grupos de doentes com disfagia: doentes com carcinoma cervicofacial e com disfagia neurológica.
- Avaliação da associação do Zinco sérico com a albumina e transferrina marcadores séricos nutricionais e/ou inflamatórios.
- Avaliação do Zinco no sangue total e da associação entre o Zinco no sangue total e o Zinco sérico.

Estudo 2

2) "**Serum trace elements in dysphagic gastrostomy candidates before endoscopic gastrostomy for long term enteral feeding**". Estudo realizado no momento da gastrostomia que envolveu todos os doentes e os oligoelementos em estudo e que respondeu à primeira pergunta da dissertação. Teve como objetivos:

- Avaliação da concentração sérica de oligoelementos (Zn, Cu, Se, Fe e Cr) em doentes com disfagia referenciados para gastrostomia para nutrição entérica de longa duração;
- Comparação da concentração sérica de oligoelementos entre dois grupos de doentes com disfagia: doentes com carcinoma cervicofacial e com disfagia neurológica submetidos a gastrostomia endoscópica;
- Associação entre a concentração sérica de oligoelementos e as categorias do Índice de Massa corporal (IMC);
- Associação entre a concentração sérica de oligoelementos e os marcadores séricos de desnutrição e/ou inflamação (albumina e transferrina séricas).

Para avaliação da concentração sérica durante 4 a 12 semanas de uso da gastrostomia endoscópica percutânea:

Estudo 3

3) "**Selenium in dysphagic patients that underwent endoscopic gastrostomy for long term enteral feeding**". Estudo realizado com o objetivo de avaliar o papel dos alimentos de preparação doméstica na evolução da concentração sérica de Se.

- Avaliar a evolução sérica de selénio em doentes com disfagia submetidos a gastrostomia endoscópica para nutrição entérica de longa duração em 3 momentos: no momento da gastrostomia (T0), após 4 semanas (T1) e após 12 semanas (T3) de nutrição entérica por gastrostomia. Paralelamente avaliar a evolução da concentração sérica de albumina e transferrina e a evolução do IMC nos mesmos 3 momentos.
- Explorar a influência da natureza da doença subjacente, carcinoma cervicofacial e disfagia neurológica na evolução sérica do selénio, albumina e transferrina e no Índice de Massa Corporal nos mesmos 3 momentos.

Estudo 4

4) **"Serum zinc evolution in dysphagic patients that underwent endoscopy gastrostomy for long term enteral feeding**". Estudo realizado com o objetivo de avaliar o papel dos alimentos de preparação doméstica na evolução da concentração sérica de Zn. Pretendeu-se:

- Observar a evolução do zinco sérico em doentes com disfagia submetidos a gastrostomia endoscópica para nutrição entérica de longa duração.
- Comparar a evolução da concentração do zinco sérico em doentes com disfagia submetidos a gastrostomia endoscópica para nutrição entérica entre os dois grupos de doenças subjacentes: carcinoma cervicofacial e disfagia neurológica.
- Comparar o zinco sérico em 3 momentos de avaliação: no momento da gastrostomia (T0), após 4 semanas (T1) e após 12 semanas (T3) de nutrição entérica por gastrostomia.

- Avaliar a relação entre o zinco sérico e a concentração sérica da albumina e transferrina e a sua evolução em doentes com disfagia submetidos a gastrostomia endoscópica para nutrição entérica.

Estudo 5

5) "**Serum Copper evolution in patients that underwent endoscopic gastrostomy for long term enteral feeding**" Estudo realizado com o objetivo de avaliar o papel dos alimentos de preparação doméstica na evolução da concentração sérica de Cu.

- Avaliar a evolução sérica de cobre em doentes com disfagia submetidos a gastrostomia endoscópica para nutrição entérica de longa duração em 3 momentos: no momento da gastrostomia (T0), após 4 semanas (T1) e após 12 semanas (T3) de nutrição entérica por gastrostomia. Paralelamente avaliar a evolução da concentração sérica de albumina e transferrina e a evolução do IMC nos mesmos 3 momentos.
- Explorar a influência da idade, género, natureza da doença subjacente, carcinoma cervicofacial e disfagia neurológica na evolução sérica do cobre, nos mesmos 3 momentos.

CAPITULO 3

Estudo 1

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

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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 (-80°C) 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

	Patients					
Parameters	*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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Estudo 2

"Serum trace elements in dysphagic gastrostomy candidates before endoscopic gastrostomy for long term enteral feeding"

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Original article

Serum trace elements in dysphagic gastrostomy candidates before endoscopic gastrostomy for long term enteral feeding

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SUMMARY

Background & aims: Patients who underwent endoscopic gastrostomy (PEG) present protein-energy malnutrition, but little is known about Trace Elements (TE), Zinc (Zn), Copper (Cu), Selenium (Se), Iron (Fe), Chromium (Cr). Our aim was the evaluation of serum TE in patients who underwent PEG and its relationship with serum proteins, BMI and nature of underlying disorder.
Methods: A prospective observational study was performed collecting: patient's age, gender, underlying disorder, NRS-2002, BMI, serum albumin, transferrin and TE concentration. We used ferrozine colorimetric method for Fe; Inductively Coupled Plasma-Atomic Emission Spectroscopy for Zn/Cu; Furnace Atomic Absorption Spectroscopy for Se/Cr. The patients were divided into head and neck cancer (HNC) and neurological dysphagia (ND).
Results: 146 patients (89 males), 21–95 years: HNC-56; ND-90. Low BMI in 78. Low values mostly for Zn ($n = 122$) and Fe ($n = 69$), but less for Se ($n = 31$), Cu ($n = 16$), Cr ($n = 7$); low albumin in 77, low transferrin in 94 and 66 with both proteins low. Significant differences between the groups of underlying disease only for Zn ($t_{140.326} = -2{,}642$, $p < 0.01$) and a correlation between proteins and TE respectively albumin and Zn ($r = 0.197$, $p = 0.025$), and albumin and Fe ($r = 0.415$, $p = 0.000$).
Conclusions: When gastrostomy was performed, patients display low serum TE namely Zn, but also Fe, less striking regarding others TE. It was related with prolonged fasting, whatever the underlying disease. Low proteins were associated with low TE. Teams taking care of PEG-patients should use Zn supplementation and include other TE evaluation as part of the nutritional assessment of PEG candidates.
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1. Introduction

Essential Trace Elements (TE) such as Zinc (Zn), Copper (Cu), Selenium (Se), Iron (Fe), and Chromium (Cr) are required in small amounts for normal metabolism and are linked together in cytosolic defense against reactive oxygen and nitrogen species [1]. Deficiency in TE has adverse health effects in immune status, inflammation, oxidative damage, and lymphocyte function. Zn is involved in three major functions, catalytic, regulatory and structural [2–4]. The World Health Organization highlighted Zn deficiency as one the 10 major factors contributing to disease in developing countries [5]. Se is an essential non-metallic trace element, the only to be specified in the genetic code. It is required for normal metabolism and is incorporated as selenocysteine at the active site of selenoproteins with antioxidant functions, anti-inflammatory, antitumorigenic, antiangiogenic, antiatherogenic and immunomodulatory effects [6–12]. Twenty five essential selenoproteinsare grouped into glutathione peroxidases, thioredoxin reductases and iodothyronine deiodinases [13–16]. Deficiencies result in deleterious repercussions, including organ

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dysfunction; poor wound healing and altered immunity [17–19]. Cu is the cofactor of several fundamental enzymes, including cytochrome-c oxidase, CuZn superoxide dismutase and ceruloplasmin. Fe acts as a catalytic centre for a broad spectrum of metabolic functions, as haemoglobin and myoglobin; it is stored as ferritin and hemosiderin and is found as a transit chelate with transferrin. Cr is critical for insulin performance that is enhanced by Cr, though influencing carbohydrate, lipid and protein metabolism [20,21]. Chromium deficiency may lead to elevated serum cholesterol and triglycerides and decreased high-density lipoprotein cholesterol. Beyond clinical apparent deficiencies of TE, which are seldom diagnosed, subclinical deficiencies may impair metabolism and must be accounted for, particularly in patients and groups of risk.

The prevalence of swallowing disorders is very high in patients with acute or chronic neurological disease, and head or neck cancer. Whatever the underlying disease, dysphagia reduces the oral intake, leading to depletion of macronutrients and micronutrients [22,23]. Percutaneous endoscopic gastrostomy (PEG) is the gold standard for enteral feeding longer than 3 weeks. When patients are referred to the PEG procedure for long term enteral feeding they have already several weeks with low ingestion and frequently present with protein-calorie malnutrition. As well as protein-calorie malnutrition, TE deficiencies may occur, but monitoring TE in ddysphagic patients is infrequent and there are few systematic studies of TE in PEG patients [24].

2. Aims

The aims of our study were:

1. Evaluation of serum TE concentration (Zn, Cu, Se, Fe and Cr) at time of the procedure in dysphagic patients referred to gastrostomy;
2. Comparison of serum TE concentration between two groups of long term dysphagic patients (head or neck cancer; neurological dysphagia) that underwent PEG;
3. Association between serum TE concentration and Body Mass Index categories (BMI).
4. Association between serum TE concentration and markers of malnutrition and/or inflammation (serum albumin and transferrin).

3. Material and methods

We performed a prospective observational study that evaluated serum TE concentration. In consecutive adult patients that were referred to and underwent endoscopic gastrostomy in order to have nutritional support for long term dysphagia (more than 3–4weeks). All adult patients were invited to participate. The only exclusion was age≤18 years and refusal to be included in the study. All subjects were informed of the purpose and procedures of the study and gave their informed consent. This study was approved by the Hospital Ethics Committee.

According to the underlying disease causing dysphagia, patients were split in two groups [1]: head and neck cancer (HNC) included oral cavity, pharyngeal, laryngeal, oesophageal proximal cancer and cervical cancers arising from other organs or tissues and [2] neurological dysphagia (ND)including acute and chronic disorders.

Collected data included patient's age, gender, clinical indication for enteral feeding through, Nutritional Risk Screening, Body Mass Index (BMI), and serum albumin, transferrin and TE concentration.

3.1. Nutritional risk identification

For nutritional screening we used the tool recommended by E.S.P.E.N., the Nutritional Risk Screening – NRS 2002.

3.2. Global nutritional assessment

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 unsuitable. Global nutritional assessment relied mostly in objective evaluation, using anthropometry - Body Mass Index (BMI) - and serum data, including albumin and transferrin. Albumin <35 g/l and transferrin <2,0 g/l were considered suggestive of malnutrition. Global Nutritional Assessment relied mostly in objective evaluation (anthropometry data) and serum data, including albumin and transferrin. 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 [25]. Malnutrition was defined as a BMI <18,5 kg/m^2 for adult patients younger than65 years and <22 kg/m^2 for patients with65 years or older [26]. Although serum proteins may be influenced by non-nutritional factors, albumin <3,5 g/l and transferrin <200 mg/dl were considered suggestive of malnutrition. A dietary recall from the previous weeks was obtain from patients, family or caregivers.

3.3. TE blood samples assays

From patients that underwent endoscopic gastrostomy, a blood sample was obtained minutes before the gastrostomy procedure. Blood samples were obtained between 8:00 and 10:00 AM following at least 12 h 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 Zn, Se, Cr and Cu assessment. After centrifugation serum samples were kept frozen (−80 °C) until the analysis. Serum Fe was evaluated through hospital routine using ferrozine colorimetric method (R1: citric acid 200 mmol/L; thiourea: 115 mmol/L; detergent. R2: sodium ascorbat: 150 mmol/L; ferrozine: 6 mmol/L; preservative). Serum concentrations of other TE were analyzed and reported from the laboratory (REQUIMTE - Rede de Química e Tecnologia Departamento de Química/Faculdade de Ciências e Tecnologiada Universidade Nova de Lisboa). Serum Zn and Cu samples were assayed using ICP-AES – Inductively Coupled Plasma-Atomic Emission Spectroscopy (washing solution 5%HNO3 in water, Fluka® patterns 1000 mg/L) and serum Se and Cr were 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 1000 mg/L). We considered reference values for the TE: Zn: 70–120 μg/dl; Se: 8–27,2 μg/dl; Cu: 70–140 μg/dl; Cr: 0,05-0.2 μg/dl; and Fe: 45–160 μg/dl [27].

3.4. Statistical analysis

It was used the Statistical Package for Social Sciences (IBM SPSS Statistics), version 22.0. The results are considered significant at a 5% significance level. To assess the normality of the data we used the Shapiro–Wilk test. Descriptive statistics were used to evaluate TE levels (Zn, Cr, Se, Fe and Cu) in dysphagic patients. Independent Samples t-test was used (since the assumption of normality was verified) to compare TE levels and proteins (albumin and transferrin) between the two groups (HNC and ND). To study the

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relationship between TE levels, albumin and transferrin, Pearson correlation was used. To compare TE levels between BMI categories, Kruskal–Wallis test was used, since the assumption of normality of data in BMI categories is not verified. To compare protein concentration between BMI categories, ANOVA was used, since the assumption of normality of data in BMI categories is verified.

4. Results

4.1. Characteristics of the study population

This study included 146 dysphagic patients who were admitted for PEG. 89 men and 57 women, ranging in age from 21 to 95 years with a mean age of 68.2 years (SD = 14.2). Of these, 90 were aged≥ 65years old. According the underlying disease, patients were divided in two groups:1-HNC group, with head and neck cancer (n = 56) and 2- ND group, with neurological dysphagia (n = 90). HNC cancers were, mostly, located in the oral cavity (n = 10), larynges (n = 15), pharynges (n = 20), and proximal oesophagus (n = 11). The ND patients comprises strokes (n = 29), dementias (n = 20), neurosurgical injuries (n = 24), amyotrophic lateral sclerosis (n = 6) and other neurological diseases (n = 11) causing dysphagia. (Table 1)

Before the PEG procedure, all patients had dysphagia for at least one month after the diagnosis of the underlying disease. Prior low oral intake was mostly variable according with the underlying disease, ranging from a few weeks to several months. Likewise, weight loss before the pre-gastrostomy evaluation was widely variable. Nevertheless, all patients had prior intake under 50% of daily caloric needs and Nutritional Risk Screening – NRS 2002 – presented a score ≥3 in every patient, signalling the nutritional risk. All patients were clinically stable at the moment of PEG and sample collection, (unstable patients are excluded or postponed). During the endoscopic gastrostomy procedure, before the PEG tube placement, all patients underwent a complete upper GI diagnostic endoscopy evaluation. No one displayed any major disorder or any potential bleeding lesion.

4.2. 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. From 146 patients, 78 (53%) showed low BMI (<18,5 kg/m^2 for patients younger than 65 years and <22 kg/m^2 for patients with65 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%).

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

Clinical characteristics	Absolute number
Age	Years
Max	95
Min	21
Mean	68,2
Standard deviation	±14.2
Gender	
Female	57
Male	89
Group diagnosis:	
Head neck cancer (HNC)	56
Oral cavity	10
Pharynx	20
Larynx	15
Proximal oesophagus	11
Neurological dysphagia (ND)	90
Stroke	29
Dementia	20
Neurosurgical injury	24
Amyotrophic Lateral sclerosis	6
Other disease	10

4.3. TE and proteins serum concentrations

4.3.1. TE concentration

Zinc: One hundred forty six patients were evaluated regarding Zn in the range 31–114 μg/dl (normal range: 70–120 μg/dl), with a mean 53,94 ± 16,20 μg/dl. From these patients,122 (84%), showed low Zn, while 24 (16%)presented normal values, albeit close to the lower bound. From these 24 patients, 17 (71%) were from neurosurgery ward, presenting acute brain lesions from trauma or surgery. From the remaining 7(29%) patients, 4 had HNC and 3 suffered from progressive neurological disorders. HNC patients presented on average a lower level than ND patients. A statistically significant differences were detected between these groups ($t_{140,326} = -2{,}642$, $p < 0.01$).

Selenium: One hundred forty six patients were evaluated regarding Se in the range 0.2–26.1 μg/dl (normal range: 8–27.2 μg/dl) with a mean 10,22 ± 3,67 μg/dl. From these patients, 115 (79%) had normal Se; 31(21%) had low values between 0.2 and 7.9 μg/dl. From these 19 (21%) were from the ND group and 11 (19.6%) were from the HNC group. No statistically significant differences were detected between these groups ($t_{142} = -0.386$, $p = 0.700$). Elderly patients group presented 14% of low values equal to the younger group.

Copper: One hundred forty six patients were evaluated regarding Cu in the range 42–160 μg/dl (normal range: 70–140 μg/dl), with a mean 97,23 ± 25.6 μg/dl. Most of patients, 130 (89%) were within the normal range, and the remaining 16(11%) presented low values, under 70 μg/dl. When divided into two groups, 13 ND patients and 3 HNC showed low Cu. No statistically significant differences were detected between the two groups (HNC and ND) ($t_{144} = 0.059$, $p = 0.953$). Elderly patients group presented 13% of low values, more than the younger group (6%).

Iron: One hundred forty six patients were evaluated regarding Fe in the range 7–243 μg/dl (normal range: 45–160 μg/dl), with a mean of 53,97 μg/dl ± 32,38 μg/dl. Globally, 77patients (53%) were within the normal range while 69 (47%) had low values (7–44 μg/dl). When divided according to the cause of dysphagia, 41% (n = 37) of ND group and 57% (n = 32) of HNC group showed low concentrations. No statistically significant differences were detected between these two groups ($t_{144} = -0.112$, $p = 0.911$) 0.45 patients from the elderly group (50%) and 25 from the younger group (45%) presented low values.

Chromium: One hundred twenty seven patients were evaluated regarding Cr in the range 0,01–7.5 μg/dl (normal range: 0,05-0.2 μg/dl), with a mean of 0,907 μg/dl ± 1,37 μg/dl. Only 7 patients (6%) had low values, 4 from HNC group and 3 from ND group. No statistically significant differences were detected between the two groups ($t_{125} = 0.235$, $p = 0.814$). Five patients with low values were from the elderly group, two from the younger patients group. (Tables 2 and 3)

4.3.2. 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 ranging

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Table 2
TE concentration (μg/dl).

TE	N	Minimum	Maximum	Mean	Std. Deviation
Zn	146	31	114	53,94	16,66
Se	146	0.2	26	10,22	3,67
Cu	146	42	160	97,23	25,61
Cr	127	0,01	7,50	0,901	1,37
Fe	146	7	243	53,97	32,43

Table 3
TE levels (μg/dl): comparison between patients with head and neck cancer (HNC) and patients with neurological dysphagia (ND).

TE	Etiology	n	Mean	Std. deviation	Std. error mean	t	df	p
Zn	HNC	56	49,71	13,173	1,760	−2,642	140,326	0,009[a]
	ND	90	56,57	18,073	1,905			
Se	HNC	56	10,07	3,200	0,428	−0,386	142	0,700
	ND	90	10,32	3,956	0,422			
Cu	HNC	56	97,39	22,376	2,990	0,059	144	0,953
	ND	90	97,13	27,552	2,904			
Cr	HNC	52	9417	1,48178	20549	0,235	125	0,814
	ND	75	8833	1,29888	14998			
Fe	HNC	56	53,59	39,394	5,264	−0,112	144	0,911
	ND	90	54,21	27,459	2,894			

[a] statistically significant differences

from 1,4–5.2 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 ranging from 74 to 331 mg/dl (normal range 200–300 mg/dl). 94 patients (65%) presented low transferrin. Sixty six patients (46%), presented low levels of both proteins.

4.4. Relationship between Albumin, transferrin and serum TE concentrations

Regarding the relationship between TE and albumin and transferrin, significant correlations were detected. A significant correlation in positive direction between albumin and Zn ($r = 0.197$, $p = 0.025$), albumin and Fe ($r = 0.415$, $p = 0.000$) was identified. Obviously, a significant correlation in positive direction was found between transferrin and Fe ($r = 0.460$, $p = 0.000$). Also, we found a significant correlation in positive direction between albumin and Cr ($r = 0.217$, $p = 0.012$). No significant differences were observed between other groups.

4.5. Relationship between BMI and serum proteins concentrations

No statistically significant differences in proteins were found between malnourished (mean = 6.419 g/dl) and nourished patients according to BMI (mean = 6.367 g/dl) ($t_{126} = 0.375$, $p = 0.708$). Only 35 patients (24,3%) showed simultaneously low BMI, albumin and transferrin.

4.6. Relationship between BMI and serum TE concentrations

Regarding TE, statistically significant differences were detected only in Fe between malnourished (mean = 48.68 μg/dl) and nourished (mean = 60.26 μg/dl) patients ($t_{110.602} = -2.039$, $p = 0.044$) (Table 4).

5. Discussion

Swallowing perturbations are frequent in patients with HNC and ND. Besides dysphagia, individual characteristics as alcoholism and tobacco consumption, cancer anorexia and therapy side effects

Table 4
Comparison between TE concentration in malnourished and nourished patients.

TE	BMI	n	Mean	Std. Deviation	Std. Error Mean	t	df	P
Zn	MMalnourished	74	53,76	17,996	2,092	0,310	137	0,757
	Nourished	65	52,88	15,127	1,876			
Se	Malnourished	74	10,03	3,014	0,350	−0,822	109,589	0,413
	Nourished	65	10,55	4,240	0,534			
Cu	Malnourished	74	94,88	25,669	2,984	−0,779	137	0,437
	Nourished	65	98,28	25,660	3,183			
Cr	Malnourished	67	0,8024	1,21921	0,14895	−0,739	120	0,461
	Nourished	55	0,9825	1,47118	0,19837			
Fe	Malnourished	74	48,68	26,280	3,055	−2,039	110,602	0,044[a]
	Nourished	65	60,26	38,622	4,791			

[a] Statistically significant differences

contribute to the development of severe malnutrition. Our patients suffered from long standing dysphagia, for more than 1 month, with daily oral intake below 50% of nutritional needs, thus having indication for immediately nutritional support by enteral feeding for long time and the Guidelines recommended the use of PEG procedure. Nutritional assessment tools that need oral communication with the patients are frequently inadequate in the context of our study, because the same disorders that induce dysphagia also lead to impaired speech capacities. We used quantitative measurements, anthropometry and laboratory assays, in order to obtain objective data to approach the nutritional status. The long standing dysphagia had reflex in the weight and in the albumin and transferrin levels, and we want to know what happened about trace elements.

Our patients presented low BMI in 53% (n = 78). These results could be worse if we had not used the usual cut-off 18,5 kg/m^2 instead of 20 kg/m^2 corresponding to NRS 2002, however 18,5 kg/m^2 is the limit adopted by the World Health Organization and it is the most widely used. During dysphagia, the patients lost weight according to low intake but, certainly, in some cases this period was not long enough to decrease BMI. This could explain our results, with 47% patients having a normal BMI. According the underlying diseases we obtained similar percentage of low BMI from the two groups, 53% (n = 47) from the ND and 54% (n = 31) from the HNC, with no statistical significant differences. We found lower BMI in the oldest group, so we believe that aging may increase the malnutrition risk.

Looking for laboratory data, we found 77 (53%) patients with low albumin and nearly two-thirds, 94 (65%) presented low transferrin. Only 66 (46%) presented low levels of both proteins and only 35 displayed low BMI, albumin and transferrin simultaneously, all values suggestive of malnutrition. The lack of association between BMI, albumin and transferrin suggests the presence of an important inflammatory process contributing for the decrease of these proteins. So, in some patients the inflammatory process may have an important contribution, triggering a complex process of stress and starvation.

Regarding TE we expected to found similar low values. Zn was severely decreased in 122 (84%) patients. From remain 24 (16%), 17 (71%) were from neurosurgery ward, and the other 7 (29%), 4 had HNC and 3 suffered from progressive ND. Most of them with normal Zn suffered from a sudden or rapidly progressive dysphagia, meaning the intake had been normal up to a few weeks before the gastrostomy and so there was not enough time to observe a decrease in the values. This could mean that the reduction of Zn seems unrelated with the nature of the underlying disease but with the duration of the starvation period induced by dysphagia.

Iron were normal in 77 patients (53%) and 69 (47%) were low. From these 69 patients 45 (65%) were from the elderly group.

Most of patients displayed normal values for remain TE. For Se, unlike Zn, only 30 (21%) patients (19ND group; 11 HNC group)

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showed low values. Our data suggest that Se can be maintained despite reduced intake of food. At least in part, this may occur because Se absorption from the diet is very efficient so that the low caloric diet prior to gastrostomy seems to be sufficient in most of patients [2]. No differences were detected according age. For Cu most of patients displayed normal values. Only 16 (11%) presented low values. However concerning age, we found 12 patients from the oldest group, suggesting that aging can influence the Cu concentration. According to literature, Cu deficiency is rare in short time semi-starvation [2]. We found similar results in our study, meaning that the period of dysphagia of our patients was not enough to cause Cu deficiency. For Cr, we obtained results from 127. Only 7 (6%) patients showed low Cr, 4 from HNC group. Concerning age, we found worse results in the oldest group (5 patients).

Concerning the relationship between TE and the underlying disorders, we found similar results for most TE. Regarding Se, no statistically significant differences were detected between HNC and ND patients. Regarding Fe, we found low values in 37 patients (41%) from ND and in 32 patients (57%) from HNC. As mentioned before all these samples were obtained just before the moment of PEG procedure. There was no endoscopic major findings in any of the patients that explained these results. No statistically significant differences were detected between these two groups. Cu deficiency was found only in 16 patients (11%), 13 from ND and 3 from HNC, without significant statistical differences. Globally, low TE seems to be unrelated with the nature of the underlying disorder causing dysphagia.

Comparing TE with BMI categories, we detected statistically significant differences only in the Fe between malnourished (mean = 48.68 μg/dl), suggesting that low Fe should be considered as a usual feature of malnutrition in these patients.

The last aim was to assess the relationship between TE and albumin and transferrin, serum markers of malnutrition and/or inflammation. A significant correlation was detected in positive direction between albumin and Zn, signifying that higher levels of albumin are associated with higher levels of Zn. Decreased Zn was found in patients with normal and low albumin and transferrin but decreased Zn cannot be only ascribed to reduce albumin binding capacity, because patients with normal serum proteins may also display low Zn. Most likely because the lack of major Zn reserves it seems to be more sensitive to shorter starvation periods than albumin or transferrin. Also a significant correlation in positive direction between Fe and albumin and transferrin (expectably) was identified. The same correlation was found between albumin and Cr. These results indicate that higher levels of albumin and transferrin are associated with higher levels of Zn, Fe and Cr. On the other hand, no relationship was found between Se and albumin and transferrin. Probably, Se may remain stable until its main enzyme, glutathione peroxidase, decrease regardless albumin and transferrin. Most of our patients displayed low proteins reflecting the reduced dietary intake and the activity of the underlying diseases. From these patients only 15% with low albumin and 14% with low transferrin were the same who presented low Se. Globally, Se variation cannot be ascribed to the concentration of albumin and transferrin. Also, no relationship was found between Cu and albumin and transferrin. Cu variation cannot be ascribed to the concentration of albumin and transferrin.

The association between proteins and Zn, Fe and Cr may be present due to several reasons. Decreased TE and proteins may result from low intake or from disease activity. Whatever the causes, dysphagic patients with low proteins should be considered as a greater risk of TE deficiency.

Our results indicate that low Zn are the rule in long term dysphagic patients and low Fe are very frequent, but not Se, Cu, and Cr. We believe that deficiencies need longer periods of low ingestion before being detectable not observed in most of our patients.

In our experience most dysphagic patients had low TE when gastrostomy was performed and intensive nutritional support begun. More striking regarding Zn, but was also frequent with Fe. It seems to be related with prolonged fasting, whatever the nature of the underlying disease. We suggest that teams taking care of PEG-fed patients should systematically use Zn supplementation, and include evaluation of other TE, mainly Fe as part of the nutritional assessment of PEG-patients when starting the nutritional support through gastrostomy.

Conflict of interest

All authors declare no conflict of interest.

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Statement of authorship

All authors have made substantial contributions and final approval the conceptions, drafting, and final version. Author contribution: Santos CA, conceived and design the study, collected and conducted the data analysis, drafted the manuscript, and final approval de version to be submitted; Fonseca J, analysed and interpreted of data, revised and contributed to final approval of the version to be submitted; Carolino E analyzed and played of data, revised and contributes to final approval, Guerreiro AS, conceived and design the study, revised and contributed to final approval of the version to be submitted. All authors had read and approved the manuscript.

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CAPITULO 4

Estudo 3

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

Carla Adriana Santos, Jorge Fonseca, Teresa Lopes, Elisabete Carolino, António Sousa Guerreiro

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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**

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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**

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

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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.

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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 (-80°C) 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 ($p = 0.002$).

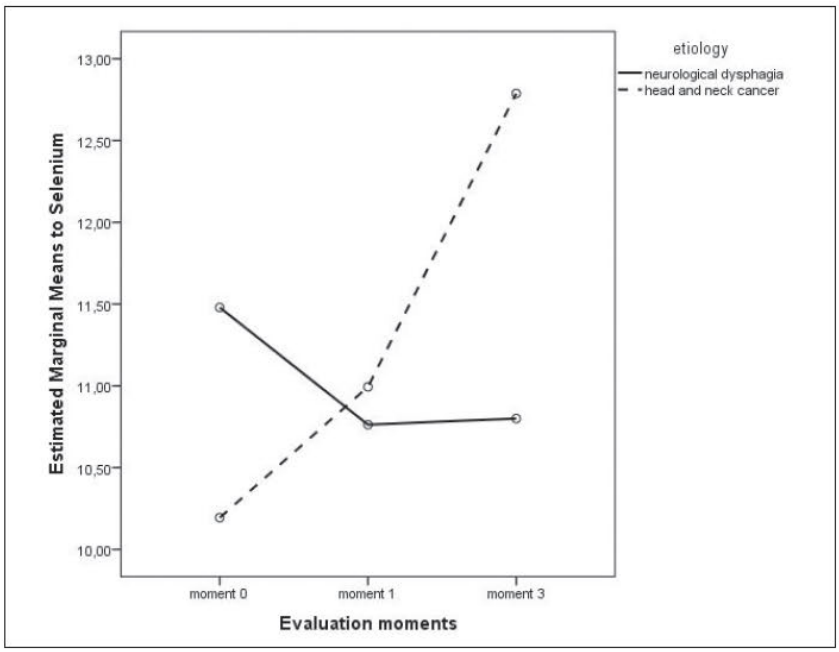

Fig. 1.

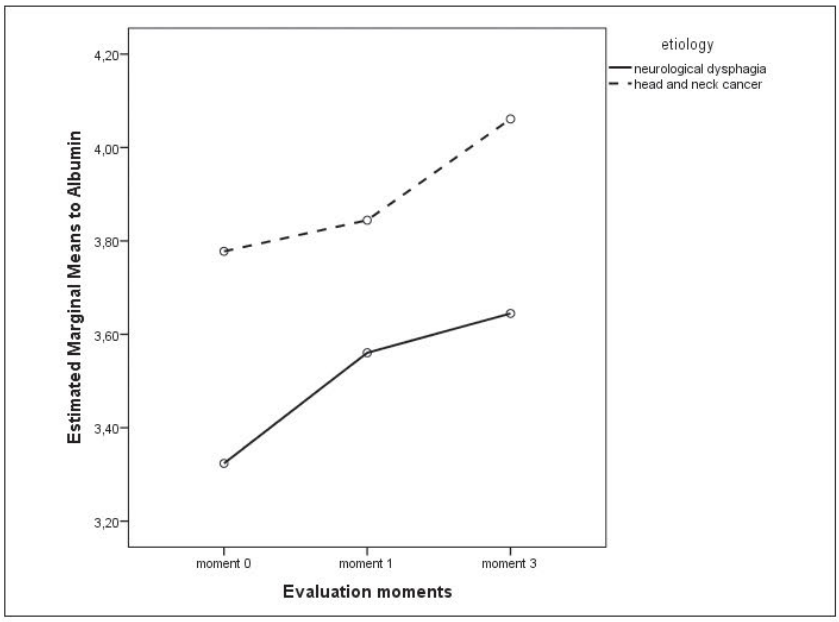

Fig. 2.

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.

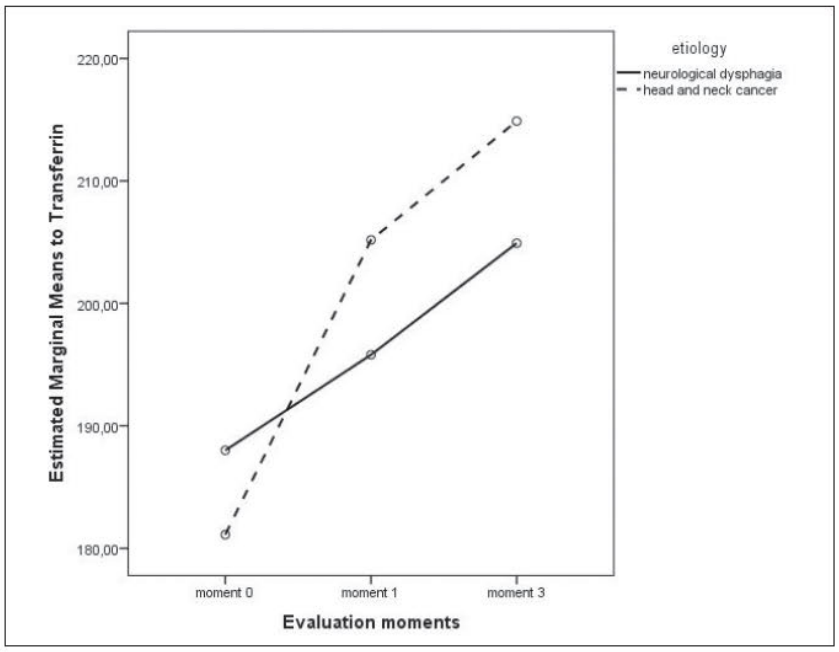

Fig. 3.

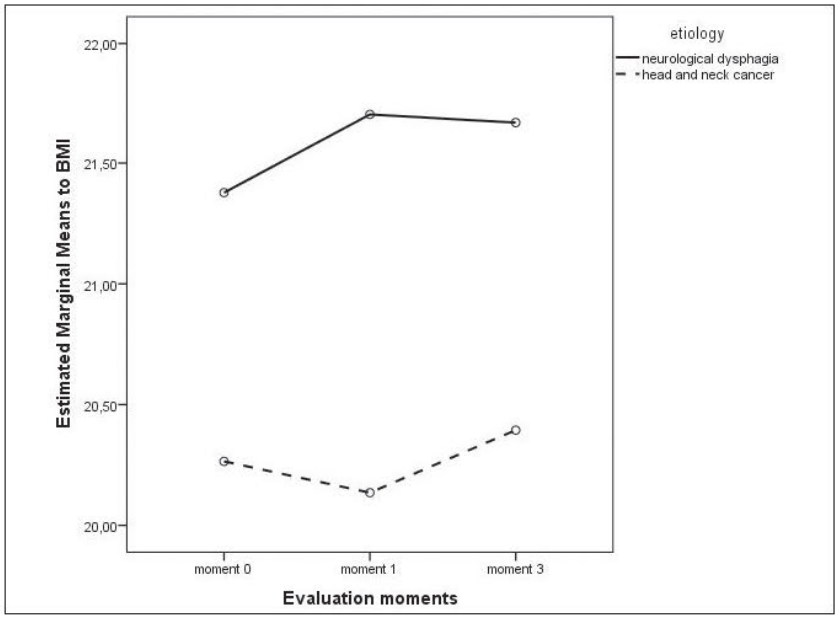

Fig. 4.

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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Estudo 4

"**Serum zinc evolution in dysphagic patients that underwent endoscopy gastrostomy for long term enteral feeding**"

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Abstract

Background: Patients that underwent endoscopic gastrostomy (PEG) present protein-energy malnutrition (PEM) but little is known about Zinc. 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: 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: 146 patients (89 males), 21-95 years: HNC-56, ND-90. 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=0.000) 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.

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 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 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.

MATERIAL 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 are 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) 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 PEG patients [21]. BMI cut-off point for malnutrition was defined for values below 18.5kg/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 remaining 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. 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, unstable patients being excluded or postponed. Nutritional Risk Screening (NRS-2002) presented a score ≥ 3 in all patients, signaling the nutritional risk.

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 53.94±16.20 µg/dl, with a median of 51 µg/dl. Zn were 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 g/l±0.35, 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 low transferrin. Looking at two main groups (HNC and ND) the mean of transferrin was 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, 33 women). Twenty five patients died and 29 were lost to follow-up. Three patients were not compliant with PEG feeding and his tube was 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 removed the tube. From the initial 24 patients normal Zn, 6 patients maintained their values, 8 decreased their values, 7 were lost to follow-up, 2 died and 1 removed his tube. From remain 89 patients, 9 had Zn into 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 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.

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

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 PEG was 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 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.

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 □ T1 (*p*=0.041), T0 □ T3 (*p*=0.011), and rejecting the hypothesis that T1 □□T3 (*p*=0.122). Analyzing the graph of Figure 1, it is found that there is a statistically significant tendency to increase Zn concentration over time. Nevertheless, most patients present los 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=0.000), verifying the paired multiple comparisons that T0 □□T1 (p=0.002), T0 □ T3 (p=0.000) and T1 □ 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 □ T1 (p=0.048), T0 □ T3 (p=0.004), and reject the hypothesis that T1 □□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 is not statistically significant (Figure 1).

Comparing Zn, albumin and transferrin concentrations in both groups (ND and HNC), statistically significant differences were found in: i) Zn concentration at T0 ($t_{138.295}$=2.321, p=0.022); ii) 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 (Figures 2).

Table 3 contains the correlations between Zn, albumin and transferrin concentration at all evaluation moments. The Zn concentration in T3 is 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 are 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 elements 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 concentration in most patients that underwent endoscopic gastrostomy [19,20]. These patients also exhibited deficiency in intracellular Zn, a harder to assess and less used [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 referred Zn deficiency in humans as a frequent dietary problem accompanying many chronic diseases, lack of Zn storage playing an important role [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. Only 4 patients with HNC had normal Zn, comparing with 20 patients from the ND group. Seventeen out of the 20 ND patients suffered traumatic brain injury, with an adequate oral intake prior to the accident. These 17 patients did not suffer a so long 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 is 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 low transferrin. Almost half of the patients (46%) presented 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 of 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.

Limitation 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 [32] and high risk patients are selected to nasogastric tube feeding. 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 long term follow-up of PEG patients.

CONCLUSION

Dysphagic PEG patients that underwent endoscopic gastrostomy are prone to present protein and energy malnutrition and Zn depletion. In our experience, serum Zn concentrations are severely decreased in the majority of patients, suggesting that low Zn is common in PEG candidates that underwent endoscopic gastrostomy. Our results also suggest that enteral nutrition using home prepared meals is not satisfactory to correct Zn deficiency but seems 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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Conflict of interest statement

The authors have no potential conflicts of interest.

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Estudo 5

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

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ABSTRACT

Background and aim: Copper (Cu) is a most 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, after 4 weeks and 12 weeks. 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: 146 patients were enrolled, 89 men, aged 21-95 years, 90 with ND, 56 with 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, low albumin in 53% (n=77), and low transferrin in 94 (65%). 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 34%, and low transferrin in 52%. Comparing age, gender, underlying disease, BMI, albumin and transferrin, there were no significant differences on serum Cu.

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.

INTRODUTION

Trace elements (TE) are inorganic elements that are required in small quantities for normal metabolic functions. Frequently, TE 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 anaemia, 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 includes all the situations when oral intake is not sufficient or safe, including neurological or mechanical dysphagia, oesophagus narrowing for benign or malign condition, and critically ill patients.[8-12] The selection of the route to delivery 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.

PATIENTS 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: (1) head and neck cancer (HNC) including oral cavity, pharyngeal, laryngeal and oesophageal proximal cancer; (2) 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.

Exclusion criteria included age ≤18 years, refusal to be included in the study, clinical instability and doubtful indication for home enteral nutrition. All subjects and legal caregivers were informed of the purpose and procedures of the study and gave their informed consent. This study was approved by the Hospital Ethics Committee.

As routine procedure, all these patients were evaluated by Enteral Feeding Team: the dietitian, the gastroenterologist and the nurse. All patients were evaluated 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 de gastrostomy, all patients were fed with homemade meals which are 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 E.S.P.E.N., the Nutritional Risk Screening – NRS 2002.[13]

Global Nutritional Assessment

Most patients present 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 and expressed as 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. [14,15] 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. [16] Although serum proteins may be influenced by a wide range of non-nutritional factors, albumin <3,5 g/l and transferrin <200mg/dl were considered suggestive of malnutrition.

TE Blood Samples Assays

From patients that underwent endoscopic gastrostomy, a blood sample was obtained minutes before the gastrostomy procedure. 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 specifically designed metal-free tubes for Cu assessment. After centrifugation serum samples were kept frozen (-80ºC) until the analysis. Serum concentration of Cu was 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 Cu samples were assayed using ICP-AES – Inductively Coupled Plasma-Atomic Emission Spectroscopy (washing solution 5%HNO3 in water, Fluka® patterns 1000mg/L). We considered reference values for Cu: 70-140 µg/dl. [17,18]

Statistical Analysis

The influence of underlying disease (ND or HNC) and Gender in Cu values 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). To study the Cu relation with age and proteins (albumin, transferrin and hemoglobin), we used the Pearson correlation coefficient. All the results are considered significant for a 5% significance level.

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 years with a mean age of 68.2 years (SD=14.2). Of these patients, 90 were 65 years or older.

Dysphagia from neurologic disease (ND) was the most common diagnostic (90 patients) which comprises 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), larynges (15), pharynges (20), and proximal oesophagus (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 score ≥ 3 in all patients, signaling the nutritional risk. All patients were clinically stable at the moment of PEG and sample collection (unstable patients were postponed).

1. Initial Evaluation

Copper serum concentrations

One hundred forty six patients were evaluated, Cu ranging 42-160 µg/dl (normal range: 70-140 µg/dl), with a mean 97.23±25.6 µg/dl. Most of 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 the two groups (HNC and ND) (t_{144}=0.059, *p*=0.953). Elderly patients group presented 13% of low values, an higher percentage than the younger group (6%).

Albumin and transferrin serum concentrations

Albumin and transferrin were evaluated in 144 patients. Regarding albumin, we obtained a mean of 3.4g/dl±0,35 ranging from 1.4 to 5.2 g/dl (normal range 3.5-5g/dl). More than half of the patients 53% (n=77) presented low albumin. Regarding transferrin we obtained a mean of 184.0mg/dl ranging from 74 to 331 mg/dl (normal range 200-300mg/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. From 146 patients, 78 (53%) showed low BMI (< 18.5 kg/m^2 for patients younger than 65 years and < 22 kg/m^2 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%). In the group of older patients, 58 (64%) presented low BMI, while in the younger group only 20 (36%) presented low BMI.

2. 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 his tube was removed. From these 89 patients, 83 (93%) had Cu into normal range and 6 (7%) had low values.

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

Albumin: From 89 patients, 30 (34%) had values under normal, and 59 (66%) patients had normal values. From the previous evaluation (T0) 39 patient maintained 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: From 89 patients, 46 (52%) had values under normal, and 43 (48%) patients had normal values. From the previous evaluation (T0) 25 patient maintained normal values, 38 maintained low values, 6 decreased values and 20 increased their values from low to the normal range. Looking at the two main study groups (HNC and ND) we found a similar mean with 205.37 mg/dl from HNC and 187.72 mg/dl from ND.

BMI: For the youngest group we found a mean of BMI of 19.88 Kg/m^2, and for the older group we found a mean of 20.98 Kg/m^2. Looking into 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 age and underlying disease we found a mean of 19.86 Kg/m^2 from HNC and 20.43 Kg/m^2 from ND from youngest group and, 19.91 Kg/m^2 and 21.20 Kg/m^2 from HNC and ND from the older. No significant differences were found.

After 12 weeks of PEG feeding, 40 patients were followed up. Ten patients died between the 4^{th} and the 12^{th} week after gastrostomy. Thirty seven were lost to follow-up and two patients PEG was 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. From 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 from HNC patients and 101.7 µg/dl from ND.

Albumin: 30 (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 the normal range and 1 decrease to low range. Looking at the two main study groups we found a similar mean for albumin with 4.06 g/l from HNC and 3.57 g/l from ND.

Transferrin: From these 40 patients, 35 (66%) had normal values while 18 (34%) 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 for 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: For the youngest group we found a mean of BMI of 20.22 Kg/m^2 and a mean of 21.51 Kg/m^2 for the older 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 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 youngest group and, 20.14 Kg/m^2 and 21.96 Kg/m^2 from HNC and ND respectively in the older group. No significant differences were found.

3. Evolution of Cu concentration after four weeks and twelve weeks, and its relationship with proteins and underlying diseases

It was not detected simultaneous significant influence the etiology and time the Cu values (Statistics with Sphericity, F_2=0.235, 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 the 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) (Figure 1). Although no differences are detected, it can be seen from Figure 1 analysis 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. To the male gender, the results were similar to those obtained previously (Figure 2, Gender: Male). Although no differences are detected, it can be seen from Figure 2, Gender: Male, analysis 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, were not detected statistically significant differences between the three evaluation moments Figure 2, (Gender: Female). Analyzing the graph of Figure 2, (Gender: Female), it is found that Cu values increased over time, and its different behavior of the male with ND.

No significant correlations were detected between the Cu values with age, albumin, transferrin, hemoglobin and Zn in any of the evaluation moments (Table 1).

DISCUSSION

Copper plays a role as a cofactor for various enzymes in the human body and is essential for the structure and function of the nervous system.[19] Cu deficiency is associated with increased osteoporosis, poor immune response, impairment of haematopoiesis and neurologic disorders. [20,21] The main causes of not-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 less than 50% of daily caloric needs, most patients maintained acceptable Cu values.

Looking the behaviour of Cu with other factors that usually had been associated with hypocuprémia such as age, gender and smoking habits we found results that suggesting that there is no relationship with no one of them. We did not find significance of the influence of the gender or age in Cu values in the three stages of evaluation. Also, we did not find any correlation between Cu and serum proteins, albumin, transferrin.

From the Cu deficiency group we found high number of patients with ND (13 from ND and 3 HNC group) but we did not found significance of the influence of underlying disease (ND or HNC) in Cu values in the three stages of evaluation. Finally, although we did not recorded smoking habits, it is known that virtually all HNC patients present heavy smoking habits and there was no significant difference with 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 rate of infections and allows the patients 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 the 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 used gastrostomy homemade meals are soups with mixed meat and fish, fruit juice, daily products with mixed cereals, and milky flour. Sometimes is difficult to reach the desired caloric intake with the homemade diet because de manipulated foods are diluted due to the tube gauge and, also, the capacity for tolerate bolus is, sometimes, diminished.[25] Nevertheless, hypocupremia was identified only in 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 explain in part because Cu is widely distributed in foods and the major contributors of Cu including organ meats (liver and kidneys), muscle meat, seafood, seeds, vegetables and cereal grains.

CONCLUSIONS

Most dysphagic PEG patients present normal serum Cu when gastrostomy is performed. Low serum Cu seems to be unrelated with age, gender, nature of the underlying disorders and normal or low BMI, serum albumin or transferrin. Our results also suggest that, for the minority of patients presenting hypocupremia before gastrostomy, homemade PEG meals seem to be effective for normalizing serum Cu.

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CAPITULO 5

DISCUSSÃO

Todas as situações clínicas que afetam a deglutição e induzem disfagia apresentam um risco aumentado de desnutrição, seja pela redução da ingestão alimentar, pelo aumento da necessidades em nutrientes específicos e/ou pelos efeitos catabólicos da doença de base.

Múltiplos estudos demonstram a necessidade de avaliar o risco nutricional e o estado nutricional [(1)] e suportam a ideia que doentes com disfagia necessitam de uma intervenção precoce e de suporte nutricional adequado para evitar ou diminuir o risco de desenvolver desnutrição.[(2-5)] No entanto, as ferramentas habituais para avaliação do estado nutricional são, na sua maioria, dependentes da expressão verbal, que está diminuída ou inexistente em muitos dos doentes disfágicos.

As equipas clínicas que seguem doentes com disfagia grave tendem, habitualmente, a apoiar-se em instrumentos objetivos tais como a antropometria e os dados laboratoriais. De entre estes últimos os mais comummente utilizados são as proteínas séricas, sobretudo a albumina e a transferrina, mas também para períodos mais curtos, a transtirretina e a proteína transportadora do retinol. Todas estas proteínas, além de poderem refletir o estado nutricional, são também proteínas de fase aguda negativas, estando diminuídas nos estados inflamatórios, pelo que a sua interpretação clínica tem de ser prudente. Os parâmetros antropométricos como o índice de massa corporal, os perímetros e pregas cutâneas refletem melhor o estado nutricional mas tendem a modificar-se mais lentamente do que os parâmetros laboratoriais.[(6)]

Nos doentes disfágicos submetidos a nutrição entérica de longa duração, como é o caso dos doentes incluídos neste estudo, a carência em macronutrientes é evidente com consequências bem conhecidas, sendo frequentes os estudos que avaliam parâmetros antropométricos e laboratoriais nas patologias que induzem disfagia como o AVC e algumas neoplasias.[(7)] O mesmo grau de conhecimento não se verifica relativamente aos oligoelementos em que as necessidades são provavelmente superiores às dos indivíduos sãos devido ao incremento do metabolismo. Assim, a existência de deficiências prévias

e/ou aumento das perdas corporais pode facilmente induzir a carência em um ou mais oligoelementos. De salientar que o reconhecimento de situações carenciais é evidente nas síndromes clássicas, em que os sinais e sintomas típicos estão bem indentificados. Pelo contrário, a carência de oligoelementos que também pode condicionar efeitos adversos importantes, é frequentemente subtil e com reduzida expressão clínica, e muitas vezes de causa não identificada. Uma alimentação monótona e/ou carente pode induzir ou a perpetuar carência de um ou mais oligoelementos.
Adicionalmente à disfagia, características individuais como o alcoolismo, tabagismo, anorexia oncológica e efeitos adversos do tratamento contribuem para o aparecimento da malnutrição.[8]

Foi objetivo deste estudo, determinar a concentração sérica de oligoelementos em doentes com disfagia referenciados e submetidos a gastrostomia endoscópica percutânea para nutrição entérica de longo prazo. A discussão será efetuada em duas partes. Na primeira parte discutem-se os resultados obtidos quando da realização de gastrostomia endoscópica percutânea. Na segunda parte analisa-se a sua evolução às 4 e 12 semanas após a gastrostomia.

1ª parte

No momento da referenciação todos os doentes (n=146) apresentavam disfagia por um período prolongado (superior a 1 mês) e ingestão calórica inferior a 50% das suas necessidades. Verificámos que mais de metade (53%) apresentava baixo IMC. Durante o período de disfagia, os doentes perderam peso relacionado com a baixa ingestão dietética mas, em alguns casos a duração da disfagia não foi suficiente para apresentarem baixo IMC por terem inicialmente peso mais elevado. Isto pode explicar alguns dos nossos resultados. Quando foram identificados os grupos de estudo, verificámos percentagens similares com baixo IMC, 53% no grupo de DN e 54% no grupo de CCF. Apesar do critério de desnutrição corresponder, no grupo dos idosos a um limiar superior ao dos adultos jovens, encontrámos mais doentes com baixo IMC nos idosos, indiciando que, nestes doentes disfágicos o risco de desnutrição aumenta com a idade.

Relativamente aos resultados laboratoriais, encontrámos 77 doentes (53%) com baixa albumina sérica e cerca de 2/3 do total, 94 doentes (65%) com redução de transferrina sérica. Encontrámos 66 doentes que exibiam redução de ambas as proteínas e de entre estes 35 apresentavam simultaneamente diminuição de todos os parâmetros sugestivos de desnutrição nomeadamente IMC, albumina e transferrina. A incompleta associação entre estes parâmetros sugere a presença de um importante processo inflamatório contribuindo para o declínio das proteínas séricas e que, em alguns doentes, poderá ter tido uma importante contribuição no desenvolvimento do processo patológico.
Relativamente aos oligoelementos, esperávamos obter igualmente valores baixos. Para avaliar a concentração de Zn foram efetuados 2 estudos. Um estudo prévio onde avaliámos a concentração de Zn no soro e no sangue total num grupo de 32 doentes. Como o Zn sérico se relaciona com a ingestão diária, esta é a forma mais fácil e comummente utilizada como marcador da sua concentração.[9-11] O Zn eritrocitário tem um turnover mais lento sendo menos sensível à diminuição da ingestão. Uma vez que também é muito mais difícil de dosear, não é pertinente a sua determinação como marcador sensitivo da ingestão dietética. Verificámos que a maioria dos nossos doentes (30/32) apresentava baixa concentração sérica de Zn, e de entre estes, cerca de metade já apresentava valores baixos de Zn no sangue total, o que reflete carência intracelular. Consideramos assim que se a redução da concentração plasmática do Zn reflete a diminuição da ingesta, os resultados por nós obtidos também confirmam a redução do seu conteúdo intracelular, com consequente compromisso das suas funções biológicas.

O segundo estudo incluiu a totalidade dos doentes avaliados (n=146). Como seria expectável a concentração sérica de Zn surge com resultados maioritariamente baixos, em que 122 doentes apresentavam valores inferiores ao normal. Dos restantes 24 doentes, 17 eram do foro neurocirúrgico e, dos outros 7, 4 pertenciam ao grupo do CCF e 3 sofriam de doença neurológica progressiva. A maioria dos doentes com Zn normal apresentava disfagia de instalação rápida, uma vez que a ingestão alimentar tinha sido adequada até ao evento que levou à disfagia, quando comparados com outros doentes. Assim não terá havido tempo suficiente para se poder observar um decréscimo nestes valores séricos. Isto parece significar que a redução de Zn não está relacionada com a natureza da doença subjacente mas sim com o tempo de duração da restrição alimentar induzida pela disfagia.

Contrariamente ao Zn no caso do Se apenas 30 doentes (21%) apresentavam valores baixos (19 do grupo da DN; 11 do grupo de CCF). Os nossos resultados sugerem que a concentração de Se consegue ser mantida dentro dos valores normais apesar da redução da ingestão dietética. Parte destes resultados podem ser explicados porque a absorção de Se da dieta é eficiente e a baixa ingestão prévia à gastrostomia foi, contudo, suficiente na maioria dos doentes para manter níveis séricos normais.[10] Não foram detetadas diferenças relacionadas com a idade dos doentes.

Para o Cu obtivemos resultados similares, com a maioria dos doentes apresentando valores dentro da normalidade. Apenas 16 doentes (11%) apresentaram valores baixos. Contudo 12 destes 16 doentes pertenciam ao grupo dos idosos sugerindo que a idade pode ter influência na concentração sérica de Cu. De acordo com a literatura a deficiência em Cu é rara em períodos curtos de baixa ingestão energética e proteica.[10] Encontrámos resultados similares no nosso estudo sugerindo que, na maioria dos doentes, o período de disfagia não foi suficiente para provocar uma carência em Cu.

À semelhança dos resultados anteriores também para o Cr verificámos que a maioria dos doentes apresentava valores dentro da normalidade. Do total de 127 doentes, apenas 7 (6%) apresentaram baixo Cr aquando da gastrostomia. Também o Cr parece permanecer estável mesmo com uma ingestão calórica e proteica reduzida, provavelmente porque a absorção do Cr está fisiologicamente adaptada à redução da ingestão. Apresenta uma absorção inversa à ingestão e mesmo pequenas doses são suficientes para manter os seus níveis séricos, como parece ter sido o caso dos doentes estudados.

Analisando os valores do Fe obtivemos valores normais em 77 doentes (53%) e valores baixos em 69 (47%) não parecendo haver diferença significativa nem com a idade nem com a doença subjacente. Contudo, quando comparámos os oligoelementos com as categorias do IMC, detectámos diferenças com significado estatístico apenas para o Fe nos doentes com baixo peso ($\bar{x}$:48.68 µg/dl), sugerindo que o Fe sérico baixo pode ser um indicador de desnutrição energética e proteica nestes doentes. Este facto poderá estar relacionado com uma variação qualitativa da ingestão alimentar, pois muito precocemente, nos estados iniciais da disfagia, ocorre expontaneamente uma mudança da consistência dos alimentos no sentido da ingestão de alimentos moles, pastosos ou líquidos. Fontes de Fe heme, como a carne, estão entre os primeiros alimentos a ser eliminados no início da

disfagia, e a carência de Fe pode ser um marcador indireto de disfagia mais prolongada do que a noção temporal que nos foi transmitida pelo doente, durante a colheita dos dados anamnésticos. Por outro lado, o Fe sérico está regularmente baixo durante os estados inflamatórios prolongados. Assim, Fe sérico reduzido e desnutrição partilham um fator causal comum, a inflamação crónica.

Quando relacionámos os valores em oligoelementos e as doenças indutoras da disfagia, não encontrámos diferenças com significado estatístico entre os doentes dos grupos de CCF e DN. Globalmente, baixas concentrações séricas de oligoelementos não estão relacionadas com a etiologia da doença causadora de disfagia. A natureza da disfagia dos doentes com CCF, capaz de induzir as alterações metabólicas e catabólicas associadas às neoplasias, bem como a típica associação do CCF com elevados consumos tabágicos e alcoólicos não influenciou significativamente a diminuição dos oligoelementos séricos. Assim, os dados recolhidos apontam claramente para que o fator dominante seja o prolongado período de disfagia.

Nesta primeira fase os nossos resultados indicam que uma baixa concentração sérica de Zn e Fe é frequente nos doentes com disfagia durante um período prolongado. Em relação ao Se, Cu e Cr, consideramos que necessitam de períodos mais prolongados de disfagia e baixa ingestão, antes de se verificar redução nos seus valores séricos.

2ª parte - Follow-up

Após 4 (T1) e 12 (T3) semanas de nutrição entérica por gastrostomia com alimentos correntes verificámos que os oligoelementos se comportaram de forma diversa.

Os valores de Zn sérico não sofreram alteração ao longo destas 12 semanas. No início do estudo 84% dos doentes apresentavam redução sérica de Zn, verificando-se que às 4 e 12 semanas, 84% e 89%, respetivamente, continuavam a apresentar valores baixos. Assim, os dados obtidos demonstraram que a alimentação com alimentos correntes não foi suficiente para corrigir a deficiência em Zn.

No respeitante aos outros oligoelementos, Se, Cu, Cr e Fe, em contraste com os níveis de Zn, a maioria parece melhorar após 12 semanas de alimentação por PEG com alimentos

correntes (dados relativos ao Cr ainda não publicados). Contudo, a redução progressiva dos doentes acompanhados ao longo do estudo, com grande número de doentes falecidos e perdidos para follow-up, não nos permite concluir com absoluta segurança.

Quanto ao Se verificámos uma tendência para a manutenção dos valores inaugurais. Inicialmente 31 dos 146 doentes (21%) apresentavam valores baixos, verificando-se que às 4 e 12 semanas, 15 dos 89 doentes (17%) e 7 de 40 (18%).

Estes dados sugerem que a reposição energética e proteica com alimentos correntes poderá impedir o agravamento de deficiência em Se. Contudo, apesar de constituir uma minoria, a identificação de Se baixo em um em cada cinco doentes submetidos a PEG poderá justificar maior atenção, dada a sua importância biológica.

Quanto ao Cu verificámos uma compensação dos valores baixos iniciais. Inicialmente 16 dos 146 doentes (11%) apresentavam valores baixos, verificando-se que às 4 e 12 semanas, 6 dos 89 doentes (7%) e 2 de 40 (5%). Aparentemente a alimentação com alimentos correntes foi suficiente para normalizar os valores do Cu e a escassa percentagem de doentes que inicialmente apresentava hipocuprémia reduziu-se progressivamente ao longo das 12 semanas de estudo. Estes dados sugerem que apesar do número limitado de doentes, a alimentação por alimentos correntes contribui para a normalização dos valores séricos do Cu. Em todo o caso as perdas de doentes ocorridas durante o follow-up e mortes dos doentes aconselham uma leitura prudente desta evolução. Estes resultados estão de acordo com a literatura que salienta que a deficiência em Cu é rara em períodos curtos de baixa ingestão calórica. [12,13]

Quanto ao Cr, inicialmente apenas 8 doentes apresentavam valores baixos. Também aqui, a percentagem de doentes com valores inicialmente baixos se reduziu ao longo do estudo sendo que às 12 semanas nenhum doente apresentava valores de Cr baixo (dados ainda não publicados). A redução do Cr não é um achado frequente e mesmo os doentes com baixo Cr parecem ter respondido à reposição dietética. Estes dados serão brevemente submetidos para publicação. Aqui também, as perdas de doentes ocorridos durante o follow-up aconselham uma leitura prudente.

O Fe que inicialmente apresentava uma percentagem elevada de doentes com valores baixos (47%) passou para 41.6% no T1 e para 37.5% no T3 (dados ainda não publicados). Este decréscimo no número de doentes com Fe baixo é discreto mas progressivo. Contudo

a análise destes dados exige uma integração mais vasta que inclui a avaliação da transferrina, ferritina, hemoglobina e vitaminais envolvidas na hematopoiese, nomeadamente o ácido fólico, que tem escassas reservas orgânicas. Também as perdas hemáticas com origem em neoplasias cervicofaciais ou em outras fontes hemorrágicas poderão ter uma importância significativa. Esta análise ultrapassa o âmbito deste estudo, pelo que estes dados serão avaliados globalmente mais tarde.

No que respeita à evolução das proteínas séricas, albumina e transferrina verificámos que quando os doentes foram referenciados para PEG, a maioria apresentava baixos valores que pode ser atribuído a uma redução energética e proteica e/ou outros fatores como da atividade da doença subjacente.[14-18] Os doentes em estudo, devido à disfagia, apresentavam baixa ingestão energética e proteica, inferior a 50% das suas necessidades, o que pode explicar, em parte, os dados acima mencionados. Analisando a evolução destas proteínas durante o período de estudo, verificámos um aumento na sua concentração o que parece sugerir uma evolução nutricional positiva e/ou uma diminuição da inflamação em ambos os grupos, CCF e DN.

Assim julgamos poder concluir que as proteínas séricas e oligoelementos, com exceção do Zn e eventualmente do Se, responderam positivamente à alimentação de com alimentos correntes administrada por PEG durante os 3 meses após gastrostomia.

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II) CONSIDERAÇÕES FINAIS

As deficiências em oligoelementos podem ser subclínicas e por isso difíceis de detetar. Os doentes com disfagia que não consigam atingir as suas necessidades energéticas e proteicas devem ser monitorizados frequentemente de modo a identificar e procurar sinais e sintomas de carência de um ou mais nutrientes, sobretudo em oligoelementos. Assim deverá ser dada especial atenção aos doentes que estão sob nutrição entérica de longa duração, especialmente aqueles que recebem preparações caseiras com alimentos correntes.

Na nossa experiência, a redução da concentração sérica de oligoelementos no momento da gastrostomia foi heterogénea, relacionada com o período prolongado de disfagia e não relacionado com a patologia subjacente. Esta carência verifica-se sobretudo em relação ao Zn e mantém-se mesmo após a implementação de suporte nutricional com alimentos correntes.

Sugerimos, assim, que as equipas que cuidam de doentes sob nutrição entérica com alimentos correntes devem suplementar sistematicamente com Zn, devendo no entanto incluir o doseamento de outros oligoelementos, principalmente Fe e Se, como parte da avaliação nutricional ao iniciar o suporte nutricional através de gastrostomia.

III) PROJETOS EM CURSO

Os trabalhos publicados na literatura relacionados com o tema desta dissertação são escassos. Assim, pretendemos prosseguir os nossos estudos com o objetivo de melhorar o suporte clínico dos doentes sob nutrição entérica prolongada.

- Está a decorrer um estudo prospectivo e randomizado comparando a evolução dos valores séricos de Zn em doentes sob nutrição por PEG, usando alimentos correntes num dos grupos e alimentação com fórmulas industriais noutro grupo. Pretendemos verificar a eficácia da alimentação com fórmulas industriais na normalização do Zn.

- Criámos uma base de dados alargada para avaliar a evolução do Fe no contexto da doença de base através da utilização de outros parâmetros, nomeadamente da transferrina, ferritina, hemoglobina e vitaminas envolvidas na hematopeiese. Pretendemos também explorar a relação da evolução do Fe com a existência de neoplasias e outras lesões potencialmente sangrantes.

- Iniciámos a avaliação dos níveis séricos de Vitamina D que presumimos constituir uma carência importante nestes doentes que associam a restrição alimentar a um défice marcado de exposição solar. Os resultados preliminares que já ultrapassam duas centenas de doentes, permitem-nos subescrever este pressuposto.