Universidade Federal do Maranhão
Centro de Ciências Biológicas e da Saúde
Programa de Pós-Graduação em Ciências da Saúde
Doutorado

SUPLEMENTAÇÃO DE AMINOÁCIDOS DE CADEIA RAMIFICADA E ÔMEGA 3: efeito clínico-nutricional no câncer

ALEXSANDRO FERREIRA DOS SANTOS

São Luís

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Tese apresentada ao Programa de Pós Graduação em Ciências da Saúde da Universidade Federal do Maranhão, como requisito para obtenção do título de Doutor em Ciências da Saúde.

Linha de Pesquisa: Pesquisa em Clínica e Cirurgia Experimental

Orientador: Prof. Dr. José Albuquerque de Figueiredo Neto

São Luís

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Viver é acalentar sonhos e esperanças fazendo da nossa fé a nossa inspiração maior. É buscar nas pequenas coisas, um grande motivo para ser feliz.

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SUMÁRIO

LISTA DE SIGLAS E ABREVIATURAS

ABEP	Associação Brasileira de Empresas de Pesquisa
AF	Ângulo de Fase
AMB	Área Muscular do Braço
BCAA	Branched chain amino acids
BIA	Bioimpedância elétrica
CB	Circunferência do Braço
CEP	Comitê de Ética em Pesquisa
CG	Grupo Controle
cm	Centímetros
CMB	Circunferência Muscular do Braço
EORTC – QLQ C30	Quality of Life Questionnarie of European Organization for Research and Treatment of Cancer
EPA	Ácido Eicosapentaenóico
FAPEMA	Fundação de Amparo à Pesquisa e ao Desenvolvimento Científico e Tecnológico do Maranhão
FC	Frequência cardíaca
FR	Frequência Respiratória
HCAB	Hospital do Câncer Aldenora Bello
HUUFMA	Hospital Universitário da Universidade Federal do Maranhão
IL – 1 e 6	Interleucinas 1 e 6
IMC	Índice de massa corporal
PAD	Pressão Arterial Diastólica
PAS	Pressão Arterial Sistólica
PCR-US	Proteína C ultra sensível
PCT	Prega Cutânea Tricipital
PPGCS	Programa de Pós-graduação em Ciências da Saúde
R	Resistência
RD24H	Recordatório de 24 horas
SBC	Sociedade Brasileira de Cardiologia
SUS	Sistema Único de Saúde

TC6	Teste da caminhada dos 6 minutos
TCLE	Termo de Consentimento Livre e Esclarecido
T_f	Término de seguimento do estudo
T_i	Baseline, início do seguimento de estudo
TNF α	Fator de necrose tumoral alfa
WHO	World Health Organization (Organização Mundial de Saúde)
Xc	Reactância
Z	Impedância
W3	Ômega 3
W3G	Grupo Suplementado com ômega 3

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RESUMO

Introdução: caquexia é uma síndrome multifatorial de relevância clínica inquestionável, preditora independente de morte, baixa resposta terapêutica e pior qualidade de vida (QV) em pacientes com câncer. **Objetivo:** Analisar o efeito da suplementação dietética de aminoácidos de cadeia ramificada (BCAA) e ácidos graxos ômega 3 (W3) na caquexia do câncer. **Material e Métodos:** ensaio clínico randomizado, aberto embasado em revisão de literatura sistemática e nos dados basais da coleta de dados, conduzida entre outubro de 2018 a outubro de 2019. A amostra aleatória simples constituída de 17 mulheres com câncer de colo uterino, com 20 anos ou mais alocadas em dois grupos (suplementado com 14,4g/dia de BCAA e Controle – CTL). O protocolo contemplou suplementação por 56 dias e orientações para alimentação saudável. Foram verificadas variáveis demográficas e sócioeconômicas, e ainda, no início e ao término da suplementação houve coleta de variáveis nutricionais, cardiorrespiratórias, capacidade funcional, QV, bioquímico-inflamatórias, clínicas e desfechos. A análise estatística foi realizada no *software SPSS*®, aplicou-se como testes *Shapiro-Wilk*, t pareado/Wilcoxon e t de student/Man-Witney à um nível de significância máximo de 5%. **Resultados:** *Capítulo I:* Foram selecionados oito estudos com indivíduos de 18 a 84 anos, amostras de 27 a 332 participantes (seguimento: 6-16 semanas). Desfechos avaliados: peso corporal, TMB, apetite, capacidade funcional, QV, fadiga, IL6, TNF-α, proteína C-reativa, albumina, pré-albumina e sobrevida. A descrição da perda amostral e a geração de uma sequência aleatória esteve presente em 75,0% dos inquéritos. *Capítulo II:* Compuseram a amostra mulheres com 38,5±5,6anos (BCAA, n=8) e 41,1±5,0anos (CTL, n=9), brancas, de baixa escolaridade e renda. Observou-se associações estatisticamente significativas ($p<0,05$): redução da circunferência do braço e da TMB no grupo BCAA comparativamente ao grupo CTL; aumento do TNF-α (165,7%) em relação ao basal no grupo BCAA e decréscimo do hematócrito no grupo CTL. *Capítulo III:* 27 mulheres foram avaliadas de forma transversal (idade 40,2±7,1anos), brancas e procedentes de São Luís. A sarcopenia teve prevalência de 33,3%. As mulheres com sarcopenia, apresentaram menor escore para os domínios Global e Capacidade Funcional, quando comparadas as mulheres não sarcopênicas. *Capítulo IV:* Observou-se um consumo médio de 62,6±16,4g/dia de proteínas, 461,8±232,1mg/dia de cálcio e 3,3±3,1mcg/dia de vitamina D. A massa magra foi de 21,3±8,4kg e a distância percorrida de 346,3±77,6m. Verificou-se uma correlação moderada, inversa e estatisticamente significativa entre distância percorrida e consumo de vitamina D. *Capítulo V:* O consumo de proteína por refeição (CPR) do almoço e do jantar atingiram a meta de 20 a 30g. Em relação a QV, houve correlação inversa e estatisticamente significativa e moderada entre FPP na mão direita e CPR no lanche e FPP na mão esquerda e CPR no desjejum, respectivamente. **Conclusão:** a suplementação com W3 é importante para modulação da caquexia no câncer, outras estratégias incluem: a adequação no consumo alimentar de vitamina D, Cálcio e Proteína e atenção no consumo alimentar de proteína em quantidade e distribuição adequada. Já a suplementação isolada de BCAA embora atenue a TMB, parece aumentar o quadro inflamatório e contribuir para piores reservas de gordura.

Palavras-Chave: Câncer. Colo Uterino. Caquexia. Suplementação. Ômega 3. Aminoácido de cadeia ramificada.

ABSTRACT

Introduction: cachexia is a multifactorial syndrome of unquestionable clinical relevance, independent predictor of death, low therapeutic response, and worse quality of life (QOL). **Objective**: To analyze the effect of dietary supplementation with branched-chain amino acids (BCAA) and omega 3 fatty acids (W3) on cancer cachexia. **Material and Methods**: randomized, open clinical trial based on a systematic literature review and baseline data collection conducted between October 2018 and October 2019. The simple random sample consisted of 17 women with cervical cancer, aged 20 years or older, divided into two groups (supplemented with 14.4g / day of BCAA and Control - CTL). The protocol included supplementation for 56 days and guidelines for healthy eating. Were verified demographic and socioeconomic variables, and at the beginning and the end of supplementation were collected nutritional, cardiorespiratory, functional capacity, QOL, biochemical-inflammatory, clinical, and outcome variables. Statistical analysis was performed using SPSS® software. Was applied the Shapiro-Wilk, paired t / Wilcoxon, and t student / Man-Witney tests at a maximum significance level of 5%. *Chapter I*: were selected eight studies with individuals aged 18 to 84 years, samples from 27 to 332 participants (follow-up: 6-16 weeks). Outcomes evaluated: body weight, BMR, appetite, functional capacity, QOL, fatigue, IL6, TNF-α, C-reactive protein, albumin, pre-albumin, and survival. The description of the sample loss and the generation of a random sequence was present in 75.0% of the surveys. *Chapter II*: the sample comprised women aged 38.5 ± 5.6 years (BCAA, n = 8) and 41.1 ± 5.0 years (CTL, n = 9), white, with low education and income. There were statistically significant associations ($p < 0.05$): reduced arm circumference and basal metabolic rate in the BCAA group compared to the CTL group; increase in TNF-α (165.7%) compared to baseline in the BCAA group and decrease in hematocrit in the CTL group. *Chapter III*: were evaluated 27 women cross-sectionally (age 40.2 ± 7.1 years), white, and from São Luís. Sarcopenia had a prevalence of 33.3%. Women with sarcopenia had a lower score for the Global and Functional Capacity domains when compared to non-sarcopenic women. *Chapter IV*: Was observed an average consumption of 62.6 ± 16.4g / day of proteins, 461.8 ± 232.1 mg/day of calcium, and 3.3 ± 3.1mcg / day of vitamin D. The lean mass was 21.3 ± 8.4 kg and the distance covered was 346.3 ± 77.6 m. There was a moderate, inverse, and statistically significant correlation between distance traveled and consumption of vitamin D. *Chapter V*: Protein consumption per meal (PCPM) for lunch and dinner reached the target of 20 to 30g. Regarding QOL, there was an inverse and statistically significant, and moderate correlation between FPP in the right hand and PCPM in the snack and FPP in the left hand and PCPM in the breakfast, respectively. **Conclusion**: supplementation with W3 is important for modulation of cachexia in cancer, other strategies include the adequacy of dietary consumption of vitamin D, calcium, and protein and attention to food consumption of protein in adequate quantity and distribution. Already the supplementation of BCAA alone, although attenuating the BMR, seems to increase the inflammatory condition and contribute to worse fat reserves.

Keywords: Cancer. Uterine lap. Cachexia. Supplementation. Omega 3. Branched-chain amino acid.

1 INTRODUÇÃO

A caquexia é definida como perda contínua de massa muscular (com ou sem perda de massa gorda), que nem sempre pode ser totalmente revertida pela terapia nutricional convencional, implicando progressivo comprometimento funcional do organismo (WAITZBERG, 2011; CAMPOS-FERRAZ et al., 2014). Trata-se de uma síndrome multifatorial que exerce impacto negativo sobre a qualidade de vida, morbidade e mortalidade de pacientes que sofrem de doenças agudas e crônicas clinicamente relevantes (LAVIANO et al., 2015; SEELAENDER et al., 2015).

Normalmente, a caquexia está associada à perda de peso corporal, degradação de proteínas musculares, perda de tecido adiposo, anorexia, inflamação, má absorção, náuseas, astenia, comprometimento da função do sistema imunitário (susceptibilidade à infecções), perturbações do metabolismo energético, fraqueza e redução da capacidade funcional (SILVA, 2006; LAVIANO et al., 2015; ARGILÉS et al., 2015; SEELAENDER et al., 2015).

Trata-se de uma condição metabólica que está sempre associada com uma doença subjacente e inflamação (ARGILÉS et al., 2015). Frequentemente esta relacionada à oncologia (OKOSHI et al., 2013; ARGILÉS et al., 2015; YOSHIDA e DELAFONTAINE, 2015). Em pacientes com câncer avançado, a prevalência de caquexia pode chegar até 80% dos casos (SEELAENDER et al., 2015). A relevância clínica deste agravo é inquestionável, destacando-se como preditor independente de morte, baixa resposta ao tratamento, bem como, de piores medidas de qualidade de vida (ARAÚJO et al., 2011; OKOSHI et al., 2013; ALI e GARCIA, 2014; KOPEĆ, 2014; SEELAENDER et al., 2015).

Vários mecanismos têm sido implicados no processo fisiopatológico da caquexia, com destaque a ação das citocinas pró-inflamatórias, onde níveis cronicamente elevados encontram-se presentes na grande maioria destes pacientes (COLETTI et al., 2006; SEELAENDER et al., 2015), e ainda, desequilíbrio entre hormônios anabolizantes e catabólicos, alterações hormonais envolvidas na regulação do metabolismo energético e do apetite (leptina, adiponectina e a grelina) (ARAÚJO et al., 2011).

Considerando-se a magnitude da caquexia, em relação à alta prevalência e importante relação com a morbimortalidade, e ainda, a baixa eficácia das terapias medicamentosas e nutricionais sobre o desenvolvimento da mesma, substâncias tem sido testadas, quanto à ação no controle do processo inflamatório objetivando melhorar o estado

nutricional, e consequentemente à qualidade de vida dos pacientes (MARQUES et al., 2013; SOUZA, 2014).

Dentre as recomendações nutricionais, a suplementação com ácidos graxos ômega-3, com reconhecido potencial antiinflamatório têm sido avaliadas em ensaios com modelos animais e humanos na redução da perda de peso, melhora da força muscular, da capacidade funcional, impedimento da perda de massa, aumento da taxa de síntese proteica, bem como, modulação da resposta imunológica e inflamatória na caquexia (GIACOSA e RONDANELLI, 2008; MARQUES et al., 2013; PAIM et al., 2014; SOUZA, 2014).

Estudos também sugerem que uma oxidação excessiva de aminoácidos de cadeia ramificada (BCAA), possa estar envolvida em mecanismos moleculares da caquexia, indicando efeito benéfico da suplementação dietética com BCAA na terapia nutricional destes pacientes, com o objetivo de melhorar o balanço nitrogenado e, principalmente, o metabolismo proteico-muscular (ELEY et al., 2007; SANTOS, 2012; CAMPOS-FERRAZ et al., 2014; BOWEN et al., 2015).

Ensaios clínicos com a utilização de suplementos nutricionais orais, de forma isolada ou combinada têm evidenciado efeitos benéficos em várias doenças crônicas (ROZENTRYT et al., 2010; CAMPOS-FERRAZ et al., 2014; SCHLEITHOFF et al., 2006; LOMBARDI et al., 2014).

No entanto, estudos de intervenção nutricional direcionados à pacientes com caquexia apresentam-se escassos, dificultando conclusões baseadas em evidências científicas (CAMPOS-FERRAZ et al., 2014).

Os dados disponíveis na literatura apresentam o câncer como grave problema de saúde pública, com elevadas taxas de incidência, prevalência e mortalidade. Nestes pacientes, a caquexia se destaca como preditor independente de morte, baixa resposta a terapia medicamentosa e nutricional, e ainda, piores medidas de qualidade de vida (BRASIL, 2015a; SEELAENDER et al., 2015).

Nesse contexto, estudos apontam a utilização dietética de aminoácidos de cadeia ramificada (ELEY et al., 2007; SANTOS, 2012; CAMPOS-FERRAZ et al., 2014; BOWEN et al., 2015) e de ômega-3 (GIACOSA e RONDANELLI, 2008; MARQUES et al., 2013; PAIM et al., 2014; SOUZA, 2014) como uma estratégia terapêutica promissora, sugerindo efeitos benéficos sobre a ingestão calórica, aumento da síntese e atenuação da taxa de degradação de

proteínas do músculo esquelético, modulação do estado inflamatório e melhora da capacidade funcional.

Face ao exposto, sabendo que há indícios que a suplementação (isolada ou combinada) pode trazer benefícios, evidencia-se a necessidade da realização de um estudo sob a Hipótese Alternativa (H_1) para testar o efeito da suplementação de aminoácidos de cadeia ramificada em associação ao ômega 3 nos parâmetros clínico-nutricionais, cardiorrespiratórios, metabólicos e qualidade de vida em pacientes com caquexia secundária ao câncer de colo uterino.

Assim, poder-se-á contribuir para elucidar a aplicação terapêutica dos referidos suplementos em pacientes portadores desta patologia, podendo-se, promover melhorias no tratamento, e ainda, proporcionar uma melhor evolução clínica de pacientes com câncer de colo uterino, que segundo Silva et al. (2014) já compreende a maior causa de morte por câncer entre as mulheres no Estado do Maranhão.

Esta tese apresenta-se no *Formato de Artigo*, cuja a organização está contida nos capítulos *Introdução* (que problematiza, apresenta e justifica esta pesquisa, além de fixar as hipóteses de estudo), *Referencial Teórico* (que fundamenta as pesquisas até aqui desenvolvidas, bem como a lacuna de conhecimento a ser preenchida), *Objetivos* (*Geral* e *Específicos*) e *Resultados* divididos em cinco Artigos, à dizer:

Capítulo I – *Effects of a Food Supplementation with Omega-3 and Branched-Chain Amino Acids in Cancer Patients with Cachexia: a Systematic Review*, o referido artigo foi submetido no periódico *Journal of International Medical Research*, uma revista B2 na área de Medicina I (Fator de Impacto = 1,287).

Capítulo II – *Suplementação de BCAA e Câncer de Colo Uterino: efeitos na antropometria, marcadores bioquímico-inflamatório e capacidade funcional* será submetido no periódico *Nutrición Hospitalaria*, uma revista B2 na área de Medicina I (Fator de Impacto = 0,888).

Capítulo III – *Sarcopenia and Quality of Life: an association study in women with cervical cancer* submetido no periódico *Quality Of Life Research*, uma revista B1 na área de Medicina I (Fator de Impacto = 2,392).

Capítulo IV – *Food Consumption for Muscle Synthesis (Protein, Calcium and Vitamin D): a study of association with muscle reserve and functional capacity in women with*

cervical cancer submetido no periódico *Nutrition in Clinical Practice*, uma revista B1 na área de Medicina I (Fator de Impacto = 2.401).

Capítulo V – *Association of protein consumption per meal with muscle strength and quality of life in patients with cervical cancer* submetido no periódico *Nutrition in Clinical Practice*, uma revista B1 na área de Medicina I (Fator de Impacto = 2.401).

Além disto, ao término dos Resultados se tece sobre os principais resultados e alcance dos objetivos da tese, bem como das limitações da tese e abertura para novas pesquisas no item Considerações Finais. Já na Conclusão, registra-se o alcance desta pesquisa.

2 REFERENCIAL TEÓRICO

2.1 Câncer de Colo Uterino

2.2.1 Epidemiologia

A infecção pelo Papiloma Vírus Humano (HPV) é muito comum. Estima-se que 80% das mulheres sexualmente ativas irão adquirí-lo ao longo de suas vidas, e aproximadamente 291 milhões de mulheres no mundo são portadoras do HPV, sendo que 32% estão infectadas pelos subtipos 16, 18 ou ambos, ou seja aqueles potencialmente oncogênicos (BRASIL, 2019).

O carcinoma de células escamosas (epidermóide) compreende aproximadamente 90% dos cânceres de colo de útero (cervicais), e o adenocarcinoma compreende aproximadamente 10% dos cânceres cervicais, já os carcinomas adenoescamosos e de pequenas células são relativamente raros. Também foram relatados sarcomas primários do colo uterino e linfomas malignos primários e secundários do colo do útero (BRASIL, 2016).

Comparando-se esse dado com a incidência anual de aproximadamente 500 mil casos de câncer de colo do útero, conclui-se que o câncer é um desfecho raro, mesmo na presença da infecção pelo HPV, ou seja, a infecção pelo HPV é um "fator necessário", mas não suficiente, para o desenvolvimento do câncer cervical uterino (BRASIL, 2019).

2.1.2 Fisiopatologia e diagnóstico

Epistemologicamente a palavra Câncer derivada do grego "*karkínos*", cujo significado é caranguejo, inicialmente a palavra foi utilizada por Hipócrates (460 a.C – 377a.C./ "pai da medicina"). Câncer é uma doença antiga, averiguada em múmias egípcias há mais de 3 mil a.C. Muito possivelmente este nome foi empregado em analogia ao modo de crescimento infiltrante/invasivo, que pode ser semelhante às pernas de um caranguejo, que as introduz entre a areia ou lama para fixar-se, o que dificulta sua remoção (SALAVERRY, 2013).

O câncer de colo do útero é o quarto câncer mais comum entre mulheres no mundo e tem a quarta maior taxa de morte por câncer entre este público (NIH, 2019). No

Brasil é o terceiro tipo de câncer mais comum, estimam-se 16.370 novos casos para cada ano, durante o biênio 2018-2019 no Brasil. A região Norte é a mais incidente (25,62/100 mil), já as Regiões Nordeste e Centro-Oeste, ocupam a segunda posição mais frequente com 20,47/100 mil e 18,32/100 mil, respectivamente. A Região Sudeste ocupa a quarta posição com 9,97/100 mil (BRASIL, 2017).

Os principais fatores de risco para o desenvolvimento deste tipo de neoplasia são: relação sexual precoce, baixo nível de escolaridade, multiparidade, múltiplos parceiros, tabagismo, uso contínuo de pílulas anticoncepcionais e a infecção pelo HPV (Papiloma vírus humano) (VERZARO; SARDINHA, 2018).

No estado do Maranhão, o câncer de colo uterino já é o terceiro tipo mais prevalente do estado e da capital, ficando atrás apenas dos cânceres de próstata e mama. Entre as mulheres especificamente, este já é o segundo mais frequente na capital e o mais frequente no estado. Em 2016 foram 970 casos novos/100 mil habitantes em todo o estado e 230/100 mil habitantes na capital de São Luís (BRASIL, 2017).

Câncer ou Neoplasias malignas englobam um conjunto de mais de 200 doenças caracterizadas pelo crescimento rápido, invasivo de células com danos em seu material genético e capazes de alterar a morfofisiologia de órgãos e sistemas. O colo do útero é revestido por dois tipos de células epiteliais: células escamosas no aspecto externo e células glandulares colunares ao longo do canal interno. A transição entre células escamosas e células colunares é uma área denominada junção escamo-colunar. A maior parte das alterações oncogênicas ocorrem nessa zona (BRASIL, 2016).

A principal causa para o desenvolvimento do câncer de colo uterino está associada à infecção persistente pelo Papilomavírus Humano (HPV), doença transmitida sexualmente, na maioria das vezes ocorre transitoriamente e regride de forma espontânea, entre seis meses a dois anos após a exposição. Nos casos em que a infecção não regride, a mesma é causada por um subtipo viral cancerígeno. Os subtipos 16 e 18 foram mais intimamente associados à displasia de alto grau e ao câncer, estes podem causar o desenvolvimento de lesões precursoras (lesão intraepitelial escamosa de alto grau e adenocarcinoma *in situ*), cuja identificação e tratamento adequado possibilita a prevenção da progressão para o câncer cervical invasivo (DUARTE et al., 2017).

Existem muitos aspectos relacionados à própria infecção pelo HPV (subtipo e carga viral, infecção única ou múltipla), e há fatores diretamente ligados à imunidade, à

genética e ao comportamento sexual que parecem influenciar os mecanismos ainda incertos que determinam a regressão ou a não infecção e também a progressão para lesões precursoras ou câncer (BRASIL, 2016).

O carcinoma surge na junção escamoso-colunar, podendo ocorrer nas células escamosas externas, nas células glandulares internas ou em ambas. A lesão precursora é a displasia: neoplasia intra-epitelial cervical (NIC) ou adenocarcinoma *in situ*, que pode posteriormente se tornar câncer invasivo. O desenvolvimento é antecedido por uma série de células anormais, que tem como características as variações na maturação citológica e histológica e irregularidades no citoplasma nuclear. A Lesão intraepitelial escamosa de baixo grau (do inglês *Low Squamous Intraepithelial Lesions - LSIL*) tem um conteúdo de DNA diplóide (dois conjuntos cromossômicos homólogos) ou poliploide (mais de dois conjuntos cromossômicos raras em organismos animais), isto está correlacionado com a tendência de reversão dos cânceres. Por outro lado, a lesão intraepitelial escamosa de alto grau (do inglês *High Squamous Intraepithelial Lesions - HSIL*) tipo NIC III é frequentemente aneuplóide, possui um maior grau de atipia celular (anormalidade celular) e é mais provável que persista e progrida. As LSIL correspondem ao NIC I, displasia leve e alterações associadas ao HPV, já as HSIL incluem as displasias moderadas e graves, o carcinoma *in situ* e as lesões previamente denominadas NIC II e NIC III (TORRES-POVEDA et al., 2014).

Este é um processo considerado lento, em pacientes com câncer cervical *in situ* não tratado, 30% a 70% desenvolverão carcinoma invasivo em um período de 10 a 12 anos. No entanto, em cerca de 10% dos pacientes, as lesões podem progredir *in situ*, podem se tornar invasivo em um período inferior a um ano. Quando se torna invasivo, o tumor rompe a membrana basal e invade o estroma cervical. A extensão do tumor no colo do útero pode finalmente se manifestar como ulceração, tumor exofítico ou infiltração extensa de tecido subjacente, incluindo bexiga ou reto (BRASIL, 2016).

O diagnóstico pode ser feito a partir da história e exame físico, exame pélvico, citologia cervical (exame de Papanicolaou), teste de HPV, curetagem endocervical, colposcopia, biópsia (NIH, 2019).

O exame citopatológico cervical uterino é a principal estratégia para a detecção precoce do câncer de colo uterino, tem como objetivo fundamental a detecção e tratamento precoce das lesões antes da sua evolução para a doença invasiva. Este exame deve ser

realizado por mulheres de 25 a 64 anos, a cada triênio após ter feito dois exames com resultados negativos anualmente (SILVA et al., 2018; VERZARO, SARDINHA, 2018).

2.1.3 Tratamento

Entre os tratamentos mais comuns para o câncer de colo uterino estão a cirurgia e a radioterapia. A escolha do método dependerá do estadiamento da doença, tamanho do tumor e fatores pessoais, como idade e desejo de preservação da fertilidade, dessa forma, o uso de cirurgia, radiação e/ou quimioterapia irão depender desses fatores (CASTELLOTTI e CAMBIAGHI, 2008).

2.1.3.1 Cirurgia

Nos estágios iniciais da doença, cirurgias conservadoras, como a conização ou traquelectomia radical com linfadenectomia por via laparoscópica, podem ser considerados. Para lesões invasivas pequenas, menores que 2cm, devem ser consideradas as cirurgias mais conservadoras, evitando-se assim as complicações e morbidades provocadas por cirurgias mais radicais. Para os estádios IB2 e IIA volumosos (lesões maiores do que 4cm), IIB, IIIA, IIIB e IVA (tumores eventualmente mais avançadas), as evidências científicas atuais orientam para tratamento quimioterápico combinado com radioterapia (BRASIL, 2019).

2.1.3.2 Quimioterapia

É um tratamento que utiliza a infusão endovenosa de compostos quimioterápicos, ou seja, agentes farmacológicos que inibem ou eliminam células de rápida proliferação. Em neoplasias, a quimioterapia é chamada de quimioterapia antineoplásica ou quimioterapia antiblástica. Os agentes quimioterápicos afetam tanto células neoplásicas como células normais, a medula óssea, mucosa do tubo digestivo e os pêlos também são atingidos, porém possuem um tempo de recuperação previsível (BRASIL, 2015b).

Dentre os efeitos colaterais da quimioterapia no sistema digestivo pode-se citar náuseas, vômitos, disfagia, anorexia, mucosite, estomatite, diarreia e/ou constipação, o que pode influenciar na ingestão alimentar do paciente, podendo levar a maior risco nutricional.

Portanto, há uma relação da desnutrição com este tipo de tratamento (SANTOS et al., 2017; SANTOS et al., 2018; GOZZO et al., 2014).

2.1.3.3 Radioterapia

A radioterapia é uma modalidade terapêutica com o objetivo de destruir células de rápido crescimento celular, como as neoplásicas, de forma que haja uma redução ou desaparecimento da neoplasia maligna. Trata-se de um tratamento que utiliza radiações ionizantes capazes de impedir a multiplicação celular neoplásica, e determinar assim a morte destes componentes celulares (ROCHA et al., 2018).

Diferentemente da quimioterapia, a ação da radioterapia restringe-se a região onde ela é aplicada. Dentre os efeitos colaterais observados nesta terapia estão: mucosite, diminuição de paladar, xerostomia, dermatites. Porém, outros efeitos a longo prazo podem ser observados, tais como a ulceração da mucosa, atrofia de tecidos, perda ou mudança do paladar, síndrome actínica, fibrose, edema, entre outros, os quais podem impactar no estado nutricional do paciente (CARNIATTO, MIOLA, CHULAM et al., 2018).

Diante dos efeitos do tumor no organismo do hospedeiro e dos efeitos colaterais do tratamento oncológico a relação com a presença de desnutrição nestes pacientes se torna eminente, podendo sua prevalência alcançar de 30 a 60% em estudos nacionais e internacionais (WAITZBERG et al., 2001; PENIÉ et al., 2005; WIE et al., 2010; BRASIL, 2013).

2.2 Câncer e Caquexia

Diante da epistemiologia, a palavra “Caquexia” vêm do grego “*kakos*” e “*hexis*”, que significa “má” e “condição”, respectivamente. Embora o estudo da caquexia no câncer seja mais frequente e discutido, este agravo não é restrito a esta doença, podendo esta condição ser empregada ainda em pacientes com insuficiência cardíaca congestiva, doenças digestivas, renais crônicas, queimaduras, sepse e ainda síndrome na imunodeficiência adquirida (SIDA). Esta condição não é completamente revertida por estratégias nutricionais tradicionais, o que pode conduzir a comprometimento funcional e consequentemente do organismo, podendo inclusive, findar-se em morte (WAITZBERG, 2011).

Quando associada ao câncer, a caquexia pode variar em função da localização do tumor, tipo de tumor, ou mesmo massa. A exemplo, tumores digestivos, mais em especificamente aqueles do trato digestivo superior, podem promover acentuada perda de peso, principalmente em função de obstruções do tráfego e diminuição da ingestão alimentar (FEARON; GLASS; GUTTRIDGE, 2012).

É importante ainda neste contexto, salientar que o câncer demonstra efeitos diretos na composição corporal do paciente oncológico, principalmente a perda de massa magra acompanhada ou não de perda de tecido gorduroso, fenômeno denominado sarcopenia, este evento associa-se ao comprometimento da capacidade funcional, aumento do risco de quedas e fraturas, maior tempo internação hospitalar e ao aumento de infecções hospitalares. A perda ponderal de peso involuntária pode afetar além da capacidade funcional, a resposta ao tratamento, a qualidade de vida e a sobrevida nestes pacientes. Não obstante, existe maior dificuldade de cicatrização de feridas, maior risco de complicações cirúrgicas e aumento dos custos hospitalares. Estas informações permitem percebermos dois conceitos semelhantes, contudo revelando agravos distintos (FRIO et al., 2015).

2.2.1 Epidemiologia

A caquexia é uma das principais causas de morbidade e morte no câncer, representando cerca de 20 a 25% de todas as causas no câncer, indicando um mau prognóstico e menor tempo de sobrevida nestes pacientes (ROGERS; MINTEER, 2019).

Além disso, grande parte dos casos de cânceres chegam a ser diagnosticados tardiamente, momento no qual o déficit energético já é cumulativo, e o quadro de caquexia já instalado em parte destes. Esta síndrome pode acometer de 80% a 90% dos pacientes oncológicos adultos e pode acabar sendo um fator contribuinte ou determinante de morte (WIEGERT, 2020).

2.2.2 Critérios de diagnóstico da Caquexia

Para diagnosticar a caquexia no câncer, pode-se citar: a perda de peso involuntária inferior à 5% associada à anorexia / alterações metabólicas, situação definida como Pré-Caquexia; quando há perda ponderal de peso involuntária de 5% ou mais ou de 2% ou mais

associada à um índice de massa corporal (IMC) inferior à 20kg/m²) ou ainda à presença de sarcopenia ou redução da ingestão alimentar ou inflamação sistêmica define-se Caquexia; por fim, quando há catabolismo intenso / baixos escores de desempenho / expectativa de vida inferior a três meses e/ou ainda falta de resposta ao tratamento antitumoral o paciente é classificado com Caquexia Refratária, conforme observa-se na Figura 1 (WAITZBERG, 2011).

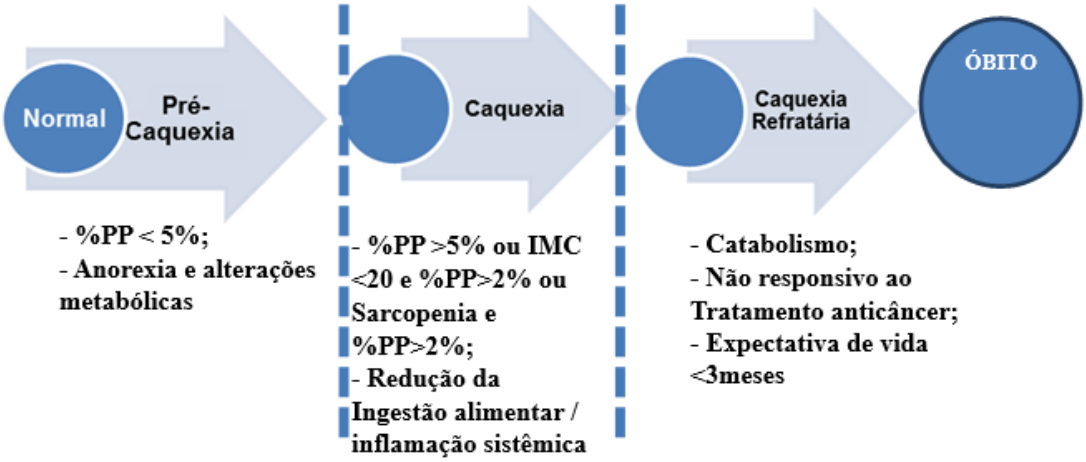

Figura 1. Estágios da Caquexia segundo Consenso Brasileiro de Caquexia Anorexia em Cuidados Paliativos; **Fonte:** WAITZBERG (2011).

2.2.3 Fisiopatologia da caquexia do câncer

2.2.3.1 Fator de mobilização de lipídios (LMF)

A depleção de tecido gorduroso, além de estimulada pelo fator de necrose tumoral alfa (TNF – α) no câncer, também é mediada pelo LMF do inglês *"Lipid Mobilizing Factor"* (Fator Mobilizador de Lipídios – LMF), uma proteína produzida por alguns tipos de tumores (e não encontrada em indivíduos saudáveis), conhecida como zinco alfa2-glicoproteína (ZAG), sendo capaz de estimular aumento da lipólise (hidrólise de triglicerídeos, ácidos graxos livres e glicerol, por meio do aumento intracelular do AMPc – monofostato de adenosina cíclico, semelhante aos hormônios lipolíticos) e redução da lipogênese nos adipócitos. Além disso, os ácidos graxos derivados da lipólise podem acabar sendo aproveitados por diferentes vias metabólicas, como o ciclo de Cori (conversão hepática de lactato à glicose com gasto de energia), um ciclo energético considerado uma via metabólica

"fútil" devido seu elevado custo-benefício ao organismo do paciente com câncer (grande gasto energético, em função de pequeno retorno energético). Nem todas as atividades do LMF são conhecidas, contudo modelos experimentais em ratos demonstraram que elevados níveis do LMF associam-se ao aumento da lipólise, similar aos níveis de pacientes com caquexia (DAS; HOEFLER, 2013; BATISTA; WAITZBERG, 2011).

2.2.3.2 Fator indutor de proteólise (PIF)

Já o PIF (do inglês "*Proteolysis Inducing Factor"*, Fator indutor de proteólise – PIF) é uma glicoproteína sulfurada também de produção tumoral, que associa-se ao catabolismo muscular (proteólise) em pacientes com câncer em processo de caquexia, onde há ativação da via proteólitica dependente de ubiquitina (ATP). Além disso, a substância é capaz de reduzir a síntese muscular (ALVES et al., 2009). A explicação para o catabolismo proteico pode ser devido aos reduzidos níveis de insulina sérica e menor sensibilidade a ação deste hormônio nos tecidos periféricos, assim como a redução da capacidade funcional nestes pacientes durante a caquexia, o que também influi diretamente no anabolismo. Além disso, há maior utilização e transporte dos aminoácidos leucina, arginina e glutamina e síntese de proteínas de fase aguda no tecido hepático (BATISTA; WAITZBERG, 2011).

2.2.3.3 Caquexia do câncer e Sistema Imunológico

Um grande número de citocinas parecem desempenhar um papel na etiologia da caquexia do câncer, entre elas a citocina pró-inflamatória interleucina-6 (IL-6) é considerada um dos principais mediadores da caquexia e um potencial marcador biológico, o estímulo de sua produção por componentes imunológicos de corpo humano parece ter estreita ligação com a instalação do tumor. Contudo, a relação entre IL-6, perda de peso e estágio do câncer ainda permanece desconhecida. Sabe-se que as citocinas são transportadas através da barreira hematoencefálica, e ali conseguem interagir com a superfície luminal de células endoteliais cerebrais, o que ocasiona a liberação de substâncias que alteram o apetite. Como exemplo, receptores para fator de necrose tumoral alfa (TNF-α) e interleucina-1 (IL-1) podem ser encontrados nas regiões hipotalâmicas do cérebro, responsáveis pela ingestão de alimentos.

Importante ressaltar, que a anorexia induzida por TNF-α e IL-6 pode ser impedida por inibidores da ciclo-oxigenase, o que sugere que prostaglandinas, como a E2 (PGE2), pode ser um agente mediador direto da supressão do apetite. Além destas citocinas, a IL-1 também aumenta sua concentração sérica durante a caquexia e seus efeitos assemelham-se ao do TNF-α. A IL-1 induz à anorexia, haja vista seu aumento contribuir para aumento nas concentrações plasmáticas de triptofano, um aminoácido que por sua vez eleva os níveis de serotonina, um regulador da saciedade precoce, e consequentemente a supressão da fome (SUZUKI et al., 2013; PENET, BHUJWALLA, 2015; AOYAGI et al., 2015; HAEHLING et al., 2015).

2.2.3.4 Mecanismos Neuroendócrinos e Metabólicos

Durante a caquexia, há alterações nos metabolismos energéticos (Figura 2), que conduzem para glicólise, glicogenólise ou ainda gliconeogênese, contribuindo para perda de peso (BATISTA; WAITZBERG, 2011).

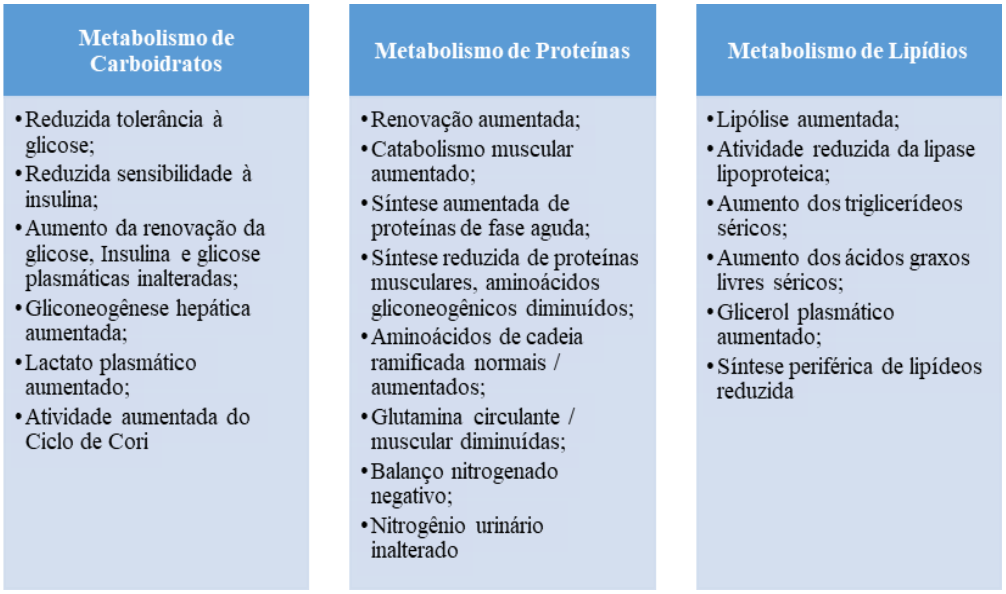

Figura 2. Alterações metabólicas na síndrome anorexia-caquexia (SAC);
Fonte: Adaptado de Batista e Waitzberg (2011).

Além do que, há um conjunto de alterações pró-inflamatórias já anteriormente citadas, que induzem/permeiam alterações neuroendócrinas e metabólicas importantes, sendo importante ressaltar alterações comuns na caquexia/perda de peso, para isto resumimos parte delas no Quadro 1 (BATISTA; WAITZBERG, 2011).

Quadro 1. Principais compostos regulatórios do consumo alimentar e alterações metabólicas na síndrome anorexia-caquexia (SAC).

Composto / Metabolismo	Local de Produção/Aletarações/Ação
Leptina	Hormônio produzido e secretado pelo tecido gorduroso. Responsável pela manutenção do peso corporal, principalmente quanto à gordura. Na perda de peso, reduz o apetite e aumenta o gasto energético.
Grelina	Hormônio peptídico predominantemente secretado ao nível gástrico. Possui ação orexígena (estimulante do apetite) em nível hipotalâmico. Pode estar reduzido na SAC
Neuropeptídio Y	No cérebro, é o mais potente hormônio orexígeno. Junto com outros peptídios orexígenos, aumenta a ingestão de alimentos, reduz o gasto energético, aumenta a lipogênese, promove balanço energético positivo e aumento da reserva adiposa. Está diminuído na presença de tumores.
Metabolismo de Carboidratos	Reduzida tolerância à glicose, Reduzida sensibilidade à insulina, Aumento da renovação da glicose, Insulina e glicose plasmáticas inalteradas, Gliconeogênese hepática aumentada, Lactato plasmático aumentado, Atividade aumentada do Ciclo de Cori
Metabolismo de Proteínas	Renovação aumentada, Catabolismo muscular aumentado, Síntese aumentada de proteínas de fase aguda, Síntese reduzida de proteínas musculares, aminoácidos (Aas) gliconeogênicos diminuídos, Aas de cadeia ramificada normais/aumentados, Glutamina circulante/muscular diminuídas, Balanço nitrogenado negativo, Nitrogênio urinário inalterado

Fonte: Adaptado de Batista e Waitzberg (2011).

2.3 Modulação da Caquexia no Câncer

Diferentes estratégias vêm sendo sugeridas para o controle / reversão da caquexia induzida pelo câncer e suas complicações (inflamação crônica, resistência à insulina, perda de massa magra, capacidade funcional, qualidade de vida e fadiga), entre elas cita-se a ação de agentes farmacológicos, treinamento físico e suplementações nutricionais (ROGERS et al., 2011; TEIXEIRA et al., 2019; FREITAS; CAMPOS, 2019; HALL et al., 2019).

O exercício físico, por exemplo, combinado ao suporte nutricional em pacientes com câncer incurável revela evidências de melhora da depressão e resistência física, qualidade de vida, fadiga, função geral e estado nutricional (HALL et al., 2019). Além disso, suplementações nutricionais como: arginina, glutamina, creatina, polifenóis, zinco, complexo vitamínicos, ácidos graxos poli-insaturados ômega 3 e aminoácidos de cadeia ramificada e seus metabólitos Hidroxi-metil-butirato (HMB) vêm sendo demonstradas com eficácia no

manejo nutricional da caquexia em estudos animais e humanos, há algum tempo, na perspectiva de maximizar reservas adiposas e musculares e minimizar lipólise e proteólise instaladas durante este evento (SIDDIQUI et al., 2006; AWA et al., 2017; CAMPOS-FERRAZ et al., 2014).

Neste contexto, vêm sendo considerada uma abordagem multimodal no tratamento deste agravo (HAß; HERPICH; NORMAN, 2019; MANTOVANI et al., 2010; HOUTHUIJZEN et al., 2017).

2.4 Suplementação alimentar como mecanismo de redução / controle da Caquexia

2.4.1 Suplementação alimentar com ácidos graxos ômega 3 (W3)

Dentre os suplementos alimentares mais estudados na modulação da caquexia do câncer (conforme destacado em letras em maior destaque e linhas mais espessas e cores mais vívidas na Figura 3), cita-se o ácido graxo polinsaturado ômega 3 (ácido graxo linolênico – W3, ilustrado na Figura 4). Os W3 são ácidos graxos polinsaturados, que possuem de 18 a 22 carbonos, com a primeira dupla ligação no terceiro carbono (extremidade ômega) e podem ser representadas por pelo menos três moléculas ativas diferentes: ácido α-linolênico (ALA; 18: 3n-3), ácido eicosapentaenóico (EPA; 20: 5n-3) e ácido docosahexaenóico (DHA 22: 6n-3), estes dois últimos produtos derivados diretos (FREITAS; CAMPOS, 2019).

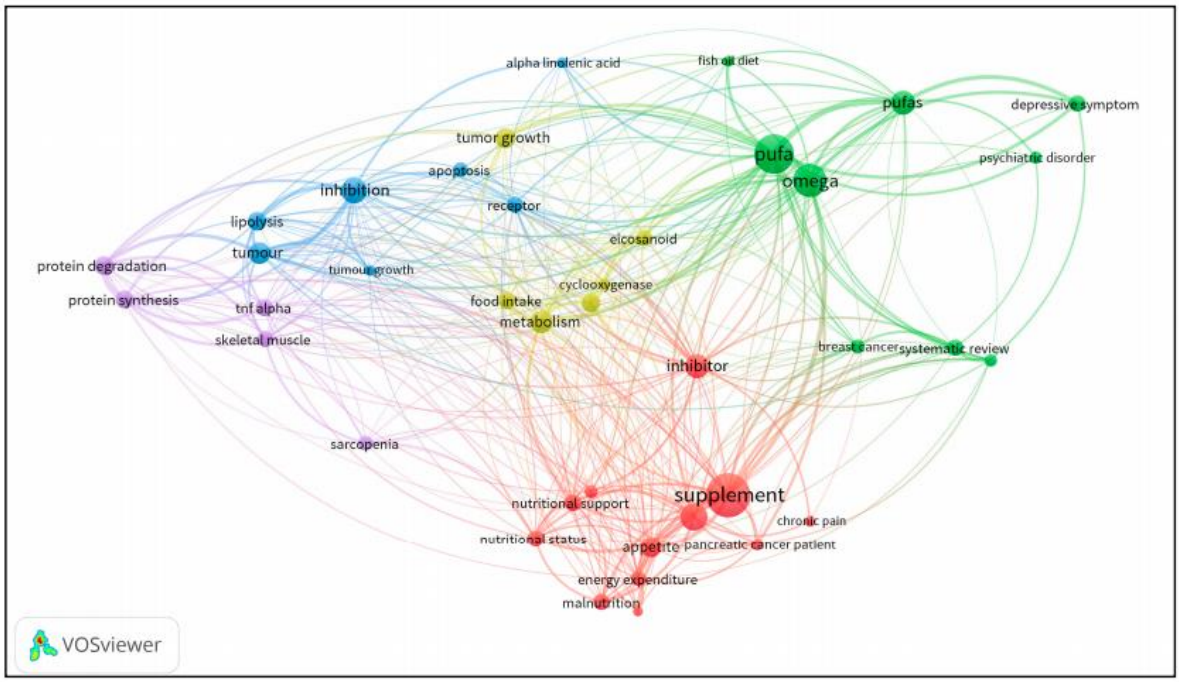

Figura 3. Citações de intervenções mais utilizadas na literatura científica sobre modulação da caquexia do câncer. **Fonte:** Freitas e Campos (2019).

Figura 4. Estrutura química ácido graxo poliinsaturado ômega 3 (ácido linolênico 18:3 n-3). **Fonte:** Garófolo e Petrilli (2006).

Apenas o ALA é sintetizado por plantas e pode ser encontrado em nozes, sementes e óleos vegetais. Já o EPA e o DHA (ácidos graxos essenciais, ou seja, não são sintetizados pelo organismo, e portanto devem ser consumidos através da dieta), possuem como fontes principais na alimentação: peixes de águas profundas/frias. É possível converter o ALA em EPA e DHA por meio de diversas reações de alongamento e dessaturação, contudo tais conversões não são capazes de produzir quantidades suficientes desses ácidos graxos no organismo (FREITAS; CAMPOS, 2019).

Os ácidos graxos ômega 6 e ômega 3 e seus derivados (ácidos araquidônico e eicosapentaenoico, respectivamente) são essenciais para a síntese de eicosanoides, e portanto para o balanço da resposta inflamatória. Durante a síntese de seus produtos (Figura 5), eles medeiam diretamente a formação de compostos pró-inflamatórios como prostanóides (TXA2, PGI2, PGE2) e leucotrienos (LTB4) da série par 2 e 4 (ácido graxo ômega 6), enquanto o ômega 3 pela modulação de agentes anti-inflamatórios (série ímpar 3 e 5), como Prostanóides (PGE3, TXA3) e Leucotrienos (LTB5), conforme ilustrado na Figura 5 (GARÓFOLO; PETRILLI, 2006).

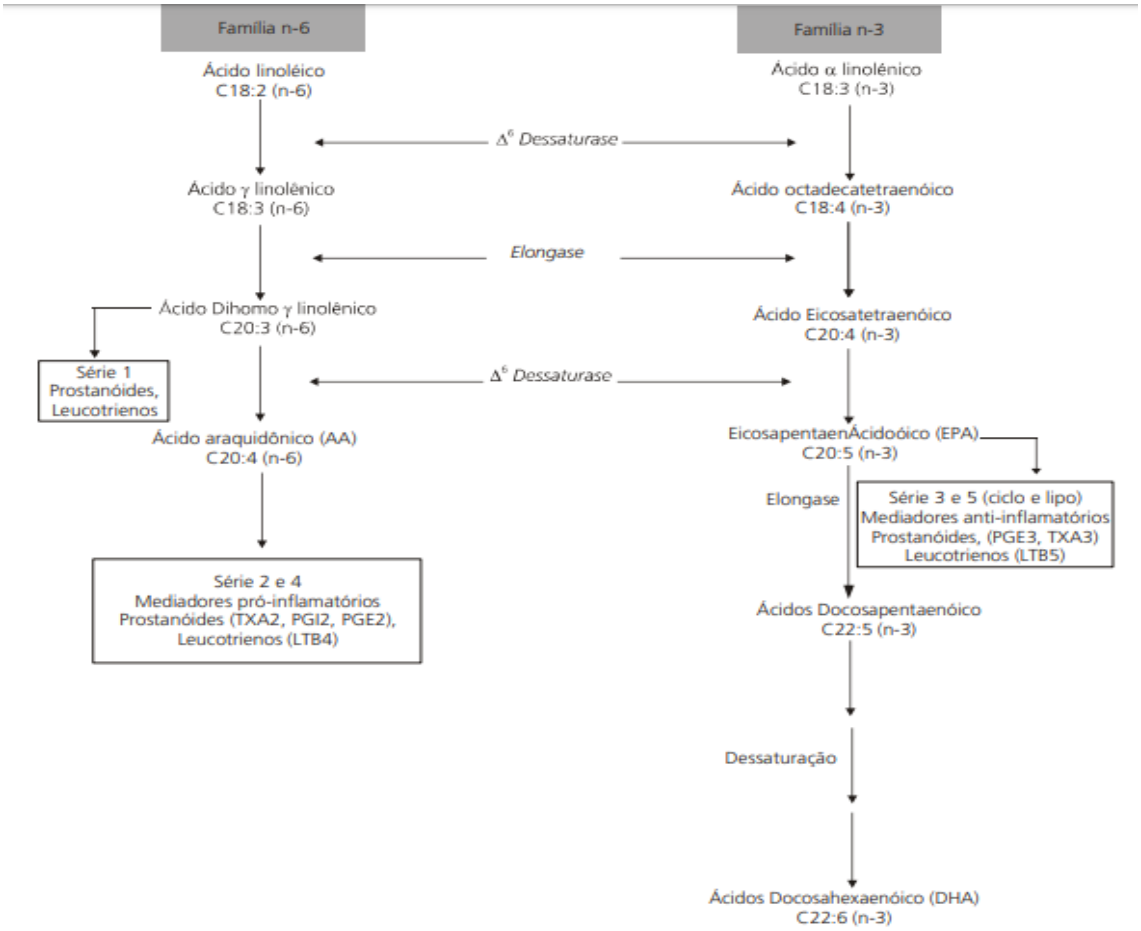

Figura 5. Esquematização da via de biossíntese dos ácidos graxos poli-insaturados.
Fonte: Garófolo e Petrilli (2006).

Sobreviventes de câncer de mama demonstraram associações inversas entre a reduzida ingestão de ácidos graxos ômega 3 e elevado consumo de ácidos graxos ômega-6 e presença de piores níveis de inflamação e fadiga (HAß; HERBICH; NORM, 2019).

Mantovani et al. (2010), ao realizar ensaio clínico com 332 pacientes caquéticos com câncer não foram capazes de confirmar que a suplementação oral enriquecida apenas EPA (2,2g/dia) foi capaz de melhorar os sintomas de fadiga ou marcadores inflamatórios, porém quando o suplemento foi combinado à 320mg de acetato de megestrol ou 4g de L-carnitina, 500mg de acetato de medroxiprogesterona e 200mg de talidomida houve melhorias profundas nos sintomas de fadiga ($p = 0,047$) e IL-6 ($p = 0,0187$) após 4 meses de intervenção.

Não obstante, o receptor de ácidos graxos livres 4 (FFA4) ou GPR120, é um receptor acoplado à proteína G (GPCR) que responde prontamente à ácidos graxos de cadeia longa, e que vêm atraindo a atenção como novo alvo terapêutico em potencial no diabetes

mellitus tipo 2, revelando que a capacidade de agonistas no FFA4 pode melhorar a disposição da glicose e aumentar a sensibilidade à insulina em modelos animais de pesquisa, vale ressaltar ainda que o padrão de distribuição deste receptor também sugere que o direcionamento do FFA4 pode contribuir em outras condições, como o câncer (MILLIGAN et al., 2017).

Contudo, a utilização de ácidos graxos ômega 3 requer alguma restrição, em relação ao tratamento quimioterápico à base de platina, pois este ácido graxo ao interagir com a platina induz resistência sistêmica a uma ampla gama de quimioterápicos. O ácido graxo ômega 3 parece exercer seu efeito ativando macrófagos esplênicos de F4 / 80 + / CD11b baixos, o que resulta na produção de lisofosfatidilcolinas (LPCs) quimioprotetoras, associada a expressão da GPR120 e seu receptor, identificando uma função nova e inesperada do GPR120 e sugerindo a utilização de antagonistas desse receptor como possíveis agentes eficazes para limitar o desenvolvimento da resistência quimioterápica, sendo necessário mais estudos que averiguem de que forma a quimioresistência a estes quimioterápicos se instala e a limitação do uso de tal suplementação alimentar (HOUTHUIJZEN et al., 2017).

Diante de seu papel, bem fundamentado como agente precursor de moléculas de sinalização anti-inflamatória na cascata inflamatória, os ácidos graxos poliinsaturados ômega-3 de cadeia longa, em especial o ácido eicosapentaenóico (EPA) e o ácido docosahexaenóico (DHA) (GARÓFOLO; PETRILLI, 2006), vêm sendo pesquisados na perspectiva de atenuação da resposta inflamatória sistêmica em pacientes com câncer, sendo refletidas na forma de reduções significativas nas concentrações plasmáticas de proteína C reativa (PCR) e interleucina-6 (BENNOUNA et al., 2019), potencialmente quando em combinação com outras substâncias (MANTOVANI et al., 2010; ROGERS et al., 2011).

2.4.2 Caquexia e Suplementação alimentar com aminoácidos de cadeia ramificada (BCAA)

Aminoácidos de cadeia ramificada (BCAA) são aminoácidos essenciais, ou seja não são produzidos pelo organismo, e portanto necessitam ser consumidos através da dieta. São três os BCAA: leucina, isoleucina, valina, sendo estes componentes responsáveis pelo efeito de sinalização de síntese muscular, e a leucina o aminoácido de cadeia ramificada responsável pela maior parte deste efeito. O mecanismo de estímulo se baseia na ativação da

etapa de ligação do mRNA durante a tradução no músculo esquelético (SIDDIQUI et al., 2006).

O catabolismo dos aminoácidos de cadeia ramificada gera produtos derivados de acil-CoA de cadeia ramificada, os quais passam por oxidação por meio de duas vias diferentes de desidrogenases. Enquanto a via da leucina é cetogênica, haja vista que forma acetil-CoA e acetoacetato, a via pela qual caminha a valina é glicogênica, por esta ser convertida em succinil-CoA (um produto intermediário do ciclo de Krebs). Isoleucina e valina são metabolizadas para succinato através da via metilmalonil-CoA. Outro produto do metabolismo da isoleucina é o acetoacetato e, portanto, a isoleucina pode ser vista como um aminoácido glicogênico e cetogênico simultaneamente (ROGERO; TIRAPEGUI, 2008). O metabolismo desses aminoácidos ficam descritos na Figura 6:

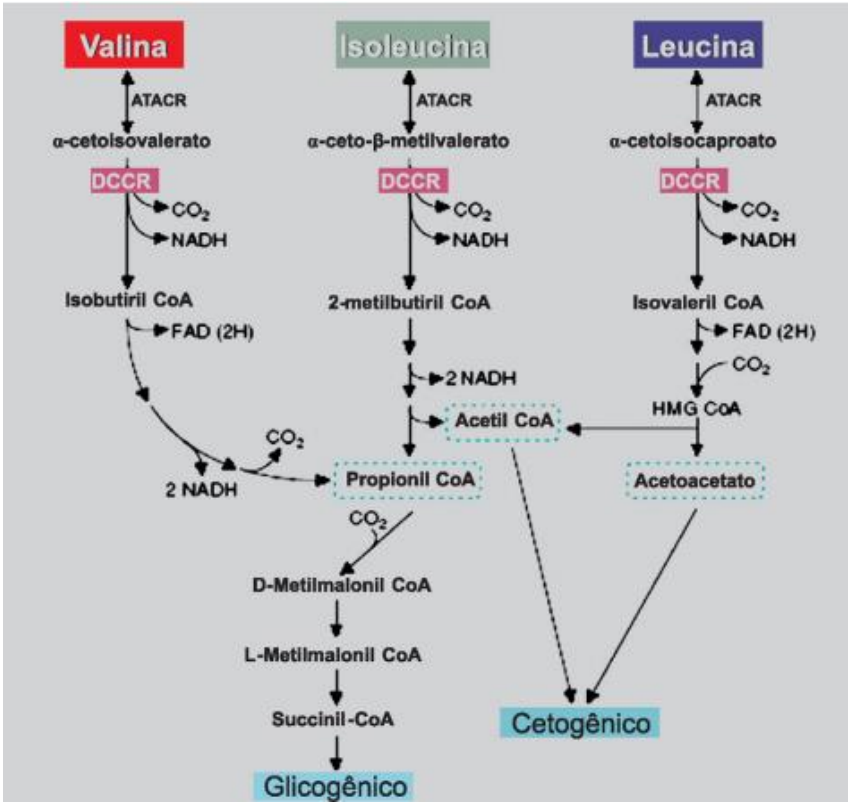

Figura 6. Metabolismo dos aminoácidos de cadeia ramificada.

Fonte: Rogero e Tirapegui (2008).

Os BCAA, neste contexto assumem propriedades anabolizantes na síntese proteica que vêm sendo estudadas há mais de 50 anos. Muito embora, até hoje, não se tenha um consenso em relação à sua efetividade terapêutica durante alguns distúrbios, supõe-se ao menos três pilares principais: (1) O catabolismo proteico-muscular (musculatura esquelética)

iniciada pela oxidação de BCAA acompanhado de liberação de alanina e glutamina no sangue; (2) A aminação de cetoácidos de cadeia ramificada (BCKAs) com BCAA; e (3) A atividade do cetoácido de cadeia ramificada desidrogenase (BCKD). Esta última, demonstraria a oxidação aprimorada do BCAA em pacientes com câncer. Apesar de serem comuns alterações no metabolismo do BCAA durante estados de injúria, e grande a necessidade de cuidados especiais durante o agravo, mais pesquisas para o entendimento da sua suplementação são necessárias (HOLEČEK, 2018).

Durante a caquexia existe uma oxidação excessiva de BCAA, sugerindo efeitos benéficos, tais como: melhoria do balanço nitrogenado e, principalmente, do metabolismo proteico-muscular, a partir da suplementação alimentar com BCAA no suporte nutricional destes pacientes (ELEY et al., 2007; SANTOS, 2012; CAMPOS-FERRAZ et al., 2014; BOWEN et al., 2015).

A suplementação de leucina, vem sendo pesquisada de maneira profunda pela sua capacidade de alteração do metabolismo proteico, tanto por meio do aumento na síntese proteica, quanto pela redução da proteólise, e portanto na redução dos efeitos da caquexia do câncer, podendo este BCAA, ter ação na preservação da massa muscular esquelética pela ativação do complexo 1 da mTOR (mTORC1), um regulador fundamental da síntese de proteínas no músculo esquelético, o que pode demonstrar que este aminoácido de cadeia ramificada pode ser um ponto chave no tratamento da caquexia relacionada ao câncer (VIANA; GOMES-MARCONDES, 2015).

A suplementação alimentar de leucina em ratos caquéticos parece modular pontos importantes da via proteasomal durante a caquexia do câncer, e portanto pode inibir a perda de massa muscular (CRUZ; OLIVEIRA; GOMES-MARCONDES, 2017). Sugere-se que a ingestão de leucina em ratos caquéticos iniba a expressão de genes da via proteassoma (SIDDIQUI et al., 2006).

Durante a caquexia há intensa degradação de tecido gorduroso e muscular, sendo a mTOR, uma substância central (proteína/gene) e potente estimuladora da síntese de proteínas. Além disso, a mTOR (sigla vinda do inglês "*Mammalian Target of Rapamycin*"), que está envolvida em outros eventos celulares, como proliferação e diferenciação celular. Neste contexto, a leucina é capaz de estimular a hipertrofia (estímulo de p70S6K em células C2C12, um subclone de linhagem de mioblastos C2, que possuem características de mioblastos normais, comumente utilizadas como modelo de estudo em proliferação e a

diferenciação celular sob ação de rapamicina), demonstrando uma possível via paralela da leucina atuante na síntese proteica e de inibição da proteólise (FAVERO; MARCONDES, 2017).

Além disso, o aminoácido de cadeia ramificada parece aumentar o consumo de oxigênio (independente da presença da mTOR), o que pode demonstrar uma capacidade do nutriente em modular o metabolismo proteico por vias de obtenção de energia diferentes não dependentes diretamente da ativação da mTOR (FAVERO; MARCONDES, 2017). Entender melhor como a suplementação com leucina pode contribuir no ganho de massa magra em pacientes com depleção músculo-esquelética se torna essencial (FAVERO; MARCONDES, 2017; VIANA; GOMES-MARCONDES, 2015).

Aminoácidos de cadeia ramificada associados à um conjunto dietético funcional contendo Coenzima Q10 e L-carnitina, quando administrados à camundongos portadores de tumor, parecem melhorar na manutenção dos músculos supra-hióideos, no apetite e na supressão do crescimento e metástase tumoral (AWA et al., 2017).

3 OBJETIVOS

3.1 Objetivo geral

Analisar o efeito da suplementação dietética de aminoácidos de cadeia ramificada e ácidos graxos ômega 3 e na caquexia do câncer.

3.2 Objetivos específicos

Caracterizar a amostra;

Verificar as evidências científicas disponíveis sobre o efeito de suplementos nutricionais com ômega-3 e aminoácidos de cadeia ramificada em pacientes com câncer e caquexia;

Verifica o efeito da suplementação de aminoácidos de cadeia ramificada em associação ao ômega 3 em parâmetros clínico-nutricionais, cardiorrespiratórios, metabólicos e qualidade de vida em mulheres com câncer de colo uterino;

Analisar a associação entre sarcopenia e a qualidade de vida em mulheres com câncer de colo uterino;

Analisar o consumo alimentar das avaliadas;

Associar a adequação do consumo alimentar de nutrientes pró-síntese muscular (proteína, cálcio e vitamina D) e melhorias da reserva muscular e capacidade funcional em mulheres com câncer de colo uterino;

Associar o consumo alimentar de proteína por refeição das avaliadas à qualidade de vida e força muscular;

4 RESULTADOS

4.1 Capítulo I – Effects of a Food Supplementation with Omega-3 and Branched-Chain Amino Acids in Cancer Patients with Cachexia: a systematic review

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12-Mar-2021

Dear Dr dos Santos:

Your manuscript entitled "Effects of a food supplementation with omega-3 and branched-chain amino acids in cancer patients with cachexia: a systematic review" has been successfully submitted online and is presently being given full consideration for publication in Journal of International Medical Research.

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Capítulo I – Effects of a Food Supplementation with Omega-3 and Branched-Chain Amino Acids in Cancer Patients with Cachexia: a systematic review

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Competing interests

The authors declare that they have no competing interests.

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Abstract

Objective: This study aims to present scientific evidence on the effect of nutritional supplements (Omega-3 and branched-chain amino acids) in oncologic patients with cachexia. **Methods**: The protocol of systematic review followed *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* - Protocols (PRISMA-P). The search for articles was between November/2018 and March/2019. **Results**: At the end of the process, eight eligible studies were quantified with participants of 18 to 84 years old, samples of 27 to 332 participants, follow-up of 6 to 16 weeks; the evaluated outcome variables were: body weight, resting energy expenditure, appetite, functional performance, quality of life, fatigue, interleukin (IL-6), tumor necrosis factor-alpha (TNF-α), protein C-Reactive, albumin, pre-albumin and survivability. The description of sample loss and the generation of an aleatory sequence was of 75.0% of the surveys. **Conclusions:** Studies have shown a favorable effect of omega-3 supplementation in the inflammatory response, attenuating muscle catabolism, and improving the quality of life, especially in the combined supplementation.

Keywords: Inflammation. Quality of Life. Dietary Supplements. Branched-chain amino acids.

Introduction

Cachexia is a multifactorial syndrome that injures the quality of life, morbidity, and mortality of patients with chronic or clinically relevant diseases [1,2].

Cancer cachexia is a multifactorial syndrome characterized by the continuous loss of skeletal muscle mass, with or without fat loss, which can’t be completely reversed by conventional nutritional support and leading to progressive functional impairment [3,4]

In cancer patients, according to the tumor type and location, the incidence of cachexia can vary from 31.0% to 87.0%, 83.0% in patients with pancreatic cancer, and more than 85.0% in patients with gastric cancer [4]. The prevalence of cachexia can be up to 80.0% in patients with advanced cancer [1,2].

Several mechanisms are affected in the pathophysiological process of cachexia, especially the action of pro-inflammatory cytokines at chronically high levels are present in the vast majority of cancer patients. Besides, can affect the imbalance of anabolic and catabolic hormones, the hormonal changes, which involve the regulation of energy metabolism and appetite (leptin, adiponectin, and ghrelin) [3].

The Omega-3 fatty acids, with recognized anti-inflammatory potential, has been evaluated in trials with animal and humans and showed to reduce weight loss, to improve the muscle strength, functional capacity, to prevent the mass loss, increase the rate of protein synthesis, as well as, to modulate the immune and inflammatory response in cachexia [5].

The excessive oxidation of Branched-Chain Amino Acids (BCAA) may be involved in molecular mechanisms of cachexia, indicating a beneficial effect of this supplementation in the nutritional therapy to improve nitrogen balance and, mainly, protein-muscle metabolism [6].

Currently, clinical trials using oral nutritional supplements, combination or not, have shown beneficial effects in several chronic diseases [7]. However, the effect of this nutritional intervention on patients with cachexia is nuclear [8].

Therefore, this systematic review aims to verify the available scientific evidence on the effect of nutritional supplements with Omega-3 and branched-chain amino acids in cancer patients with cachexia.

Methods

The protocol for this systematic review was developed following PRISMA-P [*Preferred Reporting Items for Systematic Reviews and Meta-Analyses* – Protocols] [9], and it was registered in the Prospective International Registry of Systematic Reviews (PROSPERO – CRD42018096757). To report the results of this review, the guidelines in the declaration were followed by PRISMA [10].

Data sources and research

The databases explored were MEDLINE, PubMed, IBECS, LILACS, and Scopus. Besides, was performed a manual search on the reference lists of eligible studies for systematic reviews and meta-analyses.

The descriptors were chosen according to DeCS (*Health Sciences Descriptors*, BIREME) and MeSH (*Medical Subject Headings*, PubMed). In addition to the descriptors above, Boolean operators were used "AND" and "OR" for combining terms in the database.

We also consulted the references of the selected articles to identify publications not previously located and that were relevant to the review's subject. The searches were carried out between November 2018 and March 2019.

The identified publications were organized in electronic folders and recorded in a database in the reference software *EndNote*®.

Study selection

To properly refine the articles, the inclusion criteria were randomized clinical trials that deal with the effects of dietary supplementation of Omega-3 or branched-chain amino acids in cancer patients with cachexia, which had been published from 2007 to 2017, in

Portuguese, English and/or Spanish. The population of interest included cancer patients, adults (over 18 years old), and those diagnosed with cachexia. The main exposure of interest was nutritional supplementation (combined or not) in cancer patients with cachexia.

The exclusion criteria used was qualitative, cross-sectional, case-control and cohort studies, review articles, editorials, letters to the editor, book chapters, as well as studies with surgical patients, studies with children, adolescents and pregnant women, or animal experiments, and also, studies that do not present data in the treatment and control arm, co-intervention with another treatment that is also not given in the control group, and studies that do not have a comparator or control group.

The process for the selection of the article was carried out in four stages, according to the model recommended by Cochrane Collaboration: 1 – Identification of the articles obtained, by searching the database and articles through the references of the selected articles; 2 – selection: in this phase, duplicates were excluded and titles and abstracts were independently evaluated by two reviewers; those that had no relation to the keywords in the search were disregarded; 3 – eligibility: it was assessed by two independent reviewers, who read the files in full (excluding those that did not meet the pre-established eligibility criteria), and 4: inclusion of eligible articles in the systematic review. An agreement between reviewers was quantified by Kappa's statistic.

Data extraction and risk of bias assessment

The data extraction was guided by a standard clinical form that had been previously elaborated. This process was independently carried out by two reviewers. Another reviewer assessed all data entry.

To assess the methodological quality of the studies, the evaluation tool that had been used was "*Cochrane 'Risk of Bias'*, from the *Handbook for Systematic Reviews of Interventions Version* 5.1.0 [Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011].

This tool includes the following items, which were assigned as 'low risk of bias', 'clear risk of bias' or 'high risk of bias': random sequence generation (selection bias); hiding the allocation sequence (selection bias); concealment of participants and researchers (performance bias); concealment of results evaluation (detection bias); incomplete outcome data (attrition bias); selective results report (reporting bias) and other sources of bias [11].

The risk of bias was assessed by two of the independent authors and it was presented as a summary figure of the assessment of the methodological quality of each study, as well as the risk of bias in the domains, for the studies included in the systematic review. The disagreements were resolved through consensus or discussions involving other authors of the review.

Outcomes

Clinical-nutritional and metabolic parameters within combination supplementation and the effect of Omega-3 in modulating the inflammatory response, attenuating muscle catabolism and improving the quality of life in cancer cachexia.

Results

Were obtained 442 publications through the electronic database system and manual search. After removing duplicates, 169 titles and abstracts were examined, with a subsequent selection of 29 studies to be read in full, of these 29 studies, 21 did not attend the inclusion

criteria. At the end of the process, according to the model recommended by the Cochrane Collaboration, eight articles [2,8,11-16] were quantified, which attended all pre-established eligibility criteria and were included in this systematic review.

The flowchart of the article's search and selection process is shown in Figure 1.

Study Characteristics

The eight selected studies were published between 2009 and 2017. The age of the participants ranged from ≥18 to 84 years old. The sample size ranged from 27 to 332 participants, with a follow-up period of 6 weeks to 4 months. The number of losses was demonstrated in six of the studies (75.0%). The characteristics of the included studies are described in Table 1.

In six studies, (75.0%), the form of the adopted intervention an oral supplement enriched with EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) [11-16].

The administration of capsules occurred in two of the studies (25.0%). In one of them, supplementation was performed with a daily dosage of four capsules containing EPA (510mg) and DHA (340mg) [8], and in the other one, patients were asked to take a capsule containing marine phospholipids (MPL) or fish oil (FO), three times a day. The FO capsules contained 60.0% FO and 40.0% medium-chain triglycerides (TCM), 6.9 g/100g of eicosapentaenoic acid (EPA), and 13.6 g/100g of docosahexaenoic acid (DHA). MPL capsules contained 35.0% of n-3-FA phospholipids (mainly phosphatidylcholine)**,** plus 65.0% of neutral lipids (8.5 g/100 g of EPA and 12.3 g/100 g of DHA). The final dose of W3 (Ômega 3) was of 300 mg/day in both groups [2].

The use of combined supplementation was analyzed in five of the articles included in the synthesis (62.5%) [11,12,13,14,15]. The characteristics of each study are presented in Table 1.

Interventions

In the study by Dewey et al. [16], the intervention group received a nutritional supplement containing EPA (Prosure) and the control group with a standard oral nutritional supplement without EPA (Ensure Plus).

Kanat et al. [12] divided the groups and performed an intervention with Megestrol Acetate (320 mg/day) plus Meloxicam tablets (15 mg/day) in group A, Megestrol Acetate plus Meloxicam plus an oral supplement enriched with EPA (2.2 g/day) (ProSure) in group B and group C nutritional supplement enriched with EPA plus Meloxicam.

The intervention group of the study by Kun-Yun et al. [15] received 1500 kcal/day of oral nutritional supplement, formula Ethanwell / Ethanzyme, caloric and protein nutritional supplement that contains several ingredients, including omega-3 fatty acids, glutamine, selenium and CoQ (Coenzyme q10) and Ethanzyme (enzyme product composed of multiple probiotics and vitamins) and the control group 1500 kcal/day of normocaloric oral nutritional supplement (Nestlé). In the study, the intervention improved the body weight, serum levels of albumin, and pre-albumin in patients with head and neck cancer cachexia and BMI <19. Their changes in body composition were significantly associated with the changes in serum levels of albumin and pre-albumin.

In the study by Mantovani et al. [14], all patients underwent basic treatment with polyphenols (300 mg/day) dietary source or tablets, lipoic acid (300 mg/day), carbocysteine (2.7 g/day), vitamin E (400 mg/day), vitamin A (30, 000 IU/day) and vitamin C (500 mg/day),

orally. Also, Arm 1 received Medroxyprogesterone Acetate (MPA) (500 mg/day) or Megestrol acetate (MA) (320 mg/day). Arm 2 received a supplement enriched with eicosapentaenoic acid (EPA) (2.2 g/day), in prescribed doses of two boxes/day for both ProSure (Abbott Laboratories) or 3 boxes/day for Forticare (Nutricia). Arm 3 received L-carnitine (Carnitene) (4 g/day). Arm 4 received Thalidomide (Celgene) (200 mg/day). And Arm 5, received MPA or MA plus nutritional supplement enriched with EPA plus L-carnitine and Thalidomide.

For all patients included in the study by Tanca et al. [11], polyphenols were provided as treatment (300 mg/day), obtained from alternative sources (onion, apple, orange, 150 ml of red wine, green tea) or supplemented by tablets plus antioxidant agents α-lipoic acid (300 mg/ day) plus 2.7 g/ day of carbocysteine, plus 400 mg/day of vitamin E, plus 30.000 IU/day of vitamin A and 500 mg/day of vitamin C, all orally. Added to this, Arm 1 received a progestational agent, that is, 500 mg/day of MPA) or 320 mg/day of Megestrol acetate (MA; two tablets, 160 mg/day) administered orally. Arm 2 received an enriched nutritional supplement (2.2 g/day of EPA ProSure or Forticare and 2 g/day for Resource. Arm 3 received L-carnitine (4 g/day, two bottles, 2 g/day). Arm 4 received Thalidomide (200 mg/day, two tablets, 100 mg/day), and arm 5 – MPA or MA plus nutritional support enriched with EPA plus L-carnitine plus thalidomide.

Finocchiaro et al. [8] performed an intervention with a daily dose of four capsules containing 510 mg of EPA and 340 mg of DHA for the intervention group and a daily dose of four capsules containing 850 mg placebo (olive oil) for the control group.

Werner et al. [2] supplemented patients in two groups, the first with fish oil (FO) and the second marine phospholipid supplement (MPL). Patients were assigned to take a 500 mg soft gel (MPL or FO) capsule three times a day. The final dose of w3 was 300 mg/day in both

groups. FO capsules contained 60.0% FO and 40.0% medium-chain triglycerides (MCT) (6.9 g for 100g of EPA and 13.6 g for 100 g of DHA). The MPL capsules contained 35.0% w3 phospholipids (mainly phosphatidylcholine) plus 65.0% neutral lipids (8.5 g for 100g of EPA and 12.3 g for 100g of DHA).

In the study by Solheim et al. [13], the patients underwent a multimodal intervention, that consisted of Celecoxib (300 mg) once a day, two packs of 220 mL of oral nutritional supplement (ProSure© Abbott), resulting in the intake of 2 g/day of EPA. The nutritional advice provided by a nutritionist and/or nursing team, the trial and exercise program was prepared by a physiotherapist. The control group received standard cancer treatment without nutritional interventions or exercise or non-steroidal anti-inflammatory medication.

Outcomes

The evaluated outcome variables in the studies included body weight, body composition, resting energy expenditure, appetite, functional performance, quality of life, fatigue, biochemical parameters (IL-6, TNF-α, C-Reactive protein, albumin and pre- albumin) and survival.

In four of the studies (50.0%), there was an improvement related to weight or body composition after the intervention. The study by Kun-Yun et al. [15] demonstrated that the group submitted to Ethanwell / Ethanzyme supplementation (supplementation with Ethanwell / Ethanzyme - oral nutritional formula enriched with Omega-3, micronutrients and probiotics) promoted an improvement in the participants' body weight compared to the control (Isocal) group ($p < 0.05$).

Solheim et al. [13] demonstrated that the multimodal intervention (Celecoxib, oral nutritional supplement – 2 g/day of EPA, nutritional counseling, and exercise program)

promoted an increase in body weight compared to the control group ($p < 0.001$). However, there were no statistically significant differences between groups in terms of muscle mass, physical activity, grip strength, subjective assessment generated by the patient, nutritional intake and C-reactive protein.

The studies by Tanca et al. [11] and Mantovani et al. [14], using data extracted from the same sample, demonstrated a significant increase in lean body mass through DEXA (Dual-energy X-ray Absorptiometry) in Arm 5 (supplementation with MPA or MA, nutritional supplement enriched with EPA, L-carnitine, Thalidomide ($p<0.05$, pe=0.015, respectively). Mantovani et al. [14] also showed an increase in lean body mass in Arm 5, which had been analyzed through a L3 computed tomography ($p = 0.001$).

The intervention that had been proposed in the studies by Kanat et al. [12] and Werner et al. [2] showed improvement in all groups after the intervention, with no statistically significant differences between groups. Dewey et al. [16] and Finocchiaro et al. [8] did not find statistically significant differences regarding the participants' weight and body composition between the groups at the end of the intervention, however, they highlight the improvement of these variables in the intervention groups – nutritional supplement containing EPA and daily dose of four capsules containing EPA (510 mg) and DHA (340 mg), respectively, by comparing the data before and after the intervention.

Only one study [14], demonstrated that appetite increased significantly after the intervention ($p = 0.0003$- an improvement assessed in arm 5). In the study by Werner et al. [2], with supplementation of FO or MPL, there was promising stabilization of appetite, however, there was no statistically significant difference when comparing the groups. In the study by Dewey et al. [16], there were no significant differences between groups.

In the analysis on quality of life, one study [12] demonstrated improvement after treatment in the three arms, but without statistically significant differences between groups. Two studies [2,16] also found no significant differences when comparing the groups.

The study by Mantovani et al. [14] demonstrated that the performance status of the Eastern Cooperative Oncology Group (ECOG PS) decreased significantly in Arm 5 ($p < 0.0001$), Arm 4 ($p < 0.0001$), and Arm 3 ($p = 0.0001$) after the intervention. Participants in the study by Kanat et al. [12] improved after treatment in all Arms. There were no statistically significant differences between groups. In the study by Dewey et al. [16]**,** there were also no statistically significant differences between groups.

Regarding the biochemical parameters, Kanat et al. [12] found improvement in serum levels of IL-6 and TNF-α (tumor necrosis factor) after treatment in all groups, without statistically significant differences. Mantovani et al. [14] demonstrated that IL-6 decreased significantly in Arm 5 ($p = 0.0187$) and in Arm 4 ($p = 0.0317$) and there was a tendency to decrease TNF-α in arm 5 ($p = 0.053$). In the study by Tanca et al. [11], there was a decrease of IL-6 in Arms 3 and 5, and a decrease in TNF-α in Arms 3 and 4 ($p < 0.05$). In the study by Finocchiaro et al. [8], CRP and IL-6 levels differed significantly between groups n-3 and placebo at the third assessment. Kun-Yun et al. [15] found that the Ethanwell/Ethanzyme regimen improved serum levels of albumin and pre-albumin ($p < 0.05$).

In the data from the same sample, the studies by Tanca et al. [11] and Mantovani et al. [14] demonstrated a significant improvement in fatigue in arm 5 ($p = 0.047$); being [11] showed a worsening of fatigue in arm 2 if compared to the others.

Regarding patient survival, Dewey et al. [16] found no significant difference when comparing the intervention to control group. In the study by Mantovani et al. [14], Glasgow's

prognostic index (GPS) decreased significantly in Arm 5 (p = 0.008), Arm 4 (p = 0.006) and Arm 3 (p = 0.030).

As for the Resting Energy Expenditure (REE), the study by Mantovani et al. [14] pointed out a significant reduction of REE in arm 5 (p = 0.044). Tanca et al. [11] found a worsening of REE in Arm 2 compared to the others, as well as significant REE improvement in Arm 5 (p = 0.02).

Bias risk assessment

According to the evaluation of the quality of the studies using the Cochrane risk-of-bias**,** for the eight studies included in the synthesis, it was found that the generation of the random sequence was clearly described in five of the studies (75.0%). The evaluation of concealment of the results was inaccurate in most studies, where only one study (12.5%) was classified as having a low risk of bias [22].

Three studies (37.5%) had a low risk of performance bias related to the concealment of participants and researchers [1,8], presented in Table 2.

The domains that presented more studies with low risk of bias were selection bias – generation of random sequence (75.0%) and report bias – selective report (75.0%). Detection bias – hiding the evaluation of results, followed by performance bias – hiding from participants and researchers (87.5% and 50.0%, respectively) were the domains that presented more studies with the uncertain risk of bias.

Other sources of bias were the domain that presented half of the articles classified as high risk of bias (50.0%). The frequency of judgment of the risk of bias for each domain is shown in Figure 2.

Discussion

This review synthesized the studies that deal with the effect of the intervention with nutritional supplements, Omega-3 and branched-chain amino acids, in cancer patients with cachexia. Eight randomized clinical trials involving interventions attended the inclusion criteria.

The evaluated outcome variables in the studies included body weight, body composition, resting energy expenditure, appetite, functional performance, quality of life, fatigue, biochemical parameters (IL-6, TNF-α, C-Reactive protein, albumin and pre-albumin) and survival.

Supplementation with Omega-3 fatty acids has been analyzed in several studies, in a variety of populations and clinical conditions, in the attenuation of weight loss, improvement of muscle strength and functional capacity, increasing increase of the rate of protein synthesis, as well as modulation of the immune and inflammatory response to cachexia [13,17-19].

In this research, branched-chain amino acids were not explored for their exclusive combination with Omega-3, however, trying to maintain the focus of the pre-established literature review, it sought to include all studies that maintained the combination of the two object nutrients of study combined with other approaches.

In this review, the form of intervention adopted in the studies was the use of an oral supplement enriched with Omega-3 (EPA and DHA) or administration in capsules containing EPA and DHA. In this sense, Solheim et al. [13], describe out that offering an oral nutritional supplement, if compared to the administration of capsules, can be useful, since supplements can provide extra calories, proteins and micronutrients, in addition to Omega-3 fatty acids; however, the alternative ways of administering Omega-3 fatty acids, like the capsules, are also advantageous in ensuring good adherence by patients.

Research into methods to combat cachexia has progressed towards combining agents, suggesting the need for a new approach to the management of cancer cachexia. The promising results of the study by Tanca et al. [11], Solheim et al. [13], Mantovani et al. [14] and Kanat et al. [12] suggest the effectiveness of the combined treatment with individual components.

These results are in agreement with a systematic review that has recently been published by [3], who pointed out that a single therapy may not be the best treatment regimen for cachexia, and that approaches involving different combinations are more likely to be successful.

The multimodal approach appears to be essential in cachexia treatment, which requires a combination of nutritional support, medications and an adequate exercise program to treat anorexia and metabolic changes associated [3].

In this context, Del Fabbro [20], in a systematic review of combined supplementation in the management of cachexia, highlights that the defining characteristics of cancer cachexia, for example, weight loss, reduced intake, and chronic inflammation can provide both a framework for the classification of cachexia and a justification for identifying its multiple therapeutic targets.

Researchers have carried out studies regarding the concept of “Multimodal therapy for a multidimensional problem” [20,14]. Several studies have analyzed the implementation of combined therapy, pharmacological and non-pharmacological, aimed at patients with cachexia, among which we highlight, MENAC (Multimodal-Exercise, Nutrition and Anti-inflammatory medication for Cachexia) [12,13] and ACCeRT (Auckland’s Cancer Cachexia Evaluating Resistance Training) study focused on refractory cachexia [3].

Nevertheless, EPA supplementation in an animal model with cancer cachexia demonstrated anti-lipolytic action by inhibiting the expression of zinc-α2-glycoprotein

(ZAG), a lipolytic factor of white and brown adipose tissue [21]. Du et al. [22] analyzing the effect of supplementation of EPA derived from starfish (Asterias amurensis) in an ascitic cancer cachexia model S180, noticed a reduction in ZAG, adipose triglyceride lipase (ATGL), hormone-sensitive lipase (HSL), among other anti-lipolytic factors.

These effects of EPA supplementation can be enhanced by the combination with physical exercise, especially by inhibiting the ubiquitin-proteasome system [21]. Rogers et al. [4] when developing a randomized clinical trial to stabilize muscle catabolism/anabolism and promote a potential net gain in total muscle mass in cachectic cancer patients, followed 20 patients for 20 weeks, who were randomly allocated to an Arm – supplementation with 2.09g of EPA and 300mg of COX-2 inhibitor (celecoxib) or in an Arm B, which in addition to the same interventions as Arm A, was also subjected to progressive resistance training (TPR) and 20g leucine supplementation. The results indicate an improvement in muscle mass of + 1.3 kg in Arm A and + 0.7 kg in Arm B at week 12. Besides, there were tendencies in the improvement/stability of cachexia markers (quadriceps muscle volume, serum albumin level, and C-reactive protein) in both arms.

About the effects of Omega-3 supplementation, intervention studies have shown positive effects on muscle mass with the use of oral nutritional supplementation, daily supply of 2-2.2 g of EPA [13,17] and approximately 1 g of DHA [18].

However, a systematic review developed by Ries et al. [23] on the use of fish oil/Omega-3 fatty acids (n-3-FA)/eicosapentaenoic acid (EPA) in patients with advanced cancer suffering from cachexia**,** found that there is insufficient evidence to support a benefit of n- 3-FA in cachexia in advanced cancer [23].

Morland et al. [17] point out that one of the main barriers in conducting clinical studies is associated with recruiting and retaining a satisfactory number of participants who

can guarantee a satisfactory study power to demonstrate the clear mechanisms of action of Omega 3.

Furthermore, food supplementation with leucine in cachectic rats controls important points of the proteasome pathway and therefore can inhibit the loss of muscle mass [24,25].

In cachexia, there is intense degradation of fatty and muscular tissue, with mTOR assuming the central role as a potent promoter of protein synthesis, which is strongly stimulated by the presence of leucine, which reveals a parallel pathway of the amino acid possibly active in protein synthesis and the inhibition of proteolysis [25,26]. Leucine supplementation has been linked to increased protein synthesis and decreased proteolysis, and therefore to the modulation of the effects of cancer cachexia, and this BCAA may act to preserve skeletal muscle mass [27].

Moreover, the use of branched-chain amino acids increases oxygen consumption [26] and it is possible to achieve better outcomes from the manipulation of respiratory rate, heart rate by physiotherapy, and specific physical training [28].

Despite this, attention to the supply of non-protein calories (carbohydrates and lipids) to guarantee the primary role of proteins / amino acids from food consumption also becomes an essential measure, because if this is not guaranteed, nitrogenous components can be diverted to maintenance of energy expenditure in cachexia.

It is important to note that the combined supplementation of leucine (one of the three branched-chain amino acids) with other agents (pharmacological, dietary, or even multimodal approaches) has been documented as promising for muscle synthesis in these patients [7,14,25,29-30].

In this review, the results of the study by Dewey et al.[16] showed that there was no statistically significant difference in the primary or secondary outcomes measured after the

intervention, compared to the control group; however, due to problems in execution (inadequate recruitment and attrition rates above expectations) and a high number of losses, it cannot be concluded that EPA supplements are ineffective.

Overall, studies included in this review are of moderate quality, where the risk of bias analyses revealed unclear risks and a high risk of bias for some domains.

Studies have shown heterogeneous design with an approach to different types of tumors and degrees of cachexia [2]. Future studies, with randomized clinical trials and more rigorous methodology, are needed to increase the robustness of the evidence.

As for the limitations of this systematic review, even though the research process has been extensive and detailed, important information may have been lost due to the non-use of articles published in languages other than those defined in the inclusion criteria. The heterogeneity between the studies and the differences between the evaluated results prevented the results from being combined in a meta-analysis.

However, more research is needed to explore the various aspects of the clinical application of this supplementation. It is necessary to develop rigorous well-designed clinical studies, especially high-quality randomized controlled trials**,** to better elucidate the effectiveness and mode of action of Omega-3 in combination or not with other elements.

Conclusion

The studies included in this systematic review showed a promising effect of Omega-3 in modulating the inflammatory response, attenuating muscle catabolism, and eventually improving the quality of life in cancer cachexia, mainly in supplementation combined with branched-chain amino acids, and to other multimodal approaches especially.

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Figures

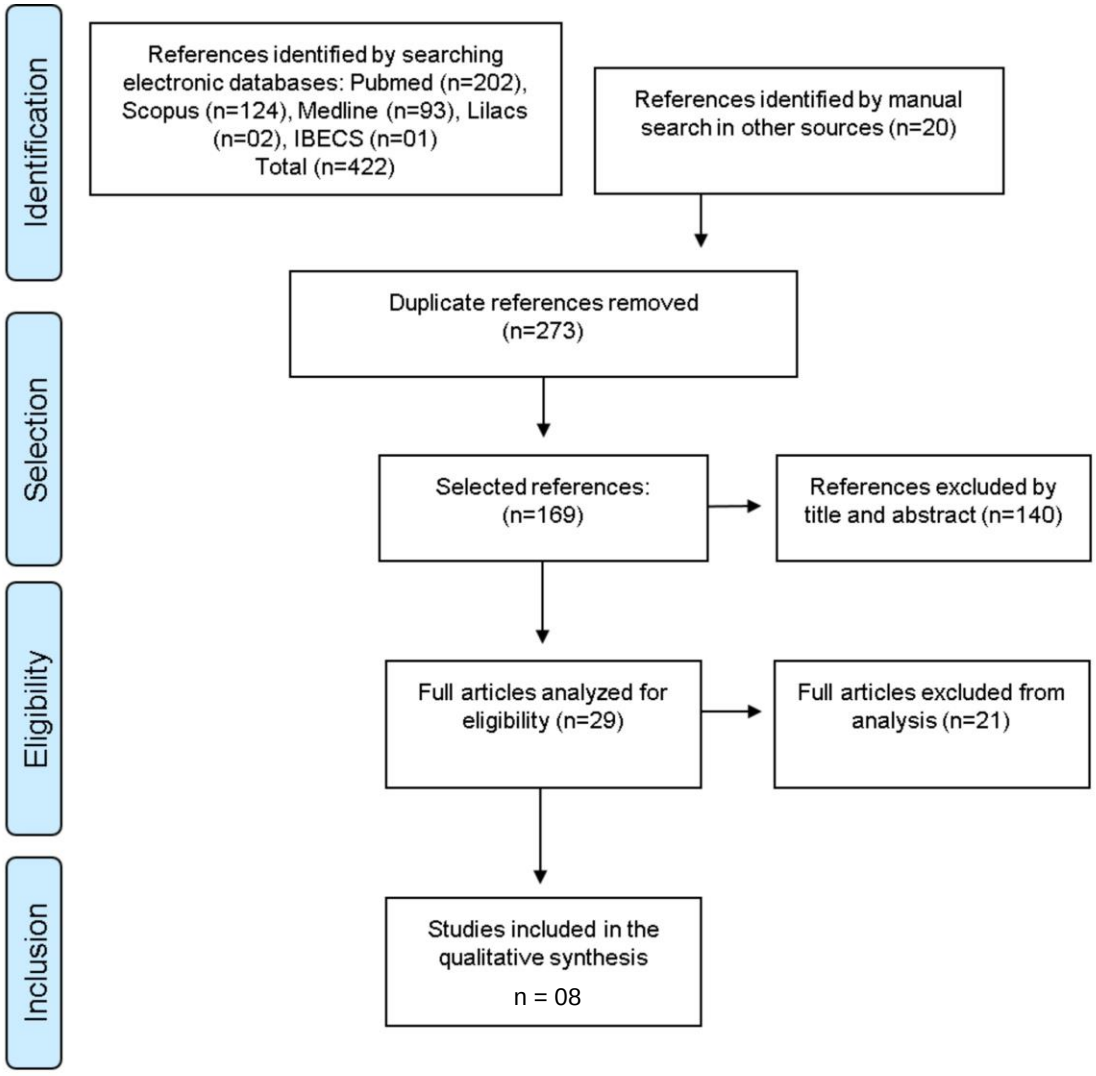

Figure 1. Flowchart of selection of articles for systematic review, according to the model of Cochrane Collaboration.

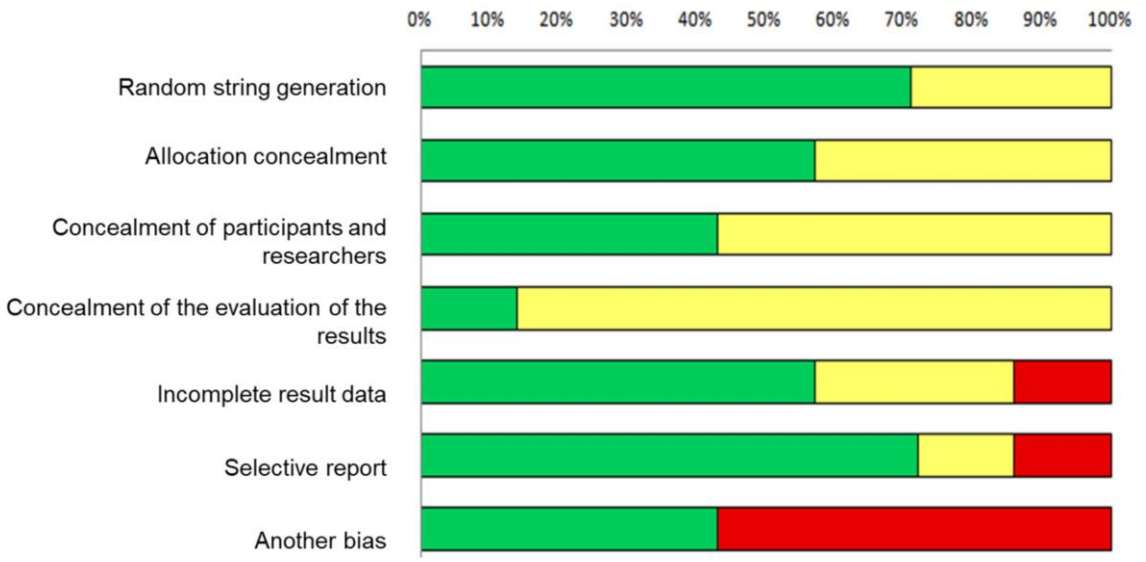

Figure 2. Risk of bias in the domains for the studies included in the systematic review, according to the Cochrane 'Risk-of-Bias'.

Tables

Table 1 - Characterization of articles included in the systematic review.

Autor	Objetivo	Amostra	Idade	Tipo de câncer	Parâmetros clínicos de interesse	Tempo de acompanhamento	Nº de perdas por Seguimento de tratamento
Werner et al. (2017) [2]	Comparar MPL de baixa formulação, que tinha a mesma quantidade e composição de n-3-FA, na estabilização de peso e apetite, melhorando a saúde (QoL) e perfis de FA plasmática em pacientes que sofrem de câncer de pâncreas.	n = 60, avaliado n = 33, braço GFO n = 18 e GMPL n = 15	≥ 18 anos	Câncer de pâncreas	Resultados primários: mudança de peso e apetite. Desfechos secundários: qualidade de vida, perfil de ácidos graxos no plasma sanguíneo, estado nutricional, parâmetros sanguíneos de rotina e adesão.	6 semanas	GFO n = 13 e GMPL n = 14
Finocchiaro et al. (2012) [8]	Investigar o efeito de EPA mais DHA no estado inflamatório, oxidativo e nutricional em pacientes com câncer de pulmão.	n = 33, CG n = 14 e IG n = 19	46 a 70 anos	Câncer de pulmão de pequenas células não avançado inoperável	Parâmetros bioquímicos (estado inflamatório [PCR, TNF-alfa, PGE2 e IL 6] e estado oxidativo [EROS e HNE - hidroxinonenal]) e parâmetros antropométricos (peso corporal).	66 dias	CG n = 0 IG n = 6
Tanca et al. (2009) [11]	Estabelecer qual foi o tratamento mais eficaz e mais seguro para melhorar as variáveis CACS / OS "chave" identificadas (desfechos primários): aumento no MCM,	n = 280, foram avaliados n = 240 avaliados e distribuídos nos 5 braços do estudo.	30 a 84 anos	Digestivo, pulmão, mama, rim, próstata, colo do útero, cabeça e pescoço e outros	Desfechos primários: MCM, gasto de energia em repouso (RGE), atividade física diária total, níveis de interleucina (IL) - 6 e fator de necrose tumoral (TNF) -α e fadiga.	4 meses	Nenhuma perda foi relatada

	diminuição no GER, aumento na diminuição física total diária de IL-6 e TNF-α e diminuição fadiga.						
Kanat et al. (2013) [12]	Compare a eficácia de três modalidades de tratamento diferentes no manejo da caquexia do câncer.	n = 69, foram avaliados n = 62: Braço A (n = 23); Braço B (n = 21) e Braço C (n = 18)	≥ 18 anos	Digestivo, pulmão, mama, testículos, próstata e outros	Peso corporal, índice de massa corporal (IMC), massa corporal magra (MCM) foram avaliados por BIA, níveis séricos de IL-6 e TNF-α, QOL (Avaliação das Funções Funcionais da Anorexia / Caquexia [ACS-12]), Horizontal Escala Visual Analógica.	3 meses	N = 7, o grupo não foi relatado
Solheim et al. (2017) [13]	Avaliar a viabilidade e segurança de uma intervenção multimodal (suplementos nutricionais de ácidos graxos poli-insaturados n-3 , exercícios e anti-inflamatórios: celecoxibe) para a caquexia do câncer em pacientes com câncer de pulmão ou pancreático incurável em quimioterapia.	n = 46 IG = 25 e CG = 21	18 a 80 anos	Câncer de pulmão ou pâncreas inoperável, em quimioterapia.	Peso corporal, índice de massa corporal (IMC); função física [usando ActivPAL e o teste de caminhada de 6 min (TC6)]; massa muscular; força muscular; Estado nutricional [Avaliação subjetiva gerada pelo paciente (aPG -SGA)]; ingestão nutricional [Escala de avaliação da ingestão nutricional (AveS)]; e fadiga [Fatigue Severity Scale (FSS)].	6 semanas	IG n = 2 CG n = 3
Mantovani et al. (2010) [14]	Estabelecer o tratamento mais eficaz e seguro para melhorar os resultados de caquexia do câncer primário - massa corporal magra (LBM), energia de repouso gasta (GER) e fadiga - e	n = 332, Braço 1 n = 44; Braço 2 n = 25; Braço 3 n = 88; Braço 4 n = 87; Braço 5 n	≥18 anos	Digestivo, pulmão, mama, rim, próstata, colo do útero, cabeça e pescoço e outros	Massa corporal magra (MCM), gasto de energia em repouso (RGE), fadiga (resultados primários); Apetite, qualidade de vida (medido pelo EORTC QLQC30 e EuroQoL [EQ] -5D), força de preensão, Índice de	4 meses	N = 12, o grupo não foi relatado

	desfechos secundários relevantes de secreções: apetite, qualidade de vida, adesão à força, o prognóstico do Índice de Glasgow (GPS) e citocinas inflamatórias.	= 88			prognóstico de Glasgow (GPS) e citocinas pró-inflamatórias (resultados secundários).		
Kun-Yun Yeh et al. (2013) [15]	Avaliar se um suplemento nutricional oral enriquecido com ácidos graxos W1-3, micronutrientes e probióticos afetaram mudanças no peso corporal (PC), albumina sérica e pré-albumina em pacientes com caquexia câncer de cabeça e pescoço.	n = 68, IG n = 31 e CG n = 37	36 a 79 anos	Câncer de cabeça e pescoço (cavidade oral, orofaringe, hipofaringe, laringe)	Alterações no peso corporal, albumina sérica e pré-albumina.	3 meses	Não houve perdas
Dewey et al. (2015) [16]	Determinar se um suplemento nutricional oral contendo ácido eicosapentaenóico de ácido graxo ômega-3 (EPA) é capaz de melhorar a qualidade de vida e o tempo de sobrevivência de pacientes com câncer de tumor sólido avançado em uma população de câncer de tipo tumor misto.	n = 27, IG = 13 e CG = 14	≥ 18 anos	Pulmão, mesotelioma, esôfago, pâncreas, estômago, próstata, mieloma	Mudanças no peso corporal e na composição corporal. Desfechos secundários: estado de apetite, estado funcional, estado de qualidade de vida e tempo de sobrevivência.	8 semanas	IG n = 4 CG n = 7

Table 2 - Results of the assessment of the methodological quality of each study included in the systematic review, according to the Cochrane 'Risk of bias'.

AUTOR	Geração de sequência aleatória (viés de seleção)	Ocultação de alocação (viés de seleção)	Ocultação de participantes e pesquisadores (viés de desempenho)	Ocultação da avaliação dos resultados (viés de detecção)	Dados de resultados incompletos (tendência de atrito)	Relatório seletivo (tendência do relatório)	Outro viés
Werner et al. (2017) [2]	Baixo	Baixo	Baixo	Incerto	Baixo	Baixo	Baixo
Finocchiaro et al. (2012) [8]	Baixo	Baixo	Baixo	Incerto	Baixo	Baixo	Alto
Tanca et al. (2009) [11]	Baixo	Incerto	Incerto	Incerto	Incerto	Baixo	Baixo
Kanat et al. (2013) [12]	Incerto	Incerto	Incerto	Incerto	Incerto	Incerto	Alto
Solheim et al. (2017) [13]	Baixo	Alto	Alto	Incerto	Baixo	Baixo	Baixo
Mantovani et al. (2010) [14]	Incerto	Incerto	Incerto	Incerto	Baixo	Baixo	Baixo
Kun-Yun Yeh et al. (2013) [15]	Baixo	Baixo	Incerto	Incerto	Baixo	Baixo	Alto
Dewey et al. (2015) [16]	Baixo	Baixo	Baixo	Incerto	Alto	Alto	Alto

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4.2 Capítulo II – Suplementação de BCAA e Câncer de Colo Uterino: efeitos na antropometria, marcadores bioquímico-inflamatório e capacidade funcional

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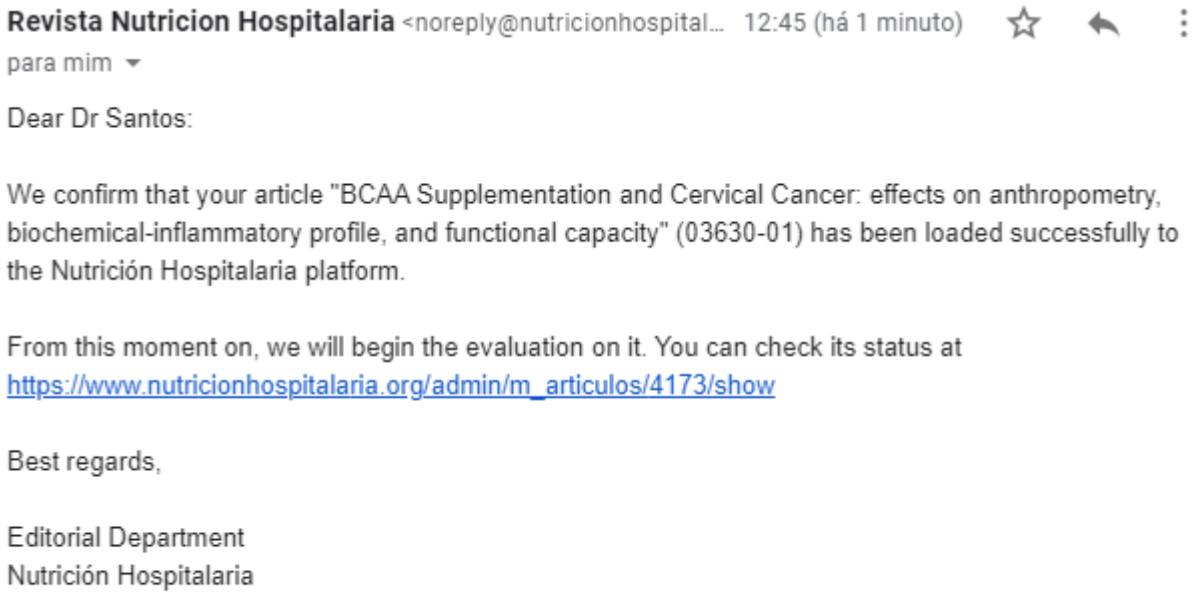

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Capítulo II – BCAA Supplementation and Cervical Cancer: effects on anthropometry, biochemical-inflammatory markers, and functional capacity

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Abstract

Introduction: Cachexia is the continuous loss of muscle with or without loss of fat mass associated with a basic disease, such as cancer, associating itself as a predictor of mortality and a low response to therapy and worse quality of life. In cachexia there is excessive oxidation of branched-chain amino acids (BCAA), suggesting beneficial effects on its supplementation. **Objective:** to analyze the effect of dietary supplementation with BCAA on anthropometric, biochemical, and inflammatory parameters and functional capacity in women with cervical cancer. **Materials and Methods**: Ensay randomized, open, with no probabilistic shows in women with cervical cancer uterine randomized electronically in groups: (i) BCAA supplementation group (n = 8); (II) Control Group (CG) (n = 9). The follow-up comprised evaluations at the beginning (T1), at the 15-day consultation (T2), at the 28-day consultation (T3), and the end (T4) of the study (56 days), nutritional, cardiorespiratory, functional capacity, quality of life and clinics, in addition to data on dietary intake and adherence to supplementation, and at T1 and T4 consultations, biochemical-inflammatory variables were collected. The statistics were provided in SPSS 25® by applying the Shapiro-Wilk test,

Student t or Mann- Witney and Wilcoxon. **Results**: 17 women with an average age of 3 8.5 ± 5.6 (BCAA) years and 41.1 ± 5.0 years (CG), white, with low education and income, were evaluated. There was a similarity between the groups and m regarding nutritional status, blood pressure, energy, and protein consumption. The arm circumference was statistical and slightly lower in the BCAA group compared to the CG group, with a decrease for other measures throughout the study. There were no statistically significant relationships ($p>0.05$) for functional capacity, quality of life, survival by standardized phase angle, body composition, IL4, IL10, IFN-γ, hemoglobin, and fasting blood glucose. The basal metabolic rate (BMR) declined significantly ($p = 0.0127$) in the BCAA, compared to the CG group. The standardized phase angle increased by T4 in the BCAA (0.47º ± 1.18) by 487.5%. TNF-α increased 165.7% compared to baseline. There was a significant decrease ($p<0.05$) in the hematocrit in the CG group. **Conclusion**: isolated supplementation with BCAA, although capable of significantly attenuating BMR, seems to have reflected in greater inflammation and a decrease in fat reserves. Further studies are needed to assess the combination of this supplementation with other inflammatory modulatory agents in cachexia.

Keywords: Cancer. Cachexia. Branched-chain amino acids. Nutritional supplementation.

Conflict of interests

We certify that there is no actual or potential conflict of interest related to this article.

Financing

Foundation for the Support of Research and Scientific Development of Maranhão (FAPEMA).

Introduction

Cachexia is the continuous loss of muscle mass (with or without loss of fat mass), which can be reversed by nutritional therapy, however, it implies a progressive functional impairment (1). It is generally associated with loss of body weight, degradation of muscle proteins, loss of adipose tissue, anorexia, inflammation, malabsorption, nausea, asthenia,

impaired immune system function, causing susceptibility to infections, metabolic disorders, weakness and decreased functional (2-4).

Several mechanisms are involved in the pathophysiology of the disease, with emphasis on not the action of proinflammatory cytokines, high concentrations which are present in large part of patients affected (4). There is also an imbalance between anabolic and catabolic hormones, hormonal changes related to the regulation of metabolism and appetite, including leptin, adiponectin, and ghrelin (5).

Cancer is a major public health problem, exhibiting high rates of incidence, prevalence, and mortality. In cancer patients, cachexia stands out as a predictor of death, low response to medication and nutritional therapy, and still shows the worse quality of life measures (4).

During cachexia there is excessive oxidation of branched-chain amino acids (BCAA), suggesting beneficial effects, such as improved nitrogen balance and, mainly, protein-muscle metabolism, from food supplementation with BCAA in the nutritional support of these patients (1, 6, 7).

The BCAA are essential amino acids, ie, are not produced by the body and therefore need to be consumed through diet. There are three BCAAs: leucine, isoleucine, valine, these components being responsible for the signaling effect of muscle synthesis, and leucine is the BCAA responsible for most of this effect. The stimulus mechanism is based on the activation of the mRNA binding step during translation into the skeletal muscle (8).

BCAAs, in this context, assume anabolic properties in protein synthesis that have been studied for more than 50 years. Although to date, there is no consensus regarding its therapeutic effectiveness during some disorders, it is assumed that there are at least three main pillars: (I) Protein-muscle catabolism (skeletal musculature) initiated by the oxidation of BCAA accompanied by a release of alanine and glutamine in the blood; (II) The amination of keto acids branched-chain BCAA; and (III) the activity of the branched-chain keto acid dehydrogenase. The latter would demonstrate the enhanced oxidation of BCAA in cancer patients. Although changes in BCAA metabolism during injury states are common, and there is a great need for special care during the disease, further research is needed to understand its supplementation (9).

Therefore, perceiving evidence that food supplementation (isolated or combined) can bring benefits (1, 6, 7), there is a need to conduct studies to test the effect of supplementation

of branched-chain amino acids on parameters clinical-nutritional, cardiorespiratory, metabolic, and quality of life in patients with cachexia secondary to cervical cancer.

Thus, it will be possible to contribute to clarifying the therapeutic application of the mentioned supplements in patients with this pathology, which will contribute to the promotion of improvements in the treatment and the clinical evolution of patients with cervical cancer (10).

In this context, we sought to analyze the effect of dietary supplementation with branched-chain amino acids on anthropometric, biochemical, and inflammatory parameters and functional capacity in women with cervical cancer.

Material and Method

An open, randomized clinical trial was conducted from October 2018 to October 2019. The collection/screening and meetings with the subjects took place at the outpatient clinic of the Hospital do Câncer Aldenora Bello, as well as the blood sample collections at Universidade CEUMA (Laboratories of Clinical Analysis and Environment).

This research was approved by the Research Ethics Committee of the Federal University of Maranhão (opinion No. 1,627,928) and was also registered in the Brazilian Registry of Clinical Trials (REBEC) (RBR-943djg and Universal Trial Number - UTN nº U1111-1195 -5621).

The non-probabilistic sample included women with cervical cancer regardless of their nutritional status, with a minimum age of 20 years. Already the simple randomization was preceded in generating the World Wide Web (internet) Randomization.com™, where each individual received the treatment according to the random order issued by the generator.

Selection Criteria

Women with cervical cancer, aged 20 years or more were included, clinically stable (no changes in the therapeutic regimen in the last 6 weeks or within the previous 3 months), and agreed signs of the Informed Consent and Informed.

Those who stated restricted vegetarianism, use of a pacemaker, in palliative care, or with any allergies to the nutritional composition of the supplement were not included.

Participants who withdrew their consent, who demonstrated adherence to an intervention of less than 75.0%, had no reason for the proposed supplementation, or had a significant loss after the intervention, were excluded.

Data collect

Supplementation protocol

After screening and capturing patients, those who agreed to participate in the study were randomized into the groups:

(I) Group supplemented with branched-chain Amino acids: BCAA Group (n = 8), women who were guided to an eating plan containing an average of 30 to 35cal / kg/day, and 1.0 to 2.0g / kg/day protein and 35.0% of total energy intake in the form of lipids (11), this caloric distribution and macronutrients were followed for both groups. Thereafter, control of food intake through a 24-hour recall (RC24). The diet plan was based on the 10 steps for an adequate/healthy diet (12), and prioritized proteins of high biological value (beef, chicken, fish, shellfish, eggs, milk, soy products, nuts, and legumes) and fats of good quality (olive oil, canola oil, nuts, seeds, and deep-water fish). Also, patients were supplemented orally with four tablets (two before lunch and two before dinner) a day with branched-chain amino acids (containing: leucine - 3.0g, isoleucine - 1.5g, and valine - 1, 5g), for 56 days (8 weeks), as approximately performed by Campos-Ferraz et al. (1).

(II) Control Group: CG Group (n = 9), women oriented with an eating plan, as proposed by Way (11) and based on the 10 steps for an adequate/healthy diet (12).

After randomization, contact was made with the patients and a date and time were defined for the first meeting at the outpatient clinic of the Hospital do Câncer Aldenora Bello. The s patients receiving the supplement at this time as drawing for the research group, in an amount sufficient for two weeks (15 days). After two weeks, in a return visit to the hospital, patients were asked about food consumption, adherence to supplementation, and other protocols, except for biochemical tests that were performed only in the first consultation and in the last. The supplements were stored in frosted packaging, without the original label so as not to blindly disclose product information.

At the beginning (T1), at the 15-day consultation (T2), at the 28-day consultation (T3), and the end (T4) of the study protocol (56 days), the variables of interest (nutritional,

cardiorespiratory, functional capacity, quality of life and clinics, in addition to data on food consumption and adherence to supplementation). At T1 and T4 consultations, biochemical and inflammatory variables were collected.

Instruments and Data Collection

The variables of interest collected included: nutritional, cardiorespiratory, functional capacity, quality of life, clinics, food consumption, adherence to supplementation and outcomes, and socio-demographic characterization. Except for biochemical inflammatory data that were verified only at the beginning (T1) and end (T4) of the study.

A semi-structured questionnaire was applied, containing demographic and socio-economic variables (age, economic classification, education level, family income, etc.). Data related to the patient's clinic (baseline diagnosis, comorbidities, use of medications, etc.), anthropometric data, food consumption, functional classification, quality of life, physical activity, handgrip strength, six-minute walk test were also recorded, as well as the results of the biochemical tests provided by the patients.

The application of the questionnaires and the obtaining of anthropometric data were carried out by properly trained researchers. Regarding anthropometric data have verified the weight, height, and body mass index, tricipital skinfold (TS), arm circumference (AC), arm muscle circumference (AMC), and arm muscle area (AMA). Tetrapolar electrical bioimpedance was used to assess body composition.

To obtain the patients' body weight, a digital platform scale with an attached stadiometer (Filizola ®) was used, with a maximum capacity of 150kg and a graduation of 100g. The measurement was performed according to the technical standard of the Food and Nutrition Surveillance System (SISVAN) (13).

The height of the patients was assessed with a stadiometer attached to the scale (Filizola®), with an accuracy of 0.50 cm. The procedure was carried out according to the SISVAN technical standard (13).

To measure the AC, an anthropometric inelastic millimeter tape, of the Sanny ® brand, was used, with a maximum extension of 200 cm and an accuracy of 1 mm. The TS was measured using a Lange caliper ®, with a scale up to 60 mm with a resolution of 1 mm. The AC and TS measurement technique followed the recommendations of Cuppari (14).

AMC was obtained using the formula [AMC = AC (cm) - (0.314 x TS)]. For the muscular area of the arm, the formula [AC (cm) - π x TS (mm) ÷ 10] 2 ÷ 4π (-6.5 for women) (15) was used. The nutritional classification of AC, TS, and AMC was performed according to Blackburn and Thornton (16) and AMA according to Frisancho (15).

For the evaluation of food consumption, the 24-hour recall was used, with the aid of a photo album with standardization of homemade measures, and the calculation of the nutritional composition was carried out with the aid of Diet Win ® software.

To assess body composition, tetrapolar electrical bioimpedance (Biodynamics ®) was used, adopting the recommendations of Cômodo et al. (17). The Standardized Phase Angle (SPA) was calculated using the equation: SPA= measured PA - mean PA (for age and sex) / population standard deviation for age and sex, the standardization can be seen in CharT1 (18, 19).

Table 1. Mean and standard deviation of the phase angle of the standard population for age and sex.

Age range (years)	Female	
	Average	Standard deviation
18 - 20	7.04	0.85
20 - 29	6.98	0.92
30 - 39	6.87	0.84
40 - 49	6.91	0.85
50 - 59	6.55	0.87
60 - 69	5.97	0.83
≥ 70	5.64	1.02

Source: Barbosa-Silva et al. (19).

Skeletal muscle mass was calculated from data obtained from bioimpedance using a predictive equation proposed by Janssen et al. (20). The basal metabolic rate (BMR) obtained in tetrapolar electrical bioimpedance was calculated using the formula of Harris and Bennedict (17).

To measure systolic (SBP) and diastolic (DBP) blood pressure, were used the Littmann® stethoscope (Saint Paul, USA) and mercury column sphygmomanometer.

To assess the quality of life in cancer patients was used the EORTC QLQ – C30 questionnaire from the European Organization for Research and Treatment of Cancer (EORTC) (21, 22).

The handgrip strength measurement (HGSM) was obtained by dynamometry. HGSM was measured using a hydraulic dynamometer (Saehan ®). The measurement was performed according to Dias et al. (23).

The 6-minute walk test (6MWT) was performed according to the recommendations of the American Thoracic Society (ATS) (24), as well as the standardization for the population (25).

Biochemical tests were collected at Ceuma University, with patients fasting for 12 hours. After collecting 2ml of blood sample in Buffered Sodium Citrate tubes, they were sent to centrifugation for 10 minutes at 2500rpm, at the Immunology Laboratory of Universidade Ceuma (NOVATÉCNICA® model NT812). The manufacturer's determinations were followed, based on the use of Bioscience®.

After centrifuging, the samples were taken to the Environment Laboratory at Ceuma University, where the plasma was separated from the rest of the blood material, with the aid of a 1000ul Micropipette (Labmate HTL variable 100-1000ul, model Labmate Pro).

UV resistant and Gilson Blue Cral 200-1000uL Tips, the plasma was stored in 5ml Eppendorf microcubes, and subsequently stored, duly identified in a -20 ° C freezer for further analysis, by the ELISA Protocol for measuring tumor necrosis factor alpha (TNF-α), IL4, IL10 and gamma interferon.

Statistical treatment

Statistical analysis was performed using the Statistical Package for the Social Sciences software (SPSS, version 25 ®, Chicago, United States of America). Normality was verified using the Shapiro-Wilk test.

Statistical parametric continuous analysis Comparisons between groups BCAA and Control were preceded by t-test Student's and the Mann Witney, as appropriate for nonparametric comparisons.

To compare numerical variables over the course of the study, the t-test for paired samples, or non-parametric equivalent, the Wilcoxon test, was applied.

The data were shown in tables, graphs, text, and all statistical associations were fixed as significant when alpha was less than 5%.

Results

Among the groups evaluated, there was a higher frequency of young women (31 to 40 years old) in the BCAA group (38.5 ± 5.6 years) and 41 years old or more in the CG (41.1 ± 5.0 years), white women, a significant percentage of those assessed live in the interior of the state in both groups (50.0% or more), with low education (BCAA = 37.5% and CG = 44.4%). All of those evaluated showed low economic class (C, D, or E) and most were in clinical support in the BCAA group (50.0%) and chemotherapy in the CG group (55.6%) (Table 1).

Mean BMI was similar between the CG and BCAA groups (25.0 ± 3.2 kgm² vs 2 5 5 ± 4.5 kgm², respectively) and blood pressure (Table 2).

The energy consumption between the BCAA and CG groups was similar (22.7 ± 6.5 vs 22.8 ± 4.6cal / kg / day, respectively), as well as protein (1.1 ± 0.3 vs 1, 2 ± 0.5g / kg / day, respectively) and glycidic (174.0 ± 42.7 vs 174.5 ± 28.8g / day, respectively). The consumption of total lipids, total cholesterol, calcium, and dietary fiber was higher in the BCAA group (Table 3).

There was a statistically significant relationship ($p < 0.05$) only for AC, which was slightly lower in the BCAA group (26.5 ± 2.7 cm) compared to the CG group (29.9 ± 1.9 cm). For all other variables (TS, BS, AMC, and AMA) there was a decrease in these measures over the evaluated time (Table 4).

An increase of 8.67% in skeletal muscle mass (kg) was noted throughout the study in the BCAA group compared to the CG group (5.23%), however without statistically significant differences ($p > 0.05$). Likewise, there was an increase in fat mass in percentage in a greater proportion in the BCAA group (13.11%) than in the CG group (1.34%) (Table 5).

And between the functional capacity measured by the walking test six minutes and the grip strength not there were statistically significant comparisons ($p > 0.05$). However, the BMR fell (- 1.05%) significantly (p = 0.0 12 7) in the BCAA group compared to the CG group in which an increase of 2.34% for this variable following T3 (Table 6).

Regarding the quality of life, there hears increased overall scores in the field of health and functional capacity, BCAA and CG group and less significant decreases symptoms in the area BCAA group, but no significant difference ($p > 0.05$) (Table 7).

In the analysis of survival using the standardized phase angle, a greater increase was observed after intervention with BCAA ($0.47^{o} \pm 1.18$, increase of 487.5%), but without significant difference ($p > 0.05$), as shown in Table 8.

In comparison, anthropometry found a significant difference ($p = 0.040$) only for the measurement of the circumference of the arm between the BCAA and CG groups T4 (Figure 1 A- E).

About body composition during follow-up no difference was observed are significant ($p > 0.05$) (Figure 2 A-C) as well as about changes in the quality of life among the evaluated during follow-up (Figure 3 A-C), distance covered in the six-minute walk test between those assessed during the study follow-up, there was no significant difference ($p > 0.05$) (Figure 4) and handgrip strength during the study, no observed a significant difference ($p > 0.05$) (Figures 5 A and 5B).

By assessing changes in basal metabolic rate during the study did not there was a significant difference ($p > 0.05$) (Figure 6).

Finally, there were no significant differences ($p > 0.05$) throughout the study between the groups in the analysis of the standardized phase angle (Figure 7).

In biochemical analysis-inflammatory difference was observed mean ($p < 0.05$) throughout the study for increased tumor necrosis factor-alpha (TNF-α) only BCAA group showing an increase of 165.7% compared to baseline (Figure 8 A-D).

There was a significant decrease ($p < 0.05$) in the hematocrit in the CG group of 57% (Figure 9 A-C).

Discussion

In this research, there was a higher frequency of adult women, white, with low education and income. The findings suggest improvements in musculoskeletal reserves, fat mass (in kg and percentage), handgrip strength (HGS) in the left hand, basal metabolic rate, and quality of life in the BCAA group.

Even without statistically significant comparisons in the BCAA group, it is possible to speculate that there was an 8.67% increase in skeletal muscle mass (kg) over the course of the study in the BCAA group compared to the CG group (5.23%). This improvement may be related to an attenuation (decrease of 1.05%, p = 0.0127) in TMB in the BCAA group, compared to the CG group, in which there was an increase of 2.34% for this variable in the T3 follow-up.

Food supplementation with leucine has taken on an important mission in mitigating the loss of muscle mass. Suggesting that leucine intake in cachectic rats inhibits the expression of genes in the proteasome pathway (8, 26).

During cachexia there is intense degradation of fat and muscle tissue, thus the consumption of BCAA contributes to the metabolite beta-hydroxy beta- methylbutyrate - (HMB), which stimulates the synthesis of mTOR, which assumes the central role in the synthesis of protein and the inhibition of proteolysis (8, 27).

Leucine supplementation has been linked to increased protein synthesis and decreased proteolysis, and therefore to the modulation of the effects of cancer cachexia, and this BCAA may act to preserve skeletal muscle mass (28).

On the other hand, the consumption of branched-chain amino acids increases oxygen consumption (27), which may reflect on the respiratory system and, consequently, on the worse performance of the BCAA group with the CG group for anthropometric measurements (AC, TS, BS, AMC, AMA), functional capacity (six-minute walk test and handgrip strength in the right hand) and fat mass (MG%).

Improving the respiratory rate through the manipulation of the heart rate through physiotherapy, specific physical training can cause better outcomes, even in the BCAA group (29).

It is also noteworthy that the supply of non-protein calories (carbohydrates and lipids) to guarantee the primary role of proteins / amino acids from food consumption also becomes an essential measure because if this is not guaranteed, the nitrogenous components can be diverted to maintenance of energy expenditure in cachexia.

Both groups (BCAA and CG) demonstrated improvements in quality of life. While the BCAA group showed a percentage increase in the score for the domain Global Health and Functional Capacity of 5.8% and 55.5%, respectively, the CG group showed an increase of 31.1% and 26.2% for the same domains. Regarding the Symptoms domain, the CG group had

the greatest decrease in the score (–53.6%, versus –25.1% in the BCAA group), which directly reflects in improvements in symptoms and quality of life. It is important to note that, until then, only the BCAA group had patients undergoing chemotherapy and who had undergone a surgical procedure, which may have directly influenced the outcomes.

I came to you that cancer treatment, especially surgical and chemotherapy, was a factor that may have directly influenced the performance of patients in functional capacity tests (6-minute walk test and handgrip strength), once they exist patients undergoing these treatments in the BCAA group. However, it is very important to note that the combined supplementation of leucine (one of the three branched-chain amino acids) with other agents (pharmacological, dietary, or multimodal approaches) has been documented as essential for muscle synthesis in these patients (1, 8, 29-32).

The outcomes obtained here could have been improved by combining the consumption of BCAA with omega 3 eco-apentaenoic fatty acids (EPFA) and physical exercise, especially by inhibiting the ubiquitin-proteasome system (33). Rogers et al. (34), when developing a randomized clinical trial to stabilize muscle catabolism/anabolism and promote a potential net gain in total muscle mass in cachectic cancer patients, followed 20 patients for 20 weeks, who were randomly allocated to one Arm A (supplementation with 2.09g of EPFA and 300mg of COX-2 inhibitor [celecoxib]) or in an Arm B, which in addition to the same interventions as Arm A, was also subjected to progressive resistance training and supplementation of 20g of leucine. The results showed a gain in muscle mass of 1.3 kg in Arm A, and 0.7 kg in Arm B at week 12, also, there were trends in the improvement/stability of cachexia markers (quadriceps muscle volume, level serum albumin, and C-reactive protein) in both arms.

Recently, a controlled, randomized, multicenter clinical trial analyzing the effect of omega-3 (W3) polyunsaturated fatty acid supplementation compared to omega-6 (W6) without controlling breast cancer-related fatigue revealed that supplementation with W6, cancer-related disease, and pro-inflammatory markers via TNF-α signaling decreased, especially in women with severe fatigue, revealing the need to elucidate new mechanisms of action (35). In the research, the supplement used still includes at least 1200mg of W6 and 1200mg of W9, which can also contribute to better performance in functional capacity tests in the BCAA group. The modulation of the true muscular patient can contribute to improving the cachexia of cancer.

The increase in the phase angle is an important survival marker and not yet widely used in the prognosis of cancer cachexia in clinical practice, even when associated with the deterioration of cell membranes, reflecting direct changes in reactance, and consequently in cell integrity, or also changes in membrane permeability or even cell composition.

Thus, the more intact the cell membranes are, the greater the energy storage and therefore, the phase angle formed (36). The increase in the measurement is positively related to reactance and negatively to resistance, therefore, the lower the phase angle values are, the greater the signs of cell death or deficits in the cell integrity of those evaluated, whereas high phase angle values are more indicative. of intact cell membranes in greater proportion (36, 37).

In this study, the BCAA group demonstrated an increase in the phase angle (+0.39º, that is, an increase of 487.5%) and the CG group, in turn, a decrease (-0.29º, that is, a reduction of 138.0%), which even without statistical significance ($p > 0.05$), showed a greater increase in the intervention group.

As regards the analysis by ELISA inflammatory profile, noted a significant increase ($p = 0.043$) for TNF-α in the BCAA group (an increase of 100.0% compared to T1) while the IL10 (increased 165.7%), however this last parameter without statistical significance ($p > 0.05$). Nevertheless, IL4 and IFN-γ showed impaired analysis due to sample losses for these data. The IL10 / TNF ratio reveals evidence of modulation of the inflammatory profile in the BCAA group (1.09pg / ml [0.0 - 3.9]) compared to the CG group (0.9pg / ml [0 - 6.5]) ($p > 0.05$) (data not tabulated).

The positive effects for muscle synthesis through supplementation with branched-chain amino acids may only appear after the modulation of inflammation through omega ga 3 or other multimodal approaches, such as physical exercise, this may explain the performance of the group BCAA.

Reduced fatty tissue reserves in the BCAA group may be a reflection of the effect of leucine metabolites (BET a-hydroxy beta-methylbutyrate [HMB]), especially between sedentary individuals (38). The reduction in fat mass and increase in lean mass are restricted to individuals who have an active life, which may explain the results found in this research. HMB can modulate protein synthesis and proteolysis in anabolic conditions, that is, during muscle renewal from periodic physical exercises (39).

Among the reasons that may have contributed to the results found are the concomitant need for supplementation with BCAA to physical exercise, healthy eating and that meets specific requirements, as well as a combination with other modulatory agents of inflammation, such as omega 3, omega 6, and megestrol (31, 35, 38).

The loss of follow-up was aggravation in the conduct of this research due to the frequency of meetings (every 15 days in the first three and 26 days for the last). Morland et al. (40), point out that this is one of the main difficulties when conducting clinical studies, the difficulty associated with recruiting and maintaining a sufficient number of participants who can guarantee a satisfactory study power to demonstrate the clear mechanisms of the intervention.

The socioeconomic class may have been another limiting factor in the sample of this study, with those evaluated belonging to economic class C or lower, which may directly influence the acquisition of food for the conduct of the diet, since the foods proposed in the diet plan include foods with higher protein content, such as meats, dairy products, and legumes that end up reflecting the most onerous foods on the Brazilian table, and consequently in reaching the caloric-protein goal. Besides, the level of previous physical activity among those assessed (sedentary or irregularly active) was another limiting factor, which deserves attention in future proposals.

It is worth mentioning that, at the beginning of 2020, measures to prevent contamination by the new Coronavirus (Sar-CoV-2) occurred in our state, which prevented the expansion of data collection in the research environment and, consequently, of the sample size and still hindered the progress of data collection from patients recruited at the end of 2019.

The form of administration of supplemental was the cause of complaints, however, not decreased d adhesion d food intervention on the part of patients.

In this regard, the form of administration should be targeted in future studies, in combination with a single product from the food supplement of branched-chain amino acids with other potentially beneficial nutrients in the modulation of cachexia. However, there is a need to expand the sample size and follow up a complete study.

Conclusion

Isolated supplementation with BCAA was able to significantly attenuate BMR by -1.05%. Moreover, there is evidence of an increase in the mass musculoskeletal (+ 8.67%) and improved d quality of life during follow-up. However, it seems to have reflected in greater inflammation and a decrease in fat reserves.

It is necessary to expand the sample size and further studies to evaluate the combination of this supplementation with other inflammatory modulatory agents in cancer cachexia.

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Tables

Tables

Table 1. Sociodemographic characteristics and treatment of women with cervical cancer. São Luís, Maranhão, Brazil, 2021.

Variables	Group			
	BCAA		Control	
	n	%	n	%
Age group (years)				
31 to 40	5	62.5	4	44.4
41 or more	3	37.5	5	55.6
Age years)	38.5 ± 5.6		41.1 ± 5.0	
Skin color				
Not white	two	25.0	3	33.3
White	6	75.0	6	66.7
Origin				
capital	4	50.0	4	44.4
Interior	4	50.0	5	55.6
Education				
Without instruction	1	12.5	0	0.0
Incomplete Fundamental	two	25.0	4	44.4
Complete Elementary School	two	25.0	0	0.0
Average	3	37.5	5	55.6
Economic class				
C	two	25.0	4	44.4
D	5	62.5	4	44.4
E	1	12.5	1	11.1
Oncological treatment				
None	0	0.0	3	33.3
Surgical	3	37.5	0	0.0
Clinical	4	50.0	0	0.0
Chemotherapy	1	12.5	5	55.6
Combined	0	0.0	1	11.1
Total	8		9	

Table 2. Anthropometric characteristics and blood pressure of women with cervical cancer at the beginning of the study follow-up (T1). São Luís, Maranhão, Brazil, 2021.

Variables	GROUP					
	BCAA			Control		
	Md±Dp	Med	(Min – Max)	Md±Dp	Med	Min – Max
Weight (kg)	56.8±7.0	57.0	(45.0-67.5)	60.4±10.2	56.4	(42.8-76.0)
BMI [a]	25.0±3.2	25.1	(19.0-29.3)	25.5±4.5	24.2	(20.6-34.2)
PAS [b]	121.9±10.9	121.0	(111.0-146.0)	127.9±13.4	128.0	(106.0-151.0)
PAD [c]	81.7±6.5	82.5	(70.0-88.0)	82.0±11.8	82.0	(66.0-100.0)

[a]Body mass index in kg / m²; [b]systolic blood pressure in mmHg; [c]diastolic blood pressure in mmHg.

Table 3. Average food consumption of energy, macro, and micronutrients of women with cervical cancer during the study follow-up. São Luís, Maranhão, Brazil, 2021.

Variables	GROUP					
	BCAA			Control		
	Md±Dp	Med	(Min–Max)	Md±Dp	Med	(Min – Max)
Energy						
cal / day	1321.6±249.1	1309.5	(975.8-1713.7)	1239.0±305.4	1200.1	(845.3-1603.5)
cal / kg / day	22.7±6.5	24.8	(11.2-29.5)	22.8±4.6	22.7	(17.3-28.6)
Proteins						
g / day	61.1±8.1	60.8	(50.8-71.5)	63.2±23.1	56.3	(42.0-97.9)
g / kg / day	1.1±0.3	1.1	(0.6-1.4)	1.2±0.5	1.2	(0.6-1.8)
Carbohydrate [a]	174.0±42.7	163.5	(133.3-241.6)	174.5±28.8	186.4	(125.5-199.7)
Lipids [a]	42.3±15.0	37.7	(26.6-63.6)	32.1±16.1	24.7	(19.2-59.9)
Total cholesterol [b]	220.5±111.5	192.2	(98.3-403.2)	167.1±73.7	150.7	(107.3-310.8)
Calcium [b]	558.1±127.4	503.2	(458.2-785.9)	467.1±359.8	396.1	(70.1-1029.3)
Dietary fiber [a]	13.4±3.7	13.5	(8.4-19.1)	12.3±2.6	11.5	(10.0-16.7)

[to]values in g / day; [b]values in mg / day.

Table 4. Comparison of anthropometry between the BCAA and Control groups. São Luís, Maranhão, Brazil, 2021.

Variables / Follow-up	Group		*p - value* *
	BCAA	Control	
	Med ± SD	Med ± SD	
Arm circumference (cm)			
T1	28.2 ± 3.5	27.7 ± 3.0	0.740
T2	28.2 ± 3.5	28.2 ± 3.1	0.982
T3	27 ± 2.8	28.7 ± 2.6	0.291
T4	26.5 ± 2.7	29.9 ± 1.9	*0.040* **
Triceps skinfold (mm^3)			
T1	19.1 ± 6.1	19.1 ± 6.4	0.988
T2	20.0 ± 6.0	18.1 ± 4.1	0.469
T3	32.7 (31.9-34.0)	32.4 (31.0-36.0)	0.699 §
T4	18.0 ± 7.2	19.1 ± 3.2	0.756
Biceps skinfold (mm^3)			
T1	11.5 ± 6.1	11.1 ± 4.9	0.889
T2	10.9 ± 6.0	9.3 ± 2.7	0.491
T3	9.8 ± 2.2	13.3 ± 3.8	0.084
T4	9.3 ± 3.5	11.7 ± 2.1	0.198
Muscle circumference of the arm (cm)			
T1	22.2 ± 3.0	21.7 ± 2.4	0.686
T2	21.9 ± 2.8	22.5 ± 2.7	0.653
T3	21.2 ± 1.9	21.8 ± 2.0	0.615
T4	20.9 ± 2.3	23.9 ± 2.4	0.065
Muscular area of the arm (cm^2)			
T1	33.5 ± 10.8	31.3 ± 7.6	0.631
T2	32.3 ± 10.2	34.5 ± 10.1	0.667
T3	29.4 ± 6.3	31.5 ± 6.7	0.594
T4	28.4 ± 7.6	39.3 ± 9.0	0.062

* Student's t-test: Mean ± SD.

Table 5. Comparison of body composition between BCAA and Control groups. São Luís, Maranhão, Brazil, 2021.

Variables / Follow-up	Group		*p - value* *
	BCAA	Control	
	Med ± SD	Med ± SD	
Skeletal muscle mass (kg)			
T1	2.3701 ± 0.40	2.1846 ± 0.35	0.325
T2	2.3699 ± 0.40	2.2901 ± 0.16	0.610
T3	2.4645 ± 0.39	2.2990 ± 0.14	0.356
T4	2.5758 ± 0.32	2.2990 ± 0.14	0.086
Fat mass (kg)			
T1	18.0 ± 8.9	22.9 ± 6.7	0.214
T2	19.2 ± 4.7	22.1 ± 7.3	0.373
T3	19.8 ± 4.4	23.8 ± 6.5	0.241
T4	18.4 ± 4.2	24.1 ± 5.6	0.093
Fat mass (%)			
T1	30.5 ± 14.9	37.2 ± 5.5	0.222
T2	34.0 ± 4.6	35.9 ± 6.2	0.519
T3	34.9 ± 3.9	37.2 ± 5.6	0.438
T4	33.5 ± 4.3	37.7 ± 3.5	0.112

* Student's t-test: Mean ± SD.

Table 6. Comparison of functional capacity and Basal Metabolic Rate between the BCAA and Control groups. São Luís, Maranhão, Brazil, 2021.

Variables / Follow-up	Group		*p - value* *
	BCAA	Control	
	Med ± SD	Med ± SD	
6-minute walk test (distance in meters)			
T1	346 (291.2-411.9)	367.7 (99.1-394.3)	0.815 §
T2	355.7 (301.8-411.5)	356.1 (140-404)	0.959 §
T3	354.3 ± 34.5	260.4 ± 164.4	0.241
T4	302.5 (295-413)	385.5 (280.9-429.6)	0.662 §
Handgrip strength (kgF) / Right Hand			
T1	19.0 (1.9-26.2)	19.5 (15.9-25.2)	0.606 §
T2	19.0 ± 6.8	21.1 ± 4.8	0.477
T3	18.0 ± 3.2	18.5 ± 2.9	0.803
T4	18.8 ± 3.4	22.6 ± 5.3	0.211
Handgrip strength (kgF) / Left Hand			
T1	17.1 ± 3.8	17.3 ± 3.4	0.883
T2	17.2 ± 3.9	18.5 ± 2.3	0.415
T3	17.8 ± 3.9	16.8 ± 3.8	0.663
T4	17.4 ± 3.1	18.3 ± 3.1	0.633
Basal metabolic rate (kcal)			
T1	1302.2 ± 74	1333.6 ± 90.7	0.450
T2	1297 ± 78.1	1331.3 ± 99.4	0.475
T3	1297.1 ± 72.2	1366.6 ± 72.7	0.012
T4	1288.5 ± 77.6	1364.9 ± 68.3	0.116

* Student's t-test: Mean ± SD; § Mann Withney test: Median (Min-Max).

Table 7. Comparison of quality of life between the BCAA and Control groups. São Luís, Maranhão, Brazil, 2021.

Quality of life	Group		*p-value* *
	BCAA	Control	
	Med ± SD	Med ± SD	
Global Health Domain			
T1	70.9 (16.7-100)	66.7 (0-100)	0.815 §
T2	76.0 ± 19.6	72.9 ± 19.3	0.753
T3	81.9 ± 22.6	79.2 ± 17.3	0.817
T4	75 (16.7-100.0)	87.5 (58.3-100.0)	0.662 §
Domain Functional Capacity			
T1	60.0 ± 24.4	70.4 ± 21.6	0.367
T2	61.4 ± 17.2	73.1 ± 21.0	0.244
T3	76.7 ± 26.2	78.9 ± 16.7	0.865
T4	93.3 (26.7-97.8)	88.9 (66.7-100.0)	0.792 §
Domain Symptoms			
T1	39.8 ± 23.9	22.2 ± 14.1	0.081
T2	35.9 (5.1-64.1)	14.1 (2.6-71.8)	0.083 §
T3	15.4 (0-87.2)	10.3 (0-35.9)	0.699 §
T4	29.8 ± 35.7	10.3 ± 11.3	0.234

* Student's t-test: Mean ± SD; § Mann Withney test: Median (Min-Max).

Table 8. Survival through the standardized phase angle between the BCAA and Control groups. São Luís, Maranhão, Brazil, 2021.

Variables / Follow-up	Group		*p-value* *
	BCAA	Control	
	Med ± SD	Med ± SD	
Standardized Phase Angle (º)			
T1	0.08 (-2.89 - 1.37)	0.21 (-2.49 - 1.12)	0.837 §
T2	0.13 ± 0.98	0.65 ± 0.59	0.199
T3	0.45 ± 1.31	-0.14 ± 0.63	0.346
T4	0.47 ± 1.18	-0.5 ± 0.58	0.108

* Student's t-test: Mean ± SD ; § Mann Withney test : Median (Min-Max).

Figures

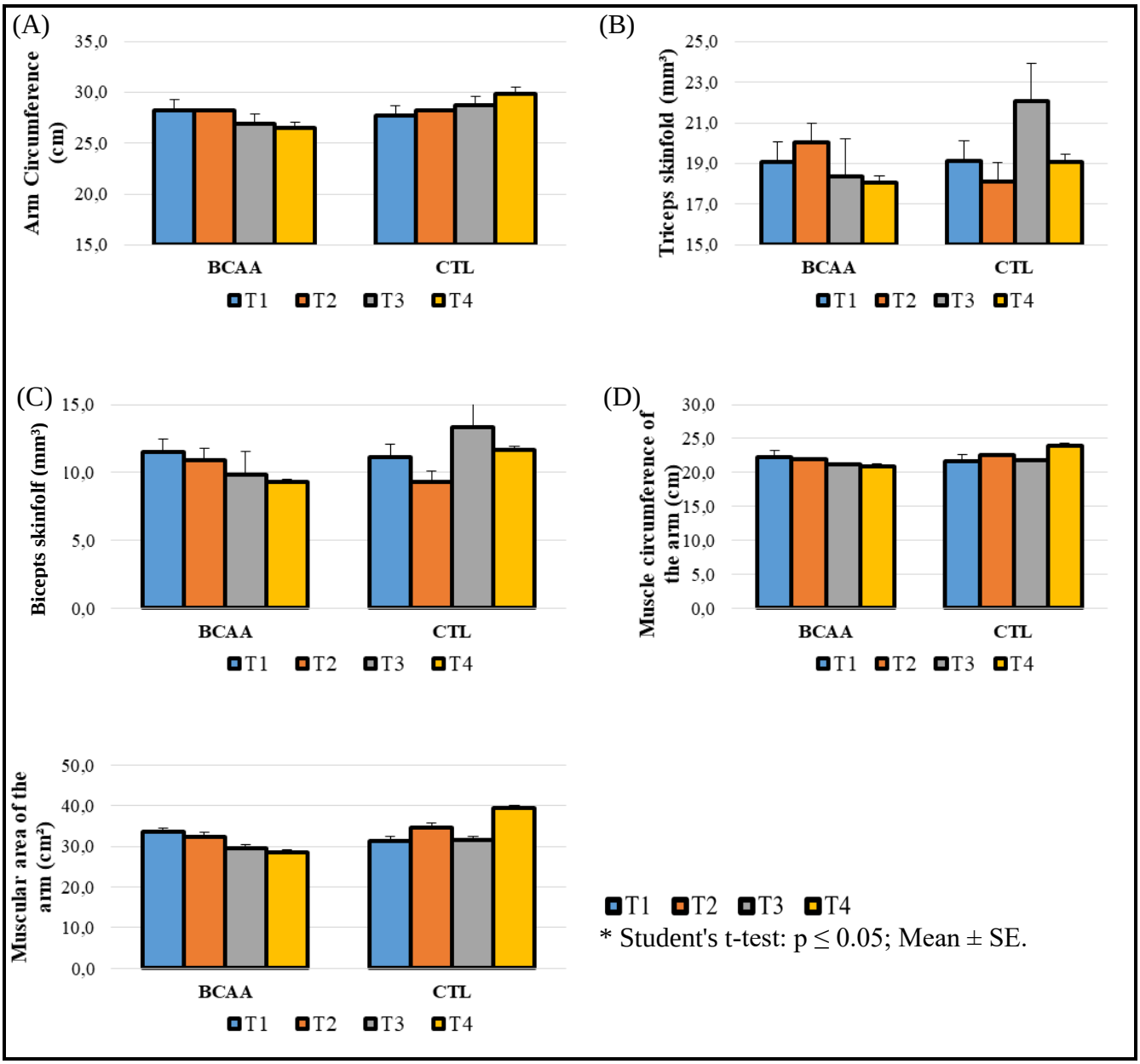

Figure 1. Comparison of the anthropometry of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) over the course of the study. São Luís, Maranhão, Brazil, 2021.

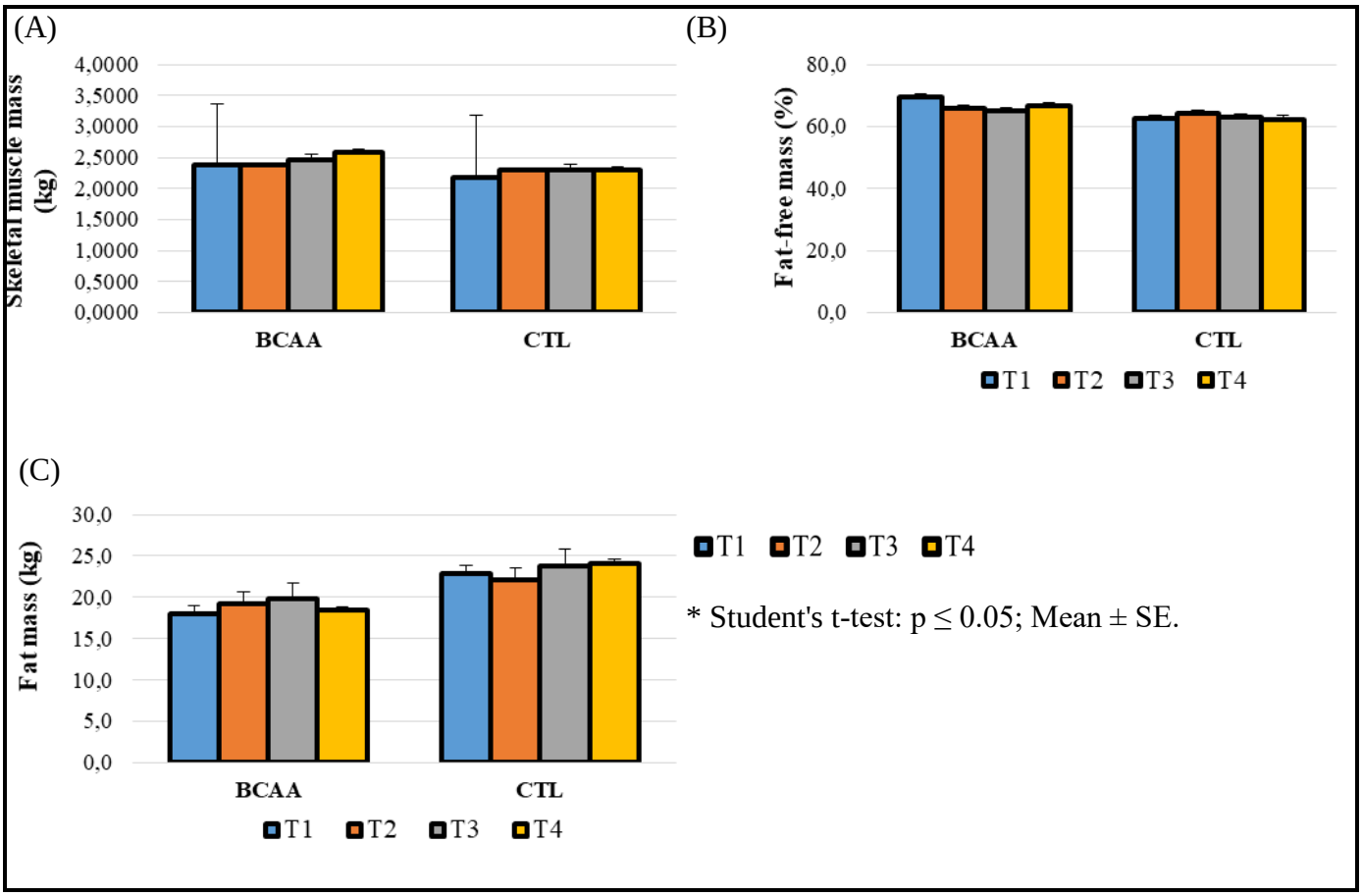

Figure 2. Comparison of the body composition of women with cervical cancer between the groups supplemented with branched chain amino acids (BCAA) and Control (CTL) throughout the study follow-up. São Luís, Maranhão, Brazil, 2021.

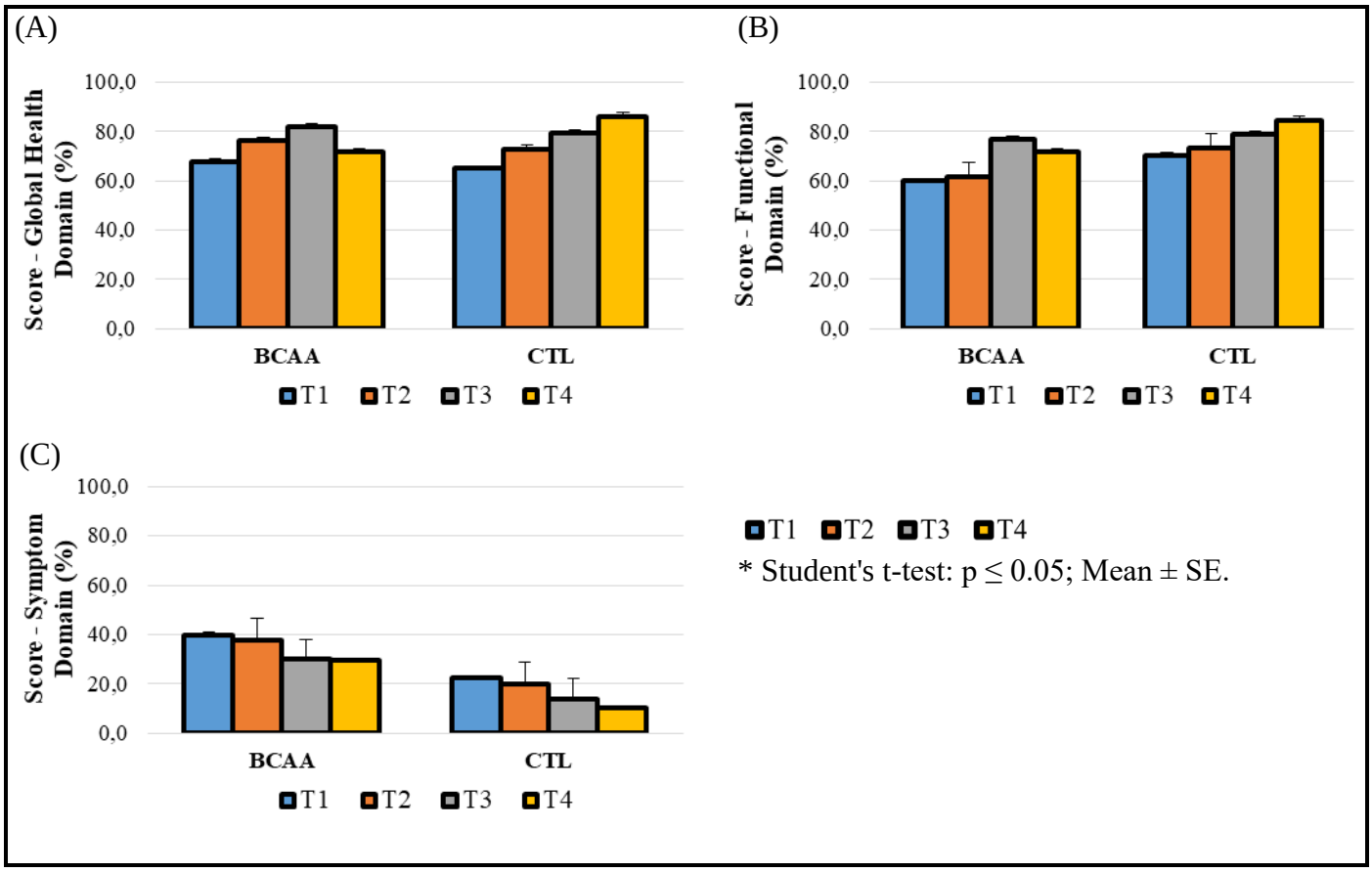

Figure 3. Comparison of the quality of life scores of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) over the course of the study. São Luís, Maranhão, Brazil, 2021.

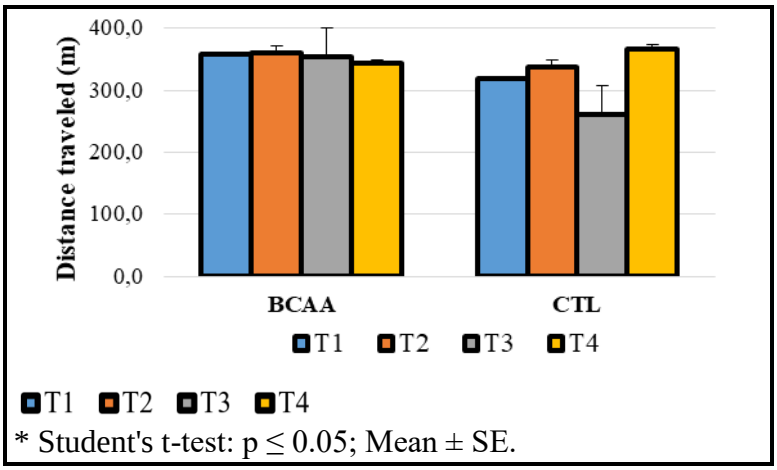

Figure 4. Comparison of functional capacity through the distance covered in the 6-minute walk test of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) throughout the study follow-up. São Luís, Maranhão, Brazil, 2021.

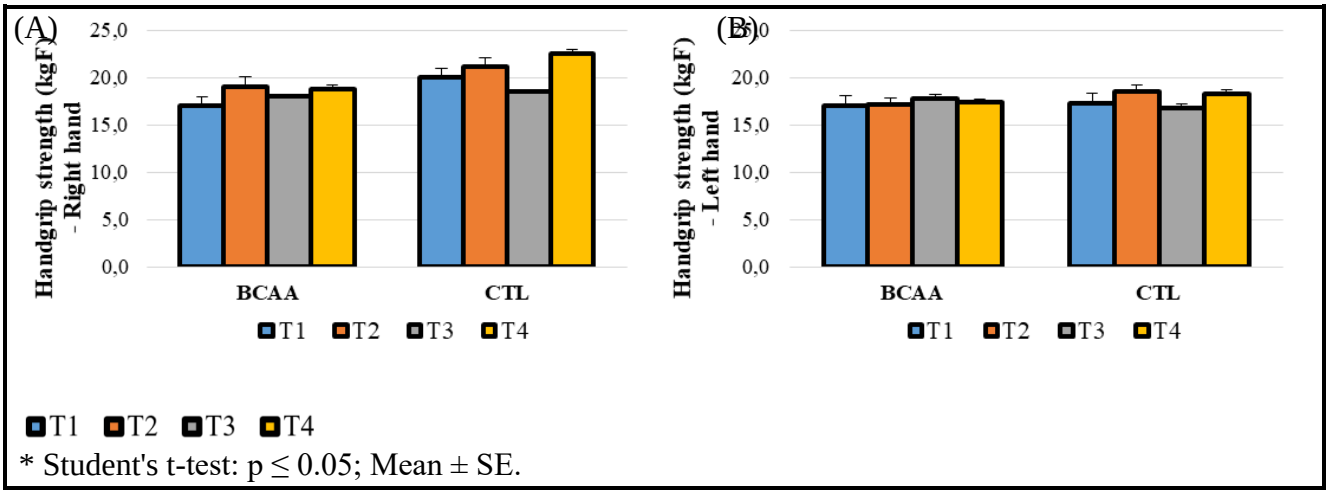

Figure 5. Comparison of handgrip strength of women with cervical cancer between groups supplemented with branched-chain amino acids (BCAA) and control (CTL) over the course of the study. São Luís, Maranhão, Brazil, 2021.

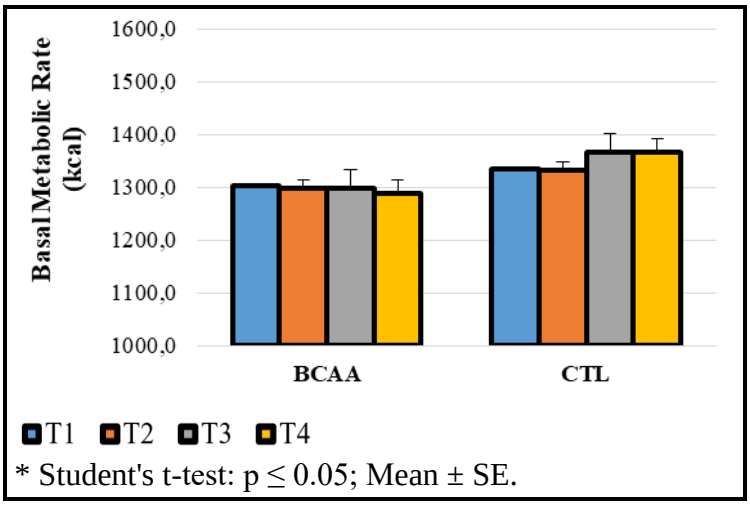

Figure 6. Comparison of the basal metabolic rate of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) throughout the study follow-up. São Luís, Maranhão, Brazil, 2021.

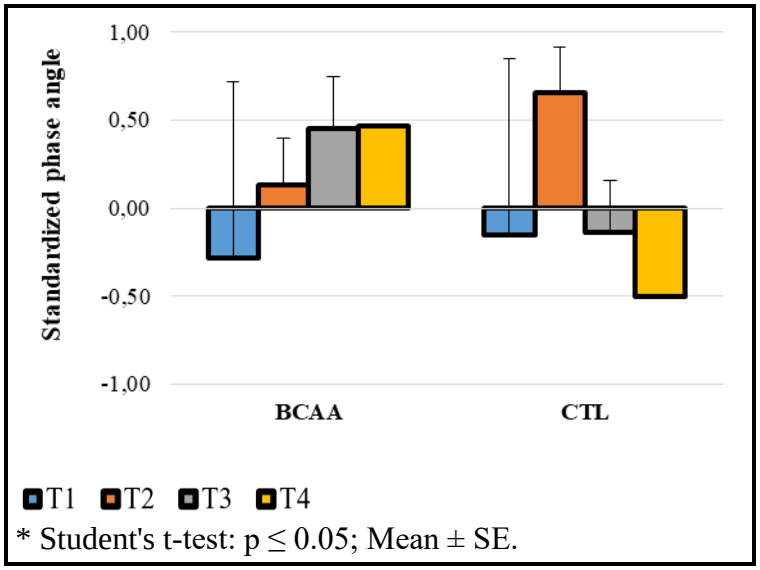

Figure 7. Comparison of the standardized phase angle of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) throughout the study follow-up. São Luís, Maranhão, Brazil, 2021.

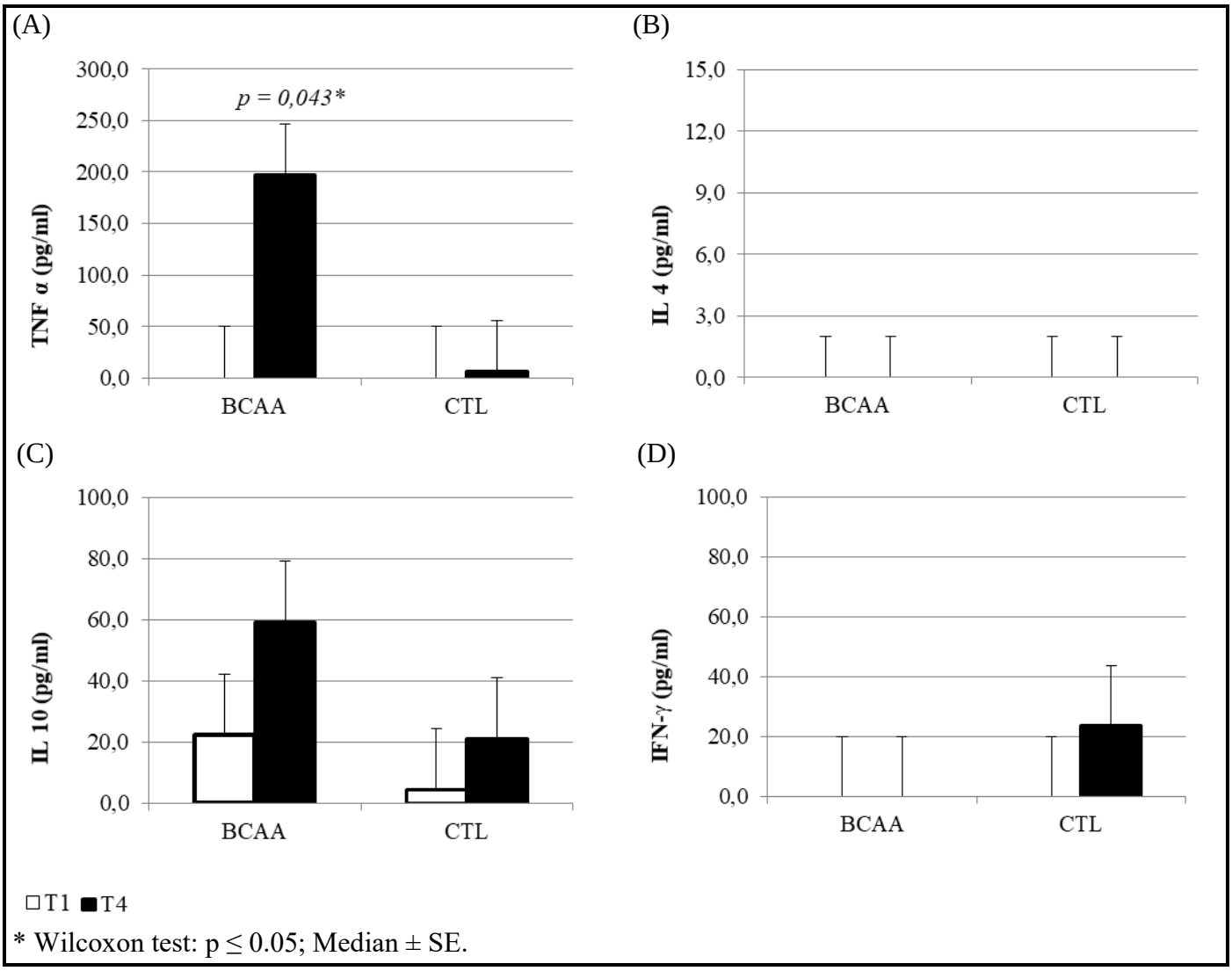

Figure 8. Biochemical-inflammatory comparison of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) throughout the study follow-up. São Luís, Maranhão, Brazil, 2021.

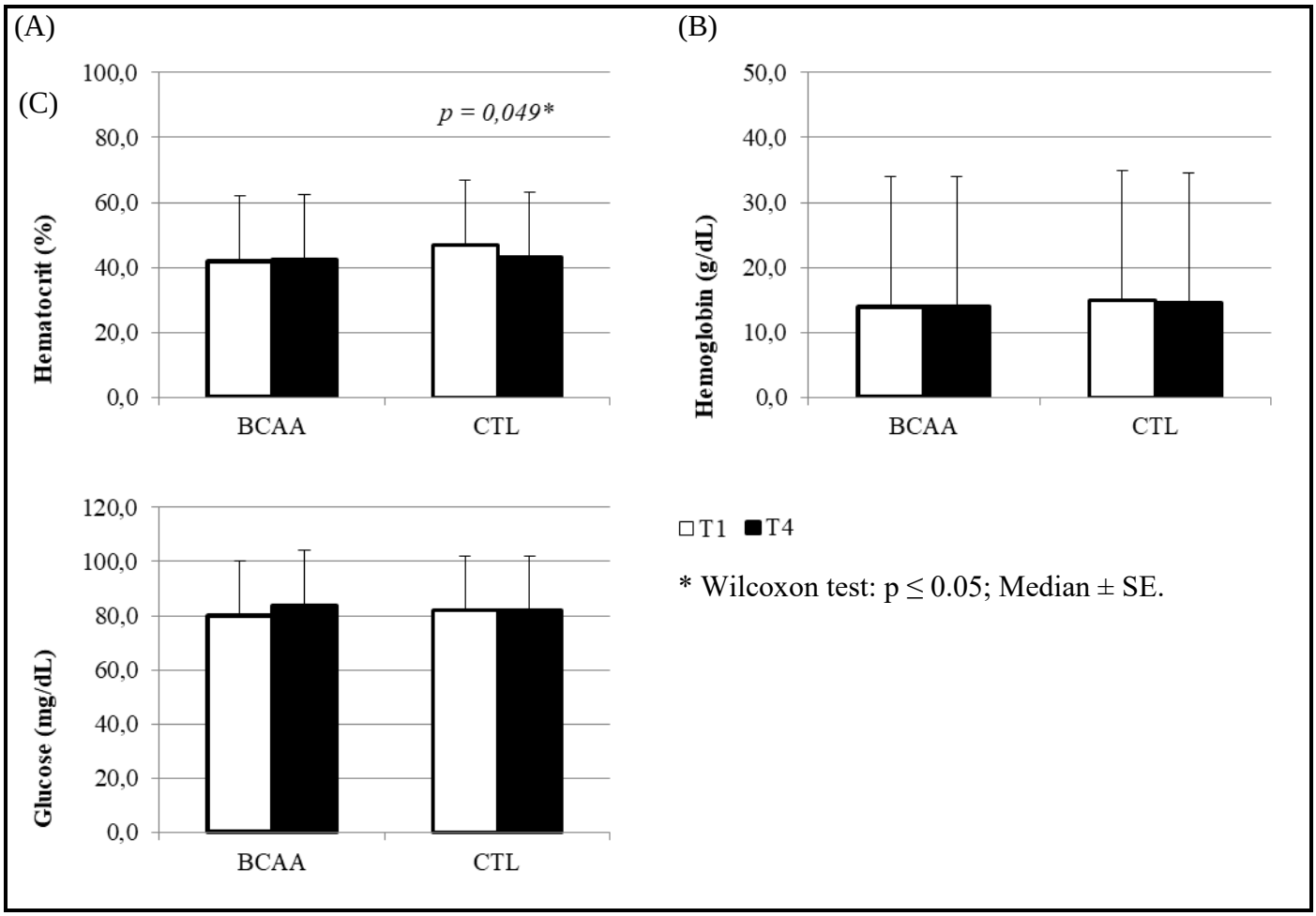

Figure 9. Comparison of hemoglobin, hematocrit and fasting glycemia of women with cervical cancer between the groups supplemented with branched-chain amino acids (BCAA) and Control (CTL) throughout the study follow-up. São Luís, Maranhão, Brazil, 2021.

NORMAS DO PERIÓDICO: Nutrición Hospitalaria

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Describe statistical methods with enough detail to enable a knowledgeable reader with access to the original data to judge its appropriateness for the study and to verify the reported results. When possible, quantify findings and present them with appropriate indicators of measurement error or uncertainty (such as confidence intervals). Avoid relying solely on statistical hypothesis testing, such as P values, which fail to convey important information about effect size and precision of estimates. References for the design of the study and statistical methods should be to standard works when possible (with pages stated). Define statistical terms, abbreviations, and most symbols. Specify the statistical software package(s) and versions used. Distinguish prespecified from exploratory analyses, including subgroup analyses.

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Present your results in logical sequence in the text, tables, and figures, giving the main or most important findings first. Do not repeat all the data in the tables or figures in the text; emphasize or summarize only the most important observations. Provide data on all primary and secondary outcomes identified in the Methods Section. Extra or supplementary materials and technical details can be placed in an appendix where they will be accessible but will not interrupt the flow of the text, or they can be published solely in the electronic version of the journal.

Give numeric results not only as derivatives (for example, percentages) but also as the absolute numbers from which the derivatives were calculated. Restrict tables and figures to those needed to explain the argument of the paper and to assess supporting data. Use graphs as an alternative to tables with many entries; do not duplicate data in graphs and tables. Avoid nontechnical uses of technical terms in statistics, such as “random” (which implies a randomizing device), “normal,” “significant,” “correlations,” and “sample.”

Separate reporting of data by demographic variables, such as age and sex, facilitate pooling of data for subgroups across studies and should be routine, unless there are compelling reasons not to stratify reporting, which should be explained.

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4.3 Capítulo III - Sarcopenia and Quality of Life: an association study in women with cervical cancer

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Capítulo III – Sarcopenia and Quality of Life: an association study in women with cervical cancer

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Abstract

Introduction: Cervical cancer is one of the more common tumors in women and the most incident in Maranhão. The cancer treatment associated with tumor factors and inflammatory cytokines can contribute to sarcopenia, which is characterized by an involuntary loss of strength and muscle mass. **Objective:** To analyze the association between sarcopenia and life quality in women with cervical cancer. **Methods:** A cross-sectional analytical study with secondary data collection was carried out from July to September 2019 at the Cancer Hospital Aldenora Bello. The studied population was women with cervical cancer age at least 20 years old, also were collected the anthropometric, sociodemographic, muscle function and quality of life data. Data analysis performed using Student T-test, Mann-Whitney test, Pearson's

Linear Correlation and Spearmen's linear correlation. The data were analyzed using the SPSS 21.0® program at a maximum significance level of 5%. **Results:** 27 women were studied, with a mean age of 40.2 (± 7.1) years, a predominance of the non-white race (37%) and from São Luís (55.6%) and sarcopenia had a prevalence of 33, 3% among those studied. Women with sarcopenia had a lower score for the Global and Functional domains when compared to non-sarcopenic women. **Conclusion:** There was no significant association between the presence of sarcopenia and quality of life, however, sarcopenic women had lower quality of life when compared to non-sarcopenic women.

Key-words: Sarcopenia. Uterine Cervical Neoplasms. Quality of life.

Conflict of interests

We certify that there is no actual or potential conflict of interest related to this article.

Financing

Foundation for the Support of Research and Scientific Development of Maranhão (FAPEMA).

Introduction

Most of the cells in our body follow a natural order (they grow, multiply and die in an orderly manner), however, cancer cells continue to grow uncontrollably, forming anomalous cells. Cancer is characterized by the proliferation of cells in an aggressive, rapid and disordered manner, with loss of control of their division (1).

Worldwide, estimates indicate that there were 18 million new cases of cancer and 9.6 million deaths in 2018, and in Brazil, an estimated 625 thousand new cases by 2022. Disregarding non-melanoma skin tumors, cervical cancer is the second most common type of cancer in the North, Northeast and Midwest and the most frequent in the state of Maranhão (2).

Cervical cancer is one of the most recurrent tumors in women and one of its main causes is an infection by some types of human papillomavirus (HPV). Infection with this virus can lead to cellular changes, which, when not diagnosed early, can trigger malignant

diseases. The use of oral contraceptives, smoking, multiparity and multiple partners are also risk factors for the development of this pathology. The diagnosis is easy to identify through the preventive exam, which is why it is extremely important to perform this periodically (1, 3).

Therapeutic approaches can bring adverse reactions to the patient, among them are nausea, dry mouth, dysphagia, alteration of smell and taste. In addition to treatment, tumor cells promote important metabolic changes in the host, such as an increase in proinflammatory cytokines, which are: interleukin-1 (IL-1), Interleukin-6 (IL-6), Tumor Necrosis Factor (TNF - α) and Interferon Gamma (IFN-γ) (4, 5, 6).

Added to this, the tumor itself produces the proteolysis-inducing factor (PIF) and the lipid-mobilizing factor (LMF) (4, 5, 6). Tumor factors, together with pro-inflammatory cytokines, play a fundamental role in suppressing appetite, altering the metabolism of macronutrients, increasing catabolism, inhibiting protein synthesis and, consequently, weight loss (5).

The inadequate protein-energy supply, aging, physical inactivity and the existence of some chronic diseases, such as cancer, can contribute to the development of sarcopenia. This pathology has its word derived from the Greek, which means “meat poverty”, that is, it is a disease characterized by the involuntary loss of strength and muscle mass and low physical performance. It is common to observe changes in functional performance first before muscle consumption (7).

Sarcopenia in cancer is related to increased toxicity due to chemotherapy, greater risk of falls and fractures, increased hospitalization, loss of independence, shorter survival and treatment tolerance, which can directly interfere with the patient's quality of life (8, 9).

Quality of life represents the individual's understanding of some aspects, such as: happiness, personal satisfaction, lifestyle, living conditions, goals and expectations (10). Understanding the relationship between sarcopenia and quality of life is extremely important since sarcopenic patients demonstrate the worse quality of life and greater symptoms of depression (11).

Associated with physical activity, nutrition is one of the main pillars used for the prevention and treatment of sarcopenia. Thus, more accurate assessments of pre-sarcopenic patients are essential, so that these interventions can be performed early, and thus reduce the

effects and severity of the disease, contributing to improving the well-being and success of antitumor treatment (12,13).

There are few studies in the literature related to sarcopenia and its consequences in cancer patients, especially those that associate sarcopenia with quality of life in patients with cervical cancer (14). Thus, the present study is relevant in being a pioneer and bringing a picture of the reality in these women.

This study analyzed the association between sarcopenia and quality of life in women with cervical cancer.

Methods

The study was an analytical cross-sectional study with secondary data collection. This research was carried out from July to September 2019 at the Cancer Hospital Aldenora Bello (HCAB). The hospital is a reference and highly complex center in oncology in the state of Maranhão, with 175 beds distributed in a clinical ward, surgical center, ICU, apartments, outpatient and radiotherapy and brachytherapy services.

This is a sub-research of the study entitled "Combined supplementation of branched-chain and omega 3 amino acids: clinical-nutritional, cardiorespiratory, metabolic impact and quality of life in pre-cachectic / cachectic patients", which had already been duly approved by the Research Ethics at the Federal University of Maranhão (UFMA) Opinion number 3,659,493, registered with the Brazilian Registry of Clinical Trials (REBEC) and Universal Trial Number (UTN) U1111-1195-5621. It is noteworthy that the objectives of this research are already duly contemplated in the base study and that data collection only occurred after approval by the Ethics Committee, as recommended by Resolution No. 466 of December 12, 2012, of the National Health Council (15).

The inclusion criteria for those evaluated in this study included: the presence of cervical cancer, minimum age of 20 years, agreement with the research, signing the Informed Consent Form (ICF), having answered a quality of life questionnaire (EORTC QLQ-30), having a handgrip strength data record (FPP) of less than 16Kg and skeletal muscle mass (MME) of less than 15Kg.

The exclusion criteria of those evaluated in this study included: the non-signature of the ICF use of a pacemaker, being a restricted vegetarian and the non-completion of the questionnaire (EORTC QLQ-30).

After the recruitment of women with cervical cancer, it was explained and asked to sign the informed consent form. Then, they were divided into two groups: sarcopenic and non-sarcopenic women. The diagnosis of sarcopenia was made according to Cruz-Jentoft et al. (13), was considered when the handgrip strength is less than 16 kg.

A pre-prepared questionnaire was applied, in which questions related to clinical, socioeconomic, demographic, anthropometric, body composition, quality of life and handgrip strength (FPP) questions were analyzed. A questionnaire was also applied for the economic classification according to the parameters established by the Brazil Economic Classification Criterion (16). This instrument consists of a variation of points that are added and classified according to the score obtained, which can be: class A1, A2, B1, B2, C1, C2, D and E.

To obtain anthropometric data, weight and height were evaluated, and for body composition, electrical bioimpedance (BIA) was used. These were applied by well-trained evaluators, being used by the same digital platform scale with an attached stadiometer (Filizola®), which has a maximum capacity of 150 kg and graduation of 100g, for the measurement of body weight. The patients were positioned in the center of the equipment, wearing light clothing, barefoot, with feet together, erect and arms parallel to the body, according to SISVAN's technical standard (18).

Regarding the patients' height, it was obtained through a stadiometer attached to the scale (Filizola®), with an accuracy of 0.50 cm. Barefoot patients, standing, with feet together, arms parallel to the body, head raised with a stare at eye level. The heels, calves, buttocks, scapulae and the back of the head against the wall or the stadiometer, and its measurement was performed according to the Food and Nutritional Surveillance System technical standard (18).

Body composition was assessed using tetrapolar bioimpedance (BIA) (Biodynamics®), after measuring weight and height. To perform electrical bioimpedance (BIA), patients should be supine, barefoot and with their lower limbs apart. They also needed to fast for 4 hours, barefoot, without metal fittings, with medications suspended from diuretics for at least 24 hours before the test was performed and to empty the bladder before the test, as recommended by Silva-Filho et al. (18).

Quality of life in women with cervical cancer was assessed using the European Organization for Research and Treatment of Cancer (EORTC), the EORTC QLQ-C30 questionnaire (18). This questionnaire contains 30 questions which are answered by the patient himself, the first part of the questionnaire covers topics related to cancer, where the answers can be: no little, moderately and a lot, with each answer having a score of 1, 2, 3 and 4, respectively. The second part of the questionnaire consists of two questions regarding the classification of the patient's health and quality of life, in grades ranging from 1 to 7, where 1 corresponds to poor quality/health and 7 to excellent.

To obtain the score, it was divided into three scales: Global health scale (referring to questions 29 and 30), Functional scales (referring to questions 1 to 7 and 20 to 27) and Symptom scales (referring to questions 8 to 19 and 28). The score for each scale is based on the average score of each of these, subtracted by 1 and divided by the maximum amplitude, the higher the score obtained on the global and functional health scales, the higher the quality of life. Regarding the symptom scale, the higher the score, the greater the presence of symptoms.

To obtain the handgrip strength (FPP), the hydraulic dynamometer (Saehan®) was used. This was performed with the patient seated in an armless chair, erect spine, forming a 90 ° flexion angle with the knee, with the elbow flexed at 90° and the arm suspended in the air with the hand positioned on the dynamometer, supported by the evaluator. This test was performed three times, where the average of the three attempts was calculated (20).

The data were tabulated in Microsoft Office Excel® and analyzed using the statistical program SPSS 21.0®. For the analysis of the results, the numerical variables were presented as mean, standard deviation, median and minimum and maximum values and the categorical variables in absolute (n) and relative (%) frequencies. Normality was verified using the Shapiro-Wilk test, with only the variable quality of life - Global Health domain being non-parametric ($p = 0.027$).

To correlate the quality of life scales with the presence of Sarcopenia, Student's T-test was performed on those scales with a normal distribution (Functional Capacity Domains and Symptoms) and Mann-Whitney test for the one without normal distribution (Global Health) and to correlate the domains Pearson's Linear Correlation was performed at the Left and Right Palmar Pressure Force on those scales with a normal distribution (Functional and Symptoms) and Spearman's Linear Correlation for those without normal distribution (Global).

Differences between groups were considered significant when $p < 0.05$.

Results

In this research, women from 33 to 43 years old (66.7%) prevailed with a mean age of 40.2 ± 7.1 years. Among these, 17 women (63%) were not white and 48,1% had completed high school (48.1%), from São Luís (55.6%). According to the economic classification criterion Brazil, 55.6% of those evaluated were class D. Regarding cancer treatment, 55.6% did not undergo chemotherapy, 81.5% did not undergo radiotherapy and 88,9% did not undergo surgery (Table 1).

It was observed that the frequency of sarcopenia was 33.3% (Graph 1).

Regarding the quality of life, in the Global Health domain there was an average of 64.2 ± 24.8%, for the Functional Capacity domain there was an average of 66.1 ± 22.1% and for the Symptoms domain, there was an average of 32, 1 ± 32.1% (Table 2).

Regarding the handgrip strength in the right and left hands, women had greater strength in the right hand, with an average of 18.8 ± 32.1% (Table 3).

Among the variables in the quality of life questionnaire, there was no significant correlation with handgrip strength (Table 4).

Sarcopenic women had the lowest EORTC QLQ-C30 score for the Global Health domain (58.3), Functional domain (63.0) and Symptoms (37.9). However, this correlation was not significant ($p > 0.05$) (Figure 1).

Discussion

In this study, women over 33 years of age, of non-white race, complete high school, from the capital and low income prevailed. Regarding cancer treatment, it was divided into surgical, chemotherapy and radiotherapy. The prevalence of sarcopenia was present in at least one-third of those evaluated, with low handgrip strength being used as a diagnostic criterion for sarcopenia.

Regarding the EORTC-QLQC30 questionnaire, the higher the score for the Global Health and Functional Capacity domains, the better the quality of life. However, for the Symptoms domain the opposite occurs, the lower the score, the higher the quality of life.

Therefore, based on the domains of this questionnaire, women with and without sarcopenia have a good quality of life, highlighting a higher score for Functional Capacity.

In this study, women with sarcopenia had a lower score for the Global Health and Functional Capacity domains when compared to non-sarcopenic women. And for the Symptoms domain, sarcopenic women had a higher score when compared to non-sarcopenic women. These findings may be a reflection of decreased muscle strength, less independence and lower quality of life.

No studies were found in the literature that associated quality of life and cervical cancer in sarcopenic patients. However, a similar study, which analyzed the association of sarcopenia with quality of life in patients with advanced cancer in palliative care, demonstrated a significant association ($p < 0.05$) between sarcopenia and lower quality of life and a prevalence of 32, 4% of sarcopenia among those evaluated. This finding was similar to that of this study, which obtained a prevalence of 33.3% of this pathology. The mentioned study was carried out with 210 volunteers, both sexes, age> 20 years and the variables of low mass and muscle strength were used to classify sarcopenia (12).

The present study has some limitations. Firstly, the sample size is small to obtain a good association between sarcopenic and non-sarcopenic patients, which may explain the lack of statistically significant associations. Second, for the classification of sarcopenia, only one variable, the handgrip strength, was taken into account, and the amount of muscle mass was not analyzed, a variable also used to confirm this diagnosis.

However, muscle strength is a better predictor of adverse results than muscle mass and, according to the European consensus on Sarcopenia, the use of handgrip strength is recommended as the main criterion for assessing evidence of sarcopenia (13).

Handgrip strength is a variable that is easy to measure and low cost and can be adopted as a measure within nutritional screening. Also, the work of the multidisciplinary team is essential in the diagnosis, consisting of a nutritionist, physiotherapist, doctor, psychologist, among others. The combination of different therapies will contribute to increasing the patient's energy consumption and protein stimulation, through food, physical exercises and medications, such as anabolic and anti-inflammatory agents, if necessary. The work of the psychologist, in turn, is fundamental to ensure greater patient compliance with treatment.

In this context, the findings of the present study reinforce the importance of an adequate and early therapeutic intervention, to reduce the negative impacts of cancer treatment and provide a better quality of life for patients (13).

Conclusion

It was found that the sample of this study did not generate statistically significant results to affirm that there is such an association. However, we observed that sarcopenic women had lower scores in the domains of quality of life questionnaires, demonstrating the lower quality of life when compared to non-sarcopenic women.

Thus, it is worth highlighting the importance of early nutritional screening for the prevention of sarcopenia, since the loss of muscle mass and strength may be related to a lower quality of life. In conclusion, the treatment of cancer-related sarcopenia requires trained professionals and represents a challenge for the multidisciplinary team, since combined multimodal approaches are essential for successful treatment.

Therefore, further studies are needed to address the association of sarcopenia and quality of life in cancer patients, as well as the development of more specific protocols for the risk, diagnosis and treatment of sarcopenia.

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Tables

Table 1. Sample and clinical characterization of women with and without Sarcopenia seen at a high complexity hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Variables	n	%
Age (years)		
22 a 32	2	7.4
33 a 43	18	66.7
44 a 53	7	25.9
Md±DP (years)	40.2±7.1	
Breed		
White	10	37.0
Not white	17	63.0
Education		
Incom. Elementary.	8	29.6
School		
Comp. Primary	4	14.8
Education.		
Comp. High. School	13	48.1
Uneducated	2	7.4
Place of origin		
Capital	15	55.6
Inland	11	40.7
Others	1	3.7
CCEB[1]		
Class C	10	37.0
Class D	15	55.6
Class E	2	7.4
Chemotherapy		
Yes	12	44.4
Not	15	55.6
Radiotherapy		
Yes	5	18.5
Not	22	81.5
Surgery		
Yes	3	11.1
Not	24	88.9
Total	27	100.0

[1]Criteria of Economic Classification Brazil.

Table 2. Quality of life (EORTC QLQ – C30) of women with and without Sarcopenia seen at a highly complex hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Scales	Average±Standard deviation	Median	Minimum – Maximum
Global Health	64.2±24.8	66.7	(0.0 – 100.0)
Functional Capacity	66.1±22.1	68.9	(28.9 – 97.8)
Symptoms	32.1±20.5	30.8	(0.0 – 71.8)

Table 3. Right and Left Palmar Grip Strength of women with and without Sarcopenia seen at a highly complex hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Variables	Average±Standard deviation	Median	(Minimum – Maximum)
FPPD[1]	18.8±6.1	19.5	(1.9 – 30.2)
FPPE[2]	16.8±3.8	16.8	(8.2 – 23.5)

[1] Palmar Grip Force - Right Hand; [2]Palmar Grip Force - Left Hand.

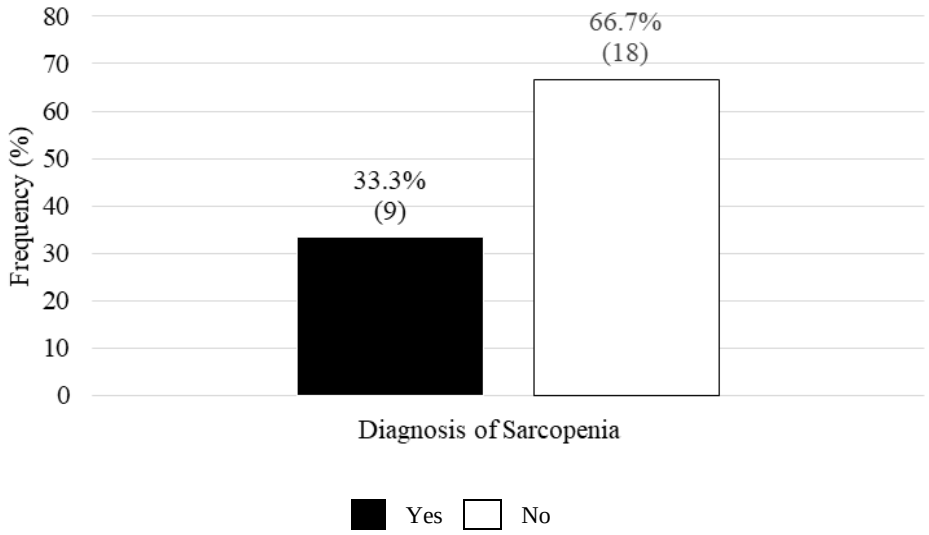
Table 4. Linear correlation between Quality of life (EORTC QLQ – C30) and Right and Left Palmar Grip Strength of women with and without Sarcopenia seen at a highly complex hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Scales	FPPD[1]	FPPE[2]
Global Health		
r*	0.30	0.07
Valor de p	0.127	0.720
Functional		
r**	0.18	0.06
Valor de p	0.357	0.750
Symptoms		
r**	-0.23	-0.13
Valor de p	0.250	0.528

[1] Palmar Grip Force - Right Hand; [2]Palmar Grip Force - Left Hand.; * Spearman Linear Correlation; ** Pearson's Linear Correlation.

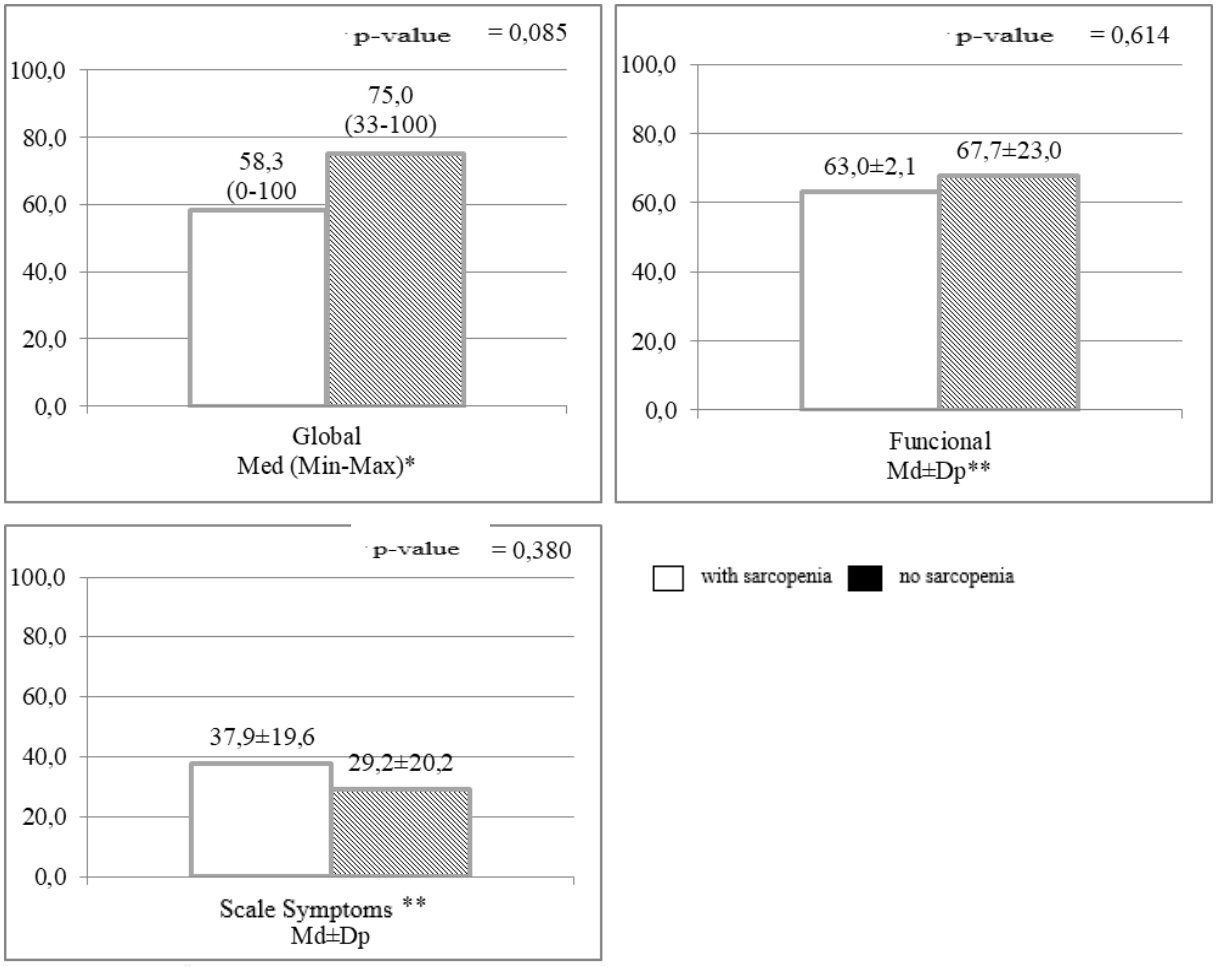
Graphs

Graph 1. Presence of Sarcopenia in women treated at a hospital of high complexity in oncology. São Luís, Maranhão, Brazil, 2020.



Figures

Figure 1. Relationship between Quality of life (EORTC QLQ – C30) and the presence of Sarcopenia in women treated at a hospital of high complexity in oncology. São Luís, Maranhão, Brazil, 2020.



* Mann Whitney test; ** Student's t-test.

NORMAS DO PERIÓDICO: Quality of Life Research

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Binge Eating Disorder is the most common eating disorder. Still, this disorder is often not addressed by the health care system, and current treatment shows poor results on a large group of these patients. Difficulties in relating to own body are linked to the development and maintenance of eating disorders in previous research and seem to influence treatment results and the risk of relapse. Basic Body Awareness Therapy is a psychomotor physiotherapeutic treatment addressing the relation to one's own body. In this study, we have explored in-depth the experiences of two patients with Binge Eating Disorder during their treatment-process with Basic Body Awareness Therapy. This study indicates that changes in how these patients related to their own bodies during the treatment processes were meaningful to them and implied a movement toward well-being and accepting one's own body. Findings from this study inspire more research on body awareness raising approaches in the treatment of patients with Binge Eating Disorder.

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Trial registration number, date of registration followed by “retrospectively registered”

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2. This result was later contradicted by Becker and Seligman [5].

3. This effect has been widely studied [1-3, 7].

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Periódico: Nutrition In Clinical Practice (Norma após o Capítulo VI)

Classificação Qualis-Periódico: B1

Área: Medicina I

Fator de Impacto: 2.401

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Capítulo IV – Food Consumption for Muscle Synthesis (Protein, Calcium and Vitamin D): a study of association with muscle reserve and functional capacity in women with cervical cancer

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ABSTRACT

Background: Cancer is a main public health problem worldwide, with the cervical type being one of the most common types. This neoplasm is the most frequent disease in Maranhão. The

treatment and the tumor itself contribute to changes in body composition, metabolic and functional capacity. The objective of the study was to compare the adequacy of food consumption of nutrients for muscle synthesis (protein, vitamin D and calcium) and in the improvements in muscle reserve and functional capacity in women with cervical cancer. **Methods**: Cross-sectional analytical research with secondary data collection was carried out from July to September 2019 at the Aldenora Bello Câncer Hospital. Participated in the research women with cervical cancer at least 20 years old, excluding restricted vegetarian women and in palliative care. Anthropometric, sociodemographic, food consumption and functional capacity data were collected. Data analysis was performed using the Shapiro-Wilk test and Spearman's Linear Correlation. The data were analyzed using the statistical program SPSS 21.0® at a maximum significance level of 5.0%. **Results**: There was an average protein consumption of 62.6±16.4 g/day, calcium of 461.8±232.1 mg/day, vitamin D of 3.3±3.1 mcg/day. The estimated lean mass was 21.3±8.4 kg (34.3±11.9%) and the distance covered in the walking test was 346.3±77.6 m. The relation between the distance covered and vitamin D was statistically significant. **Conclusion**: Even with the consumption below the expected, vitamin D was significant concerning the distance covered. Further studies on the subject are needed to make treatment more efficient.

Key-words: Cervical cancer. Food consumption. Nutritional status.

Declaration of Conflicting Interests

The Author(s) declare(s) that there is no conflict of interest

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Trial Number: U1111-1195-5621

Introduction

Malignant neoplasm or cancer is a disease characterized by the cells' disorderly development that invades tissues and organs and can extend to other regions of the body. The

presence of the disease is mostly influenced by external factors, including excessive exposure to the sun, obesity, smoking, lifestyle, or internal factors resulting from events that generate changes in the genetic material of cells (1,2).

Cancer has become a major public health problem worldwide, corresponding to the second leading cause of death worldwide. Estimates point to the existence of approximately 625 thousand new cases of cancer between the years 2020 and 2022 in Brazil, comprising any primary tumor location, gender or age (1,2).

In the North, Northeast and Midwest regions, cervical cancer is one of the most incident types, except for non-melanoma skin tumors (1). The occurrence of this type of cancer becomes more evident in women between 40 and 50 years of age (3). In Maranhão, cervical cancer appears with the highest incidence of cases, followed by breast cancer (4).

Cervical cancer is caused by persistent infection by some oncogenic types of Human Papillomavirus, being one of the most recurrent tumors in women. Infection with this virus can result in intraepithelial changes that are likely to become an invasive process. The manifestation of these changes is easily diagnosed through the test known as Papanicolau, making it essential to frequent this test (5-7).

Treatment consists of chemotherapy, surgery and radiotherapy and can be used together, but in this type of cancer, brachytherapy radiotherapy is the most used (1,5). Antitumor therapy can bring side effects that contribute to the modification of body composition, leading the patient to loss of fat and muscle reserve, in addition to functional and metabolic changes that increase their nutritional risk (1,8).

The tumor itself is capable of producing factors such as the proteolysis-inducing factor that induces degradation and inhibition of protein synthesis in skeletal musculature and lipid mobilization factor, that act directly on adipose tissue, as well as it produces an increase in

pro-inflammatory cytokines that stimulate anorexigenic receptors and inhibit orexigenic receptors causing muscle and fat loss (9,10).

Dietary proteins are fundamental components in the process of muscle mass formation and regeneration. In the natural aging process, there is an inadequate protein supply that can lead to a reduction in lean mass and, consequently, functional capacity, leaving the patient more susceptible to weakness and difficulty in performing basic activities (10,11). Thus, by increasing the frequency and load of patients' physical activity, there is an increase in the anabolic effect of amino acids and some nutrients, such as vitamin D in protein synthesis (12).

Vitamin D, in turn, when at normal levels (> 20 ng/mL) appears to have a favorable decrease in the cascade of prostaglandins associated with cancer. As for its function, it participates in the homeostasis of calcium and phosphorus, in addition to acting on the balance of parathormone which normally improves insulin sensitivity, favoring muscle synthesis and physical performance, that is, everything indicates that its deficient plasma level is associated with functional limitations (11-14).

Calcium is a mineral that makes up the skeleton, being essential in several physiological processes including muscle contraction. Its daily intake is around 1000mg, which may vary according to the body's needs (15). As well as proteins and vitamin D, in the course of age, there is a change in its metabolism leaving the patient more prone to fractures and muscle weakness, requiring an increase in the intake of this mineral (11,16).

Protein, calcium and vitamin D when properly ingested can positively affect health, resulting in the prevention of fractures and attenuation of muscle mass losses, making the patient more capable of performing basic activities (11,12). Thus, this study is necessary, as it may elucidate the association between adequate consumption of these nutrients concerning the muscle synthesis and functional capacity in women with this condition.

This study sought to associate the adequacy of food consumption of nutrients for muscle synthesis (protein, calcium and vitamin D) and improvements in muscle reserve and functional capacity in women with cervical cancer.

Methods

This was a cross-sectional analytical study with secondary data collection carried out from July to September 2019 at the Unified Health System outpatient clinic of the Hospital do Câncer Aldenora Bello, a reference hospital in oncology in the State of Maranhão with outpatient care, hospitalization, equipped with ICU, surgical beds, containing stretchers and individual offices.

The study was duly evaluated by the Research Ethics Committee of the CEUMA University, as recommended by Resolution No. 466 of December 12, 2012, of the National Health Council, under protocol number 3.659.493 and registered in the Brazilian Registry of Clinical Trials (REBEC) and Universal Trial Number U1111-1195-5621.

Participated in this study women with cervical cancer aged at least 20 years and who did not oppose signing the informed consent form. This sample excluded women who were not able to perform electrical bioimpedance, restricted vegetarian women in palliative care and who withdrew their consent.

The data collection instrument used was a pre-prepared questionnaire, which was included in the data collection form. The clinical, anthropometric and sociodemographic data of the patients were evaluated. The questionnaires and data collection were carried out by trained researchers.

Regarding anthropometric data, weight and height were analyzed with the aid of a digital platform scale with a coupled stadiometer (Filizola®), containing a maximum capacity

of 150 kg and graduation of 100 g. The patients were in the center of the equipment, with as little clothing as possible, barefoot, erect, with their feet together, arms extended along with their bodies and keeping their eyes fixed on the horizon (17).

Using a stadiometer attached to the Filizola® scale (São Paulo, BRA) with an accuracy of 0.50 cm, height was assessed and the patients were standing upright, arms extended along the body, head up, looking at a fixed point. The heels, calves, buttocks, scapulae and back of the head were leaning against the stadiometer with the feet forming a right angle with the legs (17).

For the analysis of body composition was used tetrapolar electrical bioimpedance (Biodynamics®). The patient needed to be supine at rest for at least 10 minutes before the exam, barefoot, with the lower limbs apart. The patients were instructed to remain at rest and not to practice physical activity until 8 hours before the exam, to remove all metal objects that were close to the body, in addition to suspending the use of diuretic medications at least 24 hours before the test was performed. . Patients were advised to avoid the consumption of food and drinks until 4 hours before the test. The electrodes were positioned similarly (18).

To assess functional capacity, it was necessary to use the six-minute walk test (6 MWT) applied by a properly trained professional, the patient needed to wear comfortable shoes and clothes, and in addition to being informed that the test would be performed twice with 15 minutes of walking. rest between them. It is a simple test, performed in a corridor of at least 30 meters, with no circulation of people and with a flat surface, according to the guidelines of the American Thoracic Society (19), as well as the standardization for the Brazilian population (20).

Before and after the test, blood pressure, peripheral oxygen saturation, heart rate and finally the level of dyspnea and tiredness in the lower limbs in minutes two, four and six (21).

The measurement of diastolic and systolic pressure was evaluated according to the recommendations of the VI Brazilian Guideline for Hypertension (22), the Littmann® stethoscope (Saint Paul, USA) and mercury column sphygmomanometer were used.

Data on food consumption were also investigated, through the 24 Hour Recall (24HR) on a specific form, the patient needed to be asked about her food in the last 24 hours regarding breakfast, breakfast, lunch, snack, dinner and supper. To help with this data collection, it was necessary to use a photo album with standardized homemade measures (23). After the collection of this information, it was transferred to the WebDiet® software where the calculation of the nutritional composition was performed, for which the 24HR evaluated in the software was the average of four 24HR applied every 15 days.

To obtain the economic classification was applied leaderboard specified in the Brazil Economic Classification Criterion (24). After these questions, the points were added and classified according to the score obtained, which may be: A1, A2, B1, B2, C1, C2, D and E.

The data were tabulated in Microsoft Office Excel® and analyzed using the statistical program SPSS 21.0®. For the analysis of the results, the numerical variables were presented as mean, standard deviation, median and minimum and maximum values and the categorical variables in absolute (n) and relative frequencies (%). Normality was verified using the Shapiro-Wilk test. Spearman's Linear Correlation was applied to correlate the marl mass (Kg and %) and distance covered (m) with protein (g), calcium (mg) and vitamin D (mcg).

Differences between groups were considered significant when $p < 0.05$.

Results

Of the 16 evaluated women, 50.0% were between 31 and 37 years old and 50.0% were between 38 and 45 years old. The mean age corresponded to 38.0±3.8 years. Among these, 11

women (68.8%) were non-white, 9 had completed high school (56.3%) and 75.0% were from the capital of the state (Table 1).

According to the economic classification criteria in Brazil, 50.0% of women are in class D. As for cancer treatment, 68.8% did not chemotherapy and 81.3% did not radiotherapy and surgery, each one (Table 1).

As for the consumption of nutrients, it was observed that the average consumption of proteins was 62.6±16.4 g/day, calcium was 461.8±232.1 mg/day, vitamin D was 3.3±3.1 mg/day (Table 2).

It was observed that the average lean mass was 21.3±8.4 kg (34.3±11.9%) and the distance covered in the six-minute walk test was 346.3±77.6 m (Table 3).

Among the variables compared to the consumption of nutrients for muscle synthesis, the distance traveled to vitamin D was inverse and statistically significant ($p < 0.05$) (moderate correlation: $0.5 \leq |r| < 0.7$) (Table 4 and Figure 1).

There was a moderate, inverse and statistically significant correlation between distance covered and vitamin D. It was also observed that there was no significance ($p < 0.05$) between distance covered and the nutrients protein and calcium (Figure 1).

Discussion

In this research, there was a higher frequency of non-white women, complete high school, coming from the capital and low income. As for cancer treatment, it was divided into chemotherapy, radiotherapy and surgery, with chemotherapy being the most used.

It is known that cancer patients, depending on the type, treatment, among others, require greater nutritional support, especially for protein, as this nutrient will contribute to the maintenance of lean mass. The Brazilian Guideline for Nutritional Therapy in Oncology

recommends protein intake for adult and elderly patients undergoing antineoplastic treatment and patients with obesity ranging from 1.2 to 1.5 g/kg/day (25).

Considering this parameter, it was observed that the protein consumption of the studied patients is adequate since the average value found was higher than the minimum value. Capelari and Ceni (26) in their study with cancer patients on chemotherapy treatment observed protein consumption below the recommended. In Souza et al. (27) a protein value was found within the recommended parameters. The mentioned study was carried out with 50 cancer patients, both sexes, age above 18 years old and the nutritional status, food consumption and functional capacity.

It is known that when the average protein consumption is below expectations, the protein intake is probably in deficit, this will be able to prevent these patients from being able to maintain or recover lean mass and end up losing muscle mass. And offering the amount of protein properly can compensate for its loss linked to inflammatory conditions, such as pro-inflammatory cytokines and catabolic conditions, for example, the proteolysis inducing factor and the lipid mobilization factor due to cancer itself (10,25).

In assessing calcium intake, inadequacy was observed. Likewise, Souza et al. (27) and Tartari et al. (28) found values below the recommended dietary intake (DRI), the first being similar to the present study and the second with slightly higher values. The values in the second study may have been higher due to the studied sample, the inclusion of both sexes and the type and time of cancer treatment.

Calcium is a very important mineral in our body because it participates in physiological processes, such as heart rate regulation and muscle contraction, but some factors, for example, anti-tumor treatment and even skipping meals can interfere with the absorption of this mineral. Buzzinaro et al. (29) in their review study point to the idea that

there is no positive association between the intake of dietary protein and calcium. In the same study, the positive relationship between protein intake and hip fracture is highlighted, due to the worsening of calcium metabolism. It is evident that the consumption of protein far beyond what the individual needs can affect, together with an increase in pro-inflammatory cytokines and anti-tumor treatment, the metabolism of other nutrients.

The value found for vitamin D is also below the recommendations. This vitamin has several functions in our body, because of the presence of the nuclear receptor (30) and with that, it must remain at normal levels. But for these levels to remain adequate, it is important to have control over the amount of source food that is eaten and the sun exposure.

Oliveira et al. (13) point out that vitamin D deficiency has been associated with health problems, including various types of cancer, autoimmune and metabolic diseases. There are mechanisms by which vitamin D can affect insulin sensitivity. Since this sensitivity is decreased it means that there is an increase in parathyroid hormone concentrations.

This parathyroid hormone affects insulin sensitivity by regulating the concentrations of free calcium present in the target cells. Vitamin D and parathyroid hormone have been linked to rapid signaling pathways including muscle cells, in addition to attenuating the expression of pro-inflammatory cytokines involved in insulin resistance (13).

If the parathyroid hormone is normal, insulin sensitivity will improve and will end up favoring muscle synthesis and physical performance, but for this to happen, the mineral calcium must be at normal levels along with protein intake. This favoring of muscle synthesis and physical performance is because physical exercise will increase the uptake of glucose in skeletal muscle (13,31).

Pedrosa and Castro (32) attest that the effects of vitamin D deficiency or insufficiency on the parameters of neuromuscular function have gained even more attention

from some researchers, especially in the elderly. Other effects of this vitamin on skeletal muscle cells are related to metabolism and protein synthesis. Myopathy caused by vitamin D deficiency manifests itself in a specific clinical picture of diffuse muscle pain and weakness of the proximal muscles, causing difficulties in gait and basic daily activities.

Still, in the same study, the authors state that vitamin D, through its actions on the regulation of calcium transport, protein synthesis and kinetics of contraction, is necessary to maintain the mass, strength and speed of contraction of skeletal muscle. And parallel to that, there are the elderly and people with some conditions that constantly present an attenuation of muscle mass caused by a reduction in the size and number of muscle fibers. Related to this loss there is also a decrease in muscle strength, which harms the functional capacity (32).

Regarding lean mass and the distance covered in the six-minute walk test, it was observed that lean mass was above the minimum value, assuming that it is adequate. But according to the guideline for the six-minute walk test while there is no more research related to this topic, the recommendation is that the value is expressed in absolute value, that is, the total distance the patient was able to walk during the test. However, Enright (33) in his study states that the distance covered can vary from 400 to 700 meters, however, it is emphasized that these values are for healthy people, differently from the population under study in this research (oncology population).

Still about the distance covered, this study observed a moderate ($0.5 \leq |r| < 0.7$), inverse (-r) and statistically significant ($p < 0.05$) correlation between this variable and the consumption of vitamin D, despite its present inadequate average consumption. This study also observed that there was no significance ($p > 0.05$) between the distance covered and the other nutrients (protein and calcium).

The disuse of skeletal muscles leads to muscle atrophy, which can lead to physical disability. Thus, a combination of resistance training and adequate intake of pro-synthesized nutrients becomes an alternative treatment to improve the prognosis of these women, as it stimulates the physical conditioning of patients, helping to decrease the loss of lean mass (34).

In this context, we emphasize that the literature points out that when protein, calcium and vitamin D are taken properly can positively affect health, thus being able to result in fracture prevention and attenuation of muscle mass losses, causing that the patient has a greater capacity to perform basic activities (11,12).

It is worth mentioning that, in the present study, there may have been limitations regarding the size of the sample used and the data regarding food consumption, as these were based on information provided by the patient himself, which may lead to memory bias because they are information related to the past.

Given these results, it is recommended that intervention studies or even cross-sectional studies be carried out since the market already has products available for sale, which contain the three nutrients studied here. This theme could become a promising focus of research that will facilitate nutritional therapy in cancer patients and patients with fragility syndrome (sarcopenia).

Conclusion

There was a statistically significant correlation only for distance traveled and consumption of vitamin D, even though the average intake of this vitamin was below the recommended value.

Thus, the importance of an increase in calcium and vitamin D intake and stability in protein consumption stands out, as these three nutrients consumed in a balanced way, may

have a positive effect on functional capacity and muscle reserve. Allied to this nutritional balance there is resistance training as a strategy to improve and strengthen the muscle reserve. Besides, food supplements that contain the majority of the three nutrients in their composition can be offered according to the needs and possibilities of each patient.

There is a need for more intervention or even cross-sectional studies that address this issue so that the care for these patients is even more specific and reduces the chance of a deficiency of pro-synthetic nutrients and muscle depletion, in addition to the loss of capacity to perform basic daily activities.

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Tables

Table 1. Clinical and sample characterization of women seen at a high complexity hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Variables	n	%
Age (years)		
31 to 37	8	50.0
38 to 45	8	50.0
Mean ± SD (years)		38.0 ± 3.8
Breed		
White	5	31.3
Not white	11	68.8
Education		
Incomplete primary education	3	18.8
Complete primary education	3	18.8
Complete high school	9	56.3
Without instruction	1	6.3
Origin		
Capital of the state	12	75.0
Other	4	25.0
CCEB[a]		
Class C	7	43.8
Class D	8	50.0
Class E	1	6.3
Chemotherapy		
Yes	5	31.3
Not	11	68.8
Radiotherapy		
Yes	3	18.8
Not	13	81.3
Surgery		
Yes	3	18.8
Not	13	81.3
Total	16	100.0

[a]Criteria of Economic Classification Brazil.

Table 2. Consumption of nutrients for muscle synthesis in women treated at a referral hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Nutrients	Average±Standard deviation	Median	(Minimum – Maximum)
Protein (g / day)	62.6±16.4	55.4	(41.4 – 100.1)
Calcium (mg / day)	461.8±232.1	447.0	(50.0 – 982.0)
Vitamin D (mcg / day)	3.3±3.1	2.0	(1.0 – 12.0)

Table 3. Lean mass and distance covered by women treated at a high complexity hospital in oncology. São Luís, Maranhão, Brazil, 2020.

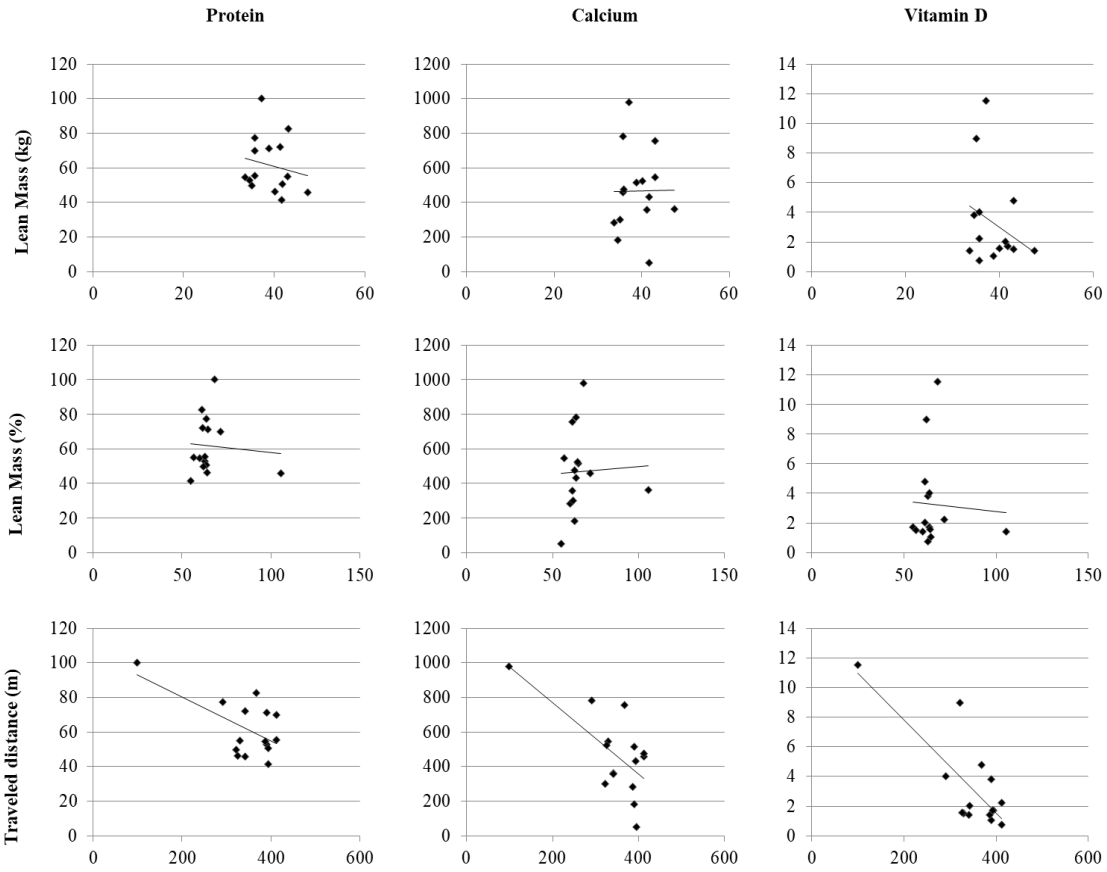
Variables	Average±Standard deviation	Median	(Minimum – Maximum)
Lean mass (Kg)	21.3±8.4	21.0	(-2.0 – 34.0)
Lean mass (%)	34.3±11.9	37.0	(-6.0 – 45.0)
Distance traveled (m)	346.3±77.6	368.0	(99.0 – 412.0)

Table 4. Spearman's linear correlation between consumption of nutrients for muscle synthesis and lean mass and distance covered by women treated at a referral hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Variables		Protein	Calcium	Vitamin D
Lean mass (kg)	r	-0.11	0.24	-0.14
	p value	0.685	0.398	0.624
Lean mass (%)	r	0,04	0.34	-0.1
	p value	0.991	0.192	0.707
Distance traveled (m)	r	-0.20	-0.46	-0.51
	p value	0.47	0.081	*0.049**

*Significant correlation.

Graph 1 . Dispersion between consumption of nutrients for muscle synthesis and lean mass and distance covered by women treated at a high complexity hospital in oncology. São Luís, Maranhão, Brazil, 2020.



4.5 Capítulo V – Associação do consumo de proteína por refeição com a força muscular e qualidade de vida em pacientes com câncer de colo uterino

Periódico: Nutrition In Clinical Practice (Norma após o Capítulo VI)

Classificação Qualis-Periódico: B1

Área: Medicina I

Fator de Impacto: 2.401

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Capítulo V – Association of protein consumption per meal with muscle strength and quality of life in patients with cervical cancer

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Abstract

Introduction: Inadequate food intake of protein causes significant impacts on the quality of life of individuals with cancer, resulting in physical and psychological changes such as anorexia, changes in taste, smell, dysphagia, nausea, and vomiting. The assessment of insufficient protein intake is necessary, as it is the main characteristic of malnutrition associated with cancer. **Objective:** To analyze the protein consumption per meal and its association with muscle strength and quality of life of patients. **Material and Method:** A cross-sectional analytical study was carried out with secondary data collection, conducted from August 2020 to October 2020 at Hospital do Câncer Aldenora Bello. With female sex patients diagnosed with cervical cancer, with minimal age of 20 years, with no changes in the therapeutic regimen in the last 6 weeks or hospitalizations in the last three months) and has signed the Conscentimento Term of Free Informed - IC. Data were collected through the quality of life questionnaires: EORTC QLQ –C30, 24-hour recorder, and muscle strength were analyzed using the dynamometer. Data analysis was performed using the Shapiro-Wilk

test and Pearson's Linear Correlation. The data were analyzed using the SPSS 21® statistical program at a significance level of 5%. **Results:** The protein consumption of lunch and dinner reached the target of 20 to 30g per meal for cancer patients with sarcopenia. Regarding the quality of life values indicate the satisfactory quality of life of patients evaluated regularly. There were no statistically significant correlations ($p > 0.05$) between Quality of life and protein consumption, however, there was an inverse and statistically significant ($p < 0.05$) and moderate ($| 0.3 | < r \leq | 0.6 |$) between right FPP and snack and left FPP and breakfast, respectively. **Conclusion:** Therefore, protein consumption per meal with handgrip strength had a significant correlation both at breakfast and at lunch concerning the quality of life.

Keywords: Cervical Cancer. Daily Intake Reference. Protein malnutrition. Quality of life.

Conflict of interests

We certify that there is no actual or potential conflict of interest related to this article.

Financing

Foundation for the Support of Research and Scientific Development of Maranhão (FAPEMA).

Introduction

Cervical cancer is one of the most frequent tumors in the female population, a neoplasm of slow evolution that initially presents small changes in cells and that if not treated at first evolve. It is caused by the persistent infection of some types of human papillomavirus (HPV), which to prevent infections is recommended to use a condom during sexual intercourse and without forgetting the Pap smear. The neoplasm also evolves due to some risk factors such as smoking, low socioeconomic status, and inadequate intimate hygiene [1].

Cancer ends up being a source of motivation for the individual to change their diet and change their lifestyle. Patients suffering from serious diseases such as cancer, usually have a variety of symptoms such as nausea, vomiting, diarrhea, constipation, food aversions, fatigue, dyspnoea, and pain, which can influence their daily lives [2, 3.]

According to the Brazilian Society of Parenteral and Enteral Nutrition (BRASPEN) [4,] a protein supply between 1.2 to 1.5g / kg/day is recommended for sarcopenic cancer patients. For patients with malnutrition, inflammation, insulin resistance, and physical inactivity present, a dose close to 2.0 g / kg/day is recommended to support protein balance. Individuals with normal renal function at a dose of 2.0g / kg/day are safe, whereas in

individuals with acute or chronic renal failure the protein supply cannot exceed 1.0 to 1.2g / kg/day. The above recommendations should be distributed throughout the day, respecting the amount of 20 to 30g of protein per meal.

Some evidence suggests that low muscle mass and the accumulation of adipose tissue in skeletal muscle are associated with muscle weakness. Thus contributing to the sensitivity and increased risk of limitations of the individual to move, being associated between the quantity and quality of skeletal muscle and decay of function in individuals with cancer, in which it is not fully understood [5].

However, the need arose in which it encouraged researchers to investigate the association of protein consumption per meal, quality of life, and muscle strength in cervical cancer patients. Thus, this study sought to analyze the patients' food consumption, classified the quality of life of those evaluated, their muscular strength was examined. associating them with protein consumption per meal.

Methods

A cross-sectional analytical study was carried out with secondary data collection. The place of study defined was the Cancer Hospital Aldenora Bello, a Center of High complexity in oncology that has a medical team working in all areas of oncology, together with a multi-professional team for better-integrated care to the patient.

175 hospitalization beds are available, divided between medical, surgical, pediatric wards, Intensive Care Units, apartments, and how treatment methods are available: radiotherapy, chemotherapy, and surgical intervention.

This study was based on the secondary data collection of the project entitled " *Combined Supplementation of Branched-Chain Amino Acids and Omega-3: clinical-nutritional, cardiorespiratory, metabolic impact and quality of life in pre-cachectic / cachectic patients* ", already approved by the Committee of Ethics in Research of the Federal University of Maranhão, with opinion: 1,627,928, and submitted and approved to the Brazilian Registry of Clinical Trial (REBEC), under the number UTN: U1111-1195-5621, respecting the ethical standards of the Resolution No. 466 of 12 December 2012 from the National Health Council [6.] Data collection started only after CEP approval. The objectives described in this research are included in the Umbrella Project criteria.

The studied population included female patients aged at least 20 years old, with a confirmed diagnosis of cervical cancer, users of the outpatient service of the Hospital do Câncer Aldenora Bello. The study sample was of the non-probabilistic type.

The study included women with a diagnosis of cervical cancer, at least 20 years old, no changes in the therapeutic regimen in the last 6 weeks or hospitalizations in the last 3

months, and the participant's consent through the Free and Informed Consent Form. Excluded from the study were women not diagnosed with cervical cancer, who had changes in the therapeutic regimen in the last 6 weeks or hospitalizations in the last 3 months, restricted vegetarians, who used a pacemaker, patients in palliative care or with metastasis, or even those that withdrew their consent to participate in the research.

The patients were initially approached and invited to participate in the research after signing the informed consent form, as soon as the research is accepted, the identification data (sex and age) of the patient were collected from a Data Collection Form developed by the researchers, as well as socioeconomic and demographic aspects (economic classification, education level, family income, etc.), clinical aspects (basic diagnosis, comorbidities, use of medications, etc.). The economic classification was defined based on the economic classification table, established under the Brazil Economic Classification Criterion [7].

The handgrip strength (FPP) was performed by a hydraulic dynamometer of the brand (Saehan), adopting the unit of measurement in kilograms (kg) [8.] For the measurement of PPF to be made, patients must sit in a chair without an arm keeping the spine erect, the knee must remain flexed at a 90 ° angle, the shoulder must be positioned in adduction and neutral rotation, the elbow flexed at 90º with the forearm in half pronation and neutral wrist, being able to move it up to 30 ° degrees of extension. The arm must remain suspended in the air with the hand positioned on the dynamometer, which is supported by the evaluator [9].

To assess food consumption, the 24-hour recall (RD24h) was applied, the schedule, the food, and drinks ate in the 24 hours were described, recalled by the study participants. The quantities of food consumed were estimated using homemade measures and food models were used to help estimate portions [10.]

Quality of life questionnaire was used EORTC QLQ-C30 from the European Organization for Research and Treatment of Cancer (EORTC) to assess the quality of life of patients globally, on symptoms perceived by them in the last seven days preceding the consultation using numerical scales with scores from 1 to 4, where 1 means not having felt the symptoms asked, 2 a little, 3 a lot, 4 a lot, and questions about the patient's perspective on her health using numeric scales from 1 to 7, where 1 is terrible and 7 is great [11, 12].

The data were tabulated in Microsoft Office Excel® and analyzed using the SPSS 21.0® statistical program. For the analysis of the results, the numerical variables were presented as mean, standard deviation, median and minimum, and maximum values, and the categorical variables in absolute (n) and relative (%) frequencies. Normality was verified using the Shapiro-Wilk test.

Pearson's Linear Correlation was applied to correlate Quality of Life (EORTC QLQ – C30) and Palmar Pressure Force (right and left) and Protein Consumption throughout the day.

Results

The sample consisted of 15 women. The age ranged from 31 to 45 years old, being from 31 to 38 years old 53.3% and from 39 to 45 years old 46.7%. More than 2/3 of the evaluated (66.7%) of the patients were not white, as for the origin, 73.3% were from the capital. Regarding education, 60% had high school and the economy class 53.3% were Class D (Table 1).

Table 2 shows the food intake of those evaluated, with a caloric consumption of 1304.7 ± 245.2kcal / day and a total protein of 61.4 ± 15.1g / day. In the analysis of protein consumption per meal, the following average consumption per meal was observed: breakfast 7.6 ± 3.0g / day, serving 1.2g / day, average lunch of 25.4 ± 7.2g / day, snack in the afternoon 4.0 ± 2.9g / day, dinner 21.0 ± 8.0g / day and at supper 2.4 ± 2.5g / day. Carbohydrate consumption was 176.7 ± 31.9 g / day whereas lipid consumption was 39.1 ± 15.4 g / day.

Table 3 shows the analysis of the quality of life of women attended, in which the Global Health Domain was 72.2 ± 24.3 points, in the Functional Domain it was 69.6 ± 22.2 points, and in the Symptoms Domain of 25, 5 ± 20.8 points.

Table 4 was analyzed the pressing force of the palm and evaluated patients were observed an average FPP in the right hand 20, 9 ± 4.8kg / F. since the test of FPP esquerda18,2 ± 3.0 Kg / F.

In Table 5, Pearson's linear correlation between the quality of life score (EORTC QLQ-C30), Palmar pressure strength (FPP), in the right and left hand with the total protein consumption and per meal of the women evaluated was analyzed. There were no statistically significant correlations ($p > 0.05$) between Quality of life and protein consumption, however, there was an inverse and statistically significant ($p < 0.05$) and moderate ($| 0.3 | < r \leq | 0.6 |$) between right FPP and snack and left FPP and breakfast, respectively.

Discussion

Regarding the sociodemographic findings, as shown in Table 1, the age group from 31 to 38 years old was the most expressive. In this age group, it is important to analyze the need for Pap tests, especially for the age group below 40 years, as some types of cancer start between 30 and 35 years [13].

The preeminence of the race / non-white color was similar to data from other studies such as the " *Profile of women with cervical cancer treated for treatment at an oncology center* ", where a higher frequency of 63.3% and 82 was found, 1% of non-white women in the existence of a diagnosis. Studies that show a higher prevalence of cervical cancer diagnosis in non-white women, being more frequent and in an advanced state [14].

Among the sociodemographic characteristics such as origin and education, these differ when compared to other studies. Thus, 73.3% are predominant in the state capital and 60% of them had completed high school and social class D presented the result of 53.3% of the evaluated women having the diagnosis. This shows that, even with several campaigns and public policies aimed at the female public, the number of women with this type of diagnosis continues to grow.

To investigate food consumption the 24-hour recall was used, in which the energy was 1304.7 ± 245.2 kcal/day. The total protein consumption was 61.4 ± 15.1 g / day. Since the protein consumption of lunch and dinner reached the target of 20 to 30g per meal for cancer patients, especially for those with sarcopenia, as recommended by the Brazilian Society of Parenteral and Enteral Nutrition [4] in its latest Nutritional Therapy Guidelines for cancer patients. This makes the result quite relevant since patients are at higher nutritional risk and are exposed to a greater risk of malnutrition and protein consumption aims to compensate for losses associated with cancer, maintaining or recovering lean mass. Since carbohydrate consumption was 176.7 ± 31.9 g / day, lipid consumption was 39.1 ± 15.4 g / day.

Regarding the quality of life of the women served, the Global Health Domain was 72.2 ± 24.3 points, in the Functional Domain it was 69.6 ± 22.2 points and in the Symptoms Domain 25, 5 ± 20.8 points, therefore, the values indicate the satisfactory regular quality of life of the patients evaluated. What according to BRASPEN [4] can relate the adequate caloric-protein consumption with a higher expectation of survival, guaranteeing a reduction in metabolic disorders and improving the maintenance of the quality of life.

The evaluation of muscle strength through the dynamometer showed mean values in the right hand of 20, 9 ± 4.8 kg / F. in the left FPP test18. 2 ± 3.0 kg / F. According to the study called " *Toxicity in patients with cancer in the gastrointestinal tract during chemotherapy: associations with sarcopenia and cachexia"*. The highest recorded value of the dominant arm was used as maximum muscle strength and the results obtained were compared with reference values according to the European Consensus (45) with a cut-off point for dinapenia < 20 kg for women [15.]

According to Pearson's linear correlation between the quality of life score (EORTC QLQ-C30), Palmar pressure strength (FPP) on the right and left hand with the total protein consumption and per meal of the women evaluated. There were no statistically significant correlations ($p > 0.05$) between Quality of life and protein consumption, however, there was

an inverse and statistically significant ($p < 0.05$) and moderate ($| 0.3 | < r \leq | 0.6 |$) between right FPP and snack and left FPP and breakfast, respectively.

Food consumption of protein per meal seems to directly influence palmar pressure strength according to data found in this study. Correlating thus the protein consumption with the muscular strength, being able even better the capacity of the individual to develop its daily activities if reached in other meals the recommended one since they are more susceptible individuals to risk of sarcopenia. According to BRASPEN, [4] doses should be distributed throughout the day, respecting the amount of 20 to 30g of protein per meal. Hyperprotein supplements can be used to supplement protein requirements.

This study has some limitations that can interfere with its results, such as the number of people in the sample was small so that the results were not expressive and significant in the research, difficulty in finding studies related or similar to the research developed in this study. Despite its limitations, there are no studies that make this type of association of protein consumption per meal with these variables in cancer patients, which makes it possible to prepare other articles as it draws attention to a theme that has not yet been discussed, such as encouraging research associated with the assessment of consumption. of protein and improves the quality of life of patients.

Conclusion

Protein consumption per meal had a significant correlation both in breakfast and in the snack with handgrip strength. Regarding the quality of life, which had no significant correlation, since if protein consumption were better, these results could be better used, consequently with a better quality of life for the women evaluated.

Revealing that food consumption of protein in adequate quantity and distribution, it is necessary to maintain or recover lean mass since its supply can compensate for losses associated with cancer since this public is often exposed to a greater risk of malnutrition due to both presence of the disease and the proposed treatments. In other words, the greater the nutritional deficit, the greater the reduction in response to treatment, with a consequent deterioration in the quality of life and the clinical outcome, among other associated factors. The protein deficit, in addition to causing muscle loss, also presents increased morbidity and mortality, physical disability, and decreased immunity, among other factors.

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Tables

Table 1. Sociodemographic and clinical characterization of women seen at a hospital of high complexity in oncology. São Luís, Maranhão, 2020.

Variables	n	%
Age years)		
31 to 38	8	53.3
39 to 45	7	46.7
Md ± Dp		37.9 ± 3.95
Breed		
White	5	33.3
Not white	10	66.7
Origin		
capital	11	73.3
Interior	4	26.7
Education		
Without instruction	1	6.7
Nurse. Fund. Incomp.	3	20.0
Nurse. Fund. Comp.	two	13.3
Ens. Medium Length	9	60.0
Economic class		
Class C	6	40.0
Class D	8	53.3
Class E	1	6.7
Diagnosis		
CA Uterine Cervix	11	73.3
CA Cervix EC IIIb	two	13.3
CA Uterine Cervix w / Invasive Injury	1	6.7
Epidermoid Carcinoma	1	6.7
Adenocarcinoma		
Total	15	100.0

Table 2. Food consumption of women treated at a hospital of high complexity in oncology. São Luís, Maranhão, Brazil, 2020.

Food Consumption	Average	Standard deviation	Median	Minimum	Maximum
Energy (Cal / day)	1304.7	245.2	1342.7	845.3	1713.7
Protein per meal (g / day)					
Breakfast	7.6	3.0	8.3	1.9	12.1
Collation	1.2	1.8	0.5	0.0	6.1
Lunch	25.4 *	7.2	24.5	16.4	41.7
Snack	4.0	2.9	3.2	0.1	9.0
Dinner	21.0 *	8.0	18.5	8.1	37.0
Supper	2.4	2.5	1.6	0.0	6.8
Total	61.4	15.1	59.2	42.0	97.9
Carbohydrate (g)	176.7	31.9	182.0	125.5	241.6
Lipids (g)	39.1	15.4	35.7	19.2	63.6

Table 3. Quality of life (EORTC QLQ - C30) of women treated at a hospital of high complexity in oncology. São Luís, Maranhão, Brazil, 2020.

Quality of Life (EORTC QLQ - 30)	Average	Standard deviation	Median	Minimum	Maximum
Global	72.2	24.3	75.0	16.7	100.0
Functional	69.6	22.2	73.3	28.9	95.6
Symptoms	25.5	20.8	23.1	0.0	71.8

Table 4. Palmar pressure strength of women treated at a hospital of high complexity in oncology. São Luís, Maranhão, Brazil, 2020.

Palmar pressure force	Average	Standard deviation	Median	Minimum	Maximum
FPP[1] Right	20.9	4.8	21.3	11.5	30.2
FPP[1] Left	18.2	3.0	18.8	12.5	23.5

[1] Palmar Pressure Force.

Table 5. Pearson's Linear Correlation between Quality of life (EORTC QLQ - C30), Palmar Pressure Force (right and left) and Protein consumption throughout the day by women treated at a highly complex hospital in oncology. São Luís, Maranhão, Brazil, 2020.

Variables	Protein						
	Breakfast	Collation	Lunch	Snack	Dinner	Supper	Total
Global							
r	0.134	-0.122	-0.052	0.172	0.004	-0.131	-0.023
p-value	0.634	0.666	0.854	0.541	0.989	0.641	0.935
Functional							
r	0.344	-0.280	0.085	0.099	-0.093	-0.095	0.011
p-value	0.210	0.313	0.764	0.726	0.742	0.737	0.970
Symptoms							
r	-0.407	0.181	0.013	-0.086	-0.016	0.037	-0.049
p-value	0.132	0.519	0.962	0.759	0.956	0.896	0.863
FPP[1] Right							
r	-0.255	-0.089	0.337	-0.527	-0.102	-0.223	-0.070
p-value	0.360	0.753	0.220	0.044 *	0.717	0.425	0.805
FPP[1] Left							
r	-0.599	0.314	0.063	-0.446	-0.164	0.079	-0.208
p-value	0.018 *	0.254	0.823	0.096	0.559	0.780	0.456

[1] Palmar Pressure Force ; * Significant correlation.

NORMAS DO PERIÓDICO: Nutrition in Clinical Practice

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Tables

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- Tables should not contain parts. For example, Table 1a, 1b should be renumbered as Table 1 and Table 2.
- Each table column should have its own unique header.
- Every table number must be mentioned in the text, eg, "as shown in Table 1" or, after referring to content in the table, you could add "(Table 2)".
- Abbreviations used in tables should be defined in a list after the table and formatted as follows (in alphabetical order): BMI, body mass index; ICU, intensive care unit…

Figures and Illustrations

- Figures should be submitted as separate files and should not be embedded in the main document.
- Figure captions should be listed in order at the end of the main document; figure numbers/captions should not be included on the actual figure files. Legends for Illustrations: Double-space captions and be brief (maximum 40 words). Indicate magnification and stain used for photomicrographs.
- Please submit figures in the accepted file formats: .eps, .jpg, .tiff, .pdf, .ppt, or .xls. Note that .doc files can be submitted only if the figure was actually created in Microsoft Word. Pictures (containing no text or graphs) typically look best in .tiff, .jpg, and .pdf formats, and graphs/line art with text typically look best in .eps, .pdf, .ppt, or .xls formats.
- Images should be submitted in high resolution. All figures need to be at least 300 dpi to ensure quality on printing. Tip: If you have a two-button mouse, simply right-click on the closed file—a drop-down list should appear. Choose the Properties option in the context menu, and then go to the Details tab to view the resolution.
- The size of the text must be large enough to be clearly visible when the figures are resized to fit the column width (~3.5 in. wide) or page width (~7 in. wide) of the journal page.
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- For identifiable photographs, see instructions in Informed Consent.
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Table S1, Table S2, etc.

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5 CONSIDERAÇÕES FINAIS

Houve uma maior frequência de estudos bem desenhados, contudo ainda existe uma quantidade importante de pesquisas com vieses metodológicos sobre a temática. Foi possível observar efeito favorável da suplementação com ácidos graxos ômega 3 na resposta inflamatória, em especial quando combinada com outras abordagens multimodais. Dentre os principais efeitos observados destacou-se: atenuação do catabolismo muscular e melhora da qualidade de vida.

Quanto a avaliação da suplementação de BCAA houve um decréscimo estatisticamente menor no grupo BCAA comparativamente ao grupo CTL para a circunferência do braço e taxa metabólica basal. O TNF-α por sua vez, aumentou em relação ao basal no grupo BCAA. Já no grupo CTL destaca-se um decréscimo significativo no hematócrito. Não houveram relações estatisticamente significativas ($p > 0,05$) para capacidade funcional, qualidade de vida, sobrevida pelo ângulo de fase padronizado, composição corporal, IL4, IL10, IFN-γ, hemoglobina e glicemia em jejum. Esses dados por sua vez nos remetem que a suplementação isolada com BCAA embora capaz de atenuar significativamente a TMB, parece ter refletido em maior inflamação e decréscimo de reservas gordurosas.

Em relação a avaliação da sarcopenia e qualidade de vida entre as avaliadas, notou-se que mulheres sarcopênicas apresentaram um escore mais baixo para os domínios Saúde Global e Capacidade Funcional quando comparadas às mulheres não sarcopênicas, contudo para esse dado não houveram associações estatisticamente significativas.

Com relação a análise do consumo alimentar pró-síntese muscular (vitamina D, Cálcio e Proteína), notou-se uma relação estatisticamente significativa entre a distância percorrida e o consumo de vitamina D. Ressaltando que esta combinação pode ambientar a proposta de suplementações nutricionais que favoreçam a síntese muscular e atenuem a proteólise.

A avaliação do consumo proteico por refeição, revelou atendimento ao preconizado nas refeições do almoço e jantar. Não houveram correlações estatisticamente significativas ($p > 0,05$) entre Qualidade de vida e consumo proteico por refeição, contudo houve correlação inversa, estatisticamente significativa e moderada entre FPP na mão direita e

o consumo de proteína no lanche e FPP na mão esquerda e o consumo de proteína no desjejum.

Devido a liberação ética da pesquisa ter ocorrido semanas antes da qualificação (dezembro de 2019), e nos meses que se sucederam ter se instalado a Pandemia de COVID-19 em todo planeta, a coleta de dados manteve-se apenas de novembro de 2019 à fevereiro de 2020, momento no qual foram suspensas todas as atividades de pesquisa do local de coleta de dados (Hospital do Câncer Aldenora Bello, São Luís, Maranhão, Brasil) até o presente momento (março de 2021), motivo pelo qual justificamos a inviabilidade de coleta de dados dos demais grupos de pacientes inicialmente planejados (Grupo suplementado com ômega 3 – GW3 e Grupo suplementação combinada – GSC), ressaltando-se ainda a coleta de dados completos de três pacientes do GSC e duas do GW3.

Não obstante, a análise bioquímico-inflamatória só foi possível após liberação dos recursos da Fundação de Amparo à Pesquisa e Desenvolvimento Científico do Maranhão (FAPEMA) aos pesquisadores, bem como adequação logística da análise sanguínea com a forma de pagamento proposta pela FAPEMA tendo sido finalizada, e portanto inserida na parte escrita deste trabalho após a primeira quinzena de março de 2021.

Na perspectiva de manter a produtividade, os pesquisadores confeccionaram os quatro artigos científicos de caráter transversais (realizados com os dados *Baseline* da pesquisa), e guiaram-se pelo Regimento Interno do Programa de Pós Graduação em Ciências da Saúde da Universidade Federal do Maranhão, que garante a defesa na presença de publicação do aluno como autor ou co-autor juntamente ao orientador (Artigo "*Implementation of a Brazilian Cardioprotect ive Nutritional (BALANCE) Program for improvement on quality of diet and secondary prevention of cardiovascular events: A randomized, multicenter trial*", publicado na *American Heart Journal*, um periódico *A2* na Medicina I – ANEXO A).

6 CONCLUSÕES

A revisão sistemática traçada (Capítulo I) revelou um efeito promissor do Ômega-3, principalmente quando combinado com aminoácidos de cadeia ramificada, e a outras abordagens multimodais, na modulação da resposta inflamatória. Além disso, foi possível observar uma quantidade limitada de ensaios clínicos bem desenhados e que pudessem garantir uma resposta mais fidedigna para a hipótese indagada.

A suplementação com BCAA isolada (Capítulo II) é capaz de atenuar significativamente a TMB, contudo parece promover maior inflamação e decréscimo de reservas gordurosas em mulheres com câncer.

Mulheres sarcopênicas apresentaram piores escores nos domínios dos questionários de qualidade de vida, quando comparadas às mulheres não sarcopênicas (Capítulo III).

Houve correlação estatisticamente significativa apenas para distância percorrida e o consumo alimentar de vitamina D, mesmo com a ingestão média dessa vitamina abaixo do valor recomendado (Capítulo IV).

O consumo de proteína por refeição apresentou correlação significativa tanto no desjejum, quanto no lanche com a força de preensão palmar (Capítulo V).

Diante dos resultados, a suplementação com ácidos graxos ômega 3 é uma estratégia importante para a modulação da caquexia no câncer, outras estratégias interessantes ainda incluem: a adequação no consumo alimentar de vitamina D, Cálcio e Proteína (consumo alimentar pró-síntese muscular) e atenção no consumo alimentar de proteína em quantidade e distribuição adequada para manter ou recuperar a massa magra visto que sua oferta pode compensar perdas associadas ao câncer.

Não obstante, a suplementação isolada de BCAA embora atenue a TMB, parece aumentar o quadro inflamatório e contribuir para redução de reservas gordurosas. Portanto, sua suplementação parece ser melhor direcionada em conjugação a outras estratégias multimodais as quais não foram foco, neste momento desta pesquisa.

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ANEXOS

ANEXO A – Artigo Publicado em Periódico A2, Medicina I (American Heart Journal).

Clinical Investigation

Medicina I
Qualis: A2
Avaliação: 2013-2016

Implementation of a Brazilian Cardioprotective Nutritional (BALANCE) Program for improvement on quality of diet and secondary prevention of cardiovascular events: A randomized, multicenter trial

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ANEXO A – Artigo Publicado em Periódico A2, Medicina I (American Heart Journal). *Continuação.*

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Abstract Background Appropriate dietary recommendations represent a key part of secondary prevention in cardiovascular disease (CVD). We evaluated the effectiveness of the implementation of a nutritional program on quality of diet, cardiovascular events, and death in patients with established CVD.

Methods In this open-label, multicenter trial conducted in 35 sites in Brazil, we randomly assigned (1:1) patients aged 45 years or older to receive either the BALANCE Program (experimental group) or conventional nutrition advice (control group). The BALANCE Program included a unique nutritional education strategy to implement recommendations from guidelines, adapted to the use of affordable and regional foods. Adherence to diet was evaluated by the modified Alternative Healthy Eating Index. The primary end point was a composite of all-cause mortality, cardiovascular death, cardiac arrest, myocardial infarction, stroke, myocardial revascularization, amputation, or hospitalization for unstable angina. Secondary end points included biochemical and anthropometric data, and blood pressure levels.

Results From March 5, 2013, to Abril 7, 2015, a total of 2534 eligible patients were randomly assigned to either the BALANCE Program group (n = 1,266) or the control group (n = 1,268) and were followed up for a median of 3.5 years. In total, 235 (9.3%) participants had been lost to follow-up. After 3 years of follow-up, mean modified Alternative Healthy Eating Index (scale 0-70) was only slightly higher in the BALANCE group versus the control group (26.2 ± 8.4 vs 24.7 ± 8.6, $P < .01$), mainly due to a 0.5-serving/d greater intake of fruits and of vegetables in the BALANCE group. Primary end point events occurred in 236 participants (18.8%) in the BALANCE group and in 207 participants (16.4%) in the control group (hazard ratio, 1.15; 95% CI 0.95-1.38; $P = .15$). Secondary end points did not differ between groups after follow-up.

Conclusions The BALANCE Program only slightly improved adherence to a healthy diet in patients with established CVD and had no significant effect on the incidence of cardiovascular events or death. (Am Heart J 2019;215:187-97.)

Unhealthy dietary patterns are important triggers in the development of chronic diseases.[1] Epidemiological studies have shown a lower risk of cardiovascular disease (CVD) incidence and mortality associated with healthy diets in individuals both with and without prior CVD.[2-6] Therefore, dietary guidelines recommend a combination of nutrient-based advice and healthy dietary patterns for the treatment and prevention of CVD and its risk factors.[7]

Efficacy of any dietary intervention is strongly influenced by degree of adherence which, in turn, is influenced by a number of factors[8] such as access to food and local culture that may determine dietary choices.[7,9] Diet quality may also vary across the socioeconomic spectrum, in which individuals with a lower social position tend to have worse dietary patterns.[10] Thus, strategies for dietary compliance that benefit those with low income are important given that higher-quality diets are associated with lower risk of cardiovascular events in these individuals as compared to those with the highest income.[6]

Guidelines have emphasized the need to adjust dietary recommendations according to personal preferences; regional foods; and cultural, ethnic, and economic aspects to improve adherence.[11] However, dietary