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Aspectos nutricionais do paciente com DPOC: comprometimento nutricional e intervenção dietética

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Tese submetida ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre como requisito para a obtenção do título de Doutor em Ciências da Saúde.

Orientador: Prof. Dr. Paulo José Zimermann Teixeira

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O mundo

Um homem da aldeia de Neguá, no litoral da Colômbia, conseguiu subir aos céus. Quando voltou, contou. Disse que tinha contemplado, lá do alto, a vida humana. E disse que somos um mar de fogueirinhas.

— *O mundo é isso* — revelou — *Um montão de gente, um mar de fogueirinhas*. Cada pessoa brilha com luz própria entre todas as outras. Não existem duas fogueiras iguais. Existem fogueiras grandes e fogueiras pequenas e fogueiras de todas as cores. Existe gente de fogo sereno, que nem percebe o vento, e gente de fogo louco, que enche o ar de chispas. Alguns fogos, fogos bobos, não alumiam nem queimam; mas outros incendeiam a vida com tamanha vontade que é impossível olhar para eles sem pestanejar, e quem chegar perto pega fogo.

Eduardo Galeano, O livro dos abraços.

DEDICATÓRIA

Dedico este trabalho à minha família.

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FORMATO DA TESE

A presente tese de doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências da Saúde, sendo apresentada através de três artigos científicos originais sobre o tema estudado:

1) Artigo original referente a estudo de coorte com coleta de dados retrospectiva sobre a associação da circunferência da panturrilha reduzida com desfechos clínicos em pacientes com Doença Pulmonar Obstrutiva Crônica encaminhados a um programa ambulatorial de reabilitação pulmonar. Esse artigo foi publicado no periódico *Journal of Parenteral and Enteral Nutrition* (ISSN 0148-6071 (Impresso) e 1941-2444 (Online); fator de impacto 4,016; qualis A2), cujas normas de publicação podem ser consultadas no Anexo 3. *Bernardes S, Silva FM, da Costa CC, de Souza RM, Teixeira PJZ. Reduced calf circumference is an independent predictor of worse quality of life, severity of disease, frequent exacerbation, and death in patients with chronic obstructive pulmonary disease admitted to a pulmonary rehabilitation program: A historic cohort study. JPEN J Parenter Enteral Nutr. 2021 Jun 26. doi: 10.1002/jpen.2214. Epub ahead of print. PMID: 34173982*.

2) Artigo original referente à análise secundária de um estudo observacional prospectivo envolvendo pacientes com Doença Pulmonar Obstrutiva Crônica exacerbada sobre a acurácia do índice de massa corporal no diagnóstico de desnutrição, assim como seu valor prognóstico em desfechos clínicos, submetido à publicação no periódico *Journal of Parenteral and Enteral Nutrition* (ISSN 0148-6071 (Impresso) e 1941-2444 (Online); fator de impacto 4,016; qualis A2), cujas normas de publicação podem ser consultadas no Anexo 3. *Bernardes S, Teixeira PJZ, Silva FM. Association of Reduced BMI, length of hospital stay, and malnutrition diagnosis in COPD patients with acute exacerbation: A secondary analysis of a cohort study.*

3) Artigo original referente à revisão sistemática com metanálise de ensaios clínicos randomizados sobre o efeito da suplementação nutricional oral em marcadores do estado nutricional de pacientes com Doença Pulmonar Obstrutiva Crônica, aceito para publicação no periódico *British Journal of Nutrition* (ISSN 0007-1145 (Impresso), 1475-2662 (Online); fator de impacto 3,718; qualis A2), cujas normas de publicação podem ser consultadas no Anexo 3. *Bernardes S, Eckert IC, Burgel CF, Teixeira PJZ, Silva, FM. Increased energy and/or protein intake improves anthropometry and muscle strength in COPD patients: a systematic review with meta-analysis on randomized controlled clinical trials*.

LISTA DE ABREVIATURAS

Termos em Português

ASG – Avaliação subjetiva global
AUC - Área sobre a curva ROC
CI – Calorimetria indireta
CP - Circunferência da panturrilha
CVF – Capacidade vital forçada
DAMPs – Padrões moleculares associados a danos
DPOC – Doença pulmonar obstrutiva crônica
ECR – Ensaio clínico randomizado
EROs – Espécies reativas de oxigênio
FPP – Força da preensão palmar
GER – Gasto energético de repouso
GET – Gasto energético total
HMB – Beta-hidroxi-beta-metilbutirato
IC – Intervalo de confiança
IL-1 – Interleucina 1
IL-6 – Interleucina 6
IL-8 – Interleucina 8
IMC – Índice de massa corporal
IMLG – Índice de massa livre de gordura
MD – diferença média
MLG – Massa livre de gordura
MM – Massa muscular
MMP-9 – Metaloproteinase de matriz 9
MMPs – Metaloproteinases de matriz
NF-kB – Fator nuclear kappa B
OMS – Organização Mundial da Saúde
PCR – Proteína C reativa
PRP – Programa de Reabilitação Pulmonar
QR – Quociente respiratório

SNO – Suplementação nutricional oral

sTNF-R – Receptores solúveis do TNF-α

TNF-α – Fator de necrose tumoral alfa

VCO^2 – Produção de dióxido de carbono

VEF_1 – Volume expiratório forçado no primeiro segundo

VO_2 – Consumo de oxigênio

Termos em Inglês

AUC - Area under the curve

BMI - Body mass index

CAT - COPD Assessment Test

CC - Calf circumference

CI - Confidence interval

COPD - Chronic obstructive pulmonary disease

ECLIPSE – Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints

ERS - European Society of Respirology

ESPEN – European Society for Clinical Nutrition and Metabolism

FFM - Fat-free mass

GBD – Global Burden of Disease

GOLD – Global Initiative for Chronic Obstructive Lung Disease

HBE – Harris-Benedict

HGS - Handgrip strength

MD – Mean Difference

mMRC – Modified Medical Research Council

MUST – Malnutrition Universal Screening Tool

NICE – National Institute for Health and Care Excellence

NOURISH – Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients

NRS-2002 – Nutritional Risk Screening

ONS – Oral nutritional supplementation

OR - Odds ratio

PROSPERO – International Prospective Register of Systematic Reviews

RCT– Randomized Clinical Trial

SMD – Standardized Mean Difference

RESUMO

A doença pulmonar obstrutiva crônica (DPOC) caracteriza-se pela obstrução crônica e progressiva do fluxo aéreo, decorrente da resposta inflamatória anormal dos pulmões. As alterações patológicas da doença envolvem também a inflamação sistêmica, que contribui para o catabolismo proteico e perda de massa muscular, aumentando o risco do comprometimento do estado nutricional nestes pacientes. No entanto, o impacto do suporte nutricional nesse grupo de pacientes é controverso. Assim, o primeiro objetivo dessa tese foi verificar a associação da circunferência da panturrilha (CP) reduzida com desfechos clínicos em pacientes com DPOC encaminhados para um programa de reabilitação pulmonar. Nessa coorte histórica de 144 pacientes, aqueles com CP reduzida eram mais propensos a apresentar piores desfechos: gravidade da doença (OR= 5,09; IC 95%, 2,00 a 12,96), exacerbações frequentes (OR = 2,34; IC 95%, 1,11 a 4,91), maior comprometimento da qualidade de vida (OR = 2,70, IC 95%, 1,22 a 6,00) e maior mortalidade (OR = 3,69; IC 95%, 1,06 a 12,87). O segundo objetivo da tese foi verificar a acurácia do índice de massa corporal (IMC) no diagnóstico de desnutrição e seu valor prognóstico para o tempo de internação e mortalidade intra-hospitalar em pacientes com DPOC internados por exacerbação da doença. Nessa análise secundária de uma coorte envolvendo 241 pacientes, o baixo IMC apresentou acurácia insatisfatória para identificar a desnutrição (AUC < 0,70), mas foi um preditor de permanência hospitalar prolongada (OR = 2,28; IC 95%, 1,17 a 4,44). O último objetivo da tese foi revisar sistematicamente o efeito de intervenções dietética com suplementação nutricional oral (SNO) calórico e/ou proteica em parâmetros do estado nutricional em pacientes com DPOC. Os resultados da revisão sistemática com meta-análise envolvendo 32 ensaios clínicos randomizados (ECR) demonstrou que as intervenções nutricionais aumentaram o peso corporal (MD = 1,44 kg; IC 95%, 0,81 a 2,08, I^2 = 73%), a massa livre de gordura (MLG) (SMD = 0,37; IC 95% 0,15 a 0,59, I^2 = 46%), a circunferência muscular do braço (MD = 0,29 mm^2; IC 95% 0,02 a 0,57, I^2 = 0%), a dobra cutânea tricipital (MD = 1,09 mm;

IC 95% 0,01 a 2,16, I^2 = 0%) e a força da preensão palmar (FPP) (SMD = 0,39; IC 95%, 0,07 a 0,71, I^2=62%) em comparação com as dietas controle. Porém, a certeza da evidência para os desfechos nutricionais variou de muito baixa a baixa. O comprometimento do estado nutricional é prevalente em pacientes com DPOC e está associado a piores desfechos clínicos. E ainda que o IMC reduzido seja um preditor independente de mortalidade, o seu uso isolado é inapropriado para a identificação de desnutrição. O aumento da oferta calórica e/ou proteica por meio de SNO promove a melhora de marcadores do estado nutricional em pacientes com DPOC.

Palavras-chave: doença pulmonar obstrutiva crônica; exacerbação; mortalidade; estado nutricional; desnutrição; terapia nutricional oral; suplementos nutricionais orais.

ABSTRACT

Chronic obstructive pulmonary disease (COPD) is characterized by chronic and progressive airflow obstruction, resulting from an abnormal inflammatory response of the lungs. The pathological changes of the disease also involve systemic inflammation, which contributes to protein catabolism and loss of muscle mass, increasing the risk of impaired nutritional status in these patients. However, the impact of nutritional support in this group of patients is controversial. Thus, the first objective of this thesis was to verify the association of reduced calf circumference (CC) with clinical outcomes in COPD patients referred to a pulmonary rehabilitation program. In this historical cohort involving 144 patients, those with reduced CC were more likely to have worse outcomes: disease severity (OR=5.09; 95% CI, 2.00-12.96), frequent exacerbations (OR=2.34 ; 95% CI, 1.11-4.91), worse total quality of life score (OR = 2.70, 95% CI, 1.22-6.00) and higher mortality (OR = 3.69; 95% CI, 1.06-12.87). The second objective of the thesis was to verify the accuracy of the body mass index (BMI) in the diagnosis of malnutrition and its prognostic value for the length of stay and in-hospital mortality in COPD patients hospitalized for exacerbation of the disease. In this secondary analysis of a cohort involving 241 patients, low BMI showed unsatisfactory accuracy in identifying malnutrition (AUC < 0.70) but was a predictor of prolonged hospital stay (OR = 2.28; 95% CI, 1.17 – 4.44). The last objective of the thesis was to systematically review the effect of dietary interventions with caloric and/or protein oral nutritional supplementation (ONS) on nutritional status parameters in COPD patients. The results of a systematic review with meta-analysis involving 32 randomized controlled trials (RCTs) showed that nutritional interventions increased body weight (MD = 1.44 kg, 95% CI, 0.81 to 2.08, I^2 = 73%), fat-free mass (FFM) (SMD = 0.37; 95% CI 0.15 to 0.59, I^2 = 46%), arm muscle circumference (MD = 0.29 mm2; 95% CI 0.02 to 0.57, I^2 = 0%), triceps skinfold (MD = 1.09 mm; 95% CI 0.01 to 2.16, I^2 = 0%) and handgrip strength (HGS) (SMD = 0.39; 95% CI, 0.07 to 0.71, I^2=62%) compared to control diets. However, the certainty of the evidence for nutritional outcomes ranged from very low to low. Impaired nutritional status is prevalent in COPD patients and is associated with worse 15

clinical outcomes. And although reduced BMI is an independent predictor of mortality, its isolated use is inappropriate for malnutrition identification. The increase in caloric and/or protein supply through ONS promotes the improvement of nutritional status markers in COPD patients.

Keywords: chronic obstructive pulmonary disease; exacerbation; mortality; nutritional status; malnutrition; oral nutritional therapy; oral nutritional supplements.

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1 REFERENCIAL TEÓRICO

1.1 IMPORTÂNCIA DO PROBLEMA

A Doença Pulmonar Obstrutiva Crônica (DPOC) é uma condição clínica comum, evitável e tratável, caracterizada por sintomas respiratórios persistentes e limitação ao fluxo aéreo decorrente de anormalidades das vias aéreas e/ou alveolares geralmente causadas por exposição significativa a partículas ou gases nocivos [1]. A limitação crônica ao fluxo aéreo própria da DPOC é causada por uma combinação de doença das pequenas vias aéreas (bronquiolite obstrutiva) e destruição do parênquima (enfisema) [1].

A prevalência da DPOC varia amplamente entre os países , assim como entre os grupos populacionais em um mesmo país, em decorrência de diferenças metodológicas das pesquisas na coleta de dados, critérios diagnósticos e análise dos dados [2]. Blanco et. al. realizaram uma busca sistemática da literatura objetivando identificar a prevalência de DPOC em estudos populacionais de amostras representativas da população em geral, entre indivíduos com idade ≥40 anos e limitação do fluxo aéreo compatível com diagnóstico de DPOC, por meio de critérios espirométricos validados [3]. Com base em 147 estudos, verificou-se uma prevalência média mundial estimada de DPOC de 13,1% (IC 95% 10,2–15,6%), com a seguinte distribuição em cada continente: Europa, 12,4% (IC 95% 8,8–16,0%); África, 13,9% (IC 95% 12,0–15,9%); América, 13,2% (IC 95% 10,5–15,9%); Ásia, 13,5% (IC 95% 10,0–16,0%); e Oceania, 11,6% (IC 95% 9,8–13,1%) [3]. Estudos epidemiológicos mais recentes estimam prevalência global de DPOC em 11,7% [4,5], com projeções de aumento nas próximas décadas devido à exposição contínua aos fatores de risco da DPOC (tabagismo, poluição ambiental e ocupacional) e ao envelhecimento da população mundial; ou seja, à medida que a longevidade aumenta, mais pessoas expressarão os efeitos a longo prazo da exposição aos fatores de risco para a doença [2].

Segundo dados do estudo *Global Burden of Disease* (GBD), a DPOC constitui uma das dez principais causas de aumento dos anos de vida ajustados por incapacidade entre indivíduos com ≥50 anos de idade e é um importante contribuinte para o aumento do peso global das doenças não transmissíveis [4]. Em todo o mundo, a DPOC representa a terceira principal causa de mortalidade, respondendo por mais de três milhões de mortes em 2019 [5].

A DPOC impõe uma sobrecarga substancial aos pacientes, que pode incluir uma variedade de sintomas respiratórios (dispneia, tosse, expectoração, sibilos, aperto no peito) de gravidade variável [6]. Além disso, os portadores da doença são susceptíveis às suas manifestações sistêmicas, que contribuem para sua gravidade, como o comprometimento do estado nutricional, observado principalmente pela redução da massa e função da musculatura esquelética [7,8]. Neste contexto, os pacientes tendem a regredir os seus níveis de atividade física quando comparados aos controles saudáveis da mesma idade [9].

O declínio na capacidade de exercício contribui ainda mais ao descondicionamento do sistema cardiovascular e musculoesquelético, aumentando a dispneia relacionada à atividade e exacerbando o sedentarismo. A menos que interrompido, este ciclo de dispneia, inatividade e descondicionamento leva à incapacidade da realização das atividades básicas da vida diária nesse grupo de doentes [6], aumentando o risco de morbidade e mortalidade, bem como os custos em saúde [10].

1.2 DPOC: FATORES DE RISCO, SINTOMATOLOGIA E DIAGNÓSTICO

Vários fatores ambientais e endógenos aumentam o risco de desenvolver DPOC [1]. Dentre os fatores de risco ambientais, o tabagismo é o mais reconhecido e estudado. No entanto, envolvem também a inalação de agentes tóxicos/irritantes provenientes do tabagismo passivo [11], poluição do ar (queima de combustíveis) [12], combustão de biomassa [13], atividades ocupacionais [14]. O baixo peso ao nascer é outro fator de risco para DPOC, provavelmente porque

a má nutrição intrauterina resulte em pulmões menores, de modo que o declínio da função pulmonar associado à idade se manifeste precocemente nesses indivíduos [15]. Nessa perspectiva, talvez o baixo nível socioeconômico seja o maior fator de risco para DPOC, já que incorpora vários fatores de risco [16].

É provável a presença de interações importantes entre os fatores ambientais e a susceptibilidade genética para desenvolver a doença [17]. Ainda que fumaça do cigarro cause inflamação nos pulmões de todos os fumantes, apenas uma minoria desenvolve obstrução significativa ao fluxo aéreo devido a um declínio acelerado da função pulmonar [18]. A taxa de declínio da função pulmonar na população geral é determinada cerca de 50% pela hereditariedade. Isso sugere que fatores genéticos podem determinar a susceptibilidade à doença. A deficiência de α-1-antitripsina - um distúrbio genético hereditário que resulta na proteção pulmonar insuficiente à ação da elastase neutrofílica e a outras agressões - é responsável por <1% dos casos de DPOC. Indivíduos com essa deficiência desenvolvem enfisema precoce, sendo a sua manifestação intensificada na presença de tabagismo, indicando uma clara predisposição genética à DPOC [17].

A dispneia crônica e progressiva é a característica sintomática mais comum na DPOC. Enquanto a tosse com escarro está presente em até 30% dos casos. Esses sintomas podem ser variáveis no dia-a-dia e podem preceder o desenvolvimento da limitação ao fluxo aéreo por muitos anos. É possível que indivíduos com limitação significativa do fluxo aéreo sejam assintomáticos e vice-versa. Comumente a procura por assistência médica é determinada pelo impacto dos sintomas na condição funcional do paciente. Mas também pode ser motivada tanto pela presença crônica ou aguda e transitória de exacerbação da sintomatologia respiratória [1].

O diagnóstico da doença é feito a partir da história de sintomalogia sugestiva e/ou da exposição aos fatores de risco, sendo confirmado por dados do exame de espirometria, pós-broncodilatador: relação VEF_1 (Volume expiratório forçado no primeiro segundo/CVF (Capacidade vital forçada) <70%

e VEF_1 <80% do normal previsto [1]. A classificação da gravidade da limitação ao fluxo aéreo é feita com base nos valores de VEF_1 [1] (**Tabela 1**). Além disso, o GOLD (*Global Initiative for Chronic Obstructive Lung Disease*) [1] propõe o uso da ferramenta de avaliação "ABCD" (**Tabela 2**), que considera a sintomatologia e a história de exacerbações como base para o início do plano terapêutico.

Tabela 1 – Classificação da gravidade da limitação ao fluxo aéreo (conforme VEF_1 pós-broncodilatador)

Em pacientes com VEF_1/CVF< 0,70:		
GOLD 1	Leve	$VEF_1 \geq 80\%$ do previsto
GOLD 2	Moderada	$50\% \leq VEF_1 < 80\%$ do previsto
GOLD 3	Grave	$30\% \leq VEF_1$ 50% do previsto
GOLD 4	Muito grave	$VEF_1 < 30\%$ do previsto

Fonte: Adaptado de Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2022 [1]

Abreviaturas: VEF_1, Volume expiratório forçado no primeiro segundo; CVF, Capacidade vital forçada.

Tabela 2 - Classificação da DPOC quanto ao impacto dos sintomas e o risco de exacerbação

História de exacerbação moderada ou grave		
≥ 2 ou ≥ 1 levando à internação hospitalar	**C**	**D**
0 ou 1 (não levando à internação hospitalar)	**A**	**B**
	mMRC 0 – 1 CAT < 10	mMRC ≥ 2 CAT ≥ 10
	Sintomas	

Fonte: : Adaptado de Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2022 [1]

Abreviaturas: mMRC: modified Medical Research Council; CAT: COPD Assessment Test.

1.3 FISIOPATOLOGIA DA DPOC

A DPOC inclui a doença das pequenas vias aéreas, uma condição na qual os bronquíolos de pequeno calibre se encontram estreitados e em menor número; enfisema, um distúrbio definido anatomicamente, caracterizado pela destruição dos alvéolos pulmonares e dilatação dos espaços aéreos; e bronquite crônica, clinicamente definida por tosse crônica e expectoração purulenta. Sendo que a maioria dos pacientes com DPOC apresenta todos os três mecanismos patológicos (doença das pequenas vias aéreas, enfisema e bronquite crônica), ainda que em graus variados [19]

O mecanismo predominante à limitação progressiva ao fluxo aéreo parece estar intimamente relacionado ao processo inflamatório, estreitamento e

fibrose nas pequenas vias aéreas, resultando na hiperinsuflação pulmonar, e consequentemente em dispneia progressiva aos esforços. Há inflamação crônica, predominantemente nas pequenas vias aéreas e no parênquima pulmonar, com aumento no número de macrófagos e neutrófilos nos estágios iniciais da doença, e mais tarde com o aumento dos linfócitos (em particular, células T citotóxicas CD8+) [20].

Os macrófagos alveolares desempenham um papel crítico na condução dessa inflamação pulmonar, liberando quimiocinas que atraem células inflamatórias, como monócitos, neutrófilos e células T para os pulmões. As células T CD8+ atuam na apoptose de células-alvo, relacionando-se à destruição pulmonar, produzem e liberam citocinas retroalimentando o processo inflamatório (ativação dos macrófagos, que então produzirão uma série de citocinas), e aumentam a expressão de receptores relacionados às quimiocinas no pulmão (responsáveis pelo recrutamento de linfócitos T) [21].

As enzimas elastolíticas são responsáveis pela destruição tecidual do enfisema e incluem a elastase de neutrófilos e metaloproteinase-9 de matriz (MMP-9). Há um desequilíbrio entre o aumento da produção de elastases e a deficiência de antiproteases endógenas, como α1-antitripina, inibidor de leucoprotease secretora e inibidores teciduais de MMPs. A MMP-9 pode ser a enzima predominantemente elastolítica que causa o enfisema e também ativa o fator de crescimento transformador-β, uma citocina que é expressa particularmente nas pequenas vias aéreas e que pode resultar na fibrose característica e estreitamento das vias aéreas [22].

O estresse oxidativo é uma característica marcante da DPOC e surge como resultado de elementos oxidantes exógenos e daqueles liberados por células inflamatórias ativadas, como neutrófilos e macrófagos, assim como possíveis alterações no sistema antioxidante endógeno decorrente de poliformismos genéticos [23]. O dano oxidativo aos tecidos circundantes leva à formação de moléculas orgânicas altamente reativas - espécies reativas de oxigênio (EROs), que podem modificar proteínas e alterar sua função, bem como resultar na formação de padrões moleculares associados a danos (DAMPs) e neoautoantígenos. O estresse oxidativo pode ativar a via do NF-kB

(Fator nuclear kappa B) e aumentar a sua expressão, que é correlacionada à limitação do fluxo aéreo. Além disso, o estresse oxidativo prejudica o processo de fagocitose, aumentando a expressão gênica inflamatória [24].

1.4 IMPACTO DA DPOC NO ESTADO NUTRICIONAL

A DPOC tem um importante componente sistêmico que manifesta-se por meio de efeitos extrapulmonares de impacto prognóstico, dentre os quais destaca-se o comprometimento nutricional, incluindo alterações do metabolismo energético e proteico, consumo alimentar, peso corporal, massa e função muscular [7,8].

O gasto energético de repouso (GER) [25,26] e o *turnover* proteico estão aumentados em pacientes com DPOC (em especial no fenótipo enfisematoso) e depleção muscular, comparado àqueles com massa muscular (MM) preservada e controles saudáveis [26]. Este estado de hipermetabolismo é associado à inflamação sistêmica crônica, dinâmica respiratória anormal [27], exacerbações agudas [28] e uso de β_2-agonistas [29].

Embora a anorexia não constitua o principal fator limitante à ingestão alimentar em pacientes clinicamente estáveis, uma vez que o apetite é geralmente preservado, e até mesmo um elevado consumo é relatado por aqueles com baixo peso, o consumo alimentar pode ser insuficiente frente ao hipermetabolismo [30]. Por outro lado, em pacientes com perda de peso observa-se uma menor ingestão, que é atribuída a vários fatores, incluindo dispneia ao se alimentar, saciedade precoce [31], o impacto emocional da doença e anorexia [32]. Os mecanismos biológicos da anorexia não são totalmente compreendidos, mas parecem estar correlacionados ao aumento na circulação de citocinas neuro-hormonais e inflamatórias, como interleucina (IL)-6, IL-8 e fator de necrose tumoral alfa (TNF–α) e quimiocinas [33].

As alterações decorrentes do processo de envelhecimento também contribuem para a redução da ingestão alimentar na DPOC, devido a maior

expressão de sintomas limitantes do consumo de alimentos (disfunção olfatória e gustativa, dificuldade de mastigação e deglutição, inapetência), problemas socioeconômicos (isolamento social ou pobreza) [34] e dependência funcional para a obtenção, preparo e/ou consumo de alimentos [32,34]. Todos esses elementos resultam em um balanço energético negativo que invariavelmente resulta na redução da massa e função muscular. O hipermetabolismo pode contribuir para a perda de peso se as necessidades de energia não forem totalmente atendidas [30].

Apesar da relativa preservação da massa gorda, a depleção muscular é observada em uma proporção substancial de pacientes, incluindo aqueles com peso corporal normal [35]. O estado inflamatório crônico de baixo grau subjacente à doença, com níveis plasmáticos elevados de citocinas, como TNF-α, IL-1 e IL-6, Receptores solúveis do TNF-α (sTNF-R) e proteína C-reativa (PCR), é um estímulo à proteólise e à inibição da síntese proteica no músculo esquelético, contribuindo para a perda de peso aguda e redução de MM [36]. Além disso, a taxa de degradação da proteína muscular é possivelmente mediada por uma elevação consistente de duas vias catabólicas: sistemas de autofagia e de ubiquitina-proteossomo [37].

Da mesma forma, a gravidade da obstrução do fluxo aéreo gera uma elevada demanda de oxigênio (aumento do trabalho respiratório) que é atendida de forma limitada, já que o fluxo sanguíneo prioriza a oferta de oxigênio a órgãos críticos (coração, sistema nervoso central e músculos ventilatórios), enquanto os tecidos periféricos, incluindo os músculos esqueléticos, desenvolvem hipóxia e déficit de nutrientes [33]. Além disso, um rearranjo das fibras musculares, que leva a maior expressão das de tipo II (glicolítica) em relação às de tipo I (via oxidativa), diminui a resistência muscular, comprometendo a capacidade de exercício e também a MM, pois as fibras musculares do tipo II respondem de forma diferente aos estímulos anabólicos e catabólicos [38].

A inatividade física sustentada, uma característica comum da DPOC, repercute negativamente sobre a massa e função do músculo esquelético

periférico [9], e mesmo em estágios leves da doença foi independentemente associada à perda do quadríceps [39], em consequência da síntese proteica diminuída e do aumento da proteólise [40].

Da mesma forma, as exacerbações agudas intensificam o catabolismo proteico e a fraqueza da musculatura esquelética pelo aumento da inflamação pulmonar e sistêmica e pelo desuso muscular devido ao repouso forçado, além da incorporação de corticoide ao esquema terapêutico (usualmente associado à miopatia) [28,41].

1.5 COMPROMETIMENTO DO ESTADO NUTRICIONAL NA DPOC

Pacientes com DPOC são susceptíveis ao comprometimento do estado nutricional, desencadeado pela interação complexa de múltiplos fatores etiológicos, sendo variável a contribuição relativa de cada um entre os indivíduos afetados [41]. As alterações nutricionais resultantes podem manifestar-se pelo baixo peso corporal, perda ponderal involuntária, mudanças na composição corporal (depleção de MM), ou pela combinação destas, como a desnutrição, sarcopenia e caquexia, que ainda podem se sobrepor. Desta forma, a prevalência de comprometimento nutricional em pacientes com DPOC varia consideravelmente, em decorrência dos diferentes critérios e pontos de corte usados, assim como das características da população estudada.

Embora muitas vezes utilizados como termos intercambiáveis para indicar o comprometimento nutricional, desnutrição, sarcopenia e caquexia são entidades distintas, que invariavelmente compartilham da depleção de MM como um dos seus marcadores.

A desnutrição é definida como um estado subagudo ou crônico em que há uma combinação de graus variados de atividade inflamatória e de subalimentação ou hiperalimentação com consequente repercussão na composição corporal e diminuição da capacidade funcional.[42] A identificação da condição requer a avaliação de diversos parâmetros de ordem nutricional,

incluindo avaliação da ingestão alimentar em relação aos requerimentos nutricionais; fatores limitantes da ingestão alimentar; histórico de peso; composição do corporal; capacidade funcional; bem-estar físico, psicológico e social; história da doença; e condição socioeconômica [43].

A sarcopenia, por sua vez, é uma doença músculo-esquelética, caracterizada pela presença da redução da força (sugestivo de sarcopenia) e MM, sendo que a concomitância do comprometimento do desempenho físico indica a gravidade da condição [44]. Até poucas décadas, a sarcopenia era entendida como perda progressiva de MM esquelética decorrente do envelhecimento, no entanto, pode ser secundária a doenças que cursam com a inflamação crônica, acometendo indivíduos independentemente da idade [45].

Já a caquexia é uma síndrome multifatorial associada à doença e caracterizada por perda de MM com ou sem perda de gordura, sendo a perda ponderal grave e progressiva associada à presença de inflamação a principal característica desta condição [46].

Em uma revisão sistemática com metanálise envolvendo pacientes admitidos em unidades de pneumologia hospitalar, a prevalência de risco nutricional foi de 32,73% (IC 95%, 31,29% a 34,17%, I^2=97,6%, 12 estudos), que foi avaliado principalmente pela ferramenta NRS-2002 (*Nutritional Risk Screening*), mas com resultados similares aos obtidos pelo MUST (*Malnutrition Universal Screening Tool*) [47]. Enquanto a prevalência de desnutrição foi de 36,95% (IC 95% 34,80% – 39,10%; I^2 = 99,7%; 11 estudos), apresentando estimativas inferiores em estudos que a identificaram por meio de parâmetros antropométricos (25,88%) do que quando a ASG (Avaliação Subjetiva Global) foi aplicada (48,81%), sugerindo que o uso exclusivo de parâmetros antropométricos, como o IMC para avaliação da desnutrição resulta na subidentificação dessa condição [47].

Recentemente, uma revisão sistemática com metanálise, que incluiu 22 estudos (n=9.416), identificou maior prevalência de sarcopenia entre pacientes com DPOC nos estudos que utilizaram um único critério diagnóstico [MM reduzida; 34%, (IC 95% 20,6–47,3)] do que naqueles que usaram >1 critério

[MM reduzida + força muscular reduzida e/ou desempenho físico reduzido; 15,5% (IC 95% 11,8–19,1)]; além disso, a condição foi mais comum naqueles em estágios mais avançados da DPOC [48]. Ainda, em dois estudos transversais envolvendo pacientes com DPOC admitidos em Programa de Reabilitação Pulmonar (PRP), a sobreposição de sarcopenia e desnutrição variou de 9,7% [49] a 24% [50].

Em uma análise secundária de dados do estudo ECLIPSE (*Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints*), a caquexia foi avaliada entre 1.483 portadores de DPOC, sendo identificada por dois critérios: 1) Consenso [perda de peso > 5% em 12 meses ou baixo IMC + presença ≥3 dos 5 seguintes parâmetros: diminuição da força muscular, fadiga, anorexia, índice de massa livre de gordura reduzido e alteração bioquímica (hemoglobina 12 g/dL ou PCR >5 mg/L)] e 2) Perda de peso: perda de peso >5% ou, na presença de IMC baixo, perda de peso >2%). A prevalência de caquexia usando a definição de consenso e a de perda de peso foi de 4,7% e 10,4%, respectivamente [51].

1.6 VALOR PROGNÓSTICO DO COMPROMETIMENTO DO ESTADO NUTRICIONAL EM PACIENTES COM DPOC

Na década de 1960 parâmetros de comprometimento nutricional como a perda e o baixo peso corporal em pacientes com DPOC despertaram interesse de pesquisadores da área, pela sua associação com menor tempo de sobrevida em indivíduos com o mesmo grau de gravidade da doença [52]. De fato, a sobreposição da depleção nutricional à DPOC intensifica o impacto sistêmico negativo de ambas, comprometendo a estrutura e função dos músculos pulmonares e esqueléticos [53,54], promovendo um balanço energético negativo, além de impactar negativamente na imunocompetência e em aspectos emocionais desses pacientes [53].

Historicamente, observa-se na literatura médica da DPOC o uso preponderante e isolado do IMC como parâmetro nutricional preditor de desfechos de morbidade e mortalidade. Em uma revisão sistemática com metanálise avaliando o valor prognóstico do IMC para a mortalidade na DPOC, após ajuste para a idade, sexo, VEF_1 (% predito) e tabagismo, pacientes com baixo IMC (<18,5 kg/m^2) apresentavam risco de morte 1,48 vezes maior (RR=1,48, IC 95% = 1,26–1,75); I^2 = 66%; 8 estudos; 14.163 participantes) comparados aqueles com valores de IMC na faixa de normalidade (18,5 kg/m^2 a 24,9 kg/m^2). Em outra revisão sistemática com metanálise envolvendo cinco ECR entre pacientes com DPOC, a taxa anual estimada de declínio do VEF_1 foi inversamente proporcional aos valores de IMC [55]. Em comparação aos pacientes na faixa normal de IMC (18,5 ou 20 a <25 kg/m^2) aqueles com baixo IMC apresentavam um declínio mais rápido do VEF_1: − 47,58 ml/ano (IC95% − 51,7 a − 43,4) e 52,9 ml/ano (IC95% − 57,3 a − 48,5), respectivamente [55].

No entanto, o uso de marcadores de MM revelam um maior valor prognóstico mais preciso que o IMC na DPOC. A análise prospectiva de pacientes encaminhados para reabilitação pulmonar identificou que o índice de massa livre de gordura (IMLG) reduzido foi independentemente associado à mortalidade em um período de dois anos (HR= 13,03, IC 95% 1,67 a 101,71), mesmo após ajustado para a idade e função pulmonar e (HR= 9,38, IC 95% 1,19 a 74,0) para a idade e capacidade de difusão, enquanto o baixo IMC não demonstrou associação com o desfecho [56]. Da mesma forma, a análise dos dados de 1.898 pacientes com DPOC do estudo de base populacional *Copenhagen City Heart Study* identificou associação do IMLG baixo com o aumento da mortalidade geral (HR=1,5; IC 95% 1,2 a 1,8) e por DPOC (HR=2,4; IC 95% 1,4 a 4,1), que persistiu mesmo em indivíduos com IMC normal para a mortalidade geral (HR=1,3; IC 95% 1,1 a 1,7) [57].

Os métodos comumente utilizados para estimar a MM na DPOC como a tomografia computadorizada, absorciometria de raios-x de dupla energia, (DEXA), ultrassonografia e bioimpedância [58] tendem a ser sofisticados e onerosos, e desta forma inacessíveis na prática clínica. Além destes métodos, a *European Respiratory Society* (ERS) reconhece o uso da antropometria

como apropriada à avaliação da MM na assistência nutricional de pacientes com DPOC [30]. Neste contexto, emerge a medida da circunferência da panturrilha (CP) como um potencial marcador de MM, dada a sua correlação positiva (r > 0,7) com a massa muscular apendicular (MMA) avaliada pelo DEXA em estudos populacionais [59,60], e por configurar-se em uma alternativa de avaliação acessível, de baixo custo, não invasiva e de fácil execução na prática clínica [61]. Além disso, valores reduzidos de CP tem sido associados a desfechos clínicos em pacientes hospitalizados, como a maior incidência de readmissão em 30 dias [62] , permanência hospitalar prolongada [63,64], presença de risco nutricional [63] e desnutrição [64]. Estudo brasileiro envolvendo pacientes com DPOC hospitalizados por exacerbação da doença a CP reduzida aumentou a chance de presença de desnutrição e de internação hospitalar superior a 11 dias [64]. Já em pacientes ambulatoriais, a CP reduzida demonstrou o maior potencial preditor para o risco de mortalidade em três anos, quando comparada à circunferência do braço e ao IMC [65]

O comprometimento nutricional manifesto tanto pelo diagnóstico de desnutrição quanto de sarcopenia ou caquexia está associado a piores desfechos em pacientes com DPOC, independente da condição clínica. De fato, pacientes desnutridos ou caquéticos apresentam risco três vezes maior de óbito [51,66] e readmissão hospitalar [67], tempo médio de hospitalização prolongado [66] e percepção de qualidade de vida reduzida [68]. Assim como, a presença de sarcopenia associa-se a piores escores de dispneia [69,70], menor força e capacidade funcional [70,71].

Dada a natureza multifatorial e a complexidade do comprometimento nutricional na DPOC, suas distintas possibilidades de expressão e respectiva associação com desfechos clínicos, a ERS propôs a estratificação dos pacientes em fenótipos metabólicos, considerando parâmetros do estado nutricional como o IMC, MM e perda ponderal [30]. Desta perspectiva, a ERS identificou e definiu seis fenótipos metabólicos (obesidade, obesidade mórbida, obesidade sarcopênica, sarcopenia), seguidos dos riscos para desfechos clínicos. Esses fenótipos foram pouco explorados até o presente momento quanto a sua validade. Um estudo envolvendo 270 pacientes com DPOC em

avaliação para admissão em PRP, revelou que os fenótipos de composição corporal estão associados à capacidade física [72]. Ainda que esse grupo de pacientes compartilhasse de características clínicas similares, aqueles com obesidade sarcopênica evidenciaram pior capacidade de exercício, força muscular periférica e respiratória e eram menos ativos fisicamente em comparação com os outros fenótipo metabólicos [72].

1.7 INTERVENÇÕES DIETÉTICAS NO MANEJO DO COMPROMETIMENTO NUTRICIONAL NA DPOC

O tratamento do comprometimento nutricional na DPOC por meio de intervenções dietéticas compartilha do racional aplicado a outras condições inflamatórias e catabólicas, associadas a doenças crônicas e agudas, nas quais a terapêutica precoce tem o potencial de reverter ou minimizar a depleção das reservas corporais, reduzindo o risco de piores desfechos [73,74].

Na DPOC, os objetivos dietoterápicos devem ser balizados pela condição clínica do paciente (estável ou em exacerbação) - determinante do background metabólico e potencial anabólico [75], além do estado nutricional, a gravidade da doença e o nível de atividade física.

Os objetivos da dietoterapia em pacientes estáveis visam manter ou aumentar o peso corporal e a MM. Enquanto durante os episódios de exacerbações agudas a proposta é minimizar a perda de peso e de MM [76], atentando ao efeito da sobrecarga calórica ao risco ou piora da hipercapnia e à intensificação dos sintomas respiratórios [77].

1.7.1 REQUERIMENTOS ENERGÉTICOS

A calorimetria indireta (CI) constitui o método mais confiável para mensurar o gasto energético de um indivíduo e orientar a prescrição

energética, porém o equipamento tem custo elevado e demanda técnicos qualificados à sua utilização, limitando a sua aplicabilidade [78]. Como alternativa, a estimativa dos requerimentos energéticos se dá pelo cálculo de equações preditivas. A literatura dispõe de equações desenvolvidas e validadas para portadores de DPOC por métodos de referência, entre as quais a proposta por Moore e Angelillo [79]. No entanto, após a aplicação da equação em pacientes estáveis e instáveis, os autores encontraram uma diferença média na estimativa de 73 kcal ± 279 e 108 kcal ± 297, respectivamente [79]. Em ambos os casos a variação foi ampla, indicando que erros de estimativa podem ser comuns e de risco para extremos calóricos indesejáveis na DPOC: subalimentação e hiperalimentação [80]. A *Academy of Nutrition and Dietetics* (AND) sugere o cálculo de 30 kcal/kg de peso corporal para estimar o gasto energético total (GET) em pacientes com DPOC sem obesidade, e orienta usar o julgamento clínico à sua determinação naqueles com IMC >30 kg/m^2 [81]. Recomenda ainda o uso de outras equações gerais disponíveis na prática clínica para o cálculo do GER, dentre estas a proposta pela Organização Mundial da Saúde (OMS), a de Harris-Benedict (HBE) ou a de Westerterp. No entanto, tais equações apresentam taxas de precisão das estimativas inferiores a 70%, a equação de HBE demanda o acréscimo do fator injúria, que não está bem estabelecido na DPOC [81], enquanto a equação de Westerterp requer informações dos valores de massa livre de gordura (obtida por impedância biolétrica), inviável à maioria dos ambientes assistenciais.

Ainda, para casos de desnutrição, encontra-se na literatura a indicação de oferta calórica de pelo menos 45 kcal/kg de peso corporal/dia, com o intuito de promover um ganho ponderal de 2 kg, que estaria associado a melhora da força muscular e da sobrevida (em quatro anos) [75,76]. No entanto, os efeitos metabólicos de impacto respiratório (aumento da produção de dióxido de carbono) devem ser ponderados quando da intenção de aumentar a oferta calórica, principalmente entre pacientes em exacerbação, já que a lipogênese resultante do excesso de energia promove o aumento significativo da produção de dióxido de carbono (VCO_2) [80].

1.7.2 REQUERIMENTOS DE MACRONUTRIENTES

Durante algumas décadas, uma das principais preocupações na terapêutica nutricional para portadores de DPOC foi a manipulação de macronutrientes, por meio da redução da proporção de carboidratos e aumento da oferta lipídica [82]. O fundamento para esta conduta baseava-se no pressuposto fisiológico do efeito individual de cada macronutriente sobre o quociente respiratório (QR). O QR é obtido por CI e definido pela razão entre a VCO_2 e o consumo de oxigênio (VO_2), sendo um marcador da metabolização de substratos energéticos: em média 0,70 para gorduras, 0,80 para proteína e 1,00 para carboidratos [80]. A prescrição de dietas hiperlipídicas e hipoglicídicas foi abandonada pela ausência de evidências robustas demonstrando o seu benefício [81].

Até o momento não há evidência sobre a distribuição percentual ideal de carboidratos e gorduras na dieta para portadores de DPOC, no entanto, a oferta destes macronutrientes deve ser estabelecida considerando-se a presença de comorbidades (doenças cardiovasculares e diabetes mellitus), estilo de vida, dificuldades financeiras e preferências pessoais [81].

A quantidade de proteína dietética recomendada na DPOC é variável, e segundo propõe o *National Institute for Health and Care Excellence* (NICE) para o manejo nutricional desses pacientes, deve ser estimada da seguinte forma: a) na ausência de risco nutricional ou desnutrição/estabilidade clínica, de 0,8 a 1,5 g de proteína/kg de peso corporal/dia e b) em períodos de agudização (exacerbados), a partir de 1,5 g de proteína/kg de peso corporal /dia [76]. No entanto, a *European Society for Clinical Nutrition and Metabolism* (ESPEN) objetivando a manutenção da força e função muscular em idosos, recomenda que a dieta deva fornecer um aporte proteico aumentado, tanto pelo declínio da resposta anabólica à ingestão de proteínas, quanto para compensar as condições inflamatórias e catabólicas associadas a doenças crônicas e agudas comuns no envelhecimento [83].

1.7.3 EFETIVIDADE DAS INTERVENÇÕES DIETÉTICAS

A intervenção dietética instituída deve considerar além dos aspectos clínicos e nutricionais, os hábitos, preferências alimentares e estilo de vida de cada indivíduo. Estruturando o plano terapêutico fundamentalmente pelo consumo de alimentos habituais, adequando a frequência e volume das refeições e/ou fortificando as preparações com alimentos de maior densidade calórica ou proteica, conforme as necessidades do paciente. Caso o paciente não consiga atingir as suas necessidades nutricionais apenas por meio das estratégias aplicadas à dieta habitual, há indicação do uso da suplementação nutricional oral (SNO) à complementação da ingestão dietética [84].

A SNO é uma das poucas estratégias de cuidado nutricional mencionadas pelo documento GOLD [1], como terapêutica relevante ao manejo da DPOC. A conduta é fundamentada principalmente pela revisão sistemática com metanálise da Cochrane (atualizada em 2012) [85] de 17 ECR, envolvendo pacientes com DPOC estáveis. Embora a SNO não tenha influenciado a função pulmonar, promoveu ganho ponderal significativo (especialmente nos desnutridos), aumento em marcadores de MM e adiposa e melhor tolerância ao exercício [85]. Sendo que, apenas nos pacientes desnutridos observou-se melhora significativa na força muscular respiratória (inspiratória e expiratória) e na qualidade de vida relacionada à saúde [85]. Similarmente, uma análise post hoc de subgrupo do estudo NOURISH (*Nutrition effect On Unplanned ReadmIssions and Survival in Hospitalized patients*) (ECR multicêntrico) envolvendo pacientes com DPOC hospitalizados e desnutridos (n= 214), demonstrou o impacto positivo da SNO hiperproteica e hipercalórica contendo betahidroxi-beta-metilbutirato (HMB) na FPP, peso corporal, concentrações plasmáticas de biomarcadores nutricionais (hemoglobina, cálcio e vitamina D) e na redução do risco de mortalidade em um período de 90 dias após a alta [86]. O benefício da SNO na DPOC estável também foi demonstrado por Collins et al. em duas revisões sistemáticas com metanálise [87,88]. Na primeira revisão [87], com 13 ECR, evidenciou-se um aumento significativo na ingestão calórico-proteica, peso corporal e em marcadores de MM e adiposa. E na segunda [88],

com 12 ECR, embora o uso de SNO não tenha repercutido em alterações na função pulmonar, resultou em incremento na força muscular respiratória (pressão inspiratória e expiratória máxima) e periférica (FPP), qualidade de vida e desempenho físico. Em contraste, uma revisão sistemática recente [89] de 22 estudos (sem restrição de delineamento) avaliou os efeitos do uso de SNO em pacientes com DPOC estáveis durante PRP, e não encontrou efeitos adicionais da intervenção em parâmetros antropométricos, capacidade e de exercício, composição corporal, função muscular respiratória e qualidade de vida.

Ainda, a partir da última década observa-se o interesse em investigar o potencial impacto da suplementação de nitrato (principalmente pela ingestão do suco de beterraba) na capacidade de exercício em portadores de DPOC [90–94] (por aumentar a disponibilidade de óxido nítrico). Os efeitos da suplementação em pacientes com doenças respiratórias crônicas foram avaliados em uma metanálise [95] de 11 ECR (n=282 participantes, dos quais, 94,7% com diagnóstico de DPOC), que verificou o benefício da suplementação no desempenho físico, somente quando da administração a longo-prazo e em associação à reabilitação pulmonar. No entanto, esta inferência é baseada em apenas um ECR [96], que por diferenciar-se dos demais pelo maior tamanho amostral (supera a soma de todas as amostras incluídas na metanálise) e tempo de intervenção (oito semanas), poderia justificar tal achado.

2 JUSTIFICATIVA

O componente extrapulmonar da DPOC, evidenciado pelos seus efeitos sistêmicos envolve entre outros, o comprometimento do estado nutricional [41], manifesto pelo baixo peso, perda ponderal involuntária, desnutrição, sarcopenia e/ou caquexia, reconhecidamente associado a piores desfechos clínicos aos portadores da doença [67,68,97,98] e maiores custos em saúde [66,99]. Neste contexto, a depleção de MM destaca-se como característica comum dessas alterações [30,48,51,68,72]. No entanto, os métodos mais indicados à avaliação da depleção muscular tendem a ser sofisticados e de alto custo [58], inviabilizando o seu uso na prática clínica. Sendo assim, faz-se necessária a identificação de parâmetros viáveis na assistência desses pacientes que possam reconhecer o comprometimento da MM e sua associação com desfechos clínicos na DPOC. Além disso, o comprometimento nutricional tende a ser subidentificado nos diferentes contextos de assistência em saúde, e decorre principalmente do uso de estratégias de avaliação inapropriadas [47]. Ainda que a suplementação nutricional hipercalórica e hiperproteica seja recomendada para pacientes com DPOC [1,76], a fim de atender os requerimentos de nutrientes e preservar ou minimizar alterações na composição corporal, a real magnitude do efeito dessa conduta sobre os parâmetros do estado nutricional requer maiores investigações.

3 OBJETIVOS

3.1 OBJETIVO GERAL

— Explorar as alterações do estado nutricional em pacientes com DPOC, assim como o uso do IMC para capturá-las e a possível associação dessas alterações com desfechos clínicos, além de revisar sistematicamente o efeito de intervenções nutricionais de suplementação oral calórico e/ou proteica em parâmetros do estado nutricional nessa população.

3.2 OBJETIVOS ESPECÍFICOS

— Avaliar a frequência de depleção de massa muscular por meio da medida da circunferência da panturrilha e a sua associação com desfechos clínicos em pacientes com DPOC encaminhados para um programa de reabilitação pulmonar;

— Avaliar a acurácia de dois pontos de corte distintos para o baixo IMC no diagnóstico de desnutrição e seu valor prognóstico em predizer tempo de internação hospitalar prolongada e mortalidade intra-hospitalar em pacientes com DPOC hospitalizados por exacerbação da doença;

— Avaliar sistematicamente o efeito de intervenções dietéticas com suplementação nutricional e/ou fortificação de alimentos sobre parâmetros do estado nutricional de pacientes com DPOC.

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4 ARTIGO 1

Reduced Calf circumference is an independent predictor of worse quality of life, severity of disease, frequent exacerbation, and death in COPD patients admitted to a Pulmonary Rehabilitation Program: a historic cohort study

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AUTHOR CONTRIBUTIONS

FMS, PJZT, and SB contributed to the conception, data analysis, and interpretation of the study. CCC and RMS contributed to data acquisition and analysis. FMS and SB drafted the manuscript. All the authors critically revised the manuscript, provided final approval, and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

DECLARATION OF INTEREST

The authors have no conflict of interest to declare.

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Abstract

Background and Aims: Muscle wasting is associated with worse outcomes in chronic obstructive pulmonary disease (COPD) patients. We assessed the association of calf circumference (CC) measurement with clinical outcomes in COPD patients referred to an outpatient pulmonary rehabilitation program (PRP).

Methods: In this single-center, retrospective observational study we analyzed demographical, clinical [spirometry test, comorbidities, COPD exacerbations, modified Medical Research Council dyspnea scale, 6-minute walk test in % predicted values, quality of life scores, body mass index, and CC), and all-cause deaths (for two years)] data from COPD patients PRP medical records. Patients were grouped according to CC in reduced CC [male (≤ 34 cm) and female (≤ 33 cm)] or adequate CC group.

Results: We evaluated a total of 144 patients (age 64.6±8.5 years; 65.3% males; forced expiratory volume in 1 second (FEV_1), 40.3±15.8 % predicted). Eighteen patients (12.5%) died during the two years follow-up. Logistic regression showed that patients with reduced CC (45%) were more likely to present worse outcomes compared with those COPD patients with adequate CC: more advanced GOLD stages (OR= 5.09; 95%CI 2.00-12.96), COPD frequent exacerbators (OR= 2.34; 95%CI 1.11-4.91), greater impairment in the total quality of life score (OR=2.70, CI 1.22-6.00), and higher mortality (OR=3.69; 95%CI 1.06-12.87).

Conclusion: Reduced CC in COPD patients under initial assessment for PRP admission was associated with disease severity, frequent exacerbation, poor health status, and higher mortality in two-years of follow-up. Considering its clinical applicability, CC measurement should be introduced in the nutritional assessment of COPD patients admitted for PRP.

Clinical Relevancy Statement

Muscle wasting is a common finding in COPD patients and it has been associated with worse outcomes. This study showed that calf circumference

(CC) measurement can be a potential muscle mass marker surrogate in this population, once the low CC demonstrated association with disease severity, frequent exacerbation, poorer total quality of life score, and higher mortality in a COPD outpatients sample referred to pulmonary rehabilitation.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by irreversible airflow limitation resulting from a mixture of airway disease (obstructive bronchiolitis) and parenchyma destruction (emphysema), which is usually progressive and associated with the abnormal inflammatory response of the lungs to harmful particles or gases [1]. According to the latest data, COPD affects 11.7% of the world population [1] and is already assumed as the third leading cause of death worldwide [2]. In addition to pulmonary involvement, the disease has an extrapulmonary component evidenced by its systemic effects, among which the loss of muscle mass (MM) [3].

Muscle wasting observed in COPD patients results from complex interaction factors involving mainly systemic inflammatory response [4]. In all stages of the disease, the imbalance between protein synthesis and breakdown can lead to intense catabolism. Other factors can lead to increased metabolism and worsening of catabolic activity, including smoking, abnormal respiratory dynamics [4], drugs such as b2-agonists, the increased effort required for breathing and eating [5], and the presence of systemic inflammation and oxidative stress [6]. Reduced MM is associated with adverse effects on exercise capacity [7], dyspnea [8], respiratory muscle function [9], and pulmonary function [7]; and is a useful predictor of COPD severity [7].

The methods often used to quantify MM in this population, as computed tomography (CT), dual-energy X-ray absorptiometry, ultrasonography, and bioelectrical impedance [10] are expensive and not always be available in clinical practice settings. The European Respiratory Society pointed those methods and anthropometry as appropriate measurements of body composition of COPD patients in clinical practice [11]. Among the anthropometric indicators of reduced MM, a simple and easy-to-perform is calf circumference (CC). In fact, in a

Brazilian study that established the cutoff points of CC to identify reduced MM using dual-energy X-ray absorptiometry as the comparator, this indicator presented specificity of 76% and satisfactory accuracy [12]. These CC cutoff points have already been associated with clinical outcomes in hospitalized patients, as the incidence of hospital readmission in 30 days [13] and prolonged hospital stay [14,15] and nutritional risk [14], and malnutrition [15].

Although relatively few investigations have evaluated CC among COPD patients, these studies demonstrated an association between this anthropometric measure and outcomes in this population [16–18]. Ho et al. [16] verified that CC was a strong predictor of exercise tolerance among 136 Taiwanese COPD outpatients (predominantly male and mean age 72.4±7.5 years), according to the logistic regression analysis. The same research group also conducted a cohort study [17] involving 104 COPD outpatients (predominantly male and mean age 74.2±6.9 years), in which low CC (< 30 cm) was positively associated with a 4.4-fold increase in mortality risk during the 3-year follow-up period, according to multivariate Cox regression analysis. Chaudhary et al. [18] compared the correlation between anthropometric, and other nutritional status markers with airflow limitation among 102 Indian COPD outpatients (predominantly <60 years) and found an inverse association between CC and severity of COPD ($p<0.001$), although researchers did not examine this association by univariate or multivariate analysis. Recently, in a Brazilian longitudinal study conducted with 176 COPD patients hospitalized by the disease's exacerbation (mean age 68.2 ± 10.4 years), Teixeira et al. (18) showed that low CC (≤ 34 cm for men and ≤ 33 cm for women) was significantly associated with malnutrition (OR 4.62) and more than 11 days hospital stay (OR 2.21) according to multivariate analysis. Given the scarce literature on this specific issue, this study aimed to assess if reduced CC is associated with clinical outcomes in COPD patients referred to an outpatient pulmonary rehabilitation program.

Methods

Design

This was a single-center, retrospective observational study using existing data of COPD patients (≥ 40 years old) of both sexes referred to an outpatient PRP. The data collection occurred during the patient's initial evaluation for admission in the PRP by a pulmonary physician and trained rehabilitation therapists, from May 2002 to October 2009. This study was conducted according to The Code of Ethics of the World Medical Association (Declaration of Helsinki). The Research Ethics Committee of the Institution approved this study protocol (number 4.08.03.06.306), and all patients gave written informed consent.

Sample

COPD patients were selected using a non-probabilistic convenience sampling, and the inclusion criteria were clinical and functional diagnosis of COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria[1] (irreversible airflow limitation defined as FEV_1/forced vital capacity [FVC] <0.70) and clinical stability indicated by no change in medication dosage or exacerbation of symptoms in the preceding four weeks. Exclusion criteria were: patients with comorbidities (psychiatric illness or dementia, uncontrolled cardiovascular diseases, orthopedic, rheumatologic, musculoskeletal or neurological disorders) that contraindicated physical activity, patients in current use or with the indication for oxygen therapy at rest or exercise, or patients that did not have available CC data. We calculated the sample size for the present study, considering the difference in CC between survivors and non-survivors COPD patients (33.4 ± 2.9 *vs* 30.9 ± 3.8, respectively) reported by Ho SC et al [17], with a power of 90%, a significance level of 5%, and an additional of 20% for adjustment in multivariate analysis and follow-up losses. The proposed calculation estimated 94 patients to conduct the study.

Data collection

Data were retrieved from the PRP medical records of each patient and included: age, gender, FEV_1, and FVC (liters and % predict) post-bronchodilator spirometry [19], modified Medical Research Council dyspnea scale (mMRC scale) [20], self-reported comorbidities history, frequencies of hospital admissions, and antibiotics requirement due to COPD exacerbations during 12 months previous to the initial assessment. As with any exacerbation treated with antibiotics, the patient also receives corticosteroids, the use of corticosteroids is implicit when prescribing antibiotics. This information was applied to categorize patients as COPD frequent exacerbators [21], if they had one or more hospitalizations and/or antibiotics use two or more times in the last year. Smoking status and history (pack-years), anthropometric measurements (weight, height, and calf circumference) [22], body mass index (BMI) [22], exercise capacity [6-minute walking test (6 MWT)] [23], BODE (Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity) index [24], health-related quality of life (HRQL) (St. George's Respiratory Questionnaire - SGRQ) [25] were collected. Also, the data of all-cause deaths in the following two years after initial assessment were obtained.

Spirometry tests were performed using the spirometer (Microlab®, United Kingdom), according to the published standard [19]. Based on the post-bronchodilator % of predicted FEV_1 values, airflow obstruction degree severity was determined using GOLD stage criteria: GOLD stage 1 (mild): ≥ 80%; stage 2 (moderate): 50-79%; stage 3 (severe): 30-49%; stage 4 (very severe) < 30% [1].

Dyspnea associated with daily activities was assessed using the mMRC scale, with scoring ranging from 0 ("Dyspnea only with strenuous exercise") to 4 ("Too dyspneic to leave house or breathless when dressing") [20].

Exercise capacity was evaluated by the 6MWT, performed following ATS/ERS guidelines [23]. Furthermore, patients were categorized into two groups, according to the walked distance in the percentage of predicted values, obtained from reference equation for Brazilian population [26]: ≥80% of the

predicted as ‘preserved performance’ and <80% of the predicted as ‘impaired performance’ [27].

To assess health-related quality of life, patients completed the self-administered SGRQ [25] under the rehabilitation staff supervision. The SGRQ consists of a total score and three components subscores: symptoms, activities, and impact (each, total score and subscores, ranging from zero [best possible health status] to 100 points [worst possible health status]).

Anthropometric measurements were performed according to the World Health Organization recommendations [22]. Weight and height were measured with a calibrated anthropometric scale (Filizola®, Brazil), and patients were requested to wear light clothing and to be barefoot. BMI was calculated based on height and weight. CC was measured with a steel measuring tape (Cescorf®, Brazil), and taken at the widest girth of right calf with the patient seated and the knee flexed to 90°. In this study, CC measurement was used as a marker of MM, and the cutoff points of ≤ 34 cm for men and ≤ 33 cm for women were adopted as indicative of ‘reduced muscle mass’ [12].

Statistical analysis

Descriptive statistics were calculated, and quantitative data are presented as mean and standard deviation or median and interquartile amplitude, while categorical data are presented as n (%). The normality of variables was tested by Kolgomorov-Smirnov. Patients with reduced MM were compared to patients with adequate MM by Student T-test (parametric variables), Mann-Whitney test (non-parametric variables), or Chi-square (categorical variables). Logistic regression was performed to evaluate the magnitude of the association between reduced CC and clinical outcomes, considering confounders variables in the adjustment based on P values < 0.20 in bivariate analyses. All analyses were performed in SPSS 21.0 and P values < 0.05 were considered statistically significant.

Results

One hundred forty-four consecutive patients were included in the study (**Figure 1**). **Table 1**[28]presents the demographic and clinical characteristics of this sample. Over half of the patients were men, with a mean age of 64.6 ± 8.5 years. GOLD stages 3 and 4 corresponded to about three-quarters of the patients evaluated and BODE index median score was 3.0 (2.8 - 5.0). Approximately 80% of the patients were former smokers and had a lifetime smoking exposure median of 42.0 (22.5 -80.0) pack-year. Patients were followed for two years and 18 deaths occurred during this time. Thirty-nine percent of patients were classified as COPD frequent exacerbators, with 26.4% and 22.2% of the total sample presenting the criteria one or more hospitalizations and antibiotics use two or more times in the last year, respectively.

Reduced CC was observed in 45.1% of patients, and it was more frequent in females (56.0%) compared to males (39.4%), although the difference did not reach statistical significance (p = 0.078). **Table 2** presents the comparisons of general and clinical characteristics of COPD patients grouped according to CC. The ‘reduced MM’ group presented lower values in spirometry parameters, a higher proportion of patients classified as GOLD 3-4 stages and increased frequency of acute exacerbations in the previous 12 months compared to the ‘adequate MM’ group. Also, the ‘reduced MM’ group presented a significant minor performance in 6MWT and a higher value in all three subscores and total SGRQ score. Otherwise, the mortality rate was significantly higher in the ‘reduced MM’ group in comparison to the ‘adequate MM’ group.

Table 3 shows the logistic regression analysis results about the association between reduced MM and clinical outcomes. Patients with reduced MM presented 5.0 times higher odds of a more advanced stage of COPD, 2.3 times higher odds of acute exacerbation history in the last 12 months, 2.7 times higher odds of worse health-related quality of life, and an increase of 3.7 times in risk of death in the following two years in comparison to patients with adequate MM.

Discussion

The present study evaluated the association between reduced CC, clinical outcomes, and mortality among COPD patients who were screened for admission to an outpatient PRP. Patients with reduced CC presented more odds for worse outcomes, namely, more advanced GOLD stages, greater impairment in total SGRQ score, higher odds of acute exacerbation history in the last 12 months, and higher mortality in two years compared with those COPD patients with adequate CC.

Reduced CC was present in 45% of studied COPD outpatients, according to the Brazilian CC cutoff points. The prevalence of reduced MM among COPD patients varies, depending on the population studied and the diagnostic approach to assess body composition. The European Respiratory Society pointed dual-energy X-ray absorptiometry, bioimpedance analysis, and anthropometry as appropriate measurements of body composition of COPD patients in clinical practice, especially to distinguish between low and normal fat-free mass (FFM) [11]. Until now reduced FFM index is the most common indicator of reduced MM applied in studies involving COPD patients and the frequency of low FFM ranged from 35.0 to 48.0% [7,29,30]. We identified only three studies [15,31,32] that assessed it by low CC and reported its prevalence data, like as in the current study: among 50 Swedish hospitalized COPD patients (mean age 75.7 ± 6.9 years) evaluated next to discharge (stable condition and free state of acute exacerbation) low CC (<31 cm) was presented in 62% of sample [31]; a Taiwanese investigation [32] with 83 COPD patients (predominantly male and > 65 years old) from a pulmonary rehabilitation unit, in which the prevalence of low CC (<30 cm for men and <27 cm for women) was 14.5%; and a Brazilian study [15] among 176 COPD hospitalized patients during an exacerbation, in which the prevalence of low CC (according to Brazilian cutoff points) was 70%. With some differences due to the cutoff point adopted for the identification of reduced MM, the current study confirmed that this condition is prevalent in COPD patients.

Muscle wasting is a common systemic manifestation of COPD and tends to follow the progressive disease course [3,4,33]. This catabolism is directed by

multiple factors interaction [3,4,33], which in turn impacts differently on each patient [4], and includes systemic inflammation [3,4,33,34], oxidative stress [4,33,34], hypoxemia [3,4,33] and hypercapnia [4,33], recurrent exacerbations [3,4,33,34], corticosteroids use [3,4,33,34], epigenetic modifications of muscle cells [34], aging [4,33,34], an imbalance between protein synthesis and degradation [4,33,34], low levels of anabolic hormones and growth factors [4,33,34], vitamin D deficiency [4,33], physical inactivity [4,33,34], cigarette smoke [4,33], and alcohol abuse [4]. The presence of reduced MM in COPD patients is related to worse outcomes [7–9].

In line with previous studies, low MM was associated with COPD severity in this sample of outpatients. Patients with reduced CC had five times more odds of presenting advanced GOLD stages compared with their counterparts with adequate CC. The Extrapulmonary Consequences of COPD in the Elderly study [35], a multicenter population-based observational study involving 460 COPD patients (mean age 75.0 ± 5.9 years) found that COPD severity was significantly, although weakly, correlated with low calf circumference (<31 cm) (Spearman correlation coefficient = -0.011). Similarly, an Indian study involving 102 COPD outpatients (majority < 60 years-old) showed a significant CC decline with increasing severity of COPD [18].

We found that COPD patients with reduced CC had an increased likelihood of acute exacerbation history in the last 12 months in 2.3 times than their counterparts with adequate CC. Muscle wasting and COPD acute exacerbations seem mutually contribute to each other. MM depletion is commonly aggravated during acute exacerbation [4,33,36], due to the contribution of several factors, including higher systemic inflammation [37], worsening of COPD symptoms of impact on food intake [38], intensification of muscle disuse and it prolongation after the acute event [37,39], and corticosteroids use [4]. In parallel, low MM is associated with frequent exacerbations [36,40]. In a Spanish prospective study [41] with 78 COPD patients hospital admitted for acute exacerbation, the readmission in the next three months was associated with less FFM. Similarly, in a post hoc analysis of a prospective observational cohort [42] with 102 stable male COPD patients, an accelerated decline in the cross-sectional area of the erector spinae muscles assessed by CT was associated

with twice frequency of moderate-to-severe exacerbations during three years of follow-up.

In the current study, patients with reduced CC exhibited 2.7 more chances of impaired total SGRQ score. To date, none study analyzed the possible association between CC measurement and HRQL in COPD patients, but it has already been related to other indicators of reduced MM. Shoup et al. [43] evaluated the relationship between nutritional status and HRQL in 50 symptomatic COPD patients (most of them had completed a PRP) and showed that patients with a low lean mass index had significantly higher subscores and total SGRQ scores than their counterparts with preserved lean mass [symptom, 69 ± 14 versus 56 ± 21; activity, 73 ± 14 versus 59 ± 21; impact, 37 ± 19 versus 25 ± 15 and total SGRQ, 53 ± 13 versus 40 ± 15]. Another study [44] investigated the relationship between the different domains of SGRQ with peripheral muscle histochemical in 29 Venezuelan COPD outpatients and verified a moderate negative correlation between total SGRQ score with type I muscle fiber proportion ($r=-0.59$; $p<0.01$). Muscle depletion appears to be more prominent in lower extremity muscle groups in COPD patients, and may also contribute to weakness in the lower limbs, which has a greater impact on the perception of health status resulting from the disease [45]. Previous studies among COPD patients reported poorer HRQL in women than in men [46,47]. In the present study, stratification by gender was not feasible to analyze, due to the small sample size. This gender-specific assessment in HRQL remains like a perspective for future studies with larger sample size.

Muscle wasting in COPD patients has been identified as an important predictor of mortality [7]. In our study, the presence of reduced CC increased 3.7 times the likelihood to die in two-years. The only study identified in the literature analyzing the relationship between CC and mortality in COPD was a Thailand cohort [17], in which low CC (<30 cm) predicted the risk of death among 104 COPD outpatients most accurately (HR= 4.40 (95% CI, 1.82-10.63), p=0.001) than mid-arm circumference and body mass index in a follow-up of three-years. Muscle wasting has also been associated with mortality in COPD in other studies [7,8,48,49] that used different parameters for the assessment of MM.

The current study presents some limitations. Its retrospective single-center design limits its results generalization. Another limitation is related to missing data for some of the patients, which may have underpowered the analysis in which these variables were included, due to its commitment to its small sample size. Moreover, the date of death unregistered precluded us to carry out the Cox regression analysis to determine the association between CC classification and mortality. The findings of mortality at two years of follow-up need to be confirmed since the CC measurement was evaluated only at the baseline, also we did not have other information related to the patient's clinical condition that could also be predictors of mortality in this period, which may have affected the results of our study. The CC cutoff points applied in this study were validated to older adults' Brazilian population; however, our sample was constituted of almost 70% of elderly patients. Another limitation that must be pointed out is the frequency of exacerbations that can change as demonstrated by Vogelmeier et al. (2019) [50]. The study included an American and English database and showed that 34.2% and 46.9% of patients with no exacerbation in the previous year had one or more exacerbations in the subsequent year and those with one exacerbation had 28.5% and 33.5% two or more exacerbation episodes [50]. As a strength, this is an original study that, with the simplicity of measuring the CC was able to reproduce outcome findings in COPD patients from previous investigations that evaluated MM using more sophisticated methodologies, and therefore, more expensive and unusual for clinical applicability. Our results can be applied in clinical practice since CC is an easy, inexpensive, accessible, and quick measure and can be obtained by any duly trained healthcare professional. It is important to reinforce the limitations of CC: limb edema precludes the measure of CC and in patients with sarcopenic obesity the established cutoff points cannot be accurate to identify reduced MM.

Considering the limitations pointed above related to its retrospective design, the current findings are more 'hypothesis-generating' than absolute conclusions. Prospective studies with large samples and preferably from different centers are desirable to confirm our results, including serial measurements of CC in PRP to assess if this multidisciplinary intervention is

effective in modifying and improving MM volume in these patients assessed by this simple indicator. Furthermore, future studies should also investigate the association between reduced CC and physical performance, since we observed a significant and clinically relevant difference in 6MWT (> 30 meters) between patients with reduced and adequate CC.

Conclusion

Reduced CC in COPD patients under initial assessment for PRP admission was associated with disease severity, acute exacerbation history in the last 12 months, poor health status, and higher mortality in two-years of follow-up. Considering its clinical applicability, the measure of CC should be introduced in the nutritional assessment of COPD patients admitted for PRP.

DECLARATION OF INTERESTS

The authors have no conflict of interest to declare.

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Table 1 – Characteristics of COPD patients (n = 144)

Variables	Descriptive Statistics
Demographic characteristics	
Age (years)	64.6 ± 8.5
≥ 60 years-old [a]	102 (70.8)
Male	94 (65.3)
Clinical characteristics	
FEV_1 (l)	1.0 (0.8 – 1.4)
FEV_1 (% predict)	40.3 ± 15.8
FVC (l)	2.3 ± 0.8
FVC (% predict)	66.9 ± 20.1
FEV_1/FVC	47.4 ± 11.9
GOLD stage	
1/2/3/4	2 (1.4)/ 35 (24.3)/ 65 (45.1)/ 42 (29.2)
COPD frequent exacerbator	56 (38.9)
Hospital-admissions in the last year [b]	38 (26.4)
Antibiotic prescriptions in the last year (≥ 2 times) [b]	32 (22.2)
Comorbidities	
Hypertension	37 (26.4)
Cardiovascular disease	12 (8.6)
Diabetes	6 (4.3)
Osteoporosis	5 (3.2)
mMRC, Dyspnea scale (n = 76)	
Scale 0/1/2/3/4	5 (6.6)/19 (25.0)/17 (22.4)/9 (11.8)/26 (34.2)
BODE Index (points) (n = 130)	3.0 (2.8 – 5.0)
Smoking (n = 138)	
Current smoker	19 (13.8)
Former smoker	113 (81.9)
Never smoker	6 (4.3)
Smoking pack-years (n = 123)	42 (22.5 -80.0)
6MWT (m) (n = 133)	375.9 ± 95.0
6MWT (% of predicted)	68.4 ± 17.2
Health-related quality of life (n = 133)	
Symptoms SGRQ score	49.5 ± 19.7
Activity SGRQ score	73.3 ± 32.4

(continued on next page)

Table 1 Continued

Variables	Descriptive Statistics
Impact SGRQ score	36.5 (22.8 – 48.0)
Total SGRQ score	49.8 ±16.5
Body weight (kg)	67.9 ± 15.3
BMI (kg/m^2)	25.1 ± 5.0
Calf circumference, cm	34.4 ± 3.7

Data are presented as mean± standard deviation or median (P25-P75) for quantitative variable and as number (%) for categorical variable.

[a] "older adults", according Brazilian legislation [27].

[b] referring to the number of events in the total sample.

Abbreviations: FEV_1, forced expiratory volume in one second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; mMRC, modified Medical Research Council dyspnea scale; BODE, Body Mass Index. Airflow Obstruction. Dyspnea and Exercise Capacity; 6MWT, 6-min walk test; SGRQ, Saint George Respiratory Questionnaire; BMI, Body Mass Index.

Table 2 – Comparison of general and clinical characteristics between COPD patients with "Adequate muscle mass" and "Reduced muscle mass" (n=144)

Variable	"Adequate muscle mass" (♂ >34 cm e ♀ >33 cm) (n=79)	"Reduced muscle mass" (♂ ≤34 cm e ♀ ≤33 cm) (n=65)	p
Age (years)	64.5 ± 8.7	64.6 ± 8.3	0.970[1]
≥ 60 years-old[a]	55 (69.6)	47 (72.3)	0.854[1]
FEV_1 (l)	1.1 (0.8-1.6)	0.8 (0.7-1.0)	< 0.001[2]
FEV_1 (% predict)	40.9 (31.9-56.2)	34.0 (26.2-42.0)	< 0.001[1]
FVC (l)	2.5 ± 0.8	2.1 ± 0.8	0.004[1]
FVC (% predict)	70.6 ± 21.0	62.4 ± 18.1	0.014[1]
FEV_1/FVC	49.9 ±11.8	44.3±11.4	0.005[2]
GOLD stage			
1 and 2	30 (38.0)	7 (10.8)	
3 and 4	49 (62.0)	58 (89.2)	< 0.001[3]
COPD frequent exacerbator	22 (27.8)	34 (52.3)	0.005 [3]
mMRC, Dyspnea scale (points)	0.0 (0.0 - 2.0)	0.0 (0.0 - 1.0)	0.508[2]
BODE Index (points)	3.0 (2.0 - 4.0)	4.0 (3.0 - 5.0)	0.001[2]
Smoking habit and history			
Current smoker	7 (9.6)	12 (18.5)	0.308[3]
Former smoker	63 (86.3)	50 (76.9)	
Never smoker	3 (4.1)	3 (4.6)	
Smoking pack-years	40.5 (21.6-80.0)	44.0 (22.5-79.5)	0.996[2]

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Table 2 Continued

Variable	"Adequate muscle mass" (♂ >34 cm e ♀ >33 cm) (n=79)	"Reduced muscle mass" (♂ ≤34 cm e ♀ ≤33 cm) (n=65)	p
Exercise capacity			
6MWT (m)	390.5 ± 87.0	357.3 ± 102.1	0.046[1]
6MWT (<80% of predicted)	58 (78.4)	46 (79.3)	0.897[3]
Health-related quality of life			
Symptom SGRQ score	46.7 ± 16.6	53.0 ± 19.2	0.063[1]
Activity SGRQ score	72 (53.0-85.3)	75 (66.0-92.0)	0.042[2]
Impact SGRQ score	31.0 (18.5-41.3)	40.5 (28.3- 52.5)	0.004[2]
Total SGRQ score	45.8 ± 16.6	54.7 ± 15.0	0.02[1]
Anthropometry			
Body weight (kg)	77.1 ± 13.0	56.7 ± 9.3	< 0.001[1]
BMI (kg/m^2)	27.9 ± 4.4	21.6 ± 3.4	< 0.001[1]
2-year mortality	4 (5.1)	14 (21.5)	0.004[4]

[1] Student's t-test. [2] Mann–Whitney U test. [3] Chi-square test. [4] Fisher's exact test.

Data are presented as means ± SDs or medians (interquartile range, IQR), or absolute (relative) frequencies.

[a] "older adults", according Brazilian legislation [27].

Abbreviations: FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council dyspnea scale; BODE: Body Mass Index. Airflow Obstruction. Dyspnea and Exercise Capacity; 6MWT: 6-min walk test; SGRQ: Saint George Respiratory Questionnaire; BMI: Body Mass Index.

Table 3 - Association between reduced muscle mass and clinical outcomes in COPD patients referred to an outpatient pulmonary rehabilitation program

	Reduced muscle mass Odds Ratio (CI 95%)[1]	P value
Gold stages 3 e 4		
Crude model	3.74 (1.46-9.53)	0.006
Adjusted model[*]	5.09 (2.00-12.96)	0.001
COPD frequent exacerbators		
Crude model	2.72 (1.34- 5.48)	0.005
Adjusted model[♯]	2.34 (1.11- 4.91)	0.025
Total SGRQ score (>49 points)		
Crude model	3.05 (1.49- 6.26)	0.002
Adjusted model[♯]	2.70 (1.22-6.00)	0.015
Mortality		
Crude model	3.55 (1.05-12.05)	0.042
Adjusted model[♯]	3.69 (1.06-12.87)	0.041

Logistic regression.

[*] Adjusted for age and smoking status

[♯] Adjusted for age, smoking status, and (FEV_1) forced expiratory volume in one second.

SGRQ: Saint-George Respiratory Questionnaire.

5 ARTIGO 2

Association of Reduced BMI, length of hospital stay, and malnutrition diagnosis in COPD patients with acute exacerbation: A secondary analysis of a cohort study

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ABSTRACT

Background: Background: Body mass index (BMI) has received attention in relation to chronic obstructive pulmonary disease (COPD) given its prognostic value; despite its limitations in detecting nutritional impairments compatible with malnutrition. This study aimed to confirm the association between BMI and in-hospital outcomes in patients with acute exacerbation of COPD (AECOPD) and its inaccuracy in diagnosing malnutrition**. Methods**: Secondary analysis of a cohort study of hospitalized AECOPD patients. Malnutrition was diagnosed by subjective global assessment (SGA), Academy of Nutrition and Dietetics - American Society for Parenteral and Enteral Nutrition (AND-ASPEN), and two cutoff values for reduced BMI (age-related and ≤ 21.0). We assessed BMI accuracy using the area under the receiver operating characteristic (AUC-ROC) curve. We evaluated in-hospital mortality and hospital stay outcomes (longer or shorter than the median) and constructed regression models. **Results:** 241 patients were analyzed, the median hospital stay was 11 (7–18) days, and 7.5% of patients died. Malnutrition prevalence according to BMI, SGA, and AND-ASPEN was 21.4%, 50%, and 54%, respectively. Reduced BMI presented low agreement with SGA and AND-ASPEN (kappa = 0.315 and 0.383) and unsatisfactory accuracy (AUC-ROC curve = 0.333 and 0.679). Age-related reduced BMI (OR=2.11; 95%CI, 1.10–4.04) and BMI ≤ 21.0 (OR=2.25; 95%CI, 1.13–4.48) were associated with hospital stays longer than the median, but not in-hospital mortality. **Conclusion:** BMI was inaccurate in identifying malnutrition in AECOPD patients and was positively associated with hospital stays longer than 10 days.

Keywords: malnutrition, COPD, hospitalization, body mass index, length of stay.

Clinical Relevancy Statement

Malnutrition is a common COPD systemic manifestation, and it is associated with impaired functional capacity and quality of life, and higher exacerbation and mortality risk. In addition, acute exacerbation episodes contribute to nutritional deterioration in COPD patients. In clinical practice, malnutrition identification is imperative and requires comprehensive assessment methods; however, the BMI value is still over-emphasized for malnutrition diagnosis. In this study involving hospitalized patients with AECOPD, we demonstrated that reduced BMI underdiagnosed malnutrition in comparison to Subjective Global Assessment and the American Society of Parenteral and Enteral Nutrition - Academy of Nutrition and Dietetics' approach for this diagnosis. Reduced BMI was associated with hospital stays longer than the median in adjusted models, but not with in-hospital mortality.

Introduction

Chronic obstructive pulmonary disease (COPD) affects about 13.1% of the World population [1] and is an important contributor to the rising burden of non-communicable diseases and increased disability-adjusted life-years. [2] Worldwide, COPD represents the third leading cause of mortality and caused more than three million deaths in 2019. . [3]

In addition to pulmonary involvement, COPD presents an extra-pulmonary component determined by systemic effects that contribute to its severity, such as malnutrition. [4] Malnutrition is common in COPD, and its prevalence varies from 14% [5] to 83%, [6] according to the assessment applied, the severity of disease, clinical setting, and patient’s socioeconomic background. Malnutrition is associated with impaired functional capacity, quality of life, and survival of these patients. In COPD patients, malnutrition results from multiple factors interaction, such as the chronic inflammatory process, reduced food intake, respiratory symptoms, physical inactivity, aging, medications, which invariably lead to protein catabolism and loss of muscle mass. [7]

Furthermore, COPD patients can still be affected by periods of exacerbation - an acute event characterized by worsening of respiratory symptoms, requiring changes in the therapeutic regimen. [4] Malnutrition and acute exacerbation in COPD act mutually. While malnutrition increases exacerbation risk, the increase of local and systemic inflammation underlying the exacerbation episode often incorporate elements (anorexia, fever, reduced physical activity, a negative energy balance, high work of breathing, and use of systemic steroids) that contribute to nutritional status deterioration. [7]

Despite the recognized unfavorable impact of malnutrition in hospitalized patient outcomes and the well-established comprehensive nutritional assessment methods to recognize it in clinical practice, [8–11] malnutrition is still diagnosed by methods less accurate, such as body mass index (BMI). A recent survey involving members of the Academy of Nutrition and Dietetics (n = 2,718) revealed that registered dietitians still use BMI to identify malnutrition, and less than half routinely applied nutrition-focused physical examination techniques during the nutritional assessment.[12] It is also observed in studies conducted with COPD patients that used BMI for diagnosing undernutrition. [13,14] However, BMI is unable to detect the nutritional impairments that meet malnutrition diagnosis criteria requirements and precede an underweight phenotype. [15] Malnutrition diagnosis involves the presence of inflammation due to chronic or acute disease, impaired nutritional intake and/or assimilation exacerbated by inflammation, and its deleterious repercussions in body composition and functional capacity. [16] Subjective global assessment (SGA) is recognized as a reference method for diagnosing malnutrition. [8] Recently other tools were also proposed: AND-ASPEN (Academy of Nutrition and Dietetics-American Society for Parenteral and Enteral Nutrition) [9] and GLIM (Global Leadership Initiative on Malnutrition). [11] In a previous study among hospitalized patients with AECOPD, [17] our research group showed that AND-ASPEN tool [9] presented an excellent accuracy and substantial concordance with SGA [8] for the diagnosis of malnutrition, as well as satisfactory predictive validity, in contrast to GLIM, [11] which showed acceptable accuracy and good agreement, and no association with clinical outcomes.

Although BMI could not be accurate to diagnose malnutrition, historically, reduced BMI has received considerable attention in COPD, given its prognostic value. [18] A meta-analysis involving 22 cohorts (21,150 COPD participants) found a higher risk of death (RR = 1.34) for underweight individuals (BMI ≤18.5 kg/m^2) compared with those having normal BMI (18.5–24.9 kg/m^2). [18] Furthermore, the literature presents different cutoff values for low BMI associated with increased risk of mortality in COPD. [19,20] Thus, this study aimed to evaluate the accuracy of two distinct cutoff values for reduced BMI on diagnosing malnutrition (compared to SGA and AND-ASPEN) and their association with hospital stay and in-hospital death in patients with AECOPD.

Methods

Participants and study design

We conducted a secondary analysis of a prospective observational study among COPD patients admitted to a Brazilian public hospital due to exacerbation of the disease, from March 2019 and March 2020, as detailed in a previous paper. [17] Briefly, inclusion criteria were: patient able to participate in a short interview and to stand in an upright position (all data obtained from the nurse staff before inviting patients to be included in the study). The exclusion criteria were limb amputation presence and COPD hospital admission reasons unrelated to respiratory conditions. The ethical Committee of Hospital approved the protocol (approval number 3.126.689), and the study conduction followed the local standards for ethics in research involving humans (http://www.conselho.saude.gov.br/resolucoes/2012/Reso466.pdf).

Data collection

Trained nutrition staff (a researcher dietitian and three undergraduate nutrition students) collected data in the first 72 hours of the participants' hospital admission. Sociodemographic (age, gender, self-reported ethnicity, and educational level) and clinical variables (smoking status and comorbidities history) were gathered from electronic records or obtained by a standardized interview with patients at bedside. Patients who claimed abstinence from

smoking for at least six months or never smoked were considered non-smokers in the analysis. The Charlson Comorbidity Index (CCI) adjusted for age was calculated based on comorbid conditions to classify the patient's severity, [21] using an electronic application recommended by Hall et al. [22]

The patients who had their spirometry test data from last year available in the electronic records had the diagnosis of COPD confirmed by the Final Expiratory Volume in the First Second/Final Vital Capacity (FEV_1/FVC) ratio <70% post-bronchodilator use. Lung function parameters such as FEV_1 (absolute and % of predicted), FVC, FEV_1/FVC were also obtained from spirometry and applied to classify patients into four spirometry stages according to the Global Initiative of Chronic Obstructive Lung Disease (GOLD) guidelines: GOLD 1 (mild) if FEV_1 >80% of the predicted value, GOLD 2 (moderate) if >50% FEV_1 <80%, GOLD 3 (severe) if >30% FEV_1 <50%, and GOLD 4 (very severe) if FEV_1 <30%. [4] Patients answered the modified Medical Research Council (mMRC) dyspnea scale to classify dyspnea level. [23]

The following parameters common to SGA[8] and AND-ASPEN [9] were collected: involuntary weight loss [actual and usual (in the previous six months) body weight information to establish the weight loss magnitude and its pattern], muscle mass and subcutaneous fat loss (nutrition-focused physical examination), and changes in food intake (amount and consistency). In addition, the nutrition staff collected specific data on SGA[8] (gastrointestinal symptoms persisting longer than two weeks, reduction of functional capacity and its duration, and metabolic demand of disease) and for AND-ASPEN [9] consensus, the diminished functional status through handgrip strength (Saehan® - Masan, Korea). We diagnosed patients as malnourished using SGA [8] tool, considering the patient's clinical history and physical examination in moderately malnourished (SGA B) or severely malnourished (SGA C) and using AND-ASPEN consensus [9], in the presence of at least two of the six recommended clinical characteristics.

Body weight (kg) and height (m) were measured using a calibrated digital scale (Plena® - São Paulo, Brazil) and a portable stadiometer brand (SECA® -

Hamburg, Germany), wearing light clothing, barefoot, and in the upright position during the measurements. BMI (kg/m^2) was calculated and for analysis purposes, we applied the BMI cutoff values for underweight in two categories, as follow: age-related reduced BMI (< 18.5 kg/m^2 for adults [24] and < 22.0 kg/m^2 for elderly [25]) and BMI < 21.0 kg/m^2. [26]

At patients' discharge, we checked the electronic records to collect the outcomes of interest: length of hospital stay (LOS) and in-hospital mortality. For data analysis, we categorized the LOS as higher if the value found in days was equal to or greater than the median of our sample.

Statistical analysis

Descriptive statistics were calculated to present data and test the normality of quantitative variables using the Kolmogorov-Smirnov test. We also calculated the sensitivity, specificity, predictive positive and negative values (PPV and NPV), as well as the area under the ROC curve with a 95% confidence interval (95% CI) and kappa coefficient. Performance metrics were classified as follows: kappa values < 0.20 as poor; 0.21–0.40 as fair; 0.41–0.60 as moderate; 0.61–0.80 as substantial; 0.81–0.99 as almost perfect; and 1.00 as perfect agreement. [27] We assumed that the sensitivity, specificity, and positive and negative predictive values from 90 to 100%, as high, from 80 to ≤89% as moderate, and ≤79% as low. [28]

We compared patients grouped by BMI by Student t, Mann-Whitney, Fisher Exact, and Chi-Square tests regarding to parametric quantitative variables, non-parametric quantitative variable, and categorical variables, respectively. Fisher Exact test was applied when less than five cases in one group presented the feature analyzed. To evaluate the association of reduced BMI with clinical outcomes, we performed Logistic Regression using higher LOS as dependent variable and Cox Regression for in-hospital death. Crude and adjusted models (mMRC scale and age included as confounders) were constructed. We included as confounders in multivariate adjusted analysis all variables with P value < 0.20 in the comparison of groups in bivariate analysis.

Although patients with BMI ≤ 21.0 kg/m^2 presented different COPD stage and FEV_1 values in comparison to patients with BMI > 21.0 kg/m^2, we did not include it as a confounder because these data were available for a subsample of 140 patients.

Data were analyzed on the SPSS 22.0 version and P values < 0.05 were considered statistically significant.

Results

A total of 241 hospitalized patients with AECOPD were included in the current study. The majority of them was males (53.5%), elderly (78.8%), self-reported white ethnicity (81.7%), actual non-smoker (94.6%), and classified as GOLD 3 or 4 (59.3% of 140 patients with FEV_1 available). Other features are summarized in **Table 1**.

Both reduced BMI groups (age-related and ≤ 21.0 kg/m2) had a higher prevalence of malnutrition by SGA and AND-ASPEN compared to those not categorized as reduced BMI. While patients with BMI < 21.0 kg/m^2, in comparison to patients with BMI > 21.0 kg/m^2, were younger, presented lower CCI adjusted for age and FEV_1/FVC ratio, and spent more days in hospital, as demonstrated in **Table 1**.

A prevalence of malnutrition was equal to 22.0%, 20.7%, 49.8%, and 53.9% by BMI age-related, BMI ≤ 21.0 kg/m^2, SGA, and AND-ASPEN, respectively.

The sensitivity and the specificity of age-related reduced BMI for malnutrition diagnosis, considering SGA[8] as a reference method was equal to 39.2% and 95.0%, respectively. The overall accuracy was 67.1%. The agreement between age-related reduced BMI and SGA[8] for malnutrition diagnosis was low, with a kappa coefficient of 0.342 ($p<0.001$), and its performance was unsatisfactory because the AUC-ROC curve was 0.671, as shown in **Table 2**. We observed similar results (with lower AUC-ROC curve value) when considering BMI ≤ 21.0 kg/m^2 cutoff to group underweight patients.

The sensitivity and the specificity of age-related reduced BMI for malnutrition diagnosis, considering AND-ASPEN [9] as a reference method, were

38.5% and 97.2%, respectively. The overall accuracy was 65.0%. PPV and PNV were 94.3% and 57.0%, respectively. The agreement between age-related reduced BMI and SGA[8] for malnutrition diagnosis was low, with a kappa coefficient equal to 0.338 ($p<0.001$); its performance was not satisfactory when compared with AND-ASPEN [9] as the reference method, since the AUC-ROC curve was equal to 0.679 (CI95% 0.611 - 0.746; $P< 0.001$), as demonstrated in **Table 2**. For the underweight group of patients (≤ 21.0 kg/m^2), we observed similar results, with the lower AUC-ROC curve.

Table 3 presents the distribution of patients with reduced BMI for the outcomes of interest: mortality and LOS. Regardless of the cutoff value adopted for the classification of reduced BMI, it was not associated with in-hospital mortality. In contrast, reduced BMI increased by two times the odds of hospital stay > 10 days after adjustment for confounders (**Table 4**).

Discussion

This study evaluated the accuracy of two distinct cutoff values for reduced BMI in diagnosing malnutrition and their association with LOS and in-hospital mortality among patients with AECOPD. The reduced BMI presented low reliability in identifying malnutrition, regardless of the cutoff value, compared with the SGA [8] and the AND-ASPEN consensus criteria. [9] In contrast, reduced BMI was associated with hospital stay longer than median after adjustments, but not in-hospital mortality.

In our study, about half of patients presented malnutrition according to SGA [8] and AND-ASPEN consensus, [9] while it was less than one-quarter considering BMI criteria. In previous investigations among hospitalized COPD patients, the prevalence of malnutrition varied widely, ranging from 14% [5] to 83%. [6] This variability may have resulted from different criteria applied for the malnutrition diagnosis, COPD clinical phenotype and severity stage, reason for hospital admission (causes related or not to respiratory conditions), history of exacerbation episodes, participants' age, and the local socio-economic conditions. BMI remains a common criterion used for diagnosing malnutrition clinical settings. [11] In a meta-analysis investigating the prevalence of

malnutrition on hospital admission in pulmonology department inpatients, among the 11 studies that assessed nutritional status, the mean prevalence of malnutrition was 37% (95% CI, 34.8%–39.1%, I^2=99.7%). [29] Of these studies, five were diagnosed with malnutrition using a comprehensive nutritional assessment method (SGA[8]), while three studies adopted BMI in isolation. The comparison between these methods revealed that BMI indicated a proportion of malnutrition five times lower than SGA. In a more recent meta-analysis conducted by our research group, including 45 observational studies with inpatients and outpatients COPD patients, we demonstrated a mean prevalence of malnutrition equal to 20% (95%CI 0.15 – 0.25; I^2 = 100%) , and it is lower in the subgroup of studies that applied BMI for malnutrition diagnosis in comparison to these studies that applied any integrative tool, such as SGA (pooled prevalence = 0.37, 95% CI 0.25 - 0.50; I^2 = 96% versus pooled prevalence = 0.15, 95%CI 0.11 - 0.21; I^2 = 100%); $p < 0.01$). [30] So, malnutrition is underdiagnosed by the BMI owing to its inherent limitations, which do not capture relevant changes in nutritional status, such as muscle mass depletion and involuntary weight loss, especially in overweight and obese individuals. [15]

In this study, BMI was inaccurate in recognizing malnourished patients considering SGA[8] and AND-ASPEN [9] as the reference methods, demonstrated by the low AUC- ROC and kappa values. This corroborates the findings of previous studies with different populations of hospitalized inpatients, assessing the agreement between the use of isolated BMI and SGA[8] for the diagnosis of malnutrition. Tran et al. assessed 693 adult patients from six general public hospitals, and although they found acceptable AUC-ROC curve values (0.70-0.73) for all BMI categories below 21.0 kg/m^2, the values were low for sensitivity (39.6-64.6%). [31] In parallel, Ng et al [24] also considered distinct BMI cutoff values to identify malnutrition in 1,152 older hospital inpatients and found a fair agreement (kappa= 0.225-0.401; $p < 0.0005$) for all BMI cutoff value categories less than 21.0 kg/m^2. [31] Similarly, among 300 hospitalized surgical patients BMI (< 18.5 kg/m^2) compared to SGA[8] showed poor agreement (kappa= 0.068, $p < 0.05$), low sensitivity [0.43, NS (95% CI 0.33-0.47)] and specificity [0.39, NS (95% CI 0.35-0.42)]. [33]

Despite the inadequacy of BMI in detecting malnutrition, our findings revealed a two-fold increase in the chance of hospital stay > 10 days in patients with reduced BMI, regardless of age adjustment. Similarly, two Indian studies among COPD patients hospitalized observed a significant negative correlation between low BMI and LOS, [33,34] suggesting the deleterious impact of nutritional depletion in the occurrence of complications and poorer response to treatment during hospitalization. In contrast, we failed to confirm the acknowledged BMI association with mortality in COPD. BMI is one of the four components of the BODE (body-mass index, airflow obstruction, dyspnea, and exercise capacity) index, [19] which has a score calculated in clinical practice, because it is a strong predictor of the risk of death among COPD patients. This association was also verified in a meta-analysis with COPD, identifying that low BMI (< 18.5 kg/m^2) increased the risk of mortality [relative risk (RR)= 1.34, CI 95%: 1.01,1.78;0.04]. [18] In addition, Schols et al. also found that, in COPD patients, low BMI increased mortality risk when patients presented normal (semistarvation) (RR= 1.23, 95% CI 1.68, 2.24) or reduced fat-free mass index (cachexia) (RR= 1.91, 95% CI 1.37, 2.67); the magnitude of association was higher in patients with cachexia, which better reflects the severity of systemic disease than does BMI. [36]

This study had some limitations: a) its single-center design and the eligibility criteria (such as the inclusion of patients able to respond to the interview and exclusion of those presenting localized or generalized fluid accumulation) reduce the generalizability of the results; b) spirometry data were missing for 42% of our sample and it precluded the inclusion of FEV_1 as a confounder in the multivariate analysis; c) we did not explore information on smoking history, since we did not collect enough data to estimate the intensity of tobacco exposure (pack-years) and its duration; d) the short follow-up probably prevented us from detecting an association between reduced BMI and mortality, which added to the low incidence of mortality; this could have compromised the power of the study to detect this association. Nonetheless, our study has important strengths. The accuracy of BMI was compared to SGA [8] - which is a recognized tool for malnutrition in the hospital setting, and AND-ASPEN [9] - which concurrent and predictive validity in COPD patients was

previously demonstrated by our research group. The study findings contribute to providing important information for clinical practitioners because it emphasizes the BMI weakness tin identifying malnutrition in hospitalized patients with AECOPD.

These findings suggest that in the nutrition care process of hospitalized COPD patients, it is relevant to diagnose malnutrition through the use of comprehensive tools which consider aspects related to disease severity, food consumption, weight history, and depletion and functionality of muscle mass. However, in a multimodal assessment, BMI can be calculated with a focus on its association with clinical outcomes, rather than a nutritional diagnostic parameter.

Conclusion

Regardless of the cutoff value applied, BMI was inaccurate to identify malnutrition in hospitalized patients with AECOPD compared with the SGA [8] and AND-ASPEN [9]. Patients with low BMI were twice as likely to have a LOS longer than 10 days, however, in our sample, low BMI was not associated with mortality.

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Table 1. Comparison of features of hospitalized patients with AECOPD with normal and reduced body mass index by age and according the cutoff value 21.0 kg/m^2

	All sample (n = 241)	Normal BMI (n = 188)	Age-related reduced BMI (n = 53)	P value	BMI > 21.0kg/m^2 (n = 191)	BMI ≤ 21.0kg/m^2 (n = 50)	P value
Age (years), mean ± SD	68.30±10.21	68.01±9.87	69.34±11.38	0.404 [1]	69.26±10.14	64.66±9.8	0.004 [1]
Elderly, n (%)	190 (78/8%)	149 (79.3%)	41 (77.4%)	0.914 [2]	156 (81.7%)	34 (68.0%)	0.056 [2]
Males, n (%)	129 (53.5%)	104 (55.3%)	25 (47.2%)	0.371 [2]	104 (55.3%)	25 (47.2%)	0.371 [2]
Self-reported white ethinicity	197 (81.7%)	158 (84.0%)	39(73.6%)	0.124 [2]	162 (84.8%)	35 (70.0%)	0.027 [2]
Smoking status							
Never/ Former smoker, n (%)	228 (94.6%)	178 (94.7%)	50 (94.3%)	1.000 [3]	178 (93.2%)	50 (100%)	0.076 [3]
CCI (points), mean ± SD	4.93±2.06	4.93±2.11	4.92±1.88	0.984 [1]	5.10±2.11	4.26±1.72	0.009 [1]
mMRC (points), mean ± SD	3.96±1.33	4.03±1.18	3.70±1.74	0.106 [1]	4.01±1.20	3.78±1.74	0.287 [1]
COPD stage*				0.356 [2]			0.017 [2]
1-2, n (%)	57 (40.7%)	49 (43.0%)	8 (30.8%)		52 (46.0%)	5 (18.5%)	
3-4, n (%)	83 (59.3%)	65 (57.0%)	18 (69.2%)		61 (54.0%)	22(81.5%)	

(continued)

Table 1 - continued

FEV_1 (%)*, mean ± SD	45.98±18.21	46.28±19.09	44.74±14.29	0.690 [1]	46.96±18.61	42.02±16.18	0.201 [1]
FVC (%)*, mean ± SD	60.39±17.45	59.97±16.86	61.99±19.79	0.582 [1]	60.55±17.51	59.75±17.49	0.827 [1]
FEV_1/ FVC (%)*, mean ± SD	72.28±22.73	73.53±22.96	67.43±21.53	0.199 [1]	74.24±22.52	64.66±22.31	0.042 [1]
Malnutrition by SGA, n (%)	120 (49.8%)	73 (39.0%)	47 (88.7%)	<0.001 [2]	72 (37.9%)	48 (96.0%)	<0.001 [2]
Malnutrition by AND-ASPEN, n (%)	130 (53.9%)	80 (43.0%)	50 (94.3%)	<0.001 [2]	83 (43.9%)	47 (94.0%)	<0.001 [2]
Length of hospital stay (days), median (P25-P75)	11.0 (7.0 - 18.0)	10.0 (7.0 - 17.8)	13.0 (8.0 - 21.0)	0.066 [4]	10.0 (7.0 17.0)	13.5 (8.8 - 25.0)	0.023 [4]
In-hospital death, n (%)	18 (7.5%)	15 (8.0%)	3 (5.7%)	0.770 [3]	16 (8.4%)	2 (4.0%)	0.379 [3]

* Data available for 140 patients.

Abbreviations: SD, standard deviation; AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index; CCI, Charlson comorbidity index; mMRC, modified Medical Research Council; COPD, chronic obstructive lung disease; FEV_1 (%) , final expiratory volume in the first second percent of predicted; FVC (%) , final vital capacity percent of predicted; SGA, subjective global assessment; AND-ASPEN, Academy of Nutrition and Dietetics-American Society for Parenteral and Enteral Nutrition; P25, 25th percentile; P75, 75th percentile.

[1] Student t test. [2] Chi-square test. [3] Fisher Exact test. [4] Mann-Whitney Test.

Table 2. Metrics of reduced BMI reliability in diagnosing malnutrition.

Test Method	**Age-related reduced BMI**		**BMI ≤ 21.0 kg/m^2**	
Reference Method	**SGA**	**AND-ASPEN** [6]	**SGA**	**AND-ASPEN** [6]
Sensitivity	39.2%	38.5%	40.0%	36.2%
Specificity	95.0%	97.2%	98.3%	97.2%
PPV	88.7%	94.3%	96.0%	94.0%
NPV	61.0%	57.0%	62.1%	56.1%
Accuracy	67.1%	65.0%	69.2%	63.8%
AUC-ROC	0.671	0.679	0.500	0.333
	(0.602 - 0.740)	(0.611 - 0.746)	(0.378 - 0.622)	(0.265 - 0.401)
Kappa	0.342	0.338	0.383	0.315

Abbreviations: BMI, body mass index; SGA, subjective global assessment; AND-ASPEN, Academy of Nutrition and Dietetics-American Society for Parenteral and Enteral Nutrition; PPV, positive predictive value; NPV, negative predictive value; AUC-ROC, area under the ROC curve

Table 3. Association between reduced BMI and clinical outcomes in COPD patients

	In-hospital death		**Length of hospital stay**	
	Survivors (n = 223)	**Non-survivors (n = 18)**	**≤10 days (n = 117)**	**> 10 days (n = 124)**
Age-related reduced BMI, n (%)	50 (22.4%)	3 (16.7%)	19 (16.2%)	34 (27.4%)
	P value = 0.770[1]		*P value =0.053*[2]	
BMI ≤ 21.0kg/m^2, n (%)	48 (21.5%)	2 (11.1%)	17 (14.5%)	33 (26.6%)
	P value = 0.379[1]		*P value = 0.031*[2]	

[1] Chi-square test. [2] Fisher Exact test.

Abbreviations: BMI, body mass index.

Table 4. Association between reduced body mass index, higher length of hospital stay, and In-hospital death in patients with AECOPD: multivariate analysis

	In-hospital death [1] HR (95% CI)	**Hospital stay higher than 10 days [2] OR (95% CI)**
Age-related reduced BMI		
Crude	0.43 (0.12 - 1.53)	1.93 (1.03 - 3.62)
Adjusted	0.51 (0.14 - 1.91) [a]	2.11 (1.10 - 4.04) [a]
BMI ≤ 21.0kg/m^2		
Crude	0.21 (0.05 - 0.93)	2.11 (1.10 - 4.05)
Adjusted [3]	0.21 (0.04 - 1.09) [b]	2.25 (1.13 - 4.48) [b]

[1] Cox Regression. [2] Logistic regression.

[a] Adjusted for modified Medical Research Council dyspnea scale score and self-reported ethinicity

.[b] Adjusted for modified Medical Research Council dyspnea scale score, age-adjusted Charlson comorbidity index, smoker and self-reported ethnicity.

Abbreviation: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index.

6 ARTIGO 3

Increased energy and/or protein intake improves anthropometry and muscle strength in COPD patients: a systematic review with meta-analysis on randomized controlled clinical trials

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Running title: oral nutritional supplements on COPD patients

Keywords: COPD; Oral Nutrition Therapy; Nutritional Status; Oral Nutrition Supplements; Food Fortification.

ABSTRACT

Compromised nutritional status is associated with a poor prognosis in COPD patients. However, the impact of nutritional support in this group of patients is controversial. The present study systematically reviewed the effect of energy and or protein supplements or food fortification on anthropometry and muscle strength of COPD patients. We searched MEDLINE (PubMed), EMBASE, Cochrane Library, and Scopus for all published randomized clinical trials (RCTs) without language restriction up to May 2021. Three reviewers performed study selection and data extraction independently. We judged the risk of bias by RoB 2 and the certainty of evidence by the GRADE approach. We included thirty-two randomized controlled trials and compiled 31 of them (1,414 participants) in the random-effects model meta-analyses. Interventions were energy and/or protein oral nutritional supplements or food fortification added to the diet for at least one week. Pooled analysis revealed that nutritional interventions increased body weight (MD=1.44 kg, 95%CI 0.81 to 2.08, I^2=73%), lean body mass (SMD=0.37; 95%CI 0.15 to 0.59, I^2=46%), midarm muscle circumference (MD= 0.29 mm2, 95% CI 0.02 to 0.57, I^2=0%), triceps skinfold (MD= 1.09 mm, 95% CI 0.01 to 2.16, I^2=0%), and handgrip strength (SMD= 0.39, 95% CI 0.07 to 0.71, I^2=62%) compared to control diets. Certainty of evidence ranged from very low to low, and most studies were judged with some concerns or at high risk of bias. This meta-analysis revealed, with limited evidence, that increased protein and/or energy intake positively impacts anthropometric measures and handgrip strength of COPD patients..

PROSPERO CRD: 42020207577

Keywords: COPD; Nutrition; Oral Nutrition Therapy; Nutritional Status; Oral Nutrition Supplements; Food Fortification.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common, preventable, and treatable clinical condition, characterized by persistent respiratory symptoms and progressive airflow limitation due to airway and/or alveolar abnormalities usually resulting from significant exposure to harmful particles or gases [1]. At a global level, COPD prevalence is about 12.2% [2], and according to World Health Organization [3], the disease was the third leading mortality cause in 2020, responsible for approximately 6% of all deaths. Recent epidemiological findings indicate an increase in COPD prevalence, associated to the world population aging [2].

In addition to pulmonary involvement, the disease has an extra-pulmonary component evidenced by its systemic effects, which affect the nutritional status of patients [1]. The nutritional abnormalities manifested mainly as reduced muscle mass, strength and/or function and involuntary weight loss - regardless of body mass index (BMI) values [4], low body weight (BW) and nutrient deficiencies [5] tend to coexist and predict worse outcomes, including poor pulmonary function [6], impaired exercise capacity [7], and health-related quality of life [8], higher hospital readmissions [9], length of hospital stay [10,11], health-costs [11,12], and mortality rates [11,13,14].

Compromised nutritional status prevalence among COPD patients has been reported to be as high as 45% [15], depending on assessment method, diagnostic criteria, and cutoffs applied, as well the studied population. The pathogenesis of nutritional abnormalities in COPD is complex and involves multiple factors interaction, including increased systemic inflammation and oxidative stress, hypoxia, acute exacerbations, corticosteroids use [16,17], COPD symptoms, and patient-related factors as age, genetics, lifestyle, and psychological aspects [17].

The impact of nutritional status on the general condition of COPD patients manifests itself mainly through weight loss and muscle wasting. Unintentional weight loss occurs in almost 50% of the patients with severe COPD and about 15% of patients with mild-to-moderate COPD [18]. The decline

in pulmonary function [19,20], acceleration in disease progression [16], and impaired resistance to infections can be expected in malnourished COPD patients [17]. In addition, COPD patients present peripheral muscle dysfunction and atrophy, expressed as muscle strength and endurance reduction [21]. Dynamometric parameters are negatively associated with the disease stage [22] and with peak inspiratory flow rate generation [23].

In clinical practice, oral nutritional supplements (ONS) or fortified food (FF) prescription is the therapeutic first choice for patients with or at risk of malnutrition [1,24,25]. However, the first meta-analysis [26]) investigating the ONS (caloric supplementation for at least 2 weeks) influence in stable COPD patients outcomes, involving nine trials (n= 277 subjects), failed to show consistent benefits on anthropometric measurements, lung function, and exercise capacity in patients with COPD. There is a growing literature on the effect of energy and protein-based supplementation or FF on nutritional and clinical outcomes in the COPD population. The latest published meta-analyses of randomized controlled trials (RCTs) evaluating the effect of nutritional support in COPD patients concluded that ONS [27–29], mainly in depleted patients, resulted in statistically significant increases in BW, midarm muscle circumference (MAMC), skinfold thickness, and in respiratory muscle strength. However, these reviews have emphasized the need for more high-quality RCTs to confirm the role of nutritional support in COPD.

Two of the meta-analyses cited above had several analytical limitations [27,28]. The authors did not report whether a dose-response gradient was performed and did not make the subgroups analysis considering features, including patients' clinical status, and energy and/or protein quantities prescribed [27,28]. In addition, since 2012, more than 40 references about this topic were published. Furthermore, a more recent systematic review [30] of 22 studies (observational and intervention design) investigated the current evidence supporting the use of any nutritional supplementation (vitamins, PUFAs, protein, carbohydrates, etc.) to improve outcomes during PR in stable COPD patients, concluded that the results are controversial and pointed to the need for further studies in this area. However, the authors performed only a

narrative synthesis of the evidence. The current systematic review aimed to overcome the limitations of previously published systematic reviews addressing the effects of energy and/or protein ONS or FF on anthropometry, body composition, and muscle strength of COPD patients and to provide an up-to-date evidence synthesis.

METHODS

Study design

This systematic review of RCTs was conducted according to the recommendations of Cochrane Handbook for Systematic Reviews of Interventions Version 6.11 [31] and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [32]. We registered its protocol in the International Prospective Register of Systematic Reviews (PROSPERO) under number CRD42020207577.

Research Question

The objective of this study was to evaluate the available evidence from RCTs for the following clinical question: “What is the effect of dietary interventions with energy and/ or protein ONS and/or FF on nutritional status parameters in COPD patients?”.

We defined the intervention as any nutritional therapy based on energy and/or protein (e.g., creatine or whey protein or amino acid metabolites) and/or amino acids (e.g., isolated or in combination form) ONS or FF added to the diet for one or more week. And we defined the control group as a usual diet or placebo or dietary advice, as reported by authors in the primary studies.

Eligibility criteria

We developed inclusion and exclusion criteria using the Patient, Intervention, Comparators, Outcome, and Study Design (PICOS) method (**Table 1**). We included all RCTs (parallel or crossover design)that assessed the effects of different ONS or FF reporting at least one of the outcomes of interest:

a) BW; b) lean body mass (LBM); c) fat mass (FM); d) peripheral muscle strength. The studies should be performed in adults over 40 years of age with a COPD diagnosis.

We excluded studies that used the following interventions: 1. Enteral or parenteral nutrition; 2. ONS with different macronutrient distribution between the groups; 3. Comparison between two active ONS, but with distinct energy proposes; 4. Comparison between two protein sources ONS; 5. ONS of antioxidants or nitrate. Moreover, we excluded studies with COPD patients under mechanical ventilation, observational studies, literature reviews, opinion papers, non-randomized trials, and abstracts with irretrievable full-text after two attempts to contact the authors.

Search methods for identification of studies

We identified studies through a comprehensive search strategy developed and conducted by S.B. and F.M.S. in the following electronic databases on September 2nd, 2020: MEDLINE (PubMed), EMBASE, Cochrane Library, and Scopus. There were no restrictions to language or date of publication. We identified appropriate controlled vocabulary (e.g. MeSH terms and Emtree terms) and free-text terms (considering, for example, spelling variants, synonyms, acronyms) in all databases: COPD (population); nutrition therapy, dietary supplements, food supplements, and FF (interventions). **Table S1** (Supporting Information) presents the full search strategy performed in PubMed. We updated the search on May 18th, 2021.

Selection of studies

We screened records by title and abstract in a reference manager software (EndNote X9.3.1, Clarivate Analytics) based on the eligibility criteria by two independent investigators (S.B. and F.M.S.) after the automatic exclusion of duplicates. Bibliographic references of all studies included in this systematic review were hand-searched to identify additional RCTs not identified through electronic searching. Also, we used the "cited by" link function in PubMed for each article included in this review to identify potential eligible RCTs. To explore the grey literature, we searched the US National Library of Medicine

(ClinicalTrials.gov). After exclusion of irrelevant records, we assessed full-text articles for eligibility through a standardized electronic form in Google Forms® by each investigator in an independent manner (S.B. and V.K./S.B. and C.F.B.). A third researcher (F.M.S.) resolved any disagreement between reviewers through discussion before inclusion.

Data collection

Data were also independently extracted by three reviewers grouped in pairs (S.B., V.K., and C.F.B.) through a standardized electronic form in Google Forms®, and subsequently cross-checked in conjunction with F.M.S. before computing entries in structured tables in Microsoft Office Excel®. We extracted the following data from each study: first author; year of publication; study design; country of study; intervention time; measured endpoints; inclusion and exclusion criteria; sample size; male percentage of sample; sample mean age; sample mean baseline values of BMI or ideal BW percentage; and sample mean baseline forced expiratory volume in the first second in liters and/or predicted%. We also collected information about the setting of nutritional intervention, considering a Pulmonary Rehabilitation setting when the study referred to it as such or if the trial applied an exercise resistance training systematic, regardless of its period and frequency. Detailed descriptions of each intervention were also extracted, as well as baseline and at the end of the intervention measurements of the outcomes values - as mean and standard deviation (SD) in each intervention. When studies report only median values, standard error, confidence interval (CI), interquartile intervals, and minimum and maximum, we transformed these values, obtained by the calculations presented in the Cochrane Handbook [31].

Assessment of risk of bias in included studies

The risk of bias within individual trials was assessed by two independent investigators (S.B. and F.M.S.) using the revised Cochrane risk-of-bias tool for randomized trials (RoB 2) [(33)], and final judgments were established by consensus. Each study was evaluated with regards to the five following

domains: 1) bias arising from the randomization process; 2) bias due to deviations from intended interventions; 3) bias due to missing outcome data; 4) bias in the measurement of the outcome; 5) bias in the selection of the reported result. The overall risk of bias judgment was: a) low risk of bias, if the trial judgment was at low risk of bias for all domains; b) some concerns, if the trial judgment raised some concerns in at least one domain for this result, but not was at high risk of bias for any domain; and c) high risk of bias, if the trial judgment was at high risk of bias in at least one domain or some concerns for multiple domains in a way that substantially lowered confidence in the results.

GRADE assessment of the certainty of the evidence

We assessed the overall certainty of the evidence for each outcome across studies following the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach [(34)]. Certainty of evidence was considered ‘high’ by default and thereafter downgraded to ‘moderate’, ‘low’ or ‘very low’ depending on the seriousness of the limitations in five criteria: within-study risk of bias, the directness of evidence, inconsistency, the precision of effect estimates and risk of publication bias.

Data synthesis and analysis

We collected the mean change of the data values between post- and pre-treatment of the study (delta) and the SD of this value (delta SD) in each arm of the study for the outcome of interest. If the primary studies did not report mean change in each group, we obtained it by subtracting the post-intervention mean from the baseline. While in delta SD absence, we estimated it assuming a correlation of 0.5 between the baseline and final measures within each group, according to the formula of Follmann et al [(35)], as proposed in the Cochrane guidelines [(31)]. Equal variance was assumed among trials and between intervention and controls.

We performed our meta-analyses using DerSimonian and Laird random-effects model regardless of statistical heterogeneity, assuming that there is not one single true effect size across studies due to clinical and methodological diversity between studies. Statistical tests of the significance of τ^2 to choose between fixed and random effects models are not recommended by the Cochrane Handbook [31] because these tests have undesirable statistical properties and fundamentally should not determine the most appropriate meta-analytic model. Instead, we used our desired inference to guide which model to use. The choice of random effects allows for *unconditional* inferences that are not restricted to the observed studies [36]. In addition, the meta-analytic model was adjusted using the Hartung-Knapp-Sidik-Jonkman method [37] to produce more robust estimates with more conservative results.

We calculated continuous outcomes and presented them as weighted mean differences (WMD) of changes from baseline with means and SD for BW, MAMC, and triceps skinfold when studies measured outcomes in the same way, and as standardized mean difference (SMD) and 95% CIs for LBM and FM, and handgrip and quadriceps strength presented as Hedges' g [31] to combine trials that measure the same outcome but used different units of measurement (eg, for fat-free mass in kg, percent, and kg/m^2). As a rough guide, effect sizes in SMDs are interpreted as suggested by Cohen [38]. Small effects "that cannot be discerned by the naked eye" are around 0.2; medium effects are around 0.5; and large effects "that can be seen by the naked eye" are around 0.8. For outcomes reported in SMD, we also performed stratified analyses based on the original measurement scale presented as WMDs to enhance the interpretability of our results. All results are presented with point estimates along with 95% confidence intervals (95% CI).

Assessment of heterogeneity, exploratory analyses, and publication bias

We assessed the magnitude of statistical heterogeneity using the I^2, accordingly the following interpretation [31]: values from 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity and 75% to 100% considerable

heterogeneity. Aiming to identify potential sources of heterogeneity and effect mediators, we planned to perform several exploratory subgroup analyses based on: a) within-study risk of bias, b) whether the intervention consisted of an energy supplement, protein supplement, or energy-protein supplement, c) clinical status (stable versus unstable patients), d) baseline overall sample BMI (with 22 kg/m² as the cutoff point). Furthermore, we performed univariate meta-regression analyses to further investigate the statistical heterogeneity and to identify potential associations between our primary outcomes and the following study-level covariates as continuous variables: a) baseline overall sample BMI; b) intervention duration (in weeks); c) total amount of prescribed supplement energy content in the intervention arm; and d) total amount of prescribed supplement protein content in the control group. In the presence of crossover RCTs design, we temporarily excluded these studies to determine whether its removal altered the results of the meta-analysis. Where there were at least ten studies (BW, LBM, HGS, and QS), we used funnel plots to visually assess the risk for publication bias and small-study effects, along with Egger's regression test. The trim-and-fill method was used to adjust for publication bias.

Changes in the review protocol

During the review process, we opted to perform two modifications in the study protocol, due to the high amount of data extracted. First, we restricted the intervention to oral nutritional supplements or food fortification adding energy and/or protein. Second, we opted by presenting the results in two independent publications: the first one is the current and will answer the research question "effect of nutrition therapy in anthropometric parameters, body composition, and peripheral muscle strength in COPD patients", while the second one will answer the research question "effect of nutrition therapy in clinical and functional outcomes in COPD patients". It was included in the PROSPERO.

RESULTS

Selection and general characteristics of included studies

We initially identified a total of 3,807 articles through database searches, of which 490 were duplicates. We assessed the full text of 48 studies for eligibility and included 32 [39,40,49–58,41,59–68,42,69,70,43–48] of them in the current systematic review (**Figure 1**). The number of studies included in the meta-analysis varied according to the outcomes. **Table S2** (Support Information) presents the list of excluded studies after inspection of the full report and a justification for this exclusion [71,72,81–86,73–80].

Table 2 presents general features of eligible studies for this systematic review. Trials were conducted in a variety of countries including Canada [51,70], Denmark [57,62], India [58], Iran [64], Italy [48,49,52,56,60], Japan [50,53], Netherlands [41,43,63,69], Spain [66], Sweden [45,59], Switzerland [68], Turkey [55,61], England [40,42,44,46,47,54], and USA [39,65,67]. The studies were published between 1987 [39] and 2020 [63,64], most of which (n=21; 1,252 participants) [41,42,54–61,63,64,43–50] from the year 2003. Almost all manuscripts were available in the English language, except for one in German [68] and another in Spanish [66]. Only one study applied a crossover design (25 participants), with eight weeks of the intervention period (no washout period reported) [51]. The remaining 31 studies were parallel-group design, with a mean intervention duration of about 12 weeks [ranging from nine days [43] to 12 months [63,68]].

The thirty-two studies included in this review randomized a total of 1,680 participants. Of these, we included 1,414 in the statistical analysis because most studies reported only an analysis per protocol, excluding participants who dropped out of the study or did not complete the protocol sufficiently. The mean sample size was equal to 52.5 participants [ranging from nine [65] to 233 [69]], with a mean age of 67.0 years [ranging from 54.2 [58] to 77.7 [50]], of which approximately 70% were male [although in six studies [50,56,66–69] gender information was unavailable]. The mean of forced expiratory volume in one second was equal to 42.1% of predicted values [ranging from 31.4 [40] to 56% [60]]- data not reported in eight studies [39,49,52,57,65,67–69] - and mean of BMI was

equal 22.3 kg/m^2 [ranging from 17.2 [61] to 30.9 kg/m^2 [60]] [data not reported in 11 studies [39,40,53,62,65,66,68–70]].

Twenty-nine studies included COPD patients in stable clinical condition (1,554) [39,40,52,54–58,60–63,41,64,68,44–47,49–51] and the majority of them were outpatient-based (1,256 participants). In 12 studies the patients participated in a pulmonary rehabilitation program (798 participants) [42,44,59,69,45,46,48,50,53–55,57]; in three studies the nutritional intervention started in inpatient base and continued in an outpatient modality after discharge (65 participants), [48,65,67] of which one study (28 participants) took place in pulmonary rehabilitation in the outpatient part, [48] and in one study (233 participants) the intervention was entirely in an inpatient pulmonary rehabilitation [69]. On the other hand, three studies included only COPD patients admitted to the hospital for an acute exacerbation (126 participants) [43,66,70].

Treatment groups of the included studies received the following interventions, stratified according to ONS composition (**Table S3** - Support Information):

(1) Supplement of energy and high-protein (≥20% of total energy from protein): it was the intervention in 14 RCTs (659 participants) [40,43,68,51,53,54,57,59,61,63,67], the mean energy density was 1.3 kcal/ml (ranging from 0.54 to 1.5), and it provided a mean of 528.6 kcal [ranging from 312.5) [59,63] to 960 [40] kcal], and 27.2 grams of protein [ranging from 10.4 [63] – 54 [40] g protein];

(2) Protein-based and amino acids supplements: it was the intervention in 10 studies (560 participants) [44–46,48,49,52,56,58,60,64], of which five used creatine (306 participants) [44–46,56,60], three prescribed essential amino acids mixture (148 participants) [48,49,52], one used whey protein (46 participants) [64], one prescribed a “protein powder”, but did not specify its sources (60 participants) [58];

(3) Energy supplement (<20% of total energy from protein): it was the intervention in eight studies (461 participants) [39,47,50,55,65,66,69,70], the mean of ONS energy density was 1.6 kcal/ml [ranging from 1.0 [50] to 2.1 [69]], and it

provided mean daily energy of 565 kcal [ranging from 400 [50] to 720 [39,65]] and 18.9 grams of protein [ranging from 9.0 [47] to 28.8 [65]].

Most comparisons involved ONS vs. placebo [42,43,62,63,69,44–46,49,54,56,59,60], but we found a variety of other comparisons including, usual diet [39,40,51,58,67] hospital diet [65,66,70], nutritional advice [41,64], leaflet providing advice (content was never discussed) [47], monthly general education program [50], normal energy diet [68], normal meals alone with dietary instruction [53], and the remaining three trials not informed the comparators [48,57,61] (**Table S3** – Support Information).

Eighteen studies assessed the compliance with the study protocol [42,43,58,59,62–64,68,69,45–48,53–55,57], of which half of them reported results [42,43,46–48,59,61,64,65] (**Table S3** – Support Information) with inconsistent definitions and measurement units, which made it impossible to estimate the general rates of patient compliance among the studies that report it. Nineteen papers did not inform regarding funding.

Risk of bias in primary studies

Figure S1 (in the Supporting Information) summarizes the bias risk assessment results for the studies included in this systematic review accordingly RoB 2 tool. Our judgment of the overall risk of bias did not result in any study ranked as “low”, while we judge 14 studies as “some concerns” [39,41,59,60,64,69,42,43,48–50,52,56,58], and 18 studies as “high” risk of bias [40,44,61–63,65–68,70,45–47,51,53–55,57].

In the first domain of RoB 2 (bias arising from the randomization process) all studies were judged as “some concerns”, except one study judged as “high” risk of bias [66]; while in the second domain (deviations from intended interventions), twelve studies were judged as “low” [42,43,60,44–47,49,54,56,59], fifteen as “some concerns” [39,41,67–70,48,50,53,55,57,61,63,64], and the five remaining studies as “high” [40,51,62,65,66]. Regarding to missing outcome data (third domain), nine studies were judged as “low” [39,41,43,48,50,58,62,64,69], fifteen as “some concerns” [40,42,65–67,49,51–57, and eight as “high” [44–47,61,63,68,70]. In addition, all studies were considered as having low risk for the domain measurement of the outcome,

while twenty-eight studies were assessed as “low” [39,40,49,50,52,55–61,41,62–67,69,70,42–48] and four studies as “some concerns” [51,53,54,68] in fifth domain (selection of the reported results). **Table S4** (in the Supporting Information) presents the reasons for these judgments.

Effect of intervention on body weight

Twenty-seven RCTs (1,164 participants) [39,40,49–53,55,58,59,62,63,41,64–70,42–48] measured BW as an outcome, of which 26 [39,40,49–53,55,58,59,62,63,41,64–67,69,70,42–48] of them reported data that could be pooled. We found a statistically significant benefit of nutritional intervention on BW using the random-effects model [MD = 1.44 kg, 95% CI 0.81 to 2.08, P < 0.01, I^2 = 73%, (1,144 participants)] (**Figure 2**). We excluded Ganzoni et al.'s study [68] from the meta-analysis because it did not report sufficient information to impute the measures of dispersion of the treatment effect. In this study, the intervention group (n = 15) received advice to follow a high-energy diet (energy supply corresponding to 1.8 times the basal metabolic rate, i. e.,~ 2,840 kcal/day) supplemented with the ONS (Fresubin®, OP 200 ml), once or twice a day, while the control group (n = 15) followed a normal energy diet. Although the intervention group obtained more weight gain (7.0 kg), the difference relative to the control group (weight gain of 2.3 kg) was not statistically significant (p=0.08).

In sensitivity analysis, the exclusion of the only crossover RCT did not materially change the results [MD = 1.18 kg, 95% CI 0.66 to 1.70, P < 0.01, I^2 = 55.1%, (1,094 participants)]. **Table 3** describes the results of the subgroup analysis for the BW outcome. The magnitude of BW gain was significantly higher in BMI <22 kg/m^2 subgroup compared to BMI ≥22 kg/m^2 subgroup, and it was also significantly higher in studies conducted with stable COPD patients compared to unstable COPD patients. On the other hand, we did not observe significant differences for BW between the three intervention subgroups, neither between the studies grouped by the risk of bias of primary studies. In univariate meta-regression analyses (**Table S5** - Support Information) for between-group

differences in BW, the amount of energy and protein prescribed, as well as the length of intervention, were able to partially explain the observed statistical heterogeneity (R^2 = 16.66 to 45.95%), but were not statistically significantly associated with between-group changes in BW. Univariate meta-regression analysis using baseline BMI as the predictor variable did not explain the heterogeneity and was not significantly associated with between-group differences in BW.

Visual inspection of the funnel plot (**Figure S2** - Supporting Information) suggests no substantial asymmetry, with non-significant Egger's test [intercept: 0.34, (CI 95% -0.83 to 1.52); p = 0.57].

We judged the certainty of evidence regarding this outcome as low, due to within-study risk of bias that was classified as some concerns in 12 studies [39,41,69,42,43,48–50,52,59,64] and high in 14 studies [40,44,65–67,70,45–47,51,53,55,62,63], the persistent inconsistency that could not be explained in subgroup analyses or meta-regression, and the low precision of effect estimates (**Table 4**).

Effect of nutritional interventions in lean body mass

Sixteen RCTs (933 participants) [42,43,56,59,60,63,64,69,44,46,48–50,52,53,55] measured LBM as an outcome; however, only 13 (n = 657) [43,44,60,63,64,46,48–50,52,53,55,56] studies included data that could be pooled of a statistically significant increase in LBM with the nutritional intervention (SMD = 0.37; 95% CI, 0.15 to 0.59, p < 0.01, I2 = 46%) (**Figure 3**). LBM was measured using bioelectrical impedance (BIA) in eight trials [43,46,49,52,55,56,60,64], while three trials used dual-energy x-ray absorptiometry (DEXA) [44,48,63] and two trials [50,53] did not report body composition assessment methods. Of the three studies that could not be included in the meta-analysis because they used different units to report LBM, two studies [59,69] found no significant improvement in the proportion of LBM [presented as fat-free mass/kg [69] and skeletal muscle mass [59]] for the ONS group, while one study [42] observed clinically relevant LBM gains only in the placebo group.

In subgroup analysis, we investigated whether the method of LBM measurement was associated with the observed results, which were not statistically significantly different between subgroups (p for interaction = 0.48). We also performed subgroup analysis for LBM according to BMI, intervention, and risk of bias. No clinically relevant differences in intervention effects between these three subgroups were found, with non-significant tests for subgroup differences (**Table 3**).

Visual inspection of the funnel plot and Egger's test [intercept: -3.63, (CI 95% 1.39 to 5.86); p = 0.0087] were compatible with publication bias (**Figure S3**). There was very-low quality evidence (risk of bias in primary studies, heterogeneity, and publication bias) for LBM outcome (**Table 4**). The results of the trim-and-fill results suggest that four trials might have been missing such that their addition would change the overall effect on LBM to [number of studies combined: k = 17 (with added 4 studies); SMD= 0.17 (95% CI, -0.0782 to 0.4267, p= 0.1762)].

Regarding midarm muscle circumference, the pooled differences in change from baseline values of seven studies (325 participants) [39,40,47,51,62,66,69] resulting in a small, but statistically significant increment circumference (MD 0.29 mm^2; 95% CI 0.02 to 0.57, p = 0.03, I^2= 0%) in the intervention group as compared to the control group (**Figure 4**). There was low-quality evidence (due to risk of bias and unfeasibility to estimate the risk of publication bias) (**Table 4**) for this outcome.

Effect of intervention in fat mass

Nine RCTs (n = 523) [42–44,46,50,53,59,60,63] reported data on FM. Pooled results showed no statistically significant differences for this outcome (SMD = 0.16; 95% CI, -0.07 to 0.40, p = 0.18, I^2 = 43%) (**Figure 5**). The certainty of evidence for FM was very low (due to risk of bias, imprecision, heterogeneity, and the unfeasibility to investigate risk of publication bias) (**Table 4**).

We included six trials (158 participants) [39,40,51,65–67] in the analysis of nutritional intervention effects on triceps skinfold. The pooled MD was 1.09 mm (95% CI, 0.01 to 2.16, p = 0.05, I^2 = 0%) (**Figure 6**), though from low-quality

evidence concerning for FM (due to risk of bias, imprecision, heterogeneity, and the unfeasibility to investigate risk of publication bias) (**Table 4**).

Effect of intervention in handgrip and quadriceps strength

Twelve trials (448 participants) [39,40,67,70,42–45,47,49,61,64] assessed peripheral muscle strength by HGS, resulting in a pooled SMD of 0.39 (95% CI, 0.07 to 0.71, p = 0.02, I^2= 62%) (**Figure 7**).

Our subgroup analysis showed that the nutritional intervention for COPD patients at stable clinical conditions resulted in a higher effect on handgrip strength than in their unstable counterparts (**Table 3**). The univariate meta-regression analysis performed, considering the length of intervention and BMI as predictors, (**Table S6** - Support Information) was unable to satisfactorily explain the substantial heterogeneity for handgrip strength. No evidence of publication bias was found based on the funnel plot visual inspection (**Figure S4** - Supporting Information) and the Egger's test was not statistically significant [intercept: -1.81 (CI 95%, -5.72 to - 2.10); p = 0.39]. There was very low-quality evidence (due to risk of bias, inconsistency, and imprecision (**Table 4**) from

Ten trials (n = 510) [42–46,50,54,57,59,63] reported the effect of intervention on QS (SMD, 0.15, 95% CI -0.04 to 0.35, p = 0.12, I^2= 15%) (**Figure 8**). Seven studies measured QS by isometric strength [42,43,46,54,57,59,63], two studies by isokinetic strength [44,45], while one study did not report the methodology applied [50]. In subgroup analysis investigating whether units of measurement was associated with the observed results, we found that only for the studies reporting QS in Newton-meters unit [43–46,54,59,63] (7 reports, 383 participants) there was a significant effect in QS (MD = 2.53; 95% CI 0.44 to 4.63, P = 0.02, I^2 = 0%), with a significant test for subgroup differences (p = 0.04). Subgroup analyses revealed no statistically significant associations between explanatory variables (clinical status, type of intervention, BMI, and overall risk of bias of primary studies) on QS outcomes, and univariate meta-regression analysis with BMI as the predictor variable only partially (R^2 = 25.93%) explained the

observed statistical heterogeneity with no significant association with the outcome (p = 0.23) (**Table S6** - Support Information).

No evidence of publication bias was found based on the funnel plot inspection and a non-significant Egger's test [intercept: 0.83, (CI 95% -2.00 to -3.65); p = 0.58] (**Figure S5** - Supporting Information). There was low-quality evidence (risk of bias and imprecision) (**Table 4**).

DISCUSSION

In this systematic review with meta-analysis of RCTs, we evaluated the effect of energy and/or protein ONS or food fortification (FF) on nutritional outcomes of COPD patients. The review identified 32 studies (1,680 participants) and showed that these nutritional interventions compared with control (placebo or usual care or dietary instruction) resulted in a significantly positive impact in several nutritional parameters. It is necessary to highlight that we identified a high risk of bias in most of the primary studies, and the certainty of the evidence was very low/low for all outcomes.

Our findings are consistent with most of the results from three meta-analyses [27–29] published between 2012 and 2013, limited to stable COPD patients, in which nutritional support, mainly in the form of ONS (for more than two weeks) compared with placebo or usual diet also revealed significant improvements in BW [27–29], midarm muscle circumference [27,29], and skinfold thickness [27,29] (especially in malnourished patients), and handgrip strength [28]. As well as a lack of benefit from nutritional interventions for free-fat mass [28] and quadriceps strength [28,29]. Notwithstanding, we observed methodological differences between the present meta-analysis and the previous ones [27–29], including intervention selection criteria (administration route, nutritional composition, and duration) and absence of information about protocol study registration.

The current review also provides a comprehensive analysis of the body of evidence by applying proper methodological safeguards to several limitations, compared to the previous ones [27,28], which used a tool (Jadad scale) to assess the risk of bias explicitly discouraged by the Cochrane Handbook for Systematic Reviews of Interventions [31]. Furthermore, such

reviews did not judge the certainty of the evidence, according to the GRADE system [34], and limited the selected studies to English only [27,28]. In this review, we also included an additional ten studies published since these meta-analyses publication [27–29].

The present meta-analyses detected substantial statistical heterogeneity for BW and handgrip-strength and a moderate statistical heterogeneity for fat-free mass. The meta-regression and the subgroup analysis were unable to explain the statistical heterogeneity, with non-significant interaction tests. However, the subgroup analyses for BW revealed a significant increase in the magnitude of effect from nutritional intervention in patients with lower BMI and clinically stable. Likewise, although the test for subgroup differences indicates that there was no statistically significant subgroup effect between the three categories of nutritional interventions, we observed greater effect size for BW with protein-based supplementation, which, according to the individual evaluation of these studies, suggests that the benefits come from the supplementation of creatine and essential amino acids. Caution is necessary in the interpretation of results on fat-free mass, since a publication bias was identified and the adjustment for funnel asymmetry by trim-and-fill method pointed to the lack of four studies and an important change in the pooled effect of the intervention. It is expected that in the presence of publication bias the summary measure shows a higher effect than the real effect, as evidenced in our results. Maybe, studies with negative results were not published and we did not identify them in our broad literature search.

The better outcomes of nutritional interventions for BW in lower BMI patients may be can be explained by the potential for improving baseline food intake and for weight gain, compared to those with normal or higher BMI. The demonstration of benefit in clinically stable patients compared to a subgroup of exacerbated patients for BW could be explained by the fact that in the last there is a marked increase in local and systemic inflammation, along with the presence of limiting factors to food intake, that negatively impact the nutritional status [17]. The purported mechanism for the effect of creatine supplementation may be associated with its orexigenic activity (as observed in animal studies) [87

and increased water retention, a consequent stimulus to increase in myofibrillar mRNA and protein content [88], promoting gains in free-fat mass. With anabolic effects in the same direction, the essential amino acids supplementation promotes protein synthesis and the resulting hypertrophy by activating translation and retarding proteolysis and expression of various atrogenes [89].

Regarding nutritional interventions, the trial protocols generated some uncertainty about the overall contribution of additional energy or proteins from nutritional supplementation to the usual food intake during interventions. About 88% of studies did not tailor the nutritional intervention based on individual estimative of the energy-protein requirements of the patients. Of the 56% of the studies that reported total energy and protein intake during the experiment, in forty percent of them, food intake was lower in the intervention group compared to the control group at the end of the follow-up. Almost 60% of the studies reported the methodology applied to assess adherence to the protocol, but only 21% of these revealed the referred level of patient adherence (with heterogeneous reporting this information). These limitations on the guarantee of the intended intervention make it impossible to recognize the true magnitude of the effect of energy and protein supplementation on the outcomes of interest. However, this brings us a pragmatic character and the need to identify strategies to facilitate patient adherence to nutritional interventions in clinical practice, resulting in an overall net benefit for outcomes relevant to the patient.

We conducted the present systematic review with meta-analysis under the latest Cochrane recommendations [31], following PRISMA guidelines [32] after a prospectively registered protocol. We assessed the certainty of the evidence for each outcome of interest using the GRADE system [33]. We identified and included all studies relevant to our research question, regardless of language. We used random-effects for all outcomes, regardless of the heterogeneity expressed by I^2 , assuming that there is not one single true effect size across studies due to their clinical and methodological divergences. Our main limitation was the inability to access one Chinese publication [90], which probably could fulfill our eligibility criteria. Yet, we need to underline the limitations for the interpretation of our results. All the RCTs included in this review had some

concerns or high risk of bias, due to problems mainly related to the randomization process (no information on the concealment of allocation sequence), due to deviations from interventions (unreported data or lack of blinding of participants and/or caregivers and/or people delivering the interventions and/or people assessing the outcomes), and due to missing outcome data (no information about follow-up loss or losses of follow-up higher than 13%). Most included studies were small sample-sized with highly variable intervention duration (1.29 to 48 weeks). The statistical heterogeneity remains high after subgroup analyses, suggesting the influence of other features between the studies, unexplored due to the impossibility to create subgroups (ex., COPD severity, since it was unreported in the majority of the studies). Furthermore, the information unavailability about patients' GOLD stage in most of the studies precluded the subgroup analysis for the disease severity.

The certainty of the evidence ranged from very low to low. The most common reasons for downgrading it were the identification of high or some concerns risk of bias in the included studies, imprecision of effect estimates, and the inconsistency from individual studies, unexplained by sensitivity analysis. For these reasons, the available evidence herein summarized is insufficient to provide clear recommendations for clinical practice due to the limited certainty of evidence and should therefore be interpreted with caution. The potential benefit of nutritional supplementation/fortification directs to protein-based nutritional supplementation particularly for COPD patients with reduced BMI and clinically stable, which should be addressed in pragmatic trials.

In future RCTs, investigations must be designed with adequate power to detect significant but realistic differences in outcomes relevant to individuals living with COPD; in addition to exploring the best protein substrate for supplements and its effective dose, if any, considering the patient's nutritional needs, establishing strategies to optimize adherence; and effectively assess total food intake. Authors should also consider the intention-to-treat analysis and then perform subgroup and sensitivity analyzes based on COPD metabolic phenotypes, pulmonary rehabilitation, and adherence to the nutritional

intervention, in addition to assessing the degree of maintenance of the identified benefits after treatment ends. When comparing the intervention to "routine care", the latter should be clearly described to allow for transparent comparisons with other trials and appropriate inferences for real-life practice.

CONCLUSION

Based on limited evidence, this meta-analysis suggests that high-energy and/or high-protein intake improves anthropometric parameters and handgrip strength in COPD patients. Conversely, the nutritional interventions showed no benefit in fat-free mass.

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AUTHOR CONTRIBUTIONS

S.B. and F.M.S. designed the study; C.F.B. and S. B. performed the data extraction F.M.S. was the third review author in case of disagreement; S.B. and FMS were responsible for quality assessment; F.M.S., I.E., and S.B. analyzed the data; F.M.S., I.E., P.Z.T., and S.B. drafted the manuscript, and all authors read and approved the final manuscript.

DECLARATION OF INTEREST

The authors have no conflict of interest to declare.

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Table 1 **PICO strategy for inclusion and exclusion criteria**

Parameter	Criteria	
	Inclusion	**Exclusion**
Participants	COPD patients	• Asthma-COPD overlap syndrome • Mechanical Ventilation
Intervention (s)	Any nutritional therapy based on energy and/or protein (e.g., creatine or whey protein or amino acid metabolites) and/or amino acids (e.g., isolated or in combination form) ONS or FF added to the diet	• Parenteral Nutrition • Enteral feeding • Anabolic steroids or drugs • Different macronutrient distribution and similar energy supply • Comparison of two levels of energy intake with the same supplement
Comparison (s)	Placebo or habitual/ usual diet or no intervention or usual medical standard or nutrition advice/ counseling	• Comparison of same caloric supply and proportion of macronutrients, differing only in a specific dietary compound source
Outcome (s)	• Body weight • Lean body mass • Fat mass • Peripheral muscle strength	
Study design	Randomized controlled trial	
Time of intervention	One week or more	

Table 2 **General characteristics of included RCTs (n=32) investigating the effect of oral nutrition therapy on nutritional parameters of COPD patients**

Author/year Country	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics				
					Randomized (n)	Analyzed (n)	Age [a] (years)	Male (%)	BMI (kg/m^2)	FEV_1 [a] [% of predict or in liters (l)]	FEV_1/FVC [a]
Lewis/1987 [39] United States	Parallel	Outpatient	8	NR	21	NR	62.1 (15.2)	71.4	NR	*0.8 (0.3) l*	31.3 (6.3)
Efthimiou/1988 [40] United Kingdom	Parallel	Outpatient	12	NR	14	NR	62 (7.9)	57.1	NR	31.4 (9.7) % *0.7 (0.2) l*	37.7 (9.2)
Knowles/1988 [51] Canada	Crossover (wash-out NR)	Outpatient	8	NR	25	25	69.0 (9.2)	84.0	NR	37.0 (11.0) %	NR
Otte/1989 [62] Denmark	Parallel	Outpatient	13	Zero	28	28	54.8 (7.9)	21.4	NR	39.9 (17.7) %	NR
Fuenzalida/1990 [65] United States	Parallel	Inpatient at CRC (part 1) and Outpatient (part 2)	6	Zero	9	9	62.4 (5.6)	100.0	NR	*1.2 (0.9) l*	NR
Entrenas - Costa/1991 [66] Spain	Parallel	Hospital	2.25	NR	37	NR	NR	NR	NR	33.0 (16.4) %	NR
Rogers/1992 [67] United States	Parallel	Inpatient at CRU and Outpatient	3	1	28	27	64.0 (7.3)	NR	NR	*1.0 (0.4) l*	35.8 (7.6)

(continued on next page)

Table 2 **Continued**

Author/year Country (ref)	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics				
					Randomized (n)	Analyzed (n)	Age [a] (years)	Male (%)	BMI (kg/m^2)	FEV_1 [a] [% of predict or in liters (l)]	FEV_1/FVC [a]
Ganzoni/1994 [68] Switzerland	Parallel	Outpatient	48	8 2 (NR)	30	20	66	NR	NR	NR	NR
Schols/1995 [69] Netherlands	Parallel	Inpatient PRP	8	30	233	217	65.0 (8.6)	NR	NR	NR	NR
Saudny-Unterberger/1997 [70] Canada	Parallel	Hospital	2	9	33	24	69.3 (8.3)	62.5	NR	33.8 (13.3) %	NR
Goris/2003 [41] Netherlands	Parallel	Outpatient	12	NR	20	19	62.0 (11.0)	55.0	19.8	40.0 (16.0) %	NR
Steiner/2003[42] United Kingdom	Parallel	Outpatient PRP	7	25	85	60	67.0 (8.5)	62.4	23.9	34.6 (13.9) % *0.9 (0.3)*	NR
Vermeeren/2004[43] Netherlands	Parallel	Hospital	1.29	9	56	47	66.5 (8.7)	66.1	21.1	34.6 (11.5) %	47.5 (14.2)
Fuld/2005 [44] United Kingdom	Parallel	Outpatient PRP	12	13	38	25	62.8 (8.9)	60.5	23.8	45.4 (14.9) % *1.1 (0.4) l*	38.5 (10.2)
Faager/2006[45] Sweden	Parallel	Outpatient PRP	8	NR	23	23	66.0 (6.0)	43.5	23.7	43 (17) % *1.2 (0.6) l*	NR

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Table 2 **Continued**

Author/year Country	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics				
					Randomized (n)	Analyzed (n)	Age [a] (years)	Male (%)	BMI (kg/m^2)	FEV_1 [a] [% of predict or in liters (l)]	FEV_1/FVC [a]
Deacon/2008 [46] United Kingdom	Parallel	Outpatient PRP	1.71	20	100	80	68.0 (7.8)	62.5	26.7	44.1 (20.4) % *1.1(0.6) l*	NR
Weekes/2009 [47] United Kingdom	Parallel	Outpatient	24	29	66	40	68.1 (9.8)	50.9	19.7	31.8 (13.6) %	0.4 (0.1)
Baldi/2010 [48] Italy	Parallel	Inpatient/ Outpatient PRP	12	2	28	26	71.6 (6.0)	71.4	20.5	42.5 (14.0) %	43.8 (14.1)
Dal Negro/2010 [49] Italy	Parallel	Outpatient	12	NR	32	NR	75.0 (7.0)	78.1	20.2	*0.9 (0.2) l*	38.5(9.4)
Sugawara/2010 [50] Japan	Parallel	Outpatient PRP	12	NR	32	32	77.7 (6.7)	NR	18.3	55.6 (25.7) % *1.3 (0.6) l*	43.8 (14.9)
Dal Negro/2012 [52] Italy	Parallel	Outpatient	12	NR	88	NR	74.0 (6.7)	69.3	20.0	*0.8 (0.3) l*	38.6 (9.74)

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Table 2 **Continued**

Author/year Country	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics				
					Randomized (n)	Analyzed (n)	Age [a] (years)	Male (%)	BMI (kg/m^2)	FEV_1 [a] [% of predict or in liters (l)]	FEV_1/FVC [a]
Sugawara/2012 [55] Japan	Parallel	Outpatient PRP	12	5	36	31	77.2 (5.3)	94.4	NR	44.5 (16.9) *%* *1.1 (0.4) l*	39.0 (10.6)
Constantin/2013 [54] United Kingdom	Parallel	Outpatient PRP	8	9	59	50	68.0 (7.2)	55.9	25.9	46.8 (16.9) % *1.1 (0.0) l*	40.2 (10.1)
Gurgun/2013 [53] Turkey	Parallel	Outpatient PRP	8	NR	30	NR	65.4 (18.0)	93.3	18.9	41.9 (28.3)	51.2 (24.2)
Marinari/2013 [56] Italy	Parallel	Outpatient	8	NR	55	NR	73.5 (8.2)	NR	30.1	42.3 (12.3) %	NR
Ahnfeldt-Mollerup/2015 [57] Denmark	Parallel	Outpatient PRP	9	18	53	35	68.4 (8.7)	43.4	23.8	NR	NR
Khan/2016 [58] India	Parallel	Outpatient	12	5	60	60	54.2 (10.3)	90	18.0	51.6 (11.8) %	67 (8.1)

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Table 2 **Continued**

Author/year Country	RCT Design	Setting	Intervention time (weeks)	Loss to follow-up	Sample		Participants characteristics				
					Randomized (n)	Analyzed (n)	Age [a] (years)	Male (%)	BMI (kg/m^2)	FEV_1 [a] [% of predict or in liters (l)]	FEV_1/FVC [a]
van de Bool/2017 [59] Netherlands	Parallel	Outpatient PRP	16	8	81	81	62.5 (8.2)	50.6	22.7	55.1 (19.8) %	43.1 (12.2)
De Benedetto[60] Italy	Parallel	Outpatient	8	NR	90	90	73 (7.0)	75.5	30.9	56 (19.9) %	NR
Degirmenci/2018 [61] Turkey	Parallel	Hospital and Outpatient	12	23	63	40	74.7 (10.3)	97.5	17.2	41.4 (20.9) %	81 (28.5)
van Beers/2020 [63] Netherlands	Parallel	Outpatient	48	20	81	81	62.5 (8.2)	51	22.7	55.1(19.6) %	43.1 (12.2)
Ahmadi/2020 [64] Iran	Parallel	Outpatient	8	2	46	44	62.8 (7.1)	100.0	21.1	43.8 (15.4) %	NR

Abbreviations: NR, Not reported; FEV_1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; CRC, Clinical Research Centre; CRU, Clinical Research Unit; PRP, Pulmonary rehabilitation program.

[a] Mean and SD

 There is one other group in this study not included in our analysis that was not considered for us since the intervention in this study arm was anabolic steroid-based.

Table 3 **Subgroup analysis for randomized controlled trials on body weight, lean mass, handgrip strength, and quadriceps strength**

Analysis	Body weight				Lean body mass			
	Studies, No. (patients, No)	MD (95% CI)	I^2, %	p-value	Studies, No. (patients, No)	SMD (95% CI)	I^2, %	p-value
Body mass index								
<22 kg/m^2	9 (384)	2.22 (0.41 to 4.03)	90		7 (295)	0.37 (0.07 to 0.67)	36	
≥22 kg/m^2	7 (295)	0.85 (0.37 to 1.33)	36	0.09	5 (331)	0.42 (0.01 to 0.82)	68	0.87
Clinical status*								
Stable	23 (1,036)	1.64 (0.93 to 2.34)	73		-	-	-	
				< 0.01				-
Unstable	3 (108)	0.26 (0.16 to 0.36)	Zero		-	-	-	
Type of intervention								
Energy	8 (328)	1.38 (0.41 to 2.35)	83		2 (62)	0.56 (-0.03 to 1.15)	24	
Energy and high-protein	10 (438)	0.90 (0.44 to 1.35)	Zero		3 (155)	0.18 (-0.14 to 0.50)	Zero	
				0.24				0.38
Protein-based	8 (378)	2.22 (0.04 to 4.40)	81		8 (440)	0.44 (0.12 to 0.77)	62	
Overall risk of bias								
Some concerns	12 (645)	1.89 (0.61 to 3.18)	74		8 (410)	0.36 (0.06 to 0.66)	53	
				0.38				
High	14 (499)	1.28 (0.75 to 1.80)	74		5 (247)	0.40 (0.04 to 0.77)	45	0.85

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Table 3 Continued

Analysis	Body weight				Lean body mass			
	Studies, No. (patients, No)	SMD (95% CI)	I^2, %	p-value	Studies, No. (patients, No)	SMD (95% CI)	I^2, %	p-value
Pulmonary rehabilitation								
Yes	10 (523)	1.27 (0.56 to 1.98)	53.3	0.65	6 (224)	0.44 (0.09 to 0.79)	34.8	
No	16 (621)	1.54 (0.61 to 2.47)	77.6		7 (433)	0.33 (0.03 to 0.63)	57.3	0.64
Study design †								
Crossover	1 (50)	2.35 (-4.05 to 8.75)	Zero	0.78	-	-	-	
Parallel	25 (1,094)	1.44 (0.81 to 2.06)	74.5		-	-	-	-
	Handgrip strength				Quadriceps strength			
Body mass index								
<22 kg/m^2	5 (154)	0.41 (-0.13 to 0.95)	77	0.75	8 (435)	0.13 (-0.09 to 0.35)	24	0.51
≥22 kg/m^2	3 (107)	0.30 (-0.08 to 0.69)	Zero		2 (75)	0. 30 (-0.16 to 0.76)	Zero	
Clinical status								
Stable	10 (383)	0.50 (0.16 to 0.84)	59	0.04	9 (467)	0.16 (-0.05 to 0.38)	25	0.88
Unstable	2 (65)	-0.13 (-0.62 to 0.36)	Zero		1 (43)	0.11 (-0.48 to 0.71)	NA	

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Table 3 Continued

Analysis	Handgrip strength				Quadriceps strength			
	Studies, No. (patients, No)	SMD (95% CI)	I^2, %	p-value	Studies, No. (patients, No)	SMD (95% CI)	I^2, %	p-value
Type of intervention								
Energy	3 (86)	-0.02 (-0.45 to 0.40)	Zero		2 (32)	0.29 (-0.21 to 0.78)	4	
Energy and high-protein	5 (183)	0.42 (0.00 to 0.84)	45	0.19	5 (315)	0.12 (-0.11 to 0.34)	Zero	
Protein-based	4 (179)	0.60 (-0.04 to 1.24)	73		3 (128)	0.18 (-0.64 to 1.00)	74	0.82
Overall risk of bias								
Some concerns	5 (257)	0.45 (-0.07 to 0.98)	75	0.68	4 (116)	0.25 (-0.02 to 0.52)	Zero	0.45
High	7 (191)	0.32 (-0.08 to 0.72)	44		6 (294)	0.09 (-0.22 to 0.40)	38	
Pulmonary rehabilitation								
Yes	3 (107)	0.30 (-0.08 to 0.69)	Zero	0.68	8 (386)	0.19 (-0.06 to 0.45)	31	0.51
No	9 (341)	0.42 (0.01 to 0.84)	69.8		2 (124)	0.05 (-0.30 to 0.40)	Zero	

Abbreviations: MD, Mean difference; SMD, Standard mean difference; BMI, body mass index.

* Analyzes for lean body mass did not perform since none study that reported this outcome was conducted with unstable patients.

† Analyzes for lean body mass did not perform since none study that reported this outcome was a crossover randomized controlled trial.

Table 4 **Summary of Findings: nutritional supplementation or food fortification compared to placebo or usual diet or no intervention effect on nutritional parameters of COPD patients**

Population: COPD patients

Settings: 1 RCT was inpatient; 3 RCTs were at hospital; 3 RCTs combined inpatient and outpatient; 25 RCTs were outpatient

Intervention: nutritional supplementation or food fortification

Comparison: placebo or usual diet or no intervention

Outcomes	Studies, No. (Patients, No)	Compiled studies	Heterogeneity (I^2, %)	Effect Size MD[1]/ SMD[2] (95% CI)	Quality of evidence (GRADE)
Body weight (kg)	26 (1,144)	[39,40,49–53,55,58,59,62,63,41,64–67,69,70,42–48]	73	1.44 (0.81 to 2.08)[1]	⊕◯◯◯ **LOW** [a]
Midarm muscle circumference (cm)	7 (325)	[39,40,47,51,62,66,69]	Zero	0.29 (0.02 to 0.57)[1]	⊕◯◯◯ **LOW** [b]
Triceps skinfold (mm)	6 (158)	[39,40,51,65–67]	Zero	1.09 (0.01 to 2.16)[1]	◯◯◯◯ **VERY LOW** [c]
Lean body mass*	13 (657)	[43,44,60,63,64,46,48–50,52,53,55,56]	46	0.37 (0.15 to 0.59)[2]	◯◯◯◯ **VERY LOW** [d]
Fat mass (kg)	9 (523)	[42–44,46,50,53,59,60,63]	43	0.16 (-0.07 to 0.40)[2]	◯◯◯◯ **VERY LOW** [e]
Handgrip strength [†]	12 (448)	[39,40,67,70,42–45,47,49,61,64]	62	0.39 (0.07 to 0.71)[2]	◯◯◯◯ **VERY LOW** [f]
Quadriceps strength[‡]	10 (510)	[42–46,50,54,57,59,63]	15	0.15 (-0.04 to 0.35)[2]	⊕◯◯◯ **LOW** [g]

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Table 4 **Continued**

GRADE Working Group grades of evidence [42]

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

Abbreviations: MD, Mean difference; SMD, Standard mean difference.

[a] due to within-study risk of bias that was classified as some concerns in 12 studies [39,41,64,69,42,43,48–50,52,58,59], and high in 14 studies [40,44,65–67,70,45–47,51,53,55,62,63], the inconsistency that could not be explained in the subgroup analysis and meta-regression, and the imprecision of effect estimates. [b] due to within-study risk of bias that was classified as some concerns in two studies [39,69] and high in five studies [40,47,51,62,66], and the unfeasibility of investigate risk of publication bias because of the reduced number of studies. [c] due to within-study risk of bias that was classified as some concerns in one study [39] high in five studies [40,51,65–67], the imprecision of effect estimates, and the unfeasibility of investigate risk of publication bias because of the reduced number of studies. [d] due to within-study risk of bias that was classified as some concerns on eight [43,48–50,52,56,60,64], studies and high in five studies [44,46,53,55,63], and the moderate heterogeneity that could not be explained in subgroup analysis and meta-regression, and publication bias. [e] due to within-study risk of bias that was classified as some concerns in five studies ([42,43,50,59,60], and high in four studies [44,46,53,63], and the imprecision of effect estimates, the moderate heterogeneity, and the unfeasibility of investigate risk of publication bias because of the reduced number of studies. [f] due to within-study risk of bias that was classified as some concerns in five studies [39,42,43,49,64], and high in seven studies [40,44,45,47,61,67,70], the inconsistency that could not be explained in the subgroup analysis and meta-regression, and the imprecision of effect estimates. [g] due to within-study risk of bias that was classified as some concerns in four studies [42,43,50,59], and high in six studies [44–46,54,57,63], and the imprecision of effect estimates.

*** Parameters and units of measurement applied in the studies for lean body mass: free-fat mass (FFM) in kilogram (kg) (n=8 studies) [41,42,44,46,47,50,51, 62], FFM index in kilogram per square meter (kg/m^2) (n= 3 studies) [48, 53,54], FFM (%) (n= 1 study) [58], and appendicular skeletal muscle mass in kg (n= 1 study) [61].**

† Units of measurement applied in the studies for handgrip strength: kilogram-force (kgf) (n=5 studies) [10,16,21,23,24] and kilogram (kg) (n= 7 studies) [11,19,22,26,30,39,41].

‡ Units of measurement applied in the studies for quadriceps strength: kgf (n= 1 study) [21], kg (n= 1 study) [29], Newton-meter (n= 7 studies) [22–25,32,37,40], and Newtons per kg (n= 1 study) [35].

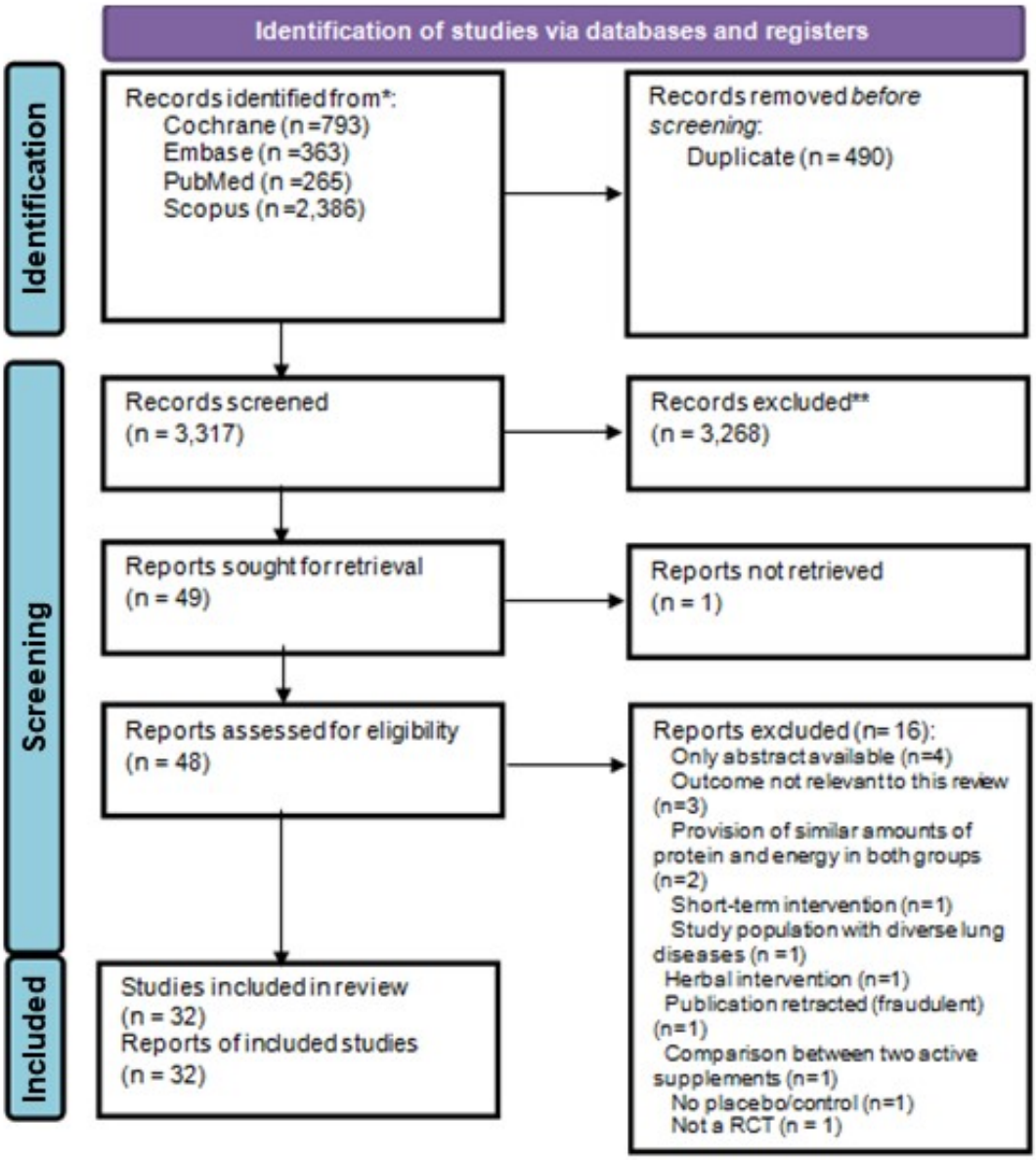

Figure 1 **Flow diagram of study selection**

Study	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Lewis, 1987	1.00	3.00	10	0.22	4.00	11	2.8%	0.78 [-2.23, 3.79]
Efthimiou, 1988	4.20	3.50	7	-0.70	9.57	7	0.6%	4.90 [-2.65, 12.45]
Knowles, 1988	0.97	11.63	25	-1.38	11.46	25	0.8%	2.35 [-4.05, 8.75]
Otte, 1989	1.52	1.41	13	0.16	0.93	15	7.0%	1.36 [0.46, 2.26]
Fuenzalida, 1990	4.44	6.82	5	3.21	6.78	4	0.5%	1.23 [-7.71, 10.17]
Entrenas Costa, 1991	-1.20	10.34	16	-1.80	11.60	21	0.7%	0.60 [-6.49, 7.69]
Rogers, 1992	1.70	5.10	15	0.40	8.26	12	1.2%	1.30 [-4.04, 6.64]
Schols, 1995	2.03	10.28	72	-0.08	11.96	63	2.0%	2.11 [-1.68, 5.90]
Saudny-Unterberger, 1997	0.21	2.54	14	-0.08	0.63	10	5.8%	0.29 [-1.10, 1.67]
Goris, 2003	0.20	1.20	11	0.30	2.35	8	4.9%	-0.10 [-1.88, 1.68]
Steiner, 2003	0.63	1.45	25	-0.58	1.54	35	7.3%	1.21 [0.45, 1.97]
Vermeeren, 2004	1.37	1.30	23	1.12	1.20	24	7.4%	0.25 [-0.47, 0.97]
Fuld, 2005	1.10	2.52	14	0.10	0.88	11	5.7%	1.00 [-0.42, 2.42]
Faager, 2006	1.24	16.28	13	1.04	13.69	10	0.2%	0.20 [-12.06, 12.46]
Deacon, 2008	0.70	1.67	38	0.20	1.92	42	7.2%	0.50 [-0.29, 1.29]
Weekes, 2009	2.01	1.10	22	-0.94	0.60	18	7.7%	2.95 [2.41, 3.49]
Baldi, 2010	3.80	2.60	13	-0.10	1.10	13	5.4%	3.90 [2.37, 5.43]
Dal Negro, 2010	5.53	8.79	16	-1.07	6.44	16	1.2%	6.60 [1.26, 11.94]
Sugawara, 2010	1.40	5.30	17	-1.00	5.85	15	1.9%	2.40 [-1.49, 6.29]
Dal Negro, 2012	5.53	8.99	44	-1.89	6.60	44	2.5%	7.42 [4.12, 10.72]
Sugawara, 2012	1.30	8.30	17	-0.20	4.30	14	1.5%	1.50 [-3.04, 6.04]
Gurgun, 2013	1.10	0.90	15	0.60	0.70	15	7.6%	0.50 [-0.08, 1.08]
Khan, 2016	1.48	3.30	30	-0.17	2.50	30	5.6%	1.65 [0.17, 3.13]
van de Bool, 2017	1.90	11.02	42	0.30	10.62	39	1.4%	1.60 [-3.11, 6.31]
van Beers, 2020	0.64	3.43	42	-0.90	3.37	39	5.6%	1.54 [0.06, 3.02]
Ahmadi, 2020	0.52	2.19	23	0.64	2.68	21	5.6%	-0.12 [-1.57, 1.33]
Total (95% CI)			**582**			**562**	**100.0%**	**1.44 [0.81, 2.08]**

Heterogeneity: $Tau^2 = 1.23$; $Chi^2 = 94.26$, df = 25 ($P < 0.01$); $I^2 = 73\%$

Test for overall effect: $P < 0.01$

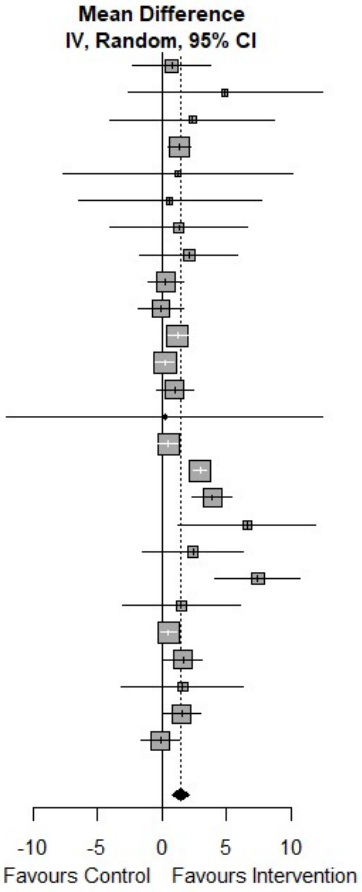

Figure 2 **Forest plot diagrams for body weight**

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Vermeeren, 2004	-0.50	2.60	21	-0.40	2.70	22	7.6%	-0.04 [-0.64, 0.56]
Fuld, 2005	2.00	1.64	14	0.40	0.89	11	4.7%	1.13 [0.27, 1.99]
Deacon, 2008	0.90	2.43	38	0.80	2.64	42	10.4%	0.04 [-0.40, 0.48]
Baldi, 2010	1.50	2.60	13	-0.10	2.30	13	5.4%	0.63 [-0.16, 1.42]
Dal Negro, 2010	3.59	4.29	16	-0.13	4.19	16	6.0%	0.86 [0.13, 1.58]
Sugawara, 2010	0.30	0.92	17	0.00	1.18	15	6.3%	0.28 [-0.42, 0.98]
Dal Negro, 2012	3.66	4.52	44	3.80	4.33	44	10.8%	-0.03 [-0.45, 0.39]
Sugawara, 2012	0.80	5.50	17	-0.10	2.49	14	6.2%	0.20 [-0.51, 0.91]
Gurgun, 2013	0.60	0.50	15	0.10	0.60	15	5.7%	0.88 [0.13, 1.64]
Marinari, 2013	3.70	5.50	30	-0.60	1.70	25	8.1%	1.00 [0.44, 1.57]
De Benedetto, 2018	1.10	4.40	45	1.00	4.40	45	10.9%	0.02 [-0.39, 0.44]
van Beers, 2020	0.17	1.36	42	-0.22	1.31	39	10.4%	0.29 [-0.15, 0.73]
Ahmadi, 2020	2.85	4.65	23	0.78	2.62	21	7.6%	0.53 [-0.07, 1.14]
Total (95% CI)			**335**			**322**	**100.0%**	**0.37 [0.15, 0.59]**

Heterogeneity: $Tau^2 = 0.07$; $Chi^2 = 22.09$, df = 12 (P = 0.04); $I^2 = 46\%$

Test for overall effect: P < 0.01

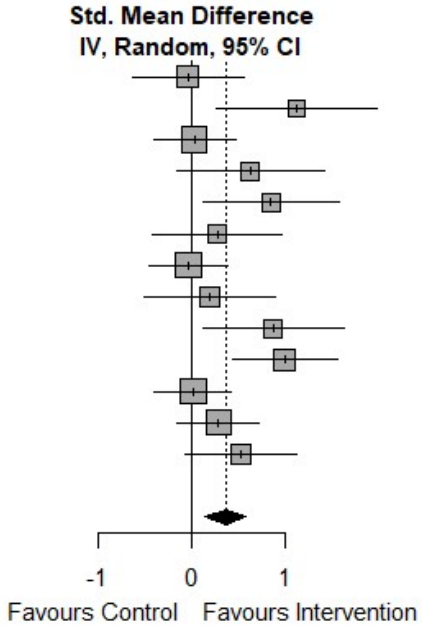

Figure 3 **Forest plot diagrams for lean body mass**

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lewis, 1987	0.10	1.61	10	0.40	3.00	11	1.8%	-0.30 [-2.33, 1.73]
Efthimiou, 1988	0.70	0.80	7	0.10	3.00	7	1.4%	0.60 [-1.70, 2.90]
Knowles, 1988	0.82	3.16	25	1.50	3.06	25	2.5%	-0.68 [-2.40, 1.04]
Otte, 1989	0.10	0.54	13	-0.03	0.58	15	42.9%	0.13 [-0.29, 0.55]
Entrenas Costa, 1991	-0.10	1.83	16	-0.50	2.15	21	4.5%	0.40 [-0.88, 1.68]
Schols, 1995	0.40	1.70	72	-0.10	1.80	63	21.0%	0.50 [-0.09, 1.09]
Weekes, 2009	-0.10	0.90	22	-0.60	0.82	18	25.9%	0.50 [-0.03, 1.03]
Total (95% CI)			**165**			**160**	**100.0%**	**0.29 [0.02, 0.57]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 3.28$, df = 6 (P = 0.77); $I^2 = 0\%$

Test for overall effect: P = 0.03

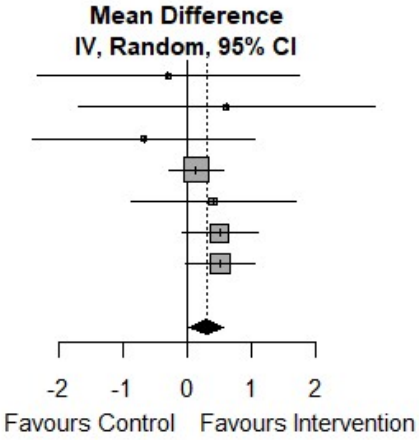

Figure 4 **Forest plot diagrams for midarm muscle circumference**

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Steiner, 2003	0.67	2.04	25	-0.76	1.66	35	11.4%	0.77 [0.24, 1.31]
Vermeeren, 2004	1.70	2.50	21	1.50	2.50	22	9.9%	0.08 [-0.52, 0.68]
Fuld, 2005	-1.70	2.16	14	-0.60	0.67	11	6.4%	-0.63 [-1.44, 0.18]
Deacon, 2008	-0.70	2.00	38	-0.40	1.92	42	13.9%	-0.15 [-0.59, 0.29]
Sugawara, 2010	-0.04	1.27	17	-0.17	1.22	15	8.1%	0.10 [-0.59, 0.80]
Sugawara, 2012	1.30	1.60	17	0.00	3.02	14	7.7%	0.54 [-0.18, 1.26]
van de Bool, 2017	1.20	2.20	42	0.20	8.45	39	14.0%	0.16 [-0.27, 0.60]
De Benedetto, 2018	-1.10	4.40	45	-1.00	4.40	45	14.8%	-0.02 [-0.44, 0.39]
van Beers, 2020	0.86	3.24	42	-0.22	1.31	39	13.9%	0.43 [-0.01, 0.87]
Total (95% CI)			**261**			**262**	**100.0%**	**0.16 [-0.07, 0.40]**

Heterogeneity: $Tau^2 = 0.05$; $Chi^2 = 13.98$, df = 8 (P = 0.08); $I^2 = 43\%$

Test for overall effect: P = 0.18

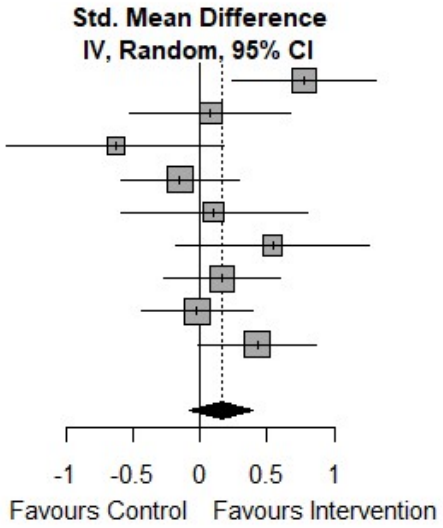

Figure 5 **Forest plot diagrams for fat mass**

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lewis, 1987	0.10	2.65	10	-0.70	3.56	11	16.3%	0.80 [-1.87, 3.47]
Efthimiou, 1988	1.50	1.60	7	-0.10	1.60	7	41.2%	1.60 [-0.08, 3.28]
Knowles, 1988	0.12	4.77	25	-0.80	4.57	25	17.3%	0.92 [-1.67, 3.51]
Fuenzalida, 1990	2.66	4.76	5	0.20	3.95	4	3.6%	2.46 [-3.23, 8.15]
Entrenas Costa, 1991	0.20	5.20	16	0.10	4.06	21	12.2%	0.10 [-2.98, 3.18]
Rogers, 1992	0.20	5.20	15	-0.20	4.06	12	9.5%	0.40 [-3.09, 3.89]
Total (95% CI)			**78**			**80**	**100.0%**	**1.09 [0.01, 2.16]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.19$, df = 5 (P = 0.95); $I^2 = 0\%$

Test for overall effect: P = 0.05

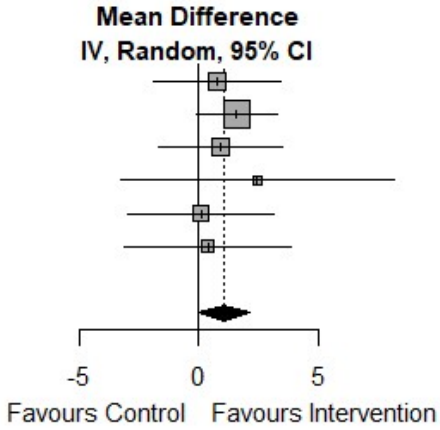

Figure 6 **Forest plot diagrams for triceps skinfold**

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Lewis, 1987	0.82	5.92	13	0.23	11.47	10	7.3%	0.07 [-0.76, 0.89]
Efthimiou, 1988	1.90	2.10	7	-0.30	2.10	7	5.1%	0.98 [-0.15, 2.11]
Rogers, 1992	2.10	2.20	15	-0.70	2.20	12	7.2%	1.23 [0.40, 2.07]
Saudny-Unterberger, 1997	-0.87	3.43	13	0.38	2.72	10	7.2%	-0.38 [-1.21, 0.45]
Steiner, 2003	0.64	1.72	25	-0.05	2.20	35	10.3%	0.34 [-0.18, 0.85]
Vermeeren, 2004	0.00	3.00	20	0.00	3.00	22	9.4%	0.00 [-0.61, 0.61]
Fuld, 2005	2.95	4.50	14	0.61	2.57	11	7.4%	0.60 [-0.21, 1.41]
Faager, 2006	0.69	7.19	12	1.70	11.08	10	7.2%	-0.11 [-0.95, 0.73]
Weekes, 2009	-0.80	2.34	22	-1.10	2.34	18	9.2%	0.13 [-0.50, 0.75]
Dal Negro, 2012	1.60	1.49	44	-0.60	1.81	44	10.9%	1.32 [0.85, 1.78]
Degirmenci, 2018	0.71	7.59	20	-0.14	6.07	20	9.2%	0.12 [-0.50, 0.74]
Ahmadi, 2020	3.06	7.08	23	0.25	7.36	21	9.5%	0.38 [-0.21, 0.98]
Total (95% CI)			**228**			**220**	**100.0%**	**0.39 [0.07, 0.71]**

Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 28.57$, df = 11 ($P < 0.01$); $I^2 = 62\%$

Test for overall effect: P = 0.02

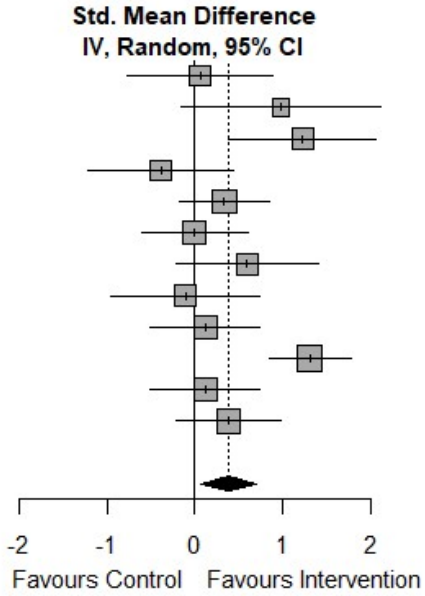

Figure 7 **Forest plot diagrams for handgrip strength**

Study	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Steiner, 2003	1.77	3.68	25	0.37	3.60	35	11.5%	0.38 [-0.14, 0.90]
Vermeeren, 2004	3.00	8.00	20	2.00	9.00	23	9.0%	0.11 [-0.48, 0.71]
Fuld, 2005	3.50	2.41	18	-0.70	5.43	18	6.9%	0.98 [0.28, 1.67]
Faager, 2006	-2.00	41.57	7	21.00	41.93	5	2.6%	-0.51 [-1.68, 0.67]
Deacon, 2008	8.90	14.60	38	10.00	10.43	42	15.0%	-0.09 [-0.53, 0.35]
Sugawara, 2010	5.00	9.73	17	-0.60	9.90	15	6.7%	0.56 [-0.15, 1.27]
Constantin, 2013	18.97	25.30	25	19.28	25.70	25	10.3%	-0.01 [-0.57, 0.54]
Ahnfeldt-Mollerup, 2015	0.27	1.05	18	0.22	0.89	17	7.6%	0.05 [-0.61, 0.71]
van de Bool, 2017	13.60	24.90	42	10.80	24.90	39	15.2%	0.11 [-0.32, 0.55]
van Beers, 2020	10.35	22.75	42	10.05	21.54	39	15.2%	0.01 [-0.42, 0.45]
Total (95% CI)			**252**			**258**	**100.0%**	**0.15 [-0.04, 0.35]**

Heterogeneity: $Tau^2 = 0.01$; $Chi^2 = 10.62$, df = 9 (P = 0.30); $I^2 = 15\%$

Test for overall effect: P = 0.12

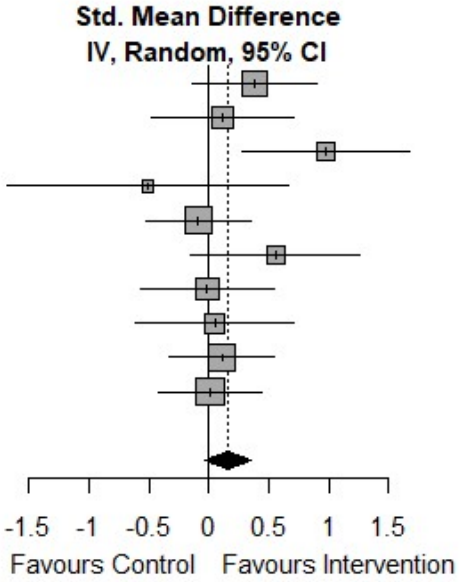

Figure 8 **Forest plot diagrams for quadriceps strength**

SUPPLEMENTARY DATA

Table S1 **Full search strategy performed on PubMed**

Table S2 **Characteristics of excluded studies [ordered by study ID]**

Table S3 **Characteristics of the interventions according to oral nutrition therapy, assessment of adherence to the planned trials' protocol, and authors' conflict of interests disclosures from primary studies**

Table S4 **Reasons for classification of risk of bias in primary studies according to RoB 2**

Table S5 **Univariate meta-regression analysis of the effect of nutritional intervention on body weight**

Table S6 **Univariate meta-regression analysis of the effect of nutritional intervention on handgrip and quadriceps strength**

Figure S1 **Risk of bias summary: review authors' judgements for individual studies included**

Figure S2 **Funnel plot for body weight**

Figure S3 **Funnel plot for lean body mass**

Figure S4 **Funnel plot for handgrip strength**

Figure S5 **Funnel plot for quadriceps strength**

Table S1 **Full search strategy performed on PubMed, lasted performed in May 18th, 2021.**

PICO Component		Search strategy in PubMed
#1	Population	((((((((((((((((((((((((((Pulmonary Disease, Chronic Obstructive [Title/Abstract]) OR (COPD[Title/Abstract])) OR (Chronic Obstructive Pulmonary Disease[Title/Abstract])) OR (COAD[Title/Abstract])) OR (Chronic Obstructive Airway Disease[Title/Abstract])) OR (Chronic Obstructive Lung Disease[Title/Abstract])) OR (Airflow Obstruction, Chronic[Title/Abstract])) OR (Airflow Obstructions, Chronic[Title/Abstract])) OR (Chronic Airflow Obstructions[Title/Abstract])) OR (Chronic Airflow Obstruction[Title/Abstract])) OR (Bronchitis, Chronic[Title/Abstract])) OR (Pulmonary Emphysema[Title/Abstract])) OR (Lung Diseases, Obstructive[Title/Abstract])) OR (Lung Disease, Obstructive[Title/Abstract])) OR (Obstructive Lung Disease[Title/Abstract])) OR (Obstructive Lung Diseases[Title/Abstract])) OR (Obstructive Pulmonary Diseases[Title/Abstract])) OR (Obstructive Pulmonary Disease[Title/Abstract])) OR (Pulmonary Disease, Obstructive[Title/Abstract])) OR (Pulmonary Diseases, Obstructive[Title/Abstract])) OR (alpha 1-Antitrypsin Deficiency[Title/Abstract])) OR (COPD, Severe Early-Onset[Title/Abstract]))) OR (Pulmonary Disease, Chronic Obstructive[Title/Abstract])) OR (Bronchitis, Chronic[Title/Abstract]))))
#2	Intervention	((Diet[Title/Abstract]) OR (Diets[Title/Abstract])) OR (Nutrition Therapy[Title/Abstract])) OR (Therapy, Nutrition[Title/Abstract])) OR (Medical Nutrition Therapy[Title/Abstract])) OR (Nutrition Therapy, Medical[Title/Abstract])) OR (Therapy, Medical Nutrition[Title/Abstract])) OR (Diet Therapy[Title/Abstract])) OR (Nutritional Support[Title/Abstract])) OR (Support, Nutritional[Title/Abstract])) OR (Dietary Supplements[Title/Abstract])) OR (Dietary Supplement[Title/Abstract])) OR (Supplements, Dietary[Title/Abstract])) OR (Dietary Supplementations[Title/Abstract])) OR (Supplementations, Dietary[Title/Abstract])) OR (Food Supplementations[Title/Abstract])) OR (Food Supplements[Title/Abstract])) OR (Food Supplement[Title/Abstract])) OR (Supplement, Food[Title/Abstract])) OR (Supplements, Food[Title/Abstract])) OR (Food, fortificated[Title/Abstract])) OR (Food, fortification[Title/Abstract])) OR (Energy intake[Title/Abstract])) OR (Protein intake[Title/Abstract])) OR (Energy drinks[Title/Abstract])) OR (Energy drink[Title/Abstract])) OR (Drink, energy[Title/Abstract])) OR (Drinks, energy[Title/Abstract])) OR (Energy supplements[Title/Abstract])) OR (Protein supplements[Title/Abstract])) OR (Calorie supplement[Title/Abstract])) OR (Protein, Whey[Title/Abstract])) OR (Proteins, Whey[Title/Abstract])) OR (Whey protein[Title/Abstract])) OR (Creatine[Title/Abstract])) OR (Amino acids[Title/Abstract])) OR (Amino Acids, Peptides,[Title/Abstract] AND Proteins[Title/Abstract])) OR (BCAA[Title/Abstract])) OR (Nutritional intervention[Title/Abstract])) OR (Enteral nutrition support[Title/Abstract])) OR (Whey peptide[Title/Abstract])) OR (Nutritional supplement therapy[Title/Abstract])) OR (Essential amino acids supplementation[Title/Abstract])) OR (Nutrient Supplementation[Title/Abstract]))
#3	Study design	((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab] NOT (animals [mh] NOT humans [mh])))))
Combined search		**#1 AND #2 AND #3**

Table S2 **Characteristics of excluded studies [ordered by study ID]**

Study	Reason for exclusion
Angelillo, 1985 [71]	Supplementation given only for five days.
Benito-Martinez, 2017 [72]	Study population with diverse lung diseases.
Cai, 2003 [73]	Herbal intervention.
Calder, 2018 [74]	Provision of similar amounts of protein and calories in both groups.
Camere, 2016 [75]	Only abstract available.
Collins, 2014 [76]	Only abstract available.
Gurgun, 2011 [77]	Only abstract available.
Ingadottir, 2020 [78]	Outcome not relevant to this review.
Laviolette, 2010 [79]	Provision of similar amounts of protein and calories in both groups.
Matsuyama, 2005 [80]	Publication retracted (fraudulent).
Ogasawara, 2018 [81]	Outcome not relevant to this review.
Planas, 2005 [82]	Comparison between two active supplementations
Raizada, 2014 [83]	Non-randomized prospective study.
Sugawara, 2011 [84]	Only abstract available.
Tümer, 2009 [85]	No placebo/control intervention.
Zongxing, 2005 [86]	Outcome not relevant to this review.

Table S3 **Characteristics of the interventions according to oral nutrition therapy, assessment of adherence to the planned trials' protocol, and authors' conflict of interests disclosures from primary studies**

Author, year	Oral nutrition therapy characteristics		Intervention time (weeks)	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)				
Lewis/1987 [39]	ONS: Isocal HCN®, 2 kcal/mL (40% CHO, 45% fat, and 15% prot), 240 – 480mL/day ONS goal: provide 500–1000 kcal/day and 19–38 g prot/day + usual diet	Usual diet	8	208 kcal/day 15.4g/day	NR	No information given
Efthimiou/1988 [40]	ONS: Build-up® (Carnation), each ONS sachet mixed with 237 mL of whole milk: 320 kcal and 18 g prot, two to four times/day ONS goal: months four to six, to reach 2,500 kcal/day and 90g prot/day (men) or 2,300 kcal/day and 80g prot/day (women) Normal diet: months one to three, and seven to nine	Normal diet	12	681 kcal/day 25.9g/day	NR	No information given
Knowles/1988 [51]	ONS: Sustacal® (54% CHO, 22% fat, and 24% prot) ONS goal: increase caloric intake about 50% above normal level	Usual diet	8	458.9 kcal/day Protein NR	Daily food diary	No information given

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)	(weeks)			
Otte/1989 [62]	ONS: Novo® (1 kcal/mL, 50% CHO, 30% fat, and 20% prot) ONS goal: 400 kcal/day and 20 g prot/day	Placebo: same consistency and taste than ONS, but 0.1 Kcal/mL, and 0.005g prot/mL	13	NR	A nurse connected to the study visited the patients every 14th day, she ensured correct administration	NOVO (Bagsvaerd, Denmark) provided the nutritional formula and reference product to the study.
Fuenzalida/1990 [65]	ONS: Sustacal HC® (1.5 kcal/mL, 50% CHO, 29% fat, and 16% prot) ONS goal: from 360 kcal to 1,080kcal/day + Hospital Diet	Hospital Diet	6	67.1 kcal/day Protein NR	NR	No information given
Entrenas Costa/1991 [66]	ONS: Pulmocare® (1.5 Kcal/mL, 28% CHO, 55.2% fat, and 16.7% prot) ONS goal: increase caloric intake with ONS by up to 1.5 times BEE	Hospital Diet	2.25	NR	NR	No information given
Rogers/1992 [67]	Varied ONS (with eating plan: 1.7 x REE and 1.5g prot /kg)	Usual diet (hospitalized at week 1 and 4 of the study)	3	NR	NR	No information given
Ganzoni/1994 [68]	ONS: Fresubin OP® 200 mL, one to two times/day Fats and carbohydrates addition in all meals (small and frequents)	Normocaloric diet	48	-25.5 kcal/day Protein NR	Caloric intake at three-month intervals was monitored, but NR the assessment method used	No information given

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)	(weeks)			
Schols/1995 [69]	ONS: high-caloric drink mix (Nutridrink®, Protifar®, Fantomalt®, and oil), 200 mL (35% CHO, 51% fat, and 14% prot) daily high caloric liquid supplement (420 kcal/200 ml: ONS goal: 420 kcal/day	No ONS	8	531.9 kcal/day Protein NR	Supplement intake was recorded daily	No information given
Saudny-Unterberger/1997 [70]	ONS: Ensure®, Ensure Plus®, or A variety of puddings, or extra snacks ONT goal: to assure a caloric intake ≥1.5x REE, if normal BMI and at ≥ 1.7x REE, if low BMI	Hospital diet	2	355 kcal/day 10g/day	NR	Supplements were provided by Abbott Laboratories, Montreal, Canada.
Goris/2003 [41]	ONS: Respifor® (1.5 kcal/mL, 60% CHO, 20% fat, and 20% prot), three times/day ONT goal: 560 kcal/day + nutritional advices from a dietitian on how to increase their energy intake.	Nutritional advices from a dietitian on how to increase their energy intake	12	143.3 kcal/day Protein NR	NR	No information given
Steiner/2003 [42]	ONS: Respifor® (1.5 kcal/mL, 60% CHO, 20% fat, and 20% prot), three times/day ONS goal: 570 kcal/day	Placebo: packed and flavored identically from ONS (non-nutritive)	7	407 kcal/day 24.1g/day	Self-reported compliance with the supplement (% cartons taken/cartons prescribed)	No information given

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time (weeks)	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)				
Vermeeren/2004 [43]	ONS: Respifor® (1.5 kcal/mL, 60% CHO, 20% fat, and 20% prot), three times/day ONS goal: 570 kcal/day	Placebo: vanilla flavored water with 0 kcal/day	1.29	355.9 kcal/day 30 g/day	Monitored by the nurses	The study was supported by Numico Research BV, The Netherlands
Fuld/2005 [44]	ONS: Creatine (Cr) + glucose polymer (5 g Cr and 35 g glucose/dose). A. Loading phase: three times/day (14 days) B. Maintenance phase: one time/day (10 wk)	Placebo: glucose polymer 40.7 g	12	NR	NR	Authors declared no COI
Faager/2006 [45]	ONS: Creatine (0.3 g/kg BW/d) first 7 d, and 0.07 g/kg BW/d next 7 wk	Placebo: glucose	8	NR	Urine 24 h 1 wk from trial start and at 8 wk, and 2 mo after the end of ONS intake	No information given
Deacon/2008 [44]	ONS: Creatine monohydrate (Cr) loaded for 5 days (22 g, divided in four doses/day), followed by maintenance during PR (3.76 g/d).	Placebo: Similar texture and appearance powder: Lactose for 5 days(24 g divided in four doses/day), followed by 4 g/day during PR	1.71	NR	Self-reported and ONS empty tub return	Authors declared no COI
Weekes/2009 [47]	Tailored dietary advice and counseling and Food Fortification (FF): whole milk powder, to "fortify" 1 pint of full-cream milk. FF goal: provide 200 to 300 kcal and 7 to 11 g of prot/day	Leaflet providing advice on nourishing snacks and drinks and encouraging FF during baseline assessment (content was never discussed)	24	194 kcal/day 11.8 g/day	5-day dietary diaries (months 1, 3, 6, 7, 9 and 12)	None declared.

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)	(weeks)			
Baldi/2010 [48]	ONS: liquid supplements of 200 mL each, Aminotrofic® (EAAs mixture 4 g), two times/day	No ONS	12	-90 kcal/day Protein NR	Assessed but NR how	Authors declared no COI
Dal Negro/2010 [49]	ONS: Aminotrofic® (EAAs mixture 4g) , two times/day	Placebo: indistinguishable from ONS	12	NR	NR	No information given
Sugawara/2010 [50]	ONS: Nutritional drink 200 mL (60% CHO, 25% fat, and 15% prot, enriched with w-3 PUFA, and vitamin A), two times/day ONS goal: 400 kcal/day + Encouraged to consume regular meal portions	Monthly 45-min education program (COPD and dyspnea control, medication and equipment use, nutrition, stress management, and relaxation techniques)	12	NR	NR	Authors declared no COI
Dal Negro/2012 [52]	ONS: Aminotrofic® (EAAs mixture 4g) , two times/day	Placebo	12	-75.5 kcal/day -5.8 g/day	NR	No information given
Sugawara/2012 [53]	ONS: Meint® 200 mL (1.0 kcal/mL, 53% CHO, 25% fat, and 20% whey protein), two times/day	Normal meals alone with dietary instruction	12	-2.5 kcal/day -1.5 g/day	Daily intake of ONS was confirmed in a diary.	Authors declared no COI
Constantin/2013 [54]	ONS: 19g prot and 49g glucose polymer in 500 mL of water.	Placebo: identical volume, noncaloric drink	8	NR	ONS intake was supervised and took place immediately after each training session (three times/wk)	None declared

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)	(weeks)			
Gurgun/2013 [55]	ONS: nutritional drink 250 mL (53.3% CHO, 30% fat, and 16.7% prot), three times/day + encouragement to continue the consumption of their own meal portions.	Usual medical standard of care	8	NR	Patient's daily intake was checked by controlling their food diary.	No information given
Marinari/2013 [56]	ONS: EufortynLios® (Creatine 170 mg + 160 mg Coenzyme Q-Ter), two times/day	Placebo: bags apparently identical to ONS	8	NR	NR	Authors declared no COI
Ahnfeldt-Mollerup/2015 [57]	ONS: Protein bar (134.8 kcal, 14.6g CHO, 4.2g fat, and 9.3 prot), two times/day	Exercise only	9	-89.6 kcal/day -2.50 g/day	Staff at the PRP distributed the protein bars to the participants and followed up on compliance regarding their intake.	Authors declared no COI
Khan/2016 [58]	ONS: protein powder PROTENIX® (2 servings: 90 Kcal, 55% CHO, 0% fat, and 45% prot), 30 g/day	Usual diet	12	NR	Based on drink consumption diaries and changes	No information given

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)	(weeks)			
van de Bool/2017 [59]	ONS: 1.5 kcal/mL, 125 mL (60% CHO, 20% fat, 20% prot, enriched with leucine, w-3 PUFA, and vitamin D), two to three times/day	Placebo: Non active constituents and flavored non-caloric aqueous solution.	16	-134.4 kcal/day -3.3 g/day	Tracked on a calendar, but also calculated from the amount of supplements provided and turned in after the ONS period.	One author employed by Nutricia Research. Two authors report grants from Netherlands Lung Foundation and Nutricia Research, during the conduct of the study. One author member of International Scientific Advisory Board of Nutricia Advanced Medical Nutrition.
De Benedetto/2018 [60]	160 mg Coenzyme QTer® + 170 mg Creatine, twice daily	Placebo	8	NR	NR	Interdisciplinary Association for Research in Lung Disease (AIMAR) Study Group and by an unrestricted grant of Scharper S.p.A None of the sponsors had an influence on the design, conduct, analysis and interpretation of the study.
Degirmenci/2018 [61]	ONS: Nutrivigor®, 220 mL (39g CHO, 11g fat, 18g prot, enriched with HMB, FOS, calcium, and vitamin D), two times/day + usual diet	No nutritional support.	12	NR	NR	No information given

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	**Control group (CG)**	**(weeks)**			
van Beers/2020 [63]	ONS: 1.5 kcal/mL, 125 mL (60% CHO, 20% fat, 20% prot, enriched with leucine, w-3 PUFA, and vitamin D) Phase 1: First 4 months, ONS three times/day Phase 2: Next 8 months, ONS one time/day (non-blinded)	Placebo: Non active constituents and flavored non-caloric aqueous solution. Phase 1: Only at first 4 months	48	-178.2 kcal/day -10.5 g/day	Tracked on a calendar, but also calculated from the number of supplements provided and turned in after the ONS period.	One author reports grants from the Lung Foundation Netherlands and Nutricia Research during the study. One author reports personal fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Novartis, GlaxoSmithKline and TEVA outside the submitted work. One author reports a grant for this study as it was financially supported by a public-private consortium of Maastricht University/NUTRIM, CIRO+ BV Horn, Nutricia Research and the Lung Foundation Netherlands, personal fees as employee at Nutricia Research during the study and personal fees as employee at Nutricia Research outside the submitted work. One author has a patent issued covering the product.

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Table S3 Continued

Author, year	Oral nutrition therapy characteristics		Intervention time	Mean difference energy and protein intake between intervention and control group	Method of adherence measure	Funding, including role in study and authors' COI disclosures
	Intervention group (IG)	Control group (CG)	(weeks)			
van Beers/2020 [63] (continued)						One author reports personal fees from Nycomed, Boehringer, AstraZeneca, GSK, Novartis and Chiesi. Prof. Schols reports grants from Nutricia Advanced Medical Nutrition.
Ahmadi/2020 [64]	ONS: Whey beverage fortified with magnesium and vitamin C (15.9 g whey protein) + dietary advice and routine care	Dietary advice and routine care	8	217.2 kcal/day 13.9 g/day	Checked based on the amount consumed by each of them	Authors declared no COI

Abbreviations: ONS, Oral nutritional supplement; %CHO, % of total energy from carbohydrate ;%fat, % of total energy from fat; %prot, % of total energy from protein; prot, protein; NR, Not reported; COI, Conflict of interests; BEE, Basal Energy Expenditure; REE, Resting Energy Expenditure; BMI, Body mass index; ONT, Oral nutrition therapy; BW, Body weight: PR,Pulmonary rehabilitation; EAAs, Essential amino acids; w-3 PUFA, omega-3 polyunsaturated fatty acids; DHA + EPA, Docosahexaenoic acid + Eicosapentaenoic acid; HMB,Hydroxymethyl Butyrate; FOS, Fructooligosaccharides.

Table S4 **Reasons for classification of risk of bias in primary studies according to RoB 2**

Study	D1	D2	D3	D4	D5	Overall	Reasons
Lewis /1987 [39]	Some concerns	Some concerns	Low	Low	Low	Some concerns	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment. It is not clear if patients differed regarding baseline features.
Efthimiou/1988 [40]	Some concerns	High	Some concerns	Low	Low	High	There is no information about the allocation sequence concealment. It is not clear if patients differed regarding baseline features. There is no information about losses of follow-up.
Knowles/1988 [51]	Some concerns	High	Some concerns	Low	Some concerns	High	It is not clear if patients differed regarding baseline features. There is no information about losses of follow-up and about the washout period.
Otte/1989 [62]	Some concerns	High	Low	Low	Low	High	There is no information about the allocation sequence concealment. Between groups comparisons of outcomes were not performed.
Fuenzalida/1990 [65]	Some concerns	High	Some concerns	Low	Low	High	There is no information about the allocation sequence concealment. Between groups comparisons of outcomes were not performed. There is no information about losses of follow-up.

(continued on next page)

Table S4 Continued

Study	D1	D2	D3	D4	D5	Overall	Reasons
Entrenas Costa/1991 [66]	High	High	Some concerns	Low	Low	High	There is no information about the allocation sequence concealment. There are some differences between groups at baseline. There is no information about losses of follow-up. Between groups comparisons of outcomes were not performed.
Rogers/1992 [67]	Some concerns	Some concerns	Some concerns	Low	Low	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment and the losses of follow-up.
Ganzoni/1994 [68]	Some concerns	Some concerns	High	Low	Some concerns	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment and patient's baseline features. Losses of follow-up were > 20%.
Schols/1995 [69]	Some concerns	Some concerns	Low	Low	Low	Some concerns	There is no information about the allocation sequence concealment. It is not clearly described if careers and people delivering the interventions aware of the assigned intervention during the trial

(continued on next page)

Table S4 Continued

Study	D1	D2	D3	D4	D5	Overall	Reasons
Saudny-Unterberger/1997 [70]	Some concerns	Some concerns	High	Low	Low	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
Goris/2003 [41]	Some concerns	Some concerns	Low	Low	Low	Some concerns	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment.
Steiner/2003 [42]	Some concerns	Low	Some concerns	Low	Low	Some concerns	There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
Vermeeren/2004 [43]	Some concerns	Low	Low	Low	Low	Some concerns	There is no information about the allocation sequence concealment.
Fuld/2005 [44]	Some concerns	Low	High	Low	Low	High	There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
Faager/2006 [45]	Some concerns	Low	High	Low	Low	High	There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
Deacon/2008 [46]	Some concerns	Low	High	Low	Low	High	There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.

(continued on next page)

Table S4 Continued

Study	D1	D2	D3	D4	D5	Overall	Reasons
Weekes/2009 [47]	Some concerns	Low	High	Low	Low	High	There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
Baldi/2010 [48]	Some concerns	Some concerns	Low	Low	Low	Some concerns	There is no information about the allocation sequence concealment. It is not clearly described if participants aware of the assigned intervention during the trial while career and people delivering the interventions aware about this.
Dal Negro/2010 [49]	Some concerns	Low	Some concerns	Low	Low	Some concerns	There is no information about the allocation sequence concealment and losses of follow-up.
Sugawara/2010 [50]	Some concerns	Some concerns	Low	Low	Low	Some concerns	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment.
Dal Negro/2012 [52]	Some concerns	Low	Some concerns	Low	Low	Some concerns	There is no information about the allocation sequence concealment and losses of follow-up.
Sugawara/2012 [53]	Some concerns	Some concerns	Some concerns	Low	Some concerns	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment. Loss of follow-up equal to 14%. Results of some outcomes of interest were not reported.

(continued on next page)

Table S4 Continued

Study	D1	D2	D3	D4	D5	Overall	Reasons
Constantin/2013 [54]	Some concerns	Low	Some concerns	Low	Some concerns	High	There is no information about the allocation sequence concealment. Loss of follow-up equal to 15%. Results of some outcomes of interest were not reported.
Gurgun/2013 [55]	Some concerns	Some concerns	Some concerns	Low	Low	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment and losses of follow-up. Groups had different body weight at baseline.
Marinari/2013 [56]	Some concerns	Low	Some concerns	Low	Low	Some concerns	There is no information about the allocation sequence concealment and the losses of follow-up.
Ahnfeldt-Mollerup/2015 [57]	Some concerns	Some concerns	Some concerns	Low	Low	High	There is no information about the allocation sequence concealment. It is not clearly described if participants aware of the assigned intervention during the trial while career and people delivering the interventions aware about this. Loss of follow-up > 20%.
Khan/2016 [58]	Some concerns	Some concerns	Low	Low	Low	Some concerns	There is no information about the allocation sequence concealment. It is not clearly described if career and people delivering the interventions aware about this while participants aware of the assigned intervention during the trial.

(continued on next page)

Table S4 Continued

Study	D1	D2	D3	D4	D5	Overall	Reasons
van de Bool/2017 [59]	Some concerns	Low	Some concerns	Low	Low	Some concerns	There is no information about the allocation sequence concealment. Loss of follow-up equal to 15%.
De Benedetto/2018 [60]	Some concerns	Low	Some concerns	Low	Low	Some concerns	There is no information about the allocation sequence concealment. Loss of follow-up equal to 15%.
Degirmenci/2018 [61]	Some concerns	Some concerns	High	Low	Low	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
van Beers/2020 [63]	Some concerns	Some concerns	High	Low	Low	High	It is not clearly described if participants, careers and people delivering the interventions aware of the assigned intervention during the trial. There is no information about the allocation sequence concealment. Losses of follow-up were > 20%.
Ahmadi/2020 [64]	Some concerns	Some concerns	Low	Low	Low	Some concerns	Careers and people delivering the interventions aware of the assigned intervention during the trial. Groups were different in baseline regarding some outcomes as lean mass and quality of life.

Table S5 **Univariate meta-regression analysis of the effect of nutritional intervention on body weight and lean body mass**

Covariate	Body weight (kg)				Lean body mass*			
	Adjusted R^2 (%)	Estimate	Confidence interval 95%	p-value	Adjusted R^2 (%)	Estimate	Confidence interval 95%	p-value
Amount of energy prescribed (kcal)	36.50	-0.0034	-0.0069 to 0.0000	0.0514	Zero	-0.0007	-0.0021 to 0.0008	0.3082
Amount of protein prescribed (g)	16.66	-0.0620	-0.1386 to 0.0147	0.1072	Zero	-0.0124	-0.0453 to 0.0206	0.4121
Duration of intervention (wk)	45.95	0.0454	-0.0089 to 0.0997	0.0974	Zero	0.0010	-0.0199 to 0.0218	0.9203
BMI (kg/m^2)	zero	-0.1783	-0.5743 to 0.2176	0.3505	Zero	-0.0046	-0.0717 to 0.0625	0.8821

Abbreviation: BMI, body mass index

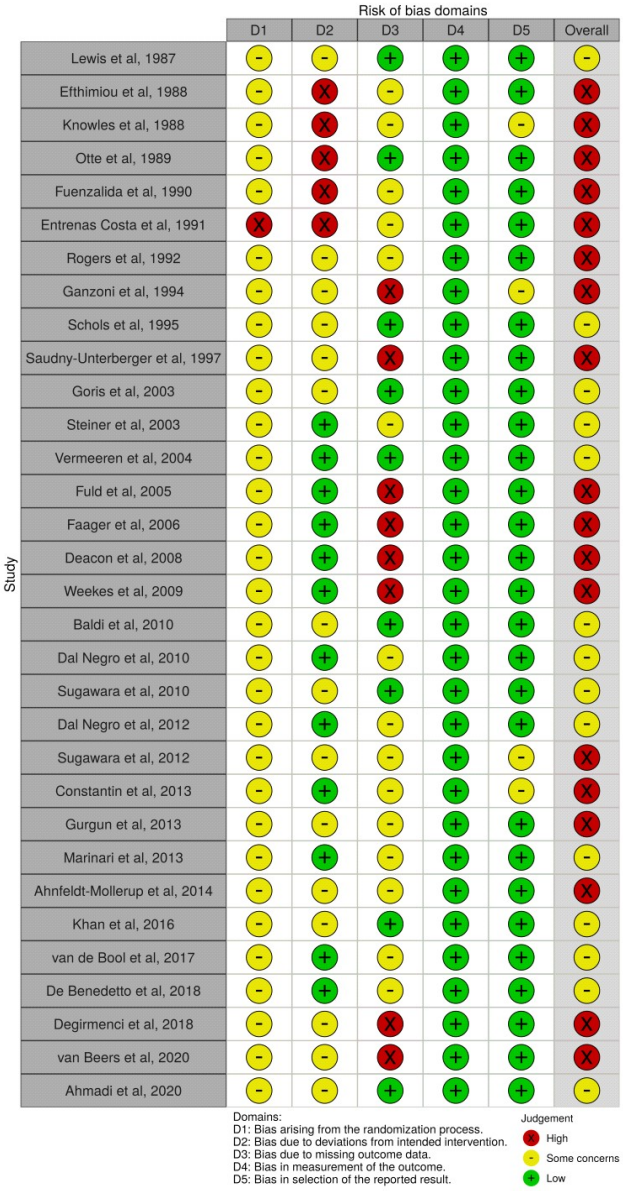
* Analyzes did not perform due to the number of studies with this information available.

Table S6 **Univariate meta-regression analysis of the effect of nutritional intervention on handgrip and quadriceps strength**

Covariate	Handgrip strength				Quadriceps strength			
	Adjusted R^2 (%)	Estimate	Confidence interval 95%	p-value	Adjusted R^2 (%)	Estimate	Confidence interval 95%	p-value
BMI (kg/m^2)	Zero	-0.0115	-0.1897 to 0.1666	0.8990	25.93	-0.0517	-0.1377 to 0.0344	0.2391
Duration of intervention (wk)	Zero	0.0106	-0.0450 to 0.0661	0.7094	Zero	-0.0015	-0.0156 to 0.0125	0.8311
Amount of protein prescribed (g)*	-	-	-	-	Zero	-0.0026	-0.0272 to 0.0220	0.8368

Abbreviation: BMI, body mass index

* Analyzes did not perform due to the number of studies with this information available.



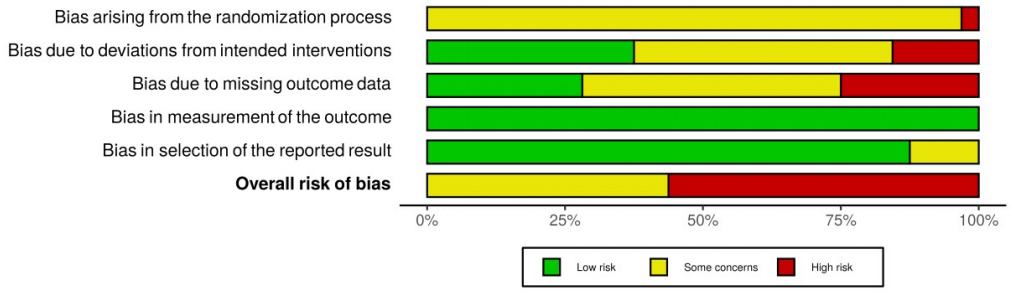
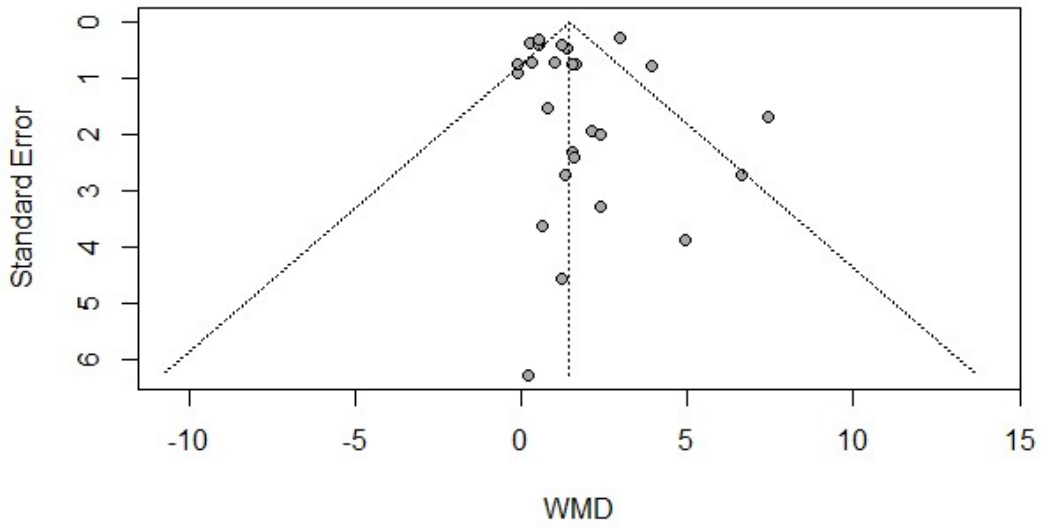
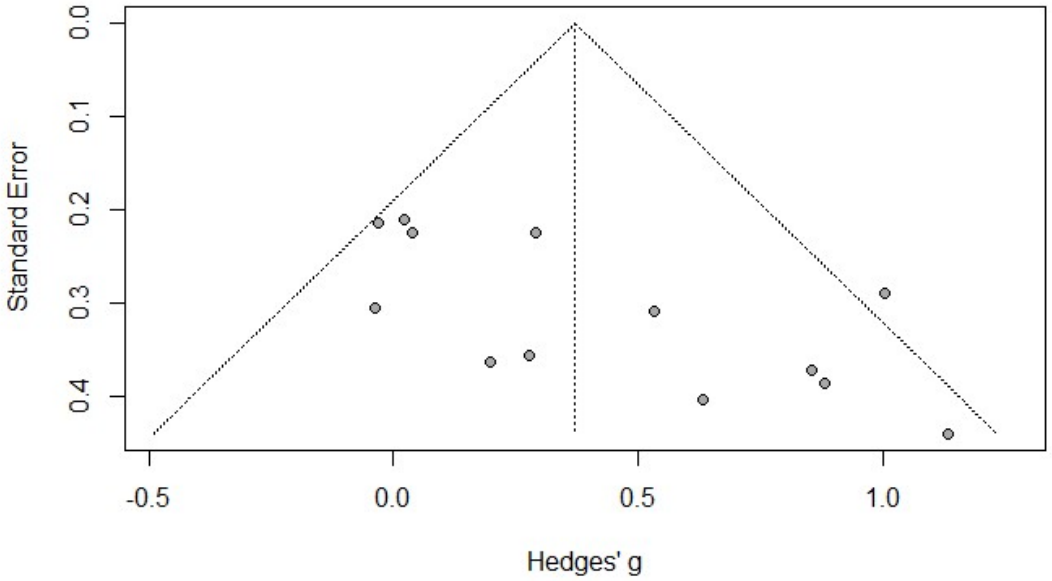


Figure S1 **Risk of bias summary: review authors' judgements for individual studies included**



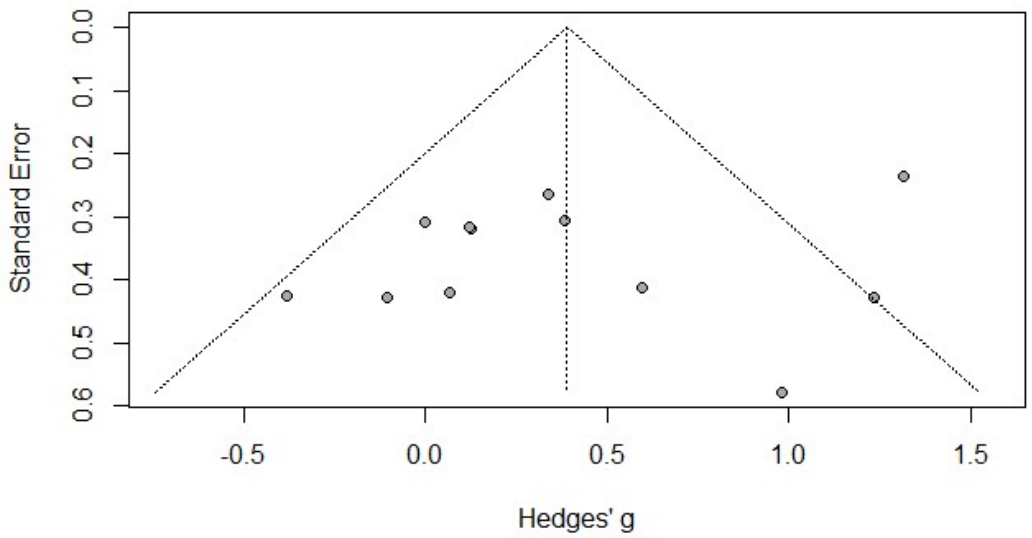
Egger's test (P=0.57)

Figure S2 **Funnel plot for body weight**



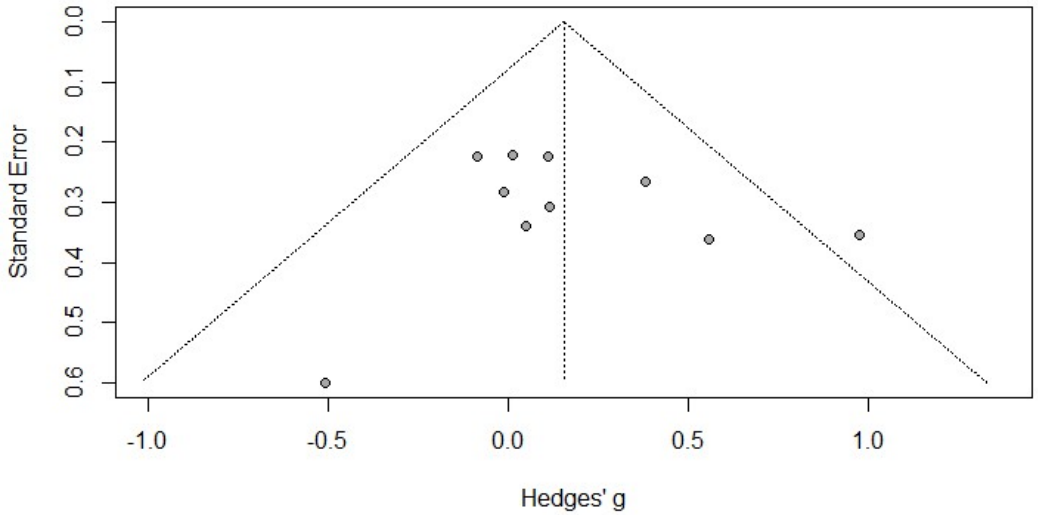
Egger's test (P=0.0087)

Figure S3 **Funnel plot for lean body mass**



Egger's test (P=0.39)

Figure S4 **Funnel plot for handgrip strength**



Egger's test (P=0.58)

Figure S5 **Funnel plot for quadriceps strength**

7 CONSIDERAÇÕES FINAIS

A DPOC é uma doença heterogênea e complexa, manifesta em distintos fenótipos clínicos, que de maneira particular interagem com a condição nutricional do paciente, resultando de alguma forma em alterações de parâmetros nutricionais. Ainda que o número e a intensidade destas alterações variem em cada caso, verifica-se que o comprometimento nutricional é frequente em pacientes com DPOC. E dado o seu valor prognóstico, se faz necessária a sua identificação precoce e pronta intervenção.

Na coorte histórica, o uso da circunferência da panturrilha reduzida, como marcador de depleção de MM foi identificada como preditora de pior prognóstico - gravidade da doença, fenótipo de exacerbação frequente, pior escore de qualidade de vida relacionada à saúde e mortalidade. Essa associação entre MM reduzida e piores desfechos clínicos já havia sido verificada em estudos prévios envolvendo pacientes com DPOC, que avaliaram a MM por meio de equipamentos mais sofisticados e, portanto, mais caros e menos disponíveis na assistência em saúde. Nossos resultados sugerem a incorporação da medida da CP como indicador de MM na avaliação nutricional desses pacientes, vista a sua aplicabilidade clínica, baixo custo, facilidade e rapidez à obtenção, sendo passível de mensuração por qualquer profissional de saúde devidamente treinado. Já a análise secundária da coorte de pacientes internados por exacerbação da doença reforçou a limitação do IMC em identificar a desnutrição, independentemente do ponto de corte utilizado. Embora tenha sido evidenciado o valor prognóstico do IMC como preditor de permanência hospitalar prolongada, o mesmo não foi preditor de mortalidade intra-hospitalar. Tais achados sinalizam a importância de uma avaliação nutricional mais detalhada, com dados antropométricos combinados a minucioso exame físico, investigação do consumo alimentar, reconhecimento de sintomas gastrointestinais e determinação da força e função muscular para

diagnóstico de desnutrição. O IMC deve ser entendido como um parâmetro complementar a ser utilizado no processo de cuidado nutricional do paciente com DPOC, haja vista seu valor prognóstico.

O comprometimento nutricional é modificável por meio de intervenções dietéticas na forma de SNO, resultando na melhora de parâmetros do estado nutricional. Através de revisão sistemática com metanálise de 32 ECR com duração média de 12 semanas, demonstrou-se que a SNO calórica e/ou proteica promove aumento do peso corporal, MLG e FPP. Sendo que a análise de subgrupos sugere um efeito mais pronunciado em pacientes com menor valor de IMC e clinicamente estáveis, e quando da SNO proteica comparada às exclusivamente hipercalóricas, em especial as fórmulas à base de creatina e aminoácidos essenciais. No entanto, a certeza da evidência sumarizada no presente estudo é de baixa a muito baixa. Ainda assim, o cuidado nutricional deve ser transversal à assistência de pacientes com DPOC e guiado pelo julgamento clínico-nutricional, a fim de estabelecer uma conduta individualizada e minimizar o risco de desfechos desfavoráveis ao pacientes.

Como perspectiva futura, com base nos achados da presente tese, pode-se enumerar alguns gaps na literatura a serem preenchidos por estudos bem delineados a fim de contribuir para aprimorar o conhecimento nas diferentes etapas do processo de cuidado nutricional de pacientes com DPOC, em especial no que diz respeito à avaliação nutricional e à intervenção dietética:

1) Avaliação do valor prognóstico da CP em pacientes com DPOC hospitalizados e de medidas seriadas tanto em pacientes ambulatoriais como naqueles hospitalizados

2) Avaliação do efeito de diferentes intervenções dietéticas em pacientes com DPOC de acordo com os fenótipos nutricionais, condição clínica e associação ou não com treinamento físico.

Tais linhas de investigação contribuiriam para que o manejo nutricional na DPOC fosse incorporado às diretrizes clínicas e embasado por evidências de mais alta qualidade, considerando-se além do impacto nutricional, desfechos clínicos e funcionais relevantes para a qualidade de vida e sobrevida do paciente.

Anexo 1 – Parecer Consubstanciado do Comitê de Ética em Pesquisa

HOSPITAL NOSSA SENHORA DA CONCEIÇÃO - GRUPO HOSPITALAR CONCEIÇÃO

Plataforma Brasil

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: Estado nutricional de pacientes com doença pulmonar obstrutiva crônica e desfechos clínicos: um estudo longitudinal prospectivo

Pesquisador: JAQUELINE FINK

Área Temática:

Versão: 1

CAAE: 05255018.4.0000.5530

Instituição Proponente: HOSPITAL NOSSA SENHORA DA CONCEICAO SA

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.126.689

Apresentação do Projeto:

Introdução: A doença pulmonar obstrutiva crônica é caracterizada pela persistente limitação do fluxo de ar, geralmente progressiva e associada à inflamação das vias aéreas. O diagnóstico é feito pelos sintomas persistentes, exposição a fatores de risco e confirmação com teste de espirometria (VEF1 < 0,7). É uma doença catabólica com alto gasto energético, com prevalência de desnutrição variando de 10 a 50%, diretamente relacionada à gravidade da doença. Além da desnutrição, pacientes com DPOC possuem prevalência elevada de sarcopenia (14% a 24%) – caracterizada pela massa muscular reduzida, perda de função e força. Na literatura, são escassos os estudos que avaliam desnutrição e sarcopenia nessa população, e poucos avaliam a associação dessas alterações no estado nutricional e funcional com função pulmonar e morbimortalidade.

Objetivo: Avaliar o estado nutricional e funcional de pacientes com DPOC e sua possível associação com desfechos clínicos.

Métodos: Estudo de coorte prospectiva com amostra prevista de 215 pacientes lúcidos, com diagnóstico de DPOC, capazes de deambular e maiores de 18 anos. Será realizado em hospital terciário da cidade de Porto Alegre – RS. A coleta de dados será realizada em até 72h da internação hospitalar na emergência ou nas unidades de internação. Serão coletados dados sócio-demográficos, de espirometria prévia, clínicos e laboratoriais de rotina. Serão aferidos peso e estatura e calculado o índice de massa corporal (IMC) e questionado o peso usual para

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cálculo do percentual de perda ponderal (%PP). Será aferida a circunferência do braço (CB) e da panturrilha (CP), a espessura do músculo adutor do polegar (EMAP) e a força do aperto de mão (FAM). Será avaliado risco nutricional de cada paciente por cinco ferramentas previamente validadas. Todos os pacientes serão classificados quanto ao estado nutricional a partir de quatro ferramentas integrativas disponíveis na literatura. Será avaliada a capacidade funcional dos pacientes através do teste "timed get up and go", o nível de dispneia pela escala Medical Research Council (MRC), e o risco para mortalidade e performance física pela ferramenta da Sociedade Europeia de Respiração. Os desfechos de interesse compreendem o tempo de internação hospitalar, a internação em unidade de terapia intensiva, a mortalidade hospitalar e a frequência de readmissão hospitalar e de mortalidade após três e seis meses da alta hospitalar. A análise dos dados será realizada nos programas SPSS e STATA com aplicação de testes estatísticos apropriados para comparação das ferramentas. O estudo iniciará após a aprovação ética e será conduzido de acordo com a Resolução 466/12. O custo previsto para a sua execução é de R$6.519,00 e tem-se a previsão de conclusão do mesmo em 24 meses.

Métodos:

População e Amostra

Pacientes adultos com DPOC internados na unidade de internação de pneumologia e emergência do Hospital Nossa Senhora da Conceição.

A amostra será composta por pacientes lúcidos, orientados, capazes de deambular, sem edema ou ascite grave, sem amputação de membros inferiores e/ou superiores. Serão excluídos do estudo pacientes sem registro de diagnóstico de DPOC em prontuário médico.

O cálculo da amostra foi realizado a partir dos resultados obtidos por Ester Marco e colaboradores acerca da associação entre mortalidade hospitalar e desnutrição, considerandose uma razão de bem nutridos/ desnutridos igual a quatro (4,0), a frequência relativa de não expostos positivos (óbito em pacientes bem nutridos) igual a 12,1% e o hazard ratio (HR) igual a 3,85. O tamanho amostral estimado, tendo como poder previsto 80% e nível de significância 5%, segundo método de Fleiss foi igual a 179 – considerando-se adicional de 20% para
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potenciais perdas a amostra estimada para o presente estudo será de 215 pacientes

ORÇAMENTO

Abaixo estão detalhados os custos com o presente projeto. Destaca-se que alguns equipamentos necessários estão disponíveis e que o custo real corresponde a R$2433,90. O mesmo será de

responsabilidade dos pesquisadores. O projeto será submetido a editais de fomento de agências regionais (FAPERGS) ou nacionais (CNPQ) no próximo ano (2019).

Objetivo da Pesquisa:

OBJETIVO GERAL

Avaliar o estado nutricional e funcional de pacientes com DPOC e sua possível associação com desfechos clínicos.

OBJETIVOS ESPECÍFICOS

Comparar o desempenho de diferentes ferramentas para identificação de risco nutricional em pacientes com DPOC.

Comparar o desempenho de diferentes ferramentas para diagnóstico de desnutrição em pacientes com DPOC.

Avaliar a validade preditiva dos parâmetros da impedância elétrica em pacientes com DPOC.

Avaliar o risco de sarcopenia em pacientes com DPOC e sua possível associação com desfechos clínicos.

Avaliar a possível associação entre FAM, tempo de internação e mortalidade em pacientes com DPOC.

Avaliar o desempenho da ferramenta da Sociedade Europeia de Respiração em predizer risco de mortalidade, cardiovascular e performance física em pacientes com DPOC.

Avaliação dos Riscos e Benefícios:

RISCOS E BENEFÍCIOS DA PESQUISA

Essa pesquisa pode gerar desconforto para o paciente ao realizar a avaliação nutricional objetiva, especialmente na aferição da PCT e do EMAP, já que o plicômetro precisa pinçar a massa adiposa e muscular, respectivamente. Para minimizar tal desconforto, a aferição dessas medidas e das demais será feita por profissional treinado. Além disso, pode haver um leve desconforto da retirada dos eletrodos que serão colocados no pé e mão dos pacientes para realização da bioimpedância.

Em relação aos benefícios, esse estudo não garantirá nenhum benefício direto ao participante. Contudo, acredita-se que com os resultados obtidos poderá ser estabelecido um aprimoramento das técnicas de diagnóstico de desnutrição, além de reconhecer o perfil nutricional dos pacientes com DPOC atendidos no Hospital Nossa Senhora Conceição, o que poderá direcionar o atendimento nutricional prestado. Sabendo-se que esses pacientes possuem

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Continuação do Parecer: 3.126.689

maiores chances de desnutrir, identificar a ferramenta mais acurada e preditora de desfechos trará mais segurança para o diagnóstico nutricional, etapa essencial para estruturação da terapia nutricional.

É importante reforçar que todo paciente identificado como tendo risco nutricional ou desnutrição será sinalizado para o nutricionista responsável pela Emergência ou pela Unidade de Pneumologia, dependendo do local onde o paciente estiver internado no momento da coleta de dados.

Comentários e Considerações sobre a Pesquisa:

Projeto de pesquisa de dissertação de mestrado.

Considerações sobre os Termos de apresentação obrigatória:

Adequados.

Recomendações:

N/A.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_DO_PROJETO_1246956.pdf	31/12/2018 10:14:46		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	tcle.pdf	31/12/2018 10:14:26	Flávia Moraes Silva	Aceito
Outros	TERMODECOMPROMISSO.pdf	12/12/2018 15:46:22	Flávia Moraes Silva	Aceito
Outros	cvbruna.pdf	12/12/2018 15:45:59	Flávia Moraes Silva	Aceito
Outros	cvflavia.pdf	12/12/2018 15:45:37	Flávia Moraes Silva	Aceito
Outros	CV_JAQUELINE.pdf	12/12/2018 15:45:12	Flávia Moraes Silva	Aceito
Projeto Detalhado / Brochura Investigador	projeto_DPOC.pdf	12/12/2018 15:44:56	Flávia Moraes Silva	Aceito

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HOSPITAL NOSSA SENHORA DA CONCEIÇÃO - GRUPO HOSPITALAR CONCEIÇÃO

Continuação do Parecer: 3.126.689

Outros	integrantes.pdf	12/12/2018 15:44:40	Flávia Moraes Silva	Aceito
Declaração de Instituição e Infraestrutura	anuencia_DPOC.pdf	10/12/2018 16:52:49	JAQUELINE FINK	Aceito
Folha de Rosto	folha_rosto_DPOC.pdf	10/12/2018 16:45:10	JAQUELINE FINK	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

PORTO ALEGRE, 30 de Janeiro de 2019

Assinado por:
Daniel Demétrio Faustino da Silva
(Coordenador(a))

Endereço: Francisco Trein, 596 - Centro Administrativo do GHC
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Anexo 2 – Protocolo PROSPERO

ID do registro do protocolos da revisão sistemática	Endereço para acessar o protocolo
CRD42020207577	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020207577

Anexo 3 - Normas dos periódicos (endereços eletrônicos)

Título	Endereço para acessar as normas
Journal of Parenteral and Enteral Nutrition	https://aspenjournals.onlinelibrary.wiley.com/hub/journal/19412444/forauthors.html
British Journal of Nutrition	https://www.cambridge.org/core/journals/british-journal-of-nutrition/information/instructions-contributors