Universidade Estadual de Londrina

FELIPE VILAÇA CAVALLARI MACHADO

ASSOCIAÇÕES ENTRE ALTERAÇÕES DE COMPOSIÇÃO CORPORAL E CARACTERÍSTICAS CLÍNICAS E FÍSICO-FUNCIONAIS EM DPOC

Londrina
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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Reabilitação (Programa Associado entre Universidade Estadual de Londrina [UEL] e Universidade Norte do Paraná [UNOPAR]), como requisito parcial à obtenção do título de Mestre em Ciências da Reabilitação.

Orientadora: Profa. Dra. Nidia Aparecida Hernandes.
Co-orientador: Prof. Dr. Fabio de Oliveira Pitta.

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Londrina, 25 de julho de 2018.

**Dedico este trabalho à minha família,
amigos e todos que me apoiaram.**

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“Try not to become a man of success, but rather try to become a man of value”
(Albert Einstein)

MACHADO, Felipe Vilaça Cavallari. **Associações entre alterações de composição corporal e características clínicas e físico-funcionais em DPOC.** 2018. 61 f. Dissertação (Mestrado em Ciências da Reabilitação) – Universidade Estadual de Londrina, Londrina, 2018.

RESUMO

Introdução: As anormalidades de composição corporal são determinantes independentes de desfechos em pacientes com DPOC. Atualmente, já se sabe que a estratificação destes pacientes em fenótipos de composição corporal (metabólicos) está associada à desfechos importantes, como capacidade de exercício e inflamação, mas não há dados comparando a atividade física na vida diária (AFVD) e força muscular entre esses fenótipos. Deste modo, o objetivo deste estudo foi comparar características clínicas e físico-funcionais em pacientes com DPOC estratificados em fenótipos metabólicos. **Métodos:** Uma análise transversal foi realizada com 270 pacientes com DPOC estável. De acordo com os percentis 10 e 90 dos valores de referência específicos para gênero, idade e índice de massa corporal (IMC) de índices de massa livre de gordura e índice de massa gorda, os pacientes foram estratificados em quatro grupos: Composição Corporal Normal (CCN), Obesos, Sarcopênicos e Obesos-sarcopênicos (OS). Os pacientes foram submetidos à avaliação da capacidade de exercício, força muscular periférica e respiratória, AFVD por meio de sensores de movimento, severidade de dispneia, estado funcional e sintomas de ansiedade e depressão. **Resultados:** A prevalência de pacientes classificados como CCN, Obesos, Sarcopênicos e OS foi de 39%, 13%, 21% e 27%, respectivamente. OS apresentaram menor distância percorrida no teste de caminhada de seis minutos (TC6min), comparado com CCN (P<0,05). Sarcopênicos e OS apresentaram pior força muscular periférica e respiratória comparados com CCN (P<0,05). Sarcopênicos apresentaram mais tempo em AFVD de moderada à alta intensidade comparados com todos os outros grupos (P<0,05) e menos tempo em AFVD sedentárias comparados com CCN e Obesos. (P<0,05). Não foram encontradas diferenças com relação a severidade de dispneia, estado funcional e sintomas de ansiedade e depressão (P>0,16). Sarcopênicos e OS apresentaram, respectivamente, 7,8 [95% IC: 1,6-37,7] e 9,5 [2,2-41,7] vezes mais chance de percorrer menos que 350 metros no TC6min. **Conclusões:** Os fenótipos metabólicos estão associados às características físico-funcionais em pacientes com DPOC. Pacientes com Obesidade-sarcopênica foram considerados os mais debilitados.

Palavras-chave: Doença Pulmonar Obstrutiva Crônica. Obesidade. Sarcopenia. Atividade Física. Tolerância ao exercício. Força muscular.

MACHADO, Felipe Vilaça Cavallari. **Associations between body composition abnormalities with clinical characteristics and physical function in COPD.** 2018. 61 p. Dissertation (Master's Degree in Rehabilitation Sciences) – Universidade Estadual de Londrina, Londrina, 2018.

ABSTRACT

Background: Abnormal body composition is an independent determinant of COPD outcomes. To date, it is already known that patient stratification into body composition (metabolic) phenotypes are associated with important outcomes, such as exercise capacity and inflammation, but there are no data comparing physical activity (PA), and muscle strength among these phenotypes. Thus, the aim of this study was to compare clinical characteristics and physical function in patients with COPD stratified into metabolic phenotypes. **Methods:** A cross-sectional analysis was conducted with 270 stable COPD patients. According to the 10th and 90th percentiles of sex-age-BMI-specific reference values for fat-free and fat mass indexes patients were stratified into four groups: Normal Body Composition (NBC), Obese, Sarcopenic, and Sarcopenic-obese (SO). Patients underwent assessment of exercise capacity, peripheral and respiratory muscle strength, PA in daily life using activity monitoring, dyspnea severity, functional status and symptoms of anxiety and depression. **Results:** The prevalence of patients classified as NBC, Obese, Sarcopenic and SO was 39%, 13%, 21%, or 27%, respectively. SO presented lower 6-minute walking distance (6MWD) compared with NBC ($P<0.05$). Sarcopenic and SO groups presented worse peripheral and respiratory muscle strength compared with NBC ($P<0.05$, for all). Sarcopenic group presented more time in moderate-to-vigorous PA compared to all other groups ($P<0.05$, for all) and less sedentary time when compared with NBC and Obese groups ($P<0.05$, for all). There were no differences regarding dyspnea severity, functional status and symptoms of anxiety and depression ($P>0.16$). Sarcopenic and SO groups had, respectively, 7.8 [95% CI: 1.6-37.7] and 9.5 [2.2-41.7] times higher odds to have a 6MWT equal or lower to 350 meters. **Conclusion:** Metabolic phenotypes are associated with physical function in patients with COPD. Sarcopenic-obese patients were the most impaired.

Keywords: Chronic Obstructive Pulmonary Disease. Obesity. Sarcopenia. Physical Activity. Exercise Tolerance. Muscle Strength.

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LISTA DE SIGLAS E ABREVIATURAS

1RM	One-repetition maximum test
6MWD	6-Minute Walking Distance
6MWT	6-Minute Walking Test
AFVD	Atividade física na vida diária
ATP	Adenosina trifosfato
ATS	American Thoracic Society
BIA	Bioelectrical Impedance Analysis
BMI	Body Mass Index
CCN	Composição corporal normal
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DEXA	Dual energy x-ray absorptiometry
DPOC	Doença pulmonar obstrutiva crônica
ERS	European Respiratory Society
FEV_1	Forced expiratory volume in the first second
FFM	Fat-free mass
FM	Fat-mass
FVC	Forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
HADS	Hospital Anxiety and Depression scale
IMC	Índice de massa corporal
LCADL	London Chest Activities of Daily Living Scale
MEP	Maximum expiratory pressure
METs	Metabolic equivalents of task
MIP	Maximum inspiratory pressure
MRC	Medical Research Council dyspnea scale
MVPA	Moderate-to-vigorous physical activity
NBC	Normal body composition
OS	Obesidade sarcopênica
PADL	Physical activity in daily life
PEMáx	Pressão expiratória máxima
PIMáx	Pressão inspiratória máxima

SO	Sarcopenic-obesity
TC6min	Teste de caminhada de seis minutos
VEF_1	Volume Expiratório Foçado no primeiro segundo

SUMÁRIO

1 INTRODUÇÃO

A Doença Pulmonar Obstrutiva Crônica (DPOC) é uma das maiores causas de morbidade e mortalidade no mundo e apresenta impacto negativo nos âmbitos social e econômico[1]. A inalação de partículas nocivas e a exposição das vias aéreas a um processo de inflamação crônica pode induzir a alterações patológicas no tecido e mecanismos de reparo e defesa pulmonares[2]. Essas alterações podem causar prejuízos na função pulmonar, como limitação ao fluxo aéreo e hiperinsuflação[2]. Sabe-se que estes pacientes não apresentam somente prejuízo na função pulmonar como também são acometidos por diversas manifestações extrapulmonares (sistêmicas)[2,3].

Dentre essas alterações sistêmicas, as anormalidades de composição corporal são prevalentes nestes indivíduos, com capacidade de afetar o prognóstico da doença[4] e predizer determinados desfechos, independentemente do prejuízo na função pulmonar[5]. De acordo com características da composição corporal, a *European Respiratory Society* recomenda a estratificação dos pacientes com DPOC em fenótipos metabólicos, para desenvolvimento de estratégias de intervenção e prevenção efetivas[5]. Os fenótipos metabólicos refletem uma interação complexa entre predisposição genética, estilo de vida e "gatilhos" da doença em músculos, ossos e tecido adiposo[5].

Alguns dos fenótipos metabólicos propostos são[5]: (1) obesidade, que apesar de ainda não estar bem estabelecido, parece ser mais prevalente em pacientes com DPOC, variando de 18 a 54% dos pacientes[6], (2) sarcopenia, uma síndrome caracterizada por progressiva e generalizada perda de massa muscular e força, e (3) a obesidade-sarcopênica (OS), que ocorre quando a sarcopenia está associada ao aumento de massa gorda[7]. Recentemente, um estudo verificou que a prevalência de sarcopenia e OS é maior em pacientes com DPOC quando comparados com indivíduos-controles e que os pacientes classificados com OS apresentam reduções na capacidade de exercício e aumento do estado inflamatório[8].

Como diversos estudos têm mostrado que a composição corporal está associada com desfechos importantes e é capaz de definir diferentes fenótipos metabólicos em pacientes com DPOC, pode-se hipotetizar que pacientes estratificados em diferentes fenótipos metabólicos apresentariam diferenças em suas características clínicas, físico-funcionais e em sua atividade física de vida diária. Desta forma, a presente dissertação teve como objetivo comparar características clínicas e físico-funcionais de indivíduos com DPOC estratificados em diferentes fenótipos metabólicos. A dissertação está em formato de artigo científico que será apresentado na seção 3.

2 REVISÃO DE LITERATURA - CONTEXTUALIZAÇÃO

2.1 Doença Pulmonar Obstrutiva Crônica

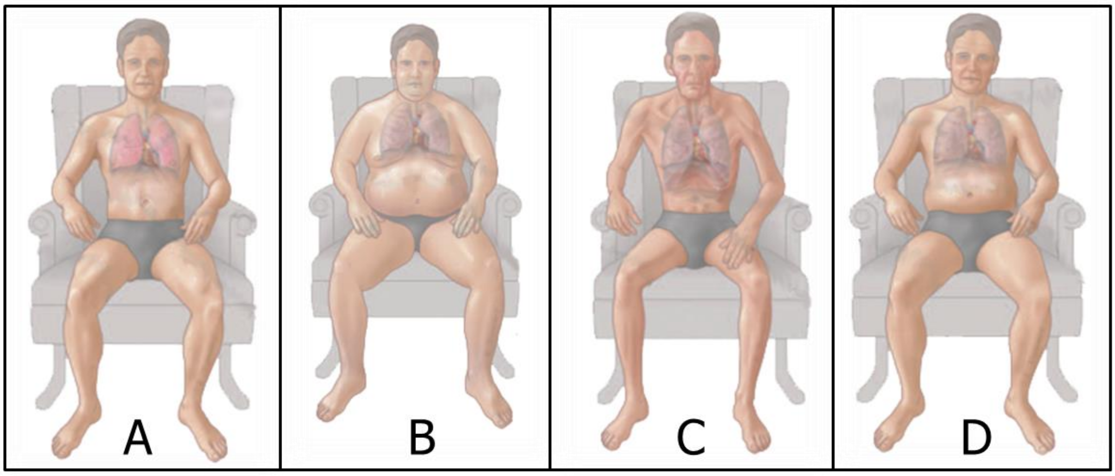
A DPOC é definida atualmente como uma doença comum, prevenível e tratável caracterizada por sintomas respiratórios persistentes e limitação ao fluxo aéreo devido a anormalidades de vias aéreas e/ou alveolares causadas geralmente pela exposição à partículas e gases nocivos[2]. A doença resulta de uma interação complexa entre fatores genéticos e ambientais, sendo o tabagismo o principal fator de risco[2]. Projeções indicam que o impacto da DPOC aumentará nas próximas décadas devido à exposição contínua aos fatores de risco para desenvolvimento da doença e ao envelhecimento da população[9].

O diagnóstico clínico de DPOC deve ser considerado em qualquer paciente com sintomas de dispneia, tosse crônica ou produção de secreção e histórico de exposição aos fatores de risco da doença[2]. Um dos principais sintomas da DPOC é a dispneia. É recomendado que, assim como a função pulmonar, este sintoma seja incluído na avaliação e classificação dos pacientes[2]. Além disso, a dispneia se mostrou um preditor de mortalidade melhor que a função pulmonar[10], bem como apresentou correlações com escalas de estado funcional[11].

Na tentativa de minimizar ou evitar os sintomas respiratórios[12], pacientes com DPOC frequentemente apresentam redução do nível de atividade física na vida diária (AFVD), mantendo um estilo de vida predominantemente sedentário quando comparados a indivíduos controles[13,14]. A inatividade física leva ao descondicionamento físico e isso, somado a respostas inflamatórias inapropriadas/excessivas, acarreta consequências extrapulmonares (sistêmicas)[2,3].

Considerando as diversas manifestações extrapulmonares que estes pacientes podem apresentar, pode-se concluir que a DPOC é uma doença complexa e heterogênea[15,16]. Heterogênea porque nem todas essas manifestações estão presentes em todos os pacientes e complexa porque essas manifestações podem apresentar diversas interações dinâmicas e não lineares[15]. Deste modo, estudos recentes descrevem a reabilitação pulmonar como uma estratégia de gerenciamento personalizada e integrada em parceria com o paciente[17], e sugerem a estratificação e caracterização fenotípica de pacientes com DPOC de acordo com determinadas características em comum, como características de composição corporal (Figura 1), para o desenvolvimento de melhores estratégias de prevenção e intervenção[5].

Figura 1 – Fenótipos metabólicos: A: Saudável (referência), B: Obesidade, C: Caquexia, D: Sarcopenia e obesidade oculta. (Adaptado de: Schols et al.[5])



2.2 Avaliação da composição corporal

Existem diversos métodos para avaliação da composição corporal, que podem ser mais ou menos apropriados para a prática clínica ou para pesquisa de acordo com a variável de interesse[5]. O quadro 1 apresenta as medidas apropriadas de composição corporal e marcadores substitutos para pesquisa e prática clínica, de acordo com cada possível variável de interesse.

Quadro 1 – Medidas apropriadas de composição corporal e marcadores substitutos para pesquisa e prática clínica.

Variável	Pesquisa	Prática clínica
Massa livre de gordura /massa gorda	Diluição de óxido de deutério	DEXA, bioimpedância elétrica (monofrequência), antropometria (dobras cutâneas).
Massa intracelular	Diluição de óxido de deutério combinada com diluição de brometo	Bioimpedância elétrica (multifrequência).
Massa muscular	Tomografia computadorizada, Ressonância magnética, biomarcadores.	DEXA, ultrassonografia, biomarcadores, antropometria (circunferência de antebraço).
Gordura abdominal	Tomografia computadorizada,	DEXA.
Gordura visceral	Ressonância magnética, biomarcadores.	Antropometria (diâmetro sagital e/ou relação circunferência cintura/quadril), ultrassonografia.
Massa e densidade óssea	DEXA	DEXA, tomografia computadorizada (alta resolução)

Adaptado de: Schols et al.[5]

A composição corporal se refere à quantidade e distribuição de tecidos no corpo humano. Indivíduos diferentes podem apresentar a mesma massa corporal, porém esta ser constituída de tecidos completamente diferentes (tecido muscular, adiposo e conjuntivo). Desta forma, mudanças no peso ou no índice de massa corporal (IMC) não levam em consideração a composição corporal[4,5]. Uma revisão sistemática verificou que, em adultos e idosos saudáveis, o IMC possui baixa sensibilidade para detectar indivíduos com aumento de gordura corporal, diagnosticando apenas metade destas ocorrências[18]. Portanto, a acurácia diagnóstica do IMC em pacientes com DPOC, que frequentemente apresentam redução de massa magra e/ou aumento de massa gorda[4,8], pode ser ainda pior, considerando que essas alterações podem ocorrer independentemente de alterações no IMC.

Um método de baixo custo e que pode ser utilizado para avaliação da composição corporal na prática clínica em pacientes com DPOC[5,19], é por meio da medida de dobras cutâneas. Estas medidas podem ser utilizadas para caracterizar a gordura subcutânea e estimar a quantidade de massa gorda corporal por meio de equações de predição[19]. Desta forma, a massa livre de gordura também pode ser estimada como a diferença entre o peso e a massa gorda corporal[20]. Apesar de sua utilização na prática clínica, a acurácia deste método é questionável, visto que alguns estudos verificaram diferenças na estimativa de massa livre de gordura obtida por meio deste método quando comparado com métodos mais sofisticados[20,21], enquanto outros estudos suportam sua utilização como um método barato e acurado[19,22]. As diferenças nestes resultados poderiam estar associadas com a utilização de diferentes equações[19] e as diferenças étnicas nas populações estudadas[20].

A avaliação da composição corporal considerando dois compartimentos (massa livre de gordura e massa gorda) também pode ser realizada por meio da análise de bioimpedância elétrica. Esta análise baseia-se no conceito de que os diferentes tecidos corporais oferecem diferentes resistências à passagem de uma corrente elétrica[23]. Consequentemente, com a realização do teste pode-se determinar a medida de resistência e reatância[23] – que dependem da composição corporal - e, por meio de equações, estimar a quantidade de massa livre de gordura e massa gorda para um determinado indivíduo[20]. Alguns dispositivos realizam essas medidas de impedância em diferentes frequências (bioimpedância elétrica multifrequência), tendo em vista que, em frequências baixas a corrente não atravessa a membrana celular, e em frequências mais altas atravessa, essa modalidade permite uma mais detalhada estratificação do compartimento de massa livre de gordura, com distinção entre a distribuição de água/massa intra e extra-celular[24]. Além disso, há dispositivos que possibilitam a colocação de um maior número de eletrodos, o que permite a análise da composição corporal de membros superiores e inferiores e tronco, separadamente (bioimpedância elétrica segmentar)[24].

A composição corporal pode ser avaliada de forma mais detalhada por meio da absortometria radiológica de dupla energia (*Dual-Energy X-ray Absorptiometry* - DEXA). Este método apresenta a vantagem de considerar três compartimentos, sendo a massa livre de gordura classificada em massa livre de gordura e conteúdo mineral ósseo[25]. A utilização da DEXA permite identificação de perda mineral óssea e a quantificação da massa muscular apendicular ou de tronco.

Além disso, é considerado por alguns estudos como padrão-ouro para análise da composição corporal e parece ser um método alternativo à diluição do óxido de deutério para avaliação da massa livre de gordura[26].

Outra técnica comumente utilizada como referência para avaliação da composição corporal é a diluição de óxido de deutério. Este método é considerado padrão-ouro para avaliação da quantidade de água total corporal. Considerando que esta variável é um dos maiores preditores da massa livre de gordura, trata-se de uma técnica altamente precisa para avaliação da composição corporal. Uma dose conhecida de água marcada com deutério é administrada e, após o equilíbrio e miscigenação com a água corporal total, sua concentração é medida em amostras de saliva, urina ou sangue, geralmente por meio da espectrometria de massa de razões isotópicas[27].

As modalidades de imagem, como a tomografia computadorizada, a ressonância magnética e o ultrassom, estão ganhando popularidade e representam novas técnicas importantes para avaliação da composição corporal[28]. A tomografia computadorizada pode ser utilizada para estimar a massa muscular, por meio da imagem do corte transversal de membros inferiores e/ou superiores. Adicionalmente, considerando a densidade específica da gordura, esta técnica é capaz de detectar infiltrações de gordura nos músculos[29]. A ressonância magnética apresenta a vantagem de estimar a composição corporal regional e estimar de maneira acurada e viável o tecido adiposo intra-abdominal[27]. Finalmente, a ultrassonografia tem se mostrado um método capaz de avaliar de maneira simples e confiável (em comparação com a tomografia computadorizada) a área de secção transversa do reto femoral[30], sendo que esta medida mostrou associações com a força muscular avaliada tanto em indivíduos saudáveis quanto em pacientes com DPOC[30].

Todos os métodos para avaliação da composição corporal apresentam vantagens e limitações (Quadro 2); então, para a escolha do método deve-se considerar sua disponibilidade, aplicabilidade e objetivo da avaliação. Por meio destes métodos pode-se comparar a composição corporal de indivíduos saudáveis daqueles com alguma doença ou ainda determinar se o indivíduo apresenta ou não anormalidades de composição corporal.

Quadro 2 – Principais vantagens e limitações dos diferentes métodos para avaliação da composição corporal

Método	Vantagens	Limitações
Dobras cutâneas	Simples, barato e de fácil aplicabilidade. Não invasivo e requer baixa cooperação do avaliado.	Acurácia depende de equações e pode variar em diferentes populações. O treinamento da técnica é importante para evitar erros intra e inter avaliador.
Bioimpedância elétrica	De fácil aplicabilidade, não invasivo e requer baixa cooperação do avaliado.	Acurácia depende de equações e pode variar em diferentes populações. Pode ser afetado por alterações de estado hídrico dos indivíduos avaliados.
DEXA	Permite a diferenciação da composição corporal em três compartimentos (incluindo massa óssea). Permite avaliação separada de tronco e membros.	Alto custo do equipamento, necessário conhecimento técnico e problemas com o uso em indivíduos com maior dimensão corporal (atletas e obesos).
Diluição de óxido de deutério	Requer baixa cooperação do avaliado. Considerado padrão ouro para massa livre de gordura total.	Uso restrito em hospitais e centros de pesquisa especializados. Pode ser afetado por alterações de estado hídrico dos indivíduos avaliados.
Modalidades de imagem	Permite a avaliação precisa de massa muscular regional. Requer baixa cooperação do avaliado.	Alto custo, limitações para indivíduos obesos, limitações para estimar quantidade total de massa livre de gordura.

2.3 Fisiopatologia e impacto das anormalidades de composição corporal em pacientes com DPOC

O entendimento da fisiopatologia e do impacto das anormalidades de composição corporal em pacientes com DPOC é essencial para o desenvolvimento de intervenções direcionadas à etiologia e às necessidades ocasionadas por essas alterações[5]. Comumente pacientes com DPOC apresentam anormalidades como: reduções na massa muscular[8], massa óssea e/ou massa gorda[5]. Por outro lado, alguns pacientes apresentam aumento da gordura corporal[6], em alguns casos com preservação da massa livre de gordura e em outros, concomitantemente com reduções na massa livre de gordura[8].

A massa muscular é determinada pelo equilíbrio entre síntese e degradação proteica; um dos fatores de estímulo para a síntese proteica é a disponibilidade de aminoácidos na corrente sanguínea[5]. Em pacientes com DPOC, evidências indicam aumento da taxa de degradação proteica[31] e diminuição na concentração sanguínea de aminoácidos de cadeia ramificada comparados com indivíduos controles[32]. Sabe-se que pacientes com DPOC que apresentam redução na massa livre de gordura apresentam prejuízo em suas características físico-funcionais e sobrevida[5]. Os pacientes podem ser classificados como tendo redução de massa livre de gordura por meio da utilização de pontos de corte, geralmente o décimo percentil dos valores de referência[5].

A perda de peso e gordura corporal pode ocorrer quando o gasto energético excede a disponibilidade de energia[5]. Sabe-se que pacientes com DPOC com perda de peso podem apresentar aumento no gasto energético em repouso[33], durante a ventilação[34] e maior custo de adenosina trifosfato (ATP) para contração muscular[34], além de, menor eficiência mecânica em membros inferiores[35,36] e requerimento diário energético aumentado[37]. Todos esses fatores parecem indicar que alguns pacientes se encontram em um estado hipermetabólico que poderia contribuir para perda de peso[5] (depleção de massa gorda e massa livre de gordura).

Obesidade é definida como o acúmulo anormal e extensivo de gordura que afeta a saúde[38]. Do ponto de vista energético, a obesidade e/ou o aumento da quantidade de gordura corporal ocorrem quando existe um balanço energético positivo indesejável, sendo a inatividade física um dos fatores que pode contribuir para este desequilíbrio. A prevalência de obesidade na DPOC, definida como o IMC $\geq$ 30, varia de 18 a 54%[6]; porém, poucos estudos realizaram uma comparação direta da prevalência de obesidade em DPOC e indivíduos controles. Quando considerados os estudos que realizaram comparações indiretas, a prevalência de obesidade em pacientes com DPOC parece ser maior que a de indivíduos controles[6].

O entendimento de como a presença da obesidade afeta o prognóstico e desfechos clínicos em pacientes com DPOC é alvo de diversos estudos atuais. Ainda não há consenso se pacientes com DPOC e obesidade apresentam maior ou menor intensidade de sensação de dispneia; entretanto, estudos indicam que pacientes com maiores valores de IMCs apresentam menor hiperinsuflação pulmonar[6,39]. Com relação à capacidade de exercício, os efeitos da obesidade parecem depender da modalidade de exercício[5]. Visto que em condições nas quais o peso não tem influência direta, como em testes realizados em bicicleta estacionária, a capacidade de exercício se mostrou semelhante entre pacientes com DPOC obesos e com peso normal[40]. Por outro lado, testes em que o peso é suportado e geram maior trabalho, como o teste de caminhada de seis minutos (TC6min), a distância percorrida pelos pacientes obesos se mostrou reduzida[40]. Outro fator que parece estar associado com essa discordância é a diferença nos protocolos dos testes[41], visto que testes em que o paciente controla o seu próprio ritmo, como o TC6min, poderiam estar mais susceptíveis a mudanças em indivíduos com maior peso, pois este pode diminuir e adequar a sua velocidade ao sentir mais dificuldade, o que não acontece em testes em que o ritmo é determinado externamente[41]. Além disso, a obesidade parece estar associada com menor mortalidade e menor risco de readmissões hospitalares por exacerbação da doença[6].

De forma mais complexa, a depleção de massa livre de gordura pode estar associada com o aumento da adiposidade (OS), tanto na população geral[42] quanto em indivíduos com DPOC[8]. É de grande interesse o entendimento do impacto da associação e interação entre estas duas anormalidades. Um crescente número de evidências indica que esta condição está associada com maior risco de saúde[43,44]. Em pacientes com DPOC, somente um estudo explorou as associações entre OS e desfechos importantes para a doença como a capacidade de exercício, o estado funcional e marcadores de inflamação sistêmica[8]. Desta forma, ainda é necessário explorar as associações entre a OS e outras características clínicas e físico-funcionais em pacientes com DPOC.

3 ARTIGO ORIGINAL

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Clinical impact of body composition phenotypes in patients with COPD.

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ABSTRACT

Background: Abnormal body composition is an independent determinant of COPD outcomes. To date, it is already known that patient stratification into body composition phenotypes are associated with important outcomes, such as exercise capacity and inflammation, but there are no data comparing physical activity (PA), and muscle strength among these phenotypes. Thus, the aim of this study was to compare clinical characteristics and physical function in patients with COPD stratified into body composition phenotypes.

Methods: A cross-sectional analysis was conducted with 270 stable COPD patients. According to the 10th and 90th percentiles of sex-age-BMI-specific reference values for fat-free and fat mass indexes patients were stratified into four groups: Normal Body Composition (NBC), Obese, Sarcopenic, and Sarcopenic-obese (SO). Patients underwent assessment of exercise capacity, peripheral and respiratory muscle strength, PA in daily life using activity monitoring, dyspnea severity, functional status and symptoms of anxiety and depression.

Results: The prevalence of patients classified as NBC, Obese, Sarcopenic and SO was 39%, 13%, 21%, or 27%, respectively. SO presented lower 6-minute walking distance (6MWD) compared with NBC ($P<0.05$). Sarcopenic and SO groups presented worse peripheral and respiratory muscle strength compared with NBC ($P<0.05$, for all). Sarcopenic group presented more time in moderate-to-vigorous PA compared to all other groups ($P<0.05$, for all) and less sedentary time when compared with NBC and Obese groups ($P<0.05$, for all). There were no differences regarding dyspnea severity, functional status and symptoms of anxiety and depression ($P>0.16$). Sarcopenic and SO groups had, respectively, 7.8 [95% CI: 1.6-37.7] and 9.5 [2.2-41.7] times higher odds to have a 6MWT equal or lower to 350 meters. **Conclusion:** Body composition phenotypes are associated with physical function in patients with COPD. Sarcopenic-obese patients were the most impaired.

Keywords: Chronic Obstructive Pulmonary Disease; Obesity; Sarcopenia; Physical Activity; Exercise Tolerance; Muscle Strength.

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airway and/or alveolar abnormalities and significant extrapulmonary (systemic) effects [1]. One of these systemic effects of COPD includes an abnormal body composition, which is highly prevalent in these patients, affects prognosis [2] and is an important independent determinant of COPD outcomes [3], such as exercise capacity and inflammation [4]. Body compostion abnormalities in this population may include an increase in fat mass (FM), a decrease in fat-free mass (FFM) or even, a shift from FFM toward FM [2].

Therefore, it is recommended to stratify these patients, in specific body composition phenotypes [3]. Considering the previous described abnormalities of body composition the commom existent body composition phenotypes in patients with COPD are characterized by low FFM [5] (sarcopenia), high FM [6] (obesity) or a combination thereof (i.e. Sarcopenic-obesity) [4]. A recent study showed that patients with COPD were 3 times more likely to present Sarcopenic-obesity compared to a non-COPD control group [4]. Additionaly, Sarcopenic-obesity was independently associated with reduced six-minute walking test (6MWT) and a higher risk of presenting with elevated systemic inflammattory biomarkes [4].

To date, it remains unknown whether and to what extent peripheral and respiratory muscle strength, physical activity in daily life (PADL), symptoms of anxiety and depression, and functional status are different after patient stratification into body composition phenotypes. Our hypothesis is that there are differences in these outcomes in patients with COPD stratified into pre-especified body composition phenotypes. This could be supported in part to the already described impact of body composition phenotypes in exercise capacity and inflammation in patients with COPD [4] and due to the already described associations between body composition and physical function in the general population [7,8]. Thus, the aim of this study was to compare clinical characteristics and physical function in patients with COPD stratified body composition phenotypes.

Methods

Participants and study design

A retrospective study with a cross-sectional analysis was conducted with patients with COPD recruited during the initial evaluation for admission in a physical training program of two already published studies [9,10] and an ongoing study (ClinicalTrials.gov number, NCT03127878). The data collection occurred at the University Hospital of Londrina, Brazil and at the Pitágoras Unopar University, Brazil, from 2006 until 2018. The initial evaluations performed in all studies were similar.

Patients from both centers were assessed for eligibility and according to the assessment of body composition classified in four different groups. The results of the assessments of clinical characteristics and physical function were compared between these groups. The inclusion criteria were diagnosis of COPD, according to GOLD [1]; clinical stability defined as the absence of exacerbations within at least one month prior the study; absence of any regular physical training in the preceding year, absence of any important comorbidities (orthopaedic, rheumatological, neurological or cardiovascular) which could interfere in the research protocol. Patients were excluded if they did not complete the assessment of body composition. All studies were approved by the Research Ethics Committee of the two institutions (number 123/09 and 377/10) and all participants signed an informed consent term.

Body Composition

Body weight and height were measured on a calibrated scale (Filizola model 21; Filizola, Brazil), and body mass index (BMI) was calculated as weight divided by height squared (kg/m^2). Body composition was assessed by bioelectrical impedance analysis (BIA) using a single-frequency analyser (Biodynamics 310TM; Biodynamics Corp, USA, in both centers) according to the protocol of Lukaski et al. [11] and manufacturer's recommendations. Participants were instructed to avoid exercising for at least 12 h before the test and refrain from the ingestion of coffee, tea, chocolate or alcoholic beverages. Body composition measurements were performed with patients lying in the supine position in the morning at the same room. In addition, patients fasted for at least 4 h before the test and urinated immediately before the evaluation.

FFM was calculated from the impedance using a specific formula derived for patients with COPD [12]. FM was calculated by subtracting FFM from body weight. FFM and FM were adjusted for differences in body surface by dividing by height squared, consequently FFM and FM indexes (FFMI and FMI, respectively) were calculated.

The FFMI and FMI values were compared with previously published age-sex-BMI specific reference values obtained from the general population [13]. Values of FFMI lower than the 10^{th} percentile and values of FMI equal or higher than the 90^{th} percentile of the reference values were considered as abnormal [4]. Therefore, patients were classified in four groups: Normal Body Composition (NBC, patients with FFMI≥10th percentile and FMI<90th percentile), Obese (FMI≥90th percentile and FFMI≥10th percentile), Sarcopenic (FFMI<10th percentile and FMI<90th percentile), or Sarcopenic-Obesity (SO, FFMI<10th percentile and FMI≥90th percentile).

Clinical Characteristics

Demographic (sex and age) data were collected. The level of functional limitation due to breathlessness in activities of daily living was assessed using the Medical Research Council (MRC) dyspnea scale [14]. The London Chest Activity of Daily Living (LCADL) scale [15] was used in order to assess functional status. Symptoms of anxiety and depression were assessed using the Hospital Anxiety and Depression Scale (HADS) [16].

Physical Function

The functional exercise capacity was assessed by the 6MWT. It was performed according to international standardization [17]. The predicted 6-minute walk distance (6MWD) was calculated according to reference values proposed by Britto et al [18]. for the Brazilian population. Peripheral muscle strength was assessed using the one-repetition maximum test (1RM), following international standardization [19], for each of three exercises performed on gymnasium equipment (CRW 1000; Embreex, Brazil): leg extension, arm extension and arm flexion. Respiratory muscle strength was assessed by digital manovacuometer (MVD 300®; Globalmed, Brazil) according to international standardization [20]. Maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) were determined and reference values used were proposed by Neder et al. [21] for the Brazilian population.

PADL was assessed during two consecutive weekdays with a validated [22,23] multisensory PA monitor (SenseWear Pro Armband, BodyMedia, Pittsburgh, USA). Patients were instructed to wear the monitor during awake time for 12 hours, starting from the time that the patient wake up [24,25]. A valid assessment day was considered if the patient wore the monitor for at least 10 hours [26,27]. The mean of the variables assessed from both days were used for the analysis. The variables used were: steps per day; average metabolic equivalents (METs) per day; sedentary time (time spent in activities below 1.5 METs [ST<1.5 METs]) [28], light activities (time spent in activities within 1.5 and 3 METs) [28], moderate-to-vigorous physical activity (time spent in activities above 3 METs [MVPA]) [28].

Statistical Analysis

Normality in data distribution was evaluated using the Shapiro-Wilk test. The results were described as mean ± standard deviation or median [interquartile range 25%-75%]. Firstly, the comparisons of continuous variables between patients from the two centers were performed with Student's *t* test for independent samples or Mann-Whitney U test. One-way ANOVA or Kruskal-Wallis test were performed for the comparisons between body composition phenotypes groups. Categorical variables were compared using the Chi-square test. An one-way ANCOVA was performed for comparisons among the body composition phenotypes groups considering adjustments for potential cofounders. All the tests with comparisons between more than two groups were followed by Bonferroni post-hoc test for pairwise comparisons. A binomial logistic regression was performed to ascertain factors associated with the likelihood of patients present a 6MWT equal or lower than 350 meters [29]. The software used was SPSS 22.0 (IBM, Armonk, NY, USA). Significance level was set at $P<0.05$.

Results

In this study a total of 279 participants were enrolled. Of these, 9 patients were excluded because they did not perform the body composition assessment. From the 270 remaining patients, 201 were recruited at the University Hospital of Londrina and 69 at the Pitágoras Unopar University. There were no differences regarding demographic, anthropometric, clinical and physical function data between patients from the two different centres ($P>0.10$ for all).

Demographic and pulmonary function characteristics of the patients are presented in **Table 1**. From the 270 patients considered in the analysis, 106 (39%) were classified as NBC, 34 (13%) were classified as Obese, 56 (21%) were classified as Sarcopenic, and 74 (27%) were classified as SO. There were no differences in the proportion of patients classified as NBC, Obese, Sarcopenic and SO between the two centers ($P>0.42$). Sarcopenic and SO groups presented lower forced expiratory volume in the first second (FEV_1) and higher proportion of patients classified as GOLD III (severe) and GOLD IV (very severe) ($P<0.01$). The proportion of female patients were higher in NBC group compared with all the other groups ($P<0.01$).

The **Table 2** presents the comparisons of clinical characteristics and physical function data among patients with COPD stratified into body composition phenotypes. There were no differences regarding symptoms of anxiety and depression, dyspnea in daily life and functional status between the groups. Sarcopenic and SO groups presented, in comparison with NBC and Obese groups, lower 6MWD and MEP in percentage of predicted (P<0.01, for all). In addition, SO group presented lower time in MVPA compared to Sarcopenic (P<0.01). Sarcopenic group presented higher average METs per day compared to all other groups (P<0.01).

Figure 1 presents the one-way ANCOVA for the comparison of absolute values of the 6MWD, peripheral muscle strength and PADL, after adjustments for confounders. Patients with SO still presented significant reductions in 6MWD after adjustments for sex, BMI and lung function. After adjustment for sex the Sarcopenic and SO groups presented lower peripheral muscle strength regarding leg extension, arm extension, and arm flexion compared with NBC. Sarcopenic group presented more time in MVPA compared to all other groups and less sedentary time when compared with NBC and obese groups, when adjusting for sex, exercise capacity and lung function.

The logistic regression model was statistically significant (*P*<0.01). From the predictor variables inserted on the model, an increasing BMI and age was associated with increased likelihood, whereas increasing VEF_1 and being male were associated with a reduction in the likelihood of presenting a distance equal or lower than 350 meters at the 6MWT (**Table 3**). Sarcopenic and SO groups had, respectively, 7.8 and 9.5 times higher odds to have a 6MWT equal or lower to 350 meters.

Discussion

The present study compared clinical characteristics and physical function after stratification into body composition phenotypes in patients with COPD. The relative prevalence of patients classified as Obese, Sarcopenic and SO were 13%, 21% or 27%, respectively, and there were a higher proportion of male in these groups. Patients with SO presented significant worse exercise capacity, peripheral and respiratory muscle strength and were less physically active compared with the other groups. On the other hand, obese patients were the less impaired and presented no differences for any of the outcomes when compared with NBC patients. Patients stratified as Sarcopenic and SO presented a higher disease severity; this finding is in accordance with the study from Joppa et al [4]. Both groups presented lower exercise capacity, peripheral and respiratory muscle strength compared with the other patients; the main differences between these two groups were that Sarcopenic group presented more time in MVPA and less sedentary time per day.

Considering exercise capacity, peripheral and respiratory muscle strength both groups with normal FFMI (NBC and Obese) presented similar results, whereas the groups with abnormally low FFMI (Sarcopenic and SO) presented significant reductions. These findings are in accordance with previous studies that show a close relationship between FFM and exercise capacity [4,30,31], skeletal muscle weakness [30,32], and respiratory muscle strength [33,34]. According to our results body compositions are less associated with clinical characteristics, since there were no differences in dyspnea, functional status and symptoms of anxiety and depression between the groups, all these outcomes frequently are impaired in patients with COPD [2] and could be considered major characteristics of the disease.

Notwithstanding, that Sarcopenic patients presented a higher average METs, time spent in MVPA and less sedentary time, whereas the number of steps were comparable with NBC and Obese groups, suggesting that these last groups of patients perform the same amount of PADL, but in a lower intensity. In addition, Sarcopenic patients also presented FM reduction (lower FMI compared with the other groups [except with NBC in male patients] (**Table 1**). It is well known that weight loss (i.e. fat and muscle loss) occurs if energy requirements are not fully met [3]. These findings raise the hypothesis that a negative energy balance in these patients could be associated with the development of these abnormalities. Although reduction of energy expenditure or PADL is not desirable in COPD patients, the energy balance could be restored by increasing their energy intake [3].

In contrast, patients stratified as Obese presented no differences in any of the assessments when compared with NBC group. Our hypothesis is that this could be partially explained by a not yet fully understood phenomenon called “obesity paradox” - associated with better survival and some functional outcomes but, on the other hand, associated with increased risk of cardiovascular and metabolic disease [30]. The obesity paradox could be related to the direct effect of adipose tissue on lung mechanics [35] or an epiphenomenon of other, yet unknown disease characteristics that confers both a reduced mortality risk and preserved fat mass and/or FFM [3] (e.g. patients in a positive energy balance or reduced protein turnover). In the present study, male obese patients presented preserved FFM and female obese patients presented higher FFM compared with NBC. It was not surprising since there is a positive correlation between BMI and FFMI [36].

In the One-way ANCOVA we adjusted the absolute values of the 6MWD for sex proportion and BMI because these are important determinants of the 6MWD in healthy Brazilians and are factors included in the reference equation for the prediction of the 6MWD [18]. Peripheral muscle strength was adjusted for sex proportion due to difference in absolute values of strength between male and female [37]. PADL were adjusted for sex, lung function and exercise capacity because these factors are associated with physical activity [38].

To our knowledge this is the first study with the aim of comparing, peripheral and respiratory muscle strength, PADL, symptoms of anxiety and depression, and functional status in patients with COPD stratified as body composition phenotypes.

The findings of the present study confirm the increasing evidence that body composition phenotypes are independently associated with outcomes in patients with COPD. And that in patients with COPD the BMI is limited to identify body composition abnormalities since, according to a widely accepted cut-off point in the classification of obesity (BMI≥30kg/m²) [8], most of patients from SO group would be classified as normal weight, whereas most of patients from NBC group would be classified as overweight/obese (**Table 1**).

Some limitations of the present study include: (1) the cross-sectional analysis, that does not allow direct cause-consequence understanding, (2) the reference values for FFMI and FMI used was not developed specifically for Brazilian population, (3) the assessment of PADL was performed in two consecutive weekdays that despite being sufficient for reliable measurement in more severe patients may not be enough for less impaired patients [38], (4) the lack of some important information, such as prevalence of comorbidities, socioeconomic status and weather conditions.

Future studies should investigate the associations of body composition phenotypes and other outcomes such as, mortality and hospital admissions as well as, confirm our results preferably, in a prospective design to better explore cause-consequence understanding. Investigate whether patients stratified in body composition phenotypes have benefits of changing to other groups. Also, investigate if patients stratified in these phenotypes present different response to the same pulmonary rehabilitation program and develop targeted interventions specifically for the different phenotypes and compare it with the effects of traditional pulmonary rehabilitation.

Conclusion

Body composition phenotypes are associated with physical function in patients with COPD. Obese patients present preserved characteristics and were similar to NBC patients. SO patients were the most impaired, considering their reductions in exercise capacity, PADL, peripheral and respiratory muscle strength. Sarcopenic patients present the same impairments in physical function compared with SO, although higher time spent in MVPA and less sedentary time per day. Clinical characteristics were similar across the different body composition phenotypes.

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Conflict of interest

All authors have disclosed no conflict of interest.

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Table 1. Anthropometrics, demographics, lung function and body composition data of COPD patients stratified into body composition phenotypes.

Variables	**NBC**	**Obese**	**Sarcopenic**	**SO**	***P* value**
6MWD (m)	465[414-505]	480[365-541]	473[416-524]	472[390-506]	0.81
6MWD (% predicted)	88[81-99]	90[73-98]	85[71-95]	83[72-90]*	<0.01
1RM Quadriceps (Kg)	17[12-21]	19[13-24]	16[13-19]	15[11-21]	0.39
1RMBiceps (Kg)	11[9-14]	12[8-15]	10[8-12]	12[9-14]	0.35
1RM Triceps (Kg)	14±5	14±5	12±4	12±5	0.09
MIP (%predicted)	78±23	74±28	69±27	70±25	0.10
MEP (%predicted)	103[89-135]	118[102-145]	83[66-111]*****†	88[75-113]*****†	<0.01
Steps/day	4441[2830-6894]	5515[2663-8552]	5520[2839-8742]	3789[2210-5355]	0.05
MVPA > 3 METs (min/day)	22[9-44]	20[7-45]	36[7-89]	16[3-31]#	<0.04
Light Activities (min/day)	211±97	206±113	224±89	214±117	0.91
ST < 1.5 METs (min/day)	465±118	470±144	418±109	482±135	0.15
Average METs/day	1.45[1.25-1.71]	1.35[1.15-1.85]	1.75[1.48-2.0]*†	1.40[1.15-1.65]#	<0.01
MRC	4[2-4]	3[2-4]	4[2-4]	4[2-4]	0.44
HADS Anxiety (pts)	5[3-10]	4[3-9]	5[3-7]	6[3-8]	0.68
HADS Depression (pts)	4[2-8]	4[1-6]	4[1-7]	4[1-8]	0.74
LCADL (pts)	22[16-28]	18[13-24]	22[17-29]	24[15-30]	0.16

Data expressed as absolute frequency, mean±SD or median [IQR 25-75%]. **NBC:** normal body composition; **SO:** sarcopenic-obese; **FVC**: forced vital capacity; **FEV_1**: forced expiratory volume in the first second; **GOLD**: Global Initiative for Chronic Lung Disease; **BMI**: body mass index; **FFMI**: fat-free mass index; **FMI**: fat-mass index;

*P<0.05 compared with NBC

†P<0.05 compared with Obese

#P<0.05 compared with Sarcopenic

Table 2. Clinical characteristics and physical function data of COPD patients stratified into body composition phenotypes.

Variables	NBC (n=106)	Obese (n=34)	Sarcopenic (n=56)	SO (n=74)	*P* value
Sex (Male/Female)	(33/73)	(25/9)*	(35/21)*	(59/15)*	<0.01
Age (years)	67±7	67±8	67±8	68±9	0.81
Heigth (cm)	157±9	161±8	160±7*	164±8*	<0.01
Weight (Kg)	68±14	83±16*	57±11*†	67±13†#	<0.01
FVC (%predicted)	72±16	70±18	79±19	65±16	0.40
FEV_1 (%predicted)	50±14	47±16	43±16*	42±16*	<0.01
FEV_1/FVC	58±13	59±17	50±12*†	54±14	<0.01
GOLD (I/II/III/IV)	(2/53/46/5)	(0/14/15/5)	(1/19/23/13)*	(1/21/31/21)*	<0.01
Male					
BMI (kg/m^2)	29.8[26.8-32.4]	29.6[24.7-34.9]	20.6[19.6-26.0]*†	25.0[22.6-28.3]*†	<0.01
FFMI (kg/m^2)	20.9±1.7	20.3±2.4	16.5±1.7*†	16.5±2.2*†	<0.01
FMI (kg/m^2)	7.4±2.6	10.4±3.9*	5.9±2.2†	8.6±2.5#	<0.01
Female					
BMI (kg/m^2)	27.3±4.6	35.7±6.4*	21.8±4.7*†	24.3±4.9.†	<0.01
FFMI (kg/m^2)	17.1±1.8	18.8±2.4*	14.0±1.3*†	13.9±1.7*†	<0.01
FMI (kg/m^2)	10.5[7.7-12.8]	16.3[14.2-20.6]*	6.9[4.8-11.2]*†	12.7[8.6-14.1]#	<0.01

Data expressed as mean±SD or median [IQR 25-75%] **NBC:** normal body composition; **SO:** sarcopenic-obese; **6MWD:** six-minute walk distance; **1RM**: one-maximum repetition; **MIP**: maximum inspiratory pressure; **MEP:** maximum expiratory pressure; **MVPA:** time in moderate-to-vigorous physical activity (above 3METs), **ST:** time in sedentary activities (bellow 1.5METs); **METs:** metabolic equivalents of task; **MRC**: Medical Research Council dyspnea scale; **HADS:** Hospital Anxiety and Depression scale; **LCADL:** London Chest Activity Daily Living scale. For 6MWD: (n=259), 1RM: (n=251); MIP and MEP: (n=267); MVPA, light activities, ST, Average METs, Steps: (n=160); MRC: (n=230); HADS: (n=159); LCADL: (n=230).

*P<0.05 compared with NBC

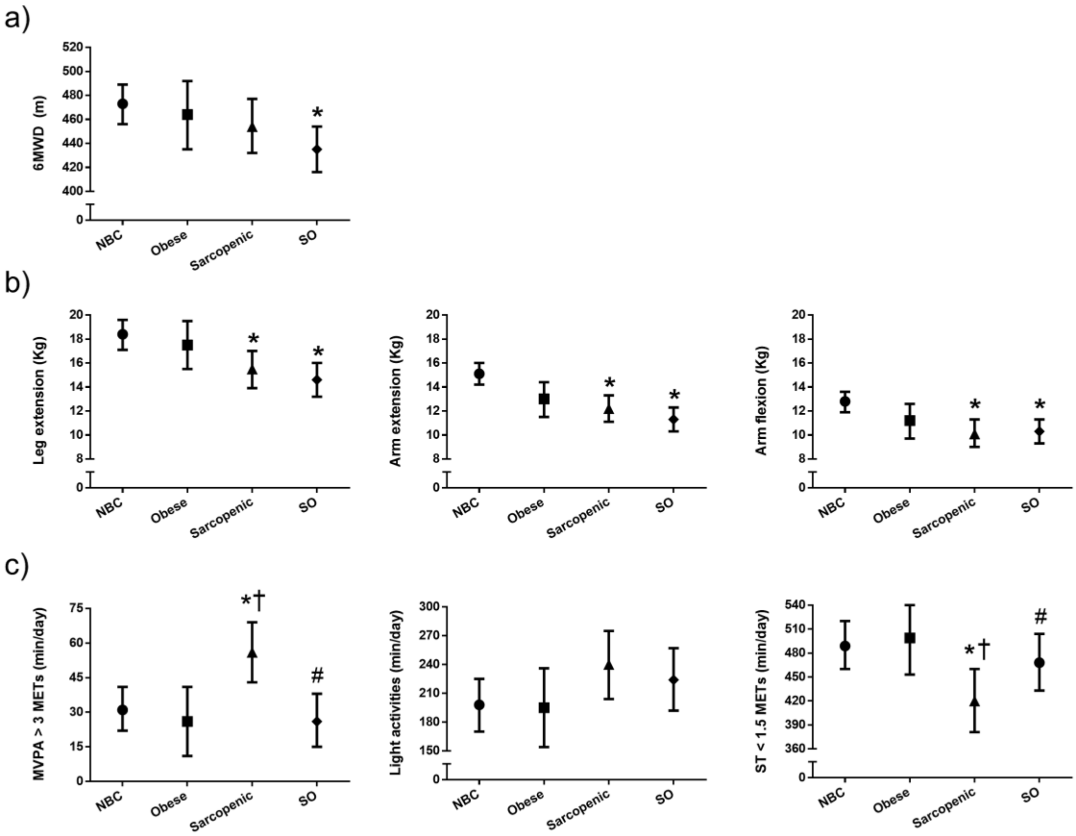
†P<0.05 compared with Obese

#P<0.05 compared with Sarcopenic

Table 3. Binomial logistic regression to ascertain factors associated with the likelihood of patients present a 6MWT equal or lower than 350 meters.

Variables	Odds Ratio	95% CI Lower	95% CI Upper	*P* value
6MWD (≤350m)				
Sex (male)	0.14	0.04	0.44	<0.01
BMI (kg/m²)	1.17	1.05	1.31	<0.01
Age (years)	1.18	1.10	1.28	<0.01
FEV_1 (%predicted)	0.97	0.94	1.00	0.03
Obese	2.80	0.50	15.68	0.24
Sarcopenic	7.85	1.63	37.70	0.01
SO	9.51	2.17	41.66	<0.01

CI: Confidence interval; **6MWD:** six-minute walk distance; **BMI:** body mass index; **FEV_1:** forced expiratory volume in the first second; **SO:** sarcopenic-obesity.



6MWD: six-minute walk distance; **NBC:** normal body composition; **SO:** sarcopenic-obese; **MVPA:** time in moderate-to-vigorous physical activity, **ST:** sedentary activities;

[a]Adjusted for: Sex, body mass index and forced expiratory volume in the first second (%predicted). NBC (n=100), Obese: (n=33); Sarcopenic: (n=53); SO: (n=73)

[b]Adjusted for: Sex. NBC (n=95), Obese: (n=32); Sarcopenic: (n=52); SO: (n=72)

[c]Adjusted for: Sex, forced expiratory volume in the first second (%predicted) and 6MWD (%predicted). For NBC (n=62), Obese: (n=21); Sarcopenic: (n=32); SO: (n=42)

*P<0.05 compared with NBC.

†P<0.05 compared with Obese.

#P<0.05 compared with Sarcopenic.

Figure 1. One-way ANCOVA with the comparison of absolute values of the 6MWD, peripheral muscle strength and PADL between patients stratified in body composition phenotypes.

4 CONCLUSÃO GERAL

A presente dissertação acrescenta à literatura atual achados que fortalecem as evidências já existentes de que a composição corporal é um fator independentemente associado com desfechos importantes para pacientes com DPOC. Pode-se concluir que as anormalidades de composição corporal podem discriminar fenótipos metabólicos que estão associados com características físico-funcionais nestes pacientes. Em resumo, a presença de obesidade-sarcopênica esteve associada com piores desfechos, visto que os pacientes apresentavam pior função pulmonar, capacidade de exercício, força muscular respiratória e periférica e menor nível de atividade física na vida diária. A presença de sarcopenia também está associada com prejuízos nas características físico-funcionais, porém estes pacientes apresentam um perfil de atividade física caracterizado por mais tempo em atividades de maiores intensidades (≥3METs) e menos tempo em atividades sedentárias (<1,5METs). Os pacientes considerados obesos apresentam características físico-funcionais preservadas quando comparados com os pacientes com composição corporal normal. Finalmente, as características clínicas como dispneia crônica na vida diária, estado funcional e sintomas de ansiedade e depressão não apresentaram associações com a composição corporal em pacientes com DPOC.

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ANEXOS

ANEXO A

Parecer do comitê de ética em pesquisa (Universidade Estadual de Londrina)

Universidade Estadual de Londrina

PARANÁ
GOVERNO DO ESTADO

COMITÊ DE ÉTICA EM PESQUISA ENVOLVENDO SERES HUMANOS
Universidade Estadual de Londrina
Registro CONEP 5231

Parecer CEP/UEL:	173/2012
CAAE:	08307812.0.0000.5231
Processo:	26336/2012
Pesquisador(a):	Fábio de Oliveira Pitta
Unidade/Órgão:	CCS – Departamento de Fisioterapia

Prezado(a) Senhor(a):

O "**Comitê de Ética em Pesquisa Envolvendo Seres Humanos da Universidade Estadual de Londrina**" (Registro CONEP 5231) – de acordo com as orientações da Resolução 196/96 do Conselho Nacional de Saúde/MS e Resoluções Complementares, avaliou o projeto:

"SEGUIMENTO A LONGO PRAZO DE UM PROGRAMA DE TREINAMENTO FÍSICO DE LONGA DURAÇÃO SOBRE ASPECTOS PULMONARES E SISTÊMICOS DE PACIENTES PORTADORES DE DOENÇA PULMONAR OBSTRUTIVA CRÔNICA (DPOC)"

Situação do Projeto: **Aprovado**

Informamos que deverá ser comunicada, por escrito, qualquer modificação que ocorra no desenvolvimento da pesquisa, bem como deverá apresentar ao CEP/UEL relatório final da pesquisa.

Londrina, 08 de outubro de 2012.

Profa. Dra. Alexandrina Aparecida Maciel Cardelli
Coordenadora do Comitê de Ética em Pesquisa Envolvendo Seres Humanos
Universidade Estadual de Londrina

Comitê de Ética em Pesquisa Envolvendo Seres Humanos - UEL -

Campus Universitário: Rodovia Celso Garcia Cid (PR 445), Km 380 - Fone (43) 3371-4000 - PABX - Fax 3328-4440 - Caixa Postal 6001 - CEP 86051-990 - Internet http://www.uel.br
LONDRINA - PARANÁ - BRASIL

Form. Código 11.764 - Formato A4 (210x297)

ANEXO B

Parecer do comitê de ética em pesquisa (Universidade Norte do Paraná)

UNOPAR

Universidade Norte do Paraná

Comitê de Ética em Pesquisa

PARECER CONSUBSTANCIADO

PROTOCOLO: *PI/0377/10*
RESPONSÁVEL: *Josiane Marques Felcar Fiale de Oliveira*
CATEGORIA DE PROJETO: *Capacitação*

O Comitê de Ética em Pesquisa da Unopar analisou e APROVOU quanto ao aspecto ético o projeto **"Efeitos do treinamento físico em solo e em água em pacientes com DPOC."**

O CEP/UNOPAR estabelece:

a) O sujeito da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (Res. CNS 196/96 – Item IV.1.f) e deve receber uma cópia do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (Item IV.2.d).

b) O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade pelo CEP/UNOPAR (Res. CNS Item III.3.z), aguardando seu parecer, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa (Item V.3) que requeiram ação imediata.

c) O CEP/UNOPAR deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso normal do estudo (Res. CNS Item V.4). É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP/UNOPAR junto com seu posicionamento.

d) Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP/UNOPAR de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas.

e) Semestralmente devem ser encaminhados relatórios parciais e ao término do projeto o relatório final.

Londrina, 09 de dezembro de 2010.

Prof. Dr. Hélio Hiroshi Suguimoto
Presidente do C.E.P. UNOPAR

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ANEXO C

Normas de formatação do periódico *Clinical Nutrition*

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References

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Divide the article into clearly defined sections.

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REVISED SUBMISSIONS

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State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

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Define abbreviations that are not standard in this field in a footnote to be placed on the first page of the article. Such abbreviations that are unavoidable in the abstract must be defined at their first mention there, as well as in the footnote. Ensure consistency of abbreviations throughout the article.
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