Universidade Estadual de Londrina

JÉSSICA FERNANDA DO NASCIMENTO FONSECA

DISFUNÇÃO MUSCULAR EM TABAGISTAS E PACIENTES COM DOENÇA PULMONAR OBSTRUTIVA CRÔNICA LEVE

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.

Orientador: Prof. Dr. Fabio de Oliveira Pitta

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Dedico este trabalho à minha família e amigos.

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“A inteligência é a capacidade de se adaptar à mudança.”

(Stephen Hawking)

FONSECA, Jéssica Fernanda do Nascimento. **Disfunção muscular periférica em tabagistas e paciente com dpoc leve.** 2018. 78 f. Dissertação (Mestrado em Ciências da Saúde) – Universidade Estadual de Londrina, Londrina, 2018.

RESUMO

Objetivo: Descrever e discutir a evidência disponível sobre função muscular e as associações entre o tabagismo e a disfunção muscular em tabagistas e pacientes com DPOC leve. **Métodos:** A busca na literatura foi conduzida nas seguintes bases de dados: Pubmed, Pedro, Cinahl, Cochrane Library, Lilacs e Embase. Os estudos eram incluídos se investigassem a força muscular e/ou endurance e/ou área de secção transversa (AST) muscular em tabagistas e/ou pacientes com DPOC classificados como GOLD I e sem câncer de pulmão. Dois revisores fizeram o rastreio e identificaram os artigos para inclusão. **Resultados:** Dezoito estudos foram identificados. Seis deles encontraram menores valores em diferentes variáveis de força muscular em tabagistas em comparação com controles não-tabagistas, enquanto outros seis encontraram valores similares entre esses grupos. Quando pacientes com DPOC classificados como GOLD I foram comparados com tabagistas, pacientes com DPOC mostraram menores valores de força muscular. Dois estudos não encontraram diferenças na AST entre tabagistas e controles não-tabagistas. Alguma evidência preliminar também mostrou que pacientes com DPOC classificados como GOLD I apresentam menores valores de AST em comparação com tabagistas. **Conclusão:** As evidências sobre disfunção muscular em tabagistas são divergentes, pois alguns estudos mostram piores resultados em variáveis de força muscular em tabagistas em comparação com controles não-tabagistas, enquanto outros não mostram. No entanto, existem evidências preliminares indicando pior disfunção muscular e menor AST em pacientes com DPOC leve em comparação com tabagistas saudáveis (ou não-DPOC).

Palavras-chave: Doença pulmonar obstrutiva crônica. Tabagismo. Músculos. Força muscular.

FONSECA, Jéssica Fernanda do Nascimento. **Muscle dysfunction in smokers and patients with mild copd.** 2018. 78 p. Dissertation (Master's degree in Health Science) – Universidade Estadual de Londrina, Londrina, 2018.

ABSTRACT

Aim: To describe and discuss the available evidence about muscle function and the association between smoking and muscle dysfunction in smokers and patients with mild COPD. **Methods:** The literature search was conducted in the following databases: Pubmed, Pedro, Cinahl, Cochrane library, Lilacs and Embase. Studies were included if they investigate muscle strength and/or endurance and/or cross-sectional area (CSA) in smokers and/or patients with COPD classified as GOLD I and without lung cancer. Two review authors screened and identified the studies for inclusion. **Results:** Eighteen studies were identified. Six of them found lower values in a variety of muscle strength variables in smokers compared with non-smoking controls, whereas six others found similar values between these groups. When comparing patients with COPD classified as GOLD I with smokers, COPD patients showed lower muscle strength. Two studies found no differences in CSA between smokers compared with non-smoking controls. Some preliminary evidence also shows that patients with COPD classified as GOLD I had lower CSA in comparison to smokers**.** **Conclusion:** Results about muscle dysfunction in smokers are divergent, since some studies have shown worse results in a variety of muscle strength variables in smokers compared with non-smoking controls, whereas others have not. Moreover, there is rather preliminary evidence indicating worse muscle dysfunction and lower CSA in patients with mild COPD in comparison to 'healthy' (or non-COPD) smokers.

Keywords: Pulmonary disease. Chronic obstructive. smoking. Muscles. Muscle strength.

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LISTA DE ABREVIATURAS E SIGLAS

BODE	Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity
DPOC	Doença Pulmonar Obstrutiva Crônica
VO_2máx	Consumo máximo de oxigênio
WHO	World Health Organization

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1 INTRODUÇÃO

A doença pulmonar obstrutiva crônica (DPOC) é uma doença prevenível e tratável, caracterizada por sintomas respiratórios persistentes e limitação ao fluxo aéreo causadas por anormalidades de vias aéreas e alveolares comumente causadas por exposição significativa a partículas ou gases nocivos[1]. Apesar da característica pulmonar, a doença cursa com manifestações sistêmicas como a disfunção muscular esquelética, desequilíbrio hormonal e anemia, entre diversas outras[2]. Entre outros fatores, as manifestações sistêmicas podem ser causadas pela inatividade, anormalidades nutricionais, uso de corticosteroides, presença de hipóxia, inflamação sistêmica[2] e ocorrência de episódios de exacerbação[1].

O principal fator etiológico no desenvolvimento da DPOC é o tabagismo, seguido por fatores ocupacionais e poluição do ar[1]. Além disso, a cessação do tabagismo é a intervenção mais efetiva na redução da morbidade e mortalidade nos pacientes com DPOC[3]. A disfunção muscular periférica é uma das maiores consequências sistêmicas da DPOC devido ao seu impacto em outros desfechos como a atividade física, tolerância ao exercício, qualidade de vida e mortalidade[4]. Adicionalmente, existem evidências que sugerem que a exposição à fumaça do tabaco poderia contribuir para a disfunção muscular mesmo antes do desenvolvimento da DPOC[5].

Sabe-se que o tabagismo é um fator de risco para o desenvolvimento da sarcopenia, que apresenta como uma de suas características a perda de massa muscular e força muscular[6]. O tabagismo parece estar associado à redução da força de alguns grupos musculares; no entanto, os resultados da literatura ainda não são aprofundados[7]. Apesar da conhecida influência de outras variáveis na disfunção muscular, como o desuso pela inatividade, o tabagismo não pode ser descartado como tendo um efeito direto na função muscular[8].

Visto que o tabagismo está altamente associado ao desenvolvimento da DPOC e que a disfunção muscular é comum nesta doença, além de poder também estar presente em tabagistas aparentemente saudáveis, faz-se importante a realização de investigações a respeito da gênese da disfunção muscular tanto na

DPOC quanto em tabagistas que ainda não desenvolveram a doença. A identificação mais aprofundada sobre os fatores envolvidos nessa disfunção pode auxiliar no desenvolvimento de terapias específicas, bem como promover informações para o aprimoramento de estratégias para o combate ao tabagismo e suas consequências.

2 REVISÃO DE LITERATURA – CONTEXTUALIZAÇÃO

2.1 Doença Pulmonar Obstrutiva Crônica (DPOC)

A doença pulmonar obstrutiva crônica (DPOC) é um grande desafio de saúde pública, representando uma importante causa de morbidade e mortalidade no mundo[1]. Estimativas apontam que cerca de 64 milhões de pessoas no mundo tem DPOC, resultando em mais de 800 mil hospitalizações ao ano[9]. A doença tornou-se recentemente a terceira causa de mortalidade no mundo[10], posição que ocuparia apenas em 2030 de acordo com estimativas da Organização Mundial da Saúde[11]. Além disso, o fardo da DPOC está projetado para aumentar nas próximas décadas devido a exposição continuada a fatores de risco e envelhecimento da população[1].

A DPOC é uma doença prevenível e tratável, caracterizada por sintomas respiratórios persistentes e limitação ao fluxo aéreo causadas por anormalidades de vias aéreas e alveolares, comumente ligadas à exposição significativa a partículas ou gases nocivos[1]. A inalação das partículas nocivas causa uma resposta inflamatória nos pulmões, que quando se torna crônica pode induzir destruição do parênquima pulmonar e perturbação do mecanismo normal de reparação e defesa, ocasionando o aprisionamento de ar e limitação progressiva ao fluxo aéreo[1]. A obstrução crônica ao fluxo aéreo é caracterizada por um misto de doença das pequenas vias aéreas e destruição do parênquima pulmonar, e a proporção dessas duas características pode variar entre os indivíduos[1]. A doença apresenta como sintomas respiratórios mais comuns a dispneia, tosse e/ou produção de secreção. Além disso, períodos de exacerbação podem ser comuns e são caracterizados por piora dos sintomas respiratórios[1].

O maior fator etiológico para desenvolvimento da doença é o tabagismo, seguido por fatores ocupacionais e poluição do ar (como a combustão de biomassa)[1]. O desenvolvimento da doença também está associado a fatores genéticos, idade, hiperresponsividade brônquica ou crescimento e desenvolvimento pulmonar deficitário na infância[1,12]. O diagnóstico é realizado por meio da avaliação

da função pulmonar pela espirometria, na presença da relação entre volume expiratório forçado no primeiro segundo e capacidade vital forçada menor do que 0.70 após o uso de broncodilatador, o que evidencia a presença de limitação persistente ao fluxo aéreo[1]. Ao avaliar o paciente com DPOC, deve-se levar em consideração fatores como a gravidade da anormalidade espirométrica e seu impacto no estado de saúde e risco de futuras exacerbações, admissões hospitalares ou morte, além da presença e magnitude dos sintomas e presença de comorbidades[1].

Muito além de uma doença unicamente dos pulmões, a DPOC pode ser considerada como uma doença sistêmica[2]. Dentre as manifestações sistêmicas, podem ser citadas a disfunção muscular esquelética, alterações de humor, desequilíbrio hormonal e anemia, entre diversas outras. As causas para essas alterações podem ser desde o descondicionamento causado pela inatividade até anormalidades nutricionais, uso de corticosteroides, presença de hipóxia e inflamação sistêmica[2]. Adicionalmente, pacientes com DPOC podem apresentar estresse oxidativo acentuado, que pode inclusive piorar com as exacerbações[1].

Algumas das comorbidades mais comuns e importantes na DPOC são a osteoporose, ansiedade, depressão e apneia obstrutiva do sono que podem estar associadas com pior estado de saúde e prognóstico[1]. Além disso, também é comum a presença de doenças cardíacas, hipertensão, diabetes, obesidade, síndrome metabólica e câncer de pulmão[1,2,13], que são capazes de gerar um impacto significante nos sintomas e desfechos clínicos[14]. De fato, algumas dessas comorbidades podem ser oriundas de fatores de risco em comum para ambas as condições, como no caso do tabagismo[14].

2.2 Tabagismo

O tabagismo é o responsável por aproximadamente 7 milhões de mortes no mundo anualmente, das quais cerca de 12% são de não-tabagistas, mas apenas expostos secundariamente ao tabaco[15]. A fumaça do tabaco contém mais de 7 mil componentes químicos prejudiciais ao corpo humano[16]. Esses componentes da fumaça do cigarro e seus metabólitos são capazes de causar dano genético na

expressão de fatores envolvidos na oncogênese e supressão tumoral[17], tornando os tabagistas mais suscetíveis ao desenvolvimento de câncer, não apenas no trato respiratório, mas também em outros sistemas.

O tabagismo também é uma causa tratável de diversas doenças globais como o acidente vascular encefálico, doenças coronarianas e múltiplos tipos de câncer[18,19]. Ele é capaz de causar uma variedade de efeitos negativos no sistema musculoesquelético, como uma menor densidade óssea, maior risco de fraturas e alterações articulares, além de piores desfechos no período pós-operatório de procedimentos articulares e ligamentares[7].

Atualmente, o tabagismo é o principal fator etiológico para o desenvolvimento da DPOC e a sua cessação é a intervenção mais efetiva para reduzir a morbidade nesses indivíduos, devido à melhora da função pulmonar em pacientes de grau moderado a grave e interrupção do declínio da função pulmonar nos pacientes mais graves, além da redução dos sintomas respiratórios, com consequente prevenção da progressão da doença[3]. A cessação tabágica também é capaz de reduzir progressivamente as taxas de mortalidade por todas as causas mesmo após anos de abstinência do tabagismo[3], bem como a redução da carga tabágica, que também já se mostra eficiente na redução da mortalidade[20]. Cerca de 30-40% dos pacientes com DPOC que apresentam sintomas ainda fumam[21], um fato que nos alerta para desenvolvimento e aprimoramento de estratégias para que a cessação tabágica aconteça nesses pacientes.

Apesar da redução progressiva na prevalência do tabagismo desde os anos 2000, em 2015 essa prevalência no Brasil ainda era de 19,3%[22]. Em um estudo de 2018 realizado em 28 países, a prevalência de tabagismo reportada foi de 22,5%[23]. Neste mesmo estudo, foi revelado que apesar de 73 a 95% dos indivíduos terem conhecimento de que o tabagismo causa doenças como acidente vascular encefálico, ataque cardíaco e câncer de pulmão, apenas 42,5% haviam realizado uma tentativa de cessação no último ano[23].

Uma variedade de intervenções tem sido desenvolvida objetivando a cessação tabágica, como a terapia de reposição de nicotina, tratamentos farmacológicos, terapias de comportamento cognitivo e até aplicativos para

smartphones[24]. Desde a implementação da *WHO Framework Convention on Tobacco Control*[25] pela Organização Mundial da Saúde em 2005, houve uma redução na prevalência de tabagismo, ainda com futuras reduções previstas na morbidade e mortalidade relacionada ao tabagismo nos próximos anos. Entre essas medidas, estão incluídas diretrizes para proibições de publicidade ao tabaco, aumento dos impostos, auxílio para a cessação, monitorização do uso do tabaco, políticas de prevenção e aviso sobre os perigos do tabagismo[26]. No entanto, apesar da meta para redução do tabagismo em 30% até o ano de 2030, esse processo na cessação do tabagismo ainda tem sido lento[27].

Atualmente, os problemas do tabagismo têm sido observados também por outros pontos de vista, como por exemplo as suas consequências ambientais e sociais de produção, como o cultivo, processamento, descarte e mão de obra[28], nos mostrando que o tabagismo vai além dos efeitos negativos altamente conhecidos sobre a saúde, porém não tornando esse tópico menos importante.

2.3 Disfunção muscular

A disfunção muscular é definida como a redução das propriedades de força e/ou endurance muscular[4]. A atrofia e a fraqueza trazem consequências importantes como dificuldades no engajamento na atividade física, intolerância ao exercício e prejuízo na qualidade de vida[4]. O declínio progressivo na massa muscular esquelética é uma mudança associada ao envelhecimento humano, que pode causar a redução da força muscular e da funcionalidade[6].

A redução da massa muscular esquelética associada à redução da força muscular e/ou baixa performance física são os critérios diagnósticos para a sarcopenia[6]. A sarcopenia representa um estado de saúde debilitado e com alto custo pessoal, com desordens de mobilidade, aumento do risco de quedas e fraturas, inabilidade para realização de atividades de vida diária, perda de independência e aumento do risco de morte[29,30]. Essa condição é causada por um desequilíbrio entre a síntese e degradação de proteínas, provavelmente em consequência de mudanças relacionadas ao envelhecimento[31]. Adicionalmente, a redução da força e qualidade muscular está associada à redução do equilíbrio e

aumento no risco de quedas em idosos[32-34]. As quedas comumente resultam em acometimentos como hematomas, fraturas e lacerações[35].

A redução da força muscular em adolescentes é um fator de risco para todas as causas de mortalidade na vida adulta jovem[36]. A diminuição da força de preensão palmar está associada à perda de independência em idosos, assim como é capaz de predizer o risco aumentado de limitações funcionais, incapacidade em idade avançada, assim como doenças cardiovasculares, mortalidade por causas cardiovasculares e também por todas as causas em adultos saudáveis[37-40].

2.4 Disfunção muscular na DPOC

A disfunção muscular periférica é uma das maiores consequências sistêmicas da DPOC devido ao seu impacto na atividade física, tolerância ao exercício, qualidade de vida e mortalidade [4]. Altamente prevalente na DPOC, essa disfunção reflete adaptações estruturais e metabólicas como alterações nos tipos de fibra (do tipo I para tipo II), redução da capacidade oxidativa, disfunção mitocondrial, redução da capilarização[41] e perda de massa muscular[42].

A etiologia da disfunção muscular em pacientes com DPOC é multifatorial. Entre os fatores relacionados podem ser citados a inflamação sistêmica, estresse oxidativo, desequilíbrio nutricional, hipoxemia e principalmente a inatividade física[41,43]. Além disso, a disfunção muscular ainda pode ser agravada pela miopatia causada pelo uso crônico de corticosteroides, inflamação local e pelos episódios de exacerbações[44], que também impactam negativamente no estado de saúde e progressão da doença[45,46.] A integridade muscular também pode estar indiretamente relacionada com elementos relevantes como a suscetibilidade a infecções, densidade mineral óssea ou frequência de episódios de exacerbação[47].

Atualmente, o melhor tratamento para disfunção muscular na DPOC é o treinamento físico[41]. O treinamento físico é um pilar indispensável na reabilitação pulmonar nesses indivíduos, devido aos seus efeitos positivos na melhora na força muscular periférica, além da melhora também da capacidade de exercício, dispneia e qualidade de vida, mesmo sem melhoras na função pulmonar[13,41,48-50]. A avaliação da disfunção se faz importante tanto como base para o início de um treinamento

físico como para identificação de pacientes de risco, visto que a força muscular pode ser associada a diversos desfechos negativos. A força de preensão palmar está independentemente associada com o risco aumentado de exacerbações[51-52], enquanto a redução da força muscular dos membros inferiores está associada a um alto risco de desenvolver incapacidade, independente do comprometimento pulmonar[53]. Adicionalmente, a massa muscular avaliada tanto pela área de secção transversa quanto pela circunferência do membro, está intimamente relacionado à sobrevida e mortalidade, respectivamente[54].

Existe uma heterogeneidade entre os indivíduos na prevalência da disfunção muscular na DPOC[41]. Alguns estudos apontam que a força muscular de diversos grupos musculares não apresenta correlação com o grau de obstrução ao fluxo aéreo ou com o risco de mortalidade estimado pelo índice BODE enquanto outros mostram correlações moderadas[51]. Apesar da maior prevalência de fraqueza muscular se encontrar no grupo mais grave, pacientes com a doença mais leve já podem apresentar fraqueza muscular enquanto uma parcela dos pacientes com maior gravidade da doença pode nem sequer apresentar fraqueza muscular[55]. Portanto, ao levar-se em consideração a heterogeneidade da disfunção muscular de pacientes com DPOC, a presença de fenótipos específicos relacionados à força muscular nessa população parece uma explicação plausível[41].

2.5. Disfunção Muscular em Tabagistas.

Acredita-se que a exposição à fumaça do tabaco poderia contribuir para a disfunção muscular mesmo antes do desenvolvimento da DPOC[5]. Apesar da influência de outras variáveis na disfunção muscular, como por exemplo o desuso, não se pode excluir um efeito direto do tabagismo sobre a função muscular[8]. O tabagismo é um fator de risco para o desenvolvimento da sarcopenia, que é caracterizada pela perda de massa muscular e força muscular relacionadas à incapacidade física e outros desfechos negativos[6].

Existem achados na literatura de que tabagistas apresentam menos fibras musculares do tipo I e IIa do que não-tabagistas[56], indicando uma atrofia das fibras de característica oxidativa, ou seja, as fibras mais resistentes à fadiga. Sabe-se também que tabagistas, em comparação com não-tabagistas, podem apresentar uma redução da oxihemoglobina local nos músculos, redução nos níveis de catalase (i.e., uma enzima extremamente importante na desintoxicação de produtos do metabolismo celular), e aumento nos níveis de marcadores inflamatórios, apesar de valores similares de VO_2máx, concentração de hemoglobina, lactato e capilarização durante exercícios de membros inferiores[7]. Esses achados apontam que aparentemente algumas alterações anatômicas e/ou metabólicas já podem ser observadas mesmo em tabagistas aparentemente saudáveis.

Existem evidências de que o tabagismo está associado à redução da força muscular de extensão da coluna, força de preensão palmar e de extensores de joelho[7]. Em um estudo publicado em 2015, em comparação com não-tabagistas ao início de um treinamento físico, tabagistas do gênero masculino apresentaram um menor volume do músculo reto femoral, apesar do ganho de massa muscular após o treinamento físico ter sido independente do histórico de tabagismo[57]. Apesar dos efeitos negativos no sistema musculoesquelético, sabe-se que a cessação do tabagismo pode estar associada ao aumento da força muscular de membros inferiores e preensão palmar, além do ganho de peso com aumento da massa magra e densidade óssea[58].

Entretanto, alguns resultados sobre diferenças na força muscular em tabagistas e não-tabagistas ainda se apresentam conflitantes, pois alguns estudos encontraram valores similares de força muscular nesses dois grupos[7]. Entre os

músculos estudados estão o quadríceps femoral, oblíquos externos e reto abdominal, que apresentaram valores similares entre tabagistas e não tabagistas, embora exista também evidências de que tabagistas apresentaram maiores valores de contração voluntária máxima do que não-tabagistas[7]. Adicionalmente, não havia ainda disponível na literatura uma revisão sistemática sobre a presença (e gravidade) da disfunção muscular em tabagistas e pacientes com DPOC leve, o que não permitia neste momento uma visão cientificamente abrangente sobre o tema.

3 ARTIGO

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ABBREVIATION LIST

1RM – One-repetition maximum

CSA – Cross-sectional area

COPD – Chronic obstructive pulmonary disease

FVC – Forced vital capacity

MTC – Maximal torque capacity

MVC – Maximal voluntary contraction

MVC/CSA – Maximal voluntary contraction/Cross-sectional area

PA – Physical activity

QMVC – Quadriceps maximum voluntary contraction

TNF-α – Tumor necrosis factor alfa

TwQpot – twitch quadriceps potentiated

FEV_1 – forced expiratory volume in the first second

REVIEW ARTICLE

Title: Muscle dysfunction in smokers and patients with mild COPD: A Systematic Review.

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ABSTRACT

Purpose: To describe and discuss the available evidence about muscle function and the association between smoking and muscle dysfunction in smokers and patients with mild COPD.

Methods: The literature search was conducted in the following databases: Pubmed, Pedro, Cinahl, Cochrane library, Lilacs and Embase. Studies were included if they investigate muscle strength and/or endurance and/or cross-sectional area (CSA) in smokers and/or patients with COPD classified as GOLD I and without lung cancer. Two review authors screened and identified the studies for inclusion.

Results: Eighteen studies were identified. Some studies found lower values in a variety of muscle strength variables in smokers compared with non-smoking controls, whereas others found similar values between these groups. When comparing patients with COPD classified as GOLD I with smokers, COPD patients showed lower muscle strength. Two studies found no differences in CSA between smokers compared with non-smoking controls. Some preliminary evidence also shows that patients with COPD classified as GOLD I had lower CSA in comparison to smokers.

Conclusion: Results about muscle dysfunction in smokers are divergent, since some studies have shown worse results in a variety of muscle strength variables in smokers compared with non-smoking controls, whereas others have not. Moreover, there is rather preliminary evidence indicating worse muscle dysfunction and lower CSA in patients with mild COPD in comparison to 'healthy' (or non-COPD) smokers.

Keywords: Pulmonary Disease, Chronic Obstructive; Smoking; Muscles; Muscle Strength.

SHORT ABSTRACT

The study describes and discusses the available evidence about the association between smoking and muscle dysfunction in smokers and mild COPD. Results showed that there is still insufficient solid evidence about the presence and characteristics of muscle dysfunction when comparing smokers versus non-smokers and smokers versus mild COPD.

INTRODUCTION

In addition to the persistent and usually progressive airway obstruction[1], chronic obstructive pulmonary disease (COPD) is characterized by several systemic manifestations related to worsening of muscle function, quality of life and functional status[2]. Examples of those manifestations are nutritional depletion[3], weight loss[4,5], malnutrition[4], deconditioning and reduction in physical activity[6], among others. Skeletal muscle dysfunction is a very common condition in patients with COPD, and plays an important role in limiting exercise performance and capacity in these patients, with implications in their health status[7]. The peripheral muscle strength of upper limbs, lower limbs and trunk are important determinants of exercise capacity and function[8]. Poor muscle status is a marker of exacerbation risk[9], as well as it has been associated with a reduced health status[10] and has also been shown to predict morbidity, mortality and disability regardless of the airway obstruction[11-13].

Muscle dysfunction is characterized by a decline in either strength or endurance in patients with COPD[7]. Both local and systemic factors play a relevant role in its pathogenesis[14]. Deconditioning due to reduced physical activity (PA) is the main driver of peripheral muscle dysfunction. Other systemic contributors to muscle dysfunction in patients with COPD are tobacco use, exacerbations, local and systemic inflammation, myopathy due to chronic use of corticosteroids[15], low levels of circulating anabolic hormones and changes in their efficacy, nutritional depletion[16], reduction of amino acid metabolism, hypoxia, hypercapnia[15,17] and oxidative stress[7,17,18]. Other changes in muscle structure and function include changes in fiber type, reduced capillarity, decreased oxidative enzyme capacity and altered cellular bioenergetics[7,18].

Smoking is one of the most important risk factors for the development of chronic obstructive pulmonary disease[19]. It is suggested that cigarette smoke exposure contributes to the development of skeletal muscle dysfunction even before the beginning of a lung disease[20]. While patients with COPD commonly suffer from exercise intolerance, a reduction in exercise capacity may already be evident in smokers without the disease. So, it is possible that reductions in exercise capacity in smokers are related to changes in skeletal muscle which precede the onset of symptoms in COPD. Studies reported some type of muscle dysfunction in smokers in comparison with non-smokers[12,21] while another did not observe the same even after matching smokers and non-smokers for levels of PA[22]. These results suggest that disuse may play a role in the loss of muscle strength in smokers. Summarizing, an effect of smoking *per se* on muscle force cannot be excluded; however, large study populations may be required to address this issue[23].

As previously mentioned, skeletal muscle dysfunction in COPD is multifactorial and several factors and biological mechanisms are involved in its etiology[18]. Therefore, investigations into the origin of muscular dysfunction in patients with COPD and smokers (due to the large influence on the development of COPD) are necessary for a better understanding of the genesis of this dysfunction. Understanding the mechanisms which play a role in muscle dysfunction in COPD is important in order to develop early therapies not only to improve but also to prevent dysfunction[24] and consequent disability in patients with COPD[25] and even in smokers, in case dysfunction is present in them. Furthermore, it is important to inform people whether smoking is itself associated with muscle weakness. So, the aim of this review was to describe and discuss the available evidence about muscle function and the association between smoking and muscle dysfunction in smokers and patients with mild COPD.

METHODS

The literature search for this systematic review article was conducted in the following databases: Pubmed, Pedro, Cinahl, Cochrane library, Lilacs and Embase. The main search strategy used was: ((((COPD[Title/Abstract]) OR pulmonary disease, chronic obstructive[MeSh terms])) AND ((smok*[Title/Abstract]) OR Tobacco[Title/Abstract]) AND ((((((((function[Title/Abstract]) OR dysfunction[Title/Abstract]) OR weakness[Title/Abstract]) OR disease[Title/Abstract]) OR force[Title/Abstract]) OR strength[Title/Abstract]) OR mass[Title/Abstract]) OR cross-sectional[Title/Abstract])) in Pubmed. Further, bibliographic references of the included studies were hand searched. Articles in any language were screened, and no restrictions were applied in terms of publication date.

Studies were included if they: investigate muscle strength and/or endurance and/or cross-sectional area in smokers and/or patients with COPD classified as GOLD I (forced expiratory volume in the first second[FEV_1]/forced vital capacity[FVC] ratio <0.70 and $FEV_1 \geq 80\%$)[1] and without lung cancer. Excluded studies comprised those which did not perform separate analysis of patients classified as GOLD I, as well as congress abstracts. Two authors (JF and AGN) independently conducted the search and in case of disagreement between the selected studies, an agreement was tried between these two authors. If agreement was not possible, a decision was made by a third author (FP).

RESULTS

Information on the screening of the studies is provided in figure 1. The last search was performed on January 25th, 2018. The initial search yielded 2310 articles, whereas 18 were included after the exclusions. Table 1 shows the characteristics of the included studies, such as sample size, variables analyzed, equipment and methodology of the main assessments. Main results regarding muscle strength, muscle endurance and muscle cross-sectional area (CSA), among other variables, are shown in table 2. Due to the heterogeneity in the nature of the included studies, it was not possible to find a suitable tool for their quality assessment.

A number of outcomes and variables were used to represent muscle strength in the available studies. By using total work extension as the chosen outcome, Neves et al.[26] found lower values in smokers compared with non-smokers, although they found similar values of peak torque of flexion and extension between groups. Orlander et al.[23] found lower values of dynamic strength in smokers compared with non-smokers, whereas Larsson et al.[27] did not find differences between smokers and non-smokers or smokers and ex-smokers also by the isokinetic method.

Concerning isometric strength, Barreiro et al.[21] and Orlander et al.[23] found lower values of isometric quadriceps maximal voluntary contraction (MVC) in smokers compared with controls. On the other hand, several authors found no differences in isometric quadriceps MVC, maximal torque capacity (MTC), MVC/body mass index, twitch quadriceps potentiated (TwQpot) and MVC/CSA when comparing smokers and controls[22,27-30]. By using the one-repetition maximum (1RM) method, Sanchez et al.[31] did not find differences between smokers and non-smokers in terms of biceps and triceps brachialis, knee extensors, hip extensors and ankle flexor muscles. Al-Obaidi et al.[32]

found similar values in smokers and non-smokers when assessing isometric lumbar extension strength across several angles; the only observed difference was between the mean strength among all angles, so that smokers had lower values than non-smokers.

Concerning handgrip and pinch strength, Boyer et al.[33], found similar values in non-smokers, smokers and patients with COPD. Similarly, Lee et al.[34] found only small differences between male never smokers, ex-smokers and current smokers. Furthermore, when comparing patients with COPD classified as GOLD I with healthy controls, Kovarik et al.[35] found no differences in handgrip strength and handgrip endurance time, as well as in the area under the curve (endurance time/handgrip strength). On the other hand, Saito et al.[36] showed that, among men, smokers with age between 20 and 39 years had lower muscle strength than non-smokers, what was not observed in older subjects. In the same study, heavy smokers showed lower values of handgrip strength than light smokers, even after adjusting for age, height, body weight and exercise habits.

Dynamic endurance of the quadriceps femoris was found in one study to be similar in smokers and non-smokers[27]. Also, only one study compared muscle strength between healthy controls and patients with COPD classified as GOLD I, and found lower values of QMVC in the sample of patients[37]. Moreover, in that same sample, QMVC was quite similar between GOLD stages, with the only significant difference found between GOLD I and IV. Singer et al.[8] found quadriceps strength to be less than 50% of the predicted value in 11.1% of patients with COPD classified as GOLD I, whereas a similar frequency was found across all GOLD stages.

Regarding muscle mass, smokers and non-smokers had no differences of quadriceps femoris CSA according to Wüst et al.[22] and Morse et al.[29]. Accordingly, no differences

in mid-arm CSA were also found between smokers and non-smokers in the study by Sanchez et al.[31], although in that study higher values of mid-thigh CSA were found in non-smokers[31]. In addition, Shrikrishna et al.[37] found lower values of rectus femoris CSA in COPD classified as GOLD I compared with healthy non-smokers, whereas Tanimura et al.[38] found lower values of pectoralis major and erector spinae muscles CSA in COPD classified as GOLD I compared with smokers. Moreover, Table 3 shows that Kok et al.[19] found an association between smoking and loss of muscle strength. According to that study, smoking 100 grams of tobacco per week results in a loss in strength of the knee muscles of 0.136 kg in males and 0.169 kg in females, with little change when adjusting for cardiopulmonary fitness and PA or other confounders[19].

DISCUSSION

Contrasting results were found when comparing muscle strength and other variables related to muscle dysfunction between smokers and non-smokers. Some studies found lower values in a variety of muscle strength variables in smokers compared with non-smoking controls(21,23,26,32,34,36), whereas others found similar values between these groups(22,27-29,33,38). When comparing patients with COPD classified as GOLD I with smokers, no differences were found,(30) whereas when comparing patients with COPD classified as GOLD I with healthy individuals, one study found lower values of muscle strength in COPD(37) while other study found no differences(35). A very limited number of studies reported reduced isometric and dynamic endurance and lower CSA in smokers compared with non-smoking controls(31,23), whereas two studies found no differences in CSA between these groups(22,29). Finally, some preliminary evidence also shows that patients with COPD classified as GOLD I had lower CSA in comparison to smokers(38).

Out of the six studies that did not find differences in muscle function between smokers and non-smokers, three showed shorter smoking histories (represented by mean ± standard deviation pack-years: 9.9±10.7;(22) 2.5±3.1(29) and median [minimum-maximum]: 13[1.1-52](26)) than the studies that found significant differences. One of the studies did not report mean and SD of pack-years and another showed a wide range of pack years (mean ± standard deviation: 38±28)(28). Therefore, there might be some bias when comparing these studies if we suppose that the intensity of consumption may influence the results. Furthermore, the study which presented higher values of pack years did not find differences between smokers, non-smokers and patients with COPD, however it did not assess the most evaluated muscle by the other studies, the quadriceps femoris(33).

Physical inactivity and dyspnea

Physical inactivity is associated with muscle dysfunction in patients with COPD[37], and smoking and PA appear to be negatively associated[(39)]. Only four studies had the groups matched by PA and three of them found no differences in muscle strength, endurance or CSA[(22,27,29,32)]. In those studies assessing PA, this was done only by questionnaires, which in itself may be a bias due to the risk of inaccuracy[(40)]. Some of these questionnaires were validated[(22,27,29)] and one was not[(32)], whereas the other studies did not carry out PA assessment. Seymour et al.[(12)] have suggested that some patients with COPD may reduce PA before symptoms or a significant airflow obstruction occur, and this reduction in PA caused by dyspnea leads to muscle atrophy. Furlanetto et al.[(41)] showed that smokers presented a reduced level of PA in comparison with matched non-smokers. Also, most of the studies included by Kaczynski et al.[(39)] in a review, showed negative correlations between smoking and PA in adults. They also mention that studies in which different levels of PA was assessed, smokers engage in lesser amount of vigorous activity than non-smokers. Indeed, we can speculate whether the reduction in muscle strength found in some studies can be due to physical inactivity and consequently deconditioning.

It seems that in COPD dyspnea contributes more as a predictive factor of quadriceps weakness than the degree of airflow obstruction[(12,42)], and with the progression of the disease patients become more sedentary due to the progressive increase of breathless, becoming also increasingly weaker[(5)]. Furlanetto et al.[(43)] showed that inactive patients with COPD present worse strength for biceps and triceps brachialis and quadriceps femoris compared with active patients. Limb muscle dysfunction due to deconditioning is justified by the presence of similar changes previously described for muscle disuse (e.g., fiber atrophy, decreased percentage of aerobic fibers, reduction in

the activity of oxidative enzymes and capillary density, oxidative stress and early lactate release during exercise), also taking into account that these findings are partially reversible by training[14,44]. Since this relation between PA and muscle weakness may be "mediated" by disuse, perhaps the fact that PA level was matched between smokers and non-smoking controls in some studies prevented those smokers from presenting reduction of muscle strength.

Fatigue

Although part of the studies did not find reduction in muscle strength in smokers compared to non-smokers, mainly in quadriceps femoris, Wüst et al.[22,45] showed that resistance to fatigue is lower in smokers than non-smokers, even though no differences were found in quadriceps MVC, MTC and CSA. In accordance with these studies, Morse et al.[29] also found no differences in quadriceps MVC, MVC/CSA and other contractile properties between smokers and physical activity-matched non-smokers, but reported a decrease in fatigue resistance in smokers. A few studies state that even patients showing only mild to moderate airway obstruction have reduced muscle endurance and relatively normal PA level, although these studies did not perform an analysis according to the severity of the disease or between those patients with mild COPD and healthy controls[46,47].

Mild COPD

Even though some studies did not find differences between smokers and non-smokers in strength of various muscle groups, Sanchez et al.[31] found lower values of mid-tight CSA in smokers compared with non-smokers. Likewise, Tanimura et al.[38]

found lower values of pectoralis major and erector spinae muscles CSA in patients with COPD classified as GOLD I compared with smoking controls. This reduction was related to disease severity, but still present in some patients with mild disease. Shrikrishna et al.[37] have found that both rectus femoris CSA and quadriceps MVC force are reduced in patients with mild disease and independently associated with PA level. In other words, even though finding few differences between smokers, mild COPD and controls in muscle function, there are more marked differences in terms of CSA.

Only two studies have compared patients with mild COPD and healthy controls, one of which found lower values of muscle strength in mild COPD[37] whereas the other found no differences[35]. Moreover, no study has yet compared patients with mild COPD with “healthy” smokers (or “non-COPD” smokers) in order to verify if muscle strength or endurance is similar between them. There is a considerable heterogeneity in the presence or absence and the degree of limb muscle dysfunction in patients with COPD, since patients with severe disease may not show marked dysfunction and patients with mild disease may present it. This suggests that only disease progression and ventilatory impairment by themselves may not be the main causes of muscle dysfunction in those patients[14]. Similarly, exercise capacity is somewhat related to lung function, although the degree of deconditioning varies across patients with similar values of FEV_1[48], showing that extra-pulmonary manifestations may start in parallel with the lung disease as a result of the same insult[14]. Peripheral muscle injury is evident in mild, moderate and severe stages of COPD even in the absence of respiratory failure, hypercapnia, chronic steroid treatment, low body weight, or some coexisting disease[47]. Of note, some changes as inflammation, oxidative stress[48], hypoxemia, nutritional imbalance[2] or depletion[3], weight loss[4,5], altered muscle structure and biology[18], mitochondrial dysfunction[48] may not be observed in peripheral muscles of patients with mild to moderate COPD[5,7].

Furthermore, alterations in peripheral muscles such as the decrease in the proportion of type I fibers are also more pronounced in patients with more severe COPD, while patients with mild disease may be affected by changes in fiber type and impairment in contractile function only in the diaphragm, and not necessarily in peripheral muscles[18,14,49].

Local and systemic changes in smokers and patients with mild COPD

Smokers who have not yet developed the disease or even symptoms may already present local or systemic changes involved in muscle dysfunction, some of them similar to those present in COPD patients, such as increased protein oxidation in quadriceps[21], TNF-α serum levels increased[50], oxidative fiber atrophy, increased glycolytic capacity, reduced expression of the constitutive nitric oxide synthases (supporting some muscular structural and metabolic damage)[51], interleukin-1β[52], higher peripheral leukocyte counts, decline in diffusing capacity for carbon monoxide[38,53], lower catalase and superoxide dismutase activity, lower levels of antioxidant capacity[41,54], marked reduction in muscle protein synthesis[55] and diminished fibrillar space mitochondria volume fraction[23]. Further, CSA of muscle fibers and proportion of type I fibers was significantly lower in smokers[51], as well as increased incidence of type IIB fibers[23]. Smokers can also present lower weight, fat mass, lean mass and bone mineral content compared with never smokers[46]. Either weight and muscle mass loss may be involved in muscle dysfunction, combined with other manifestations such as systemic inflammation[5]. Ten to 15% of patients with mild COPD may have weight loss, in contrast to 50% of patients with severe disease[5].

Even with some smokers presenting worse strength compared with non-smokers, patients with COPD may have even worse values than smokers. The condition of hormonal changes, use of corticosteroids and poor nutrition, which may be present in those patients, may exaggerate these changes(56). It should be noted that during exacerbations, systemic inflammation is also more evident(14), in addition to infection, physical inactivity and negative energy imbalance(9,14). Corticosteroids can induce acute and chronic myopathies(17) resulting in weakness characterized by rhabdomyolysis, loss of thick myosin filaments, atrophy of type II fibers, abnormalities in carbohydrate metabolism and a negative balance in protein metabolism(14). Despite the fact that the systemic use of corticosteroids has decreased(14), its use may still be common in patients with severe exacerbations (therefore mainly those patients with more severe disease), making the myopathies less likely to happen due to the use of corticosteroids in patients with mild COPD. Some of the pharmacological agents used by patients with COPD in order to improve lung function and the frequency of severe acute COPD exacerbations(57) can lead to changes in muscles and their function such as reduced effects of insulin, higher susceptibility to muscle fatigue, attenuation in muscle regeneration, dyselectrolytemia and reduction in the contractile reaction time by changes in calcium channel blockers(9,14).

Boyer et al.(33) found similar values of handgrip and pinch strength in smokers, non-smokers and patients with COPD. The authors justify the absence of evidence of reduction in handgrip strength in patients with early-stage COPD by the fact that the evaluation of muscle strength by handgrip strength is controversial as a surrogate of isokinetic dynamometry of lower limbs, in addition to the fact that upper limb muscle strength is more preserved than in the lower limbs(58,59). Possibly, the use of the upper limbs and shoulder girdle in daily PA may reduce the impairment of the upper limbs by

disuse[60]. On the other hand, handgrip strength has been previously shown to be associated with upper and lower body strength, gait speed, PA and the probability of disability[61], besides being a predictor of all-cause mortality in middle-aged and elderly persons[62].

Limitations

Some limitations can be mentioned in this study regarding the methodology of the included studies, which is very variable and do not allow us to make adequate comparisons between them. As an example, differences in the protocols and variables of evaluation of muscle strength and endurance and of PA are noticeable. Furthermore, variable average and range of pack-years of smoking history are observed, in addition to the lack of data, assessment details and comparisons between groups with mild COPD and smokers or between patients with COPD and healthy controls. Furthermore, it should be considered that factors other than exposure to tobacco may predispose individuals to develop COPD, including genetic abnormalities, abnormal lung development and accelerated aging[1], and perhaps these factors could be confounders involved in the controversial results. Therefore, some caution is required when analyzing these results.

APPLICATION TO PRACTICE

In-depth knowledge about the presence of muscle dysfunction in mild COPD allows us to develop therapies in order to treat the dysfunction as early as possible. Furthermore, the presence of muscle dysfunction in any smoker, even those with no diagnosis of COPD, motivates us even more to reinforce and strengthen campaigns in favor of smoking cessation, as well as to develop therapeutic options capable of reversing this harm.

CONCLUSION

Results about muscle dysfunction in smokers are divergent, since some studies have shown worse results in a variety of muscle strength variables in smokers compared with non-smoking controls, whereas others have not. Methodological aspects of the available studies may at least in part explain these contrasting results. Moreover, there is rather preliminary evidence indicating worse muscle dysfunction and lower CSA in patients with mild COPD in comparison to ‘healthy’ (or non-COPD) smokers. Further research is needed to better understand muscle dysfunction in smokers and patients with mild COPD in order to develop strategies for its prevention and treatment, which is frequent in the COPD population and may be associated with smoking, the main agent in the development of COPD.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest. The authors alone are responsible for the content and writing of the paper.

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AUTHORS' CONTRIBUTIONS

JF was responsible for the literature review, conception and design of the study, acquisition of data and writing of the paper. AGN contributed for the literature review, conception and design of the study. FP was responsible for critically advising the study and for intellectual input, as well as for the final correction and approval of the version to be published.

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Figure 1 – PRISMA flow diagram of study selection process.

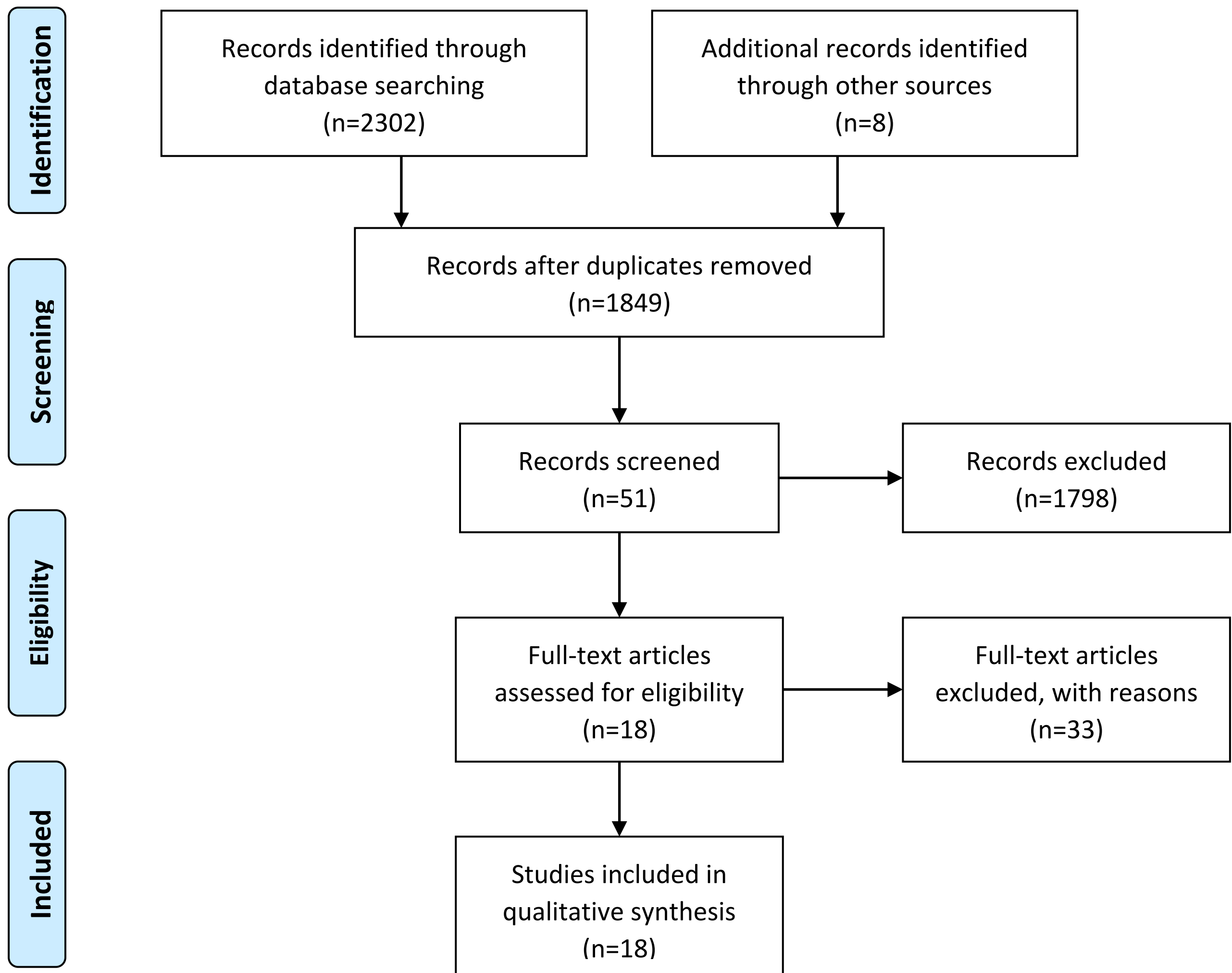

Table 1 - Characteristics of the studies

Authors/year	Groups (n)	Muscle groups evaluated	Variables analyzed	Equipment	Assessment characteristics
Neves et al. 2016[26]	Smokers (20) Non-smokers (20)	Knee extensor muscles	Peak torque of flexion and extension of the knee at a speed of 60°s-1 (Nm) Total work of extension of the knee at a speed of 180°s-1 (J)	Isokinetic dynamometer (BiodexMedical Systems Inc.s, USA)	Isokinetic knee flexor and extensor testing in a concentric–concentric regime by 5 maximum repetitions at a speed of 60°/s and 30 at 180°/s.
Larsson et al. 1984[27]	Non-smokers (6) Smokers (6) Non-smokers (4) Ex- smokers (4)	Knee extensor muscles	Isometric strength (Nm) Dynamic strength (Nm) Dynamic endurance (% of decline in peak torque)	Isokinetic dynamometer (Cybex 11, Lumex Inc., New York)	Maximum isometric and dynamic strength was measured in the left knee at speed of 0, 30, 60, 120, 180 and 300°/s. Measured as the ability to maintain tension output during 50 repeated maximal dynamic contractions performed on the isokinetic dynamometer at a speed of 80 /s. The endurance capacity was calculated as the relative (%) decline in peak torque from the mean of the three initial contractions to the mean of the three final contractions.
Barreiro et al. 2010[21]	Controls (10) Smokers (9) Severe COPD (10)	Knee extensor muscles	Isometric quadriceps MVC (kg)	Isometric dynamometer (Biopac Systems) connected to a digital polygraph (Biopac Systems) Exercise platform (Domyos HGH 050; Decathlon, Lille, France	Patients were seated at an exercise bench with both trunk and thigh fixed on a rigid support. The highest value from three reproducible quadriceps MVC maneuvers (<5% variability between values) of the dominant leg during 3 s was included in the analysis.
Orlander et al. 1979[23]	Smokers (18) Non-smokers (25)	Knee extensor muscles	Maximum isometric strength (Nm) Maximum dynamic strength (Nm) Dynamic endurance (s) Isometric endurance (%)	Isokinetic dynamometer (Cybex 11, Lumex Inc., New York)	Left knee-extensor muscles assessed with subjects seated in an adjustable chair with support for the back, shoulders and hips. The hip angle was fixed at 90° and the lower leg moved the lever of the dynamometer. For dynamic strength, the angular movement of the knee joint was from 100° to 0° at a speed of 60°/s, 120°/s and 180°/s. Two attempts were allowed at each knee angle and velocity. Measures were made in sequence from slow to fast speeds with 30s recovery between each contraction. For isometric strength the position was 30° 60° and 90°. Muscle endurance measured in both legs simultaneously. Maximum isometric strength was taken as the highest force value obtained during a series of 5 contractions. After 3 min of rest, isometric endurance time was recorded, measured as the maximum time during which a

					tension level of 50% of maximum isometric strength could be maintained. Dynamic endurance was measured at a speed of 180°/s as the ability to maintain tension output during 50 maximum contractions and was calculated by determining the relative (%) decline in peak torque from the mean of the 3 initial contractions
Wüst et al. 2008[22]	Male non-smokers (22) Male smokers (19) Female non-smokers (23) Female smokers (21)	Knee extensor muscles	Quadriceps MVC (Nm) Quadriceps MTC (MTC corrected for voluntary activation) (Nm) CSA (cm^2)	Cybex norm dynamometer (Ronkonkoma, New York, USA) Fixed 0.2-T MRI scanner (E-Scan; ESA-OTEBiomedica, Genova, Italy)	Participants undertook a standardized warm-up before the measurements and were given visual feedback and verbal encouragement during the isometric MVC of the quadriceps with the hip joint at 90° of flexion and knee at 60, 70 and 80°. Participants were familiarized with the testing procedures on a separate day. CSA of the quadriceps was measured with MRI at 50% of femur length. Scans were obtained with a T1 weighted, high resolution, gradient echo profile, with the following scanning parameters: time to echo – 16 ms; repetition time – 100 ms; field of view – 330 mm · 254 mm – matrix: 256 · 256, and a slice thickness of 5 mm.
Patel et al. 2016[28]	Never smokers (13) Healthy smokers (13) COPD (61)	Knee extensor muscles	Quadriceps MVC (kg) Quadriceps MVC/BMI	Strain gauge	Participants were assessed seated in an adjustable, straight-backed chair with the dominant lower leg dependent and the knee flexed to 90°. Pelvis was secured by an adjustable belt. Force was measured with a strap looped round the leg just proximal to the malleoli.
Morse et al. 2007[29]	Smokers (9) Non-smokers (10)	Knee extensor muscles	Knee extension torque (Nm) MVC/CSA (Nm cm^{-2}) Quadriceps CSA (cm^2)	Cybex norm dynamometer (Ronkonkoma, New York, NY, USA) Fixed 0.2-T MRI scanner (E-Scan; ESA-OTEBiomedica, Genova, Italy), at50%of femur length	Measurements were performed on the right leg with participants seated with the hip joint at 90º flexion with the hip and shoulders strapped and a knee joint angle at 80º. Participants were familiarized with the testing procedures on a separate session and performed a warm-up. Isometric MVC of the quadriceps was maintained for 4s with 2 min of rest in between each contraction. Visual feedback of the torque signal and verbal encouragement was given to all participants. Scans were obtained with aT1 weighted, high resolution, gradient echo profile, with the following scanning parameters: time to echo – 16 ms; repetition time – 100 ms; field of view – 330 mm · 254 mm – matrix: 256 · 256, and a slice thickness of 5 mm.

Gagnon et al. 2014[30]	COPD GOLD I (37) Healthy smokers (19)	Knee extensor muscles	Mean potentiated quadriceps twitch force obtained at baseline –TwQpot (kg) Quadriceps MVC (kg).	(data not shown)	Subjects positioned in a recumbent chair and the dominant leg was assessed by supramaximal magnetic stimulation of the femoral nerve 3 seconds following an isometric quadriceps MVC. TwQpot was obtained 5 s after a 3 s quadriceps MVC. A set of six potentiated twitches was performed at 100% stimulator output. Each maneuver was separated by 30 s and Verbal encouragements were provided during the maneuver.
Sanchez et al. 2011[31]	Controls (23) Smokers without COPD (18) COPD (55)	Knee extensor, hip extensor, knee flexor and ankle flexor muscles (leg press) Elbow extensor muscle Elbow flexor muscle	1 Repetition maximum (kg) Mid-thigh CSA Mid-arm CSA	Weight training equipment Scanner, Shimadzu SCT-7000 TS, Japan	Subjects performed one-repetition maximum (1RM) test in kg on weight training equipment. They performed a pre-test warm-up of 10 repetitions with a light load and the 1RM test was initiated at a weight near the suspected maximum. A 2 to 3min rest was permitted between repetitions. Mid-thigh cross-sectional area was measured halfway between the pubic symphysis and the femur inferior condyle and MA cross-sectional area between the head of the humerus and the olecranon. Each image was 10 to 20 mm thick
Al-Obaidi et al. 2004[32]	Non-smokers without low back pain (21) Non-smokers with low back pain (20) Smokers without low back pain (18) Smokers with low back pain (17)	Lumbar extensor muscles	Isometric lumbar extensor strength (torque value in ft-lb (1 ft-lb = 1.3558 Nm) at 72°,60°,48°,36°,24°, 12° and 0° Mean isometric lumbar extensor strength	The MedX lumbar extension machine (Ocala, FL) Sensitive load cell	Subjects with stabilized pelvis and a sensitive load cell attached to the movement arm of the MedX. Subjects were encouraged to perform maximally during each isometric contraction at 7 angles of spinal flexion, (72°,60°,48°,36°,24°, 12° and 0°).
Boyer et al. 2015[33]	Non-smokers (101) Smokers without COPD (100) COPD (100)	Palm and fingers flexors	Grip test (kg) Pinch test (kg)	Handgrip dynamometer and pinch gauge (Baseline evaluation Intruments, NY, USA)	Pinch and grip strengths were assessed using a standard handgrip dynamometer and pinch gauge
Shrikrishna et. al 2012[37]	Healthy control (40) COPD (161) GOLD I (38) GOLD II (45) GOLD III (41) GOLD IV (37)	Knee extensor muscles	Isometric quadriceps MVC (kg)	Strain gauge	Subjects seated on a modified chair with pelvis secured by an adjustable belt and their knee fixed at 90º. Force was measured with a strap looped round the leg just proximal to the malleoli and performed at least three sustained isometric MVC of the quadriceps for 1s.
Singer et al. 2012[8]	COPD (828) GOLD I (126) GOLD II (362) GOLD III (233) GOLD IV (107) Healthy controls (302)	Knee extensor muscles Hip flexor muscles	Quadriceps force (lbs of force) Quadriceps force (% predicted from values generated from healthy controls) Hip flexors force (lbs of force) Hip flexors (%predicted from values generated from healthy controls)	Hand-held dynamometer (MicroFet2 dynamometer; Saemmons Preston, Bolingbrook, IL)	Peak force values recorded for 3 trials isometric contraction on each side in alternating fashion.
Tanimura et al. 2015[38]	COPD GOLD I (23) COPD GOLD II (61)	Erector spine muscle Pectoralis muscles	Erector spine muscle CSA Pectoralis muscles CSA	Chest CT scans (Aquilion 64;	Chest CT scans were obtained with the use of 0.5-mm collimation, a

	COPD GOLD III (34) COPD GOLD IV (12) Smoking control (20)			Toshiba, Tokyo, Japan)	scan time of 500 milliseconds, 120 kilovolts peak
Kok et al. 2011[19]	Smokers 21y (68) non-smokers 21y (113) Smokers 27y (53) Non-smokers 27y (88) Smokers 32y (84) Non-smokers 32y (342) Smokers 36y (93) Non-smokers 36y (280)	Knee extensor muscles	Peak torque of the knee f lexor and extensor Strength index: Peak torque adjusted by weight (N/s/kg) Knee muscle strength (KMS): the highest peak torque of the flexion and extension of both legs and dividing this score by 4	CYBEX II (Cybex, Hanley, USA) and CYBEX Norm (Cybex)	Isokinetic strength of the knee extensor and flexor muscles performed at 300°/s. First leg was chosen randomly.
Lee et al. 2017[34]	Male never smokers (136) Male ex-smokers (328) Male current smokers (133)	Palm and fingers flexors muscles	Handgrip strength (kg)	Digital grip strength dynamometer (TKK 5401; Takei Scientific Instruments Co., Ltd., Tokyo, Japan)	HGS measured 3 times in each hand. Subjects seated and holding the dynamometer with the second finger nodes of the working hand at 90° and were instructed to the handle and to squeeze as firmly as they could with 60-second rest period after each measure. The highest value of 6 measures was used for analysis.
Saito et al. 2012[36]	Smokers 20-29y (379) Non-smokers 20-29y (477) Smokers 30-39y (437) Non-smokers 30-39y (591) Smokers 40-49y (375) Non-smokers 40-49y (526) Smokers 50-59y (292) Non-smokers 50-59y (598) Smokers 60-69y (113) Non-smokers 60-69y (429) Smokers 70-79y (22) Non-smokers 70-79y (110)	Grip strength muscles Knee extensor msucles	Grip strength (kg) Isometric leg strength (kg)	Dynamometer (THP-10, Sakai, Tokyo, Japan for grip strength and COMBIT CB-1, Minato, Osaka, Japan for leg strength)	Muscle strength measurements were recorded in 2 trials; the strongest performance was the one used for analysis. Isometric leg strength was measured by seating the subject in a chair, instructing him or her to grasp the armrests to fix the body position, and instructing the subject to extend his leg to 60° with a dynamometer attached to the ankle joint by a strap.
Kovarik et al. 2017[35]	COPD GOLD I (7) Control (25)	Grip strength muscles	Maximum grip strength (N) Endurance time (s) Area under de curve (endurance time/strength)	Pinch/Grip Analyser (MIE Medical Research Ltd., Leeds, UK) with Clinical Analysis Software (CAS)	Maximum strength assessed on both limbs. Patients were instructed to squeeze the handle as much as possible for 3–5 s. Three repetitions of the test were performed with rest of at least 1 minute. The dominant limb was determined according to the best performance. The results of maximum strength were also corrected for body weight, amount of FFM, and forced vital lung capacity.

MVC: quadriceps maximal voluntary contraction; MTC: maximal torque capacity; CSA: cross-sectional area; y: years; MRI: magnetic resonance imaging; BMI: body mass index; TwQpot: Twich quadriceps potentiated.

Table 2 – Comparison between groups in the included studies.

Authors/year	Results (p value)

Neves et al. 2016[26]	**Control vs. Smokers** Total work of extension of the knee at a speed of 180°s-1 (J): 2718±389.2 vs 2341±413.3 (P=0.010) Peak torque of flexion of the knee at a speed of 60°s-1 (N.m): 113.6±25.15 vs. 101.7±28.15 (P=0.189) Peak torque of extension of the knee at a speed of 60°s-1 (N.m): 215.9±24.08 vs 199.3±31.83 (P=0.087)
Larsson et al. 1984[27]	**Smokers vs non-smokers** Isometric strength (Nm): 187±19 vs 174±14 (P>0.05) Dynamic strength at 30°/s; 60°/s; 120°/s; 180°/s; 300°/s (Nm): 173±17 vs 170±15; 164±15 vs 155±16; 138±12 vs 138±12; 118±10 vs 121±12; 93±11 vs 93±9 (P>0.05) Dynamic endurance (% of decline in peak torque): 54±4 vs 48±6 (P>0.05) **Smokers vs ex-smokers** Isometric strength (Nm): 187±32 vs 182±19 (P>0.05) Dynamic strength at 30°/s; 60°/s; 120°/s; 180°/s; 300°/s (Nm): 178±31 vs 189±21; 166±25 vs 168±19; 131±20 vs 137±18; 116±17 vs 120±8; 88±13 vs 83±10 (P>0.05) Dynamic endurance (% of decline in peak torque): 52±8 vs 49±2 (P>0.05)
Barreiro et al. 2010[21]	**Control vs Healthy smokers** MVC (kg): 38.50±1.7 vs 36.78±1.5 (P<0.05) **Healthy smokers vs COPD** MVC (kg): 36.78±1.5 vs 28.20±1.31 (P<0.001) **Control vs COPD** MVC (kg): 38.50±1.7 vs 28.20±1.31 (P<0.05)
Orlander et al. 1979[23]	**Smokers vs non-smokers** Isometric strength (Nm): 180.9±9.5 vs 216.5±6.6 (P<0.01) Dynamic strength at 60°/s; 120°/s; 180°/s (Nm): 165.9±8.4 vs 194.2±6.0 (P<0.01); 143.0±5.4 vs 162.6±5.1 (P<0.05); 121.7±7.0 vs 131.0±4.2 (P>0.05) Dynamic strength at 60°/s,;120°/s; 180°/s (%):93.0±0.03 vs 90.3±0.02 (P>0.05); 80.9±0.03 vs 75.5±0.02 (P>0.05); 68.5±0.04 vs 60.8±0.01 (P<0.05) Maximum isometric endurance (s): 51.9±4.8 vs 65.2±6.9 (P>0.05) Maximum dynamic endurance (%):50.0±2.9 vs 49.0±5.1 (P>0.05)
Wüst et al. 2008[22]	**Male non-smokers vs. Male smokers:** MVC (Nm): 286±21 vs 280±18 (P>0.05) MTC (Nm): 330±18 vs 300±19 (P>0.05) CSA (cm^2): 72±2 vs 65±3 (P>0.05) VA%: 85.9±3.0 vs 92.0±2.3 (P<0,05) **Female non-smokers vs. Female smokers:** MVC (Nm): 190±12 vs. 204±15 (P>0.05) MTC (Nm): 213±12 vs. 219±15 (P>0.05) ACSA (cm^2): 53±2 vs 52±2 (P>0.05) VA%: 88.1±2.2 vs 90.0±3.3 (P>0.05)
Patel et al. 2016[28]	**Healthy smokers vs. COPD** MVC (kg): 40.1±12 vs. 30.5±10 (P<0,05) MVC/BMI: 1.44±0.4 vs. 1.20±0.4 (P>0.05) **Never smokers vs. Healthy smokers** MVC (kg): 37.9±9 vs. 40.1±12 (P>0,05) MVC/BMI: 1.45±0.3 vs. 1.44±0.4 (P>0.05)
Morse et al. 2007[29]	**Smokers vs non-smokers** MVC (kg): 335±73 vs 351±72 (P>0.05) MVC/CSA (Nm cm^{-2}): 4.5±0.5 vs 4.5±0.9 (P>0.05) CSA (cm^2): 74.9±11.6 vs 78.9±6.7 (P>0.05)
Gagnon et al. 2014[30]	**COPD GOLD I vs control** No diferences in mid-tight CSA, MVC and TwQpot.
Sanchez et al. 2011[31]	**Controls vs Smokers without COPD** 1RM Biceps (kg): 24.6±1.4 vs 22.5±1.8 (P>0.05) 1RM Triceps (kg): 20.1±1.2 vs 17.6±1.6 (P>0.05) 1RM Leg press (kg): 82.9±5.8 vs 79.6±7.3 (P>0.05) Mid-arm CSA (cm^2) :37.8 ± 1.8 vs 34.6 ± 2.0 (P>0.05) Mid-thigh CSA (cm^2): 138.8 ± 4.8 vs 120.0 ± 5.2 (P<0.05)

	Controls vs COPD 1RM Biceps (kg): 24.6±1.4 vs 20.2±0.9 (P>0.05) 1RM Triceps (kg): 20.1±1.2 vs 19.0±0.8 (P>0.05) 1RM Leg press (kg): 82.9±5.8 vs 83.3±3.7 (P>0.05) Mid-arm CSA (cm^2): 37.8 ± 1.8 vs 36.4 ± 1.2 (P>0.05) Mid-thigh CSA (cm^2): 138.8 ± 4.8 vs 124.6 ± 3.2 (P<0.05)
Al-Obaidi et al. 2004[32]	**Non-smokers vs Smokers** Mean isometric lumbar extension at 72° 60° 48° 36° 24° 12° 0° (ft-lb): 410.3 ± 106.8 vs 283.1 ± 68.5; 370.5 ± 92.4 vs 245.7 ± 72.0; 352.8 ± 86.2 vs 251.8 ± 71.0; 346.6 ± 67.8 vs 216.4 ± 67.2; 340.8 ± 68.0 vs 185.2 ± 76.2; 317.5 ± 76.2 vs 184.5 ± 42.3; 295.7 ± 57.0 vs 178.6 ± 71.3 (P>0.05) Mean isometric lumbar extension (ft-lb): 347.7 ± 79.2 vs 220.8 ± 66.9 (P<0.001)
Boyer et al. 2015[33]	**Non-smokers vs Smokers without COPD vs COPD** Pinch test (kg): 7 [5–9] vs 6 [5–8] vs 6 [5–8] (P=0.08) Grip test (kg): 38 [26–48] vs 38 [26–45] vs 36 [27–42] (P=0.39)
Shrikrishna et al. 2012[37]	**Control vs GOLD I** MVC (kg): 34.3±8.8 vs 29.6±7.2 (P<0.0001) USRFCSA (cm^2): 640±136 vs 530±116 (P<0.0001) **GOLD I vs GOLD II vs GOLD III** MVC (kg): 29.6±7.2 vs 27.9±7.3 vs 27.3±8.8 (P>0.05) USRFCSA (cm^2): 530±116 vs 511±135 vs 504±122 vs 509±122 (P>0.05) **GOLD I vs GOLD IV** MVC (kg): 29.6±7.2 vs 25.3±6.8 (P<0.002) USRFCSA (cm^2): 530±116 vs 509±122 (P<0.002)
Singer et al. 2012[8]	**Frequency of subjects with quadriceps strength less than 50%:** GOLD I: 11.1%; GOLD II: 8.3; GOLD III: 10.3%; GOLD IV: 15% (P=0.23)
Tanimura et al. 2015[38]	**COPD GOLD I vs Smoking control** Erector spinae CSA (cm^2): 31.3±7.2 vs. 39.2±7.0 (P<0.01) **COPD vs Smoking control** Erector spinae CSA (cm^2): 25.91±7.41 vs 39.04±10.50 (P<0.0001) Pectoralis major CSA (cm^2): 29.77±6.97 vs 39.20±6.98 (P<0.0001)
Lee et al. 2017[34]	**Male never smoker vs male ex-smoker vs male current smoker (not considered aged):** Handgrip strength (kg): 37.6±6.9 vs 38.2±6.9 vs 39.6±7.2 kg (P=0.002) **Male never smoker vs male ex-smoker vs male current smoker (<65 years):** Handgrip strength (kg): 41.5±7.1 vs 42.4±6.4 vs 42.3±6.7 (P=0.566) **Male never smoker vs male ex-smoker vs male current smoker (≥65 years):** Handgrip strength (kg): 35.3±5.7 vs 36.0±6.0 vs 35.3±5.4 (P=0.388)
Saito et al. 2012[36]	**Current smokers vs Nonsmokers (20-29 years):** Right grip strength (kg): 47.3±7.7 vs 46.4±7.6 (P=0.10) Left grip strength (kg): 44.8±7.5 vs 43.8±7.3 (P= 0.05) Leg strength (kg): 71.6±16.3 vs 72.7±16.7 (P= 0.33) **Current smokers vs Nonsmokers (30-39 years):** Right grip strength (kg): 46.7±7.2 vs 45.9±7.7 (P=0.11) Left grip strength (kg): 44.6±7.0 vs 43.6±7.3 (P= 0.02) Leg strength (kg): 69.7±16.7 vs 71.1±16.8 (P= 0.17) **Current smokers vs Nonsmokers (40-49 years):** Right grip strength (kg): 45.7±7.4 vs 45.3±7.8 (P= 0.45) Left grip strength (kg): 43.8±6.9 vs 43.5±7.3 (P= 0.44) Leg strength (kg): 68.6±15.3 vs 67.7±16.2 (P= 0.41) **Current smokers vs Nonsmokers (50-59 years):** Right grip strength (kg): 42.1±7.1 vs 42.4±7.5 (P= 0.62) Left grip strength (kg): 40.3±6.7 vs 40.5±7.5 (P=0.82) Leg strength (kg): 60.7±14.8 vs 61.6±14.4 (P= 0.41) **Current smokers vs Nonsmokers (60-69 years):** Right grip strength (kg): 36.8±6.9 vs 37.4±6.8 (P= 0.43) Left grip strength (kg): 36.0±6.5 vs 36.0±6.6 (P= 0.99) Leg strength (kg): 51.4±12.4 vs 53.2±13.0 (P= 0.19) **Current smokers vs Nonsmokers (70-79 years):** Right grip strength (kg): 33.5±7.4 vs 32.3±7.0 (P= 0.45)

	Left grip strength (kg): 31.3±7.3 vs 30.7±6.7 (P= 0.71) Leg strength (kg): 41.3±12.2 vs 41.6±10.5 (P= 0.85) **Heavy current smoker vs Light current smoker* (^{1}adjusted for age; ^{2}adjusted for age, height, body weight, and exercise habits):** Right grip strength (kg): 43.8±8.0 vs 46.2±7.8 (P<0.001; P^1<0.001; P^2=0.004) Left grip strength (kg): 41.9±7.5 vs 44.1±7.5 (P<0.001; P^1<0.001; P^2=0.001) Leg strength (kg): 64.0±16.7 vs 69.5±16.6 <0.001 (P<0.001; P^1<0.001; P^2=0.37)
Kovarik et al. 2017[35]	**Control vs COPD GOLD I:** Maximum grip strength (N): 371±90 vs 375±96 (P>0.05) Endurance time (s): 104 [88-128] vs 104 [94-123] (P>0.05) Area under de curve (endurance time/strength): 18.9 [16.0-4.2] vs 18.5 [15.5-1.8] (P>0.05)

Data reported as mean ± standard deviation or median [interquartile range]. MVC: quadriceps maximal voluntary contraction; MTC: maximal torque capacity; CSA: cross-sectional area; VA: voluntary activation; BMI: body mass index; USRFCSA: ultrasound rectus femoris cross-sectional area; 1RM: one-maximum repetition; MRI: magnetic resonance imaging;; TwQpot : Twich quadriceps potentiated; *Brinkman index (number of cigarette consumed per day multiplied by years of smoking) greater than or equal to 400 was classified as a heavy current smoker and less than 400 was a light current smoker.

Table 3 – Correlations between smoking and loss of strength.

Authors/year	Main Results (p value)
Kok et al. 2011[19]	**Muscle strength vs smoking:**
	Male smokers (100g tobacco a week)
	–0.136 (–0.248 to –0.023) (p=0.018)[a]
	–0.131 (–0.235 to –0.027) (p=0.014)[b]
	–0.116 (–0.232 to 0.000) (p= 0.050)[c]
	–0.193 (–0.306 to –0.080) (p=0.001)[d]
	–0.136 (–0.252 to –0.020) (p=0.022)[e]
	Female smokers (100g tobacco a week)
	-0.169 (–0.305 to –0.032) (p=0.015)[a]
	–0.172 (–0.297 to –0.046) (p=0.007)[b]
	–0.181 (–0.317 to –0.046) (p=0.008)[c]
	–0.187 (–0.309 to –0.065) (p=0.003)[d]
	–0.200 (–0.321 to –0.079) (p=0.001)[e]
Saito et al. 2012	**Current smokers (Brinkman index <400)**[f]
	Right grip strength (kg): 0.983 (0.968, 0.998)[g]
	Left grip strength (kg): 0.987 (0.971, 1.002)[g]
	Leg strength (kg): 0.993 (0.985, 1.000)[g]
	Leg strength/body weight: 0.609 (0.360, 1.031)[g]
	Nonsmokers[f]
	Right grip strength (kg): 0.974 (0.963, 0.986)[g]
	Left grip strength (kg): 0.971 (0.960, 0.983)[g]
	Leg strength (kg): 0.997 (0.991, 1.003)[g]
	Leg strength/body weight: 0.819 (0.548, 1.224)[g]

[a]Crude model; [b]Adjusted for cardiopulmonar fitness and physical activity; [c]Adjusted for vitamin C and E intake and alcohol; [d]Adjusted for body weight and percentage of body weight fat; [e]Adjusted for all possible covariates; [f]adjusting for age, height, body weight, and exercise habits; [g]data expressed as odds ratio (95% confidence interval).

4 CONSIDERAÇÕES FINAIS

Os resultados sobre a disfunção muscular em tabagistas são divergentes, visto que alguns estudos mostram piores resultados em diversas variáveis de força muscular em tabagistas em comparação com não-tabagistas, enquanto outros estudos não encontraram essa diferença. Alguns aspectos metodológicos dos estudos disponíveis devem ser levados em consideração, pois podem explicar, em parte, os resultados contrastantes entre eles.

Por outro lado, essa revisão traz resultados de evidências preliminares indicando uma disfunção muscular mais acentuada e menor área de secção transversa muscular em pacientes com DPOC leve em comparação com indivíduos tabagistas aparentemente saudáveis (não-DPOC)

As indefinições apontadas nesta revisão indicam que a literatura científica desse tema ainda deve avançar consideravelmente para melhor entendimento da disfunção muscular em tabagistas e pacientes com DPOC leve. Além da definição do verdadeiro grau de disfunção muscular nesses indivíduos, esse avanço deve também ter o objetivo de desenvolver estratégias para sua prevenção e tratamento, devido à sua prevalência na população com DPOC e por sua eventual associação com o tabagismo, o principal agente no desenvolvimento da DPOC.

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ANEXOS

ANEXO A

NORMAS PARA SUBMISSÃO NO PERIÓDICO *JOURNAL OF CARDIOPULMONAR REHABILITATION AND PREVENTION*

ETHICAL/LEGAL CONSIDERATIONS

A submitted manuscript must be an original contribution not previously published (except as an abstract or a preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Wolters Kluwer Health (WKH). Each person listed as an author is expected to have significantly participated in the study. Although the editors, reviewers, and publisher evaluate the manuscript, the validity of the published manuscripts is solely the responsibility of the authors.

REQUIREMENTS FOR ALL CATEGORIES OF SUBMISSIONS

- Manuscripts must conform to "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" (*N Engl J Med*. 1997;336:309-315).
- Manuscripts may not contain previously published material or material that is under consideration for publication elsewhere.
- If an author has other work that is in preparation, has been previously submitted or published, or is in press and potentially overlaps the submitted manuscript, that work must be submitted as an attachment with the current submission.
- The cover letter accompanying the manuscript must include the following statement: "All authors have read and approved submission of the manuscript and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language except as an abstract."
- The manuscript text should be submitted as a Microsoft Word file (not as a PDF) using Times New Roman font, 12-point. The entire manuscript and references should be double-spaced. Page numbers must be on each text page, appearing in the upper right header. Do not use bold, italics, or underline for any terms or phrases in the abstract or manuscript, as these should only be used for headings.
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- All sources of support and potential conflicts of interest must be stated in the submission letter and the title page.
- Word count for the text-only portion of the manuscript should be stated in the title page.

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Information on the title page should include the following in this order:

- Type of submission: Original Investigation, Scientific Review, Brief Report, or Case Report at the top left of the page
- Full title of the article and (in the header for each page); capitalize the first letter of each major word in the title
- Full name, academic degree, hospital or university affiliation, city, state and country (if not the United States) of each author. If an author's present affiliation is different from that under which the work was done, both should be given.
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- The name, full mailing address, phone, fax, and e-mail of the corresponding author
- Three to five key words
- All sources of support must be provided, including disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and any other funding agencies. For example, Source of Funding: Author B is currently receiving a grant (#12345) from Organization Y. Authors C, D, E have no disclosures of funding.
- Any potential conflicts of interest must be stated. These include financial, consultant, institutional, and other relationships that might lead to bias or a conflict of interest. If there is no conflicts of interest, this should also be explicitly stated as either, "All authors declare no conflicts of interest." or "Drs. A and B declare no conflicts of interest.". All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included under the heading "Conflicts of Interest". For example: Conflicts of Interest and Source of Funding: Author A has received honoraria from Company Z. Author B is currently receiving a grant (#12345) from Organization Y, and is on the speaker's bureau for Organization X—the CME organizers for Company A. Authors C, D, and E declare no conflicts of interest.
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ABSTRACTS

All submissions should include **two abstracts**: a Structured Abstract (≤250 words) and a Condensed Abstract (≤50 words; for use in the Table of Contents). The structured abstract must use the following four headings (except for Review articles and Case Reports), labeled as Purpose, Methods, Results, and Conclusions. They should briefly describe, respectively, the rationale for the study, how the study was conducted, salient results, and what the authors conclude from the findings. The Condensed Abstract does not use any subheadings.

SCIENTIFIC REVIEW

Scientific Reviews must be limited to no more than 4000 words and no more than 75 references. Reviews must follow this outline: 1) Title page; 2) Structured Abstract and Condensed Abstract; 3) Introduction, ending with a clear statement of purpose; 4) Review of Relevant Literature, as appropriate to article; 5) Discussion; 6) Application to Practice; 7) Summary; 8) References; 9) Figure Legends; 10) Tables; and 11) Figures. The word “Review” should appear in the title (eg, “A Systematic Review” or “A Review”).

REFERENCES

References should be listed in the order in which they appear in the article using superscripts. Journal references should include authors’ surnames followed by initials (without punctuation), title of article, name of journal in italics as abbreviated in *Index Medicus* (if not included in *Index Medicus*, the journal name should be spelled out), year of publication, volume number, and inclusive page numbers. If there are six or fewer authors, all authors should be listed. If there are seven or more authors, the first three authors followed et al is used. References should be formatted as shown in the American Medical Association Manual of Style, 10th edition (https://www.lib.jmu.edu/citation/amaguide.pdf). See examples below.

Authors are responsible for the completeness and accuracy of all references. No more than two references in a foreign (non-English) language may be used. Personal communications and unpublished data should be included within the text of the manuscript or as footnotes, not as references.

Reference Examples

Six or fewer authors:

Jones NL, Schneider PS, Kaminsky LA, Riggin K and Taylor AM. An assessment of the total amount of physical activity of patients participating in a phase III cardiac rehabilitation program. *J Cardiopulm Rehabil Prev*. 2007;27:81-85.

Seven or more authors:

Hamm LF, Sanderson BK, Ades PA, et al. Core competencies for cardiac rehabilitation/secondary prevention professionals: 2010 update: Position statement of

the American Association of Cardiovascular and Pulmonary Rehabilitation. *J Cardiopulm Rehabil Prev*. 2011;31:2-10.

Journal article online:

Williams PA, Franklin BA. Reduced Incidence of Cardiac Arrhythmias in Walkers and Runners. *PLoS One*. 2013;8(6):e65302. doi: 10.1371/journal.pone.0065302.

Entire Book

Myers JN. *Essentials of Cardiopulmonary Exercise Testing*. Champaign, IL: Human Kinetics; 1996.

Book Chapter

Welk GW. Use of accelerometry-based activity monitors to assess physical activity. In: *Physical Activity Assessments for Health-Related Research*. Welk GW. ed. Champaign, IL: Human Kinetics: 2002:125-142.

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FIGURES AND TABLES

Figures/Digital Artwork

Standard figures of graphs (eg, line, bar) should be created in MS Office program, Send the native (DOC, PPT, XLS) file.

Creating Digital Artwork Guidelines

- **Important:** All figures must meet the requirements for Digital Artwork: http://links.lww.com/ES/A42
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.
- Artwork should be saved as TIFF, EPS, or MS Office (DOC, PPT, XLS) files. High resolution PDF files are also acceptable.
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs, and other halftone images must be saved at a resolution of at least 300 dpi.
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- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed in the text.
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The journal accepts for publication color figures that will enhance an article. Authors who submit color figures will receive an estimate of the cost for color reproduction. If they decide not to pay for color reproduction, they can request that the figures be converted to black and white at no charge. Figures included in Supplemental Digital Content (SDC) may be in color at no additional expense.

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Create tables using the table creating and editing feature of the word processing software (ie, Microsoft Word). Do not use Excel or comparable spreadsheet programs. Cite tables consecutively in the text and number them in that order.

Include the table title, appropriate column heads, and explanatory legends (including definitions of any abbreviations used as a footnote to the table). Each table should be self-explanatory and should supplement, rather than duplicate, the material in the text.

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