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Treinamento Muscular Inspiratório Melhora a Força Muscular Respiratória e Capacidade Funcional em Pacientes com Insuficiência Renal Crônica em Hemodiálise

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Orientador: Prof. Dr. Rodrigo Della Méa Plentz

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RESUMO

A fraqueza muscular respiratória em pacientes com insuficiência renal crônica (IRC) está associada à redução da capacidade funcional e influencia diversos sistemas desses pacientes. O treinamento muscular inspiratório (TMI) surge como uma opção de tratamento que pode promover efeitos positivos nos aspectos respiratório, funcional e inflamatório. **Objetivo**: Revisar sistematicamente os efeitos do TMI sobre a força muscular respiratória, capacidade funcional, função pulmonar, qualidade de vida, função endotelial e estresse oxidativo de pacientes com IRC em hemodiálise (HD). **Metodologia**: revisão sistemática de ensaios clínicos randomizados (ECRs) conduzida de acordo com a recomendação PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) e seguindo as recomendações propostas pela Colaboração Cochrane. Serão utilizadas as bases de dados MEDLINE (via PubMed), Embase, Scientific Electronic Library Online (Scielo), Cochrane Central Register of Controlled Trials e Physiotherapy Evidence Database (PEDro) para busca dos artigos potencialmente relevantes publicados. Serão selecionados estudos que avaliaram o efeito do IMT na força muscular respiratória, capacidade funcional, função pulmonar, função endotelial, qualidade de vida ou estresse oxidativo de pacientes adultos com IRC em HD em comparação com o controle, TMI placebo ou fisioterapia convencional foram selecionados. Dois revisores independentes extrairão os dados usando um formulário de extração de dados predefinido. O risco de viés será avaliado com RoB 2.0 e e a qualidade da evidência pelo sistema Grading of Recommendatons Assessment, Development and Evaluaton (GRADE). **Resultados:** Oito estudos foram incluídos, totalizando 246 pacientes. A metanálise mostrou que o TMI aumentou a pressão máxima inspiratória (PImáx) em 22,53cmH_2O, a pressão máxima expiratória (PEmáx) em 19,54cmH_2O, a distância percorrida no teste de caminhada de 6 minutos (TC6M) 77,63m. Não foram observadas alterações na função pulmonar e qualidade de vida. Não foi possível analisar quantitativamente os dados de função endotelial e stress oxidativo. **Conclusão:** O TMI melhora a PImáx, PEmáx e a capacidade funcional de pacientes com IRC em HD, porém a qualidade de evidência varia de baixa a muito baixa. O TMI não demonstrou resultados significativos para função pulmonar e

qualidade de vida. Os efeitos sobre a função endotelial e capacidade oxidativa permanecem incertos.

Palavras-chave: Insuficiência Renal Crônica, Diálise Renal, Força Muscular.

ABSTRACT

Respiratory muscle weakness in patients with chronic renal failure (CRF) is associated with reduced functional capacity and influences several systems in these patients. Inspiratory muscle training (IMT) appears as a treatment option that can promote positive effects in the respiratory, functional and inflammatory aspects. Objective: To systematically review the effects of TMI on respiratory muscle strength, functional capacity, lung function, quality of life, endothelial function and oxidative stress in patients with CKD undergoing hemodialysis (HD). **Methodology**: systematic review of randomized controlled trials (RCTs) conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyzes) recommendation and following the recommendations proposed by the Cochrane Collaboration. MEDLINE (via PubMed), Embase, Scientific Electronic Library Online (Scielo), Cochrane Central Register of Controlled Trials and Physiotherapy Evidence Database (PEDro) will be used to search for potentially relevant published articles. Studies evaluating the effect of IMT on respiratory muscle strength, functional capacity, lung function, endothelial function, quality of life or oxidative stress in adult patients with CKD on HD in comparison with control, placebo TMI or conventional physical therapy will be selected. Two independent reviewers will extract the data using a predefined data extraction form. The risk of bias will be assessed with RoB 2.0 and the quality of evidence will be assessed by the Classification of Assessment, Development and Assessment of Recommendations (GRADE) system. **Results**: Eight studies were included, totaling 246 patients. The meta-analysis showed that IMT increased the maximum inspiratory pressure (MIP) by 22.53cmH2O, the maximum expiratory pressure (MEP) by 19.54cmH2O, the distance covered in the 6-minute walk test (6MWT) by 77.63m. Changes in lung function and quality of life were not observed. It

was not possible to quantitatively analyze data on endothelial function and oxidative stress. **Conclusion**: IMT improves MIP, MEP and functional capacity of patients with CKD on HD, but the quality of evidence varies from low to very low. IMT did not demonstrate significant results for lung function and quality of life. Effects on endothelial function and oxidative capacity remain uncertain. A evidência para esses benefícios pode ser influenciada por algumas fontes de viés.

Keywords: Chronic Renal Failure; Renal Dialysis; Muscle Strength.

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IRC	Insuficiência Renal Crônica
QV	Qualidade de vida

HD	Hemodiálise
TMI	Treinamento Muscular Inspiratório
TC6M	Teste de caminhada de 6 minutos
ISWT	Teste de caminhada incremental
KDQOL-SF	Kidney Disease Quality of Life – Short Form
SF-36	Short Form Health Survey 36
Pimáx	Pressão Máxima Inspiratória
PEmáx	Pressão Máxima Expiratória
VEF_1	Volume Expiratório Forçado no Primeiro Segundo
CVF	Capacidade Vital Forçada
ICAM-1	Intercellular Adhesion Molecule 1
VCAM-1	Vascular Cell Adhesion Protein 1
GRADE	Grading of Recommendations Assessment, Development, and Evaluation System
IC	Insuficiência Cardíaca
PCR	Proteína C Reativa
STNFR2	Receptor 2 Do Fator De Necrose Tumoral Solúvel

SUMÁRIO

1 REVISÃO DE LITERATURA

As referências que embasam o referencial teórico foram encontradas nas bases de dados Pubmed, Medline, Embase, Scielo e pela busca manual das referências dos estudos encontrados. Os principais termos utilizados para a pesquisa foram: *Chronic Kidney Disease, Renal Insufficiency, Renal dialysis, Hemodialysis, Muscle strength, Muscle weakness* e seus respectivos similares na língua portuguesa.

1.1 INSUFICIÊNCIA RENAL CRÔNICA: DEFINIÇÃO, EPIDEMIOLOGIA CLASSIFICAÇÃO, MANIFESTAÇÕES SISTÊMICAS E INFLAMATÓRIAS

A doença renal é considerada um importante problema de saúde pública que consiste em lesão renal e perda progressiva e irreversível da função dos rins, seja ela glomerular, tubular ou endócrina. Em sua fase mais avançada, quando o paciente está no estágio considerado crônico da doença, os rins não conseguem manter a normalidade do meio interno do paciente, tornando-se necessário realizar terapias renais substitutivas, como as diálises ou transplante renal (JUNIOR, 2004).

No Brasil, mais de 50 mil pacientes encontram-se realizando hemodiálise gerando um gasto médio com o programa de diálise e transplante renal de 1,4 bilhões de reais ao ano (SBN. Censo da Sociedade Brasileira de Nefrologia, 2013). Mundialmente, 2618 milhões de pessoas receberam terapias substitutivas em 2010, sendo que 2050 milhões desses pacientes realizaram diálise, o que corresponde a 78% dessa população. Estima-se que no ano de 2030, 5439 milhões de pacientes com insuficiência renal crônica (IRC) necessitarão de terapias substitutivas, com maior crescimento em países de baixa renda (LIYANAGE *et al*., 2015).

A diálise pode ser dividida em dois tipos, a hemodiálise e a diálise peritoneal, que se diferenciam pelo local onde ocorre a limpeza e filtração do sangue. Na hemodiálise, ocorre remoção do excesso de líquidos e de substâncias tóxicas do sangue por meio da máquina de hemodiálise e um dialisador. Já na diálise peritoneal esse processo ocorre dentro do corpo do paciente com auxílio da sua membrana peritoneal. Nesse procedimento, o líquido de diálise é colocado na cavidade abdominal e drenado por um cateter (SBN, 2004; KDOQI, 2006).

De acordo com a Kidney Disease Outcome Quality Initiative (KDOQI) (2006) e as Diretrizes Brasileiras de IRC (JUNIOR, 2004), a avaliação da taxa de filtração glomerular é a melhor medida de avaliação e classificação da funcionalidade dos rins em indivíduos normais ou em pacientes com doença renal. Essa classificação pode ser divida em seis estágios funcionais que variam de acordo com a função renal do paciente. Na primeira fase, incluem-se pessoas que não desenvolveram a IRC, mas que fazem parte dos grupos de risco, como hipertensos, diabéticos e que possuem parentesco com IRC. Já na segunda fase encaixam-se pessoas que já possuem lesão renal, porém com filtração glomerular preservada (acima de 90 ml/min/1,73m^2). A terceira, quarta e quinta fases compõem respectivamente a insuficiência renal leve, insuficiência renal moderada e insuficiência renal grave. Por último, a sexta fase compreende a insuficiência renal crônica.

Na insuficiência renal leve, ocorre o início da perda de função dos rins, onde os níveis de ureia e creatinina plasmáticos ainda são normais e os rins conseguem manter razoável controle do meio interno com ritmo de filtração glomerular entre 60 e 89 ml/min/1,73m^2. Não há sinais ou sintomas clínicos importantes de insuficiência renal. No estágio moderado, a avaliação laboratorial simples normalmente já demonstra níveis elevados de ureia e de creatinina plasmáticos, com faixa de ritmo de filtração glomerular compreendido entre 30 e 59 ml/min/1,73m^2. Nessa fase, o paciente já apresenta de forma discreta alguns sinais e sintomas da uremia (National Kidney Foundation, 2002; JUNIOR, 2004).

Na insuficiência renal grave, o ritmo de filtração glomerular fica entre 15 a 29 ml/min/1,73m^2 e o paciente já apresenta sinais e sintomas marcados de uremia, como a anemia, a hipertensão arterial, o edema, a fraqueza, o mal-estar e os sintomas digestivos. Na última fase, a insuficiência renal crônica corresponde à faixa de função renal na qual os rins perderam o controle do meio interno com ritmo de filtração glomerular inferior a 15 ml/min/1,73m^2. Nesse estágio, o paciente encontra-se intensamente sintomático e suas opções terapêuticas são os métodos de depuração artificial do sangue (diálise peritoneal ou hemodiálise) ou o transplante renal (National Kidney Foundation, 2002; JUNIOR, 2004).

Segundo a National Kidney Foundation (NKF), com a progressão da doença o

acúmulo de resíduos no sangue pode levar ao desenvolvimento de complicações como hipertensão arterial, anemia, distúrbios no metabolismo mineral ósseo, desnutrição, além de doenças cardiovasculares. Além disso, o declínio da função renal tem sido associado a um pior desempenho físico e maior fragilidade independente da idade do paciente, sexo, raça, índice de massa corporal (IMC) ou comorbidades. Essa fragilidade envolve características como velocidade lenta na marcha, fraqueza muscular, baixo nível de atividade física, cansaço e perda de peso não intencional (REESE *et al*., 2013).

Atualmente, tem-se considerado o papel da imunorregulação da inflamação subclínica na progressão das doenças crônico-degenerativas (GERARD, ROLLINS, 2001; SULIMAN, STENVINKEL, 2008). Nesse contexto, existem evidências de ativação do sistema imune em estágios precoces e tardios da IRC, controlando ou exacerbando seu estado e, por fim, tornando-se um fator preditor independente de mortalidade (SULIMAN, STENVINKEL, 2008; STENVINKEL *et al.*, 2005, TASHIRO *et al.*, 2002, PECOITS-FILHO *et al.,* 2002, ZIMMERMANN *et al.,* 1999, NASCIMENTO *et al.,* 2002). A inflamação aumenta o risco cardiovascular e a mortalidade dos pacientes com IRC terminal (ZIMMERMANN *et al.,* 1999; NASCIMENTO *et al.*, 2002), pois se sabe que os fatores de risco tradicionais para a doença cardiovascular tais como hipertensão arterial sistêmica (HAS), *diabetes melittus* (DM), dislipidemia e obesidade não seriam suficientes para elevar de tal forma a incidência de complicações cardiovasculares nos pacientes com IRC terminal (CHEUNG *et al.,* 2000). Sendo assim, o processo inflamatório, associado aos efeitos do estresse oxidativo, da resistência à insulina e da disfunção endotelial são considerados fatores de risco para doença cardiovascular nos pacientes com IRC (CHEUNG *et al.,* 2010).

A via final comum da IRC é caracterizada pela progressiva fibrose glomerular e/ou túbulo-intersticial, lesão capilar peritubular por hipóxia e perda de funcionamento dos néfrons por esclerose glomerular e atrofia tubular, independentemente do mecanismo primário que desencadeou a lesão renal (EDDY *et al.* 2005). Nesse processo fisiopatológico de progressão da lesão renal, tem sido cada vez mais detectada a participação dos mecanismos inflamatórios (RUIZ-ORTEGA *et al.,* 2001). A deterioração da função renal tem sido associada ao aumento dos níveis séricos de

proteína C reativa, de citocinas e dos receptores solúveis para estas citocinas nos diferentes estágios da IRC (STREETZ *et al*., 2001).

As citocinas, ao interagirem com seus receptores localizados na membrana celular, regulem a transcrição de inúmeros genes e determinam modificações do comportamento das células presentes no tecido, inclusive no renal (COUSER *et al*., 1998). Dentre as citocinas pró-inflamatórias que têm sido associadas à fisiopatologia da doença renal destacam-se a interleucina-1 (IL-1), interleucina-6 (IL-6) e o fator de necrose tumoral-alfa (TNF-alfa) (STREETZ *et al*., 2001).

O TNF-alfa é uma citocina pró-inflamatória, cuja produção é estimulada pela angiotensina II e associa-se à fibrose intersticial pela diferenciação de miofibroblastos. Em modelo pré-clínico, tanto a deficiência genética de TNF-alfa quanto a sua inibição farmacológica atenuaram o desenvolvimento das lesões glomerulares (VIANNA *et al*., 2011). Ele tem sido considerado um regulador da cascata de citocinas que fornece uma forma rápida de defesa do hospedeiro contra a infecção, mas em excesso pode causar perda de massa muscular (FRIEDRICH *et al*., 2015). O TNF-alfa é altamente multifuncional com efeitos sobre o metabolismo de lipídios, da coagulação, da resistência à insulina, e disfunção endotelial (STENVINKEL *et al*., 2005).

Já a IL-10 é um produto das células imunoativas, principalmente os monócitos e linfócitos, que tem sido considerada como uma das citocinas anti-inflamatórias de imunorregulação mais importantes. A liberação de IL-10 sempre segue a de fatores pró-inflamatórios, com uma latência de algumas horas, auxiliando para que uma resposta inflamatória seja regulada depois de algum tempo (STENVINKEL *et al*., 2005).

A IRC está associada a uma resistência ao hormônio anabólico IGF-1 (WANG *et al*., 2006) que juntamente com os altos níveis circulantes de marcadores inflamatórios como TNF-alfa são uma das causas mais importantes do catabolismo proteico aumentado e perda de massa muscular esquelética nesses pacientes (SOUZA *et al.,* 2015). O IGF-1 é predominantemente produzido pelo fígado, porém estudos recentes apontam fortemente que os macrófagos são a principal fonte extra-hepática de IGF-1 (GOW *et al*., 2010). Os macrófagos M1 são os responsáveis pela degradação e são ativados por citocinas pró-inflamatórias e os M2 tem a função restauradora pela produção de citocinas anti-inflamatórias, como o IL-10 (MOUNIER *et al*., 2013).

O hormônio do crescimento (GH), o IGF-1 e a insulina são fatores anabólicos potentes que promovem o ganho de massa muscular. O GH é o principal promotor do crescimento em crianças e exerce ações anabólicas também em adultos, mediadas pelo IGF-1, como síntese de proteínas e aumento da gliconeogênese. O eixo GH/IGF-1 é controlado por uma variedade de fatores, tais como sexo, idade, hormônio grelina, exercício, sono e a massa de gordura (STENVINKEL *et al*., 2015). Para o músculo esquelético, o IGF-1 coordena fatores de crescimento adicionais para promover a proliferação de mioblastos, diferenciação e a formação da fibra durante o crescimento normal, bem como durante a regeneração após a lesão. Estas ações podem resultar em hipertrofia muscular, e este aumento na massa muscular melhora a capacidade funcional do músculo esquelético (PHILIPPOU, BARTON 2014).

Em pacientes com IRC, os níveis de IGF-1 parecem estar diminuídos (HU *et al*., 2015), o que pode prejudicar a manutenção do metabolismo das proteínas e provocar a hipotrofia muscular (STENVINKEL *et al*., 2015). Além disso, a avaliação desse marcador somado a análise das citocinas pró e anti-inflamatória nessa população podem ser de extrema importância para compreender as repercussões da IRC sobre a função muscular periférica.

1.2 REPERCUSSÕES DA IRC NA FUNÇÃO MUSCULAR ESQUELÉTICA E QUALIDADE DE VIDA

A perda de massa e fraqueza muscular é comum em pacientes com IRC (WORKENEH, MITCH, 2010). Recentemente tem-se utilizado o termo sarcopenia urêmica (FAHAL, 2014) ou disfunção muscular urêmica (SOUZA *et al*., 2015) para descrever o processo de perda de massa e força muscular progressiva e cumulativa na IRC, que ocorre desde os seus estágios iniciais (FAHAL, 2014).

A sarcopenia urêmica é multifatorial e está associada de forma inversamente proporcional à idade e função renal desses pacientes (FAHAL, 2014; SOUZA *et al*., 2015). Existem dois principais fatores para que essas alterações na função muscular ocorram nessa população: o aumento da degradação de proteína muscular e a diminuição de síntese proteica (STENVINKEL *et al*., 2015).

O aumento do catabolismo proteico muscular é responsável pelo aumento de

degradação da proteína muscular. O catabolismo excessivo é influenciado pela disfunção metabólica e renal, além de mecanismos adicionais, como a ativação de vias de danos endoteliais, a inflamação, acidose metabólica, alteração intracelular do IGF-1 e sinalização de insulina (BONANNI *et al*., 2011). Estudos com modelos animais de IRC indicam que inadequadas sinalizações intracelulares estimulam o catabolismo proteico muscular gerando degradação das proteínas musculares (WORKENEH, MITCH, 2010). Além disso, como agravante, pacientes com IRC possuem o sistema antioxidante deficiente causando lesões de células e tecidos. Este desequilíbrio do sistema oxidante/antioxidante possivelmente está relacionado à idade avançada, diabetes, inflamação crônica, septicemia e bio-incompatibilidade das membranas e soluções de diálise (BONANNI *et al*., 2011).

Outros fatores de risco para o aumento da degradação de proteína muscular são as comorbidades presentes nesses pacientes, como insuficiência cardíaca, acidose metabólica e depressão, além de fatores genéticos, aumento da carga de estresse crônico, com elevação plasmática dos níveis de citocinas pró-inflamatórias e o estilo de vida (sedentarismo, obesidade, tabagismo e bebidas alcoólicas) (STENVINKEL *et al*., 2015). Já a diminuição da síntese proteica muscular pode ocorrer devido ao estilo de vida de pacientes com IRC, fatores hormonais (IGF-1, GH e insulina), uso de corticóides e fatores nutricionais como baixa ingestão proteica, de antioxidantes e vitamina D (STENVINKEL *et al*., 2015).

O desequilíbrio entre esses fatores leva à redução de massa e força muscular que causam incapacidades e prejudicam a qualidade de vida desses pacientes (WORKENEH, MITCH, 2010), aumentando o risco de morbidades e mortalidade (STENVINKEL *et al*., 2015). Um denominador comum tanto para a degradação quanto para a diminuição de síntese proteica é o estilo de vida sedentário. Em um estudo com IRC em HD, Johansen *et al*., (2003) observaram que esses pacientes apresentam nível reduzido de atividade física, e que este fator pode induzir à perda de proteínas musculares e hipotrofia muscular, a qual está associada à fraqueza muscular, redução de atividade física e desempenho físico.

Além disso, a redução de força muscular e capacidade de exercício nesses pacientes com IRC pode estar relacionada com alterações bioquímicas e morfológicas

nas fibras musculares. Lewis *et al*., (2012) mostraram que pacientes em hemodiálise apresentavamm redução da atividade de enzimas oxidativas mitocondriais e também da capacidade oxidativa das fibras musculares em vasto lateral. Ainda foi observada uma maior proporção de fibras tipo I juntamente com uma menor percentagem de fibras do tipo II, apontando uma possível compensação para a diminuição global na capacidade oxidativa, visto que a proporção de fibras associadas com a maior capacidade de resistência foi aumentada. Estas alterações podem prejudicar a produção de energia, bem como a entrega do substrato e oxigênio, contribuindo para a intolerância esforço e capacidade de resistência reduzida.

Percebe-se, portanto, que a disfunção muscular presente em pacientes com IRC está intimamente relacionada com fraqueza e fadiga muscular, contribuindo para um estilo de vida sedentário, que afeta tanto a composição muscular quanto a capacidade de exercitar-se, gerando efeitos negativos diretos sobre as atividades físicas de vida diária e qualidade de vida desses pacientes.

1.3 TREINAMENTO MUSCULAR RESPIRATÓRIO

O treinamento específico dos músculos respiratórios pode ser uma alternativa útil para pacientes com IRC, pois o condicionamento e o fortalecimento dos músculos respiratórios podem retardar as complicações da perda de massa muscular (FIGUEIREDO et al., 2012), produzindo benefícios significativos na força muscular respiratória, capacidade funcional, função pulmonar e qualidade de vida (MEDEIROS et al., 2017). Sua realização pode resultar em efeitos como modificação do fenótipo dos músculos respiratórios, aumento da força e resistência dos músculos respiratórios (RAY; PENDERGAST; LUNDGREN, 2010).

Em outras populações, como pacientes com insuficiência cardíaca (IC), existem evidências que o TMI melhora a fraqueza muscular inspiratória, a aptidão cardiorrespiratória e a qualidade de vida, apresentando efeitos positivos na sensação de dispneia em repouso e durante o exercício e no metaborreflexo dos músculos respiratórios (FERNANDEZ-RUBIO et al., 2020). Já em pacientes com doença pulmonar obstrutiva crônica (DPOC), foi observado que o TMI melhorou a força e

resistência muscular inspiratória, a capacidade de exercício, dispneia e a qualidade de vida. Além disso, nos pacientes com fraqueza muscular inspiratória, a adição de TMI a um programa geral de treinamento aumentou a pressão máxima inspiratória e demonstrou uma tendência a melhorar o desempenho funcional durante os exercícios(GOSSELINK et al., 2011). Nesses pacientes, benefícios na resistência muscular inspiratória parece ter relação com aumentos significativos na proporção das fibras do tipo I e no tamanho das fibras do tipo II nos intercostais externos após TMI (ALBA RAMIREZ-SARMIENTO, MAURICIO OROZCO-LEVI, ROSA GU¨ELL, 2002).

O TMI tem sido utilizado também como uma terapia eficaz na prevenção de complicações por hospitalizações prolongadas e na redução das taxas de mortalidade intra-hospitalar (NEPOMUCENO et al., 2017), devido a sua boa tolerância e por ser considerado um treinamento viável e seguro (VORONA et al., 2018).

Nesse contexto no qual se sabe que a fraqueza muscular respiratória está associada à redução da capacidade funcional e influencia diversos sistemas de pacientes com IRC (FIGUEIREDO et al., 2017), o treinamento muscular inspiratório (TMI) surge como uma opção de tratamento que pode promover efeitos positivos nos aspectos respiratório, funcional e inflamatório, sendo uma alternativa de baixo custo e fácil execução nas unidades de HD (FIGUEIREDO PHS, LIMA MMO, COSTA HS, MARTINS JB, FLECHA OD, GONÇALVES PF, ALVES FL, RODRIGUES VGB, MACIEL EHB, MENDONÇA VA, LACERDA ACR, VIEIRA ÉLM, TEIXEIRA AL, DE PAULA F, 2018).

2 OBJETIVOS

2.1 Objetivo Geral

Revisar sistematicamente os efeitos do treinamento muscular inspiratório (TMI) sobre a força muscular respiratória e a capacidade funcional de pacientes com insuficiência renal crônica em hemodiálise.

2.2 Objetivos Secundários

Verificar o efeito do TMI sobre a função pulmonar, qualidade de vida, função endotelial e estresse oxidativo de pacientes com insuficiência renal crônica em hemodiálise.

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4 ARTIGO

Revista enviada: Journal of Physiotherapy

Inspiratory muscle training improves respiratory muscle strength and functional capacity in patients with chronic renal failure on haemodialysis: meta-analysis of randomised clinical trials

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Abstract

Question: Does inspiratory muscle training (IMT) improve respiratory muscle strength, functional capacity, lung function, quality of life, endothelial function, and oxidative stress in patients with chronic renal failure (CKD) on haemodialysis (HD)?

Design: Systematic review and meta-analysis of randomised clinical trials.

Participants: Patients with chronic renal failure CKD on HD.

Intervention: IMT.

Outcome measures: Primary outcomes were: respiratory muscle strength and functional capacity. Secondary outcomes were: lung function, quality of life, endothelial function, and oxidative stress.

Results: Eight studies were included, totalling 246 patients. The meta-analysis revealed that IMT increased the maximum inspiratory pressure (MIP) by 22.53cmH2O, the maximum expiratory pressure (MEP) by 19.54cmH2O, the distance covered in the 6-minute walk test (6MWT) by 77.63m. Changes in lung function and quality of life were not observed. It was not possible to quantitatively analyse data on endothelial function and oxidative stress.

Conclusion: IMT improves MIP, MEP, and functional capacity of patients with CKD on HD, but the quality of evidence varies from low to very low. IMT did not demonstrate significant results for lung function and quality of life. Effects on endothelial function and oxidative capacity remain uncertain.
Registration: PROSPERO CRD42020172137.
Keywords: Chronic Renal Failure, Respiratory Training, Renal Dialysis, Respiratory Muscles, Muscle Strength.

Introduction

Chronic kidney failure (CKF) is a worldwide public health issue that was responsible for the death of more than 16,000 people in Brazil in 2019[1]; it consists of progressive and irreversible lesion and loss of kidney function for a period greater or equal to three months. At a more advanced stage, the accumulation of non-excreted substances can lead to the development of complications, such as alterations in endocrine and metabolic functions, as well as hydroelectrolytic and acid-base disturbances. At this stage, it becomes necessary to perform renal replacement therapies, such as dialysis or renal transplant[2,3].

Because CKF is a systemic disease, the decline in renal function has been associated with impaired muscle, pulmonary, and endothelial function[4]. Changes in peripheral and respiratory musculature are common in patients with CKD since their early stages and are inversely proportional to these patients´ age and their renal function[5,6]. In these patients, there is an imbalance between factors that lead to increased muscle catabolism and decreased protein synthesis, causing a reduction in muscle mass and strength that impair their quality of life (QoL)[7,8].

Respiratory muscle strength, lung function, and functional capacity are lower in patients with CKD on haemodialysis (HD) than in the general population, with muscle strength being the most affected respiratory component in those individuals[4]. Both the pathophysiology of CKF and the effects of HD therapy impair the strength and endurance of the respiratory muscles[9], due to protein breakdown, muscle atrophy of type I and II fibres, as well as impaired oxygen transport, uptake, and consumption[10–12].

In the evolution of renal function deterioration, the participation of inflammatory mechanisms has been detected, such as increased serum levels of C-reactive protein, cytokines, and soluble receptors for these cytokines in different stages of CKD[13]. This inflammatory process associated with the effects of oxidative stress, insulin resistance, and endothelial dysfunction are considered risk factors for cardiovascular disease for these patients[14], increasing their risk of mortality[15,16]. Furthermore, reductions in the activity of mitochondrial oxidative enzymes and in the oxidative capacity of muscle fibres seem to be related to the worsening of muscle strength and exercise capacity in CKD[17,18]. Therefore, evaluating these markers in this population can be of utmost importance to understand the impact of CKD on peripheral and respiratory muscle function.

It is well established that respiratory muscle weakness is associated with reduced functional capacity and influences several systems of patients with CKD[19]. In this context, IMT emerges as a treatment option that can promote positive effects on respiratory, functional, and inflammatory aspects, as well offer a low-cost and easy-to-perform alternative in HD[20] units. In other populations, such as patients with heart failure (HF), there is evidence that IMT improves inspiratory muscle weakness, cardiorespiratory fitness, and quality of life[21]. In addition, IMT has also been used as an effective therapy to prevent complications from prolonged hospitalizations and to reduce in-hospital mortality rates[22], as it is a tolerable, feasible, and safe training.

Notably, the previous systematic review by Medeiros et al (2017)[24] did not include endothelial function and oxidative capacity outcomes. Given the importance of this subject and the growing body of research on this issue in recent years, the research question for this systematic review was: Does IMT improve respiratory muscle strength, functional capacity, lung function, QoL, endothelial function, and oxidative stress of patients with CKD on HD?

Methods

This systematic review was conducted according to the Cochrane Handbook for Systematic Reviews of Interventions[25] and reported according to the Preferred

Reporting Items for Systematic Reviews and Meta-Analysis[26]. The protocol registration is in the Prospective Register of Systematic Reviews under number CRD42020172137.

Identification and selection of studies

Randomized controlled trials (RCTs) that evaluated the effects of IMT with a linear inspiratory loading in adult patients (> 18 years) with CKD on HD for at least 3 months were included. Secondary outcomes were functional capacity, lung function, quality of life, endothelial function, and oxidative stress. Respiratory muscle strength should be assessed by a manovacuometer; functional capacity could be assessed by the 6-minute walk test (6MWT), incremental shuttle walk test (ISWT) or ergospirometry, and pulmonary function should be measured by spirometry. Quality of life should be assessed using the Kidney Disease Quality of Life – Short Form (KDQOL-SF) questionnaire. Endothelial function could be assessed by flow-mediated dilation or blood markers and oxidative stress by pro and antioxidant markers. The comparison group could be controls, placebo, or conventional physical therapy. Animal studies, studies evaluating the acute effect of therapy, and studies with incomplete data (abstracts) were excluded. The inclusion criteria are listed in Box 1.

All citations identified were entered into the reference management software (EndNote X7.7) and duplicates were excluded. The titles and abstracts of all articles identified by the search strategy were independently evaluated by two researchers (AB and NR). Studies that did not meet the eligibility criteria according to titles or abstracts were excluded. All abstracts that did not provide enough information were selected for full-text evaluation. Disagreements regarding the eligibility of the studies were discussed between the two reviewers, and in the event consensus was not reached, disagreements were resolved by a third reviewer (JS).

Databases and research

MEDLINE (via PubMed), Embase, Scientific Electronic Library Online (Scielo), Cochrane Central Register of Controlled Trials and Physiotherapy Evidence Database (PEDro) databases were used to retrieve potentially relevant articles published until December 2021. References included in the identified published articles were used as

an additional source to identify other studies. Search terms included “kidney failure, chronic”, “renal insufficiency, chronic”, “renal dialysis”, “breathing exercises,” and “inspiratory muscle training”. A combination of free and conventional descriptors (MESH, DeCs) was used to search databases related only to population and treatment, aiming at greater sensitivity. No search restrictions were applied regarding the year or language of publication; however, in the selection of articles, only studies published from the year 2000 to the date of the search were selected, as most of the scientific production regarding this intervention has been published in the last 20 years. The descriptors and full search strategies are available on the eAddenda (Appendix 1).

Assessment of characteristics of studies

After reading and selecting the full texts, the same reviewers (AB and NR) independently extracted data from the included studies using a predefined data extraction form. The extracted data included study characteristics and outcomes of interest.

Regarding methodological quality, two reviewers (AB and NR) independently assessed the risk of bias of the included studies. The Cochrane Risk of Bias Tool for Randomized Studies (RoB 2.0)[27] for RCT was used. The domains evaluated were: Randomisation process, Deviations from the intended interventions, Loss results data, Result measurement, and Selection of the reported result. The risk of bias for each domain was classified as “low risk”, “high risk”, or “some concerns”; subsequently, an overall score was given for each outcome assessed. In the event of disagreement, a third reviewer (JS) was asked to resolve the conflict. The overall quality of evidence was assessed using the Grading of Recommendations Assessment, Development, and Evaluation system[28].

Data analysis

Wherever possible, data was grouped using a meta-analytic approach. After data extraction, pooled effect estimates were obtained by comparing the change from baseline to the end of the study for each group. A random effects model, with the DerSimonian and Laird variance estimator was used, and the results were presented as

mean difference with 95% confidence intervals. A value of $p \leq 0.05$ was considered significant. Statistical heterogeneity between studies was assessed using the I2 statistic. To reduce statistical heterogeneity, a sensitivity analysis was performed considering the type of training for the functional capacity outcome. All meta-analyses were performed using R statistical software version 3.5, with meta package version 4.8-1. Studies not included in the meta-analysis were described.

Results

Identification and selection of studies

The electronic search strategy identified a total of 435 studies and one study was found through other sources. Eight studies met the inclusion criteria[9,20,29–34] for this systematic review, gathering data from 246 patients. Seven studies were included in the meta-analysis[9,29–34] because one study[20] had no control group. It was not possible to perform a meta-analysis for the outcomes of endothelial function and oxidative stress, as the studies[20,29,30] that evaluated these variables used different assessment methods and biochemical markers, respectively. Figure 1 shows the study selection flowchart.

Characteristics of studies

The characteristics of the included studies are detailed in table 1.

The equipment used for respiratory muscle training were Threshold® IMT and PowerBreathe®. Training volume was planned through sets (3-5 sets) with fixed number of repetitions (10-30 repetitions) or by training time (1 minute), and in most studies[9,20,29,31,33,34] it was performed three times a week. The most used load was set at 50% of the maximum inspiratory pressure (Pimax) and the training program time ranged from five to 24 weeks.

Risk of bias

The eight RCTs included in this review were assessed using the RoB 2.0 tool and only Medeiros et al (2018)[32] presented “low risk of bias” for all domains assessed. Campos et al (2018)[29] obtained “low risk of bias” in all domains of the tool to assess the

outcomes of endothelial function and oxidative stress, while Dipp et al (2019)[30] reported only for endothelial function. For all other outcomes analysed, two studies[20,30] showed “some concerns” for the overall domain and five other studies [9,29,31,33,34] demonstrated “high risk of bias”. The domain “randomisation process” presented “low risk of bias” for all outcomes of the studies included in this review, with the exception of Pellizzaro et al, (2013)[9], who presented “some concerns”. The domain with the greatest problems was "outcome measure" because three studies[29,31,33] had "high risk of bias" and three[9,20,30] had "some concerns" about the blinding of outcome evaluators. Table 2 of the supplementary material presents the full analysis of the risk of bias.

Effect of intervention

Respiratory muscle strength

MIP was assessed in eight studies[9,20,29–34] and seven[9,29–34] studies were included in the meta-analysis, for a total of 124 patients. Compared to the control group, IMR increased MIP by 22.53 cmH2O (95% CI 11.77 to 33.30; I2:99%; $p < 0.001$); and yet, despite the significant increase, heterogeneity was high. Sensitivity analysis was performed considering volume and type of training; however, heterogeneity remained unchanged, so all studies were kept in the analysis (Figure 2A).

The only study not included in the meta-analysis for MIP was that conducted by Figueiredo et al (2018)[20], as the authors assessed IMT in a group that performed aerobic exercise and groups that combined aerobic exercised with IMT. The authors found an increase of 34.5 cmH2O (95% CI 22.4±46.7; $p < 0.001$) in MIP after IMT, compared to the control period and after the intervention period, however without differences in MIP between the IMT group and the groups that underwent aerobic training and aerobic training combined with IMT ($p = 0.81$).

Maximal expiratory pressure (MEP) was assessed in six studies[9,29,31–34] and five[9,29,32–34] were included in the meta-analysis covering 94 patients. Despite the positive effects of IMT on this variable (MD = 24.38 cmH2O; 95% CI, 7.78 to 40.98; I2:99%; $p = 0.004$), heterogeneity was also high and a sensitivity analysis was performed. The study by Campos et al (2018)[29] was excluded from the analysis because it was the only study that performed IMT with a fixed load regardless of the

value of the MIP assessed; moreover, the study presented a small confidence interval. Thus, the meta-analysis with four studies and 65 patients showed that IMT increased MEP when compared to the control group with moderate heterogeneity (MD = 19.54cmH2O; 95% CI, 13.40 to 25.67; I2:54%; $p < 0.001$) (Figure 2B).

The study conducted by Figueiredo et al (2012)[31] was not included in the MEP meta-analysis because it did not present post-training values for the control group. Contact with the authors was attempted to retrieve these data, but without success. The results of the study demonstrated that the IMR was able to increase MEP from 73.13±5.10 to 82.50±6.74 cmH2O ($p = 0.007$), but no difference was reported in relation to the control group.

Functional capacity

Four studies[9,29,30,32] evaluated the functional capacity through the 6MWT and another through the ISWT[20], only a meta-analysis was performed with the studies that used the 6MWT. The meta-analysis of four studies and 66 patients showed no significant improvement for the IMT group compared to the control group for this outcome (MD = 58.92m; 95% CI, −2.17 to 120.01; I2:20%; $p = 0.0587$). After the sensitivity analysis, the study by Dipp et al (2019)[30] was excluded from the meta-analysis for having a large confidence interval and negative effect size. Three studies[9,29,32] remained in the meta-analysis with a total of 52 patients demonstrating an increase in the distance covered in the 6MWT after IMT (MD = 77.63m; 95% CI, 12.55 to 142.72; I2:11%; $p = 0.0194$) (Figure 3).

Figueiredo et al (2018)[20] evaluated the functional capacity by the ISWT and demonstrated an increase of 96.7m in the IMT group after the control period and also after the intervention period (95% CI 5.6±187.9, $p < 0.001$). The authors reported that both groups showed improvements in functional capacity, with no differences between IMT and aerobic training and aerobic training combined with IMT ($p = 0.65$).

Pulmonary function

The meta-analysis of the four studies[29,32–34] that evaluated lung function included 83 patients and showed that IMT did not show significant improvement for the outcome

forced expiratory volume in the first second (FEV1) (MD = 0.17; 95% CI, −0.23 to 0.58; I2:41%; *p* = 0.4062) (Figure 4A). As for forced vital capacity (FVC), five studies[9,29,32–34] and 94 patients were included and also showed no effects of IMT when compared to the control group (MD = 0.23; 95% CI, -0.10 to 0 .55; I2:0%; *p* = 0.16) (Figure 4B).

The study by Figueiredo et al (2012)[31] was not included in the meta-analysis of FEV1 and FVC because it did not present post-training values for the control group, and we were not successful in contacting the authors. The results showed a significant improvement in FVC (2.45±0.17 to 2.85±0.16; *p* = 0.001) and FEV1 (2.18±0.16 to 2.46±0.14; *p* = 0.01) before and after IMT. The result compared to the control group was not reported.

Quality of life

The Kidney Disease Quality of Life – Short Form questionnaire was used to assess quality of life in four studies[9,32–34], which were included in the meta-analyses performed for the “symptoms” domain, totalling 65 patients. IMT showed no significant effects when compared to the control group (MD = 0.14; 95% CI, −6.95 to 7.23; I2:15%; *p* = 0.9693) (Figure 5A). For the domains “sleep”, “pain” and “energy”, three studies[9,21,30] were included in the meta-analysis (n = 42 patients included in each analysis) and also did not demonstrate significant favourable effects to the IMT group (sleep MD = 10 .69; 95% CI, −14.54 to 35.92; I265%; *p* = 0.9693; pain MD = 9.60; 95% CI, −20.72 to 39.92; I2:64%; *p* = 0.5348; energy MD = 10.61; 95% CI, −14.36 to 35.57; I2:59%; *p* = 0.40). Figures 5B, 5C, 5D correspond to the sleep, pain and energy analyses, respectively.

Figueiredo et al (2018)[20] also assessed QoL through the KDQL-SF questionnaire and observed significant effects of IMT in the pain domain during the control period (71.8, 95% CI 52.5 to 91.5 vs 89.7 95% CI 79.2 to 100.3; *p* = 0.01). The authors also found improvement in the energy domain before and after intervention in IMT, aerobic exercise and combined groups with an increase after 16 weeks of training compared to 8 weeks and to baseline. However, after post hoc analysis, the effects remained only in the group that underwent IMT combined with aerobic exercise (baseline: 67.7 95% CI 47.3 to 88.2; 8 weeks: 73.2 95% CI 51.8 to 94.6; 16 weeks: 90.0 95% CI 79.6 to 97.1; *p*

= 0.01). There was no statistical significance for the other domains of the KDQOL-SF questionnaire.

Endothelial function

Two studies[29,30] evaluated the effects of IMT on endothelial function. Dipp et al (2019)[30] (n = 25 patients) used the flow mediated dilation (FMD) method and did not find any significant difference either after IMT (7.4±3.5 vs 9.1±3.1%; *p* = 0.127) or when compared to the control group (mean difference after IMT: 1.9 95% CI -1.7 to 5.6, *p* = 0.287). Campos et al (2018)[29] evaluated the endothelial function of 41 patients measuring the plasma markers of endothelial activation intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion protein 1 (VCAM-1) and also found no significant difference between IMT and control groups (mean change ICAM-1: −26.2 ng/mL 95% CI −132.5 to 80.0, *p* = 0.620; VCAM-1: 112.9 ng/mL, 95% CI, −221 0.9 to 447.8, *p* = 0.498). However, the authors found changes in other biomarkers. At the end of the study, the IMT group had lower concentrations of syndecan 1 (−84.5 ng/mL; 95% CI −148.1 to −20.9; *p* = 0.011), angiopoietin-2 (− 480 pg/mL; 95% CI −1003.7 to −97.0; *p* = 0.034) and endothelin-1 (−8.4 pg/mL; 95% CI −14.3 to −2.4; *p* = 0.015), compared to the control group.

Oxidative stress

Figueiredo et al (2018)[20] (n = 26 patients) evaluated the effects of IMT associated with aerobic exercise on oxidative stress measured by thiobarbituric-acid-reactive substances (TBARS) and malondialdehyde (MDA). The authors found no differences between IMT, IMT associated with aerobic exercise, and aerobic exercise groups, as well as no changes in the intragroup redox status parameters (IMT: baseline: 0.3 95% CI 0.1 to 0.4; 8 weeks: 0.2 95% CI 0.1 to 0.4; 16 weeks: 0.1 95% CI 0.0 to 0.2; Aerobic exercise: baseline: 0.2 95% CI 0.1 to 0.2 ; 8 weeks: 0.2 95% CI 0.1 to 0.2; 16 weeks: 0.2 95% CI 0.1 to 0.2; IMT combined with aerobic exercise: baseline: 0.2 95% CI 0, 1 to 0.3; 8 weeks: 0.2 95% CI 0.1 to 0.3; 16 weeks: 0.2 95% CI 0.1 to 0.4; *p* = 0.37 intragroup; *p* = 0.18 between groups).

Supporting the findings of the study conducted by Figueiredo et al (2018)[20], other authors[29] conducted a study with 41 patients to assess the effects of IMT compared to a control group and also found no difference between groups for TBARS MDA markers (mean change between groups 0.69 nmol/mL; 95% CI -0.49 to 1.87; *p* = 0.243).

GRADE assessment

The quality of evidence, assessed using the Grading of Recommendations Assessment, Development, and Evaluation System (GRADE), suggests low confidence for the outcomes expiratory muscle strength, functional capacity, and FVC, and very low confidence for inspiratory muscle strength, FEV1, and QoL. For endothelial function and oxidative stress, the narrative option was used. The evidence profile is available in table 3 of the supplementary material.

Discussion

This systematic review with meta-analysis demonstrated that IMR in patients with CKD on HD improves MIP, MEP, and functional capacity of these patients. As demonstrated by several studies, patients with CKD on HD presented a reduction in inspiratory muscle strength[4,30,35] with a pressure of 82 cmH2O, being a good cut-off point to stratify respiratory muscle weakness in these patients[36].

According to the literature, IMT generates adaptations in the inspiratory muscles, promoting hypertrophy, increased proportion of type I fibres, reduction of type II fibres, and greater cross-sectional area of the diaphragm, reflecting the improvement of inspiratory muscle weakness and an increase of MIP[32–34]. In this review, IMT was able to increase MIP by 22.53 cmH2O and MEP by 19.54 cmH2O, corroborating the results of a previous systematic review that found an improvement in MIP of 23cmH2O and MEP 26cmH2O in HD[24] patients; however, our review presents more robust data, namely twice the number of studies presented in the review by Medeiros et al (2017)[24].

Expiratory muscle strength is also reduced in HD patients with inspiratory muscle weakness[4,35]. Although no expiratory muscle training has been performed, in several studies[9,29,31,32] there was also a significant increase in MEP after IMT, which may be

related to the work imposed on the abdominal muscles during the intervention[37]. It is also believed that with training, the inspiratory muscles become stronger and are able to generate greater traction and chest opening. This more expanded position means greater elastic recoil of the lungs and chest wall, which may have led to a greater mechanical advantage for performing the MEP maneuver[24].

Some studies[9,36] reported a correlation between MIP and the distance covered in the 6MWT, in which it was observed that reductions in MIP contributed to decreasing functional capacity of patients on HD, suggesting that the strength training of inspiratory muscles can improve functional performance of these patients.

This review found that the IMT caused positive effects on exercise tolerance assessed by the 6MWT, increasing the distance walked by 77.63m. Two other systematic reviews with meta-analysis in HD patients also found an improvement in functional capacity by the 6MWT with an increase of 80m[24] and 117.62m[38] after IMT. This finding becomes relevant, since, for every 100m covered in the 6MWT, there is an increase in survival in this population of 5%[39].

Figueiredo et al (2018)[20] carried out a study comparing the effects of IMT alone and combined with aerobic training and found positive effects of IMT on the functional capacity assessed by the ISWT for both groups. The increase in functional capacity after IMT was 96.7m, a distance greater than the minimal clinically important difference (20m) proposed for patients with CKD not on dialysis[40].

In addition, the authors[20] also reinforced that IMT increased functional capacity at a similar magnitude to aerobic training with a cycle ergometer, being a therapeutic approach of low cost and easy to perform in HD units when conventional aerobic exercise cannot be implemented. Similarly, Pellizaro et al (2013)[9] demonstrated that IMT increased the distance covered in the 6MWT with a magnitude greater than that found for the peripheral muscle training group.

These findings support the idea that functional capacity is influenced by cardiorespiratory fitness and not merely by peripheral factors, such as muscle weakness. Therefore, the impairment of functional capacity can be attenuated by the gain in respiratory muscle strength.

The improvement in functional capacity after IMT can be explained by a mechanism that has already been well studied in HF: the attenuation of the metaboreflex. In patients with HF, the blood flow requirements of the respiratory muscles significantly increase during exercise and blood flow is diverted from the locomotor muscles to accommodate the respiratory work[41,42] due to respiratory muscle weakness associated with the hyperactivity of cardiovascular reflexes. Thus, strategies that reduce inspiratory muscle work and attenuate the inspiratory metaboreflex can improve exercise tolerance[42].

Patients with CKD on HD have impaired lung function indicated by spirometry[4,33]. The effects of IMT on lung function are still unclear. This systematic review demonstrates that IMR did not significantly improve FEV1 and FVC outcomes compared to the control group. The meta-analysis by Medeiros et al (2017)[24] found an increase in IMR when compared to breathing exercises for FEV1; however, the authors compared IMT to a control group with breathing exercises.

Two not controlled clinical trials with 15 patients each also yielded controversial results. Silva et al (2011)[43] found no statistically significant difference in lung function at the end of an 8-week training with a load adjusted to 40% of MIP. Heba et al (2018)[44] observed that IMR increased FEV1 and FVC after 12 weeks of training at 50% PImax. These results do not seem to be related to training volume and intensity, as the studies included in this meta-analysis that did not find positive results performed IMT for 8 to 24 weeks with training ranging from 30 to 50% of MIP[9,32,33]; those that reported positive results in pulmonary function[29,31,34] performed protocols of 6 to 8 weeks using a 40% load of MIP.

The absence of effects on lung function is probably due to the fact that IMT aims to improve inspiratory muscle strength rather than lung volumes and capacities. The worsening of pulmonary function in HD patients is influenced by several factors, such as chronic and subclinical pulmonary oedema, interstitial fibrosis, calcification of the lung parenchyma and bronchial tree, recurrent infections and alveolitis due to treatment with corticosteroids[4,35]. In addition, chronic vascular congestion may be another explanation for the decrease in lung compliance[35]. Reversible airway obstruction caused by fluid

accumulation seems to be more related to decreased lung function[45], which would justify the absence of IMR results on this variable.

This was the first systematic review with meta-analysis to assess the effects of IMT on QoL of patients with CKD on HD. Our findings do not demonstrate significant effects of IMT on this outcome when compared to the control group. This is probably due to the fact that QoL involves physical, social, and emotional aspects, with IMT being a very specific intervention. Figueiredo et al (2018)[20] reported improvement in self-perception of pain during the control period in the IMT group and also demonstrated that the addition of aerobic exercise to IMT improved the physical domains of health-related quality of life. The literature reports that intradialytic aerobic training generates an increase in the dimensions of physical, social, and mental health functioning[46,47]; therefore, the association of IMT with aerobic exercise seems to positively influence factors related to physical aspects in the QoL of patients on HD[20].

The two studies included in this systematic review[29,30] did not demonstrate improvement in endothelial function after IMT. Conversely, the study by Campos et al (2018)[29] pointed out changes in other biomarkers related to the endothelium. There was a significant reduction in endothelial glycocalyx syndecan-1 and angiopoietin-2 lesion biomarkers, in addition to a reduction in endothelin-1 levels, indicating better blood pressure control during IMT.

The reduction of endothelin-1 is an interesting marker given its other functions. In addition to being a potent vasoconstrictor, it can also be considered a marker of endothelial dysfunction, exerting vascular smooth muscle cell contraction activity, increasing renal vascular resistance and reducing renal plasma flow and glomerular filtration rate[48,49].

Similarly, a study in patients with HF[50] found no improvement in endothelial function after IMT, as assessed by venous occlusion plethysmography. The authors reported that although high-intensity IMT increased HR and SBP in maximal respiratory effort, indicating a possible increase in pulsatile flow, this result did not cause a systemic effect.

Dipp et al (2019)[30] evaluated the endothelial function of 25 patients with CKD on HD using FMD and also found no significant effects of IMT on this outcome. Corretti et

al (2002)[51] highlight in their guidelines that studies aiming to assess the effects of interventions on endothelial function should include a sample size of 40-60 subjects to detect a 1.5% to 2% change in vessel diameter, as it is an insensitive measure. The studies included in this review[29,30] that evaluated endothelial function after IMT in HD patients had a small sample size and a short intervention period, which could at least partially explain the absence of positive results.

None of the studies included in this review[20,29] showed favourable results for the modulation of oxidative stress after IMT. However, knowing that oxidative stress is able to activate transcription factors that regulate inflammatory mediators and that chronic inflammation can cause an increase in oxidative stress[13,52], it is worth mentioning that Pellizaro et al (2013)[9] found a reduction in levels of C-reactive protein (CRP) in the training group after 10 weeks of IMT. A direct correlation between lipid and protein oxidation markers and CRP levels has been proven in HD[53] patients.

Figueiredo et al (2018)[20] also found positive results of IMT on inflammatory markers. The authors reported reductions in plasma soluble tumour necrosis factor receptor 2 (sTNFR2) levels after interventions in all groups when compared to baseline and at 8 weeks. The reduction in the level of sTNFR2 may be clinically relevant because it is an independent predictor of mortality[54]. This reduction in sTNFR2 occurred concomitantly with the increase in adiponectin and resistin levels. In individuals without CKD, serum resistin is related to CRP and oxidative stress[55] and adiponectin to cell protection and inflammation reduction[56], suggesting positive effects of IMT in the modulation of anti-inflammatory activity as well as an antioxidant action induced by training, especially when associated with IMT to aerobic training.

Although improvements were observed in certain biochemical and inflammatory markers, a direct cause-and-effect relationship with IMT cannot be determined for the redox state because other factors influencing the metabolic status of these patients were not evaluated in the aforementioned studies.

This review has some limitations: the small number of randomised clinical trials for some outcomes (endothelial function and oxidative stress), which may affect the conclusions, as well as the quality of evidence found (low to very low). Still, the heterogeneity regarding the training protocols used by the different studies makes it

difficult to establish a consensus on the most appropriate type of IMT; however, better results were observed with training periods from 8 weeks and pressures between 40-50 % of PImax.

Despite the limitations, this is the first systematic review to present the effects of IMT on QoL of patients with CKD on HD through a meta-analysis and gathers evidence regarding the effects of this therapy on the outcomes of endothelial function and oxidative capacity. Furthermore, we emphasize that this review presents a significant number of new studies on this topic when compared to the review by Medeiros et al (2017)[24], which reinforces and makes the results more robust.

In conclusion, IMT improves MIP, MEP, and functional capacity of patients with CKD on HD, but the quality of evidence varies from low to very low. IMT did not demonstrate significant results for lung function and quality of life. The effects of this therapy on endothelial function and oxidative capacity remain uncertain. Based on these findings, new RCTs should be carried out with a larger sample size with emphasis on outcomes, such as endothelial function and oxidative stress.

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Box 1. Inclusion criteria

Design

• Randomised controlled trials

Participants

• Adults (>18 years)

• Chronic kidney failure on haemodialysis

• Haemodynamically stable

Intervention

• Inspiratory muscle training using linear load

Outcomes

• Primary: respiratory muscle strength, functional capacity

• Secondary: lung function, quality of life, endothelial function, oxidative stress

Comparisons

• Inspiratory muscle training versus controls or placebo intervention

• Inspiratory muscle training versus conventional physical therapy

Appendix 1. Search strategy performed in MEDLINE (PubMed) and adapted to other databases

#1	"Kidney Failure, Chronic"[Mesh] OR “End-Stage Kidney Disease” OR “Disease, End-Stage Kidney” OR “End Stage Kidney Disease” OR “Kidney Disease, End-Stage” OR “Chronic Kidney Failure” OR “End-Stage Renal Disease” OR “Disease, End-Stage Renal” OR “End Stage Renal Disease” OR “Renal Disease, End-Stage” OR “Renal Disease, End Stage” OR “Renal Failure, End-Stage” OR “End-Stage Renal Failure” OR “Renal Failure, End Stage” OR “Renal Failure, Chronic” OR “Chronic Renal Failure” OR “ESRD”
#2	"Kidney Diseases"[Mesh] OR "Kidney Diseases” OR “Disease, Kidney” OR “Diseases, Kidney” OR “Kidney Disease”
#3	"Renal Insufficiency, Chronic"[Mesh] OR "Renal Insufficiency, Chronic" OR “Chronic Renal Insufficiencies” OR “Renal Insufficiencies, Chronic” OR “Chronic Renal Insufficiency” OR “Kidney Insufficiency, Chronic” OR “Chronic Kidney Insufficiency” OR “Chronic Kidney Insufficiencies” OR “Kidney Insufficiencies, Chronic” OR “Chronic Kidney Diseases” OR “Chronic Kidney Disease” OR “Disease, Chronic Kidney” OR “Diseases, Chronic Kidney” OR “Kidney Disease, Chronic” OR “Kidney Diseases, Chronic” OR “Chronic Renal Diseases” OR “Chronic Renal Disease” OR “Disease, Chronic Renal” OR “Diseases, Chronic Renal” OR “Renal Disease, Chronic” OR “Renal Diseases, Chronic”
#4	"Renal Dialysis"[Mesh] OR "Renal Dialysis" OR “Dialyses, Renal” OR “Renal Dialyses” OR “Dialysis, Renal” OR “Haemodialysis” OR “Hemodialyses” OR “Dialysis, Extracorporeal” OR “Dialyses, Extracorporeal” OR “Extracorporeal Dialyses” OR “Extracorporeal Dialysis”
#5	#1 OR #2 OR #3 OR #4 OR
#6	"Breathing Exercises"[Mesh] OR “Exercise, Breathing” OR “Respiratory Muscle Training” OR “Muscle Training, Respiratory” OR “Training, Respiratory Muscle”
#7	“Inspiratory muscle training”
#8	“IMT”
#9	#7 OR #8

#10	randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial [tw]) OR ((singl*[tw] OR doubl* [tw] OR trebl*[tw] OR tripl*[tw] AND (mask* [tw] OR blind*[tw])) OR (“latin square” [tw]) OR placebos [mh] OR placebo* [tw] OR random*[tw] OR research desing [mh:noexp] OR comparative study [mh] evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] Or control* [tw] OR prospectiv* [tw] Or volunteer [tw]) NOT (animal [mh] NOT human [mh]
#11	#5 AND #9 AND #10

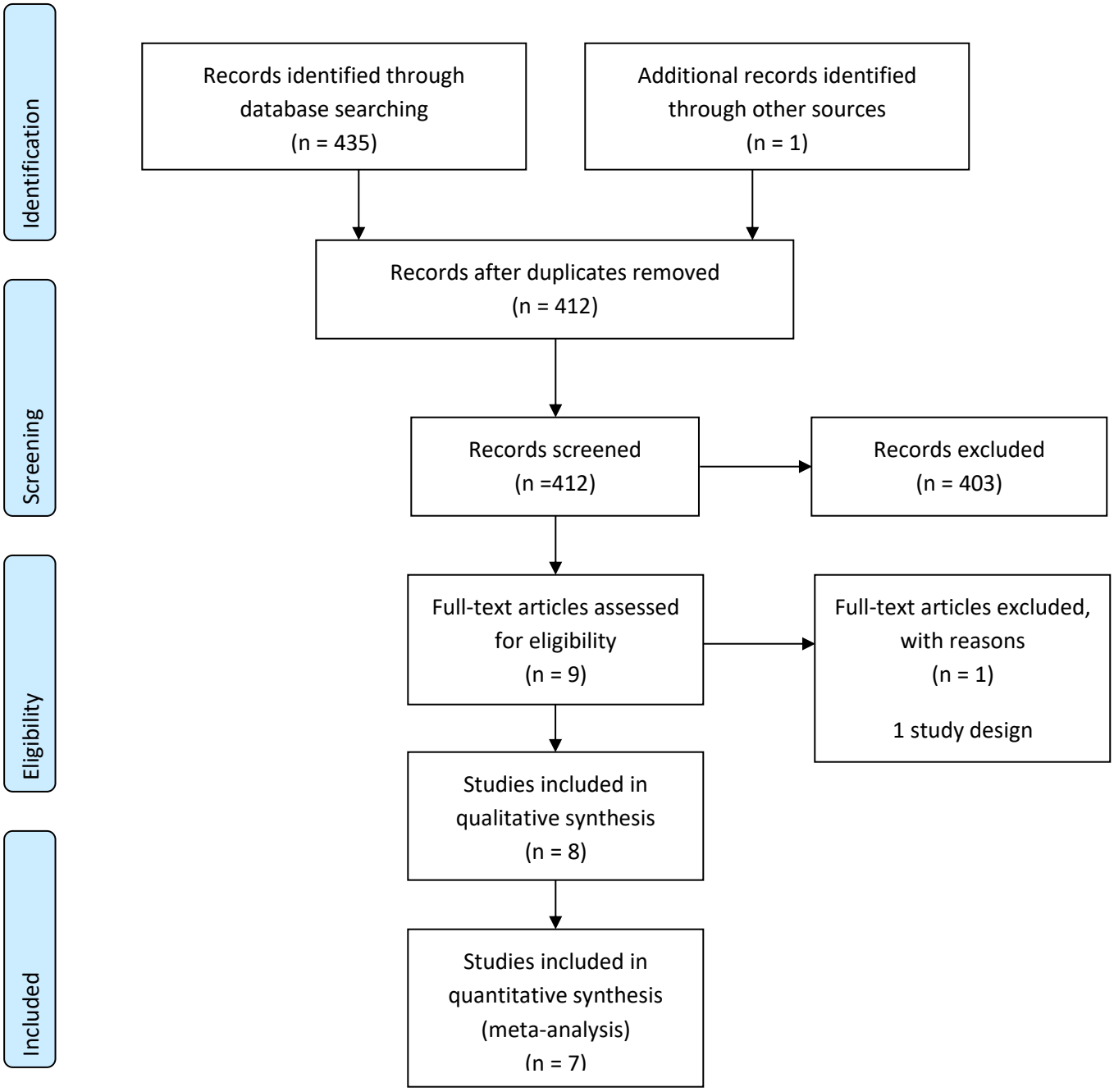

Figure 1. Study selection flow diagram

Table 1 Study characteristics

Author, Year	Participants	Intervention	Comparison	Sample (n)	Sex F/M (%)	Age ± SD (years-old)	Protocol	Outcome measures of interest and instruments
Campos et al, 2018	CKF patients on HD	IMT	Control Group	41 patients IG: 29 CG: 12	IG: 41.4/58.6 CG: 41.7/58.3	IG: 48.86 ± 12.97 CG: 52.67 ± 14.61	IG: Threshold PEP; 15cmH_2O-20cmH_2O; 12 repetitions; 30min-40min; 3x/week; 8 weeks. CG: No physiotherapeutic intervention.	- Inspiratory and expiratory muscle strength by manovacuometer (MIP and MEP - cmH_2O) - Functional capacity by 6MWT (m) - Pulmonary function by Spirometry (FVC – L/min and FEV1 – L/min) - Endothelium function (VCAM-1, ICAM-1 Syndecan-1, angiopoietin-2, endothelin-1) - Oxidative stress (malondialdehyde, TBARS)
Dipp et al, 2019	CKF patients on HD	IMT	Control Group	25 patients	IG: 14.3/85.7	IG: 60 ± 9	IG: PowerBreathe; 50%, 60% and 70%; 5x10 repetitions with	- Inspiratory muscle strength by manovacuometer (MIP

				IG: 14 CG: 11	CG: 36.4/63.6	CG: 55 ± 13	2min of rest; 20min; 6x/week (3 on HD and 3 at home); 5 weeks. CG: No physiotherapeutic intervention.	- cmH_2O) - Functional capacity by 6MWT (m) and Sit-to-stand test (30seg) - Endothelial function by FMD
Figueiredo et al, 2018	CKF patients on HD	IMT+Aerobic training IMT	Aerobic training	26 patients IG: 13 CG: 13	IG: 30.8/69.2 CG: 23.1/76.9	IG: 45.2 ± 19.04 CG: 49.5 ± 14.44	IG: Threshold IMT or Power Breathe; 50% MIP; 3x15 with 1min of rest; 20min; 3x/week; 8 weeks. CG: Cycle ergometer; ≥50 rpm; 40min.	- Inspiratory muscle strength by manovacuometer (MIP - cmH_2O) - Functional capacity by Incremental Shuttle Walk Test - Quality of life by KDQOL-SF - Oxidative stress (TBARS, MDA)
Figueiredo et al, 2012	CKF patients on HD	IMT	Control Group IMT with biofeedback	26 patients IG: 16	IG: 43.75/56.25 CG: 40/60	IG: 40.46 ± 11.16 CG: 50 ±	IG: Threshold IMT; 40% MIP; 1min breathing effort and 1min of rest; 20min; 3x/week; 6 weeks	- Inspiratory and expiratory muscle strength by manovacuometer (MIP and MEP - cmH_2O) - Pulmonary function by Spirometry (FVC -

				CG: 10 IMTb: 15	IMTb: 46.7/53.3	22.77 IMTb: 41.2 ± 3.4	CG: No physiotherapeutic intervention. IMTb: Respiratory biofeedback system (1 min breathing effort and 1 min resting) for 20min; 40% MIP	L and FEV1 - L)
Medeiros et al, 2018	CKF patients on HD	IMT	Sham Group	24 patients IG: 12 SG: 12	IG: 58.3/41.7 CG: 66.7/33.3	IG: 45.50 ± 11.45 CG: 47.33 ± 13.68	IG: PowerBreathe - IMT program; 50% MIP; 3x30 with 1min of rest; 2x/day, 7x/week; 8 weeks. CG: 5 cmH_2O for the sham group	- Inspiratory and expiratory muscle strength by manovacuometer (MIP and MEP - cmH_2O) - Pulmonary function by Spirometry (FVC - L and FEV1 - L) - Functional capacity by 6MWT (m) - Quality of life by KDQOL-SF
Pellizzaro et al, 2013	CKF patients on HD	IMT	Control Group Peripheral Muscle	25 patients IG: 11	IG: 27.3/72.7 CG: 42.9/57.1 PMT: 50/50	IG: 43 ± 13.8 CG: 51.9 ± 11.6	IG: Threshold Loader; 50% MIP; 3x15 with 1min of rest; 3x/week; 10 weeks. CG: No physiotherapeutic	- Inspiratory and expiratory muscle strength by manovacuometer (MIP and MEP - cmH_2O) - Functional capacity by 6MWT

			Training (PMT)	CG: 14 PMT: 14		PMT: 48.9 ± 10.1	intervention. PMT: knee extensor muscles training with free leg weights; 50% of 1MR.	- Pulmonary function by Spirometry (FVC - L) - Quality of life by KDQOL-SF
Soares et al, 2017	CKF patients on HD	IMT	Control Group	35 patients IG: 19 CG: 16	IG: 15.8/84.2 CG: 37.5/62.5	IG: 54.7 ± 10.4 CG: 49.3 ± 16.3	IG: Power Breathe; 30% MIP; 3x10; 72 sessions; 3x/week, 24 weeks. CG: No physiotherapeutic intervention.	- Inspiratory and expiratory muscle strength by manovacuometer (MIP and MEP - cmH_2O) - Pulmonary function by spirometry (FVC - L and FEV1 - L) - Quality of life by KDQOL-SF
Yuenyongchaiwat et al, 2020	CKF patients on HD	IMT	Sham Group	44 patients IG: 23 SG: 21	IG: 21.74/78.26 SG: 38.10/61.90	IG: 54.87 ± 12.27 SG:49.14 ± 10.84	IG: 40% MIP; 3x15 repetitions with 1min of rest; 3x/week; 8 weeks. SG: 0% MIP or lowest pressure of MIP; 3x15 repetitions with 1min of rest; 3x/week; 8 weeks.	- Inspiratory and expiratory muscle strength by manovacuometer (MIP and MEP - cmH_2O) - Pulmonary function by spirometry (FVC – L and FEV1 – L) - Quality of life by

Note: CKD: Chronic Kidney Disease; HD: Haemodialysis; IMT: Inspiratory muscle training; IG: Intervention group; CG: control group; MIP: Maximal inspiratory pressure; MEP: Maximal expiratory pressure; 6MWT: 6-Minute Walk Test ; FVC: Forced vital capacity; FEV1: forced expiratory volume in the first second; VCAM-1: vascular cell adhesion protein 1; ICAM-1: intercellular adhesion molecule 1; TBARS: thiobarbituric-acid-reactive substances; MAD: malondialdehyde; FMD: flow mediated dilation; KDQOL-SF: Kidney Disease Quality of Life – Short Form.

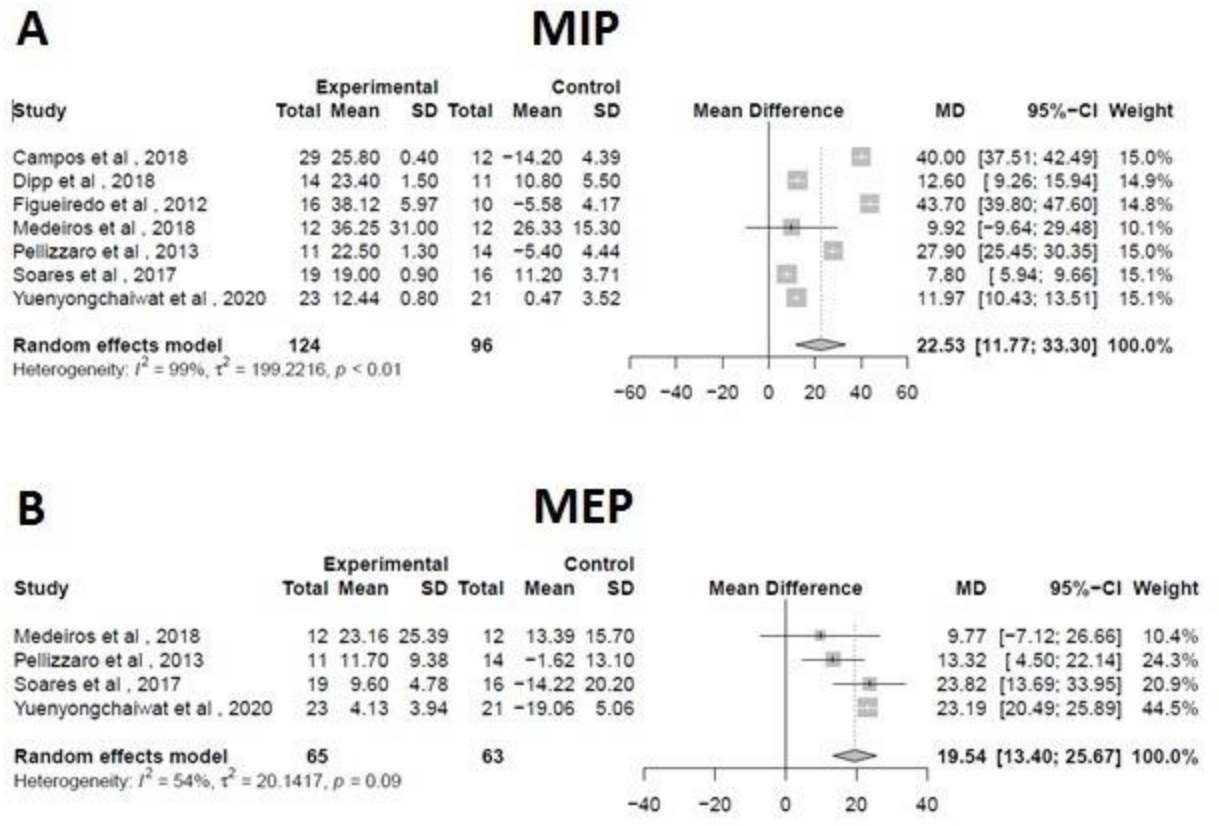

Figure 2. - MD and 95% CI in (A) MIP and (B) MED for IMT vs control group. Abbreviations: CI, confidence interval; MD, mean difference.

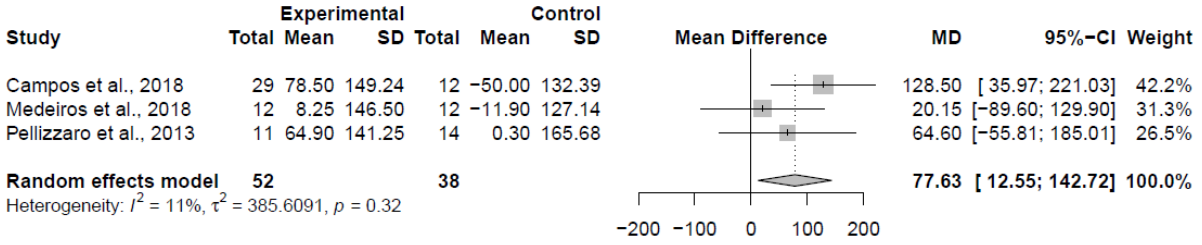

Figure 3. MD and 95% CI in functional capacity for IMT vs control group. Abbreviations: CI, confidence interval; MD, mean difference.

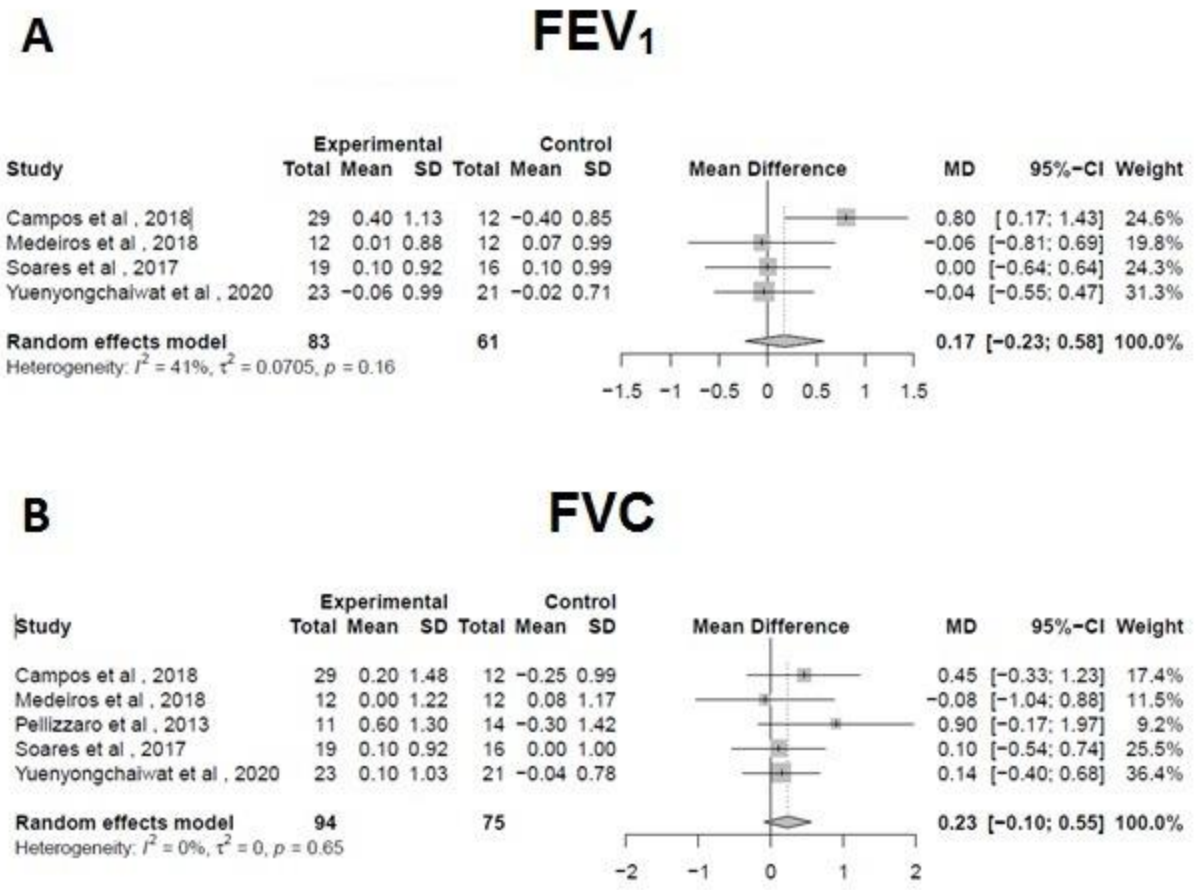

Figure 4. MD and 95% CI in (A) FEV_1 and (B) FVC for IMT vs control group. Abbreviations: CI, confidence interval; MD, mean difference.

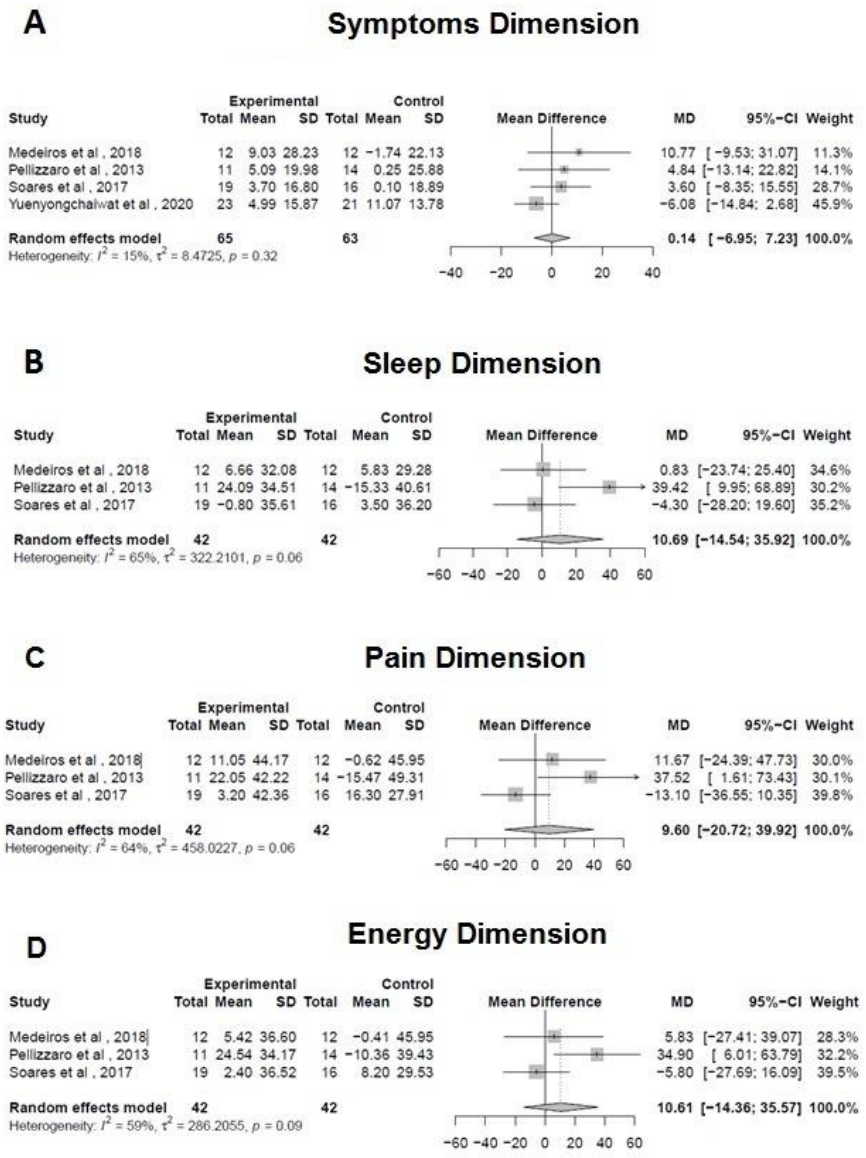

Figure 5. MD and 95% CI (A) symptoms, (B) sleep, (C) pain, (D) energy dimension for IMT vs control group. Abbreviations: CI, confidence interval; MD, mean difference.

Table 2 - Risk of Bias RoB 2.0

Author, Year	RoB 2.0 Randomisation process	Deviations from intended intervention	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall bias
Campos et al, 2018						
MIP and MEP	Low	Low	Low	High	Low	High
FVC and FEV1	Low	Low	Low	High	Low	High
6MWT	Low	Low	Low	High	Low	High
Endothelium function	Low	Low	Low	Low	Low	Low
Oxidative stress	Low	Low	Low	Low	Low	Low
Dipp et al, 2019						
MIP	Low	Low	Low	Some concerns	Low	Some concerns
6MWT	Low	Low	Low	Some concerns Low	Low	Some concerns
Endothelial function	Low	Low	Low		Low	Low
Figueiredo et al,				Some		

2018 MIP and MEP ISWT Oxidative stress Oxidative stress KDQOL-SF	Low Low Low Low Low	Low Low Some concerns Some concerns Some concerns	Low Low Low Low Low	concerns Some concerns Low Low Some concerns	Low Low Low Low Low	Some concerns Some concerns Some concerns Some concerns Some concerns
Figueiredo et al, 2012 MIP and MEP FVC and FEV1	Low	Some concerns	Low	High	Some concerns	High
Medeiros et al, 2018 MIP and MEP FVC and FEV1 6MWT	Low	Low	Low	Low	Low	Low

KDQOL-SF						
Pellizzaro et al, 2013 MIP and MEP FVC 6MWT KDQOL-SF	Some concerns	High	Low	Some concerns	Some concerns	High
Soares et al, 2017 MIP and MEP FVC and FEV1 KDQOL-SF	Low	High	High	High	Low	High
Yuenyongchaiwat et al, 2020 MIP and MEP FVC and FEV1 KDQOL-SF	Low	High	High	Low	Low	High

Table 3 - Assessment of the quality of evidence

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMT	CONTROL	Relative (95% CI)	Absolute (95% CI)		
Maximum Inspiratory Pressure												
7	randomised trials	serious[a]	very serious[b]	not serious	not serious	none	124	96	-	MD **22.53 higher** (11.77 higher to 33.3 higher)	⨁◯◯◯ Very low	IMPORTANT
Maximum Expiratory Pressure												
4	randomised trials	serious[a]	serious[c]	not serious	not serious	none	65	63	-	MD **19.54 higher** (13.4 higher to 25.67 higher)	⨁⨁◯◯ Low	IMPORTANT
Forced Maximum Capacity												
6	randomised trials	very serious[a]	not serious	not serious	not serious	none	94	75	-	MD **0.23 higher** (0.1 lower to 0.55 higher)	⨁⨁◯◯ Low	IMPORTANT
Forced expiratory volume in the first second												
5	randomised trials	very serious[a]	serious[c]	not serious	serious[d]	none	99	71	-	MD **0.17 higher** (0.23 lower to 0.58 higher)	⨁◯◯◯ Very low	IMPORTANT
6-min walk test												
3	randomised trials	serious[e]	not serious	not serious	serious[d,f,g]	none	52	38	-	MD **77.63 higher** (12.55 higher to 142.72 higher)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMT	CONTROL	Relative (95% CI)	Absolute (95% CI)		
KDQOL Symptoms												
4	randomised trials	very serious[a]	not serious	not serious	serious[f,h]	none	65	63	-	MD **0.14 higher** (6.95 lower to 7.23 higher)	⨁◯◯◯ Very low	IMPORTANT
KDQOL Sleep												
3	randomised trials	very serious[a]	very serious[b]	not serious	very serious[d,f]	none	42	42	-	MD **10.69 higher** (14.54 lower to 35.92 higher)	⨁◯◯◯ Very low	IMPORTANT
KDQOL Pain												
3	randomised trials	very serious[a]	very serious[b]	not serious	very serious[d,f]	none	42	42	-	MD **9.6 higher** (20.72 lower to 39.92 higher)	⨁◯◯◯ Very low	IMPORTANT
KDQOL Energy												
3	randomised trials	very serious[a]	serious[c]	not serious	very serious[d,f]	none	42	42	-	MD **10.61 higher** (14.36 lower to 35.57 higher)	⨁◯◯◯ Very low	IMPORTANT
Endothelial function												
2	randomised trials	not serious	not serious	not serious	not serious	none	2 studies, total 46 patients. Dipp et al, 2019: IMT group pre 7.4±3.5 vs post 9.1±3.1, $p = 0.127$; control group 8.2 ±5.4 vs post 7.2±4.7, $p = 0.624$; IMT vs control group IMT $p = 0.287$. Campos et al, 2018: IMT vs control (mean change ICAM-1: −26.2 ng/mL 95% CI −132.5 to 80.0, $p = 0.620$; VCAM-1: 112.9 ng/mL, 95% CI , −221.9 to			⨁⨁⨁⨁ High	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IMT	CONTROL	Relative (95% CI)	Absolute (95% CI)		
							447.8, *p* = 0.498)					

Oxidative Stress

2	randomised trials	not serious	not serious	not serious	not serious	none	2 studies, total of 67 patients. Figueiredo et al, (2018): IMT: baseline: 0.3 95% CI 0.1 to 0.4; 8 weeks: 0.2 95% CI 0.1 to 0.4; 16 weeks: 0.1 95% CI 0.0 to 0.2; Aerobic exercise group: baseline: 0.2 95% CI 0.1 to 0.2; 8 weeks: 0.2 95% CI 0.1 to 0.2; 16 weeks: 0.2 95% CI 0.1 to 0.2; IMT group combined with aerobic exercise: baseline: 0.2 95% CI 0.1 to 0.3; 8 weeks: 0.2 95% CI 0.1 to 0.3; 16 weeks: 0.2 95% CI 0.1 to 0.4; *p* = 0.37. intragroup; *p* = 0.18 between groups Campos et al, 2018: mean change between IMT and control groups 0.69 nmol/mL; 95% CI -0.49 to 1.87; *p* = 0.243.	⊕⊕⊕⊕ High	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

a. It has a high risk of bias in domains that can reduce reliability.

b. High heterogeneity (> 60%).

c. Moderate heterogeneity (40-60%).

d. Large CI.

e. Limitations are unlikely to detract from reliability.

f. Small number.

g. Significant *p*.

h. Moderate CI.

5 CONCLUSÃO GERAL

O objetivo geral deste trabalho foi revisar sistematicamente os efeitos do treinamento muscular inspiratório sobre a força muscular respiratória e a capacidade funcional de pacientes com insuficiência renal crônica em hemodiálise.

A disfunção muscular presente em pacientes com IRC está intimamente relacionada com fraqueza e fadiga muscular, contribuindo para um estilo de vida sedentário, que afeta tanto a composição muscular quanto a capacidade de exercitar-se, gerando efeitos negativos diretos sobre as atividades físicas de vida diária e qualidade de vida desses pacientes.

O treinamento muscular inspiratório aumenta a pressão inspiratória máxima, a pressão expiratória máxima e a capacidade funcional de pacientes com insuficiência renal crônica em hemodiálise em comparação com fisioterapia convencional ou controles e intervenção placebo. A melhora da capacidade funcional nessa população é de extrema importância devido à sua relação com a sobrevida desses pacientes.

6 IMPACTO DO TRABALHO

A fraqueza muscular respiratória em pacientes com insuficiência renal crônica está associada à redução da capacidade funcional e influencia vários sistemas nesses pacientes. O treinamento muscular inspiratório surge como uma opção de tratamento que pode promover efeitos positivos nos aspectos respiratório, funcional e inflamatório.

Os resultados presentes neste trabalho trazem impactos científicos e clínicos, adicionando informações relevantes à literatura atual sobre o tema, melhorando a sua confiabilidade e trazendo dados importantes para o trabalho de reabilitação pulmonar. Além disso, também traz impactos econômicos, tendo em vista que o treinamento muscular inspiratório é um tratamento de baixo custo e fácil execução nas unidades de hemodiálise.