UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE:

CARDIOLOGIA E CIÊNCIAS CARDIOVASCULARES

Dissertação de Mestrado

DIFERENTES MODALIDADES DE TREINAMENTO INTRADIALÍTICO EM PACIENTES COM DOENÇA RENAL CRÔNICA TERMINAL

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Orientador: Prof. Dr. Ricardo Stein

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Dissertação de mestrado apresentada como requisito parcial para obtenção do título de Mestre em Ciências Cardiovasculares, à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Ciências da Saúde: Cardiologia e Ciências Cardiovasculares.

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LISTA DE SIGLAS E ABREVIATURAS

CF - Capacidade Funcional

DCVs - Doenças Cardiovasculares

DRC - Doença Renal Crônica

DRCT - Doença Renal Crônica Terminal

ELFI - Eletroestimulação Funcional Intradialítica

HD - Hemodiálise

Kt/V - Depuração Fracional de Ureia

PCR - Proteína C-reativa

TAI - Treinamento Aeróbico Intradialítico

TCI - Treinamento Combinado Intradialítico

TC6M - Teste de Caminhada de 6 Minutos

TF - Treinamento Físico

TFI - Treinamento Físico Intradialítico

TMI - Treinamento Muscular Inspiratório

TRI - Treinamento Resistido Intradialítico

SUMÁRIO

RESUMO

Objetivo: Pacientes com doença renal crônica terminal (DRCT) em hemodiálise comumente apresentam baixa aptidão cardiorrespiratória e pior prognóstico. Foi realizada uma revisão sistemática e meta-análise para se avaliar o efeito de diferentes tipos de treinamento físico intradialítico (TFI) em pacientes com DRCT.

Métodos: Foram pesquisados em sete bases de dados, ensaios clínicos randomizados publicados até julho de 2019.

Resultados: Foram incluídos 50 estudos (n = 1.757). Comparado aos cuidados usuais, o TFI aeróbico melhorou a depuração fracional de ureia (Kt/V), capacidade funcional (CF), pressão arterial sistólica e proteína C-reativa. O treinamento combinado aumentou a CF e reduziu a pressão arterial diastólica. O treinamento resistido, a eletroestimulação funcional e o treinamento muscular inspiratório melhoraram a CF. Não houve mudanças nos níveis de colesterol total, interleucina-6 ou hemoglobina. Não houve diferença na incidência de eventos adversos entre os grupos TFI e controle. A certeza da evidência foi variável de acordo com a escala GRADE, com a maioria dos resultados classificados com uma certeza muito baixa. O risco de viés dos estudos primários mostrou risco pouco claro na sua maioria.

Conclusões: Os cinco tipos de TFI demonstraram algum tipo de benefício para pacientes com DRCT. Esses achados devem ser interpretados à luz do risco de viés incerto dos artigos primários, e da baixa à muito baixa certeza de evidências dos desfechos avaliados.

Palavras-chave: Doença renal em estágio final; treinamento intradialítico; eficácia da diálise; meta-análise.

ABSTRACT

Objective: Patients with end-stage renal disease (ESRD) undergoing hemodialysis usually have low cardiorespiratory fitness, and worse prognosis. We performed a systematic review and meta-analysis to assess the impact of different types of intradialitic training (IDT) on patients with ESRD.

Methods: The search was performed in seven databases up to July, 2017.

Results: Fifty studies were included (n=1,757). Compared to usual care, aerobic IDT improved fractional urea clearance (Kt/V), functional capacity (FC), systolic blood pressure and C-reactive protein. Combined training increased CF and reduced diastolic blood pressure. Resistance training, functional electrostimulation and inspiratory muscle training improved FC. There was no impact on total cholesterol, interleukin-6, or hemoglobin levels. There was no difference in incidence of adverse events between the IDT and control groups. The certainty of evidence was variable according to the GRADE scale, with most outcomes rated very low certainty. The risk of bias assessment of primary studies showed unclear risk in most.

Conclusions: The five types of IDT have demonstrated benefits for patients with ESRD. Our data should be interpreted in light of the unclear risk of bias of most evaluated articles and the low to very low certainty of evidence for evaluated outcomes.

Keywords: End-stage renal disease; intradialytic exercise; dialysis efficacy; meta-analysis.

INTRODUÇÃO

A doença renal crônica (DRC) é uma síndrome grave e complexa, caracterizada pela perda gradual da função renal ao longo do tempo.[1] Considerada um importante problema de saúde pública no Brasil e no mundo, a DRC – quando não tratada adequadamente – pode evoluir para o seu último estágio, conhecido como DRC terminal (DRCT).[2] A prevalência da DRCT avança progressivamente, impulsionada pelo envelhecimento populacional e pela "epidemia" de fatores de risco muito bem estabelecidos, destacando-se o diabetes mellitus e a hipertensão arterial sistêmica.[3,4]

Evidências demonstraram que os pacientes com DRCT estão mais propensos à inatividade física e sintomas depressivos. Por sua vez, isto se traduz em redução significativa da capacidade funcional e qualidade de vida, assim como em um pior prognóstico.[5,6] Dessa forma, o treinamento físico (TF) realizado durante as sessões de hemodiálise (HD), conhecido como treinamento físico intradialítico (TFI), surgiu como uma terapia alternativa e atrativa nesse cenário. O TFI pode ser realizado sob a supervisão de profissionais especializados nas unidades de HD, o que traz maior segurança e confiança aos pacientes, além de deixá-los menos propícios a uma sessão de HD mais enfadonha.

Apesar de o TFI promover efeitos benéficos comprovados por uma série ensaios clínicos randomizados publicados nos últimos 20 anos,[7-10] bem como por revisões sistemáticas e meta-análises,[6,11-13] informações sobre qual a modalidade de TFI mais eficaz para estes pacientes permanecem escassas. Portanto, após uma descrição inicial dos principais conceitos, sinais/sintomas, tratamento e prognóstico dos pacientes com DRCT, esta revisão aborda e discute os efeitos de diferentes modalidades de TFI como tratamento adjuvante à HD. Em um capítulo subsequente, é apresentado um estudo que

buscou resumir as respostas individuais de cinco diferentes modalidades de TFI sobre sete desfechos considerados como de alta relevância no cenário da DRCT.

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2. REVISÃO DA LITERATURA

2.1. DOENÇA RENAL CRÔNICA

2.1.1 Conceitos

A doença renal crônica (DRC) é uma condição caracterizada pela deficiência dos rins em realizarem de forma adequada as suas funções fisiológicas. Apresentando-se em seis estágios distintos, o último deles é denominado de DRC terminal (DRCT). Nesta etapa, o rim evidencia um prejuízo funcional muito avançado.[1,2] Com frequência, estes pacientes cursam com anemia, insônia, cansaço, cãibras (tipicamente piores à noite), náuseas, vômitos, emagrecimento repentino e anorexia, edema periférico, oligúria e hematúria, entre outros sinais e sintomas.[3,4]

A DRC também pode cursar inicialmente sem sinais e sintomas, o que lhe traz a alcunha de "assassino silencioso". Assim, com o passar do tempo a doença vai progredindo e muitas vezes os sintomas só surgem quando a doença está em uma fase mais avançada. Enfermidades que são consideradas como alguns dos maiores fatores de risco para DRC e DRCT – o diabetes mellitus e a hipertensão arterial sistêmica[5] – também podem ser doenças silenciosas, dificultando a sua identificação, assim como um tratamento precoce.

Por fim, a qualidade de vida relacionada à saúde é substancialmente mais baixa nos pacientes com DRC quando comparados à população em geral, e tende a reduzir ainda mais conforme a taxa de filtração glomerular também declina.[4,6] Os pacientes devem receber uma reabilitação focada na educação para lidar com a doença e prevenir complicações, levando em consideração aspectos somáticos, mentais e sociais, os quais podem prolongar a vida e diminuir a mortalidade. Intervenções que visem a educação e mudança no estilo de vida desses indivíduos podem impactar sobremaneira na melhora desse preocupante cenário.

2.1.2 Epidemiologia

A DRC é um problema de saúde pública global que afeta mais de 750 milhões de pessoas em todo o mundo.[7] Nos Estados Unidos (EUA), a incidência de DRCT ajustada para idade, sexo, raça e etnia foi de 386 casos por milhão/ano em 2003 e, respectivamente, 356, 352 e 351 casos por milhão/ano em 2011, 2012 e 2013.[8]

No Brasil, a DRC também é uma condição altamente prevalente e preocupante; em uma população de 200 milhões de indivíduos – 70% considerados adultos – estima-se que até 22 milhões tenham algum grau de insuficiência renal.[9] No sul do Brasil, em estudo com mais de 5 mil indivíduos (18-87 anos de idade) selecionados aleatoriamente de uma região urbana, observou-se prevalência de DRC de 11,4%, sendo tal frequência associada a fatores de risco como o diabetes, hipertensão, idade e obesidade.[10]

O diabetes e a hipertensão são as principais entidades nosológicas que levam à DRC, particularmente nos países de média e alta renda.[11] Diante do exposto e sendo digno de nota, em 2016, um em cada onze indivíduos no mundo era portador de diabetes[12] – fator ao qual são atribuídos aproximadamente 44% dos casos incidentes e 38% dos casos prevalentes de DRCT nos EUA.[13] Quanto à hipertensão, em 2025 estima-se que afetará 1,56 bilhão de adultos.[14] Ademais, cerca de 80% dos pacientes em HD podem apresentar esta enfermidade, com apenas 30% tendo um controle adequado dos seus níveis pressóricos.[15] Portanto, com a incidência e prevalência de casos de diabetes e hipertensão, é esperado que a DRC e DRCT continuem a crescer nesse cenário. Outros fatores de risco relacionados à DRC são o histórico familiar, tabagismo, exposição a nefrotoxinas, etnia (mais comum em negros do que em caucasianos), dentre outros.[16-18]

Em 2010, aproximadamente três milhões de pessoas receberam tratamento dialítico em todo o mundo, e esse número pode se aproximar de seis milhões até 2025.[19]

No Brasil, um levantamento recente realizado por Thomé et al. em cerca de 300 centros de diálise (HD e diálise peritoneal) verificou que mais de 126 mil pacientes encontravam-se em tratamento dialítico.[20] Tal estudo aponta para o crescimento no número absoluto de pacientes que necessitam de diálise em nosso país.

Cursando com um prognóstico reservado, os pacientes com DRCT em HD apresentam diferentes comorbidades e são, portanto, muito propensos a complicações. Foi demonstrado que estes indivíduos têm mortalidade significativamente maior quando comparados a seus pares da mesma idade sem DRCT,[21] com uma sobrevida cumulativa de três anos estimada em 50%.[22] Além disso, a DRC representou 2.968.600 (1%) dos anos de vida ajustados por incapacidade e 2.546.700 (1% a 3%) dos anos de vida perdidos em 2012.[4] Corroborando com esses números, em um estudo bastante recente foi relatado que a DRC continua apresentado um prognóstico reservado, sendo considerada a 16ª principal causa de anos de vida perdidos em todo o mundo.[23]

Por outro lado, após análise dos dados de quase dois milhões de crianças e adultos americanos com DRCT incidente (1995 a 2013), Foster et al. verificaram redução no excesso de risco de morte por todas as causas nesses indivíduos durante este período. Entretanto, foi relatado que a mortalidade geral por DRC aumentou em mais de 30% nos últimos 10 anos, colocando esta entidade como uma das principais causas de morte, ao lado do diabetes e da demência.[24] Mais exatamente, a DRC figura como a 12ª causa mais comum de morte,[25] e o *Global Burden of Disease Study* apresentou uma estimativa de 1,2 milhão de óbitos a ela atribuídos em 2015.[7] No Brasil, em levantamento realizado em 2017, englobando 291 unidades de diálise através da coleta de dados por meio de um questionário *on-line*, foi descrita uma taxa anual de mortalidade bruta ao redor de 20%.[20]

Por sua vez, a principal causa de morte na população mundial são as doenças cardiovasculares (DCVs),[26,27] e isso também é verdadeiro para os pacientes com DRCT.[28] A elevada taxa de mortalidade por DCVs nesses indivíduos pode ser parcialmente explicada pela alta prevalência de marcadores inflamatórios pró-aterogênicos (ex.: proteína C-reativa, interleucina 6) e de dislipidemia,[29,30] além do diabetes e da hipertensão, como explicitado anteriormente, os quais podem predispor à aterosclerose e morte prematura.[28] Muito recentemente, em um grande estudo de base populacional realizado nos EUA, observou-se que os pacientes que iniciaram tratamento dialítico entre 1997-2014 apresentaram altas taxas de eventos cardiovasculares, o que fortalece os dados prévios que classificam indivíduos com DRCT como de muito alto risco cardiovascular.[31]

Por sua vez, crianças que necessitam de HD também evidenciam elevada mortalidade associada à DCVs, a qual não deve ser negligenciada, sendo até mil vezes superior do que naquelas consideradas saudáveis.[32] Em um estudo de coorte com 33.156 crianças e jovens com DRCT que iniciaram terapia de substituição renal entre 2003 e 2013, as DCVs teve um papel significativo, sendo responsável por quase 40% das mortes neste período.[33]

2.1.3 Diagnóstico e tratamento

A respeito do diagnóstico, costuma-se identificar a DRC pela presença de uma anormalidade da estrutura e/ou função renal por um período de pelo menos 3 meses.[4,34] Por sua vez, a taxa de filtração glomerular é uma medida considerada padrão-ouro para se determinar o nível da função renal, bem como o estágio da doença, caso esta esteja presente. Divide-se a doença em seis estágios, desde ≥90 mL/min/1,73 m^2 até <15 mL/min/1,73 m^2,[35] conforme detalhado na **Tabela 1.** Outras formas complementares de

diagnóstico são as medidas de albumina na urina (albuminúria em amostra ou de 24 horas), assim como de creatinina e ureia séricas ou na urina.[36] Quando há presença de leve/moderada excreção de proteína pela urina, já se estabelece um quadro de microalbuminúria (30-300 mg/dia). Por sua vez, o estágio mais avançado de excreção de proteína e de lesão renal passa a ser chamado de macroalbuminúria (>300 mg/dia).[37]

Tabela 1. Classificação da doença renal crônica baseado na taxa de filtração glomerular[35]

			Categorias de albuminúria persistente		
			A1	A2	A3
			Normal ou levemente aumentada	Moderadamente aumentada	Severamente aumentada
			<30 mg/g	30-300 mg/g	>300 mg/g
Estágio 1	≥90 mL/min/1,73 m^2	Normal			
Estágio 2	60-89 mL/min/1,73 m^2	Redução leve			
Estágio 3[a]	45-59 mL/min/1,73 m^2	Redução leve-moderada			
Estágio 3[b]	30-44 mL/min/1,73 m^2	Redução moderada-severa			
Estágio 4	15-29 mL/min/1,73 m^2	Redução severa			
Estágio 5	<15mL/min/1,73 m^2	Insuficiência renal			

Verde: baixo risco (se não há nenhum outro marcador de doença renal: sem DRC); Amarelo: risco moderadamente aumentado; Laranja: alto risco; Vermelho: muito alto risco.

Quando a doença progride e atinge o último estágio, os rins não são mais capazes de realizar as suas funções fisiológicas e acabam por falharem permanentemente; assim, os pacientes passam a necessitar de tratamento dialítico ou transplante renal para sobreviver. Apesar da HD não ser capaz de substituir completamente a função renal perdida, o tratamento dialítico tem como objetivo a

remoção de líquidos acumulados (denominado de ultrafiltração) e resíduos do sangue, restauração dos níveis de eletrólitos e o controle da pressão arterial, características estas de função renal normal. Opções de diálise incluem diálise peritoneal e HD.[38-40] A HD, especificamente, é definida como o transporte de solutos (ex.: ureia) do sangue arterial do paciente para uma máquina denominada dialisador, através de uma fístula arteriovenosa ou cateter. Então, o sangue é exposto à solução de diálise (chamada de dialisato) através de uma membrana semipermeável, devolvendo, posteriormente, o sangue limpo para o paciente por via venosa.[40] Geralmente, as sessões de HD são realizadas três vezes por semana,[41] durando um período relativamente longo, que varia de 3 a 4 horas.[42]

Algumas fórmulas estão disponíveis para estimarem a dose de diálise do paciente. Entre elas, existem a taxa de redução de ureia (URR) e a depuração fracional de ureia (Kt/V).[43] Na fórmula do Kt/V, especificamente, o (K) é definido pela depuração de ureia do dialisador, multiplicada pelo tempo de tratamento (t), sendo estes divididos pelo volume de distribuição de ureia do paciente (V). O K depende do tamanho do dialisador, da taxa de fluxo de sangue e do fluxo do dialisato. O t normalmente dura entre 3 e 4 horas (180-240 minutos por sessão de diálise), mas pode ser ajustado. O volume de distribuição de ureia do paciente (V) é estimado por meio de uma equação antropométrica, a qual leva em consideração: gênero, idade, altura e peso do indivíduo (por exemplo: equação de Watson).[44,45] A dose padrão adequada de HD é estimada para os pacientes que são submetidos a três sessões por semana. A sua adequação é fixada pelas diretrizes do *National Kidney Foundation Disease Outcomes Quality Initiative* (NKF-DOQI), recomendando-se um Kt/V maior que 1,2.[46]

2.2 TREINAMENTO FÍSICO EM PACIENTES COM DOENÇA RENAL CRÔNICA

Os pacientes com DRC são comumente inativos, comportamento este que acaba por prejudicar a sua capacidade funcional.[47,48] Além de redução na força muscular,[49] prejuízos na densidade mineral óssea,[50] dentre outros fatores, eles também tendem a apresentar um menor consumo máximo de oxigênio (VO_2máx) quando comparados à população geral.[51] Um paciente em HD pode permanecer internado, em média, um total de 11 dias por ano. Após a alta, pode apresentar chance de readmissão de aproximadamente 40% dentro de um mês, o que induz ainda mais à perda de massa muscular. Juntamente com estimativas de quatro a seis semanas por ano de imobilização, há um declínio ainda maior da capacidade física nesses pacientes.[52]

Como descrito nos capítulos anteriores, os indivíduos com DRC estão mais suscetíveis às DCVs, decorrente, em parte, do seu comportamento sedentário. Portanto, serem fisicamente ativos não significa apenas uma melhora na sua capacidade funcional e na qualidade de vida; mais do que isso, é possível que o risco de desenvolvimento e progressão das DCVs possa ser substancialmente reduzido por um estilo de vida ativo.

Como recomendação, aconselha-se que os pacientes com DRC estejam engajados em pelo menos 30 minutos de TF por dia, cinco vezes por semana,[53] sendo que ao longo desses dias, três devam ser destinados ao TF aeróbico de intensidade leve à moderada, e dois dias de TF resistido leve à moderado, com séries variando entre 10-15 repetições.[51] Entretanto, aconselhamento sobre a importância do TF para este grupo de pacientes parece ser uma realidade ainda escassa. Em uma pesquisa realizada com quase 200 nefrologistas, todos eles concordaram que a atividade física era um componente importante para os seus pacientes; no entanto, mais de 1/3 deles não pensaram que os seus pacientes estariam abertos a uma discussão sobre o assunto.[54]

Liu et al. demonstraram uma associação entre a presença de DRC, incapacidade de mobilidade e declínio na velocidade da marcha, o que destaca a perda de independência física nesta população.[55] Dessa forma, a identificação dos pacientes em maior risco e com maiores limitações funcionais pode permitir o desenvolvimento de estratégias interdisciplinares que visem a sua educação e conscientização à respeito dos benefícios do TF, proporcionando ganhos de força muscular e capacidade de realizar as suas atividades diárias com segurança.

2.3. **TREINAMENTO FÍSICO INTRADIALÍTICO**

O exercício deveria ser um componente de rotina para os pacientes com DRCT submetidos à HD, dado os seus potenciais benefícios.[56-58] Tendo em vista a alta prevalência de comorbidades nestes pacientes, muitos podem não se sentir seguros ou mesmo estimulados a praticarem o TF fora do ambiente hospitalar. Como as sessões de HD costumam durar cerca de 4 horas, a monotonia é quase inevitável. Além disso, foi descrito que aproximadamente 80% dos indivíduos dormem durante as sessões de HD. É importante mencionar que o risco de morte nos pacientes que dormem mais do que 9 horas por dia pode ser até 50% maior quando comparados àqueles que dormem por menos tempo.[59] Assim, foi desenvolvido um programa de treinamento para ser realizado durante as sessões de HD – conhecido como TF intradialítico (TFI).[60,61] Nesse sentido, o TFI pode ser mais vantajoso para os pacientes quando comparado ao treinamento fora do ambiente dialítico. Por exemplo, pode haver uma maior taxa de assiduidade, motivação e segurança através de um monitoramento regular mais rigoroso. Por fim, os pacientes mais idosos e com problemas mais graves de saúde também podem se beneficiar deste tipo de programa, se sentindo mais confiantes com profissionais supervisionando e orientando a prática do treinamento.

Alguns dos benefícios que podem ser decorrentes do TFI são: melhora na capacidade funcional (VO_2máx[62,63] e teste de caminha de 6 minutos (TC6M)),[64-66] força muscular,[67,68] melhora da ansiedade,[69] fadiga,[70] e até redução no uso de medicamentos antihipertensivos.[71,72]

Neste tipo de programa, é possível a realização de diversas modalidades de treinamento, a citar: 1) aeróbico (com bicicletas ergométricas adaptadas);[73] 2) resistido (utilizando-se halteres livres, caneleiras, bandas elásticas, *leg press* adaptado, etc.);[74-76] 3) combinado (aeróbico + resistido);[77-79] 4) treinamento muscular inspiratório (com dispositivos específicos);[80,81] e 5) eletroestimulação funcional (realizada com eletrodos que geram correntes elétricas na musculatura que se quer estimular.[82,83]

Para que os diferentes protocolos de treinamento sejam os mais seguros possíveis e que se evitem eventos adversos, há algumas contraindicações antes de se iniciar o TFI, como por exemplo: a) hipertensão não controlada; b) arritmias potencialmente letais (incluindo taquicardia ventricular sustentada); c) angina instável; d) doença hepática ativa; e) diabetes não controlada; f) doença cerebral avançada; e g) hipercalemia persistente antes da HD.[84]

2.3.1. **Treinamento aeróbico intradialítico**

Tradicionalmente, o EF aeróbico é definido como aquele no qual as atividades envolvam gasto calórico acima do despedido no repouso por diferentes grupos musculares (ex.: caminhadas, corridas e andar de bicicleta).[85] Como o TFI é realizado durante as sessões de HD, no treinamento aeróbico intradialítico (TAI) geralmente utiliza-se bicicletas ergométricas ou cicloergômetros adaptados à cadeira ou à maca do paciente. Portanto, é possível se pedalar sentado quanto deitado.

Diversos ensaios clínicos randomizados avaliaram a importância do TAI em pacientes com DRCT.[65-67,86-92] A frequência destes protocolos pode variar. Por exemplo, há estudo onde foi aplicada apenas duas sessões semanais de TAI;[67] entretanto, a grande maior tende a aplicar três vezes por semana.[64,65,88,90,92]As intensidades geralmente são de leve à moderada, e podem ir aumentando gradativamente, conforme a tolerância do paciente.

Liao et al. submeteram 40 pacientes com DRCT à TAI de intensidade moderada (12-15 na Escala de Borg) em cicloergômetro, três vezes por semana, 30 minutos/dia, durante 12 semanas. Ao final deste período, houve redução significativa nos níveis de PCR ultra-sensível quando comparado ao grupo controle sem treinamento físico (1,25 mg/dL para 0,78 mg/dL *versus* 1,24 mg/dL para 1,23 mg/dL), respectivamente.[93] Corroborando com estes achados, Afshar et al. aplicaram treinamento em cicloergômetro três vezes por semana, 20-40 minutos por sessão, observando marcada redução nos níveis de creatinina sérica no grupo arrolado para o TAI *versus* grupo controle (sem exercício) (11,1 mg/dL para 3,82 mg/dL *versus* 9,11 mg/dL para 9,22 mg/dL), respectivamente. Além disso, os autores também descreveram uma importante melhora nos níveis de PCR ultra-sensível no grupo ativo *versus* grupo controle sem qualquer treinamento que, ao contrário, apresentou aumento deste marcador inflamatório ao final de 8 semanas (5,45 mg/L para 0,88 mg/L *versus* 4,08 mg/L para 4,14 mg/L), respectivamente.[94] Uma vez que os pacientes com DRCT em HD estão mais propensos a complicações cardiovasculares, as quais podem ser potencializadas com o aumento nos marcadores inflamatórios (especialmente a PCR),[30] estes resultados sustentam a importância da aplicação do TAI nesta população.

Além de melhoras nos níveis plasmáticos de PCR, o TAI tem se mostrado uma estratégia interessante para melhora da capacidade funcional dos pacientes. Dobsak et

al. aplicaram o TAI por 30-50 minutos, três vezes semanais durante 20 semanas, com intensidade moderada (60% da frequência cardíaca máxima), e evidenciaram ganhos significativos (aproximadamente 60 metros) no TC6M, ao passo que houve redução no grupo controle.[95] Esses dados vão ao encontro daqueles encontrados por Liao et al.[93] e, mais recentemente por Fernandes et al.[64] Em um estudo de coorte com 52 pacientes com DRCT acompanhados por 12 anos, a sobrevida aumentou em aproximadamente 5% a cada 100 metros percorridos no TC6M,[96] fortalecendo a importância do aumento na capacidade funcional para estes pacientes, além de expor o TC6M como método de valor prognóstico na prática clínica.

Além do TC6M, outro parâmetro amplamente aceito e consolidado para mensuração da capacidade cardiorrespiratória é o VO_2máx (ou de pico). Koufaki et al. estudaram 48 pacientes em HD, com idade variando entre 50 e 58 anos, os quais foram submetidos a TAI em cicloergômetro com aumento gradual da intensidade e do volume de treinamento. Nas semanas 1-4 eram realizados 20 minutos de exercício; semanas 5-8, 20 minutos; e finalmente, semanas 9-12, 40 minutos. A frequência utilizada também foi de três vezes por semana. Ao final dos três meses, o grupo de exercício apresentou um aumento de 2,9 $mL.kg^{-1}.min^{-1}$, ao passo que no grupo controle, sem exercício, houve decréscimo nos valores de VO_2máx.[97] Cabe salientar que em estudo publicado no já longínquo anos de 1995, pacientes submetidos ao TAI apresentaram ganho médio de 3,7 $mL.kg^{-1}.min^{-1}$, sem mudança no grupo que não realizou treinamento.[98] Por sinal, vinte e três anos mais tarde, McGregor et al. observaram melhora de 2,46 $mL.kg^{-1}.min^{-1}$ no VO_2máx de pacientes com DRCT submetidos à TAI por 10 semanas, três vezes semanais, com duração diária de 50-60 minutos.[62] Corroborando com os resultados supracitados, os pacientes que não foram engajados no programa de treinamento apresentaram redução nos valores de VO_2máx ao fim do estudo. É importante citar que

Sietsema et al. estudaram uma coorte de 175 pacientes em HD durante um período médio de 3 anos e meio, e destacaram o VO_2máx como um importante preditor de sobrevida nesta população, se sobrepondo até outras variáveis prognósticas tradicionais. Aliás, aqueles pacientes com VO_2máx acima de 17,5 $mL.kg^{-1}.min^{-1}$ evidenciaram uma sobrevida significativamente maior do que aqueles com valores mais baixos.[99] Desta forma, a capacidade de exercício aeróbico pode fornecer informações prognósticas adicionais nos pacientes com DRCT submetidos à HD. Assim, recomenda-se o TAI como um componente importante neste cenário.

Em relação ao Kt/V, os resultados são conflitantes. Dobsak et al.,[95] Mohseni et al.[100] e Paluchamy & Vaidyanathan[101] descreveram ganhos significativos no Kt/V no grupo submetido ao TAI quando comparado a grupos sem treinamento, e esses resultados puderam ser explicados por uma redução significativa na recuperação do soluto após o exercício, devido ao aumento da perfusão dos músculos esqueléticos.[102] Entretanto, Giannaki et al.,[90] Liao et al.[93] e Afshar et al.[94] não observaram qualquer alteração nesta variável com o TAI, fazendo com que a melhora no Kt/V com TAI ainda permaneça um tópico a ser explorado.

2.3.2. **Treinamento resistido intradialítico**

O treinamento resistido, também conhecido como treinamento contra-resistência, geralmente é realizado com auxílio de pesos, e visa, dentre outros benefícios, a melhora da força e aumento ou manutenção da massa muscular.[103,104] Esta modalidade deve englobar o treinamento de todos os principais grupos musculares em dois ou mais dias da semana.[105]

A DRC provoca uma série de alterações na função muscular dos pacientes, podendo ser observado catabolismo muscular, sarcopenia, neuropatia, atrofia das fibras

musculares tipo I e II e fraqueza, o que contribui para redução na atividade física, seja no dia a dia ou como exercício.[106] Seguindo este raciocínio, foi relatado que pacientes com DRC (estejam eles em HD ou não), têm um risco aumentado quando apresentam redução na massa muscular,[107] ao passo que a presença de uma maior massa corporal magra foi associada a menor risco de mortalidade em uma grande coorte de pacientes nefropatas.[108,109] Ren et al. seguiram de forma prospectiva 131 pacientes em HD, relatando alta incidência de sarcopenia, a qual piorou de forma gradativa com o avançar da idade. Em um ano de acompanhamento, o risco de morte naqueles sarcopênicos era maior do que o de pacientes não sarcopênicos,[109] o que corrobora com achados de outros estudos[107,108] e fortalece a importância da manutenção da massa muscular nesta população. Por sua vez, Johansen et al. mostraram que a força muscular foi associada como um importante preditor da velocidade da marcha em pacientes em HD.[110] Além disso, a força muscular isocinética também parece desempenhar importante papel sobre VO_2máx desses indivíduos.[111] Sendo assim, o treinamento resistido pode auxiliar de forma importante na reversão ou atenuação destas complicações, e talvez ter influência na sobrevida destes pacientes.

Diversos equipamentos ou acessórios vêm sendo utilizados para o treinamento resistido intradialítico (TRI). Nos diferentes estudos foram utilizados halteres de peso livre,[112,113] bandas elásticas e Theraband®,[63,114,115] bolas elásticas[116] e até equipamentos para o músculo quadríceps, como *leg press* adaptado.[116,117]

Cigarroa et al. estudaram treze pacientes relativamente jovens (idade média de 38 anos), os quais foram submetidos a TRI duas vezes por semana, durante 2 meses. Os músculos predominantemente treinados foram quadríceps, glúteos e isquiotibiais. Inicialmente, os pacientes pedalavam por 5 minutos em bicicleta estacionária em uma intensidade leve-moderada (50-60% da frequência cardíaca máxima) como forma de

aquecimento. Após, eram estimulados a realizarem três séries de 10 repetições para cada exercício. Por fim, como desaquecimento, alongamento auto-assistido com faixas elásticas de baixa resistência era realizado. Ao final do estudo, melhora significativa foi observada na força muscular e nos questionários de qualidade de vida; ainda, houve declínio na pressão arterial diastólica, além de ganhos importantes em metros percorridos no TC6M.[118]

Em outro estudo com aplicação de TRI em 10 pacientes em HD, também foram observados alguns resultados animadores. O protocolo seguiu-se por três meses, com 2 sessões semanas de TRI supervisionado, englobando aquecimento de 5-10 minutos, seguido por até 9 exercícios de fortalecimento muscular com a utilização de pesos livres, com intensidade sendo aumentada gradativamente conforme tolerância do paciente. Além disso, os pacientes foram encorajados à realização de treinamento não-supervisionado em casa através do uso de *Theraband*®, seguindo dicas e instruções por vídeos. Ao final de três meses, foi observada melhora no teste de sentar e levantar (de 10 vezes), assim como na distância percorrida no TC6M. Também é importante ressaltar que houve ausência de complicações ou lesões relacionadas ao treinamento supervisionado e não-supervisionado.[119]

2.3.3. **Treinamento combinado intradialítico**

Quando se combina o treinamento aeróbico e o treinamento de força, há a modalidade conhecida como treinamento combinado. O treinamento aeróbico visa, principalmente, uma melhoria na capacidade cardiorrespiratória e cardiovascular; já o treinamento de força objetiva a melhora da força muscular e preservação ou aumento da massa magra, como mostrado no capítulo anterior. Portanto, a combinação desses treinamentos tem o intuito de alcançar ambos os benefícios.

Peres et al. submeteram 58 pacientes a um programa de treinamento combinado intradialítico (TCI) supervisionado por 2 meses. Os exercícios eram realizados três vezes por semana, com 1 hora de duração, sempre durante as duas primeiras horas de HD. Após um período de aquecimento, os pacientes treinavam em cicloergômetro e, posteriormente, realizavam exercícios de força com pesos, bolas e elásticos; o desaquecimento era feito no cicloergômetro em baixa velocidade. Ao final dos dois meses houve melhora significativa na capacidade funcional (mensurada através do TC6M e do VO_2máx). Além disso, foram observados ganhos na força muscular do quadríceps.[120]

Estudos que aplicaram o TCI em idosos com DRC também evidenciaram bons resultados.[121,122] Em um desses, a aplicação do TCI foi de baixa intensidade (com aumento gradual). Semelhante ao estudo descrito anteriormente, o treinamento também foi realizado nas duas primeiras horas de HD. A duração variou entre de 45-50 minutos, duas vezes por semana, durante 3 meses. Os exercícios eram prescritos de forma individualizada. O treinamento aeróbico foi feito em cicloergômetro, e o treinamento de força utilizando faixas de resistência elástica, halteres e *medicine ball*. Após 12 semanas, os idosos apresentaram ganhos na força muscular mensurada pelo *handgrip* (kg) (16,6 para 18,2), força máxima de extensão do quadríceps (kg) (10,5 para 12,9), e na capacidade funcional avaliada pelo TC6M (234 metros para 274 metros).[121] Alguns mecanismos, como maior liberação de lactato sanguíneo, recrutamento de unidades motoras, formação de capilares e conteúdo mitocondrial, além do próprio ganho de força do quadríceps, são fatores que podem explicar a melhoria na capacidade funcional promovida pela combinação de exercícios aeróbicos e de força.[123]

Tais dados foram corroborados por uma série de ensaios clínicos randomizados que também avaliaram o efeito do TCI sobre a força muscular e capacidade

funcional.[63,77-79,115,124,125] Por exemplo, Ouzouni et al. submeteram os pacientes a um protocolo de TCI três vezes por semana, durante 10 meses. Inicialmente os indivíduos realizavam 5 minutos de aquecimento, 20 minutos em cicloergômetro e 5 minutos de desaquecimento, seguido por 30 minutos de exercícios de força (com auxílio de *theraband* e pesos livres) e de flexibilidade, com intensidade variando entre 13-14 na Escala de Borg (sensação de um pouco difícil). Um ganho importante foi observado no VO_2máx dos pacientes submetidos ao treinamento (20,9 $mL.kg^{-1}.min^{-1}$ para 25,3 $mL.kg^{-1}.min^{-1}$), ao passo que nenhuma alteração foi observada no grupo controle sem treinamento durante os 10 meses (20,3 $mL.kg^{-1}.min^{-1}$ para 20,1 $mL.kg^{-1}.min^{-1}$).[78] Dados semelhantes também foram observados por outros ensaios clínicos randomizados,[63,77,79,115] o que faz dessa modalidade de treinamento uma estratégia atrativa para indivíduos em HD.

Esses resultados devem ser vistos com entusiasmo pelos prestadores de cuidados desses pacientes, uma vez que o VO_2máx é um preditor importante de sobrevida nos pacientes em HD, se sobrepondo até muitas variáveis prognósticas tradicionais (como hemoglobina e níveis de creatinina).[99] Dessa forma, a literatura mostra que o TCI tem o potencial de melhorar significativamente a capacidade funcional, podendo ter assim uma repercussão positiva até na sobrevida.

2.3.4. **Eletroestimulação funcional intradialítica**

A eletroestimulação funcional é uma forma de tratamento que pode melhorar a função muscular e a aptidão cardiorrespiratória através da indução de contrações musculares sem necessidade de esforço voluntário, não requerendo participação ativa do indivíduo. Nesse sentido, pode ser uma estratégia útil e eficiente para pacientes mais graves e com limitações funcionais importantes.[126,127] Além disso, como o número de

pessoas idosas em HD continua a crescer, e até 70% deles podem apresentar algum grau de fragilidade física,[128] a eletroestimulação funcional se torna uma modalidade de treinamento atraente para este subgrupo de pacientes.

Apesar de ainda ser escasso o número de estudos que avaliaram os efeitos da ELF intradialítica (ELFI) nos pacientes com DRCT, aqueles que o fizeram mostraram resultados animadores. Brüggemann et al. aplicaram um protocolo de ELFI composto por um total 12 sessões, 3 vezes por semana, durante 1 hora cada. Os pacientes tinham idade média de 55 anos e os grupos foram divididos em ELFI de baixa frequência (5Hz e intensidade média de 13,85mA) e alta frequência (50 Hz e intensidade média de 72,90 mA). Ao final do estudo, a distância percorrida no TC6M aumentou em ambos os grupos, não havendo diferença significativa entre eles: 403 para 420 metros *versus* 435 para 457 metros nos grupos baixa e alta frequência, respectivamente.[129]

Em um ensaio clínico randomizado com 40 adultos, a ELFI também evidenciou efeitos benéficos sobre a função pulmonar e a capacidade funcional. Ela foi aplicada no quadríceps femoral dos pacientes durante 30 minutos, três vezes por semana, durante dois meses. Foi determinada uma frequência de 50 Hz por dois segundos, e um repouso por dez segundos. A intensidade da corrente elétrica foi determinada pela tolerância de cada paciente. O teste de uma repetição máxima e a distância percorrida no TC6M foram maiores após o protocolo no grupo de tratamento. Além disso, foi observada redução na pressão arterial sistólica.[82] Dentre os mecanismos propostos para estes resultados, destaca-se o fato de que a eletroestimulação funcional, através da ativação das fibras musculares, é capaz de contribuir com a melhora do torque muscular, podendo promover maior resistência à fadiga.[130,131]

2.3.5. **Treinamento muscular inspiratório intradialítico**

O treinamento muscular inspiratório (TMI) é uma técnica utilizada com o auxílio de dispositivos específicos, com o intuito de se melhorar o sistema cardiovascular e a atividade/função dos músculos respiratórios, especialmente o diafragma.[132] Consequentemente, a capacidade funcional e a realização das atividades de vida diária podem ser otimizadas. A realização deste treinamento deve ser controlada, específica e repetida em intervalos regulares.

O TMI já provou ser benéfico para a função respiratória de pacientes com doenças crônicas.[133,134] Por exemplo, está bem estabelecido que indivíduos acometidos por insuficiência cardíaca e fraqueza muscular inspiratória podem obter melhora acentuada da força muscular inspiratória e da capacidade funcional (ex.: incremento no TC6M e no VO_2máx) com a prática do TMI;[134] por sua vez, pacientes com doença pulmonar obstrutiva crônica têm benefício significativo na força e resistência muscular respiratória, redução da dispneia e aumento na resistência ao esforço.[135]

Os pacientes com DRC, especificamente, não raramente apresentam quadros de desnutrição, atrofia muscular de fibras I e II e perda de massa muscular (descrito em capítulos anteriores). Dessa maneira, pode haver redução da força e função dos músculos respiratórios, comprometendo, inclusive a capacidade funcional.[136] Em 1994, evidências já apontavam para uma tendência de redução ao redor de 40% na força muscular inspiratória dos pacientes com DRCT, quando comparados a indivíduos saudáveis.[137] Por sua vez, Figueiredo et al. evidenciaram a fraqueza muscular inspiratória como um preditor independente de comprometimento da capacidade funcional em indivíduos submetidos à HD.[138] Dessa forma, o TMI pode ser visto como uma forma importante de treinamento adjuvante neste cenário, de modo especial destinado para aqueles (mas não somente) pacientes em HD e com importantes

limitações neuromusculares, parcela não desprezível dessa população. Além de diversas complicações já descritas neste documento, mais da metade dos pacientes em HD podem estar se exercitando menos de uma vez por semana,[139] o que também contribui para as limitações frente ao exercício. Assim, intervenções de fácil aplicabilidade e baixo custo, a exemplo do TMI, podem ser realizadas durante as sessões de HD e contribuir para redução das complicações oriundas de um comportamento sedentário.

Apesar dos benefícios bem estabelecidos do TMI, ensaios clínicos randomizados com aplicação de TMI intradialítico são escassos, mas corroboram evidenciando ótimos resultados. Em um destes estudos, Campos et al. estudaram 41 pacientes com idade média de 50 anos, submetidos a TMI supervisionado, aplicados 3 vezes por semana, através do *Threshold* (um dos dispositivos utilizados para realização do TMI). Os participantes eram instruídos a respirar (treinamento inspiratório) e expirar (treinamento expiratório). A intensidade do TMI foi aumentada gradativamente. De forma detalhada, as primeiras 12 sessões tinham duração de 30 minutos cada e resistência de 15 cmH_2O; as últimas 12 sessões duravam 40 minutos cada, com resistência estabelecida em 20 cmH_2O. Após dois meses, uma melhora significativa foi observada no ganho de metros percorridos avaliado através do TC6M, quando se comparou o grupo TMI *versus* o grupo controle (sem treinamento): 380,5 metros ± 108,0 para 459,0 metros ± 103,0 *versus* 388,5 metros ± 99,7 para 338,5 metros ± 87,1, respectivamente. A diferença média entre os grupos foi de 126,5 metros.[140]

Em outro ensaio clínico randomizado, Pellizzaro et al. também submeteram pacientes com DRCT a um programa de TMI intradialítico com intensidade determinada de 50% da pressão inspiratória máxima. Este experimento que teve duração de 10 semanas, consistiu na realização de 30 sessões de treinamento nas primeiras 2 horas de HD. Os pacientes eram orientados a realizarem 15 inspirações com descanso

de 1 minuto entre elas, três vezes por semana. Semelhante ao estudo descrito anteriormente, o treinamento foi realizado com auxílio do *Threshold.* Ao final do estudo, também foi observada melhora significativa no TC6M no grupo TMI, com ganho médio de 65 metros, ao passo que não houve nenhuma alteração no grupo controle (sem treinamento).[80]

Em um ensaio clínico randomizado com 25 pacientes ~~e~~ realizado no Brasil, pacientes com DRCT foram submetidos a um protocolo de TMI intradialítico de alta intensidade, executado com o dispositivo *POWER breathe Plus Light Resistance*®. Os pacientes se exercitaram por cinco semanas, 6 vezes por semana, com cada sessão consistindo de 5 séries de 10 repetições. Com a carga sendo ajustada semanalmente, o TMI era iniciado com 50% da pressão inspiratória máxima (1ª semana), 60% da pressão inspiratória máxima (2ª e 3ª semanas), até atingir 70% da pressão inspiratória máxima na 4ª e 5ª semanas. A intensidade era ajustada semanalmente, com utilização de um manovacuômetro digital. Ao fim do estudo, apesar melhora na força muscular inspiratória, surpreendentemente não houve diferença significativa na capacidade funcional avaliada através do TC6M entre o grupo intervenção e o controle.[141] Como descrito pelos autores, diferenças entre percentual de sedentários nos grupos, além de valores de hematócrito abaixo dos valores normais no grupo intervenção, podem explicar parcialmente estes resultados.

O TMI realizado durantes as sessões de HD pode ser uma alternativa de fácil aplicabilidade, especialmente para os pacientes mais frágeis. Os ganhos de força nos músculos respiratórios podem se traduzir em melhora da capacidade funcional, a qual pode ter repercussão direta na qualidade de vida dos pacientes. Todavia, as evidências neste cenário ainda são escassas e futuros estudos bem delineados são necessários para se determinar o real efeito do TMI intradialítico, além da melhor forma, volume e

intensidade para gerar os maiores benefícios para os pacientes com DRCT em HD.

Em síntese, os diversos tipos de programas de treinamento físico disponíveis e aplicados para os pacientes com DRCT em HD demonstram algum grau de benefício sobre algum importante desfecho para esses indivíduos – seja ele o aeróbico, resistido, combinado, o TMI ou até mesmo a ELF. Entretanto, deve-se ter em mente que o corpo de informações sobre qual a modalidade de treinamento é a mais eficaz/efetiva ainda é limitado. Nesse particular, estudos melhor delineados, assim como novas revisões sistemáticas e meta-análises destes experimentos serão muito bem-vindas.

Por fim, mesmo com lacunas a serem preenchidas, as evidências disponíveis sobre os diferentes tipos de treinamento já apontam para inúmeros benefícios promovidos nesta população, os quais foram amplamente descritos neste manuscrito. O que fica é que os pacientes com DRCT em HD merecem ter a opção de utilizá-los no seu mundo real.

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OBJETIVOS

Objetivo geral

Avaliar o efeito de cinco diferentes métodos de treinamento intradialítico sobre oito diferentes desfechos, como pressão arterial e marcadores funcionais e bioquímicos considerados de alta relevância para pacientes com doença renal crônica em fase terminal submetidos à hemodiálise.

Objetivos específicos

- Realizar uma revisão sistemática e meta-análise de ensaios clínicos randomizados para sintetizar os efeitos isolados dos treinamentos intradialíticos aeróbico, resistido, combinado (aeróbico + resistido), treinamento muscular inspiratório e eletroestimulação funcional sobre os seguintes desfechos: a) Kt/V; b) pressão arterial; c) VO_2máx; d) teste de caminhada de 6 minutos; e) proteína C-reativa; f) interleucina-6; g) hemoglobina; e h) colesterol total;
- Realizar análises de sensibilidade para estratificação de estudos de acordo com protocolos que possam influenciar nas meta-análises realizadas, como estudos com sessão única de treinamento, ou também com possível aplicação de treinamento intradialítico associado a treinamento pré e/ou pós sessão de hemodiálise.

ARTIGO

Intradialytic Training in Patients With End-Stage Renal Disease:

A Systematic Review and Meta-Analysis of Randomized Clinical Trials Assessing the Effects of Five Different Training Interventions

Treinamento Intradialítico em Pacientes Com Doença Renal em Estágio Final:

Revisão Sistemática e Meta-Análise de Ensaios Clínicos Randomizados Avaliando os Efeitos de Cinco Diferentes Intervenções de Treinamento

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Intradialytic Training in Patients With End-Stage Renal Disease:

A Systematic Review and Meta-Analysis of Randomized Clinical Trials Assessing the Effects of Five Different Training Interventions

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Abstract

Objective

Patients with end-stage renal disease (ESRD) undergoing hemodialysis may have reduced dialysis adequacy (Kt/V), low cardiorespiratory fitness (CRF), and worse prognosis. Different types of intradialytic training (IDT) may serve as an adjunct therapy for the management of the ESRD. This systematic review and meta-analysis aimed to assess the impact of different types of IDT on clinical outcomes and functional parameters in ESRD.

Methods

PubMed, Embase, CINAHL, Cochrane CENTRAL, Scopus, SPORTDiscus, and Google Scholar were searched for randomized clinical trials in adult patients with ESRD which compared IDT with usual care (UC), without language restrictions and published up to July 2019; a handsearch of references was also performed. Certainty of evidence was assessed using GRADE, and risk of bias in primary studies with the RoB 1.0 tool.

Results

Fifty studies were included (n=1,757). Compared to UC, aerobic IDT improved Kt/V (WMD = 0.08), VO_2peak (WMD = 2.07 mL.kg.$^{-1}$.min^{-1}), 6-minute walk test (6MWT) distance (64.98 m), reduced systolic blood pressure (-10.07 mmHg) and C-reactive protein (-3.28 mg/L). Resistance training increased 6MWT distance (68.50 m). Combined training increased VO_2peak (5.41 mL.kg.$^{-1}$.min^{-1}) and reduced diastolic blood pressure (-5.76 mmHg). Functional electrostimulation (FES) and inspiratory muscle training (IMT) improved 6MWT distance (54.14 m and 117.62 m, respectively). There was no impact on total cholesterol, interleukin-6, or hemoglobin levels. There was no difference in incidence of adverse events between the IDT and control groups. The certainty of evidence was variable according to the GRADE scale, with most outcomes rated very low certainty. The risk of bias assessment of primary studies showed unclear risk in most.

Conclusions

Aerobic, resistance, and combined training during hemodialysis, as well as FES and IMT, demonstrated to be effective for the treatment of the patient with ESRD. Our data should be interpreted in light of the unclear risk of bias of most evaluated articles and the low to very low certainty of evidence for evaluated outcomes.

Keywords

End-stage renal disease; intradialytic exercise; dialysis efficacy; meta-analysis.

Prospero registration ID

CRD42017081338.

Data Sharing Repository

https://osf.io/fpj54/.

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None.

Data Sharing Policy Statement

We followed the International Committee of Medical Journal Editors Data Sharing Statement for the data sharing policy of this study. All the data and materials related to this study are available at https://osf.io/fpj54/ (Creative Commons CC-By Attribution 4.0), without restrictions to authors request, timing and purpose of use.

Introduction

Patients with end-stage renal disease (ESRD) usually have a series of cardiovascular risk factors [1]. Hypertension [2], increased levels of inflammatory markers [3], dyslipidemia [4], and physical inactivity [5] are highly prevalent in this setting. Hemodialysis (HD) is the primary treatment for ESRD, and optimization of adjunctive therapies may improve prognosis [6]. Recently, structured intradialytic training (IDT) has been proposed as an effective complementary therapy for patients with ESRD by increasing dialysis adequacy (Kt/V) and other clinically relevant outcomes, such as blood pressure (BP) and cardiorespiratory fitness (CRF) when compared to usual care [7-9]. Kong et al. [10] showed a 14% improvement in Kt/V after IDT, at least partially explained by a significant reduction in solute rebound following exercise due to increased perfusion of the skeletal muscles, and suggested that patients could thus save 20 minutes of HD per day. Although most studies have used aerobic, resistance, or combined exercise interventions [11-13], recent evidence has considered other types of IDT; inspiratory muscle training (IMT) and functional electrostimulation (FES) have emerged as attractive strategies, especially for the most debilitated patients [14, 15]. On the other hand, evidence from primary studies regarding the efficacy and expected benefit of IDT is conflicting [16].

There is a lack of robust evidence on the impact of different exercise strategies as IDT when compared to patients' usual care. In addition, some well-established adjuvant therapies, such as IMT and FES, have not been adequately studied as IDT modalities. Within this context, we evaluated the impact of different types of IDT on some parameters important for patients with ESRD, through a systematic review and meta-analysis (SRMA) of randomized clinical trials (RCTs) that primarily evaluated outcomes such as Kt/V, CRF, and blood pressure (BP), as well as other secondary outcomes.

Methods

This SRMA was prospectively registered at inception in the International Prospective Register of Systematic Reviews (PROSPERO) under identification number CRD42017081338, containing pre-specified primary and secondary outcomes, full eligibility criteria, and methods. In compliance with reproducibility standards, all materials and raw data are available at **https://osf.io/fpj54/**. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement [17] was used to guide the reporting of this manuscript. There were no deviations from any of the pre-specified methods.

Eligibility criteria

Eligible studies were required to meet the following criteria: (1) Population: adult (≥18 years old) patients with ESRD undergoing HD, regardless of sex; (2) Intervention: IDT, defined as aerobic, resistance, or combined training; FES or IMT, regardless of duration of exposure; (3) Comparison group: usual care or sham exercises (e.g., stretching), regardless of duration of exposure; (4) Outcomes: Kt/V (primary outcome), office BP, CRF (VO_2peak or VO_2max), 6-minute walk test (6MWT), hemoglobin, C-reactive protein (CRP), interleukin-6 (IL-6), and total cholesterol (TC) (secondary outcomes); (5) Design: RCTs (parallel, crossover or factorial). Crossover trials were considered in their full form if a washout period of at least 2 weeks was respected; otherwise, only the first phase of the trial was included, to avoid carryover effects. Factorial designs were eligible if there was demonstrable absence of interactions between treatments.

Sources of data and research strategies

Seven electronic databases – PubMed/MEDLINE®, Cochrane Controlled Register of Trials (CENTRAL), EMBASE, Scopus, SPORTDiscus, CINAHL and Google Scholar – were queried for published results (and the ClinicalTrials.gov database, for potential unpublished results), from inception until July 2019. We also e-mailed authors of published results to seek information about any unregistered ongoing studies, and those of registered RCTs to seek potentially relevant data for inclusion. All databases were searched using terms for IDT and specific modalities (e.g., "intradialytic exercise"), as well as for outcomes and clinical condition (e.g., "extracorporeal dialysis"), combined with MeSH terms, synonyms, truncations, and Boolean operators. For PubMed/MEDLINE, a highly sensitive filter for RCTs was also used [18].We further searched the reference lists of included studies for other potentially eligible reports. The complete search strategy for all databases is presented in **Supplemental data 1**.

Assessment of study eligibility

Initially, one researcher searched the databases, generated reference lists, created the libraries, and excluded duplicates. The eligibility assessment process was then carried out in two stages: (a) review of potentially eligible studies by checking titles and abstracts in a reference manager software [19]; (b) a final full-text assessment of the remaining reports. Reports not presented in form of an original article (e.g., conference abstracts) were not excluded from the assessment. The two steps were conducted separately and by independent teams of two reviewers. Disagreements were resolved by consensus. The list of included and excluded reports, with their reasons for inclusion or exclusion, can be found at **https://osf.io/fpj54/**.

Data extraction

Data were extracted into a spreadsheet developed by the authors, pilot-tested on the first three eligible studies and then refined accordingly. Two independent reviewers extracted the data; disagreements were solved by consensus or by a third reviewer's opinion. Reviewers were not blinded to authors, institutions, or journals. The parameters of interest were (1) publication (e.g., journal name, year of publication, conflicts of interest), (2) demographics (e.g., age, sex, duration of ESRD and HD), (3) exercise interventions (e.g., modalities, duration, and frequency), (4) outcomes (unit, point-estimates, dispersions, *P*-values), and (5) design (parallel, crossover, or factorial RCT). The full glossary of extracted variables with their definitions is available at **https://osf.io/fpj54/.**

Risk of bias in primary studies

The risk of bias or primary studies was assessed with the Risk of Bias Tool 1.0 from Cochrane Collaboration in its full format (without addition or exclusion of domains) [20].Two reviewers (FF and DS) independently evaluated seven domains of bias in each study, relying on the information presented in the study report or available protocols. The domains considered were: (a) Selection bias due to random sequence generation, (b) Selection bias due to allocation concealment, (c) Performance bias, (d) Detection bias, (e) Attrition bias, (f) Reporting bias, and (g) Other bias. We followed the supporting material of the RoB 1.0 tool. Whenever available, protocols were checked for selective outcome reporting and for potential deviations. Discrepancies between the two reviewers were resolved by consensus. Raw data with commentary from the reviewers can be found at **https://osf.io/fpj54/**.

Summary measures

Weighted mean differences (WMD) by the inverse variance of primary studies with 95% confidence intervals (95%CI) of dialysis efficacy were our primary measure of effect. For qualitative data synthesis, data were entered into a comprehensive table containing detailed information about population, intervention, comparison group, outcomes (with directions), experimental design, and source of funding. Adverse events were only summarized qualitatively.

For the meta-analysis, we pooled the means and estimates of variances (i.e., standard deviations – SD) of the final observations of the per-protocol analysis. Hence, whenever necessary, change-from-baseline effect sizes (point-estimate and dispersion) were transformed to final observations. Ten of the studies included in this review used intention-to-treat analysis.

If any study presented the results as standard error, they were transformed to SD [21].In case of any skewed data presented as median and interquartile ranges, the SD was approximated based on the interquartile range (Q4–Q1) using the method of Wan et al. [22], which takes the sample size into account. In case of missing data, we imputed the narrowest point-estimate and the largest dispersion unit from our available outcome dataset, to exclude possibilities of self-benefit in our synthesis (i.e., a conservative approach). If any result was presented as mean and confidence interval, the SD was calculated on the basis of the respective confidence interval. In samples with $n<30$, the SD was calculated using Student's t-distribution, by applying the formula SD = margin of error x squared root of *N* divided by *t*. We also transformed the measurement units of outcomes (e.g., log to mg/L) whenever necessary for pooling purposes. If any study presented values as median (range), the SD was imputed as recommended by Hozo et al. [23]. The formula utilized takes into account sample size, median, minimum value,

and maximum value. All formulas and transformations are described in detail at **https://osf.io/fpj54/.**

Meta-analysis was conducted in Rev Man 5.3 software [24] within a random effects model. As for the primary outcome, secondary outcomes were presented as WMD and 95% CIs as the measure of treatment effect, to preserve the original units and improve interpretation. Adverse events were meta-analyzed through random effects for binary outcomes; relative risk with 95% CIs was presented as a summary measure. Study heterogeneity was assessed by the Cochrane Q test and I^2 inconsistency analysis, in which values >50% were considered as suggestive of heterogeneity [25].

The risk of bias across studies was assessed by investigating the asymmetry of results. This was done by visual inspection of a funnel plot of effect sizes against their respective inverses of standard errors [26] whenever more than 10 studies were available [27], as well as with Egger's test [26].

Sensitivity analyses were done by removing from meta-analysis those studies that applied only a single exercise session, not only to account for heterogeneity but also considering the observed average duration of interventions.

An α value of 0.05 and 0.10 was considered for statistical significance of summary measures and asymmetry tests, respectively. The final model consisted of the five types of IDT compared with a control group. Raw data for all statistical analyses are available at **https://osf.io/fpj54/.**

Certainty of the evidence

The overall certainty of the evidence was assessed using the Grades of Recommendations Assessment, Development and Evaluation (GRADE) instrument

[28]. Overall within-study certainty of evidence was classified as either very low, low, moderate, or high [28]. GRADE was applied by one independent reviewer.

Results

Study selection

The initial search identified 3,118 titles and abstracts, of which 967 were excluded as duplicates. Two additional potentially eligible studies were identified in the reference lists of other studies [29, 30]. Thus, we screened the remaining 2,153 titles and abstracts for eligibility. Of these, we excluded a further 2,052. Thus, 101 potentially eligible studies were read in full, of which 51 were excluded. In total, 50 published original articles [7, 8, 11-13, 29-73] were included in the review. A flow diagram of study search and selection is shown in **Figure 1**. The list of included and excluded studies is available as metadata at **https://osf.io/fpj54/**.

<<< Figure 1>>>

Study characteristics

All studies were RCTs and included patients undergoing HD for ESRD. The duration of follow-up ranged from 1 day [42] to 12 months [51]. In 33 trials (79%), participant concealment was unclear, while the other nine (21%) were explicitly unblinded; the exact same proportion applied to provider blinding. Only four studies (9%) explicitly reported assessor blinding.

Overall, 2,062 patients were randomized; data were analyzed for 1,757. The size of the randomized sample ranged from 15 to 103 participants. The mean age of participants varied from 20 to 73.9 years. Soliman et al. [30] and Paluchamy & Vaidyanathan [61] did not report the mean age of their participants. Most of the studies included both men and women, but, consistent with the sex distribution of dialysis-dependent ESRD, there was a male predominance. Only two studies included male patients exclusively [11, 32]. The characteristics of the analyzed studies are summarized in **Supplemental Table 1**.

Intervention characteristics

Twenty-nine studies used aerobic training [7, 8, 11-13, 29, 30, 32, 36, 38-41, 43-46, 49, 52, 57-59, 61, 62, 65, 66, 71-73], thirteen used resistance training [11, 31, 34, 35, 37, 38, 41, 47, 55, 56, 63, 67, 70], seven used a combination of aerobic and resistance training compared to a control group [48, 50, 51, 53, 54, 60, 64], two used IMT compared to a control group [33, 63], one compared resistance training versus IMT and a control group [63], and three compared FES training with a control group [40, 68, 69]. Three studies used protocol with rotation, flexion and extension of the ankles and wrists, which we consider as very low intensity aerobic exercise [30, 52, 58]. Four studies did not report dropout rates [11, 12, 40, 59] and among those that did, these rates varied widely (from 2.4% [71] to 56.2% [29]).

The structure of interventions – intensity, frequency, volume (duration in minutes), and sets (for resistance training, length of exposure and supervision) – also varied widely among the different interventions. As an example, regarding length of exposure, Dungey et al. [42] applied only a single aerobic training session, while Kouidi et al. [51] exposed patients to 48 months of combined exercise training. The same applies to

frequency; all studies exposed patients to IDT three times a week, except Dungey et al. [42] (unique session). Furthermore, important data were missing from several trials. Twelve studies [29, 30, 47, 53-55, 59, 61-63, 68, 69] failed to report whether IDT was supervised, while thirty-eight studies were supervised; in the study by Cooke et al. [36], there was no supervision. Almost all studies (90%) used a control group without any exercise. In the studies of Curado Lopes et al. [37], DePaul et al. [39], Martins do Valle et al. [56], and Wu et al. [73], control groups performed light stretching exercises; Kirkman et al. [47] and Rosa et al. [67] used sham exercise (very low intensity, no load or progression) for their controls. Detailed information on the characteristics of the included interventions can be found in **Supplemental Table 2.**

Outcomes

Among trials comparing IDT to usual care, those of aerobic exercise studies evaluated the outcomes Kt/V, hemoglobin, VO_2peak, 6MWT, CRP, IL-6, TC, systolic BP, and diastolic BP. Trials of resistance training evaluated the outcomes Kt/V, hemoglobin, 6MWT, CRP and TC. FES studies evaluated the outcomes Kt/V and 6MWT. IMT studies evaluated only 6MWT as an outcome, for a total of 23 outcomes analyzed overall. When compared to patients randomized to usual care, those allocated to any IDT strategy showed significant differences in WMD with respect to efficacy (when analyzed for the same outcome).

For Kt/V, effect sizes varied from 0.08 to 0.10, with aerobic intervention reaching statistical significance (WMD = 0.08, 95%CI = 0.00 to 0.15, I^2 = 56%, P = 0.04). As for office systolic BP, effect sizes varied from –4.33 mmHg to –10.07 mmHg, with aerobic intervention achieving the largest effect size (WMD = –10.07 mmHg, 95%CI = –16.35

to –3.78, I^2 = 44%, P = 0.002). As for office diastolic BP, WMDs ranged from –2.96 mmHg to –5.76 mmHg, with combined intervention achieving the largest effect size (WMD = –5.76 mmHg, 95%CI = –8.83 to –2.70, I^2 = 0%, P = 0.0002). Regarding VO_2peak, effect sizes varied from 2.07 $mL.kg^{-1}.min^{-1}$ to 5.41 $mL.kg^{-1}.min^{-1}$, with combined exercise achieving the most pronounced effect (WMD = 5.41 $mL.kg^{-1}.min^{-1}$, 95%CI = 4.03 to 6.79, I^2 = 0%, P <0000.1). For 6MWT, effect sizes varied from 36.37 m to 117.62 m, with IMT achieving most pronounced effect (WMD = 117.62 m, 95% CI = 67.26 to 167.99, I^2 = 0%, P <0.00001). As for CRP, effects sizes varied from –0.50 mg/L to –3.24 mg/L, with the aerobic exercise achieving most pronounced effect (WMD = –3.24 mg/L, 95%CI = –4.52 to –1.97, I^2 = 0%, P <0.00001). No intervention had an impact on hemoglobin, IL-6, or TC.

Sensitivity analyses were carried out to investigate the impact of the single-session study on the summary effect [42], as well as that of studies that applied pre-dialysis or post-dialysis exercise [8, 39]. The large heterogeneity in the analysis of the impact of aerobic exercise on hemoglobin (61%) disappeared when we omitted the study conducted by Soliman et al. [30]. Notably, this was the only study that used an IDT intervention markedly different from the others, consisting only of rotation of the wrists, ankles, and other joints. Summary measures for each individual meta-analysis and efficacy outcomes (primary and sensitivity analyses) are presented in **Table 1**, and forest and funnel plots are available as **Supplemental Figures.**

Reported adverse events were also collected. Among studies that reported this type of information, adverse events included partial muscle injury, hypotension, angina, tachycardia at rest, access problem, cramp, joint pains, and back lacerations in trials of resistance training [34, 35, 37, 47]; and hypotension, muscle pain, cramp, headache, chest pain, palpitations, nausea and/or vomiting, and tachyarrhythmia in studies of

aerobic training [39, 46, 49, 73]. One patient withdrew from the DePaul et al. study [39] because of fatigue. The prevalence of major adverse events (nausea/vomiting; musculoskeletal complications; cardiovascular complications, e.g., angina) between the IDT and control groups was not significantly different (RR 1.43, 95% CI 0.73 to 2.83, I^2 = 0%, P = 0.30). This summary is available in **Supplemental figures** and **Supplemental table 1**. Finally, data on conflicts of interests, the DOIs and registry numbers of included studies, and information on financial support is presented in **Supplemental table 3.**

<<<**Table 1**>>>

Risk of bias of the included studies

For the vast majority of studies, we were unable to reach precise conclusions regarding risk of bias due to the high prevalence of "unclear" judgment, except in the attrition bias domain. We found the following frequencies for "low risk of bias", "unclear risk of bias" or "high risk of bias", respectively: (a) selection bias due to random sequence generation: 38%, 60%, and 2%; (b) selection bias due to allocation concealment: 16%, 82%, and 2%; (c) performance bias: 0%, 78%, and 22%; (d) detection bias: 6%, 74%, and 20%; (e) attrition bias: 84%, 14%, and 2%; (f) reporting bias: 6%, 86%, and 8%; and (g) other bias: 10%, 84%, and 6%. The full assessment of risk of bias is shown in **Figure 2**, and individual assessments of each study in **Supplemental Figures**.

Asymmetry of evidence

Asymmetry of evidence was assessed through visual inspection of the funnel plot and the formal Begg's and Egger's tests whenever reasonable ($k \geq 10$). Hemoglobin was the only outcome that could be assessed for asymmetry. No evidence of asymmetry was found by visual inspection nor by Begg's and Egger's tests ($P = 0.000$). This may suggest no evidence of publication bias.

Certainty of evidence

The certainty of evidence was classified as very low to low in 74% of the outcomes evaluated. The full assessment of all outcomes can be found in the Summary of Findings Table (**Table 2**).

<<<Table 2>>>

Discussion

This SRMA was designed to assess the impact of five different types of IDT (aerobic, resistance, aerobic plus resistance, IMT, and FES) on eight outcomes (clinical and functional parameters) in patients with ESRD, and to provide additional information regarding distinct physical training protocols performed during HD. The main conclusion of this study is that the five different types of IDT appear to have some beneficial effect in the HD scenario.

Previous reviews and meta-analyses have examined the effects of IDT on some of our evaluated outcomes [9, 74, 75]. However, these publications did not systematically review all the available evidence, nor did they explore the influence of some IDT

modalities comprehensively. On the other hand, we meta-analyzed 50 RCTs (n=1,757) and evaluated two intradialytic interventions that have been the subject of little study to date: IMT and FES. For example, Salhab et al. [76] recently published an interesting SRMA evaluating IDT. However, their meta-analysis incorporated only 12 RCTs; in addition the authors focused this SRMA specifically on aerobic IDT. Thus, we believe that our data can be seen as a broad addition to the literature, including a series of sensitivity analyses. Two studies [8, 39] included in our SRMA used pre-dialysis or post-dialysis training. As this might influence estimates of final effect, a sensitivity analysis was performed excluding each of these studies, as presented in **Table 1**.

Our findings suggest that IDT improves Kt/V, BP, and functional capacity without adverse events, in line with what was described by Pu et al [77]. However, it is important to note that we analyzed the impact of each type of training (aerobic, resistance, and combined) separately on each outcome. As Pu et al. [77] did not use eligibility criteria as strict as those of in this SRMA, the final results of their study may have been influenced (e.g., RCTs in which the control group was instructed to walk home while wearing a pedometer).

Aerobic IDT improved Kt/V when compared to usual care (no exercise intervention) alone. It is important to emphasize that one study included a protocol of aerobic pre-dialytic training [8]. When we performed a sensitivity analysis omitting this study, there was no difference. Thus, the impact of aerobic IDT on Kt/V remains controversial. Interestingly, Vanholder et al. [78] recently debated the true utility of Kt/V due to the nature of the typical stage IV patient profile (elderly, frail, and thin with comorbidities), which may lead to overestimation of true Kt/V values.

In terms of functional capacity, both aerobic and combined IDT improved VO_2peak; the greatest improvement was observed with combined IDT (an increase of 2.07 mL.kg^{-1}.min^{-1} and 5.41 mL.kg^{-1}.min^{-1}, respectively). Low VO_2peak has been reported as an independent mortality factor in ESRD patients [79], and values less than 17.5 mL.kg^{-1}.min^{-1} are strong mortality predictors [80]. In turn, combined IDT improved CRF while also reducing diastolic BP (–5.76 mmHg) and systolic BP (–4.33 mmHg, nonsignificant difference). On the other hand, in the group that underwent aerobic IDT there was a reduction of 10.07 mmHg in systolic BP. However, the analysis showed moderate heterogeneity (44%). Despite exploring possible divergences in primary studies that might explain this heterogeneity, again, we were unable to find plausible explanations. We then performed sensitivity analyses, excluding one study at a time. When the Liao et al. [12] and Soliman et al. [30] studies were removed, the heterogeneity disappeared. Indeed, these studies were inconsistent with the others, reporting a very large reduction in systolic BP after aerobic exercise. Possible differences in BP measurement methods (not reported in most studies) may explain these divergences.

Specifically, in relation to IMT and FES, both strategies promoted gains in 6MWT distance (117.62 and 54.14 meters, respectively). As the 6MWT is an established predictor of increased risk of mortality, cardiovascular events, and hospitalization in these patients, these results seem auspicious and may be useful in the management of patients on HD [81].

Inflammation, whether chronic or acute, is a feature of ESRD [82, 83], and CRP, IL-6 and hemoglobin levels can be impacted. This meta-analysis indicates that aerobic IDT results in a reduction in CRP levels. One possible explanation may be related to the reduction of adipose tissue – the main source of inflammatory cytokines – in these patients [84]. However, IL-6 levels did not change after aerobic and resistance IDT.

Again, among studies aerobics evaluating IL-6, that conducted by Dungey et al. [42] differed from the others by applying an acute IDT intervention (single-session protocol). A sensitivity analysis was performed, and when this study was omitted, the heterogeneity and weighted mean difference remained unchanged.

Our analyses of hemoglobin levels included several studies of aerobic, resistance, and combined IDT and indicate that none of the protocols altered this parameter. In contrast to our findings, Chung et al. [74] conducted a SRMA and reported that IDT had significant effects on hemoglobin levels. However, these authors evaluated only 11 studies and did not separate training modalities; on the other hand, our analysis encompassed almost twice as many studies and analyzed different types of training separately, which yields more reliable results. Regarding TC levels, no differences were found in studies of aerobic or resistance IDT.

Despite the important benefits and promising results associated with exercise, patients with chronic kidney disease still have a high rate of physical inactivity. A lack of knowledge by healthcare providers and a lack of motivation by patients may represent important barriers to engagement in regular physical exercise. Hannan et al. [85] recently pointed out fatigue and low energy levels as the most commonly reported barriers to exercise in this patient population. These findings are in agreement with those reported by Moorman et al. [86], where fatigue, shortness of breath, and weakness were also the main barriers encountered. It is essential that health care providers be aware of these difficulties and to be able to devise strategies to make HD patients more physically active.

Strengths and Limitations

This SRMA has several notable strengths. First, the analysis was based on a larger sample, with more events and a substantially larger number of patients, than in previous publications. This translates into greater power, more accurate estimates of effect, and a broader collection of the available evidence on the topic. Second, different IDT modalities were examined, one of which – FES –, had never before been subjected to meta-analysis. Third, our findings show that different types of IDT seem to have beneficial effects; this may serve as a useful input to policy-making for patients with ESRD. As these patients often have significant that preclude certain types of training [87], they may derive particular benefit from some of the IDT modalities evaluated. Finally, to the best of our knowledge, this review is the first to report on strength of the evidence using GRADE in the IDT scenario.

The aforementioned strengths notwithstanding, some limitations need to be considered. First, the risk of bias could not be assessed in all studies due to incorrect reporting. This may have affected the results of the primary studies and their estimates; readers should thus interpret our findings in light of these limitations. Second, among the protocols that used only intradialytic resistance training, seven studies did not report the duration of the intervention [35, 38, 41, 47, 55, 56, 63]. Moreover, ten of the studies included an intent to treat analysis. Some interventions were represented by a small number of studies in the analysis (combined IDT for 6MWT, systolic and diastolic BP, and hemoglobin; resistance IDT for IL-6 and TC; IMT for 6MWT; and FES for Kt/V and 6MWT). Therefore, in light of these circumstances, readers should interpret our findings with caution. In addition, the high risk of bias in most studies in different domains and the uncertainty of evidence should also be taken into account. It is noteworthy that an analysis of hard outcomes (e.g., mortality, cardiovascular events, etc.) was not possible given the absence of these data in the studies. Finally, rigid eligibility criteria were used

in the different studies, which may have resulted in randomization of “healthier” patients.

Conclusions

Aerobic, resistance, and combined training, as well as FES and IMT, all appear to be important IDT strategies. They were effective for in patients with ESRD overall, although not for all outcomes of interest. Our data should be interpreted in light of the high prevalence of unclear risk of bias in most studies and low to very low certainty of evidence for the outcomes evaluated.

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Table 1. Full results.

Outcome	Intervention*	Nº of trials/groups	WMD	95% CI	I^2	*p*-value
Hemoglobin	Aerobic exercise	14	0.15 g/dL	–0.24 to 0.53	59%	0.46
	Resistance exercise	8	0.01 g/dL	–0.18 to 0.19	0%	0.95
	Combined exercise	3	0.03 g/dL	–0.27 to 0.33	0%	0.85
VO_2peak	Aerobic exercise	7	2.07 $mL.kg^{-1}.min^{-1}$	0.42 to 3.72	0%	0.01
	Combinedexercise	5	5.41 $mL.kg^{-1}.min^{-1}$	4.03 to 6.79	0%	< 0.00001
6MWT	Aerobic exercise	6	64.98 m	43.86 to 86.11	0%	< 0.00001
	Resistance exercise	6	68.50 m	29.05 to 107.96	36%	0.0007
	Combined exercise	2	36.37 m	–13.73 to 86.46	0%	0.15
	IMT	2	117.62 m	67.26 to 167.99	0%	< 0.0001
	FES	3	54.14 m	17.57 to 90.71	0%	0.004
Kt/V	Aerobic exercise	12	0.08	0.00 to 0.15	56%	0.04
	Resistance exercise	6	0.10	–0.01 to 0.20	6%	0.06
	FES	2	0.08	–0.29 to 0.45	81%	0.67
CRP	Aerobic exercise	6	–3.28 mg/L	–4.68 to –1.88	0%	< 0.00001
	Resistance exercise	6	–0.50 mg/L	–1.52 to 0.52	10%	0.34

IL-6	Aerobic exercise	3	–0.75 pg/mL	–1.81 to 0.31	0%	0.16
	Resistance exercise	2	–0.00 pg/mL	–0.49 to 0.49	18%	1.00
TC	Aerobic exercise	5	–2.71 mg/dL	–10.36 to 4.94	0%	0.49
	Resistance exercise	2	–11.30 mg/dL	–25.39 to 2.79	0%	0.12
SBP	Aerobic exercise	10	–10.07 mmHg	–16.35 to –3.78	44%	0.002
	Combined exercise	2	–4.33 mmHg	–9.75 to 1.08	0%	0.12
DBP	Aerobic exercise	10	–2.96 mmHg	–7.71 to 1.78	65%	0.22
	Combined exercise	2	–5.76 mmHg	–8.83 to –2.70	0%	0.0002
Sensitivity analyses						
IL-6 (SA_1)	Aerobic exercise	2	–0.81 pg/mL	–1.92 to 0.31	0%	0.16
SBP (SA_2)	Aerobic exercise	8	–5.82 mmHg	–10.68 to –0.95	0%	0.02
SBP (SA_3)	Aerobic exercise	8	–11.36 mmHg	–19.73 to –2.99	54%	0.008
DBP (SA_4)	Aerobic exercise	8	–3.37 mmHg	–10.17 to 2.64	70%	0.25

6MWT (SA_5)	Aerobic exercise	5	68.85 m	46.45 to 91.26	0%	< 0.00001
Kt/V (SA_6)	Aerobic exercise	11	0.09	–0.00 to 0.17	58%	0.05
VO_2peak (SA_7)	Aerobic exercise	6	2.13 $mL.kg^{-1}.min^{-1}$	0.32 to 3.94	0%	0.02
TC (SA_8)	Aerobic exercise	4	–3.36 mg/dL	–11.88 to 5.16	0%	0.44

6MWT = Six-minute walk test; CRP = C-reactive protein; TC = Total cholesterol; IL-6 = Interleukin 6; SBP = Systolic blood pressure; DBP = Diastolic blood pressure.

SA_1: Sensitivity analysis. When we removed Dungey et al.[41] from the analysis, because it applied only one training session, there was no significant change in overall analysis.

SA_2: Sensitivity analysis. When we removed Liao et al.[12] and Soliman et al.[29] from the analysis, the heterogeneity disappeared. These studies were inconsistent with the others, reporting a very large reduction in systolic BP.

SA_3: Sensitivity analysis. When we removed van Vilsteren et al.[8] due to use of pre-dialysis strength training and DePaul et al.[38] due to use of pre-dialysis or post-dialysis strength training, there was no significant change in the overall analysis.

SA_4: Sensitivity analysis. When we removed van Vilsteren et al.[8] due to use of pre-dialysis strength training and DePaul et al.[38] due to use of pre-dialysis or post-dialysis strength training, there was no significant change in the overall analysis.

SA_5: Sensitivity analysis. When we removed DePaul et al.[38] due to use of pre-dialysis or post-dialysis strength training, there was no significant change in the overall analysis.

SA_6: Sensitivity analysis. When we removed van Vilsteren et al.[8] due to use of pre-dialysis strength training, the analysis did not show any difference.

SA_7: Sensitivity analysis. When we removed van Vilsteren et al.[8] due to use of pre-dialysis strength training, there was no significant change in the overall analysis.

SA_8: Sensitivity analysis. When we removed van Vilsteren et al.[8] due to use of pre-dialysis strength training, there was no significant change in the overall analysis.

Table 2. Summary of findings

Patient or population: End-stage renal disease on hemodialysis

Setting: Rehabilitation

Intervention: Different types of intradialytic training

Comparison: Usual care or stretches

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intradialytic training	Usual care	Relative (95% CI)	Absolute (95% CI)		
Kt/V – Aerobic												
12	randomized trials	serious [a,b]	serious [c]	not serious	not serious	publication bias strongly suspected strong association [a]	188	182	-	MD **0.08 higher** (0 to 0.15 higher)	⨁⨁◯◯ LOW	IMPORTANT
Hemoglobin – Resistance												
8	randomized trials	serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected [a]	116	109	-	MD **0.01 higher** (0.18 lower to 0.19 higher)	⨁⨁◯◯ LOW	IMPORTANT
Hemoglobin – Combined												
3	randomized trials	serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected	76	70	-	MD **0.03 higher** (0.27 lower to 0.33 higher)	⨁⨁◯◯ LOW	IMPORTANT
VO2peak – Combined												
5	randomized trials	serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected very strong association	105	96	-	MD **5.41 higher** (4.03 higher to 6.79 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
VO2peak – Aerobic												
7	randomized trials	serious [a,b]	not serious	not serious	serious [d]	publication bias strongly suspected strong association	127	121	-	MD **2.07 higher** (0.42 higher to 3.72 higher)	⨁⨁◯◯ LOW	IMPORTANT
Kt/V – Resistance												

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intradialytic training	Usual care	Relative (95% CI)	Absolute (95% CI)		
6	randomized trials	serious [a,b]	not serious	not serious	serious [d]	publication bias strongly suspected	109	111	-	MD **0.1 higher** (0 to 0.2 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

C-reactive protein – Resistance

6	randomized trials	serious [a,b]	not serious	not serious	serious [d]	publication bias strongly suspected	103	97	-	MD **0.5 lower** (1.52 lower to 0.52 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Kt/V - Functional electrostimulation

2	randomized trials	serious [a,e]	very serious [f]	not serious	serious [g]	publication bias strongly suspected	31	30	-	MD **0.08 higher** (0.29 lower to 0.45 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Total cholesterol – Resistance

2	randomized trials	serious [a,e]	not serious	not serious	serious [d]	publication bias strongly suspected	27	27	-	MD **11.3 lower** (25.39 lower to 2.79 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Interleukin-6 – Aerobic

3	randomized trials	serious [a,e]	not serious	not serious	serious [g]	publication bias strongly suspected	34	36	-	MD **0.75 lower** (1.81 lower to 0.31 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

C-reactive protein – Aerobic

6	randomized trials	serious [a,e]	not serious	not serious	not serious	publication bias strongly suspected strong association	99	99	-	MD **3.28 lower** (4.68 lower to 1.88 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

6MWT – Resistance

6	randomized trials	serious [a,b]	not serious	not serious	very serious [d]	publication bias strongly suspected strong association	107	104	-	MD **68.5 higher** (29.05 higher to 107.96 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

6MWT – Combined

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intradialytic training	Usual care	Relative (95% CI)	Absolute (95% CI)		
2	randomized trials	serious [a,h]	not serious	not serious	serious [g]	publication bias strongly suspected	19	18	-	MD **36.37 higher** (13.73 lower to 86.46 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

6MWT – Electrostimulation

3	randomized trials	serious [a,e]	not serious	not serious	serious [g]	publication bias strongly suspected strong association	42	40	-	MD **54.14 higher** (17.57 higher to 90.71 higher)	⨁⨁◯◯ LOW	IMPORTANT

6MWT - Inspiratory muscle training

2	randomized trials	serious [a,b]	not serious	not serious	serious [g]	publication bias strongly suspected very strong association	40	26	-	MD **117.62 higher** (67.26 higher to 167.99 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT

Interleukin 6 – Resistance

3	randomized trials	serious [a,b]	not serious	not serious	serious [d]	publication bias strongly suspected	51	40	-	MD **0** (0.49 lower to 0.49 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

6MWT – Aerobic

6	randomized trials	serious [a,b]	not serious	not serious	not serious	publication bias strongly suspected very strong association	93	95	-	MD **64.98 higher** (43.86 higher to 86.11 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT

Total cholesterol – Aerobic

5	randomized trials	serious [a,e]	not serious	not serious	serious [d]	publication bias strongly suspected	95	88	-	MD **2.71 lower** (10.36 lower to 4.94 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

Hemoglobin – Aerobic

14	randomized trials	serious [a,e]	serious [i]	not serious	serious [d]	publication bias strongly suspected	184	182	-	MD **0.15 higher** (0.24 lower to 0.53 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

SBP – Aerobic

Certainty assessment							No. of patients		Effect		Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Intradialytic training	Usual care	Relative (95% CI)	Absolute (95% CI)		
10	randomized trials	serious [a,e]	not serious	not serious	serious [d]	publication bias strongly suspected very strong association	172	160	-	MD **10.07 lower** (16.36 lower to 3.78 lower)	⨁⨁⨁◯ MODERATE	IMPORTANT

SBP – Combined

2	randomized trials	serious	not serious	not serious	serious [d]	publication bias strongly suspected	41	35	-	MD **4.33 lower** (9.75 lower to 1.08 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

DBP – Combined

2	randomized trials	serious [a,e]	not serious	not serious	not serious	publication bias strongly suspected very strong association	41	35	-	MD **5.76 lower** (8.83 lower to 2.7 lower)	⨁⨁⨁⨁ HIGH	IMPORTANT

DBP – Aerobic

10	randomized trials	serious [a,e]	serious [j]	not serious	serious [d]	publication bias strongly suspected	173	161	-	MD **2.96 lower** (7.71 lower to 1.78 higher)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; **MD:** Mean difference

Explanations

a. Unclear risk of bias.

b. The risk of bias observed is due to the lack of information on allocation concealment and blinding of outcome assessment in most studies.

c. Analysis showed 56% heterogeneity.

d. Wide confidence interval.

e. The risk of bias observed is due to the lack of information on random sequence generation, allocation concealment, and blinding of outcome assessment in most studies.

f. Analysis showed 81% heterogeneity.

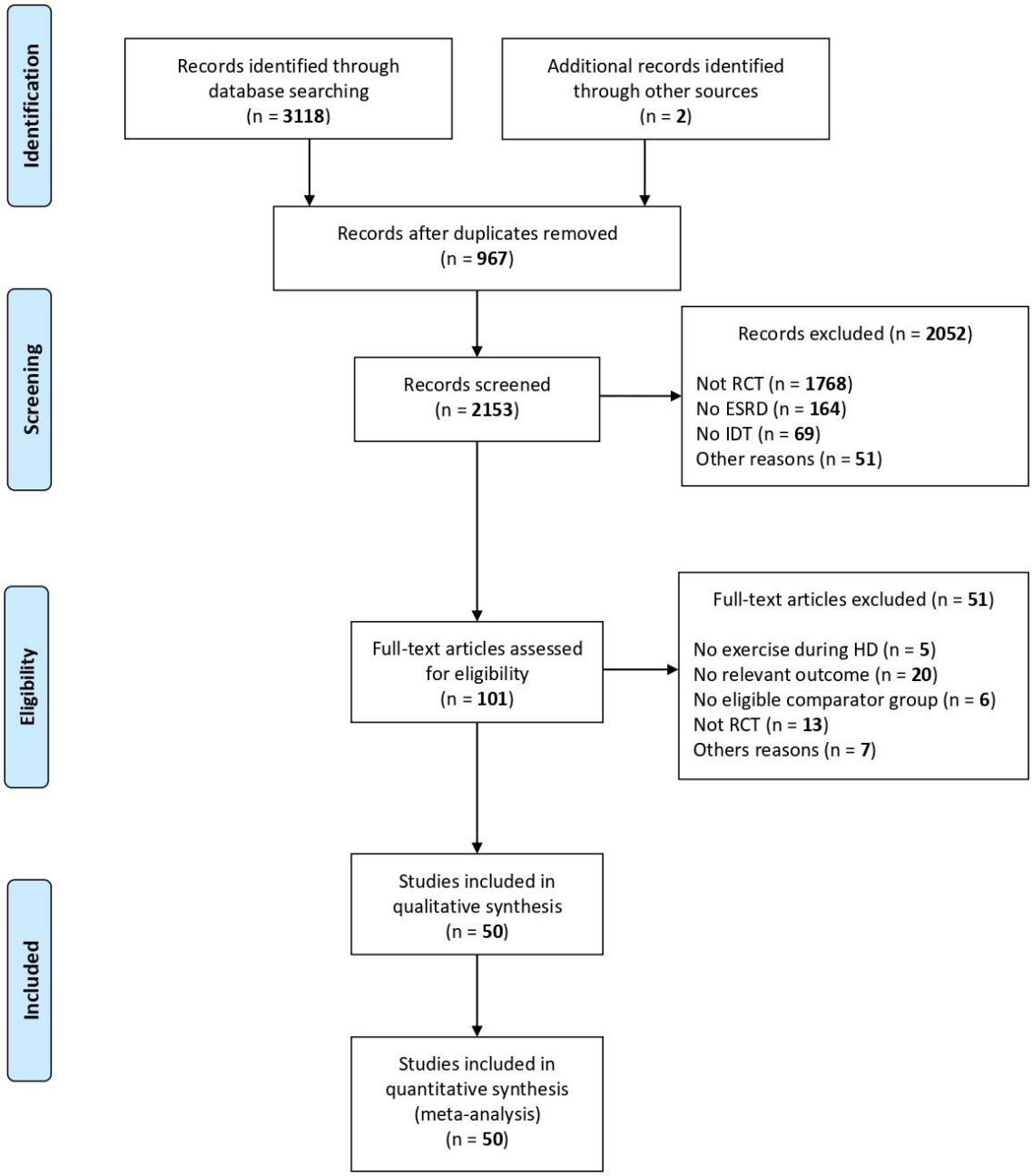
g. Small sample size.

h. The risk of bias observed is due to the lack of information on random sequence generation, allocation concealment, blinding of outcome assessment, selective reporting, and other bias in most studies.

i. Analysis showed 59% heterogeneity.

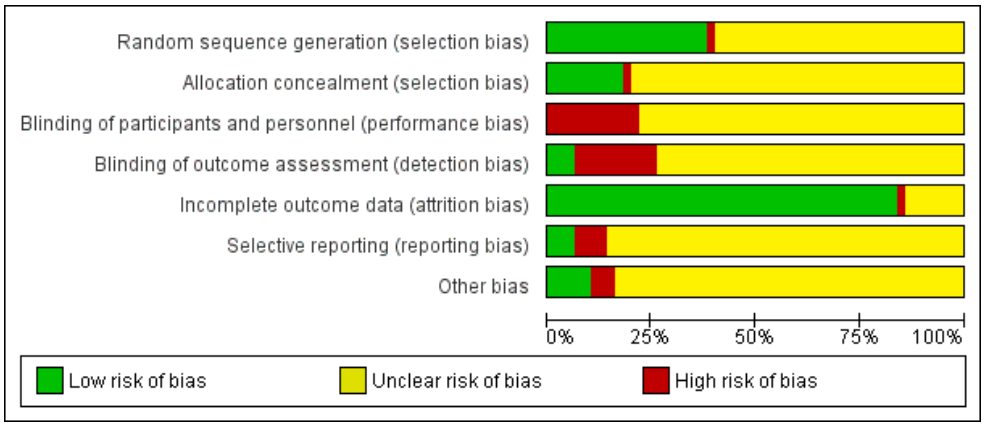
j. Analysis showed 65% heterogeneity.

Figure 1. Flow of information through the different phases of a systematic review and meta-analysis.



RCT: Randomized clinical trial; ESRD: End-stage renal disease; HD: Hemodialysis.

Figure 2. Risk of bias classification according to the RoB 1.0 Cochrane tool.



Supplemental data 1. The search strategies were tested previously with and without descriptors (e.g.[tiab], [mesh], [ti]) and the one that returned the maximal titles and abstracts values waschosen. Search date: July 26, 2019.

PubMed/MEDLINE

#1 (intradialytic[tiab] OR intra-dialytic[tiab] OR hemodialysis[tiab] OR haemodialysis[tiab] OR renal dialysis[MeSH] OR extracorporeal dialysis OR extracorporeal dialyses OR dialysis[MeSH] OR dialyses OR HD) AND (hemodialysis efficacy OR Kt/V OR hemodialysis dose OR hemodialysis frequency OR hemoglobin OR cholesterol OR total cholesterol OR interleukin-6 OR C-reactive protein OR 6MWT OR six-minute walk test OR 6-minute walk test OR 6-min walk test OR VO2peak OR VO2 OR blood pressure OR systolic blood pressure OR diastolic blood pressure)

#2 exercise[MeSH] OR exercises OR resistance exercise OR resistance training[MeSH] OR strength training OR aerobic exercise OR aerobic exercises OR exercise aerobic OR aerobic training OR aerobic versus strength OR strength versus aerobic OR physical fitness[MeSH] OR physical training OR exercise therapy[MeSH] OR combined training OR aerobic plus strength training OR aerobic plus resistance exercise OR aerobic plus resistance training OR concurrent training OR concurrent exercise or electrostimulation or electro-stimulation or inspiratory muscle training

#3 randomized controlled trial[pt] OR controlled clinical trial[pt] OR clinical trial[pt] OR randomized controlled trials[mh] OR random allocation[mh] OR double-blind method[mh] OR singleblind 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 design[mh:noexp] 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])
#1 AND #2 AND #3

Cochrane Library

#1 MeSH descriptor: [Renal Dialysis] explode all trees

#2 MeSH descriptor: [Dialysis] explode all trees

#3 intradialytic or hemodialysis or haemodialysis or extracorporeal dialysis or extracorporeal dialyses or dialyses or HD

#4 #1 or #2 or #3

#5 MeSH descriptor: [Exercise] explode all trees

#6 MeSH descriptor: [Resistance Training] explode all trees

#7 MeSH descriptor: [Physical Fitness] explode all trees

#8 MeSH descriptor: [Exercise Therapy] explode all trees

#9 exercises or resistance exercise or strength training or aerobic exercise or aerobic exercises or exercise aerobic or aerobic training or physical training or combined training or aerobic plus strength training or aerobic plus resistance exercise or aerobic plus resistance training or concurrent training or concurrent exercise or aerobic versus strength or strength versus aerobic or inspiratory muscle training or IMT or electrostimulation or electro-stimulation

#10 #5 or #6 or #7 or #8 or #9

#11 hemodialysis efficacy or KtV or hemodialysis dose or hemodialysis frequency or hemoglobin or cholesterol or total cholesterol or interleukin-6 or C-reactive protein or 6MWT or six minute walk test or 6 minute walk test or 6 min walk test or VO2peak or VO2 or blood pressure or systolic blood pressure or diastolic blood pressure

#12 #4 and #10 and #11 in Trials

Embase

#1 intradialytic OR haemodialysis OR renal dialysis OR extracorporeal dialysis OR extracorporeal dialyses OR dialyses OR HD OR 'hemodialysis'/exp OR 'dialysis'/exp

#2 exercises OR resistance exercise OR strength training OR aerobic exercises OR exercise aerobic OR aerobic training OR physical fitness OR physical training OR exercise therapy OR combined training OR aerobic plus strength training OR aerobic plus resistance exercise OR aerobic plus resistance training OR concurrent training OR concurrent exercise OR 'exercise'/exp OR 'training'/exp OR 'resistance training'/exp OR

'aerobic exercise'/exp OR electrostimulation OR electro-stimulation or inspiratory muscle training

#3 random$ OR doubl$ adj blind$ OR singl$ adj blind$ OR assign$ OR allocat$ OR 'randomized controlled trial'/exp

#1 AND #2 AND #3

Scopus

#1 (TITLE-ABS(intradialytic) OR KEY(renal AND dialysis OR dialysis) OR ALL(hemodialysis OR haemodialysis OR extracorporeal AND dialysis OR extracorporeal AND dialyses OR dialyses OR HD))

#2 KEY(exercise OR resistance AND training OR physical AND fitness OR exercise AND therapy) OR ALL(exercises OR resistance AND exercise OR strength AND training OR aerobic AND exercise OR aerobic AND exercises OR exercise AND aerobic OR aerobic AND training OR aerobic AND versus AND strength OR strength AND versus AND aerobic OR physical AND training OR combined AND training OR aerobic AND plus AND strength AND training OR aerobic AND plus AND resistance AND exercise OR aerobic AND plus AND resistance AND training OR concurrent AND training OR concurrent AND exercise OR electrostimulation OR electro-stimulation OR inspiratory AND muscle AND traning)

#3 randomized AND controlled AND trial OR controlled AND clinical AND trial OR clinical AND trial OR random*

#1 AND #2 AND #3

SPORTDiscus

#1 (MH "dialysis" OR "hemodialysis") OR intradialytic OR haemodialysis OR renal dialysis OR extracorporeal dialysis OR extracorporeal dialyses OR dialyses OR HD

#2 (MH "exercise" OR "resistance training" OR "physical fitness") OR exercises OR resistance exercise OR strength training OR aerobic exercise OR aerobic exercises OR exercise aerobic OR aerobic training OR aerobic versus strength OR strength versus

aerobic OR physical training OR exercise therapy OR combined training OR aerobic plus strength training OR aerobic plus resistance exercise OR aerobic plus resistance training OR concurrent training OR concurrent exercise

#3 ((MH "randomized controlled trials") OR controlled clinical trial OR random*) NOT (PT review)

#1 AND #2 AND #3

CINAHL

#1 (MH "dialysis" OR "hemodialysis") OR intradialytic OR haemodialysis OR renal dialysis OR extracorporeal dialysis OR extracorporeal dialyses OR dialyses OR HD

#2 (MH "exercise" OR "resistance training" OR "physical fitness") OR exercises OR resistance exercise OR strength training OR aerobic exercise OR aerobic exercises OR exercise aerobic OR aerobic training OR aerobic versus strength OR strength versus aerobic OR physical training OR exercise therapy OR combined training OR aerobic plus strength training OR aerobic plus resistance exercise OR aerobic plus resistance training OR concurrent training OR concurrent exercise or electrostimulation or electro-stimulation or inspiratory muscle training

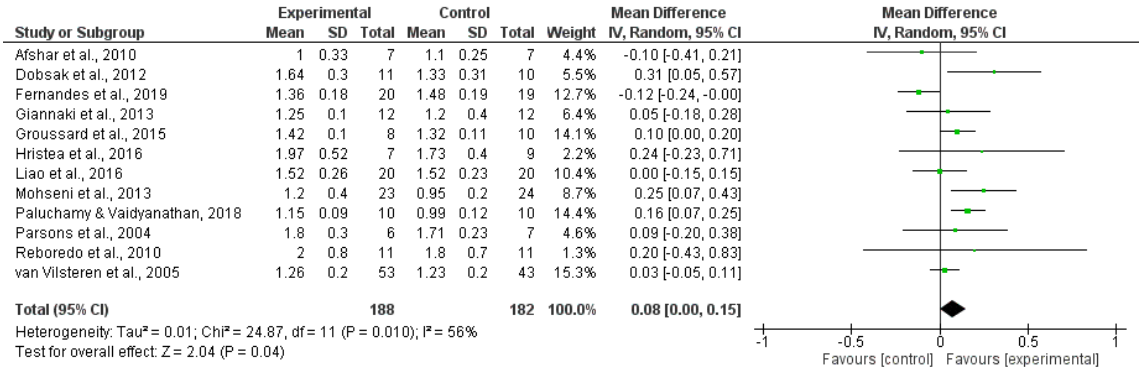
#3 ((MH "randomized controlled trials") OR controlled clinical trial OR random*) NOT (PT review)

#1 AND #2 AND #3

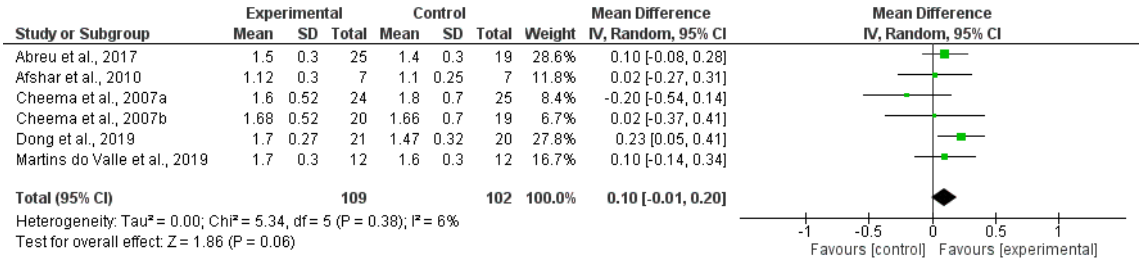
Supplemental Figures

1. Kt/V

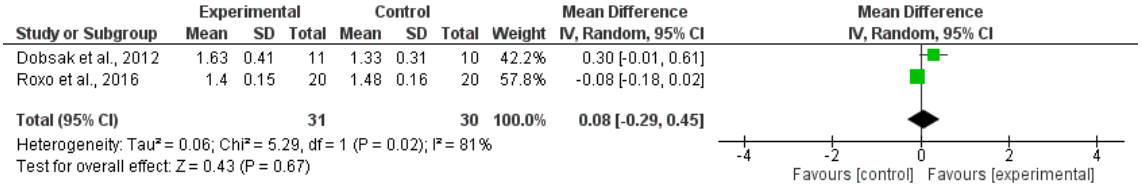
1.1. Aerobic training vs usual care



1.2. Resistance training vs usual care



1.3. Electrostimulation vs usual care

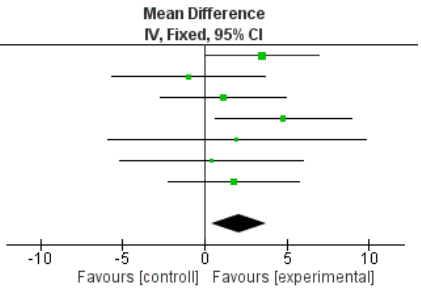


2. VO_2peak

2.1. Aerobic Training vs usual care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Carmack et al., 1995	14.4	4.7	10	10.9	3.1	11	22.9%	3.50 [0.06, 6.94]
Groussard et al., 2015	14.3	6.51	8	15.3	1.9	10	12.5%	-1.00 [-5.66, 3.66]
Koufaki et al., 2002	19.9	6.3	18	18.8	4.9	15	18.6%	1.10 [-2.72, 4.92]
McGregor et al., 2018	20.71	6.85	16	15.93	5.17	18	16.0%	4.78 [0.66, 8.90]
Painter et al., 2002	22.12	10.78	10	20.16	7.23	12	4.4%	1.96 [-5.87, 9.79]
Reboredo et al., 2011	29	7	12	28.6	7	12	8.7%	0.40 [-5.20, 6.00]
van Vilsteren et al., 2005	28.02	8.8	53	26.25	10.8	43	16.9%	1.77 [-2.23, 5.77]
Total (95% CI)			**127**			**121**	**100.0%**	**2.07 [0.42, 3.72]**

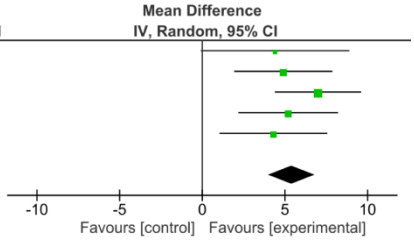
Heterogeneity: Chi² = 4.60, df = 6 (P = 0.60); I² = 0%
Test for overall effect: Z = 2.46 (P = 0.01)



2.2. Combined Training vs usual care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Konstantinidou et al., 2002	20.2	5.7	10	15.8	4.8	12	9.5%	4.40 [-0.06, 8.86]
Kouidi et al., 2009	21.4	6.8	30	16.5	4.5	29	22.0%	4.90 [1.97, 7.83]
Kouidi et al., 2010	22.33	4.9	24	15.33	3.79	20	28.7%	7.00 [4.43, 9.57]
Ouzouni et al., 2009	25.3	5.3	19	20.1	3.4	14	21.4%	5.20 [2.22, 8.18]
Petraki et al., 2008	25.1	6.1	22	20.8	4.6	21	18.3%	4.30 [1.08, 7.52]
Total (95% CI)			**105**			**96**	**100.0%**	**5.41 [4.03, 6.79]**

Heterogeneity: Tau² = 0.00; Chi² = 2.26, df = 4 (P = 0.69); I² = 0%
Test for overall effect: Z = 7.70 (P < 0.00001)

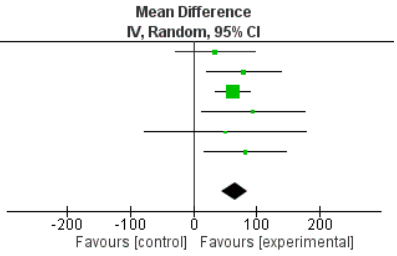


3. 6-minute walk test

3.1. Aerobic training vs Usual Care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
DePaul et al., 2002	464	94	15	430	80	14	11.1%	34.00 [-29.40, 97.40]
Dobsak et al., 2012	445.8	72.6	11	366.5	65.6	10	12.8%	79.30 [20.19, 138.41]
Fernandes et al., 2019	386.9	19.38	20	325	59.8	19	56.1%	61.90 [33.70, 90.10]
Groussard et al., 2015	500	84.85	8	406	91.71	10	6.7%	94.00 [12.22, 175.78]
Hristea et al., 2016	346.28	134.88	7	295.77	121.07	9	2.7%	50.51 [-76.93, 177.95]
Wu et al., 2014	441	135	32	359	132	33	10.6%	82.00 [17.07, 146.93]
Total (95% CI)			**93**			**95**	**100.0%**	**64.98 [43.86, 86.11]**

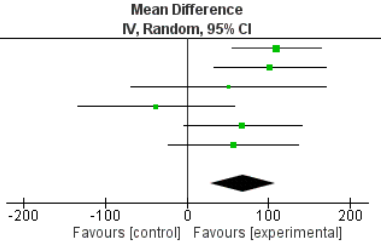
Heterogeneity: Tau² = 0.00; Chi² = 1.99, df = 5 (P = 0.85); I² = 0%
Test for overall effect: Z = 6.03 (P < 0.00001)



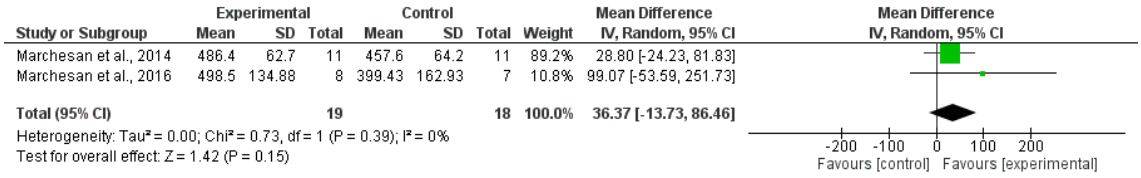
3.2. Resistance training vs usual care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cheema et al., 2007a	513.3	94.6	24	403.5	99.9	25	24.9%	109.80 [55.34, 164.26]
Cheema et al., 2007b	515.6	96.6	20	414.1	119.5	19	19.5%	101.50 [33.09, 169.91]
Kirkman et al., 2014	571	101	9	520	160	10	8.9%	51.00 [-68.11, 170.11]
Martins do Valle et al., 2019	457.3	155.6	12	494.8	66.9	12	12.5%	-37.50 [-133.33, 58.33]
Pellizzaro et al., 2013	475	74.1	14	407	116.7	14	18.2%	68.00 [-4.41, 140.41]
Rosa et al., 2018	526.45	126.15	28	469.42	162.93	24	16.0%	57.03 [-23.17, 137.23]
Total (95% CI)			**107**			**104**	**100.0%**	**68.50 [29.05, 107.96]**

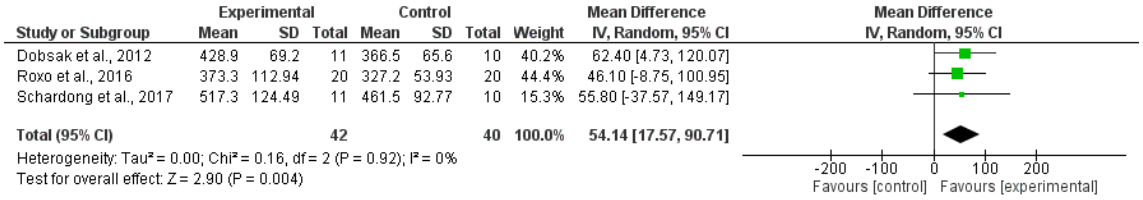
Heterogeneity: Tau² = 857.79; Chi² = 7.82, df = 5 (P = 0.17); I² = 36%
Test for overall effect: Z = 3.40 (P = 0.0007)



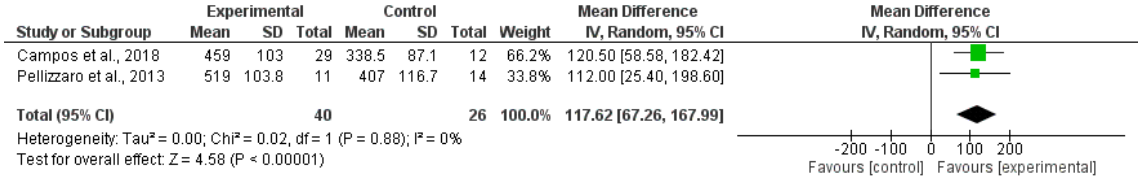
3.3. Combined training vs usual care



3.4. Electrostimulation vs usual care

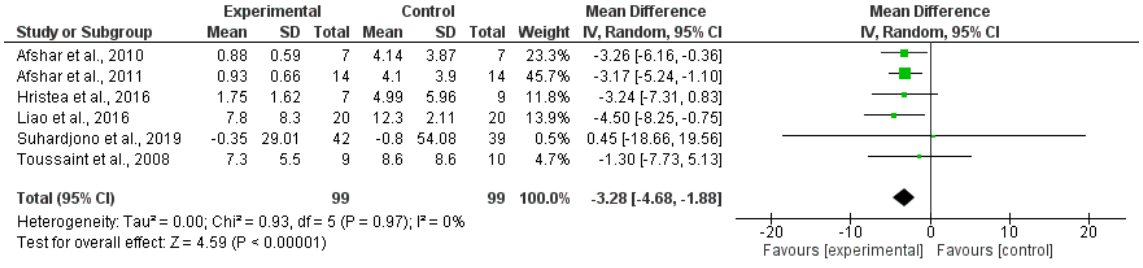


3.5. Inspiratory muscle training vs usual care

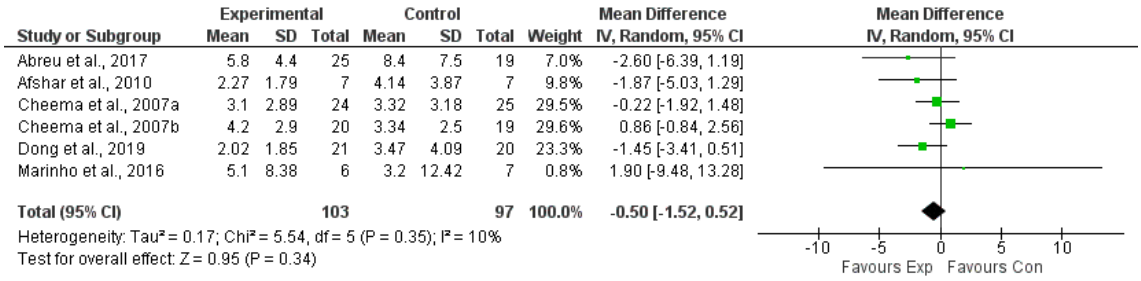


4. C-reactive protein

4.1. Aerobic training vs usual care

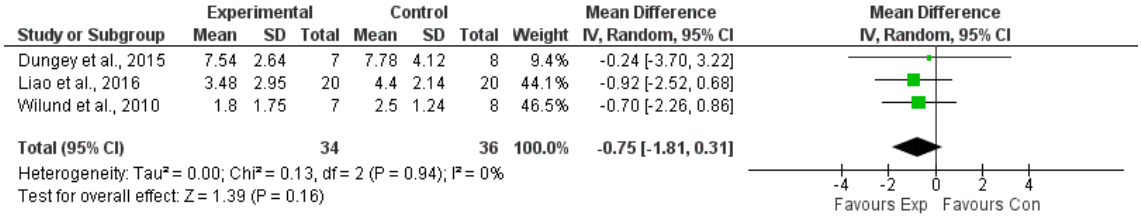


4.2. Resistance training vs usual care

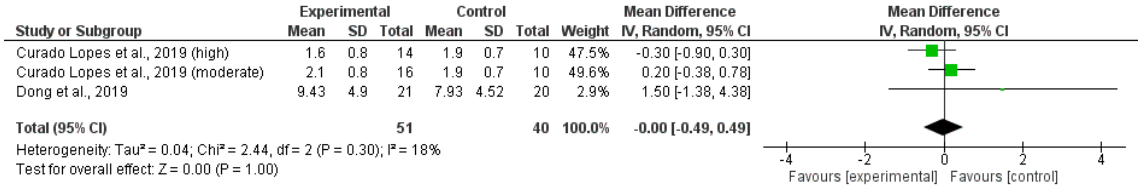


5. Interleukin 6

5.1. Aerobic training vs usual care



5.2. Resistance training vs usual care

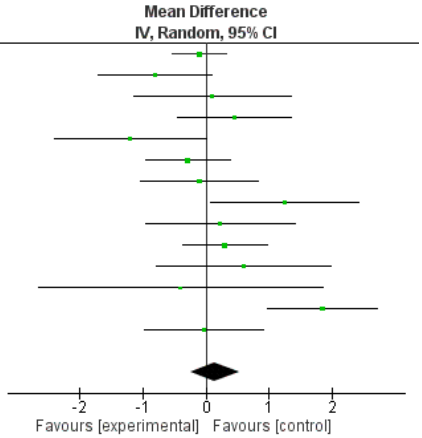


6. Hemoglobin

6.1. Aerobic training vs usual care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Afshar et al., 2010	10.1	0.5	7	10.2	0.3	7	11.5%	-0.10 [-0.53, 0.33]
de Lima et al., 2013	10.3	0.9	10	11.1	1.2	11	7.8%	-0.80 [-1.70, 0.10]
DePaul et al., 2002	11.3	2	15	11.2	1.4	14	5.6%	0.10 [-1.15, 1.35]
Fernandes et al., 2019	10.7	1.14	20	10.25	1.66	19	7.8%	0.45 [-0.45, 1.35]
Groussard et al., 2015	11.3	1.7	8	12.5	0.4	10	5.8%	-1.20 [-2.40, 0.00]
Hristea et al., 2016	10.92	0.69	7	11.21	0.66	9	9.6%	-0.29 [-0.96, 0.38]
Koufaki et al., 2002	12.1	1.3	18	12.2	1.4	15	7.6%	-0.10 [-1.03, 0.83]
Makhlough et al., 2012	9.87	2.01	25	8.62	2.14	23	6.0%	1.25 [0.07, 2.43]
Momeni et al., 2014	10.03	2.07	20	9.8	1.7	20	6.0%	0.23 [-0.94, 1.40]
Painter et al., 2002	10.7	0.9	10	10.4	0.7	14	9.6%	0.30 [-0.37, 0.97]
Parsons et al., 2004	11.7	0.7	6	11.1	1.7	7	4.9%	0.60 [-0.78, 1.98]
Reboredo et al., 2010	10.9	2.8	11	11.3	2.6	11	2.4%	-0.40 [-2.66, 1.86]
Soliman et al., 2015	11.04	1.53	18	9.19	0.89	12	8.0%	1.85 [0.98, 2.72]
Toussaint et al., 2008	12.24	0.99	9	12.27	1.1	10	7.5%	-0.03 [-0.97, 0.91]
Total (95% CI)			**184**			**182**	**100.0%**	**0.15 [-0.24, 0.53]**

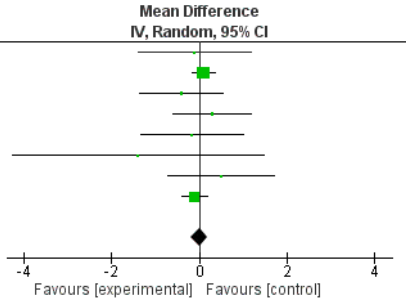
Heterogeneity: Tau² = 0.29; Chi² = 31.64, df = 13 (P = 0.003); I² = 59%
Test for overall effect: Z = 0.74 (P = 0.46)



6.2. Hemoglobin – Resistance training vs usual care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Abreu et al., 2017	10.5	1.9	25	10.6	2.3	19	2.1%	-0.10 [-1.37, 1.17]
Afshar et al., 2010	10.3	0.2	7	10.2	0.3	7	46.8%	0.10 [-0.17, 0.37]
Cheema et al., 2007b	12.2	1.7	20	12.6	1.3	19	3.7%	-0.40 [-1.35, 0.55]
de Lima et al., 2013	11.4	0.9	11	11.1	1.2	11	4.3%	0.30 [-0.59, 1.19]
Dong et al., 2019	10.34	1.8	21	10.5	2.02	20	2.4%	-0.16 [-1.33, 1.01]
Marinho et al., 2016	10.6	2.22	6	12	3.03	7	0.4%	-1.40 [-4.26, 1.46]
Martins do Valle et al., 2019	10.8	1.7	12	10.3	1.3	12	2.3%	0.50 [-0.71, 1.71]
Pellizzaro et al., 2013	11.1	0.4	14	11.2	0.4	14	38.0%	-0.10 [-0.40, 0.20]
Total (95% CI)			**116**			**109**	**100.0%**	**0.01 [-0.18, 0.19]**

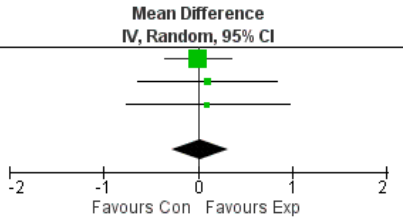
Heterogeneity: Tau² = 0.00; Chi² = 3.77, df = 7 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.07 (P = 0.95)



6.3. Combined training vs usual care

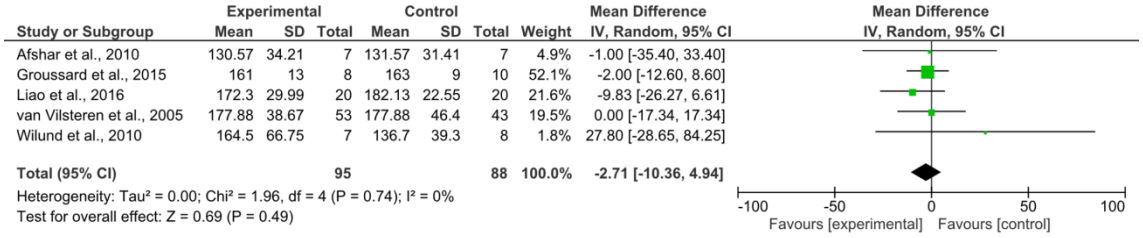
Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Kouidi et al., 2009	11	0.7	30	11	0.7	29	71.5%	0.00 [-0.36, 0.36]
Kouidi et al., 2010	11.3	1.2	24	11.2	1.3	20	16.4%	0.10 [-0.65, 0.85]
Petraki et al., 2008	11.8	1.4	22	11.7	1.5	21	12.1%	0.10 [-0.77, 0.97]
Total (95% CI)			**76**			**70**	**100.0%**	**0.03 [-0.27, 0.33]**

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 2 (P = 0.96); I² = 0%
Test for overall effect: Z = 0.19 (P = 0.85)

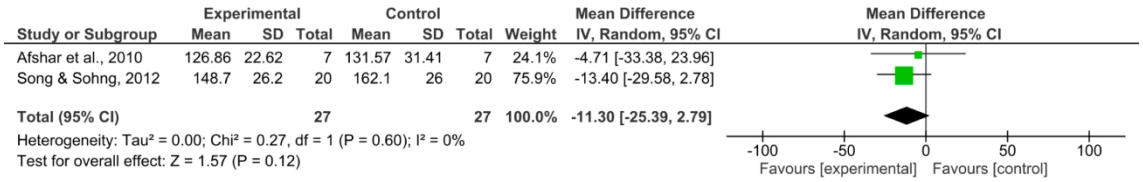


7. Total Cholesterol

7.1. Aerobic training vs usual care

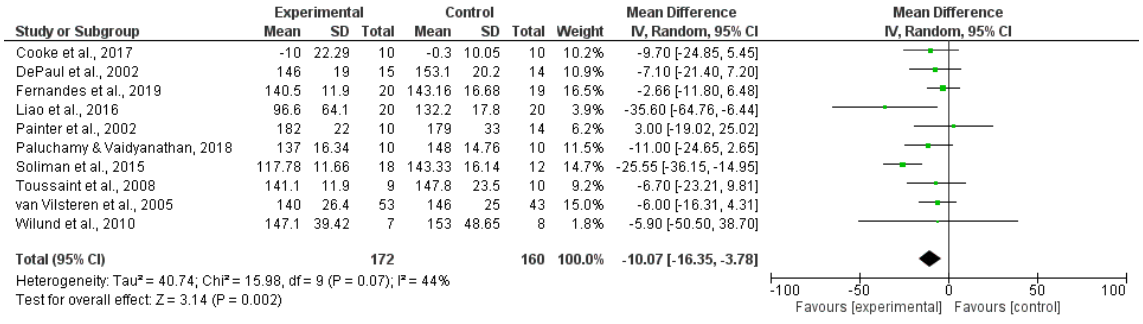


7.2. Resistance training vs usual care

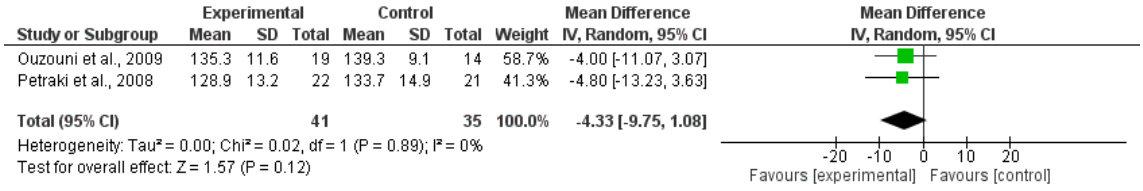


8. Systolic Blood Pressure

8.1. Aerobic training vs usual care



8.2. Combined training vs usual care

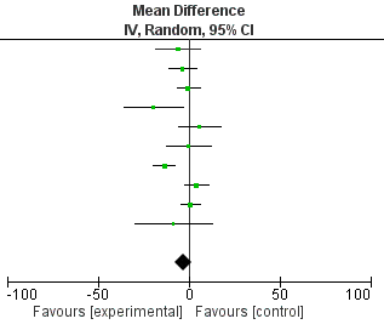


9. Diastolic Blood Pressure

9.1. Aerobic training vs usual care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Cooke et al., 2017	-5.3	17.05	10	0.5	10.49	10	7.9%	-5.80 [-18.21, 6.61]
DePaul et al., 2002	81.7	8.6	15	85.2	11.7	14	12.1%	-3.50 [-11.02, 4.02]
Fernandes et al., 2019	86	6.6	20	86.32	12.52	19	13.3%	-0.32 [-6.65, 6.01]
Liao et al., 2016	53.1	34.9	20	72.4	12.1	20	5.7%	-19.30 [-35.49, -3.11]
Painter et al., 2002	87	14	10	81	14	14	8.7%	6.00 [-5.36, 17.36]
Paluchamy & Vaidyanathan, 2018	83	14.19	10	83	14.19	10	7.9%	0.00 [-12.44, 12.44]
Soliman et al., 2015	77	8.24	18	90.42	8.11	12	13.6%	-13.42 [-19.38, -7.46]
Toussaint et al., 2008	77.2	5.7	9	72.8	9.4	10	12.7%	4.40 [-2.51, 11.31]
van Vilsteren et al., 2005	80	14.9	53	79	12	43	14.2%	1.00 [-4.38, 6.38]
Wilund et al., 2010	77.3	23.02	8	85.7	21.78	9	3.8%	-8.40 [-29.78, 12.98]
Total (95% CI)			**173**			**161**	**100.0%**	**-2.96 [-7.71, 1.78]**

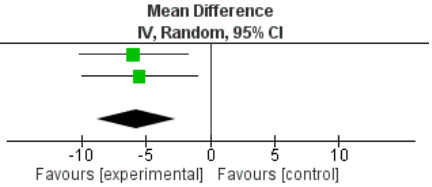
Heterogeneity: Tau² = 33.77; Chi² = 25.86, df = 9 (P = 0.002); I² = 65%
Test for overall effect: Z = 1.22 (P = 0.22)



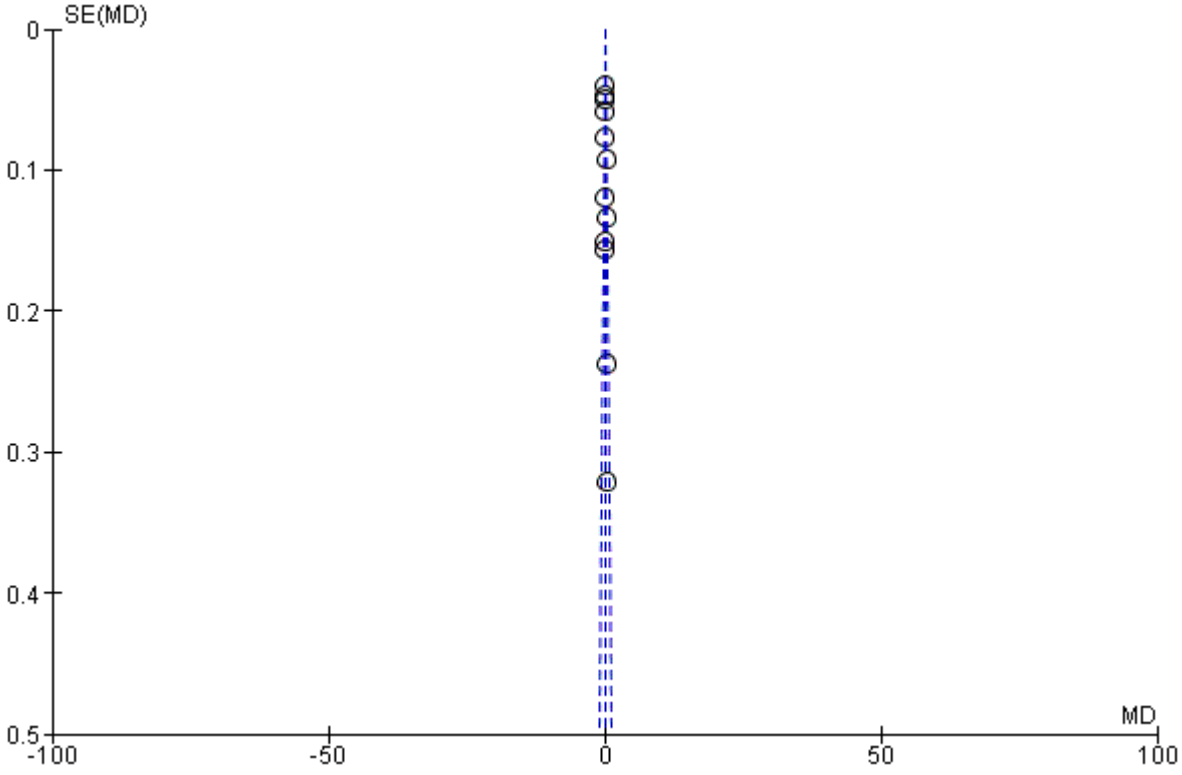
9.2. Combined training vs usual Care

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Ouzouni et al., 2009	79.2	7.7	19	85.2	4.6	14	52.7%	-6.00 [-10.22, -1.78]
Petraki et al., 2008	76.9	7.9	22	82.4	7	21	47.3%	-5.50 [-9.96, -1.04]
Total (95% CI)			**41**			**35**	**100.0%**	**-5.76 [-8.83, -2.70]**

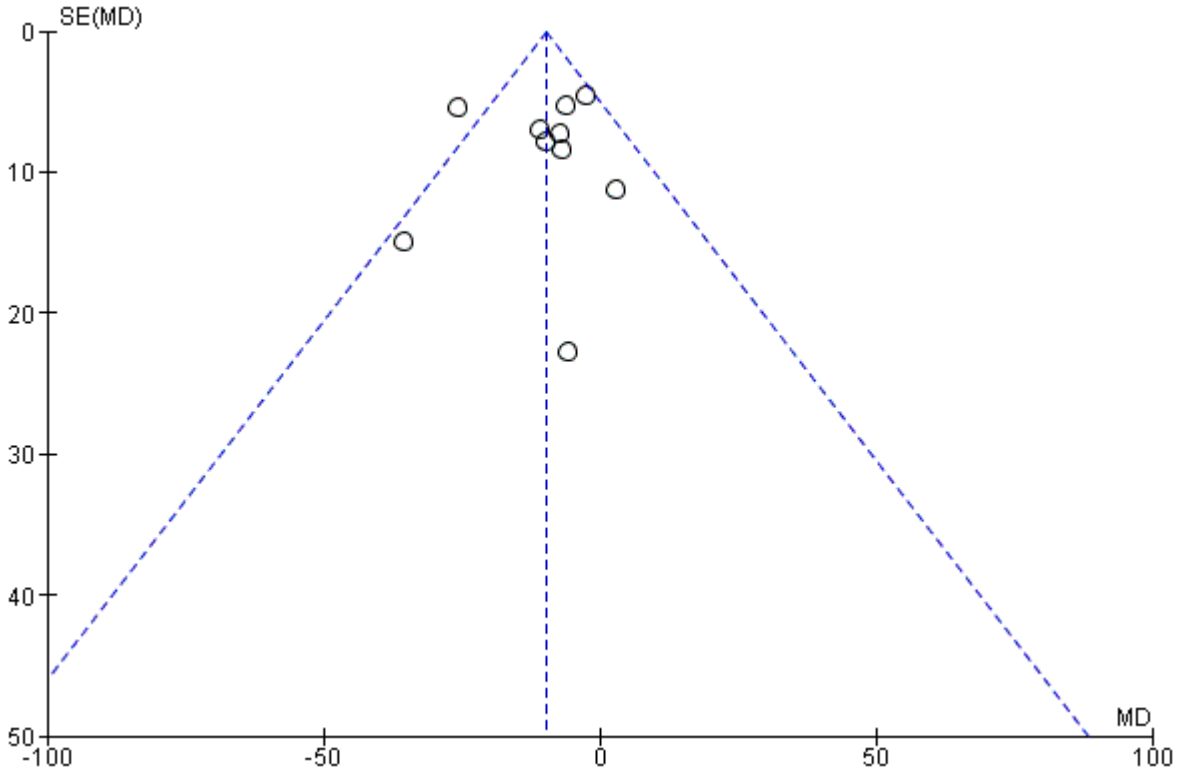
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.87); I² = 0%
Test for overall effect: Z = 3.69 (P = 0.0002)



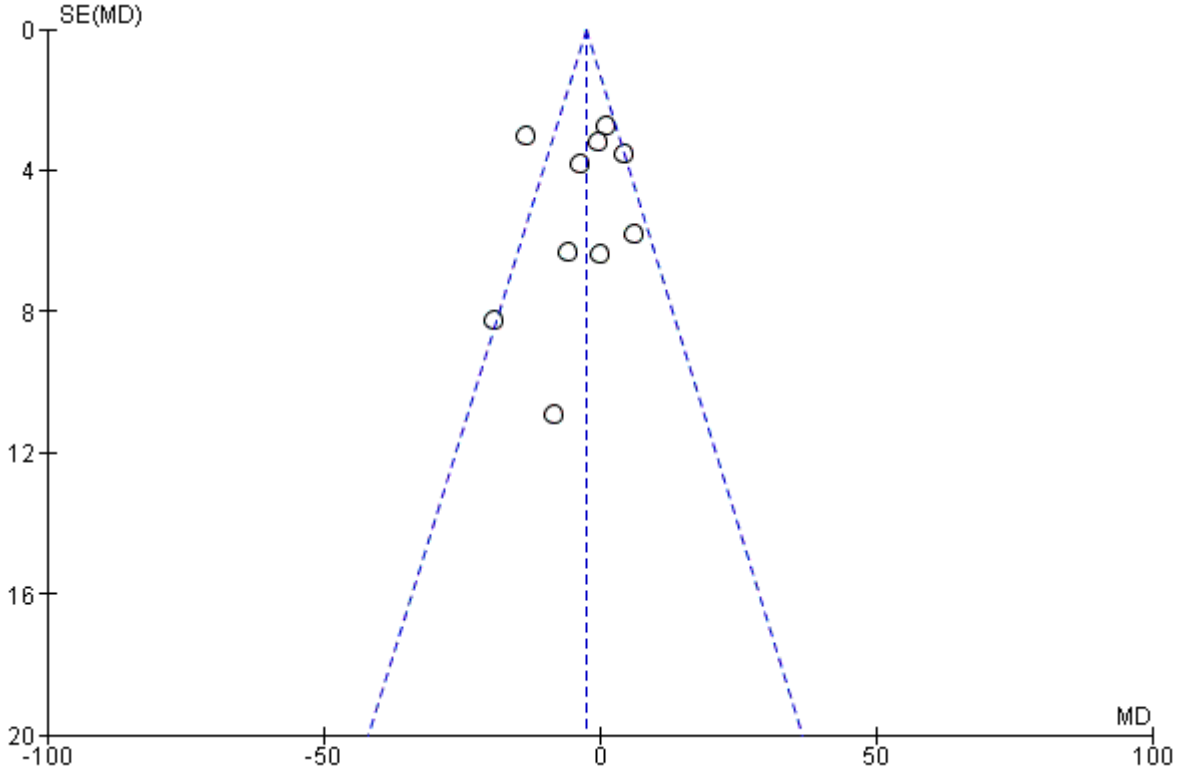
10. Funnel plot Kt/V – Aerobic training vs usual care



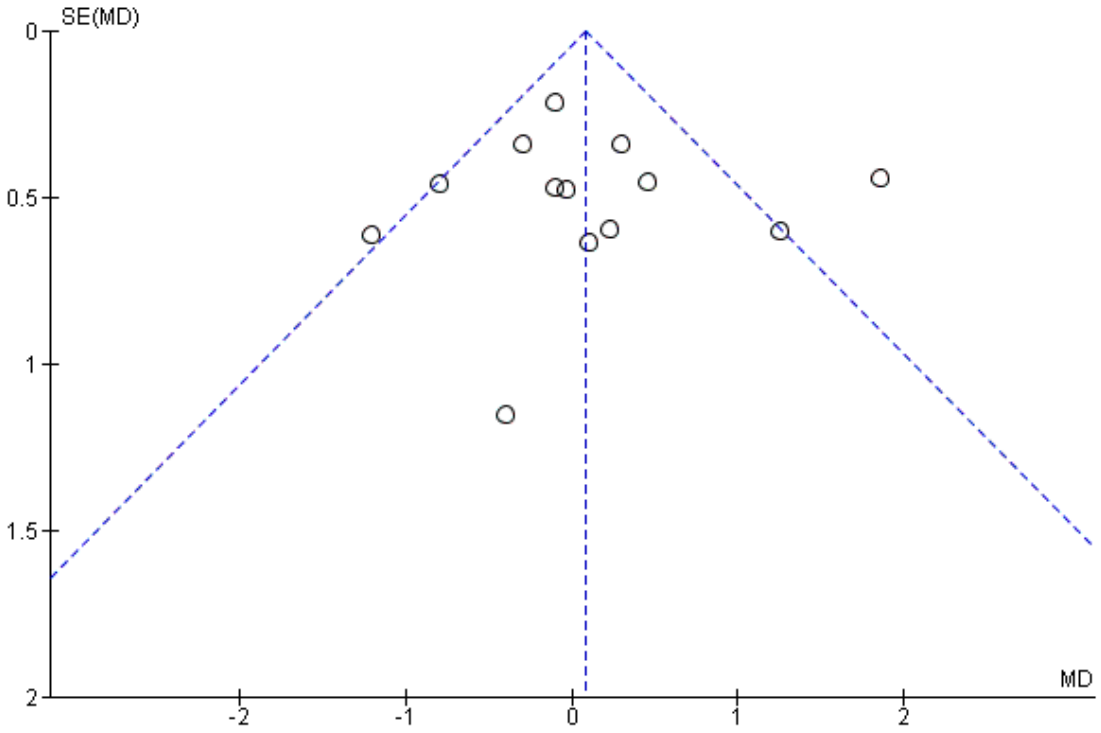
11. Funnel plot systolic blood pressure – Aerobic training vs usual care



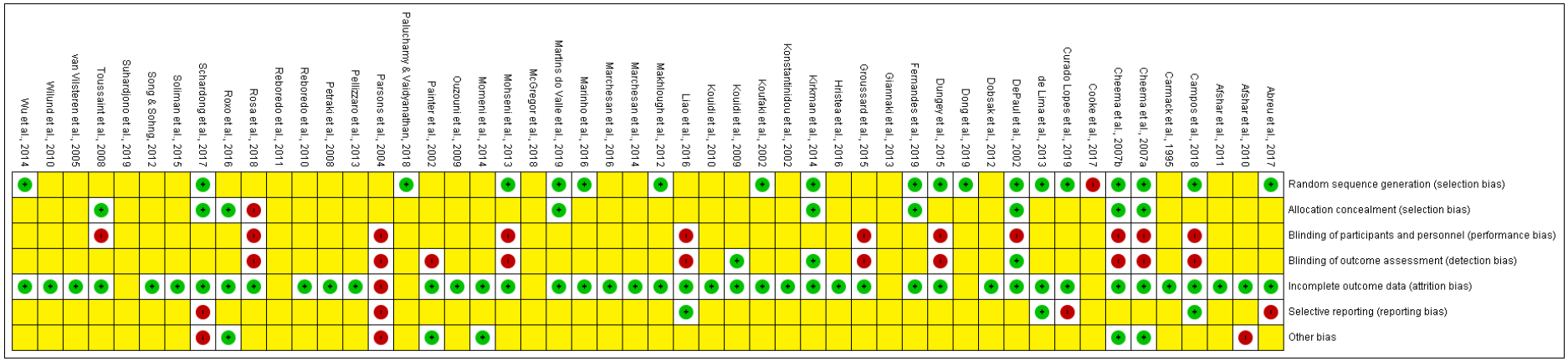
12. Funnel plot diastolic blood pressure – Aerobic training vs usual care



13. Funnel Plot hemoglobin – Aerobic training vs usual care



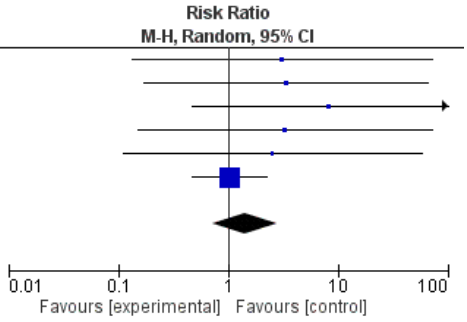
14. Risk of bias classification according to the RoB 1.0 Cochrane tool for studies included in the meta-analysis.



15. Overall effect size of major adverse events between intradialytic training vs usual care

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Cheema et al., 2007a	1	24	0	25	4.7%	3.12 [0.13, 73.04]
Curado Lopes et al., 2019	2	30	0	20	5.2%	3.39 [0.17, 67.05]
DePaul et al., 2002	4	20	0	18	5.7%	8.14 [0.47, 141.49]
Kirkman et al., 2014	1	9	0	10	4.9%	3.30 [0.15, 72.08]
Koufaki et al., 2002	1	18	0	15	4.7%	2.53 [0.11, 57.83]
Wu et al., 2014	9	32	9	33	74.9%	1.03 [0.47, 2.26]
Total (95% CI)		**133**		**121**	**100.0%**	**1.43 [0.73, 2.83]**
Total events	18		9			

Heterogeneity: Tau² = 0.00; Chi² = 3.35, df = 5 (P = 0.65); I² = 0%
Test for overall effect: Z = 1.04 (P = 0.30)



Supplemental table 1.

Study	Sample size	Men/Women	Dropouts	Mean age (y)	Outcomes	Adverse events
Abreu et al. 2017 [31]	61 (44)	41 / 20	17 (27.8%)	45.3	Kt/V, hemoglobin, CRP	NR
Afshar et al. 2010 [11]	21	21 / 0	NR	51.6	Kt/V, TC, CRP, hemoglobin	NR
Afshar et al. 2011 [32]	36 (28)	28 / 0	8 (22.2%)	20	CRP	NR
Campos et al. 2018 [33]	56 (41)	24 / 17	15 (26.7%)	50	6MWT	NR
Carmack et al. 1995 [29]	48 (21)	15 / 6	27 (56.2%)	44.1	VO_2peak	NR
Cheema et al. 2007a [34]	49 (44)	34 / 15	5 (10.2%)	62.6	Kt/V, 6MWT, CRP	Partial injury of a muscle
Cheema et al. 2007b [35]	49 (39)	34 / 15	10 (20%)	62.6	Kt/V, 6MWT, CRP, hemoglobin	One rotator cuff tear (supraspinatus)
Cooke et al. 2018 [36]	27 (20)	14 / 6	7 (25.9%)	55.4	SBP, DBP	None
Curado Lopes et al. 2019 [37]	80 (50)	30 / 20	30 (37.5%)	54.2	IL-6	Hypotension, angina, tachycardia at rest, access problem
de Lima et al. 2013 [38]	33 (32)	18 / 14	1 (3%)	45.5	Hemoglobin	NR
De Paul et al. 2002 [39]	38 (29)	23 / 14	9 (23.6%)	54.5	6MWT	Hypotension, muscle pain
Dobsak et al. 2011 [40]	21	8 / 13	NR	59.1	Kt/V, 6MWT	NR

Dong et al. 2019 [41]	45 (41)	21 / 20	4 (8.8%)	60	Kt/V, hemoglobin, CRP, IL-6	NR
Dungey et al. 2015 [42]	15	9 / 6	0	57.9	IL-6	None
Fernandes et al. 2019 [43]	44 (39)	17 / 22	5 (11.3%)	43.4	Kt/V, 6MWT, SBP, DBP, hemoglobin	NR
Giannaki et al. 2013 [44]	24 (24)	17 / 7	0	58.6	Kt/V	None
Groussard et al. 2015 [45]	20 (18)	15 / 5	2 (10%)	71.3	Kt/V, VO_2peak, TC, hemoglobin	NR
Hristea et al. 2016 [46]	21 (16)	12 / 9	5 (23.8%)	69.7	Kt/V, CRP, 6MWT, hemoglobin	An episode of hypotension and tachyarrhythmia
Kirkman et al. 2014 [47]	32 (27)	15 / 12	5 (15.6%)	50.8	6MWT	Joint pains, lacerations on the back
Konstantinidou et al. 2002 [48]	58 (48)	32 / 26	10 (17%)	49.2	VO_2peak	None
Koufaki et al. 2002 [49]	48 (33)	13 / 35	15 (31.2%)	53.9	VO_2peak, hemoglobin	NR
Kouidi et al. 2009 [50]	63 (59)	34 / 25	4 (6.3%)	53.9	VO_2peak, hemoglobin	NR
Kouidi et al. 2010 [51]	50 (44)	26 / 18	6 (12%)	46.1	VO_2peak, hemoglobin	None
Liao et al. 2016 [12]	40	17 / 23	NR	62	Kt/V, TC, CRP, IL-6, SBP, DBP	None
Makhlough et al. 2012 [52]	47	30 / 17	0	54.6	Hemoglobin	None

Marchesan et al. 2014 [53]	33 (22)	16 / 6	11 (33.3%)	43.6	VO_2peak, 6MWT	NR
Marchesan et al. 2016 [54]	18 (15)	11 / 4	3 (16%)	64.9	6MWT	NR
Marinho et al. 2016 [55]	14 (13)	6 / 7	1 (7%)	73.9	CRP, hemoglobin	None
Martins do Valle et al. 2019 [56]	24	13 / 11	0	54.8	Kt/V, 6MWT, hemoglobin	None
McGregor et al. 2018 [57]	42 (34)	24 / 10	8 (19%)	53.2	VO_2peak	None
Mohseni et al. 2013 [58]	50 (47)	30 / 17	3 (6%)	54.5	Kt/V	None
Momeni et al. 2014 [59]	40	30 / 10	NR	43.1	Hemoglobin	NR
Ouzouni et al. 2009 [60]	35 (33)	27 / 8	2 (5.7%)	48.8	VO_2peak, SBP, DBP	None
Painter et al. 2002 [7]	65 (48)	27 / 21	17 (26.2%)	45.5	VO_2peak, hemoglobin, SBP, DBP	NR
Paluchamy &Vaidyanathan, 2018 [61]	20	18 / 2	0	NR	Kt/V, SBP, DBP	None
Parsons et al. 2004 [62]	18 (13)	7 / 6	5 (27.7%)	54.1	Kt/V, hemoglobin	NR
Pellizzaro et al. 2013 [63]	45 (39)	23 / 16	6 (13.3%)	48.3	6MWT, hemoglobin	NR
Petraki et al. 2008 [64]	70 (63)	47 / 16	7 (10%)	48.8	VO_2peak, hemoglobin	None
Reboredo et al. 2010 [65]	28 (22)	8 / 14	6 (21.4%)	46.6	Kt/V, hemoglobin	NR

Reboredo et al. 2011 [66]	28 (24)	10 / 14	4 (14.3%)	46.4	VO_2peak	NR
Rosa et al. 2018 [67]	59 (52)	35 / 17	7 (11%)	55.7	6MWT	NR
Roxo et al. 2016 [68]	42 (40)	20 / 20	2 (4%)	50.5	Kt/V, hemoglobin, 6MWT	None
Schardong et al. 2017 [69]	24 (21)	4 / 17	3 (12.5%)	61.6	6MWT	None
Soliman, 2015 [30]	40 (30)	14 / 16	10 (25%)	NR	Hemoglobin, SBP, DBP	NR
Song & Sohng, 2012 [70]	44 (40)	20 / 20	4 (9.1%)	53.4	TC	None
Suhardjono et al. 2019 [71]	83 (81)	46 / 35	2 (2.4%)	50.1	CRP	NR
Toussaint et al. 2008 [72]	20 (19)	9 / 10	1 (5%)	68.5	CRP, hemoglobin, SBP, DBP	None
van Vilsteren et al. 2005 [8]	103 (96)	64 / 32	7 (6.8%)	55	Kt/V, VO_2peak, TC, SBP, DBP	NR
Wilund et al. 2010 [13]	17 (15)	6 / 9	2 (11.8%)	59.9	TC, IL-6, SBP, DBP	NR
Wu et al. 2014 [73]	69 (65)	55 / 10	4 (5.8%)	48.8	VO_2peak, 6MWT	Cramp, headache, chest pain, palpitations, hypotension, nausea/vomit

CRP: C-reactive protein; TC: Total cholesterol; 6MWT: Six-minute walk test; IL-6: Interleukin 6; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; NR: Not reported.

Supplemental table 2.

Study	Type of exercise	Intensity	Volume	Frequency (x per wk)	Time (min)	Length (wk)	Utilized equipment	Supervision	Control Group
Abreu et al. 2017 [31]	Resistance	60% 1RM	4 types of exercise 3 sets 10 reps	3	30	36	Theraband®	Yes	Without exercise
Afshar et al. 2010 [11]	Aerobic	65-85% VO_2peak	5 min warm up 10-30 min exercise 5 min cool down	3	20-40	8	Cycle ergometer	Yes	Without exercise
	Resistance	60% 3RM	2-3 sets 8 reps				Anklet Shinguard		
Afshar et al. 2011 [32]	Aerobic	65-85% VO_2peak	5 min warm up 10-30 min exercise	3	15-35	3	Cycle ergometer	Yes	Without exercise
Campos et al. 2018 [33]	IMT	15 cmH_2O – 20 cmH_2O	12 sessions – 30 min 12 sessions – 40 min	3	30-40	8	Threshold PEP	Yes	Without exercise
Carmack et al. 1995 [29]	Aerobic	NR	20-30 min exercise	3	20-30	10	Cycle ergometer	NR	Without exercise
Cheema et al. 2007a [34]	Resistance	15-17 RPE	10 types of exercise 2 sets 8 reps	3	45	12	Free weight dumbbells	Yes	Without exercise
Cheema et al. 2007b [35]	Resistance	15-17 RPE	10 types of exercise 2 sets 8 reps	3	NR	12	Free weight dumbbells	Yes	Without exercise

Cooke et al. 2018 [36]	Aerobic	12-16 RPE	NR	3	NR	12	Cycle ergometer	No	Without exercise
Curado Lopes et al. 2019 [37]	Resistance (moderate)	According to the increase in muscle strength	Warm up wk 1-4: 1 set 15-20 max reps wk 5-8: 2 set 16-18 max reps wk 9-12: 3 set 18-20 max reps - Rest interval between sets (1 min)	3	20-40	12	Elastic bands, ankle weights	Yes	Stretching with elastic bands
	Resistance (high)		Warm up wk 1-4: 1 set 15-20 max reps wk 5-8: 2 set 8-10 max reps wk 9-12: 4 set 10-12 max reps - Rest interval between sets (1 min)						
de Lima et al. 2013 [38]	Aerobic	2-3 RPE modified	20 min exercise	3	20	8	Cycle ergometer	Yes	Without exercise
	Resistance	40% 1RM	4 types of exercise 3 sets 15 reps		NR		Ankle support		
De Paul et al. 2002 [39]	Aerobic	"Somewhat strong" - RPE	2 min warm up 20 min exercise	3	20	12	Cycle ergometer	Yes	Light stretching (30 min)
Dobsak et al. 2011 [40]	Aerobic	60% Wpeak	5 min warm up 20 min exercise in the first 5 wk and 2x20 min after wk 5	3	30-50	20	Cycle ergometer	Yes	Without exercise

			5 min cool down						
	Electro-stimulation	Gradually increased up to 60 mA	10Hz 20-s stimulation, 20-s rest Pulse width 200 ms Rise and fall time 1 s		60		Portable Stimulators/Dual Channel Battery		
Dong et al. 2019 [41]	Resistance	Tolerance of each patient	5 min warm up wk 1: ankle weight (0 kg) Quadriceps training (low intensity) Ankle weight (+0.5 kg) per week, ultil 5kg Pressure on the elastic ball and maximally (3-5 s) - 10 × 10 cycles repeatedly	3	NR	12	Quadriceps equipment, weights applied to the ankles, elastic ball	Yes	Without exercise
Dungey et al. 2015 [42]	Aerobic	12-14 RPE	5 min warm up 30 min exercise	1 (unique session)	35	1 day	Cycle ergometer	Yes	Without exercise
Fernandes et al. 2019 [43]	Aerobic	50-70% HRmax	10 min warm up (active upper and lower limb exercises) 30 min exercise 10 min cool down	3	50	8	Cycle ergometer	Yes	Without exercise
Giannaki et al. 2013 [44]	Aerobic	60-65% VO_2peak	45 min exercise	3	45	24	Cycle ergometer	Yes	Without exercise

Groussard et al. 2015 [45]	Aerobic	55-60% VO_2peak	5 min warm up 30 min exercise 5 min cool down	3	40	12	Cycle ergometer	Yes	Without exercise
Hristea et al. 2016 [46]	Aerobic	3 RPE modified	5 min warm up 30 min exercise	3	15-35	24	Cycle ergometer	Yes	Without exercise
Kirkman et al. 2014 [47]	Resistance	80% 1RM	3 sets 8-10 reps	3	NR	12	Adapted leg press	NR	Unprogressive stretches
Konstantinidou et al. 2002 [48]	Aerobic	70% FCmax	5 min warm up 20 min exercise 5 min cool down	3	60	24	Cycle ergometer	Yes	Without exercise
	Resistance	NR	30 min exercise				Theraband®, weights in legs		
Koufaki et al. 2002 [49]	Aerobic	wk 1-4: 55W wk 5-8: 61W wk 9-12: 64W	wk 1-4: 20 min wk 5-8: 30 min wk 9-12: 40 min	3	20-40	12	Cycle ergometer	Yes	Without exercise
Kouidi et al. 2009 [50]	Aerobic	13 RPE	10 min warm up 40 min exercise	3	60-90	40	Cycle ergometer	Yes	Without exercise
	Resistance		30 min 3 sets 15 reps 10 min cool down				Theraband®, weights applied to the ankles		
Kouidi et al.	Aerobic	11-13 RPE or	5 min warm up	3	60-90	48	Cycle	Yes	Without

2010 [51]		70% VO2peak	30-60 min exercise 5 min cool down				ergometer		exercise
	Resistance		20 min exercise				Theraband®, free weights		
Liao et al. 2016 [12]	Aerobic	12-15 RPE	5 min warm up 20 min exercise 5 min cool down	3	30	12	Cycle ergometer	Yes	Without exercise
Makhlough et al. 2012 [52]	Aerobic	Low	20 rpm rotating ankles and wrist (clockwise and counter-clockwise) 20x flexion/extension wrist and ankles	3	15	8	Not applicable	Yes	Without exercise
Marchesan et al. 2014 [53]	Aerobic	60% HRmax (wk 1-8) 70% HRmax (wk 9-17)	3 min warm up 10-45 min exercise	3	45	17	Cycle ergometer	NR	Without exercise
	Resistance	wk 1-4: no weight wk 5-12: 0.5 kg wk 13-17: 1 kg	3 sets 12 reps (wk 1-8) 3 sets 15 reps (wk 9-17)				NR		
Marchesan et al. 2016 [54]	Aerobic	60% HRmax (wk 1-8) 70% HRmax (wk 9-24)	15-35 min exercise	3	45	24	Cycle ergometer	NR	Without exercise

	Resistance	wk 1-4: no weight wk 5-8: 0.5 kg wk 9-24: 1 kg	3 sets 12 reps (wk 1-16) 3 sets 15 reps (wk 17-24)				Dumbbells, Shin pad		
Marinho et al. 2016 [55]	Resistance	60-70% 3RM	3 lower limbs exercises 1 hip joint exercise 1 min rest between sets and 3 min between types of exercises	3	NR	8	Theraband®	NR	Without exercise
Martins do Valle et al. 2019 [56]	Resistance	Borg ratings scores between 3-5	Lower limb stretching exercises Strengthening exercises (upper and lower limbs) wk 1: 2 sets 10 reps wk 2-12: 3 sets 10 reps	3	NR	12	Weighted ankle cuffs and dumbbells	Yes	Stretching
McGregor et al. 2018 [57]	Aerobic	12-14 RPE	5 min warm-up 40-50 min exercise 5 min cool down	3	50-60	10	Cycle ergometer	Yes	Without exercise
Mohseni et al. 2013 [58]	Aerobic	Low	20 rpm rotating ankles and wrist 20x flexion/extension wrist, elbow, ankles	3	15	8	Not applicable	Yes	Without exercise
Momeni et al. 2014 [59]	Aerobic	NR	30 min exercise	3	30	12	Cycle ergometer	NR	Without exercise
Ouzouni et al. 2009 [60]	Aerobic	13-14 RPE	5 min warm up 20 min exercise	3	60-90	40	Cycle ergometer	Yes	Without exercise

			5 min cool down						
	Resistance		30 min exercise				Theraband® and weigth		
Painter et al. 2002 [7]	Aerobic	12-14 RPE and 15-17 RPE	30 min moderate exercise Intervals of 2-3 min of intense exercise	3	30	20	Cycle ergometer	Yes	Without exercise
Paluchamy & Vaidyanathan, 2018 [61]	Aerobic	Tolerance of each patient	3-5 min warm-up 5 min exercise 3-5 min rest 5-10 min exercise 3-5 min cool down	3	10-15	12	Cycle ergometer	NR	Without exercise
Parsons et al. 2004 [62]	Aerobic	40–50% maximal work capacity	15 min exercise (3 times)	3	45	8	Cycle ergometer	NR	Without exercise
Pellizzaro et al. 2013 [63]	Resistance	50% 1RM	3 sets 15 reps	3	NR	10	Ankle support	NR	Without exercise
	IMT	50% PImax	15 inspirations Rested of 60 seconds				Threshold Loader®		
Petraki et al. 2008 [64]	Aerobic	13 RPE	5 min warm up 50 min exercise 5 min cool down	3	90	28	Cycle ergometer	Yes	Without exercise
	Resistance		30 min strengthening				Theraband®		

			and flexibility exercise				and weigth		
Reboredo et al. 2010 [65]	Aerobic	4-6 RPE modified	10 min warm up 5 min light exercise 35 min exercise 1-3 min cool down	3	60	12	Cycle ergometer	Yes	Without exercise
Reboredo et al. 2011 [66]	Aerobic	4-6 RPE modified	10 min warm up 5 min light exercise 35 min exercise 1-3 min cool down	3	60	12	Cycle ergometer	Yes	Without exercise
Rosa et al. 2018 [67]	Resistance	NR	11 types of exercise 2 sets 15-20 reps	3	40-50	12	Theraband®, free weight dumbbells, shin guards	Yes	Sham exercise (very low intensity without load and progression)
Roxo et al 2016 [68]	Electro-stimulation	Tolerance of each patient	24 sessions Pulses of 350 microseconds 50Hz frequency for 2 s Rest for 10 s	3	30	8	Neurodyn II, Ibramed, Amparo, Brazil	NR	Without exercise
Schardong et al. 2017 [69]	Electro-stimulation	Tolerance of each patient	Isometric exercise Pulses of 400 microseconds 80Hz frequency for 10 s	3	20-34	8	Neurodyn II, model N53, IBRAMED, Sao	NR	Without exercise

			Rest starting with 50 s and reducing by 10 s every 2 wk				Paulo/Brazil		
Soliman et al. 2015 [30]	Aerobic	Low	20 rpm rotating ankles and wrist (clockwise and counter-clockwise) 20x flexion/extension wrist and ankles	3	15	8	Not applicable	NR	Without exercise
Song & Sohng, 2012 [70]	Resistance	11-15 RPE	5 min warm up 20 min exercise 5 min cool down	3	30	12	Theraband®, sand bag	Yes	Without exercise
Suhardjono et al. 2019 [71]	Aerobic	40-60% HRmax	NR	2	30	8	AdirMed®-US cycle ergometer	Yes	Without exercise
Toussaint et al. 2008 [72]	Aerobic	Perception level	At least 30 min exercise	3	30	12	Cycle ergometer	Yes	Without exercise
van Vilsteren et al. 2005 [8]	Aerobic	60% VO_2peak	20-30 min exercise	2-3	20-30	12	Cycle ergometer	Yes	Without exercise
Wilund et al. 2010 [13]	Aerobic	12-14 RPE	45 min exercise	3	45	16	Cycle ergometer	Yes	Without exercise
Wu et al. 2014 [73]	Aerobic	12-16 RPE	5 min warm up 10-15 min exercise	3	15-20	12	Cycle ergometer	Yes	Stretching (10-15 min)

IMT = Inspiratory muscle training; HRmax = Heart rate maximum; RM = Repetition maximum; RPE = The Borg Rating of Perceived Exertion; Reps = Repetitions; NR = Not reported.

Supplemental table 3.

Study	DOI	Register on the Clinical Trials	Funding	Potential conflicts of interest
Abreu et al. 2017 [31]	10.1016/j.lfs.2017.09.007	Yes	Unclear	No
Afshar et al. 2010 [11]	10.4103/0971-4065.73442	Unclar	Unclear	No
Afshar et al. 2011 [32]	–	Unclear	Unclear	No
Campos et al. 2018 [33]	10.1016/j.rmed.2017.12.005	Yes	Yes	No
Carmack et al. 1995 [29]	https://doi.org/10.1007/BF02214958	Unclear	Unclear	Unclear
Cheema et al. 2007a [34]	10.1681/ASN.2006121329	Yes	Unclear	No
Cheema et al. 2007b [35]	10.1053/j.ajkd.2007.07.005	Yes	No	No
Cooke et al. 2018 [36]	10.1093/ajh/hpx191	Yes	Yes	No
Curado Lopes et al. 2019 [37]	10.1016/j.apmr.2019.06.006	Yes	Unclear	No
de Lima et al. 2013 [38]	10.3109/0886022X.2013.780977	Unclear	Unclear	No
De Paul et al. 2002 [39]	10.1053/ajkd.2002.36887	Unclear	Unclear	Unclear
Dobsak et al. 2011 [40]	10.1111/j.1525-1594.2011.01302.x	Unclear	Unclear	Unclear
Dong et al. 2019 [41]	https://doi.org/10.1007/s11255-019-02200-7	Unclear	No	No
Dungey et al. 2015 [42]	10.1159/000368535	Unclear	Unclear	Yes
Fernandes et al. 2019 [43]	https://doi.org/10.1155/2019/7857824	Yes	No	No
Giannaki 2013 [44]	10.1093/ndt/gft288	Yes	Unclear	No
Groussard et al. 2015 [45]	dx.doi.org/10.1139/apnm-2014-0357	Unclear	Unclear	No
Hristea et al. 2016 [46]	10.1111/nep.12752	Yes	Yes	No
Kirkman et al. 2014 [47]	10.1007/s13539-014-0140-3	Yes	Unclear	No
Konstantinidou et al. 2002 [48]	10.1080/165019702317242695	Unclear	Unclear	Unclear

Koufaki et al. 2002 [49]	10.1046/j.1365-2281.2002.00405.x	Unclear	Unclear	Unclear
Kouidi et al. 2009 [50]	10.1053/j.ajkd.2009.03.009	Yes	No	Unclear
Kouidi et al. 2010 [51]	10.1097/HJR.0b013e32833188c4	Unclear	Unclear	No
Liao et al. 2016 [12]	10.1097/MD.0000000000004134	Unclear	Yes	No
Makhlough et al. 2012 [52]	–	Unclear	Unclear	No
Marchesan et al. 2014 [53]	10.5007/1980-0037.2014v16n3p334	Unclear	Unclear	Unclear
Marchesan et al. 2016 [54]	10.1590/0103-5150.029.002.AO14	Unclear	Unclear	Unclear
Marinho et al. 2016 [55]	10.1053/j.jrn.2016.03.002	Unclear	Unclear	Unclear
Martins do Valle et al. 2019 [56]	10.1080/09638288.2019.1606857	Yes	Yes	No
McGregor et al. 2018 [57]	10.1371/journal.pone.0200354	Yes	Yes	No
Mohseni et al. 2013 [58]	10. 5001/omj.2013.99	Yes	Unclear	Unclear
Momeni et al. 2014 [59]	–	Unclear	Yes	No
Ouzouni et al. 2009 [60]	10.1177/0269215508096760	Unclear	Unclear	Unclear
Painter et al. 2002 [7]	10.1053/ajkd.2002.30544	Unclear	Unclear	Unclear
Paluchamy & Vaidyanathan, 2018 [61]	10.4103/1319-2442.239661	Unclear	Unclear	No
Parsons et al. 2004 [62]	10.5414/cnp61261	Unclear	Yes	Unclear
Pellizzaro et al. 2013 [63]	10.3109/0886022X.2012.745727	Unclear	Yes	No
Petraki et al. 2008 [64]	10.5414/CNP70210	Unclear	Unclear	Unclear
Reboredo et al. 2010 [65]	10.1590/S0101-28002010000400006	Unclear	Yes	Unclear
Reboredo et al. 2011 [66]	10.1016/j.apmr.2011.07.190	Yes	Unclear	No
Rosa et al. 2017 [67]	10.1177/0269215518760696	Yes	No	No
Roxo et al. 2016 [68]	10.5935/0101-2800.20160052	Unclear	Unclear	Unclear

Schardong et al. 2017 [69]	10.1111/aor.12886	Yes	Yes	No
Soliman, 2015 [30]	0.5430/jnep.v5n11p16	Unclear	Unclear	No
Song & Sohng 2012 [70]	10.4040/jkan.2012.42.7.947	Unclear	Unclear	Unclear
Suhardjono et al. 2019 [71]	10.1111/hdi.12764	Unclear	Yes	No
Toussaint et al. 2008 [72]	10.1111/j.1542-4758.2008.00262.x	Yes	Yes	Uncleart
van Vilsteren et al. 2005 [8]	10.1093/ndt/gfh560	Unclear	Unclear	No
Wilund et al. 2010 [13]	10.1093/ndt/gfq106	Unclear	Unclear	No
Wu et al. 2014 [73]	10.1177/0300060513509037	Unclear	No	No

Funding: Yes: The authors declare a funding; No: The authors declare no funding; Unclear: Insufficient information. **Register on the Clinical Trials:** Yes: The authors report at work; Unclear: Insufficient information. **Potential conflicts of interest**: Yes: The authors declare a conflict of interest; No: The authors declare no conflict of interest; Unclear: Insufficient information.

Supplemental table 4. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	58
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	60
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	62
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	62
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	63
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	63
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	64
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	64
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	64
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	65

Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	65
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	65
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	66
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	67

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	65
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	67
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	68
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	69
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	72
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	102
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	70
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	97
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	90
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	73
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	77
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	78
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	78

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

5. CONCLUSÕES

- Os métodos de treinamentos intradialíticos aeróbico, resistido e combinado são importantes estratégias para melhora de alguns importantes desfechos no cenário da doença renal em fase terminal, muito embora nem toda modalidade tenha demonstrado benefícios que se apliquem para todos os desfechos avaliados;

- Apesar de o treinamento aeróbico ter evidenciado impacto significativo sobre o Kt/V, quando a análise de sensibilidade foi realizada omitindo um estudo no qual o treinamento de força pré-diálise também foi utilizado, a significância desapareceu. Sendo assim, o impacto do treinamento intradialítico sobre o Kt/V permanece incerto;

- A eletroestimulação funcional e o treinamento muscular inspiratório – ambos realizados durante a hemodiálise – parecem alternativas eficazes para o incremento da capacidade funcional; entretanto, pelo baixo número de estudos avaliados nestes dois tipos de treinamento, os dados observados devem ser vistos à luz dessa limitação;

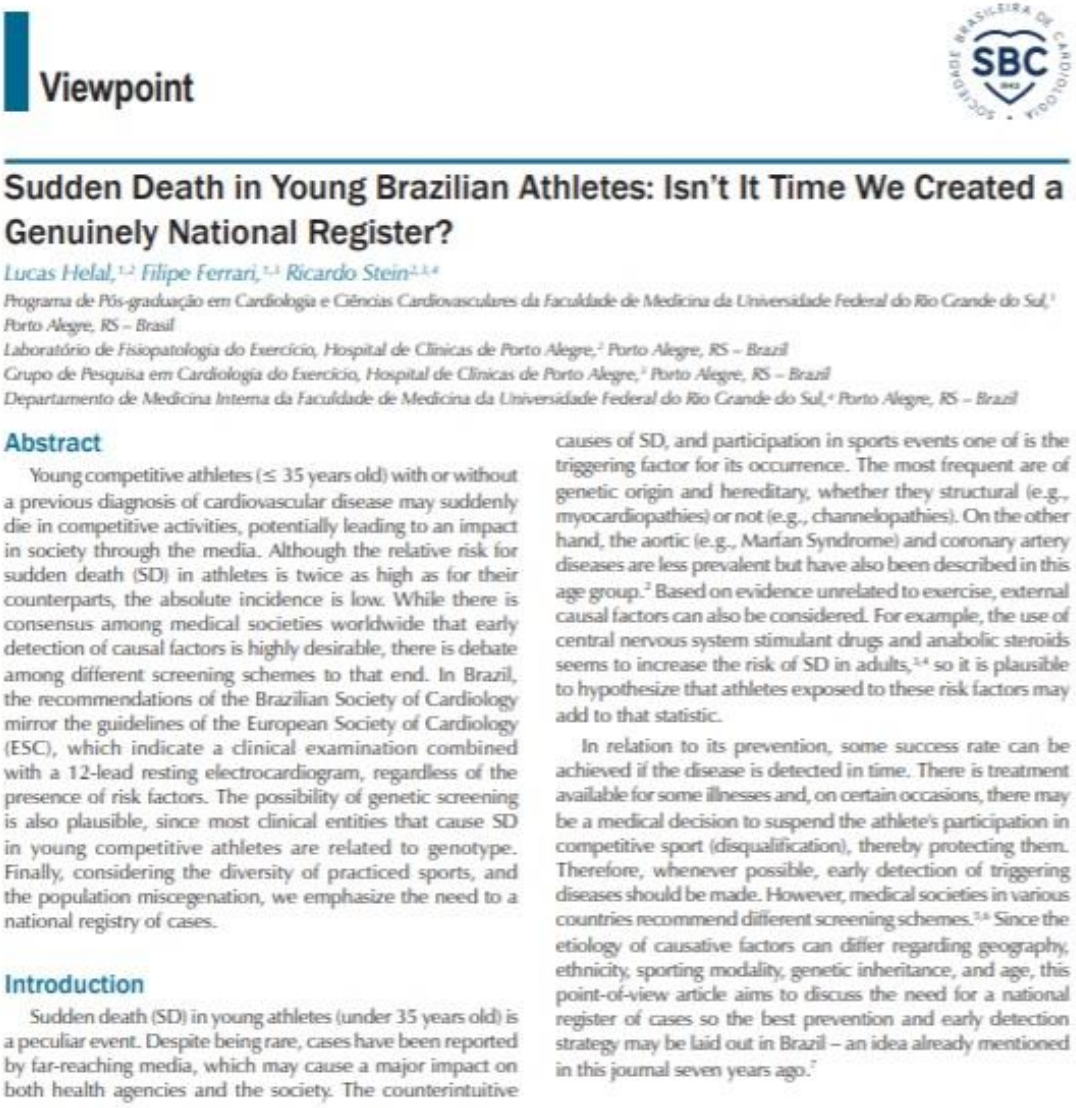
- O treinamento intradialítico pode ser realizado através de diferentes estratégias (modalidades), sendo importante considerar o serviço de hemodiálise, sempre levando em consideração às possíveis comorbidades dos pacientes;

- A imensa maioria dos estudos avaliados são de qualidade duvidosa e apresentam problemas na descrição metodológica. Dessa forma, os achados provenientes desta revisão sistemática e meta-análise devem ser interpretados com cautela, sempre se considerando o risco de viés incerto relativo à uma parcela significativa dos estudos analisados, além da certeza de evidências baixa à muito baixa para a maioria dos desfechos avaliados.

6. PRODUÇÃO CIENTÍFICA DURANTE O MESTRADO

6.1. ARTIGOS PUBLICADOS EM REVISTAS NACIONAIS

6.1.1. Sudden Death in Young Brazilian Athletes: Isn't It Time We Created a Genuinely National Register? Arq Bras Cardiol. 2018;111(6):856-859.



Viewpoint

Sudden Death in Young Brazilian Athletes: Isn't It Time We Created a Genuinely National Register?

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Abstract

Young competitive athletes (≤ 35 years old) with or without a previous diagnosis of cardiovascular disease may suddenly die in competitive activities, potentially leading to an impact in society through the media. Although the relative risk for sudden death (SD) in athletes is twice as high as for their counterparts, the absolute incidence is low. While there is consensus among medical societies worldwide that early detection of causal factors is highly desirable, there is debate among different screening schemes to that end. In Brazil, the recommendations of the Brazilian Society of Cardiology mirror the guidelines of the European Society of Cardiology (ESC), which indicate a clinical examination combined with a 12-lead resting electrocardiogram, regardless of the presence of risk factors. The possibility of genetic screening is also plausible, since most clinical entities that cause SD in young competitive athletes are related to genotype. Finally, considering the diversity of practiced sports, and the population miscegenation, we emphasize the need to a national registry of cases.

Introduction

Sudden death (SD) in young athletes (under 35 years old) is a peculiar event. Despite being rare, cases have been reported by far-reaching media, which may cause a major impact on both health agencies and the society. The counterintuitive causes of SD, and participation in sports events one of is the triggering factor for its occurrence. The most frequent are of genetic origin and hereditary, whether they structural (e.g., myocardiopathies) or not (e.g., channelopathies). On the other hand, the aortic (e.g., Marfan Syndrome) and coronary artery diseases are less prevalent but have also been described in this age group.[2] Based on evidence unrelated to exercise, external causal factors can also be considered. For example, the use of central nervous system stimulant drugs and anabolic steroids seems to increase the risk of SD in adults,[3,4] so it is plausible to hypothesize that athletes exposed to these risk factors may add to that statistic.

In relation to its prevention, some success rate can be achieved if the disease is detected in time. There is treatment available for some illnesses and, on certain occasions, there may be a medical decision to suspend the athlete's participation in competitive sport (disqualification), thereby protecting them. Therefore, whenever possible, early detection of triggering diseases should be made. However, medical societies in various countries recommend different screening schemes.[5,6] Since the etiology of causative factors can differ regarding geography, ethnicity, sporting modality, genetic inheritance, and age, this point-of-view article aims to discuss the need for a national register of cases so the best prevention and early detection strategy may be laid out in Brazil – an idea already mentioned in this journal seven years ago.[7]

6.1.2. Reabilitação nos pacientes submetidos a transplante cardíaco - Parte I. Revista do DERC. 2018;24:132-134.

ARTIGO DE REVISÃO

Rev DERC 2018;24(4):132-134

REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE I

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INTRODUÇÃO

O transplante cardíaco (Txc) é o tratamento de escolha para pacientes com insuficiência cardíaca (IC) refratária que permanecem com sintomas graves mesmo em uso de todo arsenal medicamentoso disponível e/ou realização de procedimentos cirúrgicos. O Txc tem como objetivo promover a melhora na qualidade de vida, assim como sobrevida nessa população.[1,2]

Nos últimos anos houve avanços significativos no que diz respeito ao Txc, com surgimento de novas técnicas cirúrgicas e desenvolvimento quando comparado ao de indivíduos saudáveis pareados por idade.[6,7] Alguns fatores podem explicar tais fatos: 1) imediatamente no período pós-transplante, o aloenxerto apresenta ausência de inervação simpática e parassimpática (denervação autonômica), provocando aumento da frequência cardíaca (FC) de repouso, atenuando a sua elevação natural como resposta ao exercício e prejudicando a recuperação após o esforço;[7,8] 2) disfunção muscular esquelética, na qual a terapia imunossupressora associada à IC prévia exercem papel de destaque;[9] 3) função vascular e hipertensão arterial sistêmica, diabetes mellitus e coronariopatia.[15] Por sua vez, o treinamento físico é conhecido como uma ferramenta terapêutica de excelência para o manejo dessas doenças crônicas[16,17] e também eficaz na otimização no controle autonômico.[7,18]

O treinamento físico após o Txc contribui no aumento do $\dot{V}O_2$ pico, na melhora do controle hemodinâmico, força muscular e densidade mineral óssea[19-21], podendo assim, inclusive, melhorar o prognóstico nesta população.[22] Embora existam inúmeras possibilidades de prescrição de treinamento, o método preconizado

6.1.3. Physical exercise in individuals in hemodialysis: benefits and best indications - systematic review. Rev Pesqui Fisioter. 2018;8(3):404-419.

Systematic review

Journals BAHIANA

Physical exercise in individuals in hemodialysis: benefits and best indications - systematic review

Exercício físico em indivíduos em hemodiálise: benefícios e melhores indicações - revisão sistemática

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RESUMO | INTRODUÇÃO: Cresce o número de indivíduos com doença renal crônica (DRC) submetidos à hemodiálise (HD). No Brasil, em 2012, o número de pacientes em HD era de 97.586, com taxa de mortalidade de 19%. O exercício físico (EF) é uma terapia adjuvante capaz de promover controle glicêmico, pressórico e outros ganhos relevantes para o controle da DRC. **OBJETIVO:** Descrever os benefícios sobre a qualidade de vida, os cuidados e os protocolos mais efetivos de exercício físico para indivíduos em hemodiálise. **MÉTODO:** Estudo de revisão sistemática. Consultados artigos dos bancos de dados SciELO

ABSTRACT | INTRODUCTION: The number of patients with chronic chronic disease (CKD) on hemodialysis (HD) has increased. In Brazil, in 2012, the number of patients in HD was 97,586, with a mortality rate of 19%. Physical exercise (PE) is an adjuvant therapy capable of promoting glycemic control, blood pressure and other gains relevant to CKD control. **OBJECTIVE:** To describe the benefits of quality of life, care and the most effective protocols of physical exercise for the individual on hemodialysis. **METHOD:** Systematic review study. Consultations of the SciELO and PubMed databases between 2005 and 2016 on the

6.1.4. Reabilitação nos Pacientes Submetidos a Transplante Cardíaco - Parte II: Treinamento Físico Pós-Transplante Cardíaco. Revista do DERC. 2019;25:10-13.

ARTIGO DE REVISÃO

Rev DERC 2019;25(1):10-13

REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE II: TREINAMENTO FÍSICO PÓS-TRANSPLANTE CARDÍACO

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A definição de alguns conceitos e o conhecimento dos princípios que norteiam a prescrição do treinamento físico é essencial. O termo "atividade física" caracteriza-se por qualquer movimento corporal produzido pelos músculos esqueléticos que resulte em gasto energético acima dos níveis de repouso; ao passo que "exercício físico" é uma atividade física planejada e estruturada com o objetivo de melhorar ou manter alguma valência física, sendo que as melhores adaptações fisiológicas ocorrem na realização de sessões acumuladas dentro de um trei-

cardíaco (Txc).[5] Capacidade funcional, por sua vez, é medida objetivamente pelo consumo de oxigênio de pico ($\dot{V}O_2$ pico), um poderoso marcador prognóstico nessa população, estando inversamente associada à morbidade e mortalidade.[7,8]

A Diretriz Sul-Americana de Prevenção e Reabilitação Cardiovascular[6] destaca a importância da realização de exercícios durante a internação e após a alta hospitalar. O treinamento aeróbico é o preconizado, devendo ser complementado pelo resistido a partir da sexta semana pós Txc. Neste documento,

contínuo de moderada intensidade. No estudo pioneiro de Richard et al.[5], os pesquisadores observaram que em um período de 46 meses pós Txc, pacientes que realizaram treinamento aeróbico – em média 4 vezes por semana durante três anos – apresentaram capacidade funcional e função cronotrópica semelhantes às verificadas em indivíduos saudáveis. Tal experimento lançou a hipótese do efeito favorável do exercício e deu embasamento para ensaios clínicos randomizados posteriores.

Metanálise recente da Cochrane,[10] que reuniu nove ensaios clínicos randomi-

6.1.5. Reabilitação nos Pacientes Submetidos a Transplante Cardíaco - Parte III: Recomendações Para Treinamento Pós-Transplante Cardíaco. Revista do DERC. 2019;25:38-44.

ARTIGO DE REVISÃO

Rev DERC 2019;25(2):38-44

REABILITAÇÃO NOS PACIENTES SUBMETIDOS A TRANSPLANTE CARDÍACO – PARTE III: RECOMENDAÇÕES PARA TREINAMENTO PÓS-TRANSPLANTE CARDÍACO

REHABILITATION IN PATIENTS UNDERGOING HEART TRANSPLANTATION - PART III: RECOMMENDATIONS FOR POST-TRANSPLANT CARDIAC TRAINING

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Baseado nas diversas evidências expostas nesta revisão, o efeito benéfico do treinamento físico em indivíduos pós-transplante cardíaco (Txc) parece ser claro. Esta terapia se mostra segura e exequível, podendo ser realizada no ambiente hospitalar ou residencial. No entanto, embora ambas as estratégias sejam eficazes em promover aumento na capacidade funcional, de acordo com os experimentos realizados até o momento, a magnitude do efeito é maior quando o treinamento é realizado em ambientes controlados. É sugerido que no início do programa, após as devidas avaliações, os pacientes sejam continuamente monitorados por eletrocardiograma durante as sessões. No entanto, tal medida não é obrigatória, considerando que o benefício da terapia ultrapassa os potenciais riscos, que são de pequena magnitude. O corpo de evidências tem incluído, na sua maioria, pacientes com pelo menos seis meses após o procedimento. Entretanto, parece-nos que quanto antes a intervenção for iniciada, maior o seu potencial benefício. De forma geral, diretrizes recomendam que o treinamento formal seja iniciado entre seis a oito semanas após o Txc. Essa recomendação visa à cicatrização do esterno, uma vez que a partir desse momento a maioria dos exercícios pode ser realizada. Cabe salientar que os profissionais envolvidos com o processo de

6.1.6. The Olympic Experimental Gymnasium Program and its Association with the Prevalence of Cardiovascular Risk Factors in Adolescents: A Cross-Sectional Study. Arq Bras Cardiol. 2019;112(6):775-781.

Original Article

The Olympic Experimental Gymnasium Program and its Association with the Prevalence of Cardiovascular Risk Factors in Adolescents: A Cross-Sectional Study

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Abstract

Background: Cardiovascular disease (CVD) is the leading cause of death worldwide. Physical activity (PA) and appropriate diet, if adopted in childhood and adolescence, may reduce the CVD burden in later life. The Olympic Experimental Gymnasium (OEG) project was implemented to increase the PA levels of students by means of regular physical exercise and healthy eating habits.

Objectives: To estimate and compare the prevalence of CVD risk factors in OEG schools versus regular schools (RSch) and to examine associations between the school environment and CVD risk factors.

Methods: In this cross-sectional study with a comparator group, adolescents aged 12-13 years attending three OEG schools (n = 719) and three RSch (n = 394) were evaluated after one year of the ongoing program to estimate the prevalence of overweight, pre-hypertension/hypertension, altered glycemia, and lipid profile. An α level of 0.05 was set for statistical analysis.

Results: RSch students had higher odds to have high blood pressure (OR 1.86, 1.36–2.54) and to be overweight (OR 1.49, 1.13–1.98) than OEG students. Glucose levels were not altered in most cases regardless of school type, and no differences were found in lipid profile. In the sensitivity analysis stratified by gender, girls from RSch were more likely to have high body mass index than boys.

Conclusions: Exposure of adolescents to the OEG policies was positively associated with an important reduction in CVD risk factors, including high blood pressure and overweight. (Arq Bras Cardiol. 2019; 112(6):775-781)

Keywords: Cardiovascular Diseases/mortality; Hypertension; Overweight; Dyslipidemias; Exercise; Life Style; Child; Adolescent; Diet.

6.1.7. Physical exercise in type 1 diabetes mellitus: what evidence for better prescribing? Rev Bras Fisiol Exerc. 2019;18(1):38-50.

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REVISÃO

Exercício físico no diabetes mellitus tipo 1: quais as evidências para uma melhor prescrição?

Physical exercise in type 1 diabetes mellitus: what evidence for better prescribing?

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6.1.8. Adiponectina, Doença Cardiovascular e Suas Relações com o Exercício Físico: Revisão Narrativa. Rev Soc Cardiol de São Paulo. 2019;29(1):82-87.

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REVIEW/REVISÃO

ADIPONECTIN, CARDIOVASCULAR DISEASE AND ITS RELATIONSHIP WITH PHYSICAL EXERCISE: A NARRATIVE REVIEW

ADIPONECTINA, DOENÇA CARDIOVASCULAR E SUAS RELAÇÕES COM O EXERCÍCIO FÍSICO: REVISÃO NARRATIVA

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ABSTRACT

There is a close relationship between circulating levels of adiponectin, insulin resistance and cardiovascular risk. The available evidence that evaluated the relationship between adiponectin levels and physical exercise is somewhat controversial. Recent studies have shown that aerobic training does not alter adiponectin levels without significant reduction in body weight; other studies show that modest weight loss, along with aerobic training, significantly improves the levels of this protein – even if there is no change in weight. On the other hand, it has been documented that aerobic training increases levels of adiponectin even if there is weight gain. Motivated by such inconsistencies, the purpose of this narrative review was to present and discuss the relationship between adiponectin and cardiovascular diseases, as well as the possible influence of physical exercise on blood concentrations of adiponectin and its association with improved glycemic status.

Keywords: Adiponectin; Exercise Physical; Cardiovascular Diseases.

RESUMO

6.1.9. PCSK9 Inhibitors: Clinical Relevance, Molecular Mechanisms, and Safety in Clinical Practice. Arq Bras Cardiol. 2019;112(4):453-460.

Review Article

PCSK9 Inhibitors: Clinical Relevance, Molecular Mechanisms, and Safety in Clinical Practice

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Abstract

Coronary artery disease (CAD) is one of the leading causes of mortality. High circulating levels of low-density lipoprotein (LDL) in the blood are associated with cardiovascular mortality, whether through an etiological role or through its association with the progression of CAD per se. Randomized clinical trials have shown that, when LDL levels are reduced, cardiovascular risk is also reduced, which reinforces this association. The first major trial involving a hypolipidemic agent of the statin family, the Scandinavian Simvastatin Survival Study (4S), was published in 1994 and found a significant reduction in mortality in patients at high cardiovascular risk. However, even in subsequent studies with different statins, a residual risk persisted, and this seems not to have changed over time; it is speculated that this risk may be due to statin intolerance. In this scenario, the potential exists for novel hypolipidemic agents to drive a true revolution in the therapy of dyslipidemia. The recent discovery of PCSK9 inhibitors (PCSK9i), a class of hypolipidemic monoclonal antibodies, is extremely promising. PCSK9 inhibition is capable of promoting

for almost 30% of deaths in 2013.[1] In recent decades, mounting evidence has shown a close link between low-density lipoprotein (LDL) levels and incidence of coronary artery disease (CAD).[2,3] Inadequate hepatic uptake of LDL results in increased levels of circulating LDL, and consequent incidence of premature CAD.[4]

The treatment of dyslipidemias involves a number of factors, and lifestyle changes should be part of all medical prescriptions for this purpose. Non-pharmacological interventions, such as starting a regular exercise program, not smoking or quitting smoking, and adopting a healthy diet can have a significant impact on lipid profile. However, a substantial number of patients need to add hypolipidemic drugs (e.g., statins, ezetimibe, fibrates) to the aforementioned measures to achieve recommended LDL goals.[5]

Substantial advances in lipid-lowering drugs have been achieved in recent years.[6] When used appropriately, these agents play a preponderant role in preventing adverse cardiovascular (CV) outcomes.[7] Hypolipidemic therapy with statins has been shown to have an impact both for primary prevention of atherosclerosis in patients at high CV risk[8] and

6.1.10. Importance of Genetic Testing in Dilated Cardiomyopathy: Applications and Challenges in Clinical Practice. Arq Bras Cardiol. 2019;113(2):274-281.

Artigo de Revisão

Importância do Teste Genético na Miocardiopatia Dilatada: Aplicações e Desafios na Prática Clínica

Importance of Genetic Testing in Dilated Cardiomyopathy: Applications and Challenges in Clinical Practice

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Resumo

A miocardiopatia dilatada (MCD) é uma síndrome caracterizada por dilatação ventricular esquerda e disfunção contrátil, sendo considerada a causa mais comum de insuficiência cardíaca em adultos jovens. O uso do sequenciamento de nova geração tem contribuído com a descoberta de uma grande quantidade de dados genômicos relacionados à MCD, identificando mutações que envolvem genes que codificam proteínas do citoesqueleto, sarcômero e canais iônicos, os quais são responsáveis por aproximadamente 40% dos casos classificados como MCD idiopática. Nesse cenário, geneticistas e especialistas em genética cardiovascular passaram a atuar em conjunto, agregando conhecimento e estabelecendo

miocardiopatia dilatada (MCD) a principal indicação de transplante cardíaco (TxC).[3] Atualmente, estima-se que a prevalência da MCD idiopática seja em torno de 1 caso para cada 2.500 indivíduos, mas autores como Hershberger et al.,[4] descrevem uma frequência dez vezes maior.[4] Particularmente nas últimas duas décadas obteve-se maior compreensão sobre a etiologia e o curso clínico de muitas destas doenças.[5,6] Este cenário foi proporcionado por avanços substanciais no emprego do diagnóstico genético em serviços de miocardiopatia e centros de pesquisa por todo o mundo.

Tradicionalmente, a MCD é definida como dilatação do ventrículo esquerdo (VE) ou de ambos, com consequente prejuízo no desempenho contrátil do músculo cardíaco, na

6.1.11. Global Longitudinal Strain or Measurement of Ejection Fraction: Which Method is Better in Stratifying Patients with Heart Failure? Arq Bras Cardiol. 2019;113(2):195-196.

Minieditorial

Strain Longitudinal Global ou Medida da Fração de Ejeção: Qual Método Estratifica Melhor os Pacientes com Insuficiência Cardíaca?

Global Longitudinal Strain or Measurement of Ejection Fraction: Which Method is Better in Stratifying Patients with Heart Failure?

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Minieditorial referente ao artigo: Strain Longitudinal Global é Preditor de Baixa Capacidade Funcional em Pacientes com Insuficiência Cardíaca Sistólica

A insuficiência cardíaca (IC) é uma síndrome complexa, de mau prognóstico e com estigma de alta mortalidade.[1] A prevalência atual estimada nos Estados Unidos é de seis milhões de casos, com uma incidência prevista de mais dois milhões de pacientes até 2030.[2] No Brasil, especificamente, ocorreram mais de 26 mil mortes por IC em 2012, com aproximadamente 230 mil internações sendo atribuídas a essa doença.[3]

Os principais sintomas da IC incluem dispneia progressiva, fadiga, intolerância ao esforço físico e sinais de sobrecarga volêmica, gerando redução na capacidade funcional e qualidade de vida dos pacientes e aumentando consideravelmente o risco de morbimortalidade.[4] Nesse sentido, não é raro que o consumo de oxigênio de pico (maxVO_2) seja, em

controverso.[9] Seguindo esse raciocínio, apesar da medida da FEVE ser um método validado e utilizado amplamente há décadas, a avaliação da deformação miocárdica através do *Strain* Longitudinal Global (SLG) vem demonstrando maior eficácia na análise do desarranjo global do ventrículo esquerdo quando comparado à medida da FEVE. O SLG pode fornecer valor adicional na estratificação prognóstica da IC, independentemente dos valores da FEVE, e servir como instrumento adicional na tomada de decisão terapêutica em situações clínicas específicas nessa população, como: implante de cardiodesfibriladores e ressincronizadores, indicação de dispositivos de assistência ventricular e seguimento de pacientes com cardiotoxicidade por quimioterápicos.[10]

6.1.12. The Brazilian Society of Cardiology and Brazilian Society of Exercise and Sports Medicine Updated Guidelines for Sports and Exercise Cardiology - 2019. Arq Bras Cardiol. 2019;112(3):326-368.

Atualização

Atualização da Diretriz em Cardiologia do Esporte e do Exercício da Sociedade Brasileira de Cardiologia e da Sociedade Brasileira de Medicina do Exercício e Esporte – 2019

Realização: Sociedade Brasileira de Cardiologia (SBC) e Sociedade Brasileira de Medicina do Exercício e do Esporte (SBMEE)

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6.1.13. Biochemical and Molecular Mechanisms of Glucose Uptake Stimulatedby Physical Exercise in Insulin Resistance State: Role of Inflammation. Arq Bras Cardiol. 2019. [Ahead of print]

Review Article

Biochemical and Molecular Mechanisms of Glucose Uptake Stimulated by Physical Exercise in Insulin Resistance State: Role of Inflammation

Filipe Ferrari,[1,2] Patrícia Martins Bock,[3,4,5] Marcelo Trotte Motta,[6] Lucas Helal[1,3]

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Abstract

Obesity associated with systemic inflammation induces insulin resistance (IR), with consequent chronic hyperglycemia. A series of reactions are involved in this process, including increased release of proinflammatory cytokines, and activation of c-Jun N-terminal kinase (JNK), nuclear factor-kappa B (NF-κB) and toll-like receptor 4 (TLR4) receptors. Among the therapeutic tools available nowadays, physical exercise (PE) has a known hypoglycemic effect explained by complex molecular mechanisms, including an increase in insulin receptor phosphorylation, in AMP-activated protein kinase (AMPK) activity, in the Ca2+/calmodulin-dependent protein kinase kinase (CaMKK) pathway, with subsequent activation of peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), Rac1, TBC1

Introduction

Insulin resistance (IR) at target tissues is directly related to chronic subclinical inflammation. When inadequately controlled, IR cause a permanent hyperglycemic status, characterizing the pathophysiology of type 2 diabetes mellitus (DM2).[1] Cardiovascular diseases are the main cause of morbidity and mortality in DM2 patients,[2] leading to annual costs per year of nearly 40 billion.[3]

Hyperglycemia, *per se*, is a devastating condition for the cardiovascular system. Among the complications caused by chronic hyperglycemia in patients with DM2, there is a reduction in endothelial vasodilator capacity (by reduced nitric oxide availability), increase in advanced glycation end products, in addition to increased oxidative stress, which leads

6.2. ARTIGOS COMPLETOS PUBLICADOS EM REVISTAS INTERNACIONAIS

6.2.1. Intradialytic exercise training modalities on physical functioning and health-related quality of life in patients undergoing maintenance hemodialysis: systematic review and meta-analysis. Clin Rehabil. 2018;32(9):1189-1202.

Article

CLINICAL REHABILITATION

Clinical Rehabilitation
2018, Vol. 32(9) 1189–1202

DOI: 10.1177/0269215518760380
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Intradialytic exercise training modalities on physical functioning and health-related quality of life in patients undergoing maintenance hemodialysis: systematic review and meta-analysis

Mansueto Gomes Neto[1,2,3], Filipe Ferrari Ribeiro de Lacerda[3], Antonio Alberto Lopes[4], Bruno Prata Martinez[1,3] and Micheli Bernardone Saquetto[1,2,3]

Abstract

Objective: To determine the effects of different intradialytic exercise training modalities on physical functioning and health-related quality of life of maintenance hemodialysis patients.

Methods: We searched MEDLINE, Cochrane Trials Register and CINAHL for controlled trials that evaluated the effects of intradialytic exercise training for maintenance hemodialysis patients and published from the earliest available date to December 2017. Weighted mean difference and 95% confidence interval (CI) were calculated, and heterogeneity was assessed using the I^2 test.

Results: Fifty-six studies met the study criteria, comprising a total of 2586 patients. Compared with no exercise, combined aerobic and resistance exercise resulted in significant improvement in peak VO_2 weighted mean difference (5.1 mL kg^{-1} min^{-1}; 95% CI: 3.4, 6.8 mL kg^{-1} min^{-1}), depression symptoms (−7.32; 95% CI −9.31, −5.33) and both physical function (10.67 points; 95% CI 1.08, 20.25 points) and vitality (10.01 points; 95% CI 4.30, 15.72 points) domains of health-related quality of life. Resistance exercise alone was significantly associated with improvement in the 6-minute walk test distance (30.2 m; 95% CI 24.6, 35.9 m), knee extensor strength (0.6 N; 95% CI 0.1, 1.0 N) and Physical Component Score of health-related quality of life (9.53 points; 95% CI −3.09, 22.15 points) when compared with control group. Aerobic exercise alone was not significantly associated with aerobic capacity and quality of life improvement.

Conclusion: The results provide support to interventions that combine intradialytic aerobic and resistance exercises to improve physical functioning and quality of life in end-stage renal disease patients undergoing hemodialysis.

Keywords

Exercise, hemodialysis, renal failure, health-related quality of life

6.2.2. The impact of high-intensity inspiratory muscle training on exercise capacity and inspiratory muscle strength in heart failure with reduced ejection fraction: a systematic review and meta-analysis. Clin Rehabil. 2018;32(11):1482-1492.

Article

CLINICAL REHABILITATION

Clinical Rehabilitation
2018, Vol. 32(11) 1482–1492

DOI: 10.1177/0269215518784345
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SAGE

The impact of high-intensity inspiratory muscle training on exercise capacity and inspiratory muscle strength in heart failure with reduced ejection fraction: a systematic review and meta-analysis

Mansueto Gomes Neto[1,2,3], Filipe Ferrari[4,5], Lucas Helal[4,6], Antônio Alberto Lopes[2,7], Vitor Oliveira Carvalho[3,8] and Ricardo Stein[4,5,9]

Abstract

Objective: Inspiratory muscle training (IMT) improves prognostic clinical variables in patients with heart failure. However, the optimal intensity for increasing those outcomes remains unclear. Thus, we aimed to determine whether high-intensity inspiratory muscle training (HIIMT) improves exercise capacity and respiratory muscle strength in patients with heart failure with reduced ejection fraction (HFrEF).

Methods: We searched for randomized controlled clinical trials at MEDLINE, the Cochrane Central Register of Controlled Trials, the Physiotherapy Evidence Database, SciELO and CINAHL from the earliest date available to May 2018. Primary studies on HIIMT against low-intensity IMT or sham-IMT that evaluated exercise capacity and inspiratory muscle strength were included. Two independent reviewers evaluated the eligibility of studies retrieved from the databases. Disagreements were resolved by discussion or by a third reviewer. Weighted mean difference (WMD), standardized mean difference (SMD) and 95% confidence interval (CI) were estimated by random effect models.

Results: Five studies met the eligibility criteria (138 patients). HIIMT improved VO_2peak (WMD 2.65 mL kg^{-1} min^{-1}; 95% CI: 2.2 to 3.1 mL kg^{-1} min^{-1}), walking tests (SMD 1.71; 95% CI: 0.83 to 2.59) and maximal inspiratory pressure (WMD 16.63 cmH_2O; 95% CI: 10.34 to 22.91 cmH_2O). The estimate for potential risks of adverse events was not performed because of the low prevalence of reports in primary studies.

Conclusion: HIIMT seems to be a useful strategy for improving exercise capacity and inspiratory muscle strength in HFrEF patients.

Keywords

Heart failure, high-intensity training, respiratory weakness

6.2.3. Genetics, Dyslipidemia, and Cardiovascular Disease: New Insights. Curr Cardiol Rep. 2019;21(8):68.

Current Cardiology Reports (2019) 21:68
https://doi.org/10.1007/s11886-019-1161-5

LIPID ABNORMALITIES AND CARDIOVASCULAR PREVENTION (G DE BACKER, SECTION EDITOR)

Genetics, Dyslipidemia, and Cardiovascular Disease: New Insights

Ricardo Stein [1,2,3,4] · Filipe Ferrari [1,2] · Fernando Scolari [1]

Abstract

Purpose of Review The cardiovascular (CV) risk related to lipid disorders is well established and is based on a robust body of evidence from well-designed randomized clinical trials, as well as prospective observational studies. In the last two decades, significant advances have been made in understanding the genetic basis of dyslipidemias. The present review is intended as a comprehensive discussion of current knowledge about the genetics and pathophysiology of disorders that predispose to dyslipidemia. We also focus on issues related to statins and the proprotein convertase subtilisin/kexin type 9 (PCSK9) and some of its polymorphisms, as well as new cholesterol-lowering medications, including PCSK9 inhibitors.

Recent Finding Cholesterol is essential for the proper functioning of several body systems. However, dyslipidemia—especially elevated low-density lipoprotein (LDL-c) and triglyceride levels, as well as reduced lipoprotein lipase activity—is associated with an increased risk of coronary artery disease (CAD). High-density lipoprotein (HDL-c), however, seems to play a role as a risk marker rather than as a causal factor of the disease, as suggested by Mendelian randomization studies. Several polymorphisms in the lipoprotein lipase locus have been described and are associated with variations in the activity of this enzyme, producing high concentrations of triglycerides and increased risk of CAD.

Summary Dyslipidemia, especially increased LDL-c and triglyceride levels, continues to play a significant role in CV risk. The combination of genetic testing and counseling is important in the management of patients with dyslipidemia of genetic etiology. Strategies focused on primary prevention can offer an opportunity to reduce CV events.

6.2.4. Digoxin in Atrial Fibrillation: An Old Topic Revisited. Curr Cardiol Rev. 2019 Jun 18. [Epub ahead of print]

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Digoxin in Atrial Fibrillation: An Old Topic Revisited.

Ferrari F[1], Rafael Miranda Ferreira Santander I[2], Stein R[1].

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Review Article

Digoxin in Atrial Fibrillation: An Old Topic Revisited

(E-pub Ahead of Print)

Author(s): Filipe Ferrari , Igor Rafael Miranda Ferreira Santander , Ricardo Stein* .

Journal Name: Current Cardiology Reviews

DOI : 10.2174/1573403X15666190618110941

Journal Home

6.2.5. Hemodynamic responses of patients with stable coronary artery disease to a comedy film: study protocol for a randomized controlled trial. Clin Trials Degener Dis. 2019;4:43-48.

RESEARCH ARTICLE

Hemodynamic responses of patients with stable coronary artery disease to a comedy film: study protocol for a randomized controlled trial

Rosane Maria Nery[1,2], Raquel Petry Buhler[1,2], Débora Santos Macedo[1,3], Juliana Maia Delfino[1,3], Filipe Ferrari[1,3], Anderson Donelli Silveira[1,2,3], Marco Aurélio Lumertz Saffi[1,2], Ricardo Stein[1,2,3,*]

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Abstract

Background and objective: Alternative and complementary interventions have been developed in an attempt to improve treatment and increase the survival of patients with coronary artery disease (CAD); one such intervention is laughter therapy. However, there is very little information on the effect of this therapeutic modality in patients with CAD. The present randomized controlled trial will compare the effect of 24 sessions of a comedy film and neutral documentary in patients with CAD.

Subjects and methods: This is a randomized, parallel-design, examiner-blinded and controlled clinical trial. Patients with stable CAD of both sexes, aged ≥ 18 years, receiving regular follow-up at a public university hospital in Southern Brazil will be included in the trial. Subjects will be randomly allocated to an intervention group (will watch a 30-minute comedy film) or a control group (will watch a 30-minute neutral documentary). Patient recruitment will end in December 2019. Analysis of the primary outcome measure will be completed in December 2019. The current protocol version is 1.0. The study protocol was approved by the Institutional Review Board of Hospital de Clínicas de Porto Alegre (protocol No. 13-0124) on July 9, 2013.

Outcome measures: The primary outcomes are the difference from baseline to the 2-month time point (corresponding to 24 sessions) in endothelial function, as assessed by brachial artery flow-mediated dilation measurement and peak oxygen consumption (peak VO_2) on

6.3. ARTIGOS ACEITOS PARA PUBLICAÇÃO

6.3.1. Inflamação, tabaco e doença cardiovascular. 2019. Rev Soc Cardiol de São Paulo.

Autores: Filipe Ferrari, Marcelo Trotte Motta, Ricardo Stein

6.3.2. Efficacy of chlorthalidone and hydrochlorothiazide in combination with amiloride in multiple doses on blood pressure in patients with primary hypertension: a protocol for a factorial randomized controlled trial. 2019. Trials.

Autores: Vitor Magnus Martins, Lucas Helal, Filipe Ferrari, Leonardo Grabinski Bottino, Sandra Costa Fuchs, Flávio Danni Fuchs

6.4. ARTIGOS EM FASE FINAL PARA SUBMISSÃO

6.4.1. Lipoprotein Lipase Polymorphisms, Apolipoprotein C-III Genes and Their Relationship With Coronary Artery Disease in the Afro-descendant Population: A Cross-sectional Study.

Autores: Marcelo Trotte Motta, Filipe Ferrari, Ricardo Stein, Ursula Matte, Emilio Hideyuki Moriguchi, Domingos Lázaro Souza Rios

Background and aims

A direct relationship of lipoprotein lipase (LPL) activity and apolipoprotein C-III (apoC-III) levels with the risk of coronary artery disease (CAD) has been demonstrated in the literature. We hypothesized an association between LPL polymorphisms and apoC-III genes and the risk of CAD in an afro-descendant sample considering possible interactions of smoking.

Methods

We conduced a cross-sectional study involving 759 individuals, 396 with CAD (274 smokers and 122 nonsmokers), and 363 free from CAD (213 smokers and 150 nonsmokers). All diagnosis were performed by coronary angiography. Six polymorphismsin the LPL gene were genotyped: T-93G (rs1800590), D9N (rs180117), S291N (rs268), PvuII (rs285), HindIII (rs 320) and S447X (rs 328), and one polymorphism for apoC-III gene: C-482T (rs 2854117). A multivariate logistic regression was used to estimate the odds ratios (OR) and adjusted for confounding factors. Statistical significance was stated as $p<0.05$.

Results

The carriers of allele -93T (TT + TG vs. GG) of polymorphism T-93G in the LPL gene had lower prevalence of CAD (OR: 0.435, p=0.035). On the other hand, the carriers of 447X allele (XX + SX vs. SS) of S447X polymorphism in the LPL gene showed increased prevalence of CAD, mainly in smokers (OR: 1.920, p=0.046). The -482TT homozygotes had a 1.8-fold higher chance of CAD compared to the allele carriers -482C (-482C/T and -482C/C genotypes). These differences were not observed in nonsmokers.

Conclusion

In afro-descendant individuals, the T-93G and S447X polymorphisms of the LPL and C-482T polymorphism of the apoC-III gene were associated with CAD, and this association was dependent of smoking. However, HindIII and PvuII polymorphisms were not associated with CAD in our population in both smokers and nonsmokers. Likewise, the D9N and N291S polymorphisms were also not associated with CAD.

6.4.2. Thiazide Diuretics Alone or in Combination With Potassium-Sparing Diuretics on Blood Pressure Lowering Efficacy in Patients With Primary Hypertension: A Systematic Review and Network Meta-analysis.

Autores: Vitor Magnus Martins, Filipe Ferrari, Lucas Helal, Leonardo Bottino, Marcelo Lucca, Patrícia Ziegelman, Henrique Rauchaud, Gabriela Brendel Blum, Sandra Costa Fuchs, Flávio Danni Fuchs

6.4.3. Direct-Acting Oral Anticoagulants in Atrial Fibrillation: Best Indications and Clinical Implications in Different Scenarios

Autores: Filipe Ferrari, Anderson Donelli da Silveira, Vitor Magnus Martins, Leandro Tolfo Franzoni, Leandro Ioschpe Zimerman, Ricardo Stein

6.5. PARTICIPAÇÃO EM CAPÍTULOS DE LIVROS

6.5.1. Título do livro: Dislipidemias na Prática Clínica

Editores: Dr. Renato Jorge Alves e Dr. Raul Dias dos Santos Filho

- Título do capítulo: Hipobetalipoproteinemia e Abetalipoproteinemia
- **Autores: Dr. Emilio Hideyuki Moriguchi e Me. Filipe Ferrari**
- Previsão para publicação: 2020.

6.5.2. Título do livro: A Doença Aterotrombótica e seus Fatores de Risco, 1ed

Editores: Dr. André Arpad Faludi, Dra. Maria Cristina de Oliveira Izar, Dr. José Francisco Kerr Saraiva, Dra. Adriana Bertolami, Dra. Viviane Zorzanelli Rocha Giraldez e Dr. Marcelo Heitor Vieira Assad

- Título do capítulo: Fatores de Risco Não Tradicionais: Inflamação
- **Autores: Dr. Emilio Hideyuki Moriguchi e Me. Filipe Ferrari**
- Previsão para publicação: 2020.