UNIVERSIDADE FEDERAL DE CIÊNCIAS DA SAÚDE DE PORTO ALEGRE – UFCSPA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

Graziela Valle Nicolodi

Influência da capacidade funcional e da força muscular na sobrevida de pacientes com doença renal crônica em hemodiálise: um estudo de coorte

Porto Alegre

2020

Graziela Valle Nicolodi

Influência da capacidade funcional e da força muscular na sobrevida de pacientes com doença renal crônica em hemodiálise: um estudo de coorte

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

Orientador: Dr. Rodrigo Della Méa Plentz

Porto Alegre
2020

Catalogação na Publicação

Nicolodi, Graziela Valle
Influência da capacidade funcional e da força muscular na sobrevida de pacientes com doença renal crônica em hemodiálise: um estudo de coorte / Graziela Valle Nicolodi. -- 2020.
128 p. : 30 cm.

Tese (doutorado) -- Universidade Federal de Ciências da Saúde de Porto Alegre, Programa de Pós-Graduação em Ciências da Saúde, 2020.

Orientador(a): Prof. Dr. Rodrigo Della Méa Plentz .

1. Doença Renal . 2. Análise de Sobrevida . 3. Força Muscular . 4. Diálise Renal . I. Título.

Sistema de Geração de Ficha Catalográfica da UFCSPA com os dados fornecidos pelo(a) autor(a).

Dedico esse trabalho aos meus pais, Marta e Juarez, meus maiores incentivadores que estiveram ao meu lado nessa jornada e desde criança, me ensinaram o real valor da educação.

AGRADECIMENTOS

Gostaria de agradecer a todas as pessoas que estiveram comigo e colaboraram para que meu sonho fosse realizado. Foi uma etapa marcada por muito trabalho, dedicação e estudo. Muito Obrigada:

Primeiramente a **DEUS**, por ter me dado saúde e principalmente força para superar os obstáculos que surgiram no decorrer desse caminho.

Aos meus pais, Marta e Juarez Nicolodi, que são as pessoas mais importantes da minha vida. A minha eterna gratidão por todo o apoio que deram a mim, por acreditarem e fazerem do meu sonho o de vocês também. Mas, acima de tudo, obrigada por serem os grandes mestres da minha vida, por nunca medirem esforços para que eu tivesse uma boa educação e por me ensinarem através do exemplo, valores como humildade, caráter e dignidade. VOCÊS SÃO TUDO PARA MIM.

Obrigada a minha família, em especial meu **irmão Fernando** e minha **cunhada Aline Nicolodi,** pelos conselhos, amizade e ajuda em todos os momentos que precisei de vocês. Obrigada por me darem o maior dos presentes, meu **sobrinho Heitor** que mesmo tão pequeno me ensina muito sobre viver. AMO VOCÊS.

A Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA), em especial ao **Programa de Pós-Graduação em Ciências da Saúde**, seu corpo docente e coordenação, que oportunizaram a realização de mais essa conquista em minha vida.

Ao meu orientador Rodrigo Della Méa Plentz, pessoa e profissional que admiro muito. Obrigada pela amizade e, principalmente, por ter sido o grande responsável pela escolha da trajetória acadêmica que fiz, pois foi através do seu incentivo desde cedo à pesquisa que cheguei até aqui. Obrigada por confiar em mim, pela paciência, pelo suporte nos momentos de angústia e insegurança. Saiba que me espelho em você profissionalmente e, espero também conseguir incentivar a pesquisa com meus alunos, da mesma forma que fez comigo quando eu ainda estava na graduação.

Minha gratidão **às colegas do grupo de pesquisa: Cinara Stein e Natiele Righi** pela ajuda, disponibilidade e por compartilharem o conhecimento de vocês comigo. Saibam que foram essenciais e contribuíram de forma significativa na minha trajetória. Vocês foram o exemplo de que pesquisa não se faz sozinho.

Meu muito obrigada também, **à toda equipe da Unidade de Terapia Renal do Hospital São Vicente de Paulo de Cruz Alta – RS**, em especial, ao **Dr. Paulo Moreira,** que

permitiu a realização desse trabalho na unidade. Aos pacientes que participaram desse estudo, minha eterna gratidão.

Agradeço a colaboração e ao convívio das **minhas alunas de graduação do curso de Fisioterapia da Universidade de Cruz Alta – UNICRUZ**: Alana Veiga, Rayssa Souto, Maiara Toledo, Natalia Lanius e Thayne Bassedone. A ajuda de vocês foi fundamental para a realização desse trabalho.

A Universidade de Cruz Alta - UNICRUZ, em especial aos meus colegas docentes do curso de Fisioterapia, pelo apoio, conselhos e pela amizade.

Aos meus amigos e amigas que, por muitas vezes, compreenderam a minha ausênc e, mesmo assim, estiveram ao meu lado me dando força para que eu conseguisse chegar realização do meu maior sonho.

A todas as pessoas que, de forma direta ou indireta, fizeram parte da minha formação, a minha eterna gratidão!

RESUMO

Introdução: pacientes com doença renal crônica (DRC) possuem alterações da capacidade funcional e força muscular que podem acarretar em prejuízos no tempo de sobrevida. **Objetivo:** verificar a influência da capacidade funcional e força muscular na sobrevida de pacientes com DRC em hemodiálise (HD). **Métodos:** Estudo de coorte prospectivo com 59 pacientes com DRC em HD foram acompanhados por dois anos. As avaliações consistiram em capacidade funcional pelo teste de caminhada de seis minutos (TC6'), força de membros inferiores com teste de sentar e levantar (TSL), força de preensão manual (FPM) pela dinamometria e força muscular respiratória através da manovacuometria, independência funcional pela escala de *Lawton*, nível de atividade física pelo IPAQ versão curta e qualidade de vida (QV) pelo EQ-5D. **Resultados**: Dos 59 pacientes incluídos, 55,9% eram homens com 58,1 ± 14,5 anos e mediana de tratamento de 64,6 [37,9 – 136,3] meses. Durante dois anos de acompanhamento, houveram 28,8% de óbitos. Relacionaram-se com menor tempo de sobrevida: Capacidade Funcional (HR: 9,92 IC95%: 1,31-74,89; p=0,026), FPM (HR: 3,0 IC95%: 1,17-7,88; p=0,023) e força expiratória (PEmáx) (HR: 3,8 IC95%: 1,33-10,80; p=0,012), 76,3% dos pacientes eram independentes e 61% sedentários. A QV obteve escore de 0,798 ± 0,185 e a média da percepção geral de saúde foi de 80,6 ± 10,4. Houveram associações significativas dos testes físicos entre si e com a qualidade de vida. **Conclusão:** Capacidade Funcional e força muscular influenciam na sobrevida de DRC em HD. Além disso, testes físicos possuem uma boa associação entre si no grupo de pacientes estudados.

Palavras-chave: Doença Renal; Diálise Renal; Força Muscular; Análise de Sobrevida.

ABSTRACT

Introduction: patients with chronic kidney disease (CKD) have changes in functional capacity and muscle strength that can suffer damage in times of survival. **Objective:** to verify the influence of functional capacity and muscle strength on the survival of patients with CKD on hemodialysis (HD). **Methods:** prospective cohort study with 59 HD CKD patients was followed for two years. The assessments consisted of functional capacity by the six-minute walk test (6MWT), lower limb strength with sit and stand test (STS), handgrip strength (HGS) by dynamometry and respiratory muscle strength through manovacuometry, independence functional by the Lawton scale, level of physical activity by the IPAQ short version and quality of life (QOL) by the EQ-5D. **Results:** of the 59 patients included, 55.9% were men aged 58.1±14.5 years and median treatment of 64.6 [37.9 - 136.3] months. During two years of follow-up, there were 28.8% of deaths. They were related to shorter survival time: functional capacity (HR: 9.92 95% CI:1.31-74.89; p= 0.026), HGS (HR: 3.0 95% CI: 1.17-7.88 ; p= 0.023) and maximum expiratory pressure (MEP) (HR: 3.8 95% CI: 1.33-10.80; p = 0.012), 76.3% of patients were independent and 61% sedentary. The QOL obtained a score of 0.798±0.185 and the mean of the general health perception was 80.6±10.4. There were significant associations between physical tests and quality of life. **Conclusion:** functional capacity and muscle strength influence the survival of CKD on HD. In addition, physical tests have a good association with each other in the group of patients studied.

Keywords: Kidney disease; Renal Dialysis; Muscle strength; Survival Analysis.

LISTA DE SIGLAS

DRC	doença renal crônica
TRS	terapia renal substitutiva
HD	hemodiálise
DP	diálise peritoneal
TR	transplante renal
TFG	taxa de filtração glomerular
DCV	doença cardiovascular
DM	diabetes mellitus
HA	hipertensão arterial
DCNT’s	doenças crônicas não-transmissíveis
SRAA	sistema renina-angiotensina-aldosterona
ECR	ensaio clínico randomizado
DPAC	diálise peritoneal ambulatorial contínua
DPA	diálise peritoneal automatizada
FAV	fístula arteriovenosa
EAV	enxerto arteriovenoso
CVCs	cateteres venosos centrais
PTH	paratormônio
DAC	doença arterial coronariana
TNFα	fator de necrose tumoral alfa
PCR	proteína C-reativa
EO	estresse oxidativo
ON	óxido nítrico
SNA	sistema nervoso autônomo
SNS	sistema nervoso simpático
SNP	sistema nervoso parassimpático
TC6’	teste de caminhada de seis minutos
SUP	sistema ubiquitina proteossoma
TSL	teste de sentar e levantar

PEmáx	pressão expiratória máxima
PImáx	pressão inspiratória máxima
MIF	medida de independência funcional

SUMÁRIO

APRESENTAÇÃO

Este trabalho consiste na Tese de Doutorado intitulada **Influência da capacidade funcional e força muscular na sobrevida de pacientes com doença renal crônica em hemodiálise: um estudo de coorte** a ser apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA.

As questões de pesquisa que estimularam o desenvolvimento desse trabalho possibilitaram identificar a importância de testes físicos amplamente utilizados no âmbito da Fisioterapia e suas associações com a sobrevida de pacientes com DRC em HD. Testes de fácil aplicabilidade e baixo custo que permitem uma boa avaliação e acompanhamento da evolução e prognóstico dos pacientes. O presente trabalho verificou também a necessidade de mais estudos com maiores tamanhos amostrais e maiores períodos de acompanhamento que favoreçam o nível das evidências e beneficiem o processo de reabilitação dos pacientes.

Para contribuir com as respostas, foi realizado um estudo de coorte prospectivo com acompanhamento de dois anos de pacientes com DRC em HD da Unidade de Terapia Renal do Hospital São Vicente de Paulo de Cruz Alta – RS. Os pacientes foram avaliados através de testes de capacidade funcional, força muscular periférica e respiratória, além de questionários de qualidade de vida e funcionalidade. A partir dos resultados obtidos nesse estudo, verificou-se a importância da prática de exercícios físicos nesses pacientes e dessa forma, surgiu a necessidade de investigarmos também, os efeitos do exercício em pacientes que ainda não estão em tratamento por terapia renal substitutiva. Sendo assim, foi realizada também uma revisão sistemática de ensaios clínicos randomizados afim de investigar os efeitos do exercício aeróbico em pacientes com DRC nos estágios pré-dialíticos.

Essa tese é composta de: introdução, revisão de literatura, objetivos, dois artigos científicos e, em anexo, a carta de aprovação do Comitê de Ética em Pesquisa – CEP.

1. INTRODUÇÃO

A Doença Renal Crônica (DRC) é definida por ser uma lesão renal com perda progressiva e irreversível da função dos rins, podendo ser a nível glomerular, tubular ou endócrina. A doença é um processo contínuo, que tem início a partir da perda da função de alguns néfrons e que acaba quando os demais tornam-se incapazes para a manutenção da vida, sendo necessária então, a terapia renal substitutiva (Junior, 2004), ou ainda o transplante renal (Orlandi *et al.*, 2015).

Diabetes Mellitus e Hipertensão Arterial são as principais causas da doença sendo que suas complicações mais frequentes são cardiovasculares e musculoesqueléticas, dessa forma é importante programas de tratamento eficazes que possam retardar a progressão bem como as consequências da doença (Girndt, 2017).

Vários sistemas estão incluídos nas alterações metabólicas do estado urêmico, dentre eles: sistema renal, cardiovascular, hematológico, neurológico, osteomuscular e endócrino (Romagnani *et al.*, 2017; Whaley-Connell e Sowers, 2017). Avaliações como capacidade funcional, força muscular periférica e qualidade de vida tem sido realizadas e mostrado um importante valor prognóstico nessa população, (Kohl *et al.*, 2012; Matsuzawa *et al.*, 2014; Jassal *et al.*, 2016) uma vez que as alterações decorrentes da uremia, estão presentes em 75% dos doentes (Flisinski *et al.*, 2014; Romagnani *et al.*, 2017) e todas essas alterações levam à sintomas de depressão e ansiedade (Lee *et al.*, 2013).

Com o objetivo de retardar a evolução da doença e melhorar as variáveis de aptidão física de DRC, estudos vêm sendo desenvolvidos para estudar os benefícios do exercício físico nessa população, tanto na fase pré-dialítca, dialítica ou mesmo após o transplante renal (Hiraki *et al.*, 2017; Qiu *et al.*, 2017; Schardong *et al.*, 2017; Dipp *et al.*, 2019).

Anterior ao início da prática de exercícios, avaliações físicas são importantes afim de acompanhar a evolução do paciente. Para isso, alguns testes vêm demonstrando boas correlações e valores prognósticos em DRC, tais como força de preensão palmar realizado através de dinamometria e teste de caminhada de seis minutos (TC6') (Kohl *et al.*, 2012; Hellberg *et al.*, 2014). No entanto, ainda existe a necessidade de estudos que avaliem outros testes de fácil aplicabilidade dentro da fisioterapia como por exemplo o Teste de Sentar e Levantar (TSL) e força muscular respiratória.

Com o objetivo de melhor discutir esses temas, nas próximas sessões, encontra-se uma breve revisão da literatura sobre aspectos fisiopatológicos da DRC bem como ferramentas de avaliação física que fundamentam sua utilização.

2. REVISÃO DE LITERATURA

2.1 Sistema Urinário: características morfofuncionais

O sistema urinário interfere em todas as partes do corpo humano mantendo os outros sistemas funcionando normalmente e em equilíbrio com os fluídos do corpo. Esse sistema é composto por dois rins, dois ureteres, uma bexiga urinária e uma uretra; os quais realizam um trabalho importante de filtração do sangue e formação da urina com o objetivo de manter a homeostase (De Groat, 1993).

Dentre as inúmeras funções atribuídas ao rim, podemos também citar a regulação do volume e composição do sangue, regulação da pressão arterial, contribuição para o metabolismo (gliconeogênese, secreção de eritropoetina e participação na síntese de vitamina D), atuação no sistema renina-angiotensina além do transporte, armazenamento e eliminação da urina (Wallace, 1998).

A unidade funcional do rim é o néfron, que é formado entre a 12ª e 36ª semanas de gestação e, após esse período, não são gerados novos néfrons, sendo que os disponíveis aumentam de tamanho para acomodar as demandas renais aumentadas (Romagnani *et al.*, 2017). Cada néfron é constituído pelo corpúsculo renal (que compreende o glomérulo e a cápsula de *bowman)*, túbulo contorcido proximal, alça de Henle e túbulo contorcido distal (Wallace, 1998).

Estima-se que o número aproximado de glomérulos seja cerca de 900.000 a 1 milhão por rim, no entanto, esse número pode variar na população, estando fortemente correlacionada com o peso ao nascer do indivíduo e correlacionado inversamente com a idade e com a pressão arterial (Duval *et al.*, 1985; Glassock e Rule, 2016).

O processo da formação da urina inicia no córtex renal através da filtração glomerular e continua a fluir através dos túbulos e ductos coletores onde entra nos cálices renais e na pelve renal e finalmente sai do rim para a bexiga através dos ureteres. Além disso, as paredes dos cálices, pelve renal e ureteres contém musculatura lisa as quais se contraem ritmicamente e ajudam a impulsionar a urina ao longo de seu curso (Wallace, 1998).

O processo de filtração glomerular inicia quando o sangue entra no glomérulo por meio da arteríola eferente; e através de um mecanismo de diferença de pressão que ocorre entre a pressão do capilar glomerular, pressão coloidosmótica e pressão capsular. Essa diferença de pressão chamamos de pressão de filtração, essa pressão força o fluído e alguns solutos de pequeno tamanho molecular através dos poros nas paredes dos capilares e lúmen da cápsula de *bowman*. O filtrado glomerular é semelhante ao plasma, no entanto, carece de proteínas, as

quais são muito grandes para passar pelos poros e, dessa forma, ficam retidas no sangue (De Groat e Yoshimura, 2015).

As funções de armazenamento e eliminação da urina são reguladas através de um sistema de controle neural entre o cérebro, medula espinhal e gânglios autonômicos periféricos que coordenam a atividade muscular lisa e estriada da bexiga e uretra (De Groat *et al.*, 2015; De Groat e Yoshimura, 2015).

2.2 Doença Renal Crônica

A Doença Renal Crônica (DRC) consiste em uma lesão renal com perda progressiva e irreversível da função dos rins podendo ser a nível glomerular, tubular e endócrina. Na sua fase mais avançada, chama-se de fase terminal de insuficiência renal crônica (IRC), onde os rins não conseguem mais manter o equilíbrio interno do paciente (Junior, 2004) e a partir daí se faz necessário uma forma de terapia renal substitutiva (TRS) que pode ser através da hemodiálise (HD), diálise peritoneal (DP) ou transplante renal (TR) (Levey *et al.*, 2015).

A doença é definida por uma taxa de filtração glomerular (TFG) menor que 60 mL/min/1.73m^2, albuminúria de pelo menos 30 mg por 24 horas conforme ou marcadores de dano renal como por exemplo: hematúria ou anormalidades estruturais como rins policísticos ou displásicos por pelo menos 3 meses (Andrassy, 2013; Levey *et al.*, 2015).

Estima-se que a doença afete 8 a 16% da população mundial, sendo uma das principais causas de morte em todo o mundo (Chen *et al.*, 2019). No Brasil, dados do Inquérito Brasileiro de Diálise estimam que um número de 3 a 6 milhões de brasileiros tenham DRC (Sesso, Lopes, Thome, *et al.*, 2017), destes, em Julho de 2017, cerca de 126.583 pacientes estavam em tratamento dialítico sendo a Hemodiálise a forma mais utilizada. Além disso, o número de pacientes que iniciaram o tratamento vem crescendo a cada ano, sendo que em 2017 foi estimado em 40.307 pacientes (Thomé *et al.*, 2019). Dados preliminares do Ministério da Saúde estimam que em 2018, o número de óbitos registradas devido a DRC no país foi de 8.055 pessoas sendo o maior número na região sudeste, seguido da região nordeste e sul do país. (Datasus, 2020).

Esses dados reforçam a DRC como sendo um grande problema de saúde pública uma vez que 85% dos tratamentos são pagos através do Sistema Único de Saúde (Sesso, Lopes, Thomé, *et al.*, 2017). Se faz necessário portanto, uma detecção precoce da doença renal e de condutas terapêuticas adequadas com o objetivo de retardar a sua progressão, reduzir o sofrimento dos pacientes além dos custos financeiros associados a ela (Junior, 2004; Paniagua-Sierra e Galvan-Plata, 2017).

O estadiamento da DRC é baseado no cálculo da TFG, sendo esse estadiamento classificado em:

- Estágio 1 (TFG ≥ 90 mL/min/1.73 m^2),
- Estágio 2 (TFG entre 60 e 89 mL/min/1.73 m^2),
- Estágio 3a (TFG entre 45 e 59 mL/min/1.73 m^2),
- Estágio 3b (TFG entre 30 e 44 mL/min/1.73 m^2),
- Estágio 4 (TFG entre 15 e 29 mL/min/1.73 m^2)
- Estágio 5 (TFG <15 mL/min/1.73 m^2) (Andrassy, 2013; Levey *et al.*, 2015).

A figura 1 demonstra o prognóstico da DRC pela TFG e categorias de albuminúria.

Figura 1: Prognóstico da DRC pela TFG e categorias de albuminúria

Risco baixo
Risco moderado
Risco alto
Risco muito alto

Categorias da TFG (ml/min/1,73m²)				Categorias de Albuminúria persistente		
				A1	**A2**	**A3**
				Normal ou levemente aumentado	Moderadamente aumentado	Severamente aumentado
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g > 30 mg/mmol
	G1	Normal ou alta	≥ 90			
	G2	Ligeiramente diminuída	60-89			
	G3a	Ligeira à moderadamente diminuída	45-59			
	G3b	Moderada à severamente diminuída	30-44			
	G4	Severamente diminuída	15-29			
	G5	Falência renal	<15			

Adaptado de (KDIGO Board Members, 2012)

Para a medida de da TFG estimada, vários marcadores são utilizados, sendo o mais comum a creatinina (Levey *et al.*, 2015). No entanto, novos marcadores vem sendo testados para estimar a TFG.(Horio, 2014) Um recente estudo de coorte avaliou 440.526 participantes no Reino Unido, e comparou a TFG baseada em três fórmulas. Os pesquisadores basearam-se nos valores de creatinina sérica, cistatina C e creatinina-cistatina e associaram os resultados de cada estimativa com a mortalidade por doenças cardiovasculares (DCV). Os autores encontraram que a medida baseada no cálculo da cistatina está mais frequentemente associada à DCV e à mortalidade juntamente com a albuminúria, enquanto que as medidas tradicionais com base na creatinina apresentaram uma fraca associação (Lees *et al.*, 2019).

Além disso, o teste de cistatina C para avaliar a função renal possui vantagens em potencial em relação à utilização da creatinina. Uma delas é que não é influenciada pela atividade física,

massa muscular ou sexo, podendo assim ser um método mais sensível para estimar a função renal (Shlipak *et al.*, 2013).

Os estágios iniciais da doença frequentemente são assintomáticos por isso, na maioria das vezes, são detectados durante a avaliação de comorbidades. Ainda, doenças rapidamente progressivas podem levar à insuficiência renal em poucos meses; no entanto, a maioria das doenças evolui ao longo de décadas e alguns pacientes não progridem durante muitos anos de acompanhamento (Levey e Coresh, 2012).

Dentre as principais causas relacionadas à DRC podemos citar o Diabetes Mellitus (DM) e/ou a Hipertensão Arterial (HA) (Junior, 2004). Acredita-se que as consequências adversas diretas da hipertensão em qualquer leito vascular sejam em função do grau ao que o mesmo está e na falha dos mecanismos de autorregulação renal em proteger assim a microvasculatura renal (Bidani e Griffin, 2004). Além disso, a nefroesclerose hipertensiva não possui marcadores distintos de danos nos rins, mas podem ocorrer altas concentrações de albuminúria após o início do declínio da TFG (Levey e Coresh, 2012).

Com relação ao DM, sabe-se que a hiperglicemia (distúrbio induzido pelo DM), é essencial para o desenvolvimento das lesões glomerulares observadas na nefropatia diabética (Diabetes *et al.*, 1993). A nefropatia diabética é classifica em quatro estágios principais: estágio 1: Hiperfiltração (aumento no ritmo de filtração glomerular e normoalbuminúria), estágio 2: microalbuminúria (excreção urinária de albumina entrre 30 – 300 mg/24h), estágio 3: proteinúria ou nefropatia clínica (excreção urinária de albumina atinge valores superiores a 300 mg/24h e queda progressiva da TFG), estágio 4: nefropatia terminal (pacientes com DRC em TRS e transplante renal) (Castiglioni e Savazzi, 1988; Macia Heras *et al.*, 2001; Kashihara, 2008).

A glomerulosclerose diabética é marcada pelo lento agravamento da albuminúria, hipertensão e declínio progressivo da TFG por vezes com presença de síndrome nefrótica (Levey e Coresh, 2012). caracterizada por edema que persiste por semanas e meses, ganho de peso, fadiga e perda do apetite (Nephrotic Syndrome, 2016). Anormalidade dos fatores de coagulação também podem estar associados à síndrome nefrótica (Togawa *et al.*, 2004).

Outras causas como idade avançada, obesidade, glomerulonefrite, infecções, nefro toxicidade, além de fatores sociodemográficos como por exemplo a raça (Ku *et al.*, 2019), baixa renda (Gutierrez *et al.*, 2010), baixa escolaridade e fatores genéticos podem ocorrer (Chen *et al.*, 2019). Em um estudo realizado por Tirapani e Fernandes (Tirapani e Fernandes, 2019) com o objetivo de analisar o impacto da renda, educação etnia nas Doenças Crônicas Não-Transmissíveis (DCNT's) incluindo DM, HA e DRC, analisou 161 estudos de 96 países e

encontrou que a renda, educação e a raça têm impacto na prevalência, incidência, diagnóstico, tratamento, progressão e mortalidade nos países de baixa e média renda mostrando que o tema relacionado aos fatores sociais precisa ser constante na elaboração de políticas de saúde presentes na atividade profissional.

2.3 Tratamento da DRC

2.3.1 Tratamento Conservador

Para o tratamento da DRC, cada paciente deve ter um plano de ação clínico baseado no estágio da doença. O tratamento de comorbidades, o uso de intervenções para retardar a progressão da doença, medidas para reduzir o risco de DCV devem começar nos estágios 1 e 2. Ainda, o tratamento de outras complicações decorrentes da diminuição da TFG como anemia, desnutrição, doença óssea, neuropatia e diminuição da qualidade de vida, devem ser realizados durante o estágio 3, pois a prevalência dessas complicações começam a aumentar quando a TFG cai para níveis abaixo de 60 mL/min/1,73m^2 (Levey *et al.*, 2003).

É importante também, no início da doença, direcionar o tratamento para medidas como o controle da hipertensão uma vez que a interação entre hipertensão e DRC é complexa e aumenta o risco de desfechos cerebrovasculares. Diversos mecanismos contribuem para a HAS dos quais podemos citar a desregulação do sódio, aumento da atividade do sistema nervoso simpático e atividade do sistema renina-angiotensina aldosterona (Hamrahian e Falkner, 2017).

Dentro das intervenções farmacológicas, os agentes que bloqueiam o sistema renina-angiotensina-aldosterona (SRAA) são os agentes de primeira escolha uma vez que atuam também na redução da albuminúria, existe ainda a utilização classes de medicamentos diuréticos, anti-hiperglicêmicos, estatinas, ativadores do receptor de vitamina D, estimulantes de eritropoetina também são utilizados pela equipe médica (Lambers Heerspink e De Zeeuw, 2013).

Além de medidas farmacológicas, a mudança nos hábitos de vida como a prática de exercícios físicos é incentivada. Wyngaert e cols (Vanden Wyngaert *et al.*, 2018) através de uma revisão sistemática com meta-análise revisaram os efeitos do treinamento aeróbico na função renal e cardiovascular em pacientes com DRC nos estágios 3-4. Foram incluídos 11 ensaios clínicos randomizados (ECR) com um total de 362 participantes. Os autores concluíram haver um efeito benéfico do exercício aeróbico sobre a TFG e a tolerância ao exercício quando comparados ao grupo que recebeu o tratamento padrão.

Juntamente com a prática de exercícios físicos, as mudanças nos hábitos de vida como a modificação dietética (Beto e Bansal, 2004; Anderson *et al.*, 2016) aliada ao atendimento de

um equipe multidisciplinar podem produzir melhoras no estilo de vida dos pacientes (Howden *et al.*, 2013).

2.3.2 Terapia Renal Substitutiva

Uma vez atingido o estágio terminal da IRC, geralmente é necessária uma TRS. O aconselhamento sobre as opções (DP, HD ou TR) deve ser coordenada pelo médico nefrologista e pela equipe multidisciplinar (Sumida e Kovesdy, 2017).

A modalidade de DP, se refere a um processo contínuo de TRS, no qual são trocados solutos e líquidos entre o sangue dos capilares peritoneais e a solução de diálise na cavidade do peritônio. Em média, os pacientes realizam de 3 a 4 trocas manuais por dia (Li *et al.*, 2017).

A DP é uma modalidade de diálise que pode ser realizada manualmente denominada de Diálise Peritoneal Ambulatorial Contínua (DPAC), ou com o uso de uma máquina cicladora chamada de Diálise Peritoneal Automatiza (DPA) na qual o paciente realiza em casa, normalmente no período da noite, antes de dormir (Sbn., 2020).

É uma alternativa de alta qualidade e custo-benefício (Li *et al.*, 2017). A primeira tentantiva de utilizar o peritônio humano para dialisar os solutos para a retenção da função urêmica foi realizada em 1923 e, nas décadas seguintes, com a melhor compreensão da técnica juntamente com o desenvolvimento do cateter de permanência teve aumento em sua utilização, e passou a ser aceita como TRS domiciliar (Oreopoulos *et al.*, 1978; Popovich *et al.*, 1978).

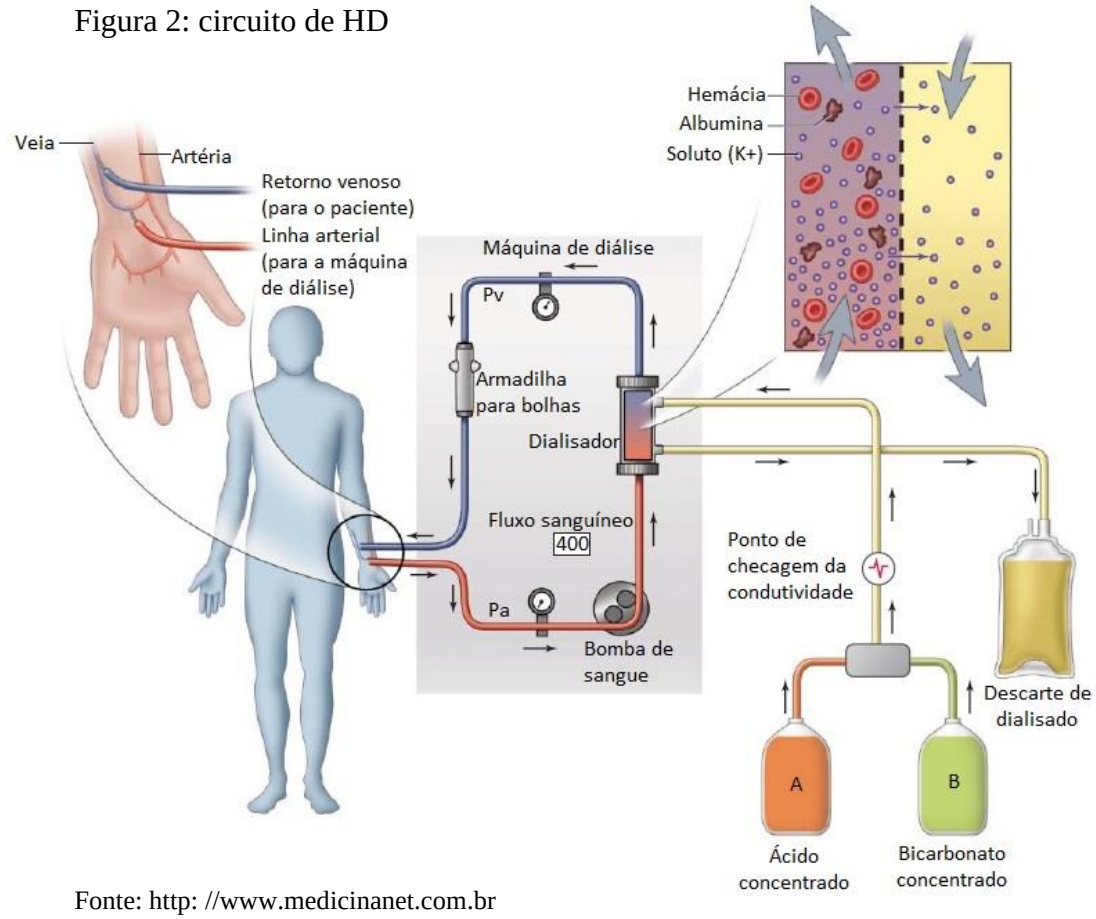
No entanto, o uso da técnica levou os nefrologistas à uma série de preocupações como alto risco de infecções, depuração inadequada e deterioração da saúde peritoneal (Oreopoulos *et al.*, 1978). Sendo assim, em meados da década de 1990 houve uma redução na proporção de pacientes tratados através da DP (Bloembergen *et al.*, 1995).

Atualmente, devido às melhoras na aplicação da DP e estudos demonstrando uma sobrevida semelhante àqueles pacientes que realizam HD e seu custo ser menor, o uso dessa modalidade vem aumentando em diversos países como China, Tailândia e Estados Unidos (Li *et al.*, 2017).

Em um estudo de coorte brasileiro (De Moraes *et al.*, 2014) que acompanhou 9.905 pacientes entre os anos de 2004 e 2011 que iniciaram a DP, se observou uma melhora na sobrevida ao longo dos anos com uma redução do Risco Relativo (RR: 0,83 IC95%: 0,72 – 0,95) nos anos de 2007/2008 e (RR: 0,69 IC95%: 0,57 – 0,83) nos anos de 2009/2010. O estudo demonstrou ainda que, a principal causa de abandono do tratamento foi o óbito, seguido de complicações como o surgimento de peritonite, a falha na ultrafiltração, disfunção de cateter e infecção refratária.

Outra forma de TRS é a hemodiálise (Levey *et al.*, 2003; Junior, 2004), a terapia foi projetada para substituir parte da fisiologia normal do rim, restaurando o ambiente entre o fluído intra e extracelular onde é realizado com uma série de mais de 10.000 pequenas fibras constituídas a partir de uma membrana semipermeável. Essas fibras possuem pequenos poros que permitem uma troca de fluídos entre o sangue e o compartimento de fluídos da diálise (Foy e Sperati, 2018). Solutos como a ureia são transportados do sangue para o dialisato e bicarbonato do dialisato para o sangue. Existe ainda um processo denominado ultrafiltração em que não há alteração nas concentrações de soluto pois seu objetivo principal é a remoção do excesso de água corporal. Torna-se importante ressaltar que para cada sessão de HD, o estado fisiológico do paciente deve ser avaliado para que a prescrição da diálise possa ser alinhada com os objetivos da sessão (Himmelfarb e Ikizler, 2010). A figura 2 demonstra como é realizado o circuito da HD.

Figura 2: circuito de HD

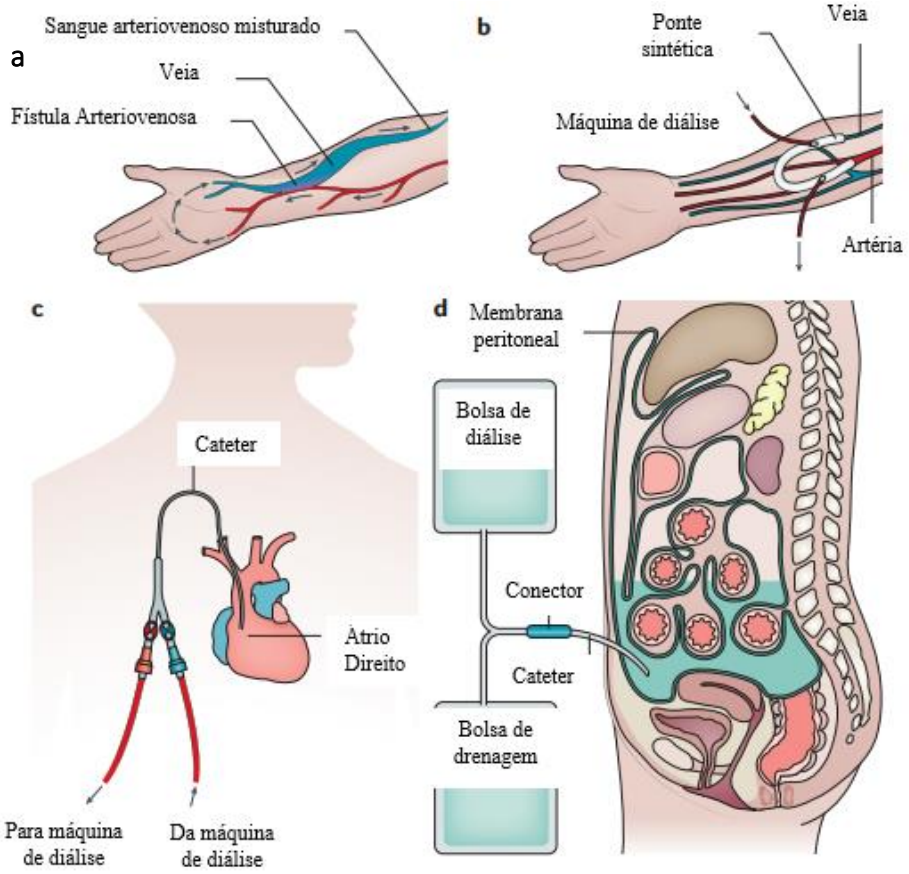


Fonte: http: //www.medicinanet.com.br

Para a HD ser realizada, é necessário que o sangue seja retirado do acesso arterial o qual circula pelo dialisador e retorne então para o paciente ao acesso do sangue venoso. (Polaschegg, 2005) Para que esse processo seja realizado, existem três alternativas de acesso: fístula arteriovenosa (FAV), enxerto arteriovenoso (EAV) ou cateter (Foy e Sperati, 2018).

Abaixo, na figura 3, estão demonstrados os tipos de acessos para o tratamento dialítico bem como os tipos de diálise.

Figura 3. Tipos de acessos para diálise.



Adaptado de Romagnani e cols (2017). a) Fístula Arteriovenosa: realizada através de uma anastomose cirúrgica de uma artéria periférica com uma veia subcutânea maior, por exemplo, no antebraço, b) enxerto arteriovenoso, c) cateter venoso central, d) cateter transcutâneo peritoneal para diálise peritoneal.

Cada forma de acesso para a HD apresenta vantagens e desvantagens distintas, atualmente, os cateteres venosos centrais (CVCs) são a forma dominante de início da HD e em casos de urgência no início da HD, provavelmente pela relativa facilidade de colocação inicial, e encaminhamento tardio do paciente ao cirurgião vascular (Foley *et al.*, 2009; Tang *et al.*, 2019).

Porém, as diretrizes atuais sugerem a colocação precoce da FAV (Vascular Access Work, 2006; Sidawy *et al.*, 2008). Os enxertos são o terceiro tipo de acesso e, apesar de terem funções bem-sucedidas nas fases iniciais, baixas taxas de infecção em comparação com os CVCs, são mais propensos a falha em comparação com a FAV (Allon e Lok, 2010). Ainda, pacientes idosos, mulheres, com fatores de risco para DCVs ou que possuam DCVs possuem

maior risco de não conseguir amadurecer a fistula, sendo então recomendado o EAV (Miller *et al.*, 2003; Lok *et al.*, 2006).

Com relação com tempo de início da diálise (precoce *verus* tardio), os dados encontrados na literatura ainda são conflitantes. As diretrizes atuais recomendam que o tratamento deve iniciar com uma abordagem mais tardia, devendo-se basear principalmente na avaliação de sinais e sintomas associados à uremia e deterioração do estado nutricional e não somente os valores da TFG (Nesrallah *et al.*, 2014; National Kidney, 2015).

Zaho e cols (2018) através de uma meta-análise de estudos observacionais estudaram o momento de início de diálise e compararam com o risco de mortalidade. Ao final do estudo verificaram que o início precoce da terapia dialítica está relacionado com aumento na mortalidade comparando com pacientes que tiveram início tardio (Zhao *et al.*, 2018).

Cooper e cols através de um estudo randomizado submeteram 828 adultos à randomização em dois grupos: início precoce com uma TFG estimada de 10 a 14 mL por minuto e início tardio com a TFG estimada entre 5 a 7 mL por minuto. Ao final do estudo, verificou-se que o início precoce da diálise não estava associado com melhora na sobrevida (Cooper *et al.*, 2010).

No entanto, o transplante renal, dentre as modalidades de substituição renal é considerado a melhor das alternativas (Farah *et al.*, 2018). Existem registros que datam que o primeiro transplante renal bem sucedido aconteceu em 1954 (Merrill *et al.*, 1956), e desde então, o método evoluiu para se tornar a alternativa de tratamento preferida entre os pacientes na fase terminal da DRC. O progresso no transplante renal melhorou a sobrevida, bem como resultados à longo prazo principalmente para os mais jovens. As pessoas mais jovens de 20 a 39 anos vivem cerca de oito anos em diálise *versus* 25 anos após o transplante renal (Augustine, 2018).

No entanto, ainda existem algumas barreiras que afetam a preferência dos pacientes pela diálise em relação ao TR, dentre essas barreiras podemos citar a falta de doadores, baixo conhecimento, barreiras religiosas e culturais (Farah *et al.*, 2018).

Com relação aos doadores, para testar a elegibilidade do órgão bem como a garantia a curto e longo prazo do bem-estar do doador, uma abrangente avaliação de saúde deve ser realizada. Testes como: compatibilidade de grupo sanguíneo, antígeno leucocitário humano, medidas de TFG, exame de imagens dos rins e trato urinário, testes cardíacos devem ser realizados (Sebille *et al.*, 2016).

Existem muitas vantagens quando o transplante é realizado de doadores vivos em comparação com doador falecido. Estima-se que a sobrevida no primeiro ano seja superior a

90% em ambos os grupos, mas em cinco anos existe uma diferença onde cerca de 80% dos pacientes com órgão de doador vivo ainda estão vivos, enquanto esse número baixa para 65% dos pacientes com um órgão de um doador falecido (Augustine, 2018).

2.4 Consequências da DRC

Os pacientes renais sofrem com frequência alterações caracterizadas de "síndrome urêmica", que resulta em efeitos biológicos de metabólitos que não são excretados ou metabolizados pelos rins e por isso, são retidos no corpo e são denominados produtos de retenção urêmica (Roberts *et al.*, 2011).

Geralmente os sintomas manifestados pela síndrome urêmica são: anemia, má nutrição, distúrbios metabólicos que resultam na diminuição da tolerância ao exercício, neuropatias motoras e autonômicas, disfunções do metabolismo ósseo, comprometimento do sistema imunológico e sinais de náusea, vômitos, insônia, fadiga, depressão, ansiedade, disfunção erétil, diminuição da libido (Parsons *et al.*, 2006).

Dentre as consequências da síndrome urêmica destacam-se os problemas cardiovasculares como Hipertensão, descompensação cardíaca, lesão da parede vascular, aterosclerose e pericardite (Vanholder *et al.*, 2016). Muitos dos fatores de risco para DCVs e DRC são similares como idade avançada, gênero masculino, diabetes, hipertensão, histórico familiar, hipercolesterolemia. No entanto, existem evidências que sugerem que outros fatores de risco relacionados à uremia possam estar relacionados às DCVs no doente renal como albuminúria, anemia, má nutrição, estresse oxidativo, inflamação, alterações no metabolismo de cálcio e fósforo, homocisteína, distúrbios do sono e alterações no equilíbrio entre óxido nítrico/endotelina (Sarnak e Levey, 2000; Sarnak *et al.*, 2003).

Com base nos fatores de risco tradicionais e os chamados não-tradicionais, todos os pacientes com DRC devem ser considerados de alto risco para DCV (Hernandez *et al.*, 2013), pois os eventos cardíacos representam quase 50% das mortes de pacientes com DRC (Heywood *et al.*, 2007).

Sabe-se que a aterosclerose é acelerada em pacientes com DRC (Balla *et al.*, 2013), vários são os mecanismos que podem explicar essa aceleração. Um deles é uma alteração denominada hiperparatiroidismo secundário como um mecanismo compensatório para controlar os níveis séricos de cálcio, fósforo e vitamina D (Sampaio, 2008). Devido à redução da absorção de vitamina D pelos intestinos, ocorre uma situação de hipocalemia, isso causa o aumento da secreção de paratormônio (PTH) gerando liberação de cálcio do osso com consequente

deposição ectópica de cálcio em artérias (incluindo coronárias), estruturas valvares, perivalvulares e miocárdio. Essa calcificação vascular é observada mais comumente em pacientes no estágio 5 da DRC (Riella, 2003; Sampaio, 2008).

Outro fator consistente e que tem sido reconhecido como um fator de risco para Doença Arterial Coronariana (DAC) em DRC é a inflamação (Stenvinkel, 2001). A calcificação do sistema arterial coronário leva à um aumento da estimulação dos macrófagos e subsequente liberação de mediadores inflamatórios como o fator de necrose tumoral alfa (TNFα) (Nadra *et al.*, 2008). Além disso, níveis elevados de outros marcadores como proteína C-reativa (PCR) e interleucina 6 (IL-6) são encontrados em pacientes com DRC nas diferentes fases da progressão (Papagianni *et al.*, 2003; Stenvinkel, 2006).

As causas de inflamação na DRC são multifatoriais e incluem estresse oxidativo, acidose metabólica, infecções recorrentes, além de fatores extracorpóreos como impurezas na água de diálise e qualidade microbiológica do dialisato (Akchurin e Kaskel, 2015; Dai *et al.*, 2017).

Hawang e cols através de um estudo de coorte com 30.703 pacientes, avaliaram as associações entre calcificação da artéria coronária, taxa de filtração glomerular estimada e mortalidade por todas as causas. Os pesquisadores investigaram se as associações diferem com a presença de inflamação sistêmica. Ao final do estudo, conclui-se que a prevalência e extensão da calcificação coronária foi maior naqueles com menor TFG e níveis maiores de PCR (Hwang *et al.*, 2016).

Estudos também têm demonstrado que pacientes nas diferentes fases da DRC possuem aumento do Estresse Oxidativo (EO) (Beetham *et al.*, 2015) com o aumento de níveis plasmáticos de peroxidação lipídica e proteica, redução na atividade antioxidante quando comparados à indivíduos normais (Boaz *et al.*, 1999; Hirayama *et al.*, 2000).

Os compostos oxidativos são produzidos como parte dos processos de reparo tecidual, inflamação e mecanismo de defesa, mas em situações patológicas como uremia, a ativação crônica inadequada dos processos oxidativos contribui para a lesão de células e tecidos (Modaresi *et al.*, 2015).

Alguns autores sugerem que a uremia é um estado pró-oxidante com aumento nos níveis de lipoperoxidação e diminuição da atividade antioxidante (Boaz *et al.*, 1999; Hirayama *et al.*, 2000). No entanto, a natureza desse estresse oxidativo e sua provável exacerbação pela diálise ainda não estão bem claros (Liakopoulos *et al.*, 2017).

Alguns estudos têm identificado na DRC, em especial em pacientes que realizam HD, aumento na produção de ERO e de espécies reativas de nitrogênio. A ativação de macrófagos pode produzir ERO, em tese: pelo acúmulo de toxinas urêmicas, bioincompatibilidade das

membranas de diálise, influxo de endotoxinas da solução de diálise (Kelly *et al.*, 2005). Além disso, condições de comorbidades que geralmente acompanham os pacientes como hipertensão, dislipidemias, síndrome metabólica, DM, idade avançada e aterosclerose também explicam o aumento do EO nessa população (Liakopoulos *et al.*, 2017).

No estudo de Yang e cols, verificou-se que nos 80 pacientes estudados, os níveis de espécies reativas de oxigênio foram 14 vezes maiores do que antes da sessão de diálise (Yang *et al.*, 2006). Ainda, o estresse oxidativo induz disfunção endotelial e progressão da aterosclerose, reduzindo a disponibilidade de óxido nítrico (Modaresi *et al.*, 2015).

O endotélio é o maior órgão do corpo que fica localizado estrategicamente entre a parede do vaso sanguíneo e o sangue (Malyszko, 2010), desempenha papéis importantes na modulação do tônus vascular, sintetizando e liberando uma série de fatores de relaxamento derivados do endotélio, incluindo prostaglandinas vasodilatadoras, óxido nítrico (ON), e fatores de hiperpolarização dependente do endotélio, bem como fatores de contração derivados do endotélio (Shimokawa, 2014).

Os mecanismos pelos quais a disfunção endotelial ocorre na DRC são variados e parecem evoluir ao longo da progressão da doença. Os mecanismos iniciais provavelmente envolvem uma redução na síntese e biodisponibilidade do ON, resultando em grande parte do estresse oxidativo e da inibição endógena da óxido nítrico sintase endotelial (Baylis, 2006).

A hiperemia reativa do antebraço, uma medida de vasodilatação que é mediada em parte pela produção do ON, está prejudicada em DRC e está diretamente associada ao aumento do risco de mortalidade (London *et al.*, 2004). Análises de um estudo transversal com 334 pacientes demonstraram que a disfunção endotelial também está presente em pacientes com DRC moderada (Landray *et al.*, 2004).

Paciente com DRC apresentam ainda, disfunção autonômica cardiovascular como uma de suas principais complicações. Além da sobrecarga adrenérgica nos indivíduos afetados, evidências indicam a presença de controle reflexo prejudicado do sistema simpático e parassimpático no coração e vasos sanguíneos (Salman, 2015).

No curso da DRC, ocorre um desequilíbrio entre os componentes do Sistema Nervoso Autônomo (SNA). A disfunção autonômica cardiovascular é uma complicação grave, porém pouco compreendida na DRC que, na maioria dos casos, está associada à hiperatividade do Sistema Nervoso Simpático (SNS) e à um bloqueio da atividade do sistema nervoso parassimpático (SNP) (Hildreth, 2011; Salman, 2015). Esse desequilíbrio simpatovagal tem sido reconhecido como um mecanismo importante de muitas comorbidades cardiovasculares em geral e, pode ser a via final comum da morte súbita, em especial em DRC (Johansson *et al.*,

2007). Estudos demonstram que a ativação simpática parece já se manifestar nos estágios iniciais da doença, estando diretamente relacionada à gravidade da doença (Grassi *et al.*, 2012).

Fukuta e cols. (Fukuta *et al.*, 2003) demonstraram que, em pacientes submetidos à diálise, a variabilidade da frequência cardíaca estava inversamente relacionada com a probabilidade de sobrevida em quatro anos. Os pesquisadores também demonstraram, que a banda espectral de alta frequência, variável que indica a modulação vagal, estava significativamente menor nos pacientes que morreram por causa cardíaca quando comparada à dos sobreviventes do mesmo período.

Outra grave consequência da DRC é a anemia (Mikhail *et al.*, 2017). Existem várias causas para a anemia nessa população, à medida que a função renal diminui, os pacientes podem desenvolver deficiência de ferro. Os pacientes podem não ser capazes de utilizar efetivamente os estoques de ferro do seu próprio corpo e, portanto, muitos em especial aqueles que estão em tratamento hemodialítico, podem precisar de tratamento adicional com ferro (Silverberg *et al.*, 1996; Tessitore *et al.*, 2001).

Além disso, com a perda da função renal, os pacientes podem precisar de tratamento adicional com uma substância denominada eritropoetina, responsável por induzir a medula óssea a produzir células sanguíneas (Richardson *et al.*, 2001).

O sintoma mais comum da anemia é a fadiga, (Joshwa e Campbell, 2017) no entanto, outros sintomas como fraquezas, tontura, dor de cabeça, dispneia e dor no peito podem ocorrer. Os sintomas são geralmente observados quando a TFG atinge valores menores que 60 mL/min/1,73m^2 e continua a piorar na medida que as funções renais diminuem. Quando a doença progride para o estágio 5, quase 90% dos pacientes possuem anemia sendo que processos de doenças como hipertrofia ventricular esquerda, insuficiência cardíaca e infarto agudo do miocárdio são resultados potenciais de anemia não tratada e sustentada nessa população (Pendse e Singh, 2005; Thomas *et al.*, 2008).

2.5 Capacidade Funcional

Pacientes que estão em tratamento dialítico possuem as maiores taxas de hospitalização e mortalidade de todas as condições crônicas e, as variáveis de capacidade funcional, podem explicar em parte tal situação (Roshanravan *et al.*, 2013; Bossola *et al.*, 2016).

A redução da capacidade funcional nesta população também está descrita em outros estudos assim como em indivíduos que estão na fase pré-dialítica (Moreira *et al.*, 1997; Padilla *et al.*, 2008; Fassbinder *et al.*, 2015; Zanini *et al.*, 2016) em crianças e adolescentes com DRC

quando comparados com indivíduos saudáveis (Watanabe *et al.*, 2016) e em pacientes que realizam o tratamento através de diálise peritoneal (Shi *et al.*, 2017).

A medida da capacidade funcional vem se mostrando uma ferramenta de avaliação importante e o teste de caminhada de seis minutos (TC6') é uma das formas de medir esses valores pois possui uma boa correlação com o teste ergométrico (Raissuni e Roul, 2018).

Kohl e cols (Kohl *et al.*, 2012) avaliaram dados de 52 pacientes em hemodiálise e encontraram uma correlação positiva (r=0.508) entre a distância percorrida no TC6' e VO_2 de pico. Os autores ainda demonstraram que para cada 100 metros percorridos no TC6' a sobrevida dos pacientes aumenta em aproximadamente 5%.

Com relação ao desempenho do TC6' na DRC, a distância média percorrida pode diminuir de 600 metros na sexta década de vida para 420 metros a partir da oitava década de vida. A massa gorda corporal e a capacidade sérica de ligação total do ferro parecem ser os principais fatores modificáveis de desempenho no teste, além do nível de dispneia percebido que pode estar associado negativamente com os níveis de hemoglobina (Bucar Pajek *et al.*, 2016). Além disso, fatores como nível educacional, força muscular periférica e depressão parecem estar associados com o baixo desempenho do TC6' nesses pacientes (Garcia *et al.*, 2017).

Ainda, fatores como alterações nos níveis de cálcio, potássio, hiperparatoroidismo, desnutrição, acidose metabólica (Moreira, 2000) podem diminuir a capacidade funcional desses indivíduos. Em associação, esses marcadores são capazes de ocasionar fraqueza e atrofia muscular, podendo então, a redução da capacidade funcional ser consequência de um quadro denominado miopatia urêmica (Dipp *et al.*, 2010; Kono *et al.*, 2014; Garcia *et al.*, 2017).

A etiologia exata da miopatia urêmica permanece incerta e estudos tem demonstrados que essa alteração não é incomum nos pacientes com DRC, estima-se que 50% dos pacientes em diálise apresentem essas alterações (Clyne, 1996). Estuda-se que a miopatia urêmica possua origem multifatorial, das quais se deva além do aumento nos valores de PTH, a deficiência de carnitina, aumento nos níveis de ferro e deficiência de vitamina D (Al-Hayk e Bertorini, 2007).

Também, alterações como anemia, anormalidades cardiovasculares e outras comorbidades podem ser fatores complicadores da doença que alteram valores de desempenho no TC6' (Kono *et al.*, 2014; Garcia *et al.*, 2017).

Além disso, foi demonstrado que a DRC promove a degradação proteica do músculo, assim como das proteínas inteiras do corpo. A fraqueza muscular presente nesses pacientes, por sua vez é predominante nos grupos musculares proximais, e em particular, músculos das

extremidades inferiores o que prejudica a autonomia da marcha, dificuldade em subir escadas e elevar os braços (Moreira, 2000; Campistol, 2002).

Estudos realizados através de biópsias musculares, demonstram alterações mitocondriais, degeneração da banda Z, perda de miofilamentos, acúmulo de glicogênio intracelular, atrofia de fibras musculares tipo II, e aumento no conteúdo de lipídeos no músculo (Shah *et al.*, 1983; Diesel *et al.*, 1993).

O melhor tratamento para a miopatia urêmica é o transplante renal, caso contrário, o tratamento consiste em na correção das causas descritas acima além do uso de eritropoetina recombinante humana a qual é eficaz na correção da anemia aumentando assim a atividade e o funcionamento cardíaco, além do manejo na qualidade da diálise, melhora do estado nutricional do paciente e a inclusão do mesmo em programas de exercício físico (Campistol, 2002; Al-Hayk e Bertorini, 2007; Bhadauria, 2012; Clarkson *et al.*, 2019).

2.6 Força Muscular Periférica e Respiratória

Fraqueza muscular e fadiga são frequentemente relatadas pelos pacientes (Zyga *et al.*, 2015). A perda de massa muscular na DRC é considerada um importante complicador, pois contribui para um estilo de vida mais sedentário podendo assim comprometer a saúde cardiovascular e aumento da morbimortalidade (Stenvinkel *et al.*, 1999).

Sabe-se que o processo do envelhecimento está associado à sarcopenia e ao aumento da incidência de DRC, dessa forma o termo sarcopenia urêmica torna implícito o efeito progressivo e cumulativo da DRC nos músculos esqueléticos (Fahal, 2014). Além disso, a sarcopenia está presente em todos os estágios da DRC e também está associada significativamente ao declínio da TFG (Zhou *et al.*, 2018).

A diminuição da massa muscular envolve tanto o tamanho da fibra (atrofia) quanto o número (hipoplasia). Tais alterações se devem à perda de energia proteica e outros fatores como fatores hormonais, imunológicos, inflamação, acidose metabólica, inatividade física, excesso de angiotensina II, redução da função de células satélites (Fahal, 2014).

Souweine e cols avaliaram as consequências da inatividade física e da perda de energia proteica em 123 pacientes em HD e concluíram que esses fatores possuem um papel importante na perda de força e massa muscular (Souweine *et al.*, 2018). Uma das prováveis explicações está no Sistema Ubiquitina-Proteossoma (SUP) que atua fisiologicamente na regulação de importantes processos fisiológicos e fisiopatológicos nos rins sendo responsável pela degradação de mais de 80% das proteínas celulares (Meyer-Schwesinger, 2019). Sabe-se que

em DRC existe uma maior ativação desse sistema decorrentes da inflamação e acidose metabólica que os pacientes apresentam. Isso explica, em parte, a perda de energia proteica encontrada nessa população (Lecker e Mitch, 2011).

Ainda, a DRC está associada ao comprometimento da regeneração do músculo esquelético que ocorre a partir da formação de novas miofibrilas por células satélites presentes no músculo esquelético (Barberi *et al.*, 2013).

Na avaliação da força muscular periférica, Wang e cols (Wang *et al.*, 2017) através de um estudo de coorte acompanharam 51 pacientes por 12 e 36 meses, os pesquisadores avaliaram a força muscular periférica dos dorsiflexores do tornozelo e observaram uma queda significativa da força desses músculos no final dos 12 meses de acompanhamento, mostrando que os parâmetros físicos apresentam queda em prazos relativamente curtos de tempo.

As alterações da musculatura esquelética também são encontradas mesmo naqueles pacientes que já realizaram o transplante renal. Van Den Ham e cols (Van Den Ham *et al.*, 2005) avaliaram a força muscular esquelética tanto de pacientes em tratamento hemodialítico quanto naqueles que realizaram o transplante renal e concluíram que a força muscular em ambos os grupos se mostrou igualmente reduzida.

A melhor compreensão dos fatores associados à perda muscular no DRC precisa ainda ser melhor elucidada, pois estudos indicam que a perda de força muscular pode ser preditor de mortalidade nesses indivíduos (Matsuzawa *et al.*, 2014).

Quando avaliada a força em membros superiores, mais especificamente o *Handgrip Test*, existem evidências que demonstram a importância da avaliação da força de membros superiores em DRC (Chang *et al.*, 2011; Hellberg *et al.*, 2014). Hellberg e cols realizaram um estudo retrospectivo com avaliação de testes funcionais com 134 pacientes. Os pesquisadores concluíram que uma redução de 50% no valor do teste de preensão manual comparado com o predito por sexo e idade, corresponde a um aumento de três vezes na mortalidade. Essa perda funcional de pequenos grupos musculares pode ser sinais da miopatia urêmica, uma das consequências comuns da DRC (Hellberg *et al.*, 2014). Resultados semelhantes também podem ser observados em doentes que realizam somente o tratamento conservador, demonstrando que a avaliação muscular de membros superiores através do *Handgrip Test* pode ser incorporado à prática clínica para a avaliação do estado nutricional e fator de prognóstico também para DRC em tratamento conservador (Chang *et al.*, 2011).

Entretanto, existem fatores limitantes quanto à utilização da avaliação da força de preensão manual em pacientes submetidos à hemodiálise, uma vez que somado a outros fatores

podem interferir nos resultados, entre eles a presença do acesso vascular e a falta de padronização da técnica (Pinto *et al.*, 2015).

Existem também, estudos que avaliam a força de membros inferiores dos pacientes com DRC e a sua relação com a mortalidade. Em um estudo de coorte, Matsuzawa e cols (Matsuzawa *et al.*, 2014) acompanharam 190 pacientes por 7 anos e avaliaram a força de membros inferiores através da dinamometria. Ao final do estudo, os autores concluíram que a diminuição de força de membros inferiores está fortemente associada com um aumento na mortalidade em pacientes em hemodiálise, no entanto, os dados desse estudo se referem à uma população japonesa.

Uma forma simples de avaliar a força de membros inferiores é o teste de sentar e levantar (TSL) pois permite em pouco tempo e em qualquer lugar que o pesquisador avalie vários aspectos do paciente tais como: flexibilidade das articulações dos membros inferiores, equilíbrio, coordenação motora, relação entre potência muscular e peso corporal (Araújo, 1999; Lira *et al.*, 2000). Existem várias formas de realizar o TSL, como o teste de sentar e levantar do chão que consiste basicamente em quantificar quantos apoios o indivíduo necessita para sentar e levantar do chão (Araújo, 1999), outra forma relativamente fácil e rápida é o teste de sentar e levantar em uma cadeira em 30 segundos em que é avaliada especificamente a força e potência muscular onde se mede o número de repetições que o indivíduo consegue realizar em 30 segundos. Esse método de avaliação parece ser sensível à detecção de intervenções de programas de exercício físico tanto em idosos quanto em jovens pois pode evidenciar o declínio da aptidão física (Jones *et al.*, 1999).

Além de alterações do sistema musculoesquelético, ocorrem também complicações no sistema respiratório dos doentes tais como derrame pleural, hipertensão pulmonar, calcificação do parênquima pulmonar, insuficiências respiratórias (Bavbek *et al.*, 2010; Palamidas *et al.*, 2014), diminuição do *endurance* e força muscular respiratória, quando comparados à indivíduos saudáveis da mesma idade (Karacan *et al.*, 2006; Kovelis *et al.*, 2008), o que leva à um dos principais sintomas respiratórios da DRC que é a dispneia, limitando ainda mais a tolerância ao exercício desses indivíduos (Palamidas *et al.*, 2014; Bucar Pajek *et al.*, 2016).

As alterações respiratórias que ocorrem com a doença também estão relacionadas com o ganho de peso no período interdialítico, maior tempo em tratamento hemodialítico, hipotrofia muscular de fibras do tipo I e tipo II, alteração de transporte, extração e consumo de oxigênio, deficiência de vitamina D, catabolismo proteico aumentado e processos inflamatórios crônicos. (Campistol, 2002; Mcintyre *et al.*, 2006; Kovelis *et al.*, 2008).

Palamidas cols (Palamidas *et al.,* 2014) observaram um comprometimento na PImax correlacionado significativamente com a duração da HD em anos. Os mesmos autores também relataram uma melhora significativa nos valores de PImax imediatamente após a HD, provavelmente devido ao aumento da contratilidade do diafragma.

Um estudo experimental (Tarasuik *et al.,* 1992) realizado com ratos em que a uremia foi induzida, mostrou diminuição da força tanto de músculos esqueléticos como o músculo sóleo, quanto de músculos respiratórios como o diafragma onde houve um atraso dos estímulos conduzidos pelo nervo frênico.

Também através de um transversal realizado com 27 pacientes com DRC em HD que avaliou a função pulmonar, força muscular respiratória e a sua correlação com desempenho físico dos participantes encontrou que tanto os valores de Pressão Inspiratória Máxima (PImáx) quanto a Pressão Expiratória Máxima (PEmáx) encontraram-se abaixo dos valores preditos por sexo e idade (38,2% e 29% respectivamente). Esses valores ainda se correlacionaram com o desempenho no TC6' e com a capacidade vital (Jatobá, 2008). Essa diminuição tanto na força expiratória quanto na força inspiratória pode permanecer abaixo dos valores normais mesmo em indivíduos que foram submetidos ao transplante renal (Tavana e Mirzaei, 2016).

Dipp e cols avaliaram 30 indivíduos com DRC em hemodiálise através de um estudo transversal e encontraram diminuição nos valores de PEmáx em relação aos valores preditos ($p=0,015$), além da redução nos valores da distância percorrida no TC6'. Ainda, os valores obtidos tanto PImáx quanto para PEmáx correlacionaram-se positivamente com o número de repetições do TSL ($r=0,476$, $p=0,008$ e $r=0,540$, $p=0,002$ respectivamente), com os níveis de fósforo circulantes ($r=0,422$, $p=0,020$; $r=0,639$, $p<0,001$ respectivamente), além disso, os valores do TC6' correlacionaram-se positivamente com a PEmáx e TSL, demonstrando assim que, a redução na PEmáx na população estudada está associada com declínio da capacidade funcional e força de membros inferiores (Dipp *et al.*, 2010).

Essas diminuições tanto na força muscular expiratória quanto na força muscular inspiratória apesar de apresentarem melhora após o transplante renal, tendem a permanecer inferiores quando comparados à uma população saudável da mesma idade (Tavana e Mirzaei, 2016). O que mostra a importância do encaminhamento desses pacientes à programas de treinamento físico dos variados tipos: aeróbico e/ou resistido (Heiwe e Jacobson, 2014) (Cigarroa *et al.*, 2016) realizado de forma domiciliar ou supervisionado (Aoike *et al.*, 2015) no período intradialítico ou interdialítico (Frih *et al.*, 2017; Pu *et al.*, 2019), além de outras formas de reabilitação como o treinamento muscular inspiratório e a estimulação elétrica funcional que

apresentam boa evidências de melhora nos sintomas relacionados à perda de capacidade funcional e força muscular (Dipp *et al.*, 2019; Schardong *et al.*, 2019).

Em relação à mortalidade, sabe-se que a disfunção pulmonar, em particular a disfunção pulmonar restritiva associa-se ao grau de comprometimento da função renal e presença de comorbidade sendo também um fator preditor independente de mortalidade nesses pacientes. No entanto ainda não existem dados na literatura que avaliaram a associação da força muscular respiratória com a mortalidade em DRC (Mukai *et al.*, 2018).

2.7 Qualidade de vida

Pacientes com DRC em muitos casos, passam a experimentar diferentes sentimentos e comportamentos devido às alterações na capacidade física, na autoestima, imagem corporal e nas suas relações sociais (Gonçalves *et al.*, 2015; De Medeiros *et al.*, 2017).

Além disso, a necessidade de terapia renal substitutiva leva à sintomas de depressão e ansiedade que estão presentes em cerca de 25% dos pacientes (Stasiak *et al.*, 2014) e são considerados fatores importantes que afetam o prognóstico e interferem na qualidade de vida de indivíduos com DRC (Lee *et al.*, 2013), pois estão associados com diminuição na aderência ao tratamento, piora na capacidade funcional e altas taxas de hospitalização (Hedayati *et al.*, 2010).

Outros fatores como ao nível de aceitação da doença podem estar positivamente correlacionados com a qualidade de vida dos doentes, ainda, fatores como maior nível de escolaridade e melhor situação financeira também estão relacionados com a maior aceitação da doença. Já fatores como fadiga, perda muscular, falta de apetite, restrição na ingestão de fluídos, sexo feminino e envelhecimento correlacionam-se com a piora dos níveis de aceitação e qualidade de vida nessa população (Jankowska-Polanska *et al.*, 2017).

Quando comparadas as taxas de prevalência de depressão em pacientes em tratamento hemodialítico e tratamento conservador estágios 3 e 4 ou transplante renal, se verificou que os sintomas de depressão e ansiedade estavam presentes em ambos os grupos no entanto, em maior número naqueles em tratamento hemodialítico (Cwiek *et al.*, 2017).

Resultados similares foram encontrados por Aggarwal e cols que através de um estudo transversal avaliaram 200 pacientes em diferentes estágios da DRC. Os autores encontraram menores scores no SF-36 em pacientes com valores menores na TFG estimada, presença de Diabetes Mellitus, doença cardiovascular e valores de PCR aumentados (Aggarwal *et al.*, 2016).

Loon e cols, (Van Loon *et al.*, 2017) através de um estudo que avaliou a qualidade de vida de 714 indivíduos de diferentes idades com DRC distribuídos em 26 centros de hemodiálise,

através do questionário de qualidade de vida específico para doentes renais: *Kidney Disease Quality of Life- Short Form* (KDQOL-SF), verificou que menores valores nos índices nos domínios de funcionalidade, saúde emocional e atividade social, estão fortemente associadas há 2 anos de mortalidade independentemente da idade. Os autores ainda concluíram que os indivíduos que obtiveram baixas pontuações domínio de atividade física, possuem um risco 3,6 vezes maior de morte em 2 anos do que aqueles que obtiveram uma melhor pontuação no questionário de qualidade de vida.

Outra ferramenta para avaliar a qualidade de vida auto relatada na DRC é o questionário *EuroQol questionnaire* (EQ-5D) (Brooks, 1996). Katayama e cols estudaram, através de uma coorte, a relação entre mudanças no nível de atividade física através de um acelerômetro e a qualidade de vida de doentes renais durante um ano de seguimento e concluíram que quanto maior o nível de atividade física dos pacientes, melhores os escores do EQ-5D (Katayama *et al.*, 2016).

Dados de um estudo de coorte realizado com 745 pacientes com DRC que avaliou a qualidade de vida através do EQ-5D demonstraram que a pontuação mais baixa no questionário está associada a um maior risco de morte (Jesky *et al.*, 2016).

Desta forma, entende-se a necessidade de profissionais da saúde em avaliar a qualidade de vida dos pacientes para assim promover transformações, oferecer estratégias de reabilitação e prevenir o comprometimento de atividades cotidianas desses pacientes (Pereira *et al.*, 2012).

2.8 Funcionalidade e Nível de Atividade Física

Pacientes que estão em tratamento dialítico possuem as maiores taxas de hospitalização e mortalidade de todas as condições crônicas e, as variáveis de funcionalidade, podem explicar em parte tal situação (Roshanravan *et al.*, 2013; Bossola *et al.*, 2016).

A dependência funcional pode ser medida usando uma variedade de escalas que avaliam a capacidade do indivíduo em executar tarefas associadas a cuidados pessoais (por exemplo comer, se vestir, usar o banheiro) e aquelas associadas à manutenção de uma casa (como compras no supermercado, preparação de refeições e tarefas domésticas). A perda da dependência funcional pode contribuir para a redução na qualidade de vida observada nos pacientes (Gill *et al.*, 2003; Boyd *et al.*, 2008; Mcclure *et al.*, 2011).

Em pacientes com DRC a independência funcional pode estar comprometida (Cook e Jassal, 2008). Jassal e cols através de um estudo de coorte acompanharam 7.226 pacientes em HD de 12 países e encontraram um alto nível de dependência funcional em todas as faixas etárias e em

todos os países avaliados. Os resultados ainda apresentaram um forte e consistente preditor de mortalidade (Jassal *et al.*, 2016). Além disso, a independência funcional pode ser crucial para permitir que os pacientes consigam sustentar a si próprio e à família financeiramente (Bennett, 2013).

Em um estudo brasileiro que avaliou a independência funcional através da Medida de Independência Funcional (MIF) de 214 pacientes em HD se verificou que o escore médio total da MIF indicou uma independência completa ou modificada dessa população. No entanto a avaliação por categorias mostrou que a locomoção e tarefa de subir e descer escadas apresentou a menor pontuação. Ainda, os pesquisadores encontraram uma correlação negativa entre o escore médio da MIF com a variável idade (r= -0,14; p=0,03), complicações relacionadas à HD (r= -0,18; p= 0,01) e comorbidades (r= -0,28; p= 0,01). Dessa forma, com o aumento da idade, número de complicações durante a HD e comorbidades, ocorre um declínio da independência funcional desses pacientes (Oller *et al.*, 2012).

Resultados similares foram encontrados por Viswanath e cols que estudaram independência funcional de 116 pacientes com DRC. Os escores totais de independência funcional apresentaram valores próximos ao máximo indicando total independência funcional. No entanto, certas tarefa específicas como atividades motoras como subir e descer escadas apresentaram os valores mais baixos (Viswanath *et al.*, 2019).

Quando avaliados através da escala de Lawton e de Katz, Matsuzawa e cols, através de um estudo de coorte com um ano de acompanhamento de 817 pacientes em HD, demonstraram que o baixo nível de independência funcional está associado com elevado risco de mortalidade, o que evidencia a importância de intervenções para manter o *status* funcional nesta população (Matsuzawa *et al.*, 2019).

Atividade física é definida como qualquer movimento corporal produzido pela contração do músculo esquelético que aumenta o gasto de energia acima do nível basal. A atividade física pode ser categorizada por modo, intensidade e objetivo, entre outros (Physical Activity Guidelines Advisory Committee report, 2008. , 2009).

No entanto, o nível de atividade física é reduzido até mesmo naqueles pacientes que estão na fase pré-dialítica, chegando à 75% à menos quando comparados com uma população saudável da mesma idade (Heiwe *et al.*, 2003). Também, observa-se que quanto maior o grau da DRC, menor o nível de atividade física (Mansur, 2007).

Nah cols avaliaram o nível de atividade física de 70 pacientes com DRC e verificou que da amostra avaliada, apenas 26% dos pacientes preenchiam os critérios para serem classificados como ativos (Nah *et al.*, 2019).

O baixo nível de atividade física está presente também nos pacientes que realizaram transplante renal, dos fatores associados com esse baixo nível de atividade física podemos citar o nível de escolaridade, o medo que os pacientes relatam de efeitos adversos, limitações físicas e a falta de motivação (Van Adrichem *et al.*, 2018).

Apesar do consenso entre os nefrologistas de que o exercício é importante e provavelmente benéfico para os pacientes, existe a necessidade de introduzir o incentivo à atividade física no manejo dos doentes. Tais intervenções são justificadas uma vez que os pacientes apresentam, independentemente da idade, alta prevalência de alterações físicas e maior fragilidade quando comparados com a população geral de idosos. Além disso, a falta de atividade física está fortemente associado à mortalidade por todas as causas (Painter e Roshanravan, 2013).

Como já descrito acima, existe na literatura evidências de que a diminuição de variáveis de capacidade funcional, força muscular e qualidade de vida possam influenciar no tempo de sobrevida de pacientes com DRC em HD. No entanto, existe a necessidade de mais estudos que verifiquem a associação entre esses testes entre si e relacioná-los com o tempo de sobrevida para que assim, o uso dessas ferramentas, possa se tornar rotina na avaliação dos pacientes.

Baseado nesses pressupostos, o objetivo do presente estudo é verificar a influência da capacidade funcional, força muscular periférica e respiratória na sobrevida de pacientes com DRC em HD.

REFERÊNCIAS

AGGARWAL, H. K. et al. Health-related quality of life in different stages of chronic kidney disease. **QJM,** v. 109, n. 11, p. 711-716, Nov 2016. ISSN 1460-2393 (Electronic) 1460-2393 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27118872 >.

AKCHURIN, O. M.; KASKEL, F. Update on inflammation in chronic kidney disease. **Blood Purif,** v. 39, n. 1-3, p. 84-92, 2015. ISSN 1421-9735 (Electronic) 0253-5068 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25662331 >.

AL-HAYK, K.; BERTORINI, T. E. Neuromuscular complications in uremics: a review. **Neurologist,** v. 13, n. 4, p. 188-96, Jul 2007. ISSN 1074-7931 (Print) 1074-7931 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/17622910 >.

ALLON, M.; LOK, C. E. Dialysis fistula or graft: the role for randomized clinical trials. **Clin J Am Soc Nephrol,** v. 5, n. 12, p. 2348-54, Dec 2010. ISSN 1555-905X (Electronic) 1555-9041 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21030576 >.

ANDERSON, C. A.; NGUYEN, H. A.; RIFKIN, D. E. Nutrition Interventions in Chronic Kidney Disease. **Med Clin North Am,** v. 100, n. 6, p. 1265-1283, Nov 2016. ISSN 0025-7125.

ANDRASSY, K. M. Comments on 'KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease'. **Kidney Int,** v. 84, n. 3, p. 622-3, Sep 2013. ISSN 1523-1755 (Electronic) 0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23989362 >.

AOIKE, D. T. et al. Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease. **Int Urol Nephrol,** v. 47, n. 2, p. 359-67, Feb 2015. ISSN 1573-2584 (Electronic) 0301-1623 (Linking). Disponível em: <https://www.ncbi.nlm.nih.gov/pubmed/25503447 >.

ARAÚJO, C. G. S. D. Teste de sentar-levantar: apresentação de um procedimento para avaliação em Medicina do Exercício e do Esporte. **Revista Brasileira de Medicina do Esporte,** v. 5, p. 179-182, 1999. ISSN 1517-8692. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1517-86921999000500004&nrm=iso >.

AUGUSTINE, J. Kidney transplant: New opportunities and challenges. **Cleve Clin J Med,** v. 85, n. 2, p. 138-144, Feb 2018. ISSN 1939-2869 (Electronic) 0891-1150 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29425089 >.

BALLA, S.; NUSAIR, M. B.; ALPERT, M. A. Risk factors for atherosclerosis in patients with chronic kidney disease: recognition and management. **Curr Opin Pharmacol,** v. 13, n. 2, p. 192-9, Apr 2013. ISSN 1471-4973 (Electronic) 1471-4892 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23291030 >.

BARBERI, L. et al. Age-dependent alteration in muscle regeneration: the critical role of tissue niche. **Biogerontology,** v. 14, n. 3, p. 273-92, Jun 2013. ISSN 1573-6768 (Electronic) 1389-5729 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23666344 >.

BAVBEK, N. et al. The effects of L-carnitine therapy on respiratory function tests in chronic hemodialysis patients. **Ren Fail,** v. 32, n. 2, p. 157-61, Jan 2010. ISSN 1525-6049. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20199175 >.

BAYLIS, C. Arginine, arginine analogs and nitric oxide production in chronic kidney disease. **Nat Clin Pract Nephrol,** v. 2, n. 4, p. 209-20, Apr 2006. ISSN 1745-8323 (Print) 1745-8323 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16932427 >.

BEETHAM, K. S. et al. Oxidative stress contributes to muscle atrophy in chronic kidney disease patients. **Redox Rep,** v. 20, n. 3, p. 126-32, May 2015. ISSN 1743-2928 (Electronic) 1351-0002 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25391884 >.

BENNETT, L. Patient independence in chronic kidney disease and anaemia: implications of the 2012 KDIGO guideline. **J Ren Care,** v. 39, n. 2, p. 108-17, Jun 2013. ISSN 1755-6686 (Electronic) 1755-6678 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23683304 >.

BETO, J. A.; BANSAL, V. K. Nutrition interventions to address cardiovascular outcomes in chronic kidney disease. **Adv Chronic Kidney Dis,** v. 11, n. 4, p. 391-7, Oct 2004. ISSN 1548-5595 (Print) 1548-5595 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15492977 >.

BHADAURIA, D. A., N. Miopatia urêmica. **Clinical Queries: Nephrology**, p. 279-283, 2012.

BIDANI, A. K.; GRIFFIN, K. A. Pathophysiology of hypertensive renal damage: implications for therapy. **Hypertension,** v. 44, n. 5, p. 595-601, Nov 2004. ISSN 1524-4563 (Electronic) 0194-911X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15452024 >.

BLOEMBERGEN, W. E. et al. A comparison of mortality between patients treated with hemodialysis and peritoneal dialysis. **J Am Soc Nephrol,** v. 6, n. 2, p. 177-83, Aug 1995. ISSN 1046-6673 (Print) 1046-6673 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/7579082 >.

BOAZ, M. et al. Serum malondialdehyde and prevalent cardiovascular disease in hemodialysis. **Kidney Int,** v. 56, n. 3, p. 1078-83, Sep 1999. ISSN 0085-2538 (Print) 0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/10469377 >.

BOSSOLA, M. et al. Functional impairment is associated with an increased risk of mortality in patients on chronic hemodialysis. **BMC Nephrol,** v. 17, n. 1, p. 72, Jul 8 2016. ISSN 1471-2369 (Electronic) 1471-2369 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27391964 >.

BOYD, C. M. et al. Recovery of activities of daily living in older adults after hospitalization for acute medical illness. **J Am Geriatr Soc,** v. 56, n. 12, p. 2171-9, Dec 2008. ISSN 1532-5415 (Electronic)

0002-8614 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19093915 >.

BROOKS, R. EuroQol: the current state of play. **Health Policy,** v. 37, n. 1, p. 53-72, Jul 1996. ISSN 0168-8510. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/10158943 >.

BUCAR PAJEK, M. et al. Six-Minute Walk Test in Renal Failure Patients: Representative Results, Performance Analysis and Perceived Dyspnea Predictors. **PLoS One,** v. 11, n. 3, p. e0150414, 2016. ISSN 1932-6203 (Electronic) 1932-6203 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26982967 >.

CAMPISTOL, J. M. Uremic myopathy. **Kidney Int,** v. 62, n. 5, p. 1901-13, Nov 2002. ISSN 0085-2538 (Print) 0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12371997 >.

CASTIGLIONI, A.; SAVAZZI, G. M. Physiopathology and clinical aspects of diabetic nephropathy. **Nephron,** v. 50, n. 2, p. 151-63, 1988. ISSN 1660-8151 (Print) 1660-8151 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/3065662 >.

CHANG, Y. T. et al. Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases. **Nephrol Dial Transplant,** v. 26, n. 11, p. 3588-95, Nov 2011. ISSN 1460-2385. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21444362 >.

CHEN, T. K.; KNICELY, D. H.; GRAMS, M. E. Chronic Kidney Disease Diagnosis and Management: A Review. **JAMA,** v. 322, n. 13, p. 1294-1304, Oct 1 2019. ISSN 1538-3598 (Electronic) 0098-7484 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31573641 >.

CIGARROA, I. et al. [Effects of a resistance training program in patients with chronic kidney disease on hemodialysis]. **Rev Med Chil,** v. 144, n. 7, p. 844-52, Jul 2016. ISSN 0717-6163 (Electronic) 0034-9887 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27661546 >.

CLARKSON, M. J. et al. Exercise interventions for improving objective physical function in patients with end-stage kidney disease on dialysis: a systematic review and meta-analysis. **Am J Physiol Renal Physiol,** v. 316, n. 5, p. F856-F872, May 1 2019. ISSN 1522-1466 (Electronic) 1522-1466 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30759022 >.

CLYNE, N. Physical working capacity in uremic patients. **Scand J Urol Nephrol,** v. 30, n. 4, p. 247-52, Aug 1996. ISSN 0036-5599 (Print) 0036-5599 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8908642 >.

COOK, W. L.; JASSAL, S. V. Functional dependencies among the elderly on hemodialysis. **Kidney Int,** v. 73, n. 11, p. 1289-95, Jun 2008. ISSN 1523-1755 (Electronic) 0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18354381 >.

COOPER, B. A. et al. A randomized, controlled trial of early versus late initiation of dialysis. **N Engl J Med,** v. 363, n. 7, p. 609-19, Aug 12 2010. ISSN 1533-4406 (Electronic)

0028-4793 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20581422 >.

CWIEK, A. et al. Association between depression and hemodialysis in patients with chronic kidney disease. **Psychiatr Danub,** v. 29, n. Suppl 3, p. 499-503, Sep 2017. ISSN 0353-5053 (Print) 0353-5053 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28953816 >.

DAI, L. et al. End-Stage Renal Disease, Inflammation and Cardiovascular Outcomes. **Contrib Nephrol,** v. 191, p. 32-43, 2017. ISSN 1662-2782 (Electronic) 0302-5144 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28910789 >.

DATASUS. **Sistema de informações sobre mortalidade**. SAÚDE, M. D. www.tabnet.datasus.gov.br 2020.

DE GROAT, W. C. Anatomy and physiology of the lower urinary tract. **Urol Clin North Am,** v. 20, n. 3, p. 383-401, Aug 1993. ISSN 0094-0143 (Print) 0094-0143 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8351765 >.

DE GROAT, W. C.; GRIFFITHS, D.; YOSHIMURA, N. Neural control of the lower urinary tract. **Compr Physiol,** v. 5, n. 1, p. 327-96, Jan 2015. ISSN 2040-4603 (Electronic) 2040-4603 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25589273 >.

DE GROAT, W. C.; YOSHIMURA, N. Anatomy and physiology of the lower urinary tract. **Handb Clin Neurol,** v. 130, p. 61-108, 2015. ISSN 0072-9752 (Print) 0072-9752 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26003239 >.

DE MEDEIROS, A. I. C. et al. Inspiratory muscle training improves respiratory muscle strength, functional capacity and quality of life in patients with chronic kidney disease: a systematic review. **J Physiother,** v. 63, n. 2, p. 76-83, Apr 2017. ISSN 1836-9561. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28433237 >.

DE MORAES, T. P. et al. Characterization of the BRAZPD II cohort and description of trends in peritoneal dialysis outcome across time periods. **Perit Dial Int,** v. 34, n. 7, p. 714-23, Nov-Dec 2014. ISSN 1718-4304 (Electronic) 0896-8608 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25185014 >.

DIABETES, C. et al. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. **N Engl J Med,** v. 329, n. 14, p. 977-86, Sep 30 1993. ISSN 0028-4793 (Print) 0028-4793 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8366922 >.

DIESEL, W. et al. Morphologic features of the myopathy associated with chronic renal failure. **Am J Kidney Dis,** v. 22, n. 5, p. 677-84, Nov 1993. ISSN 0272-6386 (Print) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8238013 >.

DIPP, T. et al. Short period of high-intensity inspiratory muscle training improves inspiratory muscle strength in patients with chronic kidney disease on hemodialysis: a randomized controlled trial. **Braz J Phys Ther**, May 6 2019. ISSN 1809-9246 (Electronic) 1413-3555 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31122717 >.

DIPP, T. et al. **Força Muscular Respiratória e Capacidade Funcional na Insuficiência Renal Terminal**. Rev Bras Med Esporte. 16 2010.

DUVAL, J. M. et al. Ultrasonographic anatomy and physiology of the fetal kidney. **Anat Clin,** v. 7, n. 2, p. 107-23, 1985. ISSN 0343-6098 (Print) 0343-6098 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/3899140 >.

FAHAL, I. H. Uraemic sarcopenia: aetiology and implications. **Nephrol Dial Transplant,** v. 29, n. 9, p. 1655-65, Sep 2014. ISSN 1460-2385 (Electronic) 0931-0509 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23625972 >.

FARAH, S. S. et al. Barriers to Kidney Transplantation as a Choice of Renal Replacement Therapy. **Transplant Proc,** v. 50, n. 10, p. 3165-3171, Dec 2018. ISSN 1873-2623 (Electronic) 0041-1345 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30577183 >.

FASSBINDER, T. R. et al. Functional Capacity and Quality of Life in Patients with Chronic Kidney Disease In Pre-Dialytic Treatment and on Hemodialysis--A Cross sectional study. **J Bras Nefrol,** v. 37, n. 1, p. 47-54, Jan-Mar 2015. ISSN 2175-8239 (Electronic) 0101-2800 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25923750 >.

FLISINSKI, M. et al. Morphometric analysis of muscle fibre types in rat locomotor and postural skeletal muscles in different stages of chronic kidney disease. **J Physiol Pharmacol,** v. 65, n. 4, p. 567-76, Aug 2014. ISSN 1899-1505. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25179089 >.

FOLEY, R. N.; CHEN, S. C.; COLLINS, A. J. Hemodialysis access at initiation in the United States, 2005 to 2007: still "catheter first". **Hemodial Int,** v. 13, n. 4, p. 533-42, Oct 2009. ISSN 1542-4758 (Electronic) 1492-7535 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19758304 >.

FOY, M.; SPERATI, C. J. What the non-nephrologist needs to know about dialysis. **Semin Dial,** v. 31, n. 2, p. 183-192, Mar 2018. ISSN 1525-139X (Electronic) 0894-0959 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29336060 >.

FRIH, B. et al. The Effect of Interdialytic Combined Resistance and Aerobic Exercise Training on Health Related Outcomes in Chronic Hemodialysis Patients: The Tunisian Randomized Controlled Study. **Front Physiol,** v. 8, p. 288, 2017. ISSN 1664-042X (Print) 1664-042X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28620308 >.

FUKUTA, H. et al. Prognostic value of heart rate variability in patients with end-stage renal disease on chronic haemodialysis. **Nephrol Dial Transplant,** v. 18, n. 2, p. 318-25, Feb 2003. ISSN 0931-0509 (Print)

0931-0509 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12543887 >.

GARCIA, R. S. A. et al. Factors Associated With Functional Capacity in Hemodialysis Patients. **Artif Organs,** v. 41, n. 12, p. 1121-1126, Dec 2017. ISSN 1525-1594 (Electronic) 0160-564X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28568475 >.

GILL, T. M.; ALLORE, H.; GUO, Z. Restricted activity and functional decline among community-living older persons. **Arch Intern Med,** v. 163, n. 11, p. 1317-22, Jun 9 2003. ISSN 0003-9926 (Print) 0003-9926 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12796067 >.

GIRNDT, M. [Diagnosis and treatment of chronic kidney disease]. **Internist (Berl),** v. 58, n. 3, p. 243-256, Mar 2017. ISSN 1432-1289 (Electronic) 0020-9554 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28194476 >.

GLASSOCK, R. J.; RULE, A. D. Aging and the Kidneys: Anatomy, Physiology and Consequences for Defining Chronic Kidney Disease. **Nephron,** v. 134, n. 1, p. 25-9, 2016. ISSN 2235-3186 (Electronic) 1660-8151 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27050529 >.

GONÇALVES, F. A. et al. Qualidade de vida de pacientes renais crônicos em hemodiálise ou diálise peritoneal: estudo comparativo em um serviço de referência de Curitiba - PR. **Brazilian Journal of Nephrology,** v. 37, p. 467-474, 2015. ISSN 0101-2800. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0101-28002015000400467&nrm=iso >.

GRASSI, G.; BERTOLI, S.; SERAVALLE, G. Sympathetic nervous system: role in hypertension and in chronic kidney disease. **Curr Opin Nephrol Hypertens,** v. 21, n. 1, p. 46-51, Jan 2012. ISSN 1473-6543 (Electronic) 1062-4821 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22080859 >.

GUTIERREZ, O. M. et al. Low socioeconomic status associates with higher serum phosphate irrespective of race. **J Am Soc Nephrol,** v. 21, n. 11, p. 1953-60, Nov 2010. ISSN 1533-3450 (Electronic) 1046-6673 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20847142 >.

HAMRAHIAN, S. M.; FALKNER, B. Hypertension in Chronic Kidney Disease. **Adv Exp Med Biol,** v. 956, p. 307-325, 2017. ISSN 0065-2598 (Print) 0065-2598 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27873228 >.

HEDAYATI, S. S. et al. Association between major depressive episodes in patients with chronic kidney disease and initiation of dialysis, hospitalization, or death. **JAMA,** v. 303, n. 19, p. 1946-53, May 2010. ISSN 1538-3598. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20483971 >.

HEIWE, S.; CLYNE, N.; DAHLGREN, M. A. Living with chronic renal failure: patients' experiences of their physical and functional capacity. **Physiother Res Int,** v. 8, n. 4, p. 167-77, 2003. ISSN 1358-2267 (Print) 1358-2267 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14730721 >.

HEIWE, S.; JACOBSON, S. H. Exercise training in adults with CKD: a systematic review and meta-analysis. **Am J Kidney Dis,** v. 64, n. 3, p. 383-93, Sep 2014. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24913219 >.

HELLBERG, M. et al. Small distal muscles and balance predict survival in end-stage renal disease. **Nephron Clin Pract,** v. 126, n. 3, p. 116-23, 2014. ISSN 1660-2110. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24713811 >.

HERNANDEZ, G. T.; SIPPEL, M.; MUKHERJEE, D. Interrelationship between chronic kidney disease and risk of cardiovascular diseases. **Cardiovasc Hematol Agents Med Chem,** v. 11, n. 1, p. 38-43, Mar 2013. ISSN 1875-6182 (Electronic) 1871-5257 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22721441 >.

HEYWOOD, J. T. et al. High prevalence of renal dysfunction and its impact on outcome in 118,465 patients hospitalized with acute decompensated heart failure: a report from the ADHERE database. **J Card Fail,** v. 13, n. 6, p. 422-30, Aug 2007. ISSN 1532-8414 (Electronic) 1071-9164 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/17675055 >.

HILDRETH, C. M. Prognostic indicators of cardiovascular risk in renal disease. **Front Physiol,** v. 2, p. 121, 2011. ISSN 1664-042X (Electronic) 1664-042X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22294981 >.

HIMMELFARB, J.; IKIZLER, T. A. Hemodialysis. **N Engl J Med,** v. 363, n. 19, p. 1833-45, Nov 4 2010. ISSN 1533-4406 (Electronic) 0028-4793 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21047227 >.

HIRAKI, K. et al. Effects of home-based exercise on pre-dialysis chronic kidney disease patients: a randomized pilot and feasibility trial. **BMC Nephrol,** v. 18, n. 1, p. 198, Jun 17 2017. ISSN 1471-2369 (Electronic) 1471-2369 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28623895 >.

HIRAYAMA, A. et al. Hemodialysis does not influence the peroxidative state already present in uremia. **Nephron,** v. 86, n. 4, p. 436-40, Dec 2000. ISSN 1660-8151 (Print) 1660-8151 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11124591 >.

HORIO, M. [New topics regarding equations for GFR estimation based on serum creatinine and cystatin C]. **Rinsho Byori,** v. 62, n. 2, p. 153-62, Feb 2014. ISSN 0047-1860 (Print) 0047-1860 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24800491 >.

HOWDEN, E. J. et al. Effects of exercise and lifestyle intervention on cardiovascular function in CKD. **Clin J Am Soc Nephrol,** v. 8, n. 9, p. 1494-501, Sep 2013. ISSN 1555-9041.

HWANG, I. C. et al. Systemic Inflammation Is Associated With Coronary Artery Calcification and All-Cause Mortality in Chronic Kidney Disease. **Circ J,** v. 80, n. 7, p. 1644-52, Jun 24 2016. ISSN 1347-4820 (Electronic)

1346-9843 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27251163 >.

JANKOWSKA-POLANSKA, B. et al. Factors affecting the quality of life of chronic dialysis patients. **Eur J Public Health,** v. 27, n. 2, p. 262-267, Apr 1 2017. ISSN 1464-360X (Electronic) 1101-1262 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28339523 >.

JASSAL, S. V. et al. Functional Dependence and Mortality in the International Dialysis Outcomes and Practice Patterns Study (DOPPS). **Am J Kidney Dis,** v. 67, n. 2, p. 283-92, Feb 2016. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26612280 >.

JATOBÁ, J. P. C. A., W. F.; ANDRADE, A. P. A.; CARDOSO, F. P. F.; MONTEIRO, A. M. H.; OLIVEIRA, M. A. M. . Avaliação da Função Pulmonar, Força Muscular Respiratória e Teste de Caminhada de Seis Minutos em Pacientes Portadores de Doença Renal Crônica em Hemodiálise. **Braz. J. Nephrol.,** v. 30, n. 4, p. 280-287, 2008.

JESKY, M. D. et al. Health-Related Quality of Life Impacts Mortality but Not Progression to End-Stage Renal Disease in Pre-Dialysis Chronic Kidney Disease: A Prospective Observational Study. **PLoS One,** v. 11, n. 11, p. e0165675, 2016. ISSN 1932-6203 (Electronic) 1932-6203 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27832126 >.

JOHANSSON, M. et al. Baroreflex effectiveness index and baroreflex sensitivity predict all-cause mortality and sudden death in hypertensive patients with chronic renal failure. **J Hypertens,** v. 25, n. 1, p. 163-8, Jan 2007. ISSN 0263-6352 (Print) 0263-6352 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/17143188 >.

JONES, C. J.; RIKLI, R. E.; BEAM, W. C. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. **Res Q Exerc Sport,** v. 70, n. 2, p. 113-9, Jun 1999. ISSN 0270-1367. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/10380242 >.

JOSHWA, B.; CAMPBELL, M. L. Fatigue in Patients with Chronic Kidney Disease: Evidence and Measures. **Nephrol Nurs J,** v. 44, n. 4, p. 337-343, Jul-Aug 2017. ISSN 1526-744X (Print) 1526-744X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29160968 >.

JUNIOR, J. Doença Renal Crônica: Definição, Epidemiologia e Classificação. **J Bras Nefrol,** v. 26, n. 3 Suppl 1, 2004. Disponível em: < http://www.jbn.org.br/artigo/detalhes/1183 >.

KARACAN, O. et al. Pulmonary function in renal transplant recipients and end-stage renal disease patients undergoing maintenance dialysis. **Transplant Proc,** v. 38, n. 2, p. 396-400, Mar 2006. ISSN 0041-1345 (Print) 0041-1345 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16549130 >.

KASHIHARA, N. [Physiopathology and treatment of diabetic nephropathy]. **Nihon Naika Gakkai Zasshi,** v. 97, n. 3, p. 614-20, Mar 10 2008. ISSN 0021-5384 (Print) 0021-5384 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22675767 >.

KATAYAMA, A. et al. Relationship between Changes in Physical Activity and Changes in Health-related Quality of Life in Patients on Chronic Hemodialysis with 1-Year Follow-up. **Acta Med Okayama,** v. 70, n. 5, p. 353-361, Oct 2016. ISSN 0386-300X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27777427 >.

KDIGO Board Members. **Kidney Int Suppl (2011),** v. 2, n. 1, p. 3, Mar 2012. ISSN 2157-1724 (Print) 2157-1716 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25028632 >.

KELLY, M.; LACOUR, B.; NGUYEN-KHOA, T. Dysregulation of superoxide dismutase in chronic kidney disease. **Nephron Clin Pract,** v. 100, n. 3, p. c103-4, 2005. ISSN 1660-2110 (Electronic) 1660-2110 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15824507 >.

KOHL, L. E. M. et al. Prognostic value of the six-minute walk test in end-stage renal disease life expectancy: a prospective cohort study. **Clinics (Sao Paulo),** v. 67, n. 6, p. 581-6, 2012. ISSN 1980-5322. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/22760895 >.

KONO, K. et al. Investigation of factors affecting the six-minute walk test results in hemodialysis patients. **Ther Apher Dial,** v. 18, n. 6, p. 623-7, Dec 2014. ISSN 1744-9987. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24674327 >.

KOVELIS, D. et al. Pulmonary function and respiratory muscle strength in chronic renal failure patients on hemodialysis. **J Bras Pneumol,** v. 34, n. 11, p. 907-12, Nov 2008. ISSN 1806-3756 (Electronic) 1806-3713 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19099096 >.

KU, E. et al. Race and Mortality in CKD and Dialysis: Findings From the Chronic Renal Insufficiency Cohort (CRIC) Study. **Am J Kidney Dis**, Nov 12 2019. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31732235 >.

LAMBERS HEERSPINK, H. J.; DE ZEEUW, D. Novel drugs and intervention strategies for the treatment of chronic kidney disease. **Br J Clin Pharmacol,** v. 76, n. 4, p. 536-50, Oct 2013. ISSN 1365-2125 (Electronic) 0306-5251 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23802504 >.

LANDRAY, M. J. et al. Inflammation, endothelial dysfunction, and platelet activation in patients with chronic kidney disease: the chronic renal impairment in Birmingham (CRIB) study. **Am J Kidney Dis,** v. 43, n. 2, p. 244-53, Feb 2004. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14750089 >.

LECKER, S. H.; MITCH, W. E. Proteolysis by the ubiquitin-proteasome system and kidney disease. **J Am Soc Nephrol,** v. 22, n. 5, p. 821-4, May 2011. ISSN 1533-3450 (Electronic) 1046-6673 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21474563 >.

LEE, Y. J. et al. Association of depression and anxiety with reduced quality of life in patients with predialysis chronic kidney disease. **Int J Clin Pract,** v. 67, n. 4, p. 363-8, Apr 2013. ISSN 1742-1241. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23521328 >.

LEES, J. S. et al. Glomerular filtration rate by differing measures, albuminuria and prediction of cardiovascular disease, mortality and end-stage kidney disease. **Nat Med,** v. 25, n. 11, p. 1753-1760, Nov 2019. ISSN 1546-170X (Electronic) 1078-8956 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31700174 >.

LEVEY, A. S.; BECKER, C.; INKER, L. A. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. **JAMA,** v. 313, n. 8, p. 837-46, Feb 24 2015. ISSN 1538-3598 (Electronic) 0098-7484 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25710660 >.

LEVEY, A. S.; CORESH, J. Chronic kidney disease. **Lancet,** v. 379, n. 9811, p. 165-80, Jan 14 2012. ISSN 1474-547X (Electronic) 0140-6736 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21840587 >.

LEVEY, A. S. et al. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification. **Ann Intern Med,** v. 139, n. 2, p. 137-47, Jul 15 2003. ISSN 1539-3704 (Electronic) 0003-4819 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12859163 >.

LI, P. K. et al. Changes in the worldwide epidemiology of peritoneal dialysis. **Nat Rev Nephrol,** v. 13, n. 2, p. 90-103, Feb 2017. ISSN 1759-507X (Electronic) 1759-5061 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28029154 >.

LIAKOPOULOS, V. et al. Oxidative Stress in Hemodialysis Patients: A Review of the Literature. **Oxid Med Cell Longev,** v. 2017, p. 3081856, 2017. ISSN 1942-0994 (Electronic) 1942-0994 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29138677 >.

LIRA, V. A.; SILVA, E. B. D.; ARAÚJO, C. G. S. D. As ações de sentar e levantar do solo são prejudicadas por excesso de peso. **Revista Brasileira de Medicina do Esporte,** v. 6, p. 241-248, 2000. ISSN 1517-8692. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1517-86922000000600004&nrm=iso >.

LOK, C. E. et al. Risk equation determining unsuccessful cannulation events and failure to maturation in arteriovenous fistulas (REDUCE FTM I). **J Am Soc Nephrol,** v. 17, n. 11, p. 3204-12, Nov 2006. ISSN 1046-6673 (Print) 1046-6673 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16988062 >.

LONDON, G. M. et al. Forearm reactive hyperemia and mortality in end-stage renal disease. **Kidney Int,** v. 65, n. 2, p. 700-4, Feb 2004. ISSN 0085-2538 (Print) 0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14717944 >.

MACIA HERAS, M.; MACIA JEREZ, M.; CORONEL, F. [Diabetic nephropathy: physiopathology and clinical course]. **Nefrologia,** v. 21 Suppl 3, p. 24-31, 2001. ISSN 0211-6995 (Print) 0211-6995 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11642203 >.

MALYSZKO, J. Mechanism of endothelial dysfunction in chronic kidney disease. **Clin Chim Acta,** v. 411, n. 19-20, p. 1412-20, Oct 9 2010. ISSN 1873-3492 (Electronic) 0009-8981 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20598675 >.

MANSUR, H. N. N., J. S.; LIMA, P. Physical Activity Levels and Cardiovascular Risk in Patients With Renal Chronic Disease. **The Journal of Strength and Conditioning Research,** v. 21, p. 1032-1036, 01/01 2007.

MATSUZAWA, R. et al. Decline in the Functional Status and Mortality in Patients on Hemodialysis: Results from the Japan Dialysis Outcome and Practice Patterns Study. **J Ren Nutr,** v. 29, n. 6, p. 504-510, Nov 2019. ISSN 1532-8503 (Electronic) 1051-2276 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30591357 >.

MATSUZAWA, R. et al. Relationship between lower extremity muscle strength and all-cause mortality in Japanese patients undergoing dialysis. **Phys Ther,** v. 94, n. 7, p. 947-56, Jul 2014. ISSN 1538-6724. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24578522 >.

MCCLURE, J. A. et al. Predicting length of stay in patients admitted to stroke rehabilitation with high levels of functional independence. **Disabil Rehabil,** v. 33, n. 23-24, p. 2356-61, 2011. ISSN 1464-5165 (Electronic) 0963-8288 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21504345 >.

MCINTYRE, C. W. et al. Patients receiving maintenance dialysis have more severe functionally significant skeletal muscle wasting than patients with dialysis-independent chronic kidney disease. **Nephrol Dial Transplant,** v. 21, n. 8, p. 2210-6, Aug 2006. ISSN 0931-0509 (Print) 0931-0509 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16504974 >.

MERRILL, J. P. et al. Successful homotransplantation of the human kidney between identical twins. **J Am Med Assoc,** v. 160, n. 4, p. 277-82, Jan 28 1956. ISSN 0002-9955 (Print) 0002-9955 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/13278189 >.

MEYER-SCHWESINGER, C. The ubiquitin-proteasome system in kidney physiology and disease. **Nat Rev Nephrol,** v. 15, n. 7, p. 393-411, Jul 2019. ISSN 1759-507X (Electronic) 1759-5061 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31036905 >.

MIKHAIL, A. et al. Renal association clinical practice guideline on Anaemia of Chronic Kidney Disease. **BMC Nephrol,** v. 18, n. 1, p. 345, Nov 30 2017. ISSN 1471-2369 (Electronic) 1471-2369 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29191165 >.

MILLER, C. D.; ROBBIN, M. L.; ALLON, M. Gender differences in outcomes of arteriovenous fistulas in hemodialysis patients. **Kidney Int,** v. 63, n. 1, p. 346-52, Jan 2003. ISSN 0085-2538 (Print)

0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12472802 >.

MODARESI, A.; NAFAR, M.; SAHRAEI, Z. Oxidative stress in chronic kidney disease. **Iran J Kidney Dis,** v. 9, n. 3, p. 165-79, May 2015. ISSN 1735-8604 (Electronic) 1735-8582 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25957419 >.

MOREIRA, P. R. et al. Avaliação da capacidade aeróbia de pacientes em hemodiálise. **Revista Brasileira de Medicina do Esporte,** v. 3, p. 1-5, 1997. ISSN 1517-8692. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1517-86921997000100002&nrm=iso >.

MOREIRA, P. R. B., E. Atualização em fisiologia e fisiopatologia renal: bases fisiopatológicas da miopatia na insuficiência renal crônica. **J Bras Nefrol.,** v. 22, n. 1, p. 34-8, 2000.

MUKAI, H. et al. Lung Dysfunction and Mortality in Patients with Chronic Kidney Disease. **Kidney Blood Press Res,** v. 43, n. 2, p. 522-535, 2018. ISSN 1423-0143 (Electronic) 1420-4096 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29627840 >.

NADRA, I. et al. Effect of particle size on hydroxyapatite crystal-induced tumor necrosis factor alpha secretion by macrophages. **Atherosclerosis,** v. 196, n. 1, p. 98-105, Jan 2008. ISSN 1879-1484 (Electronic) 0021-9150 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/17350022 >.

NAH, R. et al. Relationships between illness representations, physical activity and depression in chronic kidney disease. **J Ren Care,** v. 45, n. 2, p. 74-82, Jun 2019. ISSN 1755-6686 (Electronic) 1755-6678 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30938078 >.

NATIONAL KIDNEY, F. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. **Am J Kidney Dis,** v. 66, n. 5, p. 884-930, Nov 2015. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26498416 >.

Nephrotic Syndrome. **Am Fam Physician,** v. 93, n. 6, p. Online, Mar 15 2016. ISSN 1532-0650 (Electronic) 0002-838X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26977845 >.

NESRALLAH, G. E. et al. Canadian Society of Nephrology 2014 clinical practice guideline for timing the initiation of chronic dialysis. **CMAJ,** v. 186, n. 2, p. 112-7, Feb 4 2014. ISSN 1488-2329 (Electronic) 0820-3946 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24492525 >.

OLLER, G. A. S. A. D. O. et al. Functional independence in patients with chronic kidney disease being treated with haemodialysis1. **Revista Latino-Americana de Enfermagem,** v. 20, p. 1033-1040, 2012. ISSN 0104-1169. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0104-11692012000600004&nrm=iso >.

OREOPOULOS, D. G. et al. A simple and safe technique for continuous ambulatory peritoneal dialysis (CAPD). **Trans Am Soc Artif Intern Organs,** v. 24, p. 484-9, 1978. ISSN 0066-0078 (Print)

0066-0078 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/716044 >.

ORLANDI, P. F. et al. Long-term outcomes of elderly kidney transplant recipients. **J Bras Nefrol,** v. 37, n. 2, p. 212-20, 2015 Apr-Jun 2015. ISSN 2175-8239. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26154642 >.

PADILLA, J. et al. Physical functioning in patients with chronic kidney disease. **J Nephrol,** v. 21, n. 4, p. 550-9, Jul-Aug 2008. ISSN 1121-8428 (Print) 1121-8428 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18651545 >.

PAINTER, P.; ROSHANRAVAN, B. The association of physical activity and physical function with clinical outcomes in adults with chronic kidney disease. **Curr Opin Nephrol Hypertens,** v. 22, n. 6, p. 615-23, Nov 2013. ISSN 1473-6543 (Electronic) 1062-4821 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24100215 >.

PALAMIDAS, A. F. et al. Impact of hemodialysis on dyspnea and lung function in end stage kidney disease patients. **Biomed Res Int,** v. 2014, p. 212751, 2014. ISSN 2314-6141. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24895552 >.

PANIAGUA-SIERRA, J. R.; GALVAN-PLATA, M. E. Chronic kidney disease. **Rev Med Inst Mex Seguro Soc,** v. 55, n. Suppl 2, p. S116-7, 2017. ISSN 2448-5667 (Electronic) 0443-5117 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29697216 >.

PAPAGIANNI, A. et al. Carotid atherosclerosis is associated with inflammation and endothelial cell adhesion molecules in chronic haemodialysis patients. **Nephrol Dial Transplant,** v. 18, n. 1, p. 113-9, Jan 2003. ISSN 0931-0509 (Print) 0931-0509 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/12480968 >.

PARSONS, T. L.; TOFFELMIRE, E. B.; KING-VANVLACK, C. E. Exercise training during hemodialysis improves dialysis efficacy and physical performance. **Arch Phys Med Rehabil,** v. 87, n. 5, p. 680-7, May 2006. ISSN 0003-9993 (Print) 0003-9993 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16635631 >.

PENDSE, S.; SINGH, A. K. Complications of chronic kidney disease: anemia, mineral metabolism, and cardiovascular disease. **Med Clin North Am,** v. 89, n. 3, p. 549-61, May 2005. ISSN 0025-7125 (Print) 0025-7125 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15755467 >.

PEREIRA, É. F.; TEIXEIRA, C. S.; SANTOS, A. D. Qualidade de vida: abordagens, conceitos e avaliação. **Revista Brasileira de Educação Física e Esporte,** v. 26, p. 241-250, 2012. ISSN 1807-5509. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S1807-55092012000200007&nrm=iso >.

Physical Activity Guidelines Advisory Committee report, 2008. . **Nut Rev,** v. 67, n. 2, p. 114-20, Feb 2009. ISSN 1753-4887 (Electronic) 0029-6643 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19178654 >.

PINTO, A. et al. **Impacto da sessão de hemodiálise na força de preensão manual.** J Bras Nefrol. 4**:** 451-457 p. 2015.

POLASCHEGG, H. D. Machines for hemodialysis. **Contrib Nephrol,** v. 149, p. 18-26, 2005. ISSN 0302-5144 (Print) 0302-5144 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15876824 >.

POPOVICH, R. P. et al. Continuous ambulatory peritoneal dialysis. **Ann Intern Med,** v. 88, n. 4, p. 449-56, Apr 1978. ISSN 0003-4819 (Print) 0003-4819 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/637423 >.

PU, J. et al. Efficacy and safety of intradialytic exercise in haemodialysis patients: a systematic review and meta-analysis. **BMJ Open,** v. 9, n. 1, p. e020633, Jan 21 2019. ISSN 2044-6055 (Electronic) 2044-6055 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30670499 >.

QIU, Z. et al. Physical Exercise and Patients with Chronic Renal Failure: A Meta-Analysis. **Biomed Res Int,** v. 2017, p. 7191826, 2017. ISSN 2314-6141 (Electronic). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28316986 >.

RAISSUNI, Z.; ROUL, G. Comparison of the long-term reproducibility of the walk test and of exercise peak oxygen consumption in patients with preserved exercise capacity. **Acta Cardiol,** v. 73, n. 2, p. 155-162, Apr 2018. ISSN 0001-5385 (Print) 0001-5385 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28745141 >.

RICHARDSON, D.; BARTLETT, C.; WILL, E. J. Optimizing erythropoietin therapy in hemodialysis patients. **Am J Kidney Dis,** v. 38, n. 1, p. 109-17, Jul 2001. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11431190 >.

RIELLA, M. **Princípios de Nefrologia e Distúrbios Hidroeletrolíticos**. 4a edição. Rio de Janeiro: 2003.

ROBERTS, M. A. et al. Secular trends in cardiovascular mortality rates of patients receiving dialysis compared with the general population. **Am J Kidney Dis,** v. 58, n. 1, p. 64-72, Jul 2011. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/21458896 >.

ROMAGNANI, P. et al. Chronic kidney disease. **Nat Rev Dis Primers,** v. 3, p. 17088, Nov 2017. ISSN 2056-676X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29168475 >.

ROSHANRAVAN, B. et al. Association between physical performance and all-cause mortality in CKD. **J Am Soc Nephrol,** v. 24, n. 5, p. 822-30, Apr 2013. ISSN 1533-3450 (Electronic) 1046-6673 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23599380 >.

SALMAN, I. M. Cardiovascular Autonomic Dysfunction in Chronic Kidney Disease: a Comprehensive Review. **Curr Hypertens Rep,** v. 17, n. 8, p. 59, Aug 2015. ISSN 1534-3111 (Electronic)

1522-6417 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26071764 >.

SAMPAIO, E. A., LUGON, J.R., BARRETO, F.C. Fisiopatologia do Hiperparatireoidismo Secundário. **Braz. J. Nephrol.,** v. 30, n. (1 Suppl 1), p. 6-10, 2008.

SARNAK, M. J.; LEVEY, A. S. Cardiovascular disease and chronic renal disease: a new paradigm. **Am J Kidney Dis,** v. 35, n. 4 Suppl 1, p. S117-31, Apr 2000. ISSN 0272-6386 (Print) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/10766010 >.

SARNAK, M. J. et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. **Hypertension,** v. 42, n. 5, p. 1050-65, Nov 2003. ISSN 1524-4563 (Electronic) 0194-911X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/14604997 >.

SBN. **Sociedade Brasileira de Nefrologia** 2020.

SCHARDONG, J. et al. Effects of Intradialytic Neuromuscular Electrical Stimulation on Strength and Muscle Architecture in Patients With Chronic Kidney Failure: Randomized Clinical Trial. **Artif Organs,** v. 41, n. 11, p. 1049-1058, Nov 2017. ISSN 1525-1594 (Electronic) 0160-564X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28621488 >.

SCHARDONG, J.; STEIN, C.; DELLA MEA PLENTZ, R. Neuromuscular Electrical Stimulation in Chronic Kidney Failure: A Systematic Review and Meta-Analysis. **Arch Phys Med Rehabil**, Dec 23 2019. ISSN 1532-821X (Electronic) 0003-9993 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31877308 >.

SEBILLE, V. et al. Prospective, multicenter, controlled study of quality of life, psychological adjustment process and medical outcomes of patients receiving a preemptive kidney transplant compared to a similar population of recipients after a dialysis period of less than three years--The PreKit-QoL study protocol. **BMC Nephrol,** v. 17, p. 11, Jan 19 2016. ISSN 1471-2369 (Electronic) 1471-2369 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26785745 >.

SESSO, R. C. et al. Brazilian Chronic Dialysis Survey 2016. **J Bras Nefrol,** v. 39, n. 3, p. 261-266, Jul-Sep 2017. ISSN 2175-8239 (Electronic) 0101-2800 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29044335 >.

SESSO, R. C. et al. Brazilian Chronic Dialysis Survey 2016. **J Bras Nefrol,** v. 39, n. 3, p. 261-266, 2017 Jul-Sep 2017. ISSN 2175-8239. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29044335 >.

SHAH, A. J. et al. Muscle in chronic uremia--a histochemical and morphometric study of human quadriceps muscle biopsies. **Clin Neuropathol,** v. 2, n. 2, p. 83-9, 1983. ISSN 0722-5091 (Print) 0722-5091 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/6851301 >.

SHI, Y. et al. Six-minute walk test predicts all-cause mortality and technique failure in ambulatory peritoneal dialysis patients. **Nephrology (Carlton),** v. 22, n. 2, p. 118-124, Feb 2017. ISSN 1440-1797 (Electronic) 1320-5358 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26773829 >.

SHIMOKAWA, H. 2014 Williams Harvey Lecture: importance of coronary vasomotion abnormalities-from bench to bedside. **Eur Heart J,** v. 35, n. 45, p. 3180-93, Dec 1 2014. ISSN 1522-9645 (Electronic) 0195-668X (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25354517 >.

SHLIPAK, M. G.; MATTES, M. D.; PERALTA, C. A. Update on cystatin C: incorporation into clinical practice. **Am J Kidney Dis,** v. 62, n. 3, p. 595-603, Sep 2013. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/23701892 >.

SIDAWY, A. N. et al. The Society for Vascular Surgery: clinical practice guidelines for the surgical placement and maintenance of arteriovenous hemodialysis access. **J Vasc Surg,** v. 48, n. 5 Suppl, p. 2S-25S, Nov 2008. ISSN 1097-6809 (Electronic) 0741-5214 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/19000589 >.

SILVERBERG, D. S. et al. Intravenous iron supplementation for the treatment of the anemia of moderate to severe chronic renal failure patients not receiving dialysis. **Am J Kidney Dis,** v. 27, n. 2, p. 234-8, Feb 1996. ISSN 0272-6386 (Print) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/8659499 >.

SOUWEINE, J. S. et al. Physical inactivity and protein energy wasting play independent roles in muscle weakness in maintenance haemodialysis patients. **PLoS One,** v. 13, n. 8, p. e0200061, 2018. ISSN 1932-6203 (Electronic) 1932-6203 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30067754 >.

STASIAK, C. E. et al. Prevalence of anxiety and depression and its comorbidities in patients with chronic kidney disease on hemodialysis and peritoneal dialysis. **J Bras Nefrol,** v. 36, n. 3, p. 325-31, 2014 Jul-Sep 2014. ISSN 2175-8239. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/25317615 >.

STENVINKEL, P. Inflammatory and atherosclerotic interactions in the depleted uremic patient. **Blood Purif,** v. 19, n. 1, p. 53-61, 2001. ISSN 0253-5068 (Print) 0253-5068 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11114578 >.

_____. Inflammation in end-stage renal disease: the hidden enemy. **Nephrology (Carlton),** v. 11, n. 1, p. 36-41, Feb 2006. ISSN 1320-5358 (Print) 1320-5358 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16509930 >.

STENVINKEL, P. et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. **Kidney Int,** v. 55, n. 5, p. 1899-911, May 1999. ISSN 0085-2538 (Print) 0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/10231453 >.

SUMIDA, K.; KOVESDY, C. P. Disease Trajectories Before ESRD: Implications for Clinical Management. **Semin Nephrol,** v. 37, n. 2, p. 132-143, Mar 2017. ISSN 1558-4488 (Electronic) 0270-9295 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28410647 >.

TANG, T. T. et al. Initiation of maintenance hemodialysis through central venous catheters: study of patients' perceptions based on a structured questionnaire. **BMC Nephrol,** v. 20, n. 1, p. 270, Jul 17 2019. ISSN 1471-2369 (Electronic) 1471-2369 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31315677 >.

TARASUIK, A.; HEIMER, D.; BARK, H. Effect of chronic renal failure on skeletal and diaphragmatic muscle contraction. **Am Rev Respir Dis,** v. 146, n. 6, p. 1383-8, Dec 1992. ISSN 0003-0805. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/1456552 >.

TAVANA, S.; MIRZAEI, S. The Effect of Renal Transplantation on Respiratory Muscle Strength in Patients with End Stage Renal Disease. **Tanaffos,** v. 15, n. 2, p. 83-88, 2016. ISSN 1735-0344 (Print) 1735-0344 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/27904539 >.

TESSITORE, N. et al. The role of iron status markers in predicting response to intravenous iron in haemodialysis patients on maintenance erythropoietin. **Nephrol Dial Transplant,** v. 16, n. 7, p. 1416-23, Jul 2001. ISSN 0931-0509 (Print) 0931-0509 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/11427634 >.

THOMAS, R.; KANSO, A.; SEDOR, J. R. Chronic kidney disease and its complications. **Prim Care,** v. 35, n. 2, p. 329-44, vii, Jun 2008. ISSN 0095-4543 (Print) 0095-4543 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/18486718 >.

THOMÉ, F. S. et al. Brazilian chronic dialysis survey 2017. **Brazilian Journal of Nephrology,** v. 41, p. 208-214, 2019. ISSN 0101-2800. Disponível em: < http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0101-28002019000200208&nrm=iso >.

TIRAPANI, L. D. S.; FERNANDES, N. A narrative review of the impacts of income, education, and ethnicity on arterial hypertension, diabetes mellitus, and chronic kidney disease in the world. **Saudi J Kidney Dis Transpl,** v. 30, n. 5, p. 1084-1096, Sep-Oct 2019. ISSN 1319-2442 (Print) 1319-2442 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31696847 >.

TOGAWA, A.; YAMAMOTO, T.; HISHIDA, A. [Nephrotic syndrome: pathophysiology, classification and diagnostic criteria]. **Nihon Rinsho,** v. 62, n. 10, p. 1777-83, Oct 2004. ISSN 0047-1852 (Print) 0047-1852 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15500118 >.

VAN ADRICHEM, E. J. et al. Physical Activity, Sedentary Time, and Associated Factors in Recipients of Solid-Organ Transplantation. **Phys Ther,** v. 98, n. 8, p. 646-657, Aug 1 2018. ISSN 1538-6724 (Electronic) 0031-9023 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29757444 >.

VAN DEN HAM, E. C. et al. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. **Am J Transplant,** v. 5, n. 8, p. 1957-65, Aug 2005. ISSN 1600-6135 (Print) 1600-6135 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/15996245 >.

VAN LOON, I. N. et al. Quality of life as indicator of poor outcome in hemodialysis: relation with mortality in different age groups. **BMC Nephrol,** v. 18, n. 1, p. 217, Jul 2017. ISSN 1471-2369. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28679361 >.

VANDEN WYNGAERT, K. et al. The effects of aerobic exercise on eGFR, blood pressure and VO2peak in patients with chronic kidney disease stages 3-4: A systematic review and meta-analysis. **PLoS One,** v. 13, n. 9, p. e0203662, 2018. ISSN 1932-6203.

VANHOLDER, R. et al. Clinical management of the uraemic syndrome in chronic kidney disease. **Lancet Diabetes Endocrinol,** v. 4, n. 4, p. 360-73, Apr 2016. ISSN 2213-8595 (Electronic) 2213-8587 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26948372 >.

VASCULAR ACCESS WORK, G. Clinical practice guidelines for vascular access. **Am J Kidney Dis,** v. 48 Suppl 1, p. S248-73, Jul 2006. ISSN 1523-6838 (Electronic) 0272-6386 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16813991 >.

VISWANATH, N. et al. Functional Status in Hemodialysis - A Comparative Study with FIM, ADLQ and 7D5L Instruments. **Indian J Nephrol,** v. 29, n. 3, p. 172-178, May-Jun 2019. ISSN 0971-4065 (Print) 0971-4065 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/31142963 >.

WALLACE, M. A. Anatomy and physiology of the kidney. **AORN J,** v. 68, n. 5, p. 800, 803-16, 819-20; quiz 821-4, Nov 1998. ISSN 0001-2092 (Print) 0001-2092 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9829131 >.

WANG, A. Y. et al. Muscle strength, mobility, quality of life and falls in patients on maintenance haemodialysis: A prospective study. **Nephrology (Carlton),** v. 22, n. 3, p. 220-227, Mar 2017. ISSN 1440-1797 (Electronic) 1320-5358 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26890468 >.

WATANABE, F. T. et al. Six-minute walk test in children and adolescents with renal diseases: tolerance, reproducibility and comparison with healthy subjects. **Clinics (Sao Paulo),** v. 71, n. 1, p. 22-7, Jan 2016. ISSN 1980-5322 (Electronic) 1807-5932 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26872080 >.

WHALEY-CONNELL, A.; SOWERS, J. R. Insulin Resistance in Kidney Disease: Is There a Distinct Role Separate from That of Diabetes or Obesity? **Cardiorenal Med,** v. 8, n. 1, p. 41-49, Dec 2017. ISSN 1664-3828. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/29344025 >.

YANG, C. C. et al. Effects of vitamin C infusion and vitamin E-coated membrane on hemodialysis-induced oxidative stress. **Kidney Int,** v. 69, n. 4, p. 706-14, Feb 2006. ISSN 0085-2538 (Print)

0085-2538 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/16395251 >.

ZANINI, S. C. C. et al. Força muscular respiratória e capacidade funcional de pacientes com doença renal crônica em hemodiálise. **Fisioter. Bras,** v. 17, n. 5, p. f: 457-I: 463, 2016/10 2016. Disponível em: < http://portalatlanticaeditora.com.br/index.php/fisioterapiabrasil/article/view/681/1499

http://fi-admin.bvsalud.org/document/view/9tzaw >.

ZHAO, Y.; PEI, X.; ZHAO, W. Timing of Dialysis Initiation and Mortality Risk in Chronic Kidney Disease: A Meta-Analysis. **Ther Apher Dial,** v. 22, n. 6, p. 600-608, Dec 2018. ISSN 1744-9987 (Electronic) 1744-9979 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/30062691 >.

ZHOU, Y. et al. Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3-5. **Nephrol Dial Transplant,** v. 33, n. 2, p. 342-348, Feb 1 2018. ISSN 1460-2385 (Electronic) 0931-0509 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/28340152 >.

ZYGA, S. et al. Assessment of Fatigue in End Stage Renal Disease Patients Undergoing Hemodialysis: Prevalence and Associated Factors. **Med Arch,** v. 69, n. 6, p. 376-80, Dec 2015. ISSN 0350-199X. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/26843728 >.

3. OBJETIVOS

3.1 Objetivo geral

Verificar se a capacidade funcional e a força muscular influenciam na sobrevida de pacientes com doença renal crônica (DRC) em hemodiálise (HD).

3.2 Objetivos específicos

- Definir se a força muscular periférica de membros inferiores interfere no tempo de sobrevida na DRC;
- Descrever a associação da capacidade funcional e da força muscular (membro superior, força respiratória e de membros inferiores)
- Avaliar a qualidade de vida e verificar a associação com os desfechos avaliados.
- Identificar o nível de dependência funcional dos pacientes.

ARTIGO 1

Influence of functional capacity and muscle strength on survival of patients with chronic kidney disease in hemodialysis: a cohort study

(Artigo escrito seguindo as normas da revista **Clinical Rehabilitation**, fator de impacto 2.738, Qualis A1)

INFLUENCE OF FUNCTIONAL CAPACITY AND MUSCLE STRENGTH ON SURVIVAL OF PATIENTS WITH CHRONIC KIDNEY DISEASE IN HEMODIALYSIS: A COHORT STUDY

Graziela Valle Nicolodi[1,2] graziela.nicolodi@yahoo.com.br

Alana Martins da Veiga[2] alaanamartins@hotmail.com

Rayssa Souto Martins[2] cissa-m@hotmail.com

Maiara Toledo[2] maiiara.toledo@hotmail.com

Natalia Adriane Lanius[2] natalia_lanius@hotmail.com

Rodrigo Della Méa Plentz[1] roplentz@yahoo.com.br

[1] Federal University of Health Sciences of Porto Alegre (UFCSPA) – Porto Alegre – RS/ Brazil - Departament of physiotherapy

[2] University of Cruz Alta (UNICRUZ) – Cruz Alta - RS / Brazil - Departament of physiotherapy

Correspondence to: Rodrigo Della Méa Plentz, Sarmento Leite, 245, CEP:90050-170, Porto Alegre, RS, Brazil, Tel: +55 51 3303-8833 / Fax: +55 51 3303 8810

E-mail: roplentz@yahoo.com or rodrigop@ufcspa.edu.br

INFLUENCE OF FUNCTIONAL CAPACITY AND MUSCLE STRENGTH ON SURVIVAL OF PATIENTS WITH CHRONIC KIDNEY DISEASE IN HEMODIALYSIS: A COHORT STUDY

Abstract

Purpose: verifying the influence of functional capacity and muscle strength on the survival of patients with chronic kidney disease (CKD) undergoing hemodialysis (HD). Design, location and sample: Prospective cohort study with 59 adult patients with CKD on HD at a Renal Therapy Unit in a hospital in south of Brazil followed for two years. **Outcomes**: variables of functional capacity were assessed by the six-minute walk test (6MWT), lower limb strength with sit and stand test (TSL), handgrip strength (HGS) by dynamometry and respiratory muscle strength using manovacuometry, functional independence by the Lawton scale, level of physical activity by the IPAQ short version and quality of life (QOL) by the EQ-5D. **Results:** from the 59 patients followed up in two years, there were 28.8% of deaths. They were related to shorter survival time: Functional Capacity (HR: 9.92 95% CI: 1.31-74.89; p= 0.026), FPM (HR: 3.0 95% CI: 1.17-7.88; p= 0.023) and maximum expiratory pressure (MEP) (HR: 3.8 95% CI: 1.33-10.80; p= 0.012). 76.3% of patients were still classified as independent and 61% sedentary. The QoL obtained a score of 0.798 ± 0.185 and the average of the general health perception was 80.6 ± 10.4. There were significant associations among all physical tests and with quality of life, with the highest ones being MEP vs HGS (r= 0.605; p<0.001), 6MWT vs HGS (r= 0.479; p<0.001), STS vs 6MWT (r= 0.611; p<0.001). Conclusion: functional capacity and muscle strength influence the survival of CKD on HD. In addition, physical tests have a good association strength for the studied patients.

Keywords: Kidney disease; Renal Dialysis; Muscle strength; Survival Analysis.

INFLUENCE OF FUNCTIONAL CAPACITY AND MUSCLE STRENGTH ON SURVIVAL OF PATIENTS WITH CHRONIC KIDNEY DISEASE IN HEMODIALYSIS: A COHORT STUDY

Introduction

Chronic Kidney Disease (CKD) is defined as kidney damage with progressive and irreversible loss of kidney function, which can be at the glomerular, tubular or endocrine level (1, 2). For this, the best indicator of renal function is the glomerular filtration rate (GFR) in which international guidelines define CKD as the person who has a GFR below 60 mL/min/1.73 m^2 or markers of renal damage or both by longer than three months. When GFR reaches values below 15 mL/min/1.73 m^2, it is called the final stage of Kidney Disease, in which in these cases, renal replacement therapy is needed: peritoneal dialysis (PD) or hemodialysis (HD), or even kidney transplantation (3).

The disease has a high prevalence and constitutes a major cost burden for health systems worldwide. It is estimated that about 11 to 13% of the world population have CKD (4). Among the main causes of the disease, Arterial Hypertension and Diabetes (5) stand out, followed by chronic glomerulonephritis and polycystic kidneys (6).

Patients undergoing dialysis have the highest rates of hospitalization and mortality from all chronic conditions and, the variables of functional capacity, may partially explain this situation (7, 8). The decrease in functional capacity in HD patients may be a consequence of uremic myopathy, anemia, cardiovascular abnormalities and other associated comorbidities (9, 10). Another alteration frequently observed in this population is the reduction in muscle mass and strength that is due to physical inactivity and the decline in the glomerular filtration rate and, thus, can lead the individual to a worse prognosis (11, 12).

Studies have shown that performance in tests to assess functional capacity through the six-minute walk test (6MWT) and peripheral muscle strength, more specifically, the Handgrip test can be listed as predictors of mortality in this population (11, 13-15). However, there is still no data to demonstrate the association between these tests and their relationship with the survival time of CKD in HD.

Thus, the aim of the present study was to assess the association between functional capacity, peripheral and respiratory muscle strength and the survival of patients with CKD on HD.

Methods

Study design: this is a prospective cohort study approved by the Research Ethics Committee of the University of Cruz Alta (UNICRUZ), Cruz Alta - RS, Brazil, under number CAAE: 92318218.6.0000.5322.

Participants: this study included CKD patients undergoing HD of both genders, aged over 18 years, selected for convenience and who underwent a regular Hemodialysis program at the Renal Therapy Unit of Hospital São Vicente de Paulo in the municipality of Cruz Alta - RS, from December 2017 to December 2019. Patients with CKD on HD for more than 3 months, weekly dialysis frequency of 3 times / week, adequate urea clearance rate during HD were included. (Kt/v ≥1.2 or URR≥65%) and with complete record of clinical data available in the service's routine database. Patients with: cognitive impairment that prevented the evaluations, as well as inability to understand and sign the free and informed consent form, patients with recent stroke sequel (three months) were excluded; recent acute myocardial infarction (two months), uncontrolled hypertension (SBP> 230 mmHg and DBP> 120 mmHg), HF grade IV according to the New York Heart Association or decompensated and unstable angina.

Study variables

The outcome of this study was survival correlated with the following variables:

- **Functional capacity:** assessed by the 6-minute walk test that was performed following the recommendations of the American Thoracic Society (16). The patient was instructed to walk as far as possible for six minutes in a 30-meter flat hall, the distance covered in meters being recorded. Every minute of the test, the patient was verbally encouraged through standardized phrases. Running or walking at half-trot was not allowed. The patient was instructed to interrupt the test if he presented symptoms such as pain in the lower limbs, tachycardia or any symptom of discomfort.

- **Respiratory muscle strength:** assessed by Manovacuometry (17) where the measurement circuit consisted of a *Murenas* analog manovacuometer with a scale range of 300 cmH_2O coupled to a mouthpiece. Maximum Inspiratory Pressure (MIP) was determined, starting from the residual volume, by deep inspiration against the occluded circuit and Maximum Expiratory Presure (MEP) was obtained, starting from total lung capacity, by forced expiration against the mouthpiece of the device. For the analysis of the results, the absolute values and as a percentage of those predicted by the equations proposed by Neder et al (18) were considered.

- Handgrip strength: performed with a Jamar hydraulic handheld dynamometer. Initially, the device was adjusted for each individual according to the size of the hands, then three measurements were taken with a one-minute recovery period on the arm opposite the participants' fistula, at the end the strength record was established in kilograms/strength (kg / f) and the average of the three measurements was the value of the handgrip strength. The participants should remain in the sitting position and with the arm evaluated with 90 degree elbow flexion, in addition, they were encouraged to perform an isometric muscle contraction for a period of 3 seconds in each assessment (19).

- Lower limb muscle strength: through the sit to stand test (STS) in which the patient remained seated in a chair, with an erect back and feet shoulder width apart and fully supported on the ground. One foot should be slightly forward in relation to the other to help maintain balance. Arms crossed at the level of the wrists and against the chest. At the signal of departure, the subject should get up until standing up, returning to the sitting position. The individual was encouraged to perform the maximum number of repetitions in a time interval of 30 seconds (20).

- Quality of life: through the EuroQol EQ-5D questionnaire (EQ-5D) commonly used as a measure of quality of life in HD patients (21). The questionnaire score is based on five domains: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. In addition, the questionnaire comprises a visual analog scale where the patient must indicate his general health status, where 0 is the worst state and 100 the best state (22).

- Instrumental activities of daily living: through Lawton's scale of instrumental activities of daily living (IADL) that measures IADLs with eight activities. Higher scores on the scale indicate greater independence (23).

- Physical activity level: measured by the international physical activity questionnaire (IPAQ) in its short version, which has 8 questions in which the individual must answer the total time and days spent with moderate and vigorous activities, in addition to the time spent sitting one day of the week and the weekend. The sum of the responses, classify the individual according to their level of physical activity (24).

Were considered as factors of exposure to muscle weakness, being considered as factors of control to exposure: the practice of regular physical activity.

Follow-up

Patients were followed up monthly by the hemodialysis service team and the researchers who collected data on physical tests and mortality. The performance of kidney transplants, as well as transfers to other dialysis units, were updated during the follow-up period of the study and considered as losses. Non-deaths were considered as censored data.

Statistical analysis

Quantitative variables were described as mean and standard deviation or median and interquartile range [p25 - p75], according to their distribution, according to the Kolmogorov-Smirnov normality test; qualitative variables through frequency and percentage. Correlations between quantitative variables were verified by Spearman's Correlation test and between qualitative variables, the Chi-square test was used. Comparisons between quantitative and qualitative variables were assessed by Student's t test or ANOVA with Tukey's test for multiple comparisons. Kaplan-Meier curves were used to obtain the graphs and estimate the overall survival time during the two years of follow-up. The associations of the variables with the survival time were assessed through Cox Regression analysis, uni and multivariate with the respective Hazard Ratios (HR), with a 95% confidence interval. Significant variables in the univariate analysis were included in the multivariate analysis. The statistical significance adopted was 5% and the analyzes were performed using SPSS software version 25.0 (SPSS Inc., IBM Company, Chicago, IL, USA).

Results

Initially, 80 patients were selected, of which, 62 patients met the eligibility criteria. However, 2 underwent kidney transplantation and another was transferred to another kidney unit during the follow-up period. 59 patients remained for the final analysis. The sample was composed mostly of men (55.9%), with a mean age of 58.1 ± 14.5 years, a Body Mass Index (BMI) of 24.9 ± 4.8 Kg/m^2 and a median treatment time of 64.6 [37.9 - 136.3] months.

About the hospitalizations that occurred during the follow-up of the study, 41 patients (71%) were hospitalized at least once. There were 99 hospitalizations in total, which shows an average of 2.4 hospitalizations per patient. The most observed reasons for hospitalizations were for musculoskeletal diseases (27.3%), respiratory diseases (17.2%) and vascular access (12.1%). The other characteristics of the sample are shown in table 1.

Biochemical tests showed levels of creatinine (9.52 ± 3.83 mg/dL), potassium (5.03 ± 0.37 mEq/L) and phosphorus (5.40 ± 1.31 mg/dL) above levels normality and hemoglobin values below normal values (10.32 ± 1.71). The other values are shown in table 1.

In assessing the level of functional independence, most patients were classified as independent (n= 45; 76.3%) and 14 patients (23.7%) were classified with some degree of dependence. As for the level of physical activity, 36 patients (61%) were considered sedentary. Regarding the analysis of quality of life, the average score obtained in the EQ-5D was 0.798 ± 0.185 and the average of the general perception of health of patients was 80.6 ± 10.4 in the VAS.

Regarding the behavior in the physical tests, it is observed that the tests performed, the worst performance was in the 6MWT (345.9 ± 123.7 meters), followed by dynamometry (28 ± 8.7 Kg/f) and MEP (84.6 ± 45.2 cmH_2O). The other results regarding the values obtained in the tests are shown in table 2.

When verifying the correlation between the tests, we found moderate associations between the following evaluations: EQ-5D x Dynamometry (r= 0.432; p= 0.002), STS x 6MWT (r= 0.611; p<0.001), STS x Dynamometry (r= 0.408; p= 0.001), 6MWT x Dynamometry (r= 0.479; p<0.001), MIP x Dynamometry (r= 0.470; p<0.001), MEP x Dynamometry (r = 0.605; p<0.001). The other associations are shown in table 3.

In the analysis of variance (ANOVA), the performance in the 6MWT showed a significant difference between the level of functional independence, that is, functionally independent patients have a better performance in the 6MWT compared with the severe and moderate dependents (p= 0.004).

When analyzing the group classified as active, we observed that they reached significantly higher values in the repetitions of the STS when compared to the sedentary ones (13.5 vs 11.2; p= 0.048), better performance in the distance covered by the 6MWT (417, 3 vs 322.5 p= 0.004), greater inspiratory and expiratory strength (116.3 vs 81.6; p= 0.003 and 109.7 vs 67.1; p<0.001) respectively, in addition to greater strength in dynamometry (32,4 vs 25.5; p= 0.005).

The present study also found a significant linear association between functionality and level of physical activity (p= 0.036).

In the survival analysis, it was observed that for the 6MWT, death occurred approximately 10 times faster in those who walked less than 388.5 meters on the 6MWT (HR: 9.92 95% CI: 1.31-74.89; p= 0.026).The average survival time for patients with distance covered on the 6MWT > 388.5 meters was 23.6 months vs 20.5 months for those who walked

a distance below (Figure 1). Regarding the performance obtained in the dynamometry test, in the studied patients, death occurred 3.03 times faster in those who reached values below the values and reference (HR: 3.03 95% CI: 1.17-7.88; p= 0.023). The average survival time of patients with handgrip strength> of reference values was 22.3 months vs 19.8 for those with values below (Figure 2). The analysis of survival and respiratory muscle strength showed that patients with decreased MEP have a survival time 3.8 times shorter (HR: 3.8 95% CI: 1.33-10.80; p = 0.012). The mean survival time of patients with MEP> 70% predicted was 22.6 months vs 20.2 months for those with values below the predicted (figure 3).

The other results of the survival analysis showed no significant difference for Sex (HR: 0.8 95% CI: 0.32 - 2.15; p = 0.703), MIP (HR: 0.9 95% CI: 0.34-2 , 80 p = 0.983), and STS (HR: 0.95 95% CI: 0.85-1.08; p = 0.492).

In the multivariate analysis, it showed a significant difference for MEP when adjusted by Dynamometry and 6MWT (HR: 3.3 CI 95%: 1.18-9.64; p = 0.023).

Discussion

The main result of this study was the demonstration that functional capacity, handgrip muscle strength and expiratory muscle strength are related to the survival of patients with HD-CKD.

During the follow-up period, there were 17 deaths (28.8%) and the study showed that patients who obtained performance below 388.5 meters on the 6MWT, have a shorter survival time than those with superior performance on the test (HR: 9.92 CI 95%: 1.31 - 74.89; p= 0.026). A previous study by our research group has already shown that the distance covered in the 6MWT is reduced in these patients and interferes with mortality, therefore, the shorter the distance covered in the test, the greater the probability of death in CKD (13). Also, with regard to handgrip strength through dynamometry, this study found that patients with values below the reference values, death occurred 3.03 times faster (HR: 3.0 95% CI: 1.17-7,88; p = 0.023). Hellberg et al (25), through a retrospective study, evaluated 112 patients and concluded that a 50% reduction in handgrip strength, compared to that predicted by sex and age, is associated with an almost 3-fold increase in mortality. Similar results can also be observed in patients who undergo only conservative treatment, demonstrating that the muscular evaluation of upper limbs through dynamometry can be incorporated into clinical practice as a prognostic factor also for CKD under conservative treatment (15).

The analysis of survival and respiratory muscle strength showed that patients with decreased MEP have a survival time 3.8 times shorter (HR: 3.8 95% CI: 1.33-10.80; p = 0.012). Several studies report respiratory muscle weakness in CKD (26-28), however, as far as we know, this is the first study that describes the relationship between respiratory muscle strength and survival time in this population.

From the values obtained in the physical tests, it was observed that the 6MWT, dynamometry and MEP presented values below the predicted, these results corroborate the results of previous studies that demonstrate a decrease in the strength and functional capacity of CKD in HD (7, 10, 13, 29). These results can be explained in part by the muscle abnormalities that these patients have as a result of anemia, malnutrition, low level of physical activity, high serum calcium levels, presence of metabolic acidosis, uremic myopathy, sarcopenia, uremic neuropathy and decreased oxidative capacity muscle fibers (30, 31).

Besides the respiratory muscle weakness, complications such as pleural effusion, pulmonary hypertension, pulmonary parenchyma calcification, respiratory failure may be present leading to one of the main symptoms of CKD, which is dyspnea and further limiting exercise tolerance (32, 33).

In this study, biochemical tests also showed altered values for hemoglobin (10.32 ± 1.71 g / dL), potassium (5.03 ± 0.37 mEq/L) and phosphorus (5.40 ± 1.31 mg/dL). In another study published by our research group, we found that serum phosphorus levels may be associated with low physical-functional performance in this population (26). When assessing the associations between the values obtained in the physical tests, we found significant values of positive associations for practically all physical tests with each other and with the quality of life. These results demonstrate that the worsening of the function of distal skeletal muscles and those related to balance may be signs of uremic sarcopenia (25) in addition, they may cause greater functional impairment for patients both in the early stages of the disease and for those in more advanced stages of the CKD (12, 34).

Muscle weakness and fatigue are frequently reported by patients (35) and, among the mechanisms that can explain these changes, we can mention hormonal imbalance, malnutrition, depletion of ATP and glycogen, inadequate oxygen transport due to anemia, acidosis metabolic and electrolyte disturbance, loss of muscle mass, chronic inflammation and decrease in vitamin D that is associated with poorer performance in muscle function tests (30, 34, 36, 37). Therefore, tests to assess functional capacity and muscle strength are easily applicable and have been shown to be effective for monitoring patients with CKD (38).

In the life quality analysis, the score obtained in the EQ-5D domains as well as the EVA score (0.798 ± 0.185 and 80.6 ± 10.4) showed that patients have a good perception of health. Similar data were found by Sakthong et al (39) who assessed the quality of life through the EQ-5D of patients with CKD and found good scores for the domains and scores on the VAS (0.65 ± 0.23 and 0.65 ± 0.26 respectively). However, there are studies that report worsening quality of life during dialysis treatment (40, 41). It is important to highlight that the way each patient lives and relates is always unique and personal, depending on several factors, ranging from environmental and social conditions, family support to the attendance of health services, and the hemodialysis treatment may have meaning different for each patient (42). In addition, 76.3% of the sample was classified as independente a factor that may have influenced the questionnaire's good score.

The sample consisted of 59 patients, 55.9% men, with a mean age of 58.1 ± 14.5 years. These results are in line with the results demonstrated by the Brazilian Dialysis Survey (6) where of the number of patients in the 309 units of Renal Therapy evaluated, about 57% of the patients were men with a predominant average age of 65% of the sample from 20 to 64 years.

When hospitalizations were analyzed, we observed that 71% of the sample hospitalized at least once in two years, the main cause of hospitalization being musculoskeletal diseases (27.3%), followed by respiratory diseases (17.2%) and vascular access (12.1%). A finding similar to ours was presented by Iwagami et al (43) through a cohort of patients with CKD between stages 3 and 5 who showed that in addition to cardiovascular diseases, hip fracture and pneumonia were among the main causes of hospitalization. In addition, it is important to give due attention to the reasons that lead to the hospitalization of these patients, because in addition to having a higher number of hospitalizations compared to those without CKD, they also have a higher risk of treatment-related complications (44).

However, this study had some limitations, such as the small sample size, the lack of data records in the analyzed files and the short follow-up period for patients.

We concluded, therefore, in this study that functional capacity, handgrip strength and expiratory muscle strength influenced the survival time of patients with CKD on HD. Tests for assessing functional capacity and muscle strength, in addition to being easy to apply and low cost, have a good correlation with each other, which shows the importance of their use in rehabilitation and follow-up protocols for these patients and thus demonstrates their external validity.

Clinical Message

- Functional capacity assessed by the 6MWT, handgrip strength measured through dynamometry and maximum expiratory pressure analyzed by manovacuometira influence the survival time of CKD in HD.

Acknowledgment

We are grateful to all patients who participated in this study. We would also like to thank the team of doctors, nurses and nursing technicians at the Renal Therapy Unit of Hospital São Vicente de Paulo, Cruz Alta / RS - Brazil.

Financing: the authors have no financial interests to declare. This study has no external funding.

Conflict of Interest Statement: the authors declare that there are no potential conflicts of interest in relation to the research, authorship and/or publication of this article.

Table 1. Characteristics of the 59 patients included in the study

Variables	Mean ± DP	N (%)
Gender		
Female		26 (44.1)
Male		33 (55.9)
Deaths		17 (28.8)
City		
Cruz Alta		37 (62.7)
Nearby city		22 (37.3)
Schooling		
Elementary School		28 (47.5)
High school		10 (16.9)
University education		10 (16.9)
Not informed		11 (18.6)
marital status		
Married		33 (55.9)
Single		15 (25.4)
Divorced		4 (6.8)
Others		7 (11.8)
Income		
1 salary		23 (39)
2- 3 salaries		17 (28.8)
Not informed		19 (32.2)
Hospitalized patients		41 (71)
Causes of hospitalization		
Osteomioarticular Diseases		27 (27.3)
Respiratory diseases		17 (17.2)
Vascular Access		12 (12.1)
Cardiovascular diseases		9 (9.1)
Clinical treatment		9 (9.1)
Gastrointestinal diseases		8 (8.1)
Infectious diseases		8 (8.1)
HD complications		8 (8.1)
Not informed		4 (4.0)
Biochemical Tests		
Creatinine (mg/dL)	9.52 ± 3.83	
Albumin (g/dL)	3.71 ± 0.29	
Hemoglobin (g/dL)	10.32 ± 1.71	
Potassium (mEq/L)	5.03 ± 0.37	
Calcium (mg/dL)	9.72 ± 1.29	
Phosphor (mg/dL)	5.40 ± 1.31	
Glucose (mg/dL)	106.68 ± 48.09	

Data as mean ± SD and frequency and percentage (%)

Table 2. Performance of 59 patients on physical tests

Physical Tests	Mean ± SD
6MWT obtained (meters)	345.9 ± 123.7
6MWT predicted (meters)	540.8 ± 97.2
6MWT predicted (%)	64.4 ± 21.2
STS obtained (repetition)	11.9 ± 4
STS predicted (repetition)	12.2 ± 1.5
STS predicted (%)	97.8 ± 30.5
MIP obtained (cmH_2O)	93.2 ± 40.8
MIP predicted (cmH_2O)	100.2 ± 18
MIP predicted (%)	92.9 ± 37.6
MEP obtained (cmH_2O)	84.6 ± 45.2
MEP predicted (cmH_2O)	104.9 ± 19.5
MEP predicted (%)	78.8 ± 36.9
Dynamometry obtained (Kg/f)	28 ± 8.7
Dynamometry predicted (Kg/f)	37 ± 5.8
Dynamometry%predicted (Kg/f)	74.9 ± 17.6

Data in mean ± SD, 6MWT: six-minute walk test, STS: sit and stand test, MIP: maximum inspiratory pressure, MEP: maximum expiratory pressure

Table 3. Associations between physical tests

Variable	r	p value
EQ-5D x 6MWT	0.395	0.005
EQ-5D x PImax	0.372	0.009
EQ-5D x PEmax	0.338	0.01
EQ-5D x Dynamometry	0.432	0.002
STS x 6MWT	0.611	<0.001
STS x MIP	0.269	0.03
STS x MEP	0.272	0.03
STS x Dynamometry	0.408	0.001
6MWT x MIP	0.349	0.007
6MWT x MEP	0.332	0.01
6MWT x Dynamometry	0.479	<0.001
MIP x MEP	0.403	0.002
MIP x Dynamometry	0.470	<0.001
MEP x Dynamometry	0.605	<0.001

Spearman correlation $p \leq 0.05$ 6MWT: six-minute walk test, STS: sit-and-stand test, MIP: maximal inspiratory pressure, MEP: maximal expiratory pressure

Figure 1

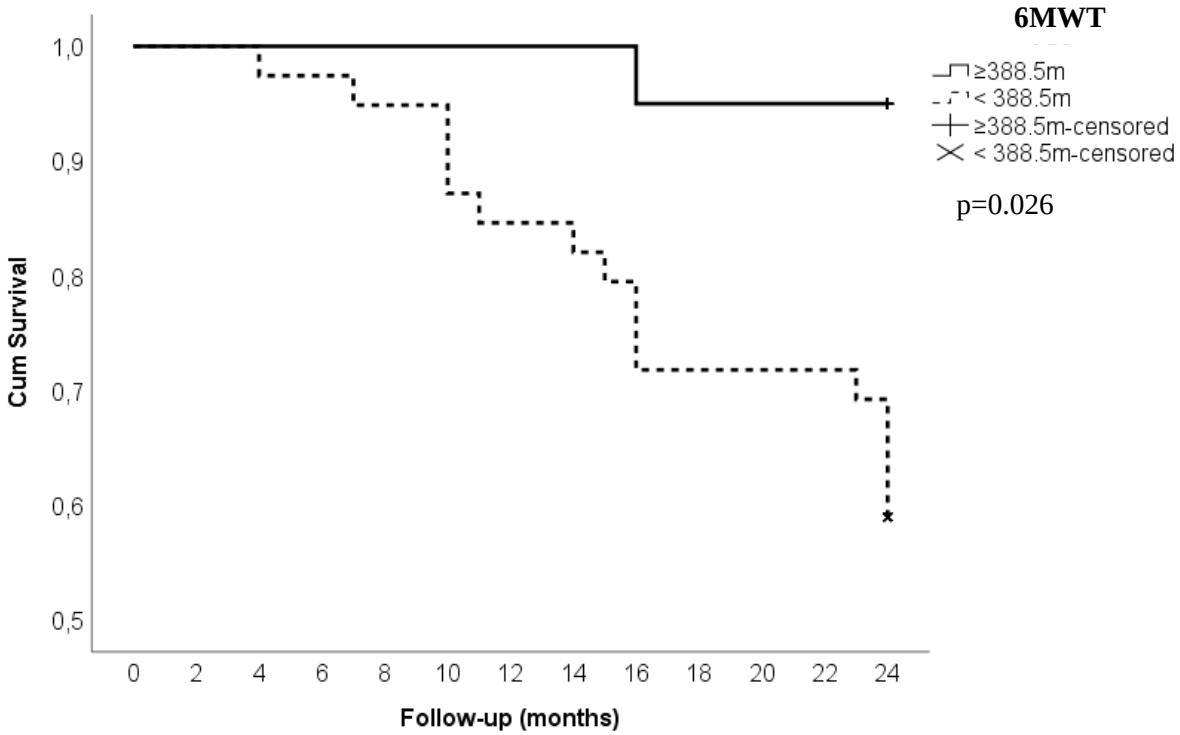


Figure 1. Kaplan-Meier survival curve according to the 6MWT

Figure 2

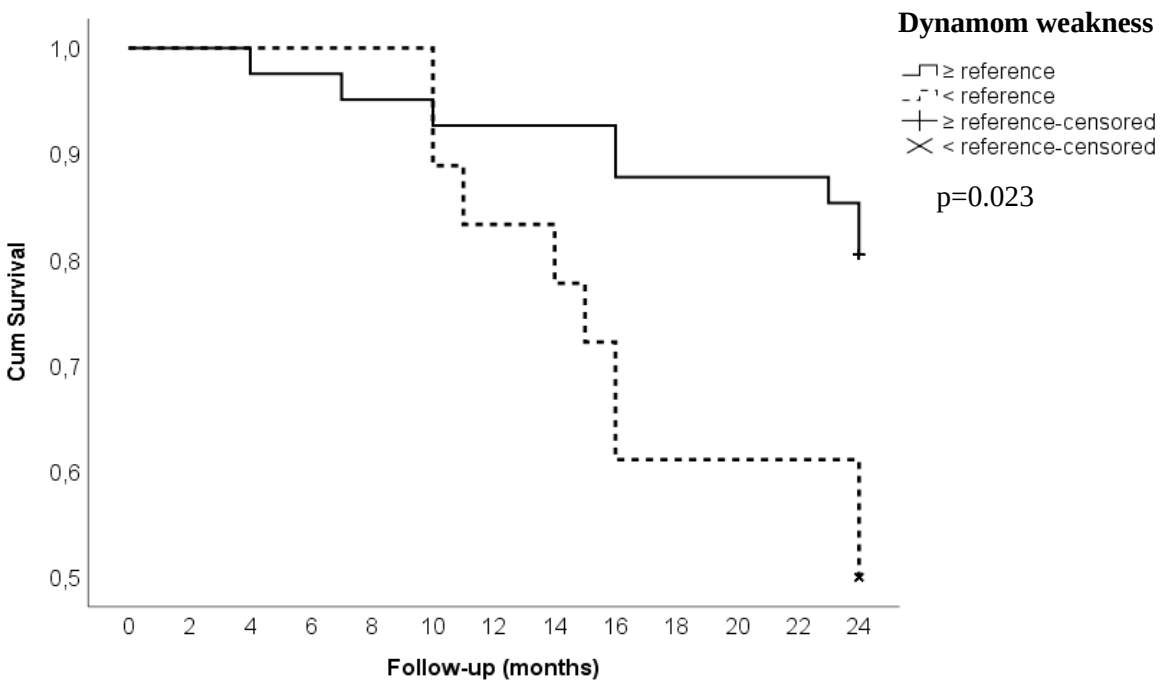


Figure 2. Kaplan-Meier survival curve according to the reference values for dynamometry.

Figure 3

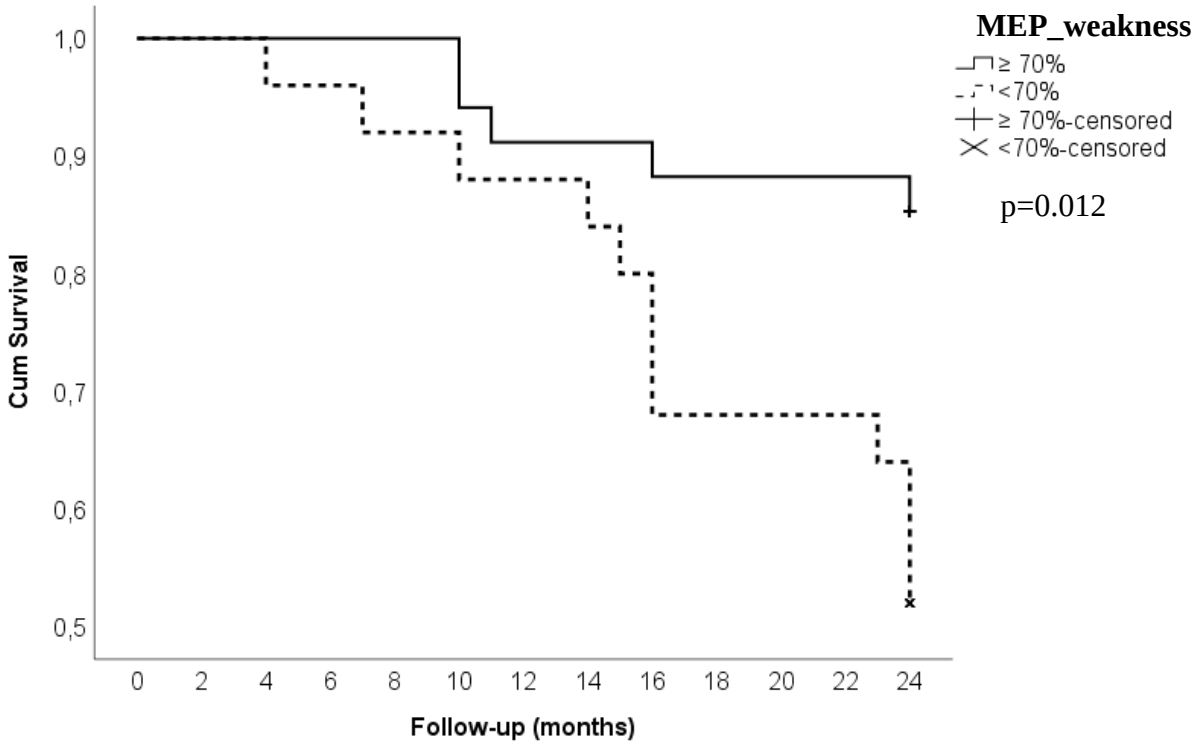


Figure 3. Kaplan-Meier survival curve for MEP values

REFERENCES

1. Junior J. Doença Renal Crônica: Definição, Epidemiologia e Classificação. J Bras Nefrol. 2004;26(3 Suppl 1).

2. Orlandi PF, Cristelli MP, Aldworth CA, Freitas TV, Felipe CR, Silva Junior HT, et al. Long-term outcomes of elderly kidney transplant recipients. J Bras Nefrol. 2015;37(2):212-20.

3. Levey AS, Becker C, Inker LA. Glomerular filtration rate and albuminuria for detection and staging of acute and chronic kidney disease in adults: a systematic review. JAMA. 2015;313(8):837-46.

4. Hill NR, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, et al. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. PLoS One. 2016;11(7):e0158765.

5. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Martins CT. Brazilian Chronic Dialysis Census 2014. J Bras Nefrol. 2016;38(1):54-61.

6. Sesso RC, Lopes AA, Thomé FS, Lugon JR, Martins CT. Brazilian Chronic Dialysis Survey 2016. J Bras Nefrol. 2017;39(3):261-6.

7. Bossola M, Di Stasio E, Antocicco M, Pepe G, Tazza L, Zuccalà G, et al. Functional impairment is associated with an increased risk of mortality in patients on chronic hemodialysis. BMC Nephrol. 2016;17(1):72.

8. Roshanravan B, Robinson-Cohen C, Patel KV, Ayers E, Littman AJ, de Boer IH, et al. Association between physical performance and all-cause mortality in CKD. J Am Soc Nephrol. 2013;24(5):822-30.

9. Kono K, Nishida Y, Moriyama Y, Yabe H, Taoka M, Sato T. Investigation of factors affecting the six-minute walk test results in hemodialysis patients. Ther Apher Dial. 2014;18(6):623-7.

10. Garcia RSA, Lucinda LMF, Ramos FA, Bueno GS, de Oliveira GMR, Bonisson LS, et al. Factors Associated With Functional Capacity in Hemodialysis Patients. Artif Organs. 2017;41(12):1121-6.

11. Morishita S, Tsubaki A, Shirai N. Physical function was related to mortality in patients with chronic kidney disease and dialysis. Hemodial Int. 2017.

12. Zhou Y, Hellberg M, Svensson P, Höglund P, Clyne N. Sarcopenia and relationships between muscle mass, measured glomerular filtration rate and physical function in patients with chronic kidney disease stages 3-5. Nephrol Dial Transplant. 2017.

13. Kohl LeM, Signori LU, Ribeiro RA, Silva AM, Moreira PR, Dipp T, et al. Prognostic value of the six-minute walk test in end-stage renal disease life expectancy: a prospective cohort study. Clinics (Sao Paulo). 2012;67(6):581-6.

14. Bossola M, Di Stasio E, Antocicco M, Pepe G, Tazza L, Zuccala G, et al. Functional impairment is associated with an increased risk of mortality in patients on chronic hemodialysis. BMC Nephrol. 2016;17(1):72.

15. Chang YT, Wu HL, Guo HR, Cheng YY, Tseng CC, Wang MC, et al. Handgrip strength is an independent predictor of renal outcomes in patients with chronic kidney diseases. Nephrol Dial Transplant. 2011;26(11):3588-95.

16. Brooks D, Solway S, Gibbons WJ. ATS statement on six-minute walk test. Am J Respir Crit Care Med. 2003;167(9):1287.

17. Nava S, Ambrosino N, Crotti P, Fracchia C, Rampulla C. Recruitment of some respiratory muscles during three maximal inspiratory manoeuvres. Thorax. 1993;48(7):702-7.

18. Neder JA, Andreoni S, Lerario MC, Nery LE. Reference values for lung function tests. II. Maximal respiratory pressures and voluntary ventilation. Braz J Med Biol Res. 1999;32(6):719-27.

19. CAPORRINO FA. Estudo populacional da força de preensão palmar com dinamômetro Jamar. Rev Bras Ortop [Internet]. 1998; 33(2):[150-4. pp.].

20. Jones CJ, Rikli RE, Beam WC. A 30-s chair-stand test as a measure of lower body strength in community-residing older adults. Res Q Exerc Sport. 1999;70(2):113-9.

21. Liem YS, Bosch JL, Hunink MG. Preference-based quality of life of patients on renal replacement therapy: a systematic review and meta-analysis. Value Health. 2008;11(4):733-41.

22. Viegas Andrade M, Noronha K, Kind P, Maia AC, Miranda de Menezes R, De Barros Reis C, et al. Societal Preferences for EQ-5D Health States from a Brazilian Population Survey. Value Health Reg Issues. 2013;2(3):405-12.

23. Lawton MP, Brody EM. Assessment of older people: self-maintaining and instrumental activities of daily living. Gerontologist. 1969;9(3):179-86.

24. Matsudo S, Araújo T, Marsudo V, Andrade D, Andrade E, Braggion G. Questinário internacional de atividade f1sica (IPAQ): estudo de validade e reprodutibilidade no Brasil. Rev bras ativ fís saúde. 2001:05-18.

25. Hellberg M, Wiberg EM, Simonsen O, Höglund P, Clyne N. Small distal muscles and balance predict survival in end-stage renal disease. Nephron Clin Pract. 2014;126(3):116-23.

26. Dipp T, SIlva A, Signori L, Strimban T, Nicolodi G, Sbruzzi G, et al. Força Muscular Respiratória e Capacidade Funcional na Insuficiência Renal Terminal. Rev Bras Med Esporte2010.

27. Tavana S, Hashemian SM, Jahromi FK. Effect of Dialysis on Maximum Inspiratory and Expiratory Pressures in End Stage Renal Disease Patients. Tanaffos. 2015;14(2):128-33.

28. Tavana S, Mirzaei S. The Effect of Renal Transplantation on Respiratory Muscle Strength in Patients with End Stage Renal Disease. Tanaffos. 2016;15(2):83-8.

29. Pinto A, Ramos C, Meireles M, Kamimura M, Cuppari L. Impacto da sessão de hemodiálise na força de preensão manual. J Bras Nefrol [Internet]. 2015; 4(37):[451-7 pp.].

30. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr. 2004;80(2):299-307.

31. Kim JK, Choi SR, Choi MJ, Kim SG, Lee YK, Noh JW, et al. Prevalence of and factors associated with sarcopenia in elderly patients with end-stage renal disease. Clin Nutr. 2014;33(1):64-8.

32. Karacan O, Tutal E, Colak T, Sezer S, Eyuboglu FO, Haberal M. Pulmonary function in renal transplant recipients and end-stage renal disease patients undergoing maintenance dialysis. Transplant Proc. 2006;38(2):396-400.

33. Kovelis D, Pitta F, Probst VS, Peres CP, Delfino VD, Mocelin AJ, et al. Pulmonary function and respiratory muscle strength in chronic renal failure patients on hemodialysis. J Bras Pneumol. 2008;34(11):907-12.

34. Souza VA, Oliveira D, Barbosa SR, Corrêa JODA, Colugnati FAB, Mansur HN, et al. Sarcopenia in patients with chronic kidney disease not yet on dialysis: Analysis of the prevalence and associated factors. PLoS One. 2017;12(4):e0176230.

35. Zyga S, Alikari V, Sachlas A, Fradelos EC, Stathoulis J, Panoutsopoulos G, et al. Assessment of Fatigue in End Stage Renal Disease Patients Undergoing Hemodialysis: Prevalence and Associated Factors. Med Arch. 2015;69(6):376-80.

36. Molina P, Carrero JJ, Bover J, Chauveau P, Mazzaferro S, Torres PU, et al. Vitamin D, a modulator of musculoskeletal health in chronic kidney disease. J Cachexia Sarcopenia Muscle. 2017;8(5):686-701.

37. Pereira RA, Cordeiro AC, Avesani CM, Carrero JJ, Lindholm B, Amparo FC, et al. Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality. Nephrol Dial Transplant. 2015;30(10):1718-25.

38. Moorthi RN, Avin KG. Clinical relevance of sarcopenia in chronic kidney disease. Curr Opin Nephrol Hypertens. 2017;26(3):219-28.

39. Sakthong P, Kasemsup V. Health utility measured with EQ-5D in Thai patients undergoing peritoneal dialysis. Value Health. 2012;15(1 Suppl):S79-84.

40. Babloyan SA. [Comparative assessment of the quality of life of kidney transplant recipients and hemodialysis patients]. Urologiia. 2018(3):39-43.

41. Wyld MLR, Morton RL, Clayton P, Wong MG, Jardine M, Polkinghorne K, et al. The impact of progressive chronic kidney disease on health-related quality-of-life: a 12-year community cohort study. Qual Life Res. 2019;28(8):2081-90.

42. Higa KK, M. T.; Soares, D. M.; Morais, M. C.; Polins, B. R.G. Quality of life of patients with chronic renal insufficiency undergoing dyalisis treatment. Acta Paul Enferm. 2008;21:203-06.

43. Iwagami M, Caplin B, Smeeth L, Tomlinson LA, Nitsch D. Chronic kidney disease and cause-specific hospitalisation: a matched cohort study using primary and secondary care patient data. Br J Gen Pract. 2018;68(673):e512-e23.

44. Nath JD, Kashem A. Etiology and frequency of hospital admissions in maintenance hemodialysis patients in chronic kidney disease. Saudi J Kidney Dis Transpl. 2019;30(2):508-12.

ARTIGO 2

Effects of aerobic exercise in patients with pre-dialysis chronic kidney disease: a systematic review of randomized controlled trials

(Artigo escrito segundo as normas da revista **Disability and Rehabilitation**, fator de impacto: 2.054, Qualis A2)

Effects of aerobic exercise in patients with pre-dialysis chronic kidney disease: a systematic review of randomized controlled trials

Graziela Valle Nicolodi[a,b], Cinara Stein[a], Natiele Camponogara Righi[a] e Rodrigo Della Méa Plentz[a]

[a] Federal University of Health Sciences of Porto Alegre (UFCSPA) – Porto Alegre – RS/ Brazil

[b] University of Cruz Alta (UNICRUZ) – Cruz Alta – RS/ Brazil

* Correspondence to: Rodrigo Della Méa Plentz, Sarmento Leite, 245, CEP:90050-170, Porto Alegre, RS, Brazil, Tel: +55 51 3303-8833 / Fax: +55 51 3303 8810

E-mail: roplentz@yahoo.com or rodrigop@ufcspa.edu.br

Effects of aerobic exercise in patients with pre-dialysis chronic kidney disease: a systematic review of randomized controlled trials

Abstract

Purpose: reviewing systematically the randomized controlled trials (RCTs) that evaluated aerobic exercise alone versus usual care in exercise tolerance, functional capacity and quality of life (QOL) in patients with pre-dialysis CKD. **Methods:** searches in the MEDLINE, Cochrane CENTRAL, EMBASE, PEDro and LILACS databases until November 2019. Included RCTs that evaluated the effects of aerobic exercise on peak VO_2, functional capacity, lower limb muscle strength and QoL. The random effect meta-analysis model was used and reported as mean difference (MD) and 95% confidence interval (CI), risk of bias through RoB2.0 and the quality of evidence by GRADE. **Results:** 11 RCTs, with 365 patients. Aerobic exercise increased 2.07 ml/kg/min (95% CI = 1.16 to 2.98; I^2= 24%, QoE moderate) at peak VO_2; 77.78m (95% CI= 33.27 to 122.30; I^2= 44.5%, QoE moderate) in the 6MWT and 7.65 repetitions (95% CI= 5.73 to 9.58; I^2= 0 %; QoE moderate) in STS-30 ”versus usual care. In QOL, studies reported improvements in the questionnaire scores. Conclusion: aerobic exercise increases VO_2 peak, functional capacity and lower limb muscle strength in patients with pre-dialysis CKD. Effects on QOL appear to be beneficial.

Keywords: kidney disease, exercise, sarcopenia, quality of life.

Implications for rehabilitation:

- Aerobic exercise should be encouraged in the rehabilitation of patients at any stage of CKD.
- Isolated and chronically, aerobic exercise promotes improved exercise tolerance,

functional capacity and muscle strength of lower limbs.

- It seems to be beneficial for quality of life, but studies with more homogeneous methodologies should be carried out.

Introduction

Chronic Kidney Disease (CKD) is defined as an abnormality of the structure or function of the kidneys, present for a period longer than three months [1]. The disease is classified into five stages according to the Glomerular Filtration Rate (GFR), and stage five is called the end stage of renal disease where a form of renal replacement therapy is needed [2]. It is estimated that there are more than 850 million people with CKD worldwide, exceeding the number of people with Diabetes, Cancer or HIV, and this shows its seriousness as a public health problem [3].

Even in the early stages of the disease, in which renal replacement therapy is not yet necessary, physical inactivity is a common condition observed in patients, which is associated with low functional and cardiopulmonary capacity [4] and a worse prognosis and independent factor of morbidity and mortality in this population [5]. The loss of muscle mass in patients who have not yet started dialysis is already present and varies between 5 and 9% [6] and is associated with the presence of some inflammatory markers such as interleukin-6 (IL-6), protein C- reactive (CRP) and tumor necrosis factor (TNF), which highlights the importance of early identification of sarcopenia and assessment of modifiable risk factors [7]. For this reason, physical exercise is encouraged by current guidelines at all stages of the disease [8, 9].

One of the exercise modalities used is aerobic exercise, which generally covers exercise durations ranging from a few minutes to several hours at varying intensities, using large muscle groups and repetitive exercises such as running, cycling, swimming and walking [10]. Positive effects of aerobic exercise on estimated GFR, exercise tolerance, cardiorespiratory function and

quality of life have been shown by two recent systematic reviews [11, 12]. Vanden et al. [12]., Observed a small beneficial effect of aerobic training on the estimated GFR and exercise tolerance. However, when assessing the effect on exercise tolerance, the authors involved modalities of resistance exercise associated with aerobic training. Still, Pei et al. [11] observed an increase in cardiorespiratory function and an improvement in the quality of life of patients with pre-dialysis and dialysis CKD.

In summary, none of the studies evaluated the isolated effect of aerobic exercise in pre-dialysis patients (phase 2-4). Thus, this study aims to systematically review randomized clinical trials (RCT) that evaluated aerobic physical exercise alone, in comparison with usual care in exercise tolerance, functional capacity and quality of life of patients with CKD in the pre-dialysis stages (phase 2-4), to verify its effectiveness and differences according to the characteristics of the protocols through meta-analysis.

Methods

Guidelines and protocol registration

The present systematic review and meta-analysis was conducted following the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [13]. The systematic review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; identification number, XXXXXX).

Eligibility criteria

Randomized clinical trials (RCTs) that assessed the effects of aerobic exercise alone of CKF patients (stages 2 to 4). We excluded studies performed with children or animals, trials in which the treatment time was less than one month, study protocols, and studies not published

in peer-reviewed journals (i.e., conference abstracts, commentaries, and reviews). We did not apply any language restrictions.

The following primary outcomes were considered in the evaluation of the studies: VO_2 peak. The secondary endpoints were functional capacity, lower limb muscle strength and quality of life (QoL).

Search strategy

We searched MEDLINE, Cochrane CENTRAL, EMBASE, PEDro, and LILACS databases from inception to November 2019 using a preplanned, systematic, comprehensive, reproducible search strategy (Supplementary table 1). Additionally, the reference lists of the retrieved articles were hand searched to detect other potentially eligible studies.

Study selection

Eligibility assessment was performed in a standardized manner. Two independent reviewers (GN and NR) screened titles and abstracts, and full-text articles separately and independently. Disagreements between the two reviewers were resolved by consensus or by involving a third reviewer (CS) for arbitration.

Data extraction and Quality Assessment

A specific form was developed for data extraction. The following data were extracted independently by two reviewers (GN and NR): author details, year of publication, country, study design, number and characteristics of participants, follow-up, description of the intervention and control group, results of evaluated outcomes.

Regarding methodological quality, again, two reviewers (GN and NR) independently assessed the risk of bias of the included studies. The tool of Cochrane Group RoB 2.0 for RCTs was used [14]. To disagreements a third reviewer (CS) was requested. The overall quality of evidence was assessed using the GRADE system [15, 16].

Data synthesis and analysis

The data were combined using the random-efect meta-analysis model, with DerSimonian-Laird estimator as variance estimator. We estimated the treatment efect using the mean diference (MD) as summary measure for continuous outcomes. Data were presented with 95% confdence intervals (CI). All analyzes were performed using software R, version 3.3.2, meta packages version 4.8-4. Statistical heterogeneity was assessed in each meta analysis using the statistics I^2. Heterogeneity was considered substantial if the I^2 was greater than 50%. Heterogeneity was explored through subgroup analysis. We assessed publication bias using funnel plot and the Egger test.

Results

Description of the studies

Initially, 3,267 studies were found, of which 11 were included [17], [18], [19], [20], [21], [22], [23], [24], [25], [26] (figure 1- flow chart). The sample consisted of 365 adult individuals with CKD in stages 2 to 4 (66% men), with a mean age of 57.41 ± 12.86 years, a mean BMI of 31.73 ± 5.86 kg/m^2 and a mean GFR 38.89 ± 13.7 mL/min. In all studies included, the AEG consisted of isolated aerobic exercise, table 1 presents in detail the characteristics of the interventions performed in the studies. VO_2 peak was assessed in all studies using the cardiopulmonary test. Functional capacity was measured in three studies [17-19], using the six-minute walk test (6MWT), as well as the strength of the lower limbs [17-19] by the sit and stand test in 30 seconds (STS-30 ”). Quality of life was assessed in five studies using SF-36 [17, 20, 24], EQ-5D [24], KDQoL-SF [26] and using a numerical value scale between 0 and 10 [25]. The follow-up of interventions ranged from 12 to 52 weeks between studies, with an average of 8.7% of losses.

Quantitative synthesis/Meta-analyses

VO_2 peak

The eleven included studies evaluated VO_2 peak (n= AEG: 204 / CG: 160). The meta-analysis showed that aerobic exercise promoted an increase of 2.46 ml/kg /min (95% CI= 1.20 to 3.72; p <0.01; I^2= 65%; moderate quality of evidence) compared to CG (figure 2a). A sensitivity analysis was performed, removing the study by Van Craenenbroeck [26] because it is a study performed with high training intensity 90% of the Maximum Heart Rate (HR max). The result after the sensitivity analysis, showed an increase of 2.07 ml/kg/min (95% CI= 1.16 to 2.98; p <0.0001; I^2= 24%) in the AEG, figure 2b. In the subgroup analysis (> 3 months and <3 months of training) there was no difference between them (p= 0.885), however the subgroup with time over 3 months showed better effects (DM= 2.38 ml/kg/min; 95% CI =1.23 to 3.52; I^2= 34%) compared to the group below 3 months of training (DM= 2.62 ml/kg/min; 95% CI= -0.46 to 5,70; I^2= 84%) figure 2c. No publication bias was detected (p= 0.11) (Supplementary figure 1).

Functional capacity

Functional capacity was assessed in three studies [17-19] (n = AEG: 63 / CG: 40). There was an increase of 77.78m (95% CI= 33.27 to 122.30; p<0.01; I^2= 44.5%) in the distance covered in the 6MWT in the AEG compared to the CG (figure 3a).

Lower limb muscle strength

Three studies [17-19] measured the muscular strength of the lower limbs (n= AEG: 63 / CG: 40). The AEG obtained an increase of 7.65 repetitions (95% CI= 5.73 to 9.58; p <0.01; I^2 = 0%) compared to the CG (figure 3b).

Qualitative synthesis

Quality of life

Five studies (n= 180 patients) evaluated the effect of aerobic exercise on the quality of life of patients with CKD. Aoike et al [17], used the SF-36 questionnaire and found improvements in quality of life scores after 24 weeks of training for both the home exercise group and the group that performed exercise at the rehabilitation center 89.62 ± 7.2 vs 90.94 ± 8.06) respectively, compared to the control group. Headley et al [20], observed improvements in the intervention group compared to the control group in the physical aspects of the questionnaire (67.67 ± 25.27 vs 79.67 ± 19.50; p = 0.02), vitality (55.33 ± 12.60 vs 81.60 ± 15.55; p= 0.05), body pain (67.33 ± 25.55 vs 77.17 ± 20.46; p= 0.02) of the SF-36. Mustata et al. [24] used two tools, the SF-36 and the EQ-5D. However, there were no differences between the intervention and control groups. Van Craenenbroeck et al. [26], evaluated the quality of life through the KDQoL-SF and found a difference between the intervention and control groups in the sleep domains (71.72 ± 19.25 vs 77.97 ± 13.29; p= 0.01), and energy / fatigue aspects (68.93 ± 15.95 vs 77.14 vs 11.04; p= 0.03). Pechter et al. [25], measured quality of life through a scale of numerical values between 0 and 10 categorizing responses from 10-8 as good health, 7-4 medium health and 3-1 poor health. However, the description of the results is inconsistent.

Risk of Bias and Quality of Evidence

Most studies were classified as “some concerns”, however, two studies [17, 18] were classified as “High”, due to the fact that the allocation is not blinded. Further details of the risk of bias assessment are shown in table 2. The quality of the evidence for each effect estimate is shown in table 3.

Discussion

This meta-analysis demonstrated that aerobic exercise when performed in isolation promotes an increase in VO_2 peak, in the distance covered by the 6MWT and in the number of repetitions in the STS-30" compared to the usual care in patients with CKD in the pre-dialysis phase. It is known that physical exercise is able to help improve many of the morbidities related to CKD, such as hypertension, cachexia and low functional capacity [27]. In a patient who is not yet undergoing renal replacement therapy, aerobic exercise decreases microalbuminuria, protects from oxidative stress and can increase the estimated GFR [12, 28].

Regarding to VO_2 peak, its measurement is considered the gold standard in the assessment of cardiorespiratory capacity, being the most used parameter, and in patients with CKD, it is considered an independent predictor of mortality [29, 30]. However, in the absence of a cardiopulmonary test, the 6MWT can be used as an initial tool to assess functional capacity, as it has a good correlation with peak VO_2 [31]. The reduction in functional capacity frequently found in patients with CKD is a consequence of cardiovascular, respiratory and muscular problems, among which the ability to extract, transport and use O_2 may be impaired [32]. It is known that the mitochondrial metabolism of skeletal muscle characterized by oxidative stress, insulin resistance and lipid metabolism are compromised [33, 34]. This mitochondrial oxidative stress mechanism is involved in the process of muscular atrophy in uremic patients and these factors are associated with a low level of physical activity leading to fatigue and less tolerance to exercise with a consequent decrease in functional capacity [35, 36]. Aerobic exercise, however, promotes an increase in mitochondrial number and volume as well as changes in the composition of organelles, such changes lead to an improvement in the oxidative capacity of the muscle and in the use of energetic substrates, thus improving the increase in exercise tolerance [37-39].

Previous systematic reviews [11, 12] have already demonstrated the benefits of exercise on peak VO_2 and functional capacity; however, this is the first to evaluate the effects of aerobic exercise in isolation. Pei et al [11] performed an analysis dividing the total training time between above and below six months for the 6MWT where they found no difference between the groups, however for the variable VO_2 peak they found an increase in both groups. However, caution is necessary regarding the total exercise time, as the subgroup analysis performed in our study showed that training for less than three months did not have an effect on VO_2 peak compared to the control group in pre-dialysis patients.

The increase in the number of repetitions in the STS-30" can be explained by the improvement in functional capacity through the mechanisms mentioned above. A study published by our research group found a positive association in performance in the STS-30" and the 6MWT ($r= 0.561$; $p= 0.001$) which demonstrates the probable involvement of the strength of the proximal muscles of the lower limbs in performance during walking [40]. A previous review [11] analyzed this variable, however, using the STS in 60 seconds, which had no effect. It is also important to highlight that, in patients with CKD in the pre-dialysis phase, one repetition performed in the STS is considered as a Clinically Important Measure (MCI) [41], and this meta-analysis found an effect measure of seven repetitions in the test after aerobic training. To the best of our knowledge, this is the first review with an analysis of the STS-30".

The studies that assessed quality of life (QOL), reported improvements in the assessed domains. It is known that even in the initial stages, patients experience a series of negative perceptions that can influence their actions to cope with the disease [42]. However, physical exercise, in addition to producing beneficial effects on the burden of symptoms of kidney disease, improves patients' mental health [43], the level of motivation, in addition to promoting greater adherence to treatment, seeking healthier lifestyle habits, decreased fatigue and

improved sleep quality [44-46]. However, the analysis tools for this variable were different between studies, and it was impossible to perform the meta-analysis.

Regarding the assessment of the risk of bias in the studies, two were classified as having a high risk of bias [17, 18], due to the lack of allocation concealment, since the participants chose right after randomization whether the intervention would be carried out at home or in the center. The rest of the studies were classified as an uncertain risk, which highlights the need for greater clarity in the methodological report. The quality of the evidence was moderate for peak VO_2, functional capacity, lower limb muscle strength and quality of life, reinforcing that aerobic exercise can be recommended for this population.

Strengths of this review should be considered. We conducted a comprehensive search of the literature with explicit criteria and eligibility and without language or date restrictions. In addition, we systematically assess the risk of bias in the studies included with RoB 2.0 and apply GRADE to determine the quality of the evidence. The study has some limitations, among them the small number of studies included in each outcome assessed, in addition, the absence of blinding study participants is a point that can influence the results, since they were compared with a group that did not perform another type of intervention. Despite these limitations, the effect estimates and small confidence intervals demonstrate a beneficial effect of isolated aerobic exercise on the variables studied, which reinforces its importance as part of the rehabilitation of patients with CKD even in its early stages.

Conclusion

Aerobic exercise performed in isolation increases VO_2 peak, functional capacity and muscle strength of lower limbs in patients with pre-dialysis CKD. The effects on QoL seem to be beneficial, but studies with more homogeneous methodologies are needed so that they can be included in a meta-analysis.

Conflict of interest statement

The authors declare that there are no potential conflicts of interest regarding the research, authorship and/or publication of this article.

Financing

The authors have no financial interests to declare. This study has no external funding.

Table 1. Characteristics of the studies inclued

Study, Year	Subjects and groups	Age mean (SD)	eGFR mean (SD)	AEG				CG	Mean Follow-up (weeks)	Outcomes
				Intervention	Frequency	Time	Intensity			
Aoike et al. (2018)	CKD stages 3 - 4 AEG home (n=12); AEG center (n=13); CG (n=15)	55.5 (7.9)	26.8 (11.7)	AEG home: walking at locations near the patient's home, such as a backyard, park or street; AEG center: walking on treadmill	3 times per week	30 min with increments of 10 min every 4 weeks until week eight	40-60% VO_2 max	Usual care	24	VO_2 peak, Functional capacity, Lower limb muscle strength and Quality of life
Aoike et al. (2015)	CKD stages 3 - 4 AEG home (n=14); CG (n=15)	55.1 (8.1)	26.8 (12.3)	Walking at locations near the patient's home, such as a backyard, park or street	3 times per week	30 min with increments of 10 min every 4 weeks until week eight	40-60% VO_2 max	Usual care	12	VO_2 peak, Functional capacity and Lower limb muscle strength
Baria et al. (2014)	CKD stages 3 - 4 AEG home (n=9); AEG center (n=10); CG (n=10)	52.1 (9.5)	27.5 (11.6)	AEG home: walking at locations near the patient's home, such as a backyard, park or street; AEG center: walking on treadmill	3 times per week	30 min with increments of 10 min every 4 weeks	40-60% VO_2 max	No exercise	12	VO_2 peak, Functional capacity and Quality of life
Headley et al. (2014)	CKD stage 3 AEG center (n=25); CG (n=21)	57.6 (8.4)	47.6 (12.2)	Continuous aerobic exercise utilizing a variety of apparati	3 times per week	15 to 30 min, increasing up until 55 min	50-60% VO_2 max	No exercise	16	VO_2 peak and Quality of life

Ikizler et al. (2018)	CKD stages 3 - 4 AEG + CR (n=30); UA + CR (n=28); AEG + UD (n=27); UA + UD (n=26)	58.2 (11.7)	36.1 (14.4)	Alternated aerobic exercise with the use of a treadmill, an elliptical crosstrainer, a Nu-Step crosstrainer, and a recumbent stationary bicycle	3 times per week	30 to 45 min	60-80% VO_2 max	Usual activity	16	VO_2 peak
Leehey et al. (2009)	CKD stages 2 - 4 AEG center (n=7); CG (n=6)	66 (19.3)	45.1 (28.4)	Walking on treadmill, outside (weather permitting) or in the research building corridors	3 times per week	30 min with increments of 5 min every 2 weeks until 40 min	25-84% VO_2 peak	No exercise	24	VO_2 peak
Miele et al. (2017)	CKD stage 3 AEG center (n=25); CG (n=21)	57.6 (8.4)	47.6 (12.2)	Aerobic exercise	3 times per week	15 to 30 min, gradually increased to a total of 55 min per session for most participants	50-60% VO_2 peak	Usual care	16	VO_2 peak
Mustata et al. (2011)	CKD stages 3 - 4 AEG center and home (n=10); CG (n=10)	68.2 (15.4)	27.5 (12.3)	Centre sessions: treadmill, stationary cycle and elliptical trainer; Home training: walking	3 times per week	5 to 20 min, increased by 5–10% weekly (to a maximum of 60 min)	40-60% VO_2 peak	Usual care	52	VO_2 peak and Quality of life
Pechter et al. (2003)	Moderate chronic renal failure AEG center (n=17); CG (n=9)	50.6 (27)	65.3 (9)	Aerobic exercise vertically in the pool with total immersion to the shoulder (24°C)	2 times per week	30 min	Low	No exercise	12	VO_2 peak and Quality of life

Van Craenenbroeck et al. (2015)	CKD stages 3 - 4 AEG home (n=25); CG (n=23)	53.2 (12.9)	38.6 (12.9)	Cycling	4 daily sessions	10 min	90% of the HR achieved at the anaerobic threshold on baseline testing	Usual care	12	VO_2 peak and Quality of life

CKD: chronic kidney disease; AEG: aerobic exercise group; CG: control group; CR: caloric restriction; UA: usual activity; UD: usual diet; n: sample size; eGFR: estimated glomerular filtration rate; SD: standard deviation; min: minutes; VO_2 max: maximal oxygen uptake; VO_2 peak: peak oxygen uptake; HR: heart rate.

Table 2. Risk of bias of RCT's included and evaluated through Rob 2.0

Study and Outcomes	Randomization process	Deviations from intended interventions	Mising outcome data	Measurement of the outcome	Selection of the reported result	Overall
Aoike et al. (2018) *VO_2 peak, Functional capacity, Lower limb muscle strength and Quality of life*	High	Low	Low	Some concerns	Low	High
Aoike et al. (2015) *VO_2 peak, Functional capacity and Lower limb muscle strength*	High	Some concerns	Low	Some concerns	Some concerns	High
Baria et al. (2014) *VO_2 peak, Functional capacity and Quality of life*	Some concerns	Some concerns	Low	Low	Some concerns	Some concerns
Headley et al. (2014) *VO_2 peak and Quality of life*	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Ikizler et al. (2018) *VO_2 peak*	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Leehey et al. (2009) *VO_2 peak*	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Miele et al. (2017) *VO_2 peak*	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Mustata et al. (2011) *VO_2 peak and Quality of life*	Some concerns	Low	Low	Low	Some concerns	Some concerns

Pechter et al. (2003) *VO_2 peak and Quality of life*	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Van Craenenbroeck et al. (2015) *VO_2 peak and Quality of life*	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns

VO_2 peak: peak oxygen uptake; Low: low risk of bias; High: high risk of bias; Some concerns: no information or uncertainty over the potential for bias.

Table 3. Quality of evidence (GRADE)

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercício aeróbico	controle	Relative (95% CI)	Absolute (95% CI)		
VO2 peak												
10	randomised trials	serious [a]	not serious	not serious	not serious	none	179	137	-	MD **2.07 more** (1.16 more to 2.89 more)	⨁⨁⨁◯ MODERATE	CRITICAL
TC6'												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	63	40	-	MD **77.78 more** (33.27 more to 122.3 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
STS 30"												
3	randomised trials	serious [a]	not serious	not serious	not serious	none	63	40	-	MD **7.65 more** (5.73 more to 9.58 more)	⨁⨁⨁◯ MODERATE	IMPORTANT
Quality of life												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Exercício aeróbico	controle	Relative (95% CI)	Absolute (95% CI)		
5	randomised trials	serious [a]	not serious	not serious	not serious	none	Five studies (n = 180 patients) evaluated the effect of aerobic exercise on the quality of life of patients with CKD. Aoike et al., Used the SF-36 scale and found an improvement in quality of life scores after 24 weeks of training for both the home exercise group and the center group (89.62 ± 7.2 vs 90.94 ± 8 , 06) respectively, compared to the control group. Headley et al., Observed improvements in the intervention group compared to the control group in physical aspects (67.67 ± 25.27 vs 79.67 ± 19.50; p = 0.02), vitality (55.33 ± 12, 60 vs 81.60 ± 15.55; p = 0.05), body pain (67.33 ± 25.55 vs 77.17 ± 20.46; p = 0.02) of the SF-36. Mustata et al. used two tools, the SF-36 and the EQ-5D. However, there were no differences between the intervention and control groups. Van Craenenbroeck et al., Assessed quality of life using the KDQoL-SF and found a difference between the intervention and control groups in the sleep domains (71.72 ± 19.25 vs 77.97 ± 13.29; p = 0, 01), and energy / fatigue aspects (68.93 ± 15.95 vs 77.14 vs 11.04; p = 0.03). Petcher et al., Measured quality of life through a numerical value scale between 0 and 10, categorizing responses from 10-8 as good health, 7-4 medium health and 3-1 poor health. However, the description of the data is inconsistent.				⊕⊕⊕◯ MODERATE	IMPORTANT

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

Explanations

a. In two studies, the randomization process presented a high risk of bias.

Figure 1. Flowchart

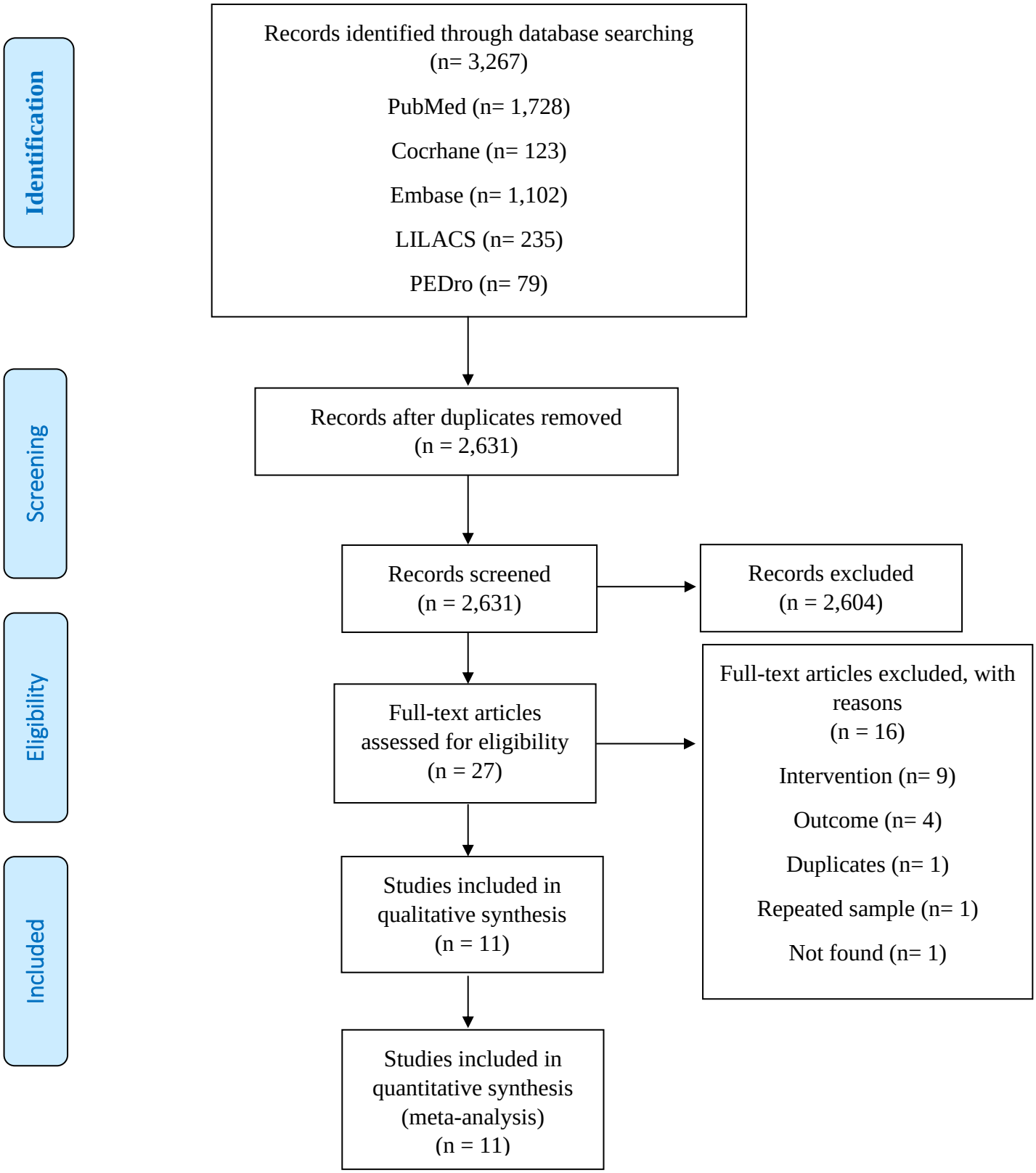
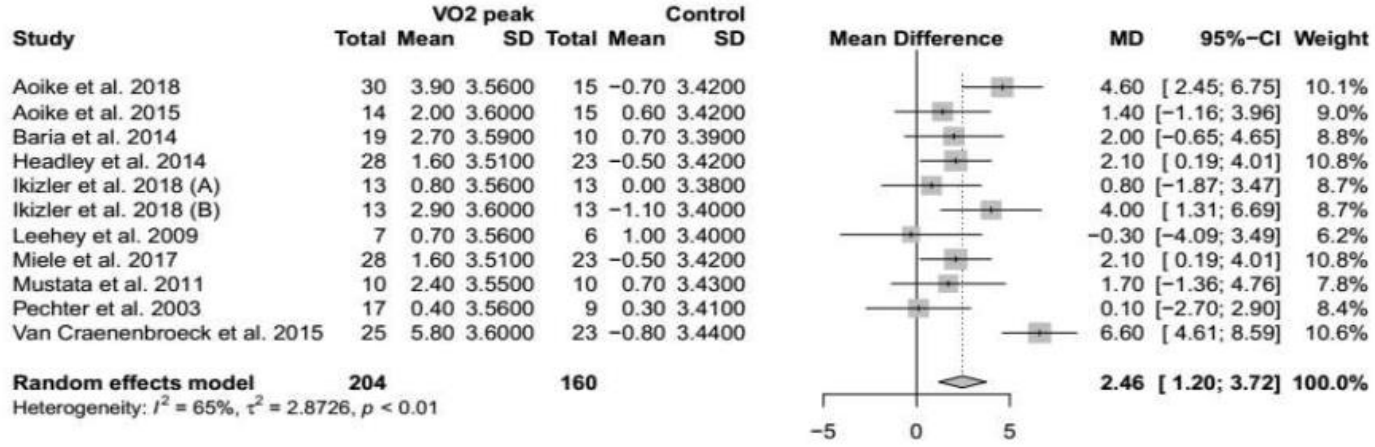
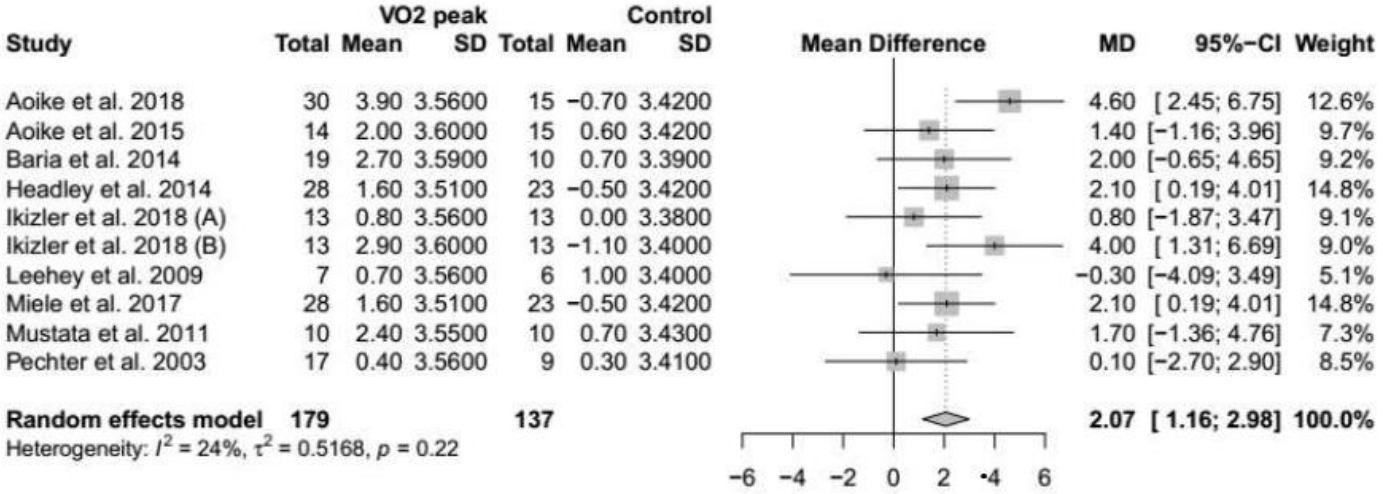


Figure 2. Effects of aerobic exercise on VO_2 peak

2a



2b



2c

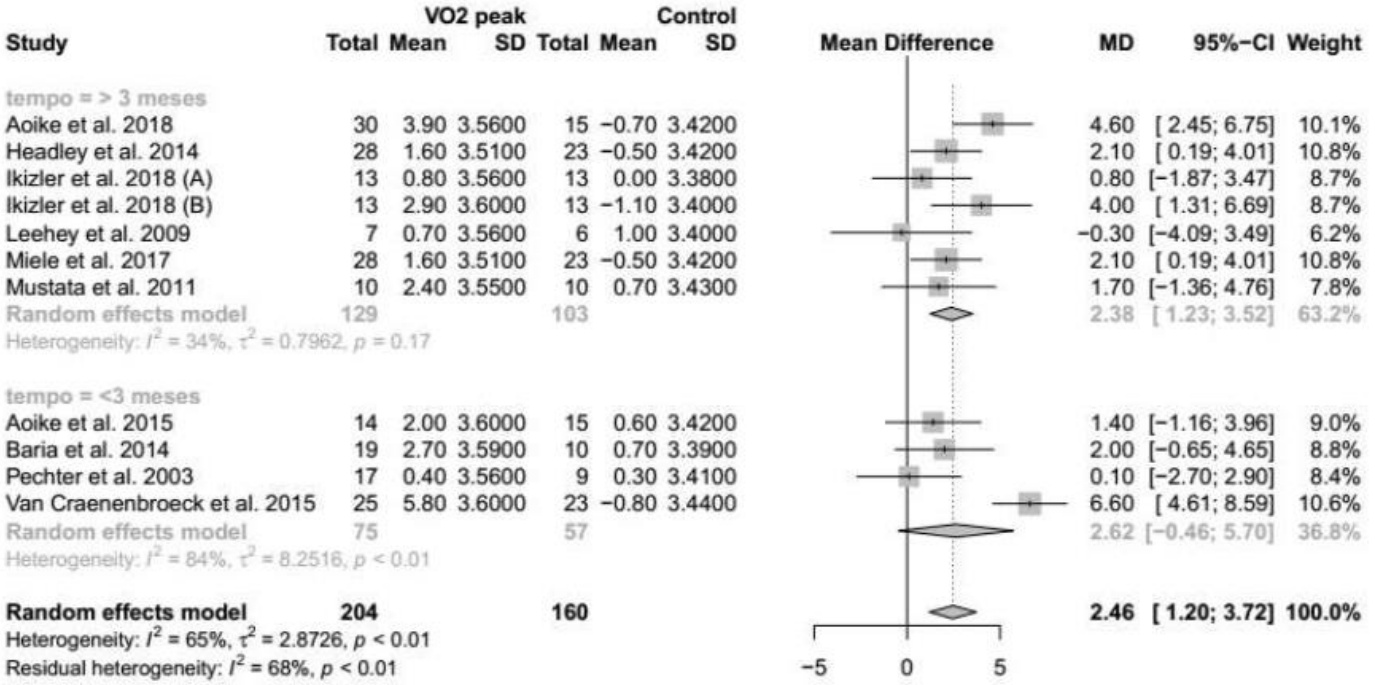
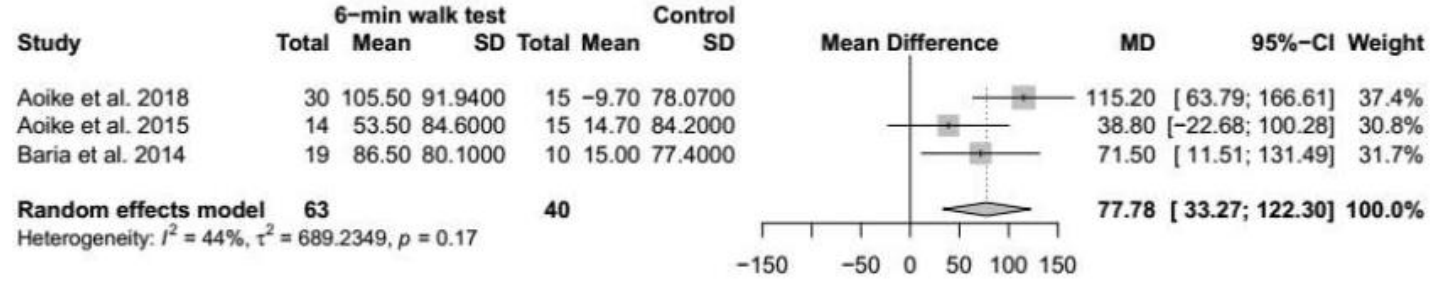
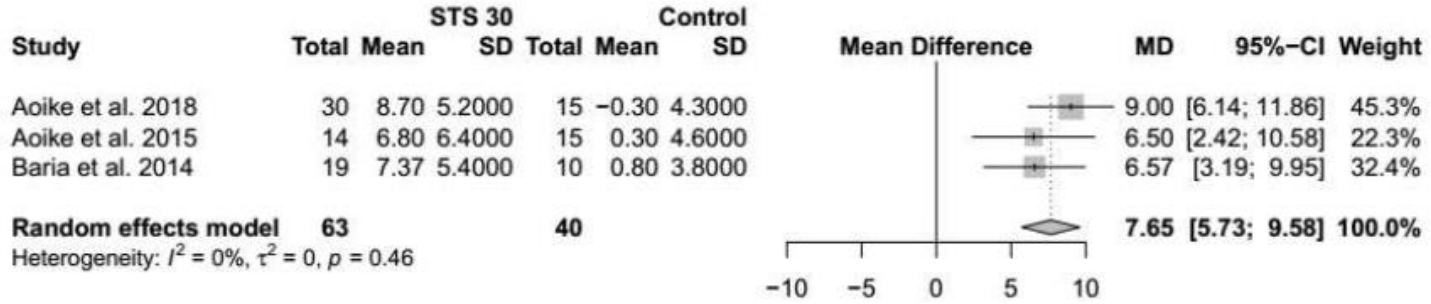


Figure 3. Effects of aerobic exercise in functional capacity and lower limb strength

3a



3b



REFERENCES

1. Kidney Disease: Improving Global Outcomes, C.K.D.M.B.D.U.W.G., *KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD).* Kidney Int Suppl (2011), 2017. **7**(1): p. 1-59.
2. Junior, J., *Doença Renal Crônica: Definição, Epidemiologia e Classificação.* J Bras Nefrol, 2004. **26**(3 Suppl 1).
3. Zuber, K. and J. Davis, *The ABCs of chronic kidney disease.* JAAPA, 2018. **31**(10): p. 17-25.
4. Fassbinder, T.R., et al., *Functional Capacity and Quality of Life in Patients with Chronic Kidney Disease In Pre-Dialytic Treatment and on Hemodialysis--A Cross sectional study.* J Bras Nefrol, 2015. **37**(1): p. 47-54.
5. Bossola, M., et al., *Functional impairment is associated with an increased risk of mortality in patients on chronic hemodialysis.* BMC Nephrol, 2016. **17**(1): p. 72.
6. Pereira, R.A., et al., *Sarcopenia in chronic kidney disease on conservative therapy: prevalence and association with mortality.* Nephrol Dial Transplant, 2015. **30**(10): p. 1718-25.
7. Schaap, L.A., et al., *Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength.* J Gerontol A Biol Sci Med Sci, 2009. **64**(11): p. 1183-9.
8. Inker, L.A., et al., *KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD.* Am J Kidney Dis, 2014. **63**(5): p. 713-35.
9. Milam, R.H., *Exercise Guidelines for Chronic Kidney Disease Patients.* J Ren Nutr, 2016. **26**(4): p. e23-5.
10. Egan, B. and J.R. Zierath, *Exercise metabolism and the molecular regulation of skeletal muscle adaptation.* Cell Metab, 2013. **17**(2): p. 162-84.
11. Pei, G., et al., *Aerobic exercise in adults with chronic kidney disease (CKD): a meta-analysis.* Int Urol Nephrol, 2019. **51**(10): p. 1787-1795.
12. Vanden Wyngaert, K., et al., *The effects of aerobic exercise on eGFR, blood pressure and VO2peak in patients with chronic kidney disease stages 3-4: A systematic review and meta-analysis.* PLoS One, 2018. **13**(9): p. e0203662.
13. Moher, D., et al., *Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement.* Ann Intern Med, 2009. **151**(4): p. 264-9, W64.
14. Higgins, J.P.S., J.; Page, M.J.; Stern, J.A. , *Revised Cochrane risk of bias tool for randomized trials (RoB 2.0).* 2016: p. 1-52.
15. Guyatt, G., et al., *GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables.* J Clin Epidemiol, 2011. **64**(4): p. 383-94.
16. saúde, M.d., *Diretrizes Metodológicas Sistema GRADE – manual de graduação da qualidade da evidência e força de recomendação para tomada de decisão em saúde.* . 2014: Brasil. p. 1-74.
17. Aoike, D.T., et al., *Home-based versus center-based aerobic exercise on cardiopulmonary performance, physical function, quality of life and quality of sleep of overweight patients with chronic kidney disease.* Clin Exp Nephrol, 2018. **22**(1): p. 87-98.
18. Aoike, D.T., et al., *Impact of home-based aerobic exercise on the physical capacity of overweight patients with chronic kidney disease.* Int Urol Nephrol, 2015. **47**(2): p. 359-67.

19. Baria, F., et al., *Randomized controlled trial to evaluate the impact of aerobic exercise on visceral fat in overweight chronic kidney disease patients.* Nephrol Dial Transplant, 2014. **29**(4): p. 857-64.

20. Headley, S., et al., *Short-term aerobic exercise and vascular function in CKD stage 3: a randomized controlled trial.* Am J Kidney Dis, 2014. **64**(2): p. 222-9.

21. Ikizler, T.A., et al., *Metabolic Effects of Diet and Exercise in Patients with Moderate to Severe CKD: A Randomized Clinical Trial.* J Am Soc Nephrol, 2018. **29**(1): p. 250-259.

22. Leehey, D.J., et al., *Aerobic exercise in obese diabetic patients with chronic kidney disease: a randomized and controlled pilot study.* Cardiovasc Diabetol, 2009. **8**: p. 62.

23. Miele, E.M., et al., *High-density lipoprotein particle pattern and overall lipid responses to a short-term moderate-intensity aerobic exercise training intervention in patients with chronic kidney disease.* Clin Kidney J, 2017. **10**(4): p. 524-531.

24. Mustata, S., et al., *Effects of exercise training on physical impairment, arterial stiffness and health-related quality of life in patients with chronic kidney disease: a pilot study.* Int Urol Nephrol, 2011. **43**(4): p. 1133-41.

25. Pechter, U., et al., *Beneficial effects of water-based exercise in patients with chronic kidney disease.* Int J Rehabil Res, 2003. **26**(2): p. 153-6.

26. Van Craenenbroeck, A.H., et al., *Effect of Moderate Aerobic Exercise Training on Endothelial Function and Arterial Stiffness in CKD Stages 3-4: A Randomized Controlled Trial.* Am J Kidney Dis, 2015. **66**(2): p. 285-96.

27. Wilkinson, T.J., N.F. Shur, and A.C. Smith, *"Exercise as medicine" in chronic kidney disease.* Scand J Med Sci Sports, 2016. **26**(8): p. 985-8.

28. Moinuddin, I. and D.J. Leehey, *A comparison of aerobic exercise and resistance training in patients with and without chronic kidney disease.* Adv Chronic Kidney Dis, 2008. **15**(1): p. 83-96.

29. Roshanravan, B., et al., *Association between physical performance and all-cause mortality in CKD.* J Am Soc Nephrol, 2013. **24**(5): p. 822-30.

30. Sietsema, K.E., et al., *Exercise capacity as a predictor of survival among ambulatory patients with end-stage renal disease.* Kidney Int, 2004. **65**(2): p. 719-24.

31. Raissuni, Z. and G. Roul, *Comparison of the long-term reproducibility of the walk test and of exercise peak oxygen consumption in patients with preserved exercise capacity.* Acta Cardiol, 2018. **73**(2): p. 155-162.

32. Cury, J.L., A.F. Brunetto, and R.D. Aydos, *Negative effects of chronic kidney failure on lung function and functional capacity.* Rev Bras Fisioter, 2010. **14**(2): p. 91-8.

33. Petersen, K.F., et al., *Impaired mitochondrial activity in the insulin-resistant offspring of patients with type 2 diabetes.* N Engl J Med, 2004. **350**(7): p. 664-71.

34. Befroy, D.E., et al., *Impaired mitochondrial substrate oxidation in muscle of insulin-resistant offspring of type 2 diabetic patients.* Diabetes, 2007. **56**(5): p. 1376-81.

35. Powers, S.K., A.N. Kavazis, and K.C. DeRuisseau, *Mechanisms of disuse muscle atrophy: role of oxidative stress.* Am J Physiol Regul Integr Comp Physiol, 2005. **288**(2): p. R337-44.

36. Powers, S.K., A.J. Smuder, and D.S. Criswell, *Mechanistic links between oxidative stress and disuse muscle atrophy.* Antioxid Redox Signal, 2011. **15**(9): p. 2519-28.

37. Hood, D.A., *Invited Review: contractile activity-induced mitochondrial biogenesis in skeletal muscle.* J Appl Physiol (1985), 2001. **90**(3): p. 1137-57.

38. Booth, F., *Effects of endurance exercise on cytochrome C turnover in skeletal muscle.* Ann N Y Acad Sci, 1977. **301**: p. 431-9.

39. Vollaard, N.B., et al., *Systematic analysis of adaptations in aerobic capacity and submaximal energy metabolism provides a unique insight into determinants of human aerobic performance.* J Appl Physiol (1985), 2009. **106**(5): p. 1479-86.

40. Dipp, T., et al., *Força Muscular Respiratória e Capacidade Funcional na Insuficiência Renal Terminal*. 2010: Rev Bras Med Esporte.

41. Wilkinson, T.J.P., et al., *Test-retest reliability, validation, and "minimal detectable change" scores for frequently reported tests of objective physical function in patients with non-dialysis chronic kidney disease.* Physiother Theory Pract, 2019. **35**(6): p. 565-576.

42. Clarke, A.L., et al., *Patient's perceptions of chronic kidney disease and their association with psychosocial and clinical outcomes: a narrative review.* Clin Kidney J, 2016. **9**(3): p. 494-502.

43. MacKinnon, H.J., J. Feehally, and A.C. Smith, *A review of the role of exercise and factors affecting its uptake for people with chronic kidney disease (CKD) not requiring renal replacement therapy.* Pril (Makedon Akad Nauk Umet Odd Med Nauki), 2015. **36**(1): p. 37-46.

44. Tang, Q., et al., *Effects of individualized exercise program on physical function, psychological dimensions, and health-related quality of life in patients with chronic kidney disease: A randomized controlled trial in China.* Int J Nurs Pract, 2017. **23**(2).

45. Wilkinson, T.J., et al., *Twelve weeks of supervised exercise improves self-reported symptom burden and fatigue in chronic kidney disease: a secondary analysis of the 'ExTra CKD' trial.* Clin Kidney J, 2019. **12**(1): p. 113-121.

46. Van Craenenbroeck, E.M., et al., *Effects of aerobic interval training and continuous training on cellular markers of endothelial integrity in coronary artery disease: a SAINTEX-CAD substudy.* Am J Physiol Heart Circ Physiol, 2015. **309**(11): p. H1876-82.

Supplementary table 1. Systematic review search strategy

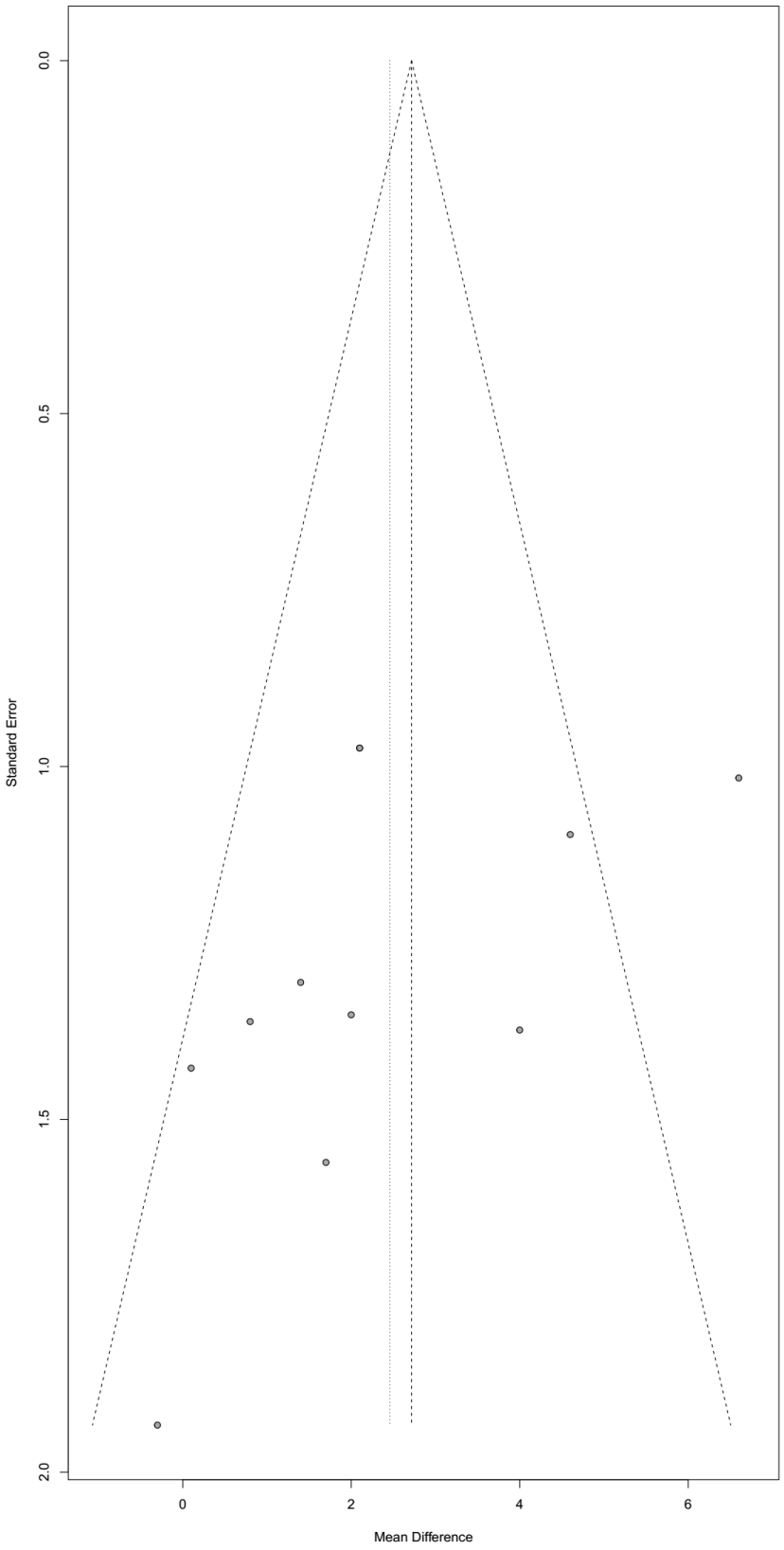
Numbers	Combiners	Terms
PubMed/MEDLINE		
#1	Population	"Renal Insufficiency, Chronic"[Mesh] OR "Renal Insufficiency, Chronic" OR “Chronic Renal Insufficiencies” OR “Renal Insufficiencies, Chronic” OR “Chronic Renal Insufficiency” OR “Kidney Insufficiency, Chronic” OR “Chronic Kidney Insufficiency” OR “Chronic Kidney Insufficiencies” OR “Kidney Insufficiencies, Chronic” OR “Chronic Kidney Diseases” OR “Chronic Kidney Disease” OR “Disease, Chronic Kidney” OR “Diseases, Chronic Kidney” OR “Kidney Disease, Chronic” OR “Kidney Diseases, Chronic” OR “Chronic Renal Diseases” OR “Chronic Renal Disease” OR “Disease, Chronic Renal” OR “Diseases, Chronic Renal” OR “Renal Disease, Chronic” OR “Renal Diseases, Chronic” OR "Kidney Failure, Chronic"[Mesh] OR "Kidney Failure, Chronic" OR "Proteinuria"[Mesh] OR "Proteinuria" OR "Glomerular Filtration Rate"[Mesh] OR "Glomerular Filtration Rate" OR “CKD”
#2	Intervention	"Exercise"[Mesh] OR “Exercise” OR “Exercises” OR “Physical Activity” OR “Activities, Physical” OR “Activity, Physical” OR “Physical Activities” OR “Exercise, Physical” OR “Exercises, Physical” OR “Physical Exercise” OR “Physical Exercises” OR “Exercise, Aerobic” OR “Aerobic Exercise” OR “Aerobic Exercises” OR “Exercises, Aerobic” OR “Exercise Training” OR “Exercise Trainings” OR “Training, Exercise” OR “Trainings, Exercise” OR “intermittent training”
#3	Study desing	(randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR (“clinical trial [tw]) OR ((singl*[tw] OR doubl* [tw] OR trebl*[tw] OR tripl*[tw] AND (mask* [tw] OR blind*[tw])) OR (“latin square” [tw]) OR placebos [mh] OR placebo* [tw] OR random*[tw] OR research desing [mh:noexp] OR comparative study [mh] evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] Or control* [tw] OR prospectiv* [tw] Or volunteer [tw]) NOT (animal [mh] NOT human [mh])
#4		**#1 AND #2 AND #3**
EMBASE		
#1	Population	Renal Insufficiency, Chronic OR Kidney Failure, Chronic OR Proteinuria OR Glomerular Filtration Rate
#2	Intervention	Exercise
#3		**#1 AND #2**
LILACS		
		tw:((tw:(kidney disease)) AND (tw:(exercise)) AND (tw:(randomized clinical trial)))
PeDro		
		Kidney disease AND Exercise

Supplementary table 2. Baseline values of outcomes

Study, Year	VO_2 peak (ml/kg/min)		Functional capacity – 6MWT (meters)		Lower limb muscle strength – STS 30" (repetitions)	
	AEG	CG	AEG	CG	AEG	CG
Aoike et al. (2018)	23.1 ± 5.4	23.6 ± 8.2	527.7 ± 88.9	546.5 ± 74.9	17.1 ± 3.8	18 ± 4.3
Aoike et al. (2015)	24.1 ± 7.1	23.6 ± 8.2	529.6 ± 83.9	546.5 ± 74.9	17.2 ± 5.3	18 ± 4.3
Baria et al. (2014)	25.6 ± 4.8	26.4 ± 7.2	556.4 ± 81.7	577 ± 65.4	17.6 ± 4	18.3 ± 3.1
Headley et al. (2014)	19.6 ± 6.7	18 ± 6	_	_	_	_
Ikizler et al. (2018)	19.8 ± 4.1	19.3 ± 4.6	_	_	_	_
Ikizler et al. (2018)*	19.4 ± 6.1	19.7 ± 5	_	_	_	_
Leehey et al. (2009)	14.9 ± 1.1	10.9 ± 1	_	_	_	_
Miele et al. (2017)	19.6 ± 6.7	18 ± 6	_	_	_	_
Mustata et al. (2011)	15.8 ± 5.2	15 ± 5.08	_	_	_	_
Pechter et al. (2003)	18.8 ± 0.9	21 ± 2.9	_	_	_	_
Van Craenenbroeck et al. (2015)	26.5 ± 5.4	24.8 ± 6.5	_	_	_	_

Values are mean ± standard deviation; *Groups with caloric restriction; AEG: aerobic exercise group; CG: control group; VO_2 peak: peak oxygen uptake; 6MWT: 6-min walk test; STS 30": Sit-to-stand test

Supplementary figure 1. Funnel plot (VO_2 peak)



4. CONCLUSÃO

A DRC promove alterações de diversos sistemas como o respiratório, o endócrino e cardiovascular. Por isso, os pacientes tendem a adotar um estilo de vida mais sedentário o que leva à diminuição da capacidade funcional, força muscular periférica e respiratória. Portanto, programas de exercícios físicos como o exercício aeróbico devem ser incentivados até mesmo para pacientes que estão nos estágios iniciais da doença (fase pré-dialítica).

Ferramentas de avaliação da qualidade de vida, capacidade funcional e força muscular são de fácil aplicabilidade e baixo custo. Os resultados deste estudo demonstram a associação entre o questionário de qualidade de vida (EQ-5D), o TC6', a manovacuometria, o TSL e a dinamometria. Além disso, a diminuição na distância percorrida no TC6', na força de preensão manual e na força muscular expiratória estão relacionadas com menor tempo de sobrevida em pacientes com DRC em HD.

ANEXOS

Anexo I – Parecer consubstanciado CEP

UNIVERSIDADE DE CRUZ ALTA - UNICRUZ/RS

PARECER CONSUBSTANCIADO DO CEP

DADOS DO PROJETO DE PESQUISA

Título da Pesquisa: CAPACIDADE FUNCIONAL E FORÇA MUSCULAR DE PACIENTES COM DOENÇA RENAL CRÔNICA EM HEMODIÁLISE.

Pesquisador: Graziela Valle Nicolodi

Área Temática:

Versão: 2

CAAE: 92318218.6.0000.5322

Instituição Proponente: Unicruz - Universidade de Cruz Alta

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.838.943

Apresentação do Projeto:
idem parecer anterior

Objetivo da Pesquisa:
idem parecer anterior

Avaliação dos Riscos e Benefícios:
idem parecer anterior

Comentários e Considerações sobre a Pesquisa:
idem parecer anterior

Considerações sobre os Termos de apresentação obrigatória:
Todas as solicitações feitas no parecer anterior foram atendidas

Conclusões ou Pendências e Lista de Inadequações:
Todas as solicitações feitas no parecer anterior foram atendidas.
Aprovado.

Considerações Finais a critério do CEP:

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Endereço: Campus Universitário Ulysses Guimarães - Rodovia Municipal Jacob Della Méa, Km 5.6 - Caixa Postal 858
Bairro: Campus Universitário Prédio **CEP:** 98.020-290
UF: RS **Município:** CRUZ ALTA
Telefone: (55)3322-1618 **E-mail:** comitedeetica@unicruz.edu.br

UNIVERSIDADE DE CRUZ ALTA - UNICRUZ/RS

Continuação do Parecer: 2.838.943

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇOES_BASICAS_DO_PROJETO_1161534.pdf	13/08/2018 12:04:07		Aceito
Declaração de Instituição e Infraestrutura	Termo_Goldani.pdf	13/08/2018 12:01:28	Graziela Valle Nicolodi	Aceito
Declaração de Instituição e Infraestrutura	Termo_Moreira.pdf	13/08/2018 12:01:16	Graziela Valle Nicolodi	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Renais.pdf	13/08/2018 12:00:53	Graziela Valle Nicolodi	Aceito
Folha de Rosto	folha_de_rosto_pdf.pdf	25/06/2018 11:33:04	Graziela Valle Nicolodi	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CRUZ ALTA, 23 de Agosto de 2018

Assinado por:
Rita Leal Sperotto
(Coordenador)

Endereço: Campus Universitário Ulysses Guimarães - Rodovia Municipal Jacob Della Méa, Km 5.6 - Caixa Postal 858
Bairro: Campus Universitário Prédio **CEP:** 98.020-290
UF: RS **Município:** CRUZ ALTA
Telefone: (55)3322-1618 **E-mail:** comitedeetica@unicruz.edu.br

Anexo II – Normas da Revista *Clinical Rehabilitation*

Clinical Rehabilitation

2018 Impact Factor: 2.738

2018 Ranking: 9/65 in Rehabilitation (SCIE)

Source: Journal Citation Reports (Web of Science Group, 2019)

eISSN: 14770873 | ISSN: 02692155 | Current volume: 33 | Current issue: 6 Frequency: Monthly

This Journal is a member of the Committee on Publication Ethics

This Journal recommends that authors follow the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals formulated by the International Committee of Medical Journal Editors (ICMJE).

Please read the guidelines below then visit the Journal's submission

site http://mc.manuscriptcentral.com/clinrehab to upload your manuscript. Please note that manuscripts not conforming to these guidelines may be returned.

Only manuscripts of sufficient quality that meet the aims and scope of Clinical Rehabilitation will be reviewed.

There are no fees payable to submit or publish in this journal.

As part of the submission process you will be required to warrant that you are submitting your original work, that you have the rights in the work, that you are submitting the work for first publication in the Journal and that it is not being considered for publication elsewhere and has not already been published elsewhere, and that you have obtained and can supply all necessary permissions for the reproduction of any copyright works not owned by you.

What do we publish?

Aims & Scope

Article types

Writing your paper

Editorial policies

Peer review policy

Authorship Acknowledgements

What do we publish?

Aims & Scope

Before submitting your manuscript to Clinical Rehabilitation, please ensure you have read the Aims & Scope.

Article Types

The journal publishes original papers, systematic reviews, Rehabilitation in Practice articles correspondence relating to published papers and short reports. Other article types should be discussed with the editor before submission.

For queries regarding the suitability of your submission please contact clinical.rehabilitation@sagepub.co.uk

Summary of manuscript structure:

A title page with names and contact details for all authors;

A **structured** abstract of **no more than 250 words** (the website checks this);

The text (usually Introduction, Methods, Results, Discussion);

Clinical Messages (2-4 bullet points, 50 words or less);

Acknowledgements, author contributions, competing interests and funding support;

References (Vancouver style);

Tables, each starting on a new page;

Figures, each starting on a new page;

Appendix (if any0

Please note that short reports follow a different format:

The main text of a short report will usually be between **1000 and 1500 words** in length.

A short report should have sufficient key references to cover all important points, but no more and usually there will be a **maximum of 15 references**.

Tables and figures can be very efficient and effective ways of presenting data. A short report will usually have **no more than three tables and figures** (in total) and most will be restricted to two.

Further information on short reports can be found here.

Writing your paper

The SAGE Author Gateway has some general advice and on how to get published, plus links to further resources.

Make your article discoverable

When writing up your paper, think about how you can make it discoverable. The title, keywords and abstract are key to ensuring readers find your article through search engines such as Google. For information and guidance on how best to title your article, write your abstract and select your keywords, have a look at this page on the Gateway: How to Help Readers Find Your Article Online.

Back to top

Editorial policies

Peer review policy

The journal's policy is to obtain at least two independent reviews of each article. It operates a single-blind reviewing policy in which the reviewer's name is always concealed from the submitting author. Referees will be encouraged to provide substantive, constructive reviews that provide suggestions for improving the work and distinguish between mandatory and non-mandatory recommendations.

All manuscripts accepted for publication are subject to editing for presentation, style and grammar. Any major redrafting is agreed with the author but the Editor's decision on the text is final.

Clinical Rehabilitation is committed to delivering high quality, fast peer-review for your paper, and as such has partnered with Publons. Publons is a third party service that seeks to track, verify and give credit for peer review. Reviewers for *Clinical Rehabilitation* can opt in to Publons in order to claim their reviews or have them automatically verified and added to their reviewer profile. Reviewers claiming credit for their review will be associated with the relevant journal, but the article name, reviewer's decision and the content of their review is not published on the site. For more information visit the Publons website.

Authorship

Papers should only be submitted for consideration once consent is given by all contributing authors. Those submitting papers should carefully check that all those whose work contributed to the paper are acknowledged as contributing authors.

The list of authors should include all those who can legitimately claim authorship. This is all those who:

Made a substantial contribution to the concept or design of the work; or acquisition, analysis or interpretation of data,

Drafted the article or revised it critically for important intellectual content,

Approved the version to be published,

Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

Authors should meet the conditions of all of the points above. When a large, multicentre group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship.

Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship, although all contributors who do not meet the criteria for authorship should be listed in the Acknowledgments section. Please refer to

the International Committee of Medical Journal Editors (ICMJE) authorship guidelines for more information on authorship.

Acknowledgements

All contributors who do not meet the criteria for authorship should be listed in an Acknowledgements section. Examples of those who might be acknowledged include a person who provided purely technical help, or a department chair who provided only general support.

Any acknowledgements should appear first at the end of your article prior to your Declaration of Conflicting Interests (if applicable), any notes and your References.

Funding

Clinical Rehabilitation requires all authors to acknowledge their funding in a consistent fashion under a separate heading. Please visit the Funding Acknowledgements page on the SAGE Journal Author Gateway to confirm the format of the acknowledgment text in the event of funding, or state that: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Declaration of conflicting interests

It is the policy of Clinical Rehabilitation to require a declaration of conflicting interests from all authors enabling a statement to be carried within the paginated pages of all published articles.

Please ensure that a ‘Declaration of Conflicting Interests’ statement is included at the end of your manuscript, after any acknowledgements and prior to the references, under a heading ‘Conflict of Interest Statement’. If no conflict exists, please state that ‘The Author(s) declare(s) that there is no conflict of interest’. For guidance on conflict of interest statements, please see the ICMJE recommendations here**.**

When making a declaration, the disclosure information must be specific and include any financial relationship that all authors of the article have with any sponsoring organization and the for-profit interests that the organisation represents, and with any for-profit product discussed or implied in the text of the article.

Any commercial or financial involvements that might represent an appearance of a conflict of interest need to be additionally disclosed in the covering letter accompanying your article to assist the Editor in evaluating whether sufficient disclosure has been made within the Conflict of Interest statement provided in the article.

Research ethics and patient consent

Medical research involving human subjects must be conducted according to the World Medical Association Declaration of Helsinki

Submitted manuscripts should conform to the ICMJE Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals, and all papers reporting animal and/or human studies must state in the methods section that the relevant Ethics Committee or Institutional Review Board provided (or waived) approval. Please ensure that you have provided the full name and institution of the review committee, in addition to the approval number.

For research articles, authors are also required to state in the methods section whether participants provided informed consent and whether the consent was written or verbal.

Information on informed consent to report individual cases or case series should be included in the manuscript text. A statement is required regarding whether written informed consent for patient information and images to be published was provided by the patient(s) or a legally authorized representative.

Please also refer to the ICMJE Recommendations for the Protection of Research Participants

Reporting guidelines

The relevant EQUATOR Network reporting guidelines should be followed depending on the type of study. For example, all randomized controlled trials submitted for publication should include a completed CONSORT flow chart as a cited figure and the completed CONSORT checklist should be uploaded with your submission as a supplementary file. Systematic reviews and meta-analyses should include the completed PRISMA flow chart as a cited figure and the completed PRISMA checklist should be uploaded with your submission as a supplementary file. The EQUATOR wizard can help you identify the appropriate guideline. Clinical Rehabilitation expects all clinical trials to be registered with a recognised registry, and the name of the registry and the registration number to be given in the paper, usually in the first paragraph in the methods section.

Other resources can be found at NLM's Research Reporting Guidelines and Initiatives Back to top

Publishing Policies

Publication ethics

SAGE is committed to upholding the integrity of the academic record. We encourage authors to refer to the Committee on Publication Ethics' International Standards for Authors and view the Publication Ethics page on the SAGE Author Gateway.

Plagiarism

Clinical Rehabilitation and SAGE take issues of copyright infringement, plagiarism or other breaches of best practice in publication very seriously. We seek to protect the rights of our authors and we always investigate claims of plagiarism or misuse of published articles.

Equally, we seek to protect the reputation of the journal against malpractice. Submitted articles may be checked with duplication-checking software. Where an article, for example, is found to have plagiarised other work or included third-party copyright material without permission or with insufficient acknowledgement, or where the authorship of the article is contested, we reserve the right to take action including, but not limited to: publishing an erratum or corrigendum (correction); retracting the article; taking up the matter with the head of department or dean of the author's institution and/or relevant academic bodies or societies; or taking appropriate legal action.

Prior publication

If material has been previously published it is not generally acceptable for publication in a SAGE journal. However, there are certain circumstances where previously published material can be considered for publication. Please refer to the guidance on the SAGE Author Gateway or if in doubt, contact the Editor at the address given below.

Contributor's publishing agreement

Before publication, SAGE requires the author as the rights holder to sign a Journal Contributor's Publishing Agreement. SAGE's Journal Contributor's Publishing Agreement is an exclusive licence agreement which means that the author retains copyright in the work but grants SAGE the sole and exclusive right and licence to publish for the full legal term of copyright. Exceptions may exist where an assignment of copyright is required or preferred by a proprietor other than SAGE. In this case copyright in the work will be assigned from the author to the society. For more information please visit the SAGE Author Gateway.

Open access and author archiving

Clinical Rehabilitation offers optional open access publishing via the SAGE Choice programme. For more information please visit the SAGE Choice website. For information on funding body compliance, and depositing your article in repositories, please visit SAGE Publishing Policies on our Journal Author Gateway.

Back to top

Preparing your manuscript for submission

Formatting

The preferred format for your manuscript is Word. LaTeX files are also accepted.

Artwork, figures and other graphics

For guidance on the preparation of illustrations, pictures and graphs in electronic format, please visit SAGE's Manuscript Submission Guidelines.

Figures supplied in colour will appear in colour online regardless of whether or not these illustrations are reproduced in colour in the printed version. For specifically requested colour reproduction in print, you will receive information regarding the costs from SAGE after receipt of your accepted article.

Supplementary material

This journal is able to host additional materials online (e.g. datasets, podcasts, videos, images etc) alongside the full-text of the article. For more information please refer to our guidelines on submitting supplementary files.

Reference style

Clinical Rehabilitation adheres to the SAGE Vancouver reference style. View the SAGE Vancouver guidelines to ensure your manuscript conforms to this reference style.

If you use EndNote to manage references, you can download the SAGE Vancouver EndNote output file.

English language editing services

Authors seeking assistance with English language editing, translation, or figure and manuscript formatting to fit the journal's specifications should consider using SAGE

Language Services. Visit SAGE Language Services on our Journal Author Gateway for further information.

Back to top

Submitting your manuscript

Clinical Rehabilitation is hosted on SAGE Track, a web based online submission and peer review system powered by ScholarOne™ Manuscripts. Visit Clinical Rehabilitation to login and submit your article online.

IMPORTANT: Please check whether you already have an account in the system before trying to create a new one. If you have reviewed or authored for the journal in the past year it is likely that you will have had an account created. For further guidance on submitting your manuscript online please visit ScholarOne Online Help.

ORCID

As part of our commitment to ensuring an ethical, transparent and fair peer review process SAGE is a supporting member of ORCID, the Open Researcher and Contributor ID. ORCID provides a unique and persistent digital identifier that distinguishes researchers from every other researcher, even those who share the same name, and, through integration in key research workflows such as manuscript and grant submission, supports automated linkages between researchers and their professional activities, ensuring that their work is recognized.

The collection of ORCID iDs from corresponding authors is now part of the submission process of this journal. If you already have an ORCID iD you will be asked to associate that to your submission during the online submission process. We also strongly encourage all co-authors to link their ORCID ID to their accounts in our online peer review platforms. It takes seconds to do: click the link when prompted, sign into your ORCID account and our systems are automatically updated. Your ORCID iD will become part of your accepted publication's metadata, making your work attributable to you and only you. Your ORCID iD is published with your article so that fellow researchers reading your work can link to your ORCID profile and from there link to your other publications.

If you do not already have an ORCID iD please follow this link to create one or visit our ORCID homepage to learn more.

Information required for completing your submission

You will be asked to provide contact details and academic affiliations for all co-authors via the submission system and identify who is to be the corresponding author. These details must match what appears on your manuscript. At this stage please ensure you have included all the required statements and declarations and uploaded any additional supplementary files (including reporting guidelines where relevant).

Publication of twitter handles:

As a way of encouraging ongoing discussion within the field, *Clinical Rehabilitation* authors are offered the option of providing their Twitter handle to be published alongside their name and email address within their article. This

way, *Clinical Rehabilitation* readers who have questions or thoughts regarding your paper can tweet you directly. Providing a Twitter handle for publication is entirely optional, if you are not comfortable with *Clinical Rehabilitation* promoting your article along with your personal Twitter handle then please do not supply it.

By providing your personal twitter handle you agree to let *Clinical Rehabilitation* and SAGE Publications use it in any posts related to your journal article. You may also be

contacted by other Twitter users. *Clinical Rehabilitation* and SAGE Publications will have no control over you or your tweets at any time. If you would like guidance on how to promote your article yourself on Twitter or other Social Media channels please

visit http://www.uk.sagepub.com/journalgateway/files/using_social_media_to_promot e.doc.

To include your Twitter handle within your article please provide this within the SAGE Track Submission form when prompted and within your title page.

Joe Bloggs, Department of Clinical Rehabilitation, Clinical Rehabilitation Hospital, Town, ST1 345, UK.

Email: JoeBloggs@email.com Twitter: @drjoebloggs

Permissions

Please also ensure that you have obtained any necessary permission from copyright holders for reproducing any illustrations, tables, figures or lengthy quotations previously published elsewhere. For further information including guidance on fair dealing for criticism and review, please see the Copyright and Permissions page on the SAGE Author Gateway.

Back to top

On acceptance and publication

SAGE Production

Your SAGE Production Editor will keep you informed as to your article's progress throughout the production process. Proofs will be sent by PDF to the corresponding author and should be returned promptly. Authors are reminded to check their proofs carefully to confirm that all author information, including names, affiliations, sequence and contact details are correct, and that Funding and Conflict of Interest statements, if any, are accurate. Please note that if there are any changes to the author list at this stage all authors will be required to complete and sign a form authorising the change.

Online First publication

Online First allows final articles (completed and approved articles awaiting assignment to a future issue) to be published online prior to their inclusion in a journal issue, which significantly reduces the lead time between submission and publication. Visit the SAGE Journals help page for more details, including how to cite Online First articles.

Access to your published article

SAGE provides authors with online access to their final article.

Promoting your article

Publication is not the end of the process! You can help disseminate your paper and ensure it is as widely read and cited as possible. The SAGE Author Gateway has numerous resources to help you promote your work. Visit the Promote Your Article page on the Gateway for tips and advice. In addition, SAGE is partnered with Kudos, a free service that allows authors to explain, enrich, share, and measure the impact of their article. Find out how to maximise your article's impact with Kudos.

Back to top

Further information

Important 'Instructions to Authors' – from the Editor

Further specific advice on editorial aspects of the journal and of writing for the journal are also available.

Click here for further information and advice on submitting to Clinical Rehabilitation.

Anexo III – Normas da Revista *Disabilty and Rehabilitation*

Thank you for choosing to submit your paper to us. These instructions will ensure we have everything required so your paper can move through peer review, production and publication smoothly. Please take the time to read and follow them as closely as possible, as doing so will ensure your paper matches the journal's requirements.

AUTHOR SERVICES
Supporting Taylor & Francis authors

For general guidance on every stage of the publication process, please visit our Author Services website.

EDITING SERVICES
Supporting Taylor & Francis authors

For editing support, including translation and language polishing, explore our Editing Services website

SCHOLARONE MANUSCRIPTS™

This journal uses ScholarOne Manuscripts (previously Manuscript Central) to peer review manuscript submissions. Please read the guide for ScholarOne authors before making a submission. Complete guidelines for preparing and submitting your manuscript to this journal are provided below.

Contents list

Health and safety

Submitting your paper

Data Sharing Policy

Publication charges
Copyright options
Complying with funding agencies
Open access
My Authored Works
Article reprints

About the journal

Disability and Rehabilitation is an international, peer reviewed journal, publishing high-quality, original research. Please see the journal's Aims & Scope for information about its focus and peer-review policy.

From 2018, this journal will be online only, and will no longer provide print copies. Please note that this journal only publishes manuscripts in English. *Disability and Rehabilitation* accepts the following types of article: Reviews, Research Papers, Case Studies, Perspectives on Rehabilitation, Reports on Rehabilitation in Practice, Education and Training, and Correspondence. Systematic Reviews should be submitted as "Review" and Narrative Reviews should be submitted as "Perspectives in Rehabilitation".

Special Issues and specific sections on contemporary themes of interest to the Journal's readership are published. Please contact the Editor for more information.

Peer review

Taylor & Francis is committed to peer-review integrity and upholding the highest standards of review. For submissions to *Disability and Rehabilitation* authors are given the option to remain anonymous during the peer-review process. Authors will be able to indicate whether their paper is 'Anonymous' or 'Not Anonymous' during submission, and should pay particular attention to the below:

Authors who wish to remain **anonymous** should prepare a complete text with information identifying the author(s) removed. This should be uploaded as the "Main Document" and will be sent to the referees. A separate title page should be included providing the full affiliations of all authors. Any acknowledgements and the Declaration of Interest statement must be included but should be worded mindful that these sections will be made available to referees.

Authors who wish to be **identified** should include the name(s) and affiliation(s) of author(s) on the first page of the manuscript. The complete text should be uploaded as the "Main Document".

Once your paper has been assessed for suitability by the editor, it will be peer-reviewed by independent, anonymous expert referees. Find out more about what to expect during peer review and read our guidance on publishing ethics.

Preparing your paper

All authors submitting to medicine, biomedicine, health sciences, allied and public health journals should conform to the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, prepared by the International Committee of Medical Journal Editors (ICMJE).

We also refer authors to the community standards explicit in the American Psychological Association's (APA) Ethical Principles of Psychologists and Code of Conduct.

We encourage authors to be aware of standardised reporting guidelines below when preparing their manuscripts:

Case reports - CARE

Diagnostic accuracy - STARD

Observational studies - STROBE

Randomized controlled trial - CONSORT

Systematic reviews, meta-analyses - PRISMA

Whilst the use of such guidelines is supported, due to the multi-disciplinary nature of the Journal, it is not compulsory.

Structure

Your paper should be compiled in the following order: title page; abstract; keywords; main text, introduction, materials and methods, results, discussion; acknowledgments; declaration of interest statement; references; appendices (as appropriate); table(s) with caption(s); figures; figure captions (as a list).

In the main text, an introductory section should state the purpose of the paper and give a brief account of previous work. New techniques and modifications should be described concisely but in sufficient detail to permit their evaluation. Standard methods should simply be referenced. Experimental results should be presented in the most appropriate form, with sufficient explanation to assist their interpretation; their discussion should form a distinct section.

Tables and figures should be referred to in text as follows: figure 1, table 1, i.e. lower case. The place at which a table or figure is to be inserted in the printed text should be indicated clearly on a manuscript. Each table and/or figure must have a title that explains its purpose without reference to the text.

The title page should include the full names and affiliations of all authors involved in the preparation of the manuscript. The corresponding author should be clearly designated, with full contact information provided for this person.

Word count

Please include a word count for your paper. There is no word limit for papers submitted to this journal, but succinct and well-constructed papers are preferred.

Style guidelines

Please refer to these style guidelines when preparing your paper, rather than any published articles or a sample copy.

Please use any spelling consistently throughout your manuscript.

Please use double quotation marks, except where "a quotation is 'within' a quotation". Please note that long quotations should be indented without quotation marks.

For tables and figures, the usual statistical conventions should be used.

Drugs should be referred to by generic names. Trade names of substances, their sources, and details of manufacturers of scientific instruments should be given only if the information is important to the evaluation of the experimental data.

Formatting and templates

Papers may be submitted in any standard format, including Word and LaTeX. Figures should be saved separately from the text. To assist you in preparing your paper, we provide formatting template(s).

Word templates are available for this journal. Please save the template to your hard drive, ready for use.

A LaTeX template is available for this journal. Please save the template to your hard drive, ready for use.

If you are not able to use the templates via the links (or if you have any other template queries) please contact us here.

References

Please use this reference guide when preparing your paper. An EndNote output style is also available to assist you.

Taylor & Francis Editing Services

To help you improve your manuscript and prepare it for submission, Taylor & Francis provides a range of editing services. Choose from options such as English Language Editing, which will ensure that your article is free of spelling and grammar errors, Translation, and Artwork Preparation. For more information, including pricing, visit this website.

Checklist: what to include

Author details. Please ensure everyone meeting the International Committee of Medical Journal Editors (ICJME) requirements for authorship is included as an author of your paper. All authors of a manuscript should include their full name and affiliation on the cover page of the manuscript. Where available, please also include ORCiDs and social media handles (Facebook, Twitter or LinkedIn). One author will need to be identified as the corresponding author, with their email address normally displayed in the article PDF (depending on the journal) and the online article. Authors' affiliations are the affiliations where the research was conducted. If any of the named co-authors moves affiliation during the peer-review process, the new affiliation can be given as a footnote. Please note that no changes to affiliation can be made after your paper is accepted. Read more on authorship.

A structured **abstract** of no more than 200 words. A structured abstract should cover (in the following order): the *purpose* of the article, its *materials and methods* (the design and methodological procedures used), the *results* and conclusions (including their relevance to the study of disability and rehabilitation). Read tips on writing your abstract.

You can opt to include a **video abstract** with your article. Find out how these can help your work reach a wider audience, and what to think about when filming.

5-8 **keywords**. Read making your article more discoverable, including information on choosing a title and search engine optimization.

A feature of this journal is a boxed insert on **Implications for Rehabilitation**. This should include between two to four main bullet points drawing out the implications for rehabilitation for your paper. This should be uploaded as a separate document. Below are examples:
Example 1: Leprosy

Leprosy is a disabling disease which not only impacts physically but restricts quality of life often through stigmatisation.

Reconstructive surgery is a technique available to this group.

In a relatively small sample this study shows participation and social functioning improved after surgery.

Example 2: Multiple Sclerosis

Exercise is an effective means of improving health and well-being experienced by people with multiple sclerosis (MS).

People with MS have complex reasons for choosing to exercise or not.

Individual structured programmes are most likely to be successful in encouraging exercise in this cohort.

Acknowledgement. Please supply all details required by your funding and grant-awarding bodies as follows: *For single agency grants*: This work was supported by the under Grant . *For multiple agency grants*: This work was supported by the under Grant ; under Grant ; and under Grant .

Declaration of Interest. This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. Further guidance on what is a declaration of interest and how to disclose it.

Data availability statement. If there is a data set associated with the paper, please provide information about where the data supporting the results or analyses presented in the paper can be found. Where applicable, this should include the hyperlink, DOI or other persistent identifier associated with the data set(s). Templates are also available to support authors.

Data deposition. If you choose to share or make the data underlying the study open, please deposit your data in a recognized data repository prior to or at the time of submission. You will be asked to provide the DOI, pre-reserved DOI, or other persistent identifier for the data set.

Supplemental online material. Supplemental material can be a video, dataset, fileset, sound file or anything which supports (and is pertinent to) your paper. We publish supplemental material online via Figshare. Find out more about supplemental material and how to submit it with your article.

Figures. Figures should be high quality (1200 dpi for line art, 600 dpi for grayscale and 300 dpi for colour). Figures should be saved as TIFF, PostScript or EPS files.

Tables. Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.

Equations. If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.

Units. Please use SI units (non-italicized).

Using third-party material in your paper

You must obtain the necessary permission to reuse third-party material in your article. The use of short extracts of text and some other types of material is usually permitted, on a limited basis, for the purposes of criticism and review without securing formal permission. If you wish to include any material in your paper for which you do not hold copyright, and which is not covered by this informal agreement, you will need to obtain written permission from the copyright owner prior to submission. More information on requesting permission to reproduce work(s) under copyright.

Declaration of Interest Statement

Please include a declaration of interest statement, using the subheading "Declaration of interest." If you have no interests to declare, please state this (suggested wording: *The authors report no conflicts of interest*). For all NIH/Wellcome-funded papers, the grant number(s) must be included in the disclosure of interest statement. Read more on declaring conflicts of interest.

Clinical Trials Registry

In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository at the beginning of the research process (prior to patient enrolment). Trial registration numbers should be included in the abstract, with full details in the methods section. The registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the WHO International Clinical Trials Registry Platform (ICTRP). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the ICMJE guidelines.

Complying with ethics of experimentation

Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All papers which report *in vivo* experiments or clinical trials on humans or

animals must include a written statement in the Methods section. This should explain that all work was conducted with the formal approval of the local human subject or animal care committees (institutional and national), and that clinical trials have been registered as legislation requires. Authors who do not have formal ethics review committees should include a statement that their study follows the principles of the Declaration of Helsinki.

Consent

All authors are required to follow the ICMJE requirements on privacy and informed consent from patients and study participants. Please confirm that any patient, service user, or participant (or that person's parent or legal guardian) in any research, experiment, or clinical trial described in your paper has given written consent to the inclusion of material pertaining to themselves, that they acknowledge that they cannot be identified via the paper; and that you have fully anonymized them. Where someone is deceased, please ensure you have written consent from the family or estate. Authors may use this Patient Consent Form, which should be completed, saved, and sent to the journal if requested.

Health and safety

Please confirm that all mandatory laboratory health and safety procedures have been complied with in the course of conducting any experimental work reported in your paper. Please ensure your paper contains all appropriate warnings on any hazards that may be involved in carrying out the experiments or procedures you have described, or that may be involved in instructions, materials, or formulae.

Please include all relevant safety precautions; and cite any accepted standard or code of practice. Authors working in animal science may find it useful to consult the International Association of Veterinary Editors' Consensus Author Guidelines on Animal Ethics and Welfare and Guidelines for the Treatment of Animals in Behavioural Research and Teaching. When a product has not yet been approved by an appropriate regulatory body for the use described in your paper, please specify this, or that the product is still investigational.

Submitting your paper

This journal uses ScholarOne to manage the peer-review process. If you haven't submitted a paper to this journal before, you will need to create an account in the submission centre. Please read the guidelines above and then submit your paper in the relevant Author Centre, where you will find user guides and a helpdesk. By submitting your paper to *Disability and Rehabilitation* you are agreeing to originality checks during the peer-review and production processes.

The Editor of *Disability and Rehabilitation* will respond to appeals from authors relating to papers which have been rejected. The author(s) should email the Editor outlining their concerns and making a case for why their paper should not have been rejected. The Editor may choose to accept the appeal and secure a further review, or to not uphold the appeal. In case of the latter, the Editor of *Disability and Rehabilitation: Assistive Technology* will be consulted.

On acceptance, we recommend that you keep a copy of your Accepted Manuscript. Find out more about sharing your work.

Data Sharing Policy

This journal applies the Taylor & Francis Basic Data Sharing Policy. Authors are encouraged to share or make open the data supporting the results or analyses presented in their paper where this does not violate the protection of human subjects or other valid privacy or security concerns.

Authors are encouraged to deposit the dataset(s) in a recognized data repository that can mint a persistent digital identifier, preferably a digital object identifier (DOI) and recognizes a long-term preservation plan. If you are uncertain about where to deposit your data, please see this information regarding repositories.

Authors are further encouraged to cite any data sets referenced in the article and provide a Data Availability Statement.

At the point of submission, you will be asked if there is a data set associated with the paper. If you reply yes, you will be asked to provide the DOI, pre-registered DOI, hyperlink, or other persistent identifier associated with the data set(s). If you have selected to provide a pre-registered DOI, please be prepared to share the reviewer URL associated with your data deposit, upon request by reviewers.

Where one or multiple data sets are associated with a manuscript, these are not formally peer reviewed as a part of the journal submission process. It is the author's responsibility to ensure the soundness of data. Any errors in the data rest solely with the producers of the data set(s).

Publication charges

There are no submission fees, publication fees or page charges for this journal.

Color figures will be reproduced in color in your online article free of charge.

Copyright options

Copyright allows you to protect your original material, and stop others from using your work without your permission. Taylor & Francis offers a number of different license and reuse options, including Creative Commons licenses when publishing open access. Read more on publishing agreements.

Complying with funding agencies

We will deposit all National Institutes of Health or Wellcome Trust-funded papers into PubMedCentral on behalf of authors, meeting the requirements of their respective open access (OA) policies. If this applies to you, please tell our production team when you receive your article proofs, so we can do this for you. Check funders' OA policy mandates here. Find out more about sharing your work.

Open access

This journal gives authors the option to publish open access via our Open Select publishing program, making it free to access online immediately on publication. Many funders mandate publishing your research open access; you can check open access funder policies and mandates here.

Taylor & Francis Open Select gives you, your institution or funder the option of paying an article publishing charge (APC) to make an article open access. Please contact openaccess@tandf.co.uk if you would like to find out more, or go to our Author Services website.

For more information on license options, embargo periods and APCs for this journal please go here.

My Authored Works

On publication, you will be able to view, download and check your article's metrics (downloads, citations and Altmetric data) via My Authored Works on Taylor & Francis Online. This is where you can access every article you have published with us, as well as your free eprints link, so you can quickly and easily share your work with friends and colleagues.

We are committed to promoting and increasing the visibility of your article. Here are some tips and ideas on how you can work with us to promote your research.

Article reprints

For enquiries about reprints, please contact the Taylor & Francis Author Services team at reprints@tandf.co.uk.