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EFEITO DO TREINAMENTO FÍSICO SOBRE A MODULAÇÃO AUTONÔMICA E TOLERÂNCIA AO EXERCÍCIO DE PACIENTES SUBMETIDOS À TERAPIA DE SUBSTITUIÇÃO RENAL: um estudo caso-controle

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São Luís
2019

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Dissertação apresentada ao Programa de Pós-Graduação em Saúde do Adulto da Universidade Federal do Maranhão para obtenção do Grau de Mestre em Saúde do Adulto.

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Orientador: Prof. Dr. Cristiano Teixeira Mostarda

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Aos meus pais, que abdicaram e entregaram de tudo para que eu pudesse “apenas” estudar

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dois anos foi quem me ouviu, me aconselhou e sempre esteve do meu lado tanto nos momentos bons, quanto nos momentos ruins, compartilhando dos meus sonhos e das minhas frustrações, das taças de vinho aos copos de lágrimas. Meu amor, espero que você alcance todos os seus sonhos e que a vida te recompense com uma felicidade do tamanho do meu amor e da minha gratidão. E junto com ela, me trouxe uma segunda família, que aprendi a amar e cuidar como se houvesse nascido de lá.

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“Eu sou apenas um rapaz, latino-americano sem dinheiro no banco, sem parentes importantes, e vindo do interior [...]”

Belchior

RESUMO

Objetivo: Analisar o efeito de um programa de treinamento físico na modulação autonômica, tolerância ao exercício, ansiedade, depressão e qualidade do sono de pacientes em hemodiálise e transplantados renais.

Desenho: Estudo caso-controle

Local: Centro de Prevenção de Doenças Renais, São Luís, Brasil

Participantes: Quatro grupos de pacientes submetidos a hemodiálise e transplantados renais tiveram seus testes bioquímicos e as avaliações da variabilidade da frequência cardíaca analisadas. Também foram avaliados os questionários de qualidade do sono, ansiedade e depressão.

Intervenções: Treinamento físico combinado

Principais medidas de desfecho: Variabilidade da frequência cardíaca e distância do teste de caminhada de seis minutos

Resultados: Ambos os grupos treinados apresentaram maiores valores na modulação autonômica cardiovascular, marcadores bioquímicos e tolerância ao exercício após o programa de treinamento físico. O grupo de pacientes transplantados renais mostrou maiores valores na modulação autonômica cardiovascular, marcadores bioquímicos e tolerância ao exercício quando comparado ao grupo de pacientes em hemodiálise treinados. Ambos os grupos mostraram maiores valores na qualidade do sono, ansiedade e depressão. Os pacientes em hemodiálise apresentaram menores valores de pressão arterial, enquanto o HDL, hemoglobina e fósforo demonstraram menores valores, alterações que não foram observadas no grupo de transplantados renais.

Conclusões: O exercício foi associado com alterações em ambos os grupos de pacientes em hemodiálise e transplantados renais. No entanto, programas de exercícios devem ser focados

principalmente na melhora dos fatores de risco cardiovascular em pacientes em hemodiálise.

Palavras-chave: Exercício; doença renal crônica; transplante; doença cardiovascular; hemodiálise

Este resumo foi estruturado de acordo com as recomendações do STROBE.

ABSTRACT

Aim: We aimed to analyze the effect of an exercise training program in autonomic modulation, exercise tolerance, anxiety, depression and sleep quality of hemodialysis and kidney-transplanted patients.

Design: Case-control study

Setting: In-hospital Center for Kidney Disease Prevention, São Luís, Brazil

Participants: Four groups of patients undergoing hemodialysis and kidney-transplanted subjects had their biochemical tests, and heart rate variability evaluations analyzed. Also, sleep quality, anxiety and depression questionnaires were evaluated.

Interventions: Combined exercise training

Main outcome measures: Heart rate variability, and six-minute walking test distance

Results: Both exercised groups showed higher values in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance after the exercise training program. The exercised kidney-transplanted patients group showed higher values in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance when compared to the exercised hemodialysis patients group. Both groups showed improvements in sleep quality, anxiety, and depression. The group of kidney-transplanted patients show higher values in the cardiovascular autonomic modulation than subjects undergoing hemodialysis. However, the patients undergoing hemodialysis showed improvements in blood pressure, HDL, hemoglobin and phosphorus, changes not observed in the kidney-transplanted group.

Conclusions: Exercise is beneficial for both hemodialysis and kidney-transplanted patients groups. However, exercise programs should be focused mainly in improving cardiovascular risk factors in the hemodialysis patients.

Keywords: Exercise; chronic kidney disease; transplantation; heart rate variability;

hemodialysis

This abstract followed the STROBE recommendations for observational studies.

LISTA DE QUADROS E TABELAS

LISTA DE ILUSTRAÇÕES

LISTA DE SIGLAS E ABREVIATURAS

DRC	Doença Renal Crônica
Ex	Exercício
HAS	Hipertensão Arterial Sistêmica
HD	Hemodiálise
K/DOQI	*Kidney Disease Outcome Quality Initiative*
KDIGO	*Kidney Disease: Improving Global Outcomes*
MAPA	Monitoramento Ambulatorial da Pressão Arterial
MDRD	*Modified Diet for Renal Disease Study*
min	Minuto
mL	Mililitros
mmol	Milimol
ND	Nefropatia Diabética
PD	Diálise Peritoneal
TC6	Teste de Caminhada de Seis Minutos
TFG	Taxa de Filtração Glomerular
TRx	Transplante renal
TSR	Terapia de Substituição Renal
VO^2	Marcador ventilatório do consumo de oxigênio

SUMÁRIO

INTRODUÇÃO

A doença renal crônica (DRC) é uma doença crônica multifatorial com prevalência aproximada de 11 a 13% na população em geral (HILL et al., 2016). As principais causas de desenvolvimento de DRC são hipertensão, diabetes, obesidade e outras doenças relacionadas ao rim como glomerulonefrite e outras infecções do trato urinário superior (HILL et al., 2016). A DRC tem uma forte relação com outras doenças cardiovasculares, como a hipertensão e o desbalanço autonômico, o qual é um forte fator de risco para morte súbita e reduzido tempo de sobrevida (SARNAK et al., 2003; SALMAN, 2015).

A diminuição da função renal está associada a maior frequência de hospitalização, menores índices de disfunção cognitiva e má qualidade de vida (GO et al., 2004; HILL et al., 2016). Além dos problemas de filtração, os pacientes com DRC submetidos à hemodiálise (HD) demonstram níveis elevados de estresse, ansiedade e depressão, além de uma má qualidade do sono (CUKOR et al., 2007; BOSSOLA et al., 2010; CAMACHO-ALONSO et al., 2018)

O principal prognóstico para o paciente em estágio final de DRC é o transplante renal (TRx) (MEIER-KRIESCHE; KAPLAN, 2002; GROUP, 2009; FEEHALLY et al., 2019). Este procedimento tem demonstrado benefícios renais, cardiovasculares, sociais e cognitivos quando comparado aos pacientes com DRC em HD, e atualmente, é o procedimento padrão-ouro para os pacientes em HD (MEIER-KRIESCHE; KAPLAN, 2002; GROUP, 2009; FEEHALLY et al., 2019).

Em ambos os casos de terapia renal substitutiva (HD e TRx), o treinamento físico tem sido usado como uma ferramenta não-farmacológica para reduzir os riscos de eventos cardiovasculares em pacientes com DRC durante a HD e após a cirurgia de TRx, melhorando em grande parte a modulação autonômica cardíaca e a função renal, todas as quais tem sido

extensivamente investigadas pelo nosso grupo de pesquisa (MORAES DIAS et al., 2015; BARROSO et al., 2016; DIAS et al., 2017).

No entanto, até essa data, nenhum estudo comparou o benefício do treinamento físico como uma comparação cruzada entre pacientes com HD e TRx. Além disso, a investigação deste tópico é de extrema importância, visto que antes e depois da cirurgia TRx, os indivíduos sedentários com DRC apresentam maior risco de eventos cardiovasculares e apresentam um estado de humor pior e uma má qualidade do sono (MORAES DIAS et al., 2015; BARROSO et al., 2016; DIAS et al., 2017).

Visto isso, buscamos comparar o efeito de um programa de treinamento físico em pacientes com HD e TRx, em relação à modulação autonômica cardiovascular, tolerância ao exercício, e níveis de ansiedade, depressão e qualidade do sono.

REFERENCIAL TEÓRICO

Doença Renal Crônica (DRC)

A DRC é uma doença crônica multifatorial que atualmente afeta entre aproximadamente seis milhões de pessoas no Brasil (MARINHO et al., 2017), e mais de 20 milhões de pessoas nos Estados Unidos (ROCCO et al., 2015)**.**

Segundo o *Kidney Disease Outcome Quality Initiave* (K/DOQI), a DRC é diagnosticada como a presença de abnormalidades renais, tanto por redução da taxa filtração glomerular (TFG; <60 mL/min/1.73m^2), albuminúria, hematúria com desfiguração de hemoglobina, ou por lesões renais visualizadas através de estudos de imagem ou biópsia renal, ocorridas por um período maior ou igual a três meses (ROCCO et al., 2015).

O método mais utilizado para a estimativa da TFG é a fórmula desenvolvida pelo estudo *Modification of Diet in Renal Disease* (MDRD), onde a idade e a concentração de creatinina sérica são levadas em consideração para o cálculo final da TFG (LEVEY et al., 2006).

(1) TFG = 186.3 x (creatinina sérica em mg/dL – 1.154) x (idade – 0.203) x (1.210 se negro, ou, 0.742 se mulher)

Segundo o K/DOQI e o *Kidney Diseases: Improving Global Outcomes* (KDIGO), a DRC é classificada em cinco estágios, classificados de acordo com a TFG e a excreção urinária de albumina, a albuminúria (Figura 1).

Categorias de Prognóstico da DRC pela TFG e Albuminúria: KDIGO 2012

Categorias da TFG (mL/min/1.73m²) Descrição e intervalos				Categorias de Albuminúria Persistente Descrição e intervalos		
				A1	A2	A3
				Normal a levemente elevado	Moderadamente elevado	Severamente elevado
				<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	Levemente reduzida	60-89			
	G3a	Levemente a moderadamente reduzida	45-59			
	G3b	Moderadamente a severamente reduzida	30-44			
	G4	Severamente reduzida	15-29			
	G5	Insuficiência renal	<15			

Verde: baixo risco (se outros sinais de doença renal ausentes, sem DRC); Amarelo: risco moderadamente elevado; Laranja: alto risco; Vermelho: muito alto risco

Figura 1. Adaptado de *Kidney Disease: Improving Global Outcomes* (KDIGO) (KDIGO, 2013)

Os maiores fatores de risco associados à DRC são a Diabetes e a Hipertensão Arterial Sistêmica (DRAWZ; RAHMAN, 2015; ROCCO et al., 2015), onde a Diabetes mais se destaca. Nos Estados Unidos, a Nefropatia Diabética (ND), lesão renal causada pelo acúmulo de glicose, é considerada a maior causa de DRC, com prevalência entre 20 e 40% dos pacientes diabéticos, e 9,6% na população em geral (KOWALSKI; KRIKORIAN; LERMA, 2015). A ND tem sido relacionada com falta de controle glicêmico adequado, levando ao aumento da produção de agentes glicolisados, responsáveis pela hipertrofia tubular e redução progressiva da TFG (WILLIAMS; GARG, 2014; KOWALSKI; KRIKORIAN; LERMA, 2015).

O diagnóstico preferido para a ND é o de utilização da albuminúria de 24h, pois é característico da ND e mais sensível a lesões glomerulares e também a mudanças de permeabilidade (KDIGO, 2013; KOWALSKI; KRIKORIAN; LERMA, 2015).

Umas das pedras-fundamentais para o tratamento da ND é o controle glicêmico, que tem sido mostrado ao longos dos anos, ser um importante fator de risco para o avanço da DRC (GROUP, 2009; KOWALSKI; KRIKORIAN; LERMA, 2015). Vários estudos tem demonstrado a relação entre o controle glicêmico deficiente no paciente com ND e complicações microvasculares (PATEL et al., 2008; KOWALSKI; KRIKORIAN; LERMA, 2015).

Ruospo et al. elaboraram uma revisão sistemática analisando o efeito de um controle glicêmico rigoroso sobre o avanço da DRC (RUOSPO et al., 2017). O estudo chegou a conclusão que indivíduos submetidos ao controle rigoroso da glicemia tinham reduzido o risco de avançar do estágio A2 para A3, de acordo com a classificação de albuminúria (a mais adequada para pacientes com DRC por origem diabética).

As recomendações atuais de controle glicêmico na DRC são baseadas na hemoglobina glicada (HbA1c), que deve ser mantida, de acordo com o K/DOQI, abaixo de 7% para reduzir o risco de complicações e o avanço de estágio da DRC (ROCCO et al., 2015). No entanto, essas recomendações devem ser individualizadas e acompanhadas por um profissional (KOWALSKI; KRIKORIAN; LERMA, 2015; ROCCO et al., 2015).

Outra recomendação não-farmacológica tão válida quanto o controle glicêmico é o exercício físico. A *American Diabetes Association* recomenda que os pacientes com ND sejam submetidos ao mínimo de 150min de atividade física moderada a intensa por semana, de acordo

com a recomendação do *American College of Sports Medicine* (GARBER et al., 2011; JOHNSON et al., 2019)

Estudos recentes tem demonstrado que o exercício físico reduz a produção de agentes glicolisados, reduzindo por consequência as lesões renais, além de melhora do perfil lipídico e glicêmico, e ainda, redução da excreção de proteínas (SANDLER; MCDONNELL, 2016; SUZUKI et al., 2017).

Um estudo recente conduzido na Finlândia (*FinnDiane Study*) acompanhou pacientes com estágios iniciais de ND durante um período de seis anos, avaliando a cada ano a albuminúria e os níveis de atividade física. Como conclusão, o estudo demonstrou que dos sujeitos que tinha elevados níveis de atividade física (>150min por semana), apenas 13% progrediram para o estágio final da DRC, comparado aos 24% do grupo com baixo nível de atividade física, indicando a importância do exercício sobre a progressão da ND (WADÉN et al., 2005; JERUMS; MACISAAC, 2015).

Outo importante fator de risco para a DRC é a Hipertensão Arterial Sistêmica (HAS). A HAS, como a DRC, é uma doença crônica multifatorial e que afeta diretamente o sistema cardiovascular e renal à longo prazo. A HAS é caracterizada como o aumento da pressão arterial a níveis acima de 130 mmHg de sistólica e 80 mmHg de diastólica, confirmado através do monitoramento ambulatorial da pressão arterial (MAPA), de acordo com as recomendações brasileiras (MALACHIAS et al., 2016).

A HAS tem relação direta com a DRC pois pode ser tanto agente iniciador quanto morbidade secundária a DRC. Alterações crônicas da pressão arterial podem levar a lesão de órgão alvo (neste caso, os rins), causando redução do número de néfrons, aumento da pressão

intra-renal, aumento da excreção de líquidos e aumento da ativação do sistema renina-angiotensina-aldosterona (BROOK; JULIUS, 2000; MORAES-SILVA et al., 2017)

Uma série de estudos tem demonstrado que a pressão arterial elevada é um importante fator de risco para o desenvolvimento da DRC, e também, após a DRC já instalada, esta pressão elevada e não-controlada é fator de risco para a evolução do paciente para os estágios finais da DRC (JAMES et al., 2014; GARGIULO; SUHAIL; LERMA, 2015).

Recentemente, uma metanálise analisou o efeito de protocolos mais restritos de controle da pressão arterial, onde os valores alvo de pressão adequada eram menores, com estudos que tinham alvos de pressão arteriais maiores. O estudo demonstrou que o grupo com alvos menores de pressão possuíam a chance de eventos cardiovasculares e avanço a estágios avançados de DRC menores do que os protocolos com níveis maiores de pressão, indicando que o controle rigoroso dos níveis de pressão arterial deve ser o foco para pacientes com DRC (XIE et al., 2016).

Terapias de Substituição Renal

As Terapias de Substituição Renal (TSR) são tratamentos que visam o auxílio ou a substituição da função renal de um indivíduo (KDIGO, 2013). Atualmente, os caso de pacientes com DRC que avançam para os estágios finais tem reduzido de forma regular, mas países como os Estados Unidos tem uma prevalência muito maior do que o resto da população mundial (Figura 2). O Brasil, por exemplo, possui uma prevalência aproximada entre 121-190 pacientes em estágio final da DRC a cada um milhão de habitantes, comparado com 260 pacientes a cada um milhão de habitantes nos Estados Unidos (FEEHALLY et al., 2019).

Atualmente, as categorias de TSR são a Diálise (Peritoneal [PD] ou Hemodiálise [HD]) e o Transplante Renal (TRx) (KDIGO, 2013). A HD é a terapia preferida como TSR por ser menos invasiva e com menor riscos de infecção, além de maior facilidade de manutenção do acesso ao sistema circulatório do paciente e menor custo, apesar de estudos não demonstrarem diferença na mortalidade entre pacientes submetidos a HD ou PD (FEEHALLY et al., 2019).

A decisão de início diálise tem sido bastante discutida nos últimos anos e varia de classificação entre países. Geralmente, indicadores como redução da TFG abaixo de 30 ml/kg/1,73m^2, aumento da albuminúria e da concentração de fósforo são fatores utilizados para a determinação do início da diálise (ROCCO et al., 2015; FEEHALLY et al., 2019). O foco da TSR é síndrome urêmica, que consiste na presença excessiva de resíduos que compõe a urina na corrente sanguínea (ROCCO et al., 2015; FEEHALLY et al., 2019).

Estudos recentes vem promovendo uma discussão sobre uma possível iniciação da diálise de forma antecipada, entretanto, um estudo recente reportou não haver diferença na mortalidade de indivíduos que começaram a diálise de forma antecipada ou não (COOPER et al., 2010; THAMER et al., 2015).

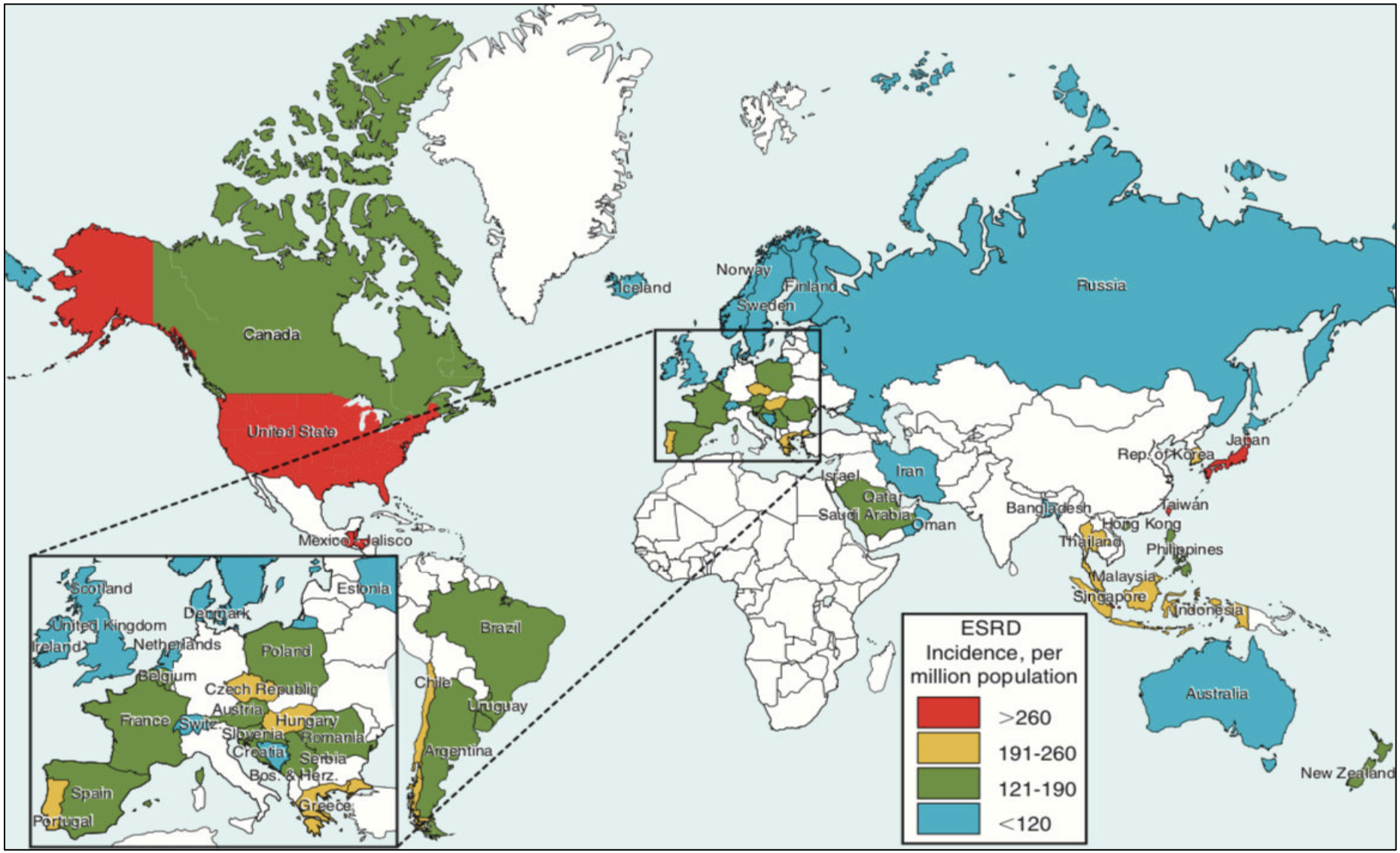

Figura 2. Distribuição geográfica mundial da prevalência de estágio final de DRC; ESRD, acrônimo em inglês para estágio final de DRC; Adaptado de Feehally et al. 2019 (FEEHALLY et al., 2019); Em branco, dados não disponíveis.

Antes das TSR's, vários esforços para o prolongamento da função renal nativa do paciente e prevenção da evolução do quadro de DRC são colocadas em prática, como podem ser vistas no Quadro 1.

Quadro 1. Recomendações para prevenção do avanço da DRC

Ingesta de Sal
Redução para <90 mmol (<2 g) por dia de Sódio (ou 5 g de Cloreto de Sódio)
Atividade física
Prática pelo menos 30 min, cinco vezes por semana
Massa corporal
Manutenção do Índice de Massa Corporal entre 20 e 25
Estado nutricional
Dieta adequada para a DRC, buscando redução de sódio, potássio, fosfato e proteínas, quando indicado

Modificado do KDOQI (ROCCO et al., 2015)

A HD funciona basicamente em substituição aos rins, ou seja, filtra o sangue retirando resíduos de alta acidez e peso molecular como uréia e potássio, e mantém outras substâncias como a glicose, por exemplo (ROCCO et al., 2015; FEEHALLY et al., 2019). A máquina de HD faz isso utilizando filtros de alta sensibilidade e diferentes permeabilidades, permitindo a passagem ou a retenção de diversos tipos de moléculas (ROCCO et al., 2015; FEEHALLY et al., 2019).

Os filtros mais utilizados atualmente são os filtros de polímeros sintéticos, como o polimetilmetacrilato e o copolímero de poliacrilonitrilometacrilato, pois possuem alta biocompatibilidade e alto fluxo de substâncias (ROCCO et al., 2015; FEEHALLY et al., 2019).

A função dos filtros é separar o compartimento com o sangue advindo do paciente, do compartimento que possui o dialisato, permitindo a troca de substância mas, não a mistura completa (ROCCO et al., 2015; FEEHALLY et al., 2019).

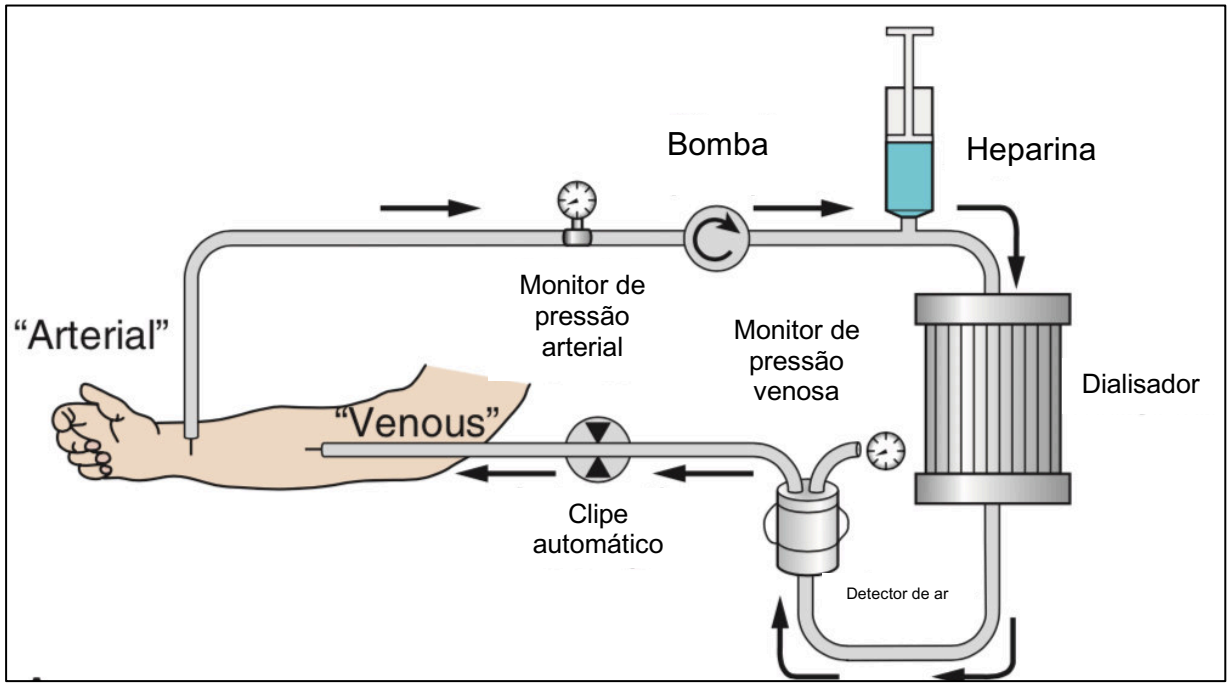

Figura 3. Esquema do funcionamento de uma máquina de HD; Adaptado de Feehally et al. 2019 (FEEHALLY et al., 2019).

Exercício Físico e Sistema Cardiovascular na DRC

O principal fator de risco para a mortalidade nos pacientes com DRC é a doença cardiovascular, que é representada principalmente pelo seus fatores de risco, como a Diabetes e HAS (RUOSPO et al., 2017). Dados recentes demonstram que dentre as oito maiores causas de morte em pacientes com DRC, quatro são por doença cardiovascular, sendo - em ordem -, morte súbita por infarto, insuficiência cardíaca, aterosclerose e acidente vascular cerebral (NIH, 2011) (Figura 4).

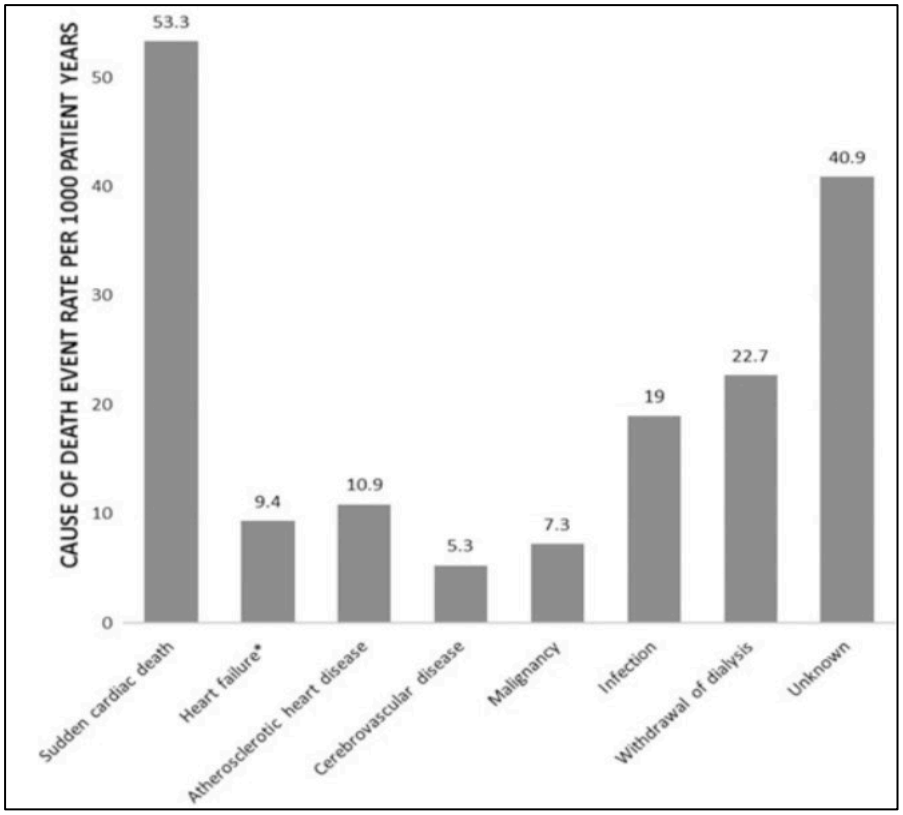

Figura 4. Maiores causas de morte em pacientes com DRC, de acordo com dados originados nos Estados Unidos; Retirado de (NIH, 2011)

No paciente com DRC, a perda da função renal desencadeia uma série de condições que são fatores de risco para eventos cardiovasculares. Inicialmente, a Diabetes e a HAS que são doenças de base fatores de risco para o desenvolvimento da DRC (WILLIAMS; GARG, 2014), também são fatores de risco para doenças cardiovasculares (SCHMIDT et al., 2011)

Além das doenças de base, outras alterações fisiológicas decorrentes da DRC, como o acidose metabólica, stress oxidativo, hipercalemia, calcificação de artérias vasculares, hipertrofia ventricular esquerda, inflamação e vários outros são fatores de risco conhecidos para doença cardiovascular, e que estão presentes no paciente com DRC (GO et al., 2004; RANGASWAMI; LERMA; RONCO, 2017)

As recomendações internacionais de atividade física recomendam a prática entre 3-5 vezes por semana, completando um total mínimo de 150 minutos semanais (NELSON et al., 2007; GARBER et al., 2011). Este ponto de corte foi determinado pelo potencial de benefícios cardiovasculares para a prática utilizando este valor, sendo que frequência semanal menor não foi associada com benefícios cardiovasculares significativos (NELSON et al., 2007; GARBER et al., 2011).

Na DRC, estudos do nosso grupo já vinham apontando para os potenciais benefícios do exercício físico nesse tipo de população, principalmente em relação à modulação autonômica, aferida através da Variabilidade da Frequência Cardíaca (MORAES DIAS et al., 2015; BARROSO et al., 2016). Estudos pioneiros com o uso do exercício em pacientes com DRC, tanto em HD como após TRx, já demonstravam melhora na modulação autonômica, melhora no VO^2 e etc. (KOUIDI, 2001; KONSTANTINIDOU et al., 2002; OUZOUNI et al., 2009).

O exercício físico além de benéfico para os riscos cardiovasculares, também têm sido associado com menores níveis de mortalidade. Um ensaio clínico randomizado e controlado feito em 2016 por Manfredini et al. demonstrou que os grupos de pacientes HD ou TRx que foram submetidos ao exercício físico de intensidade moderada e alta, respectivamente, tiveram diminuição significativa na frequência de hospitalização, e, como achado principal, que possuíam maior tempo de sobrevida quando comparado com os que não participaram do programa de treinamento, ou, iniciaram o programa e não o concluíram (MANFREDINI et al., 2017) (Figura 5).

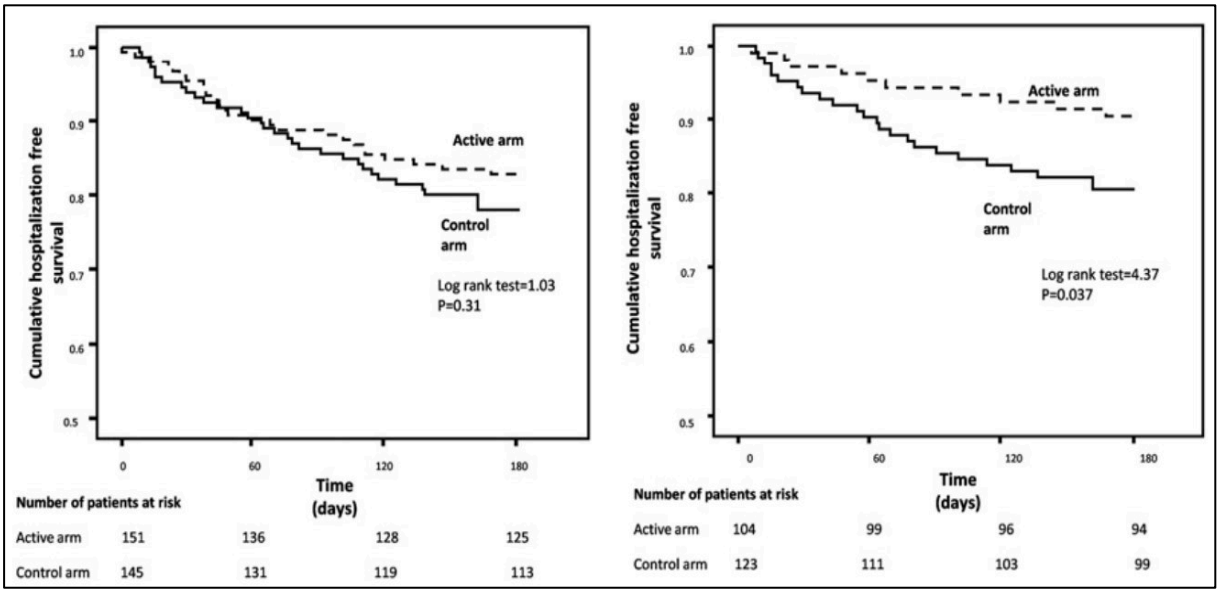

Figura 5. Pacientes com DRC que completaram o programa de treinamento (à direita) possuem maior sobrevida que pacientes que não treinaram ou não completaram o programa de treinamento (à esquerda); Adaptado de (MANFREDINI et al., 2017).

HIPÓTESE

Hipotetizamos que os indivíduos que participam de um programa de treinamento físico possuem adaptações benéficas na modulação autonômica, tolerância ao exercício, ansiedade, depressão e qualidade do sono.

OBJETIVOS

Objetivo geral

Analisar o efeito de um programa de treinamento físico em pacientes com HD e TRx, em relação à modulação autonômica cardiovascular, tolerância ao exercício, ansiedade, depressão e qualidade do sono.

Objetivos específicos

- Avaliar a modulação autonômica através da variabilidade da frequência cardíaca dos pacientes diagnosticados com DRC dos grupos controle e dos grupos submetidos ao programa de exercício

- Avaliar a tolerância ao exercício através do teste de caminhada de seis minutos (TC6) dos pacientes diagnosticados com DRC os grupos controle e dos grupos submetidos ao programa de exercício

- Avaliar os níveis de ansiedade, depressão e qualidade do sono dos pacientes diagnosticados com DRC dos grupos controle e dos grupos submetidos ao programa de exercício

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Title: A case-control study of exercise and kidney disease: hemodialysis and transplantation

Running head: Exercise and chronic kidney disease

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Abstract

We aimed to analyze the effect of an exercise training program in autonomic modulation, and exercise tolerance of hemodialysis and kidney-transplanted patients. Four groups of exercised and non-exercised patients undergoing hemodialysis and kidney-transplanted subjects had their biochemical tests, and heart rate variability evaluations analyzed. Also, sleep quality, anxiety and depression questionnaires were evaluated. Both exercised groups showed improvements in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance after the exercise training program. The exercised kidney-transplanted patients group showed better improvements in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance when compared to the exercised hemodialysis patients group. Both groups showed improvements in sleep quality, anxiety, and depression. The group of kidney-transplanted patients show better results in the cardiovascular autonomic modulation than subjects undergoing hemodialysis. However, the patients undergoing hemodialysis showed improvements in blood pressure, HDL, hemoglobin and phosphorus, changes not observed in the kidney-transplanted group. Exercise is beneficial for both hemodialysis and kidney-transplanted patients groups. However, exercise programs should be focused mainly in improving cardiovascular risk factors in the HD patients.

Keywords: Exercise; chronic kidney disease; transplantation; heart rate variability; hemodialysis

Introduction

Chronic kidney disease (CKD) is a multifactorial disease with a prevalence of 11-13% in the general population around the world (HILL et al., 2016). The leading causes of CKD development are hypertension, diabetes, obesity and other kidney-related diseases like glomerulonephritis and other upper urinary tract infections (HILL et al., 2016). CKD has a strong relationship with other cardiovascular diseases such as hypertension and autonomic imbalance, a substantial risk factor for sudden death and short survival (SARNAK et al., 2003; SALMAN, 2015). The decreased kidney function is associated with increased levels of hospitalization, cognitive dysfunction and poor quality of life (GO et al., 2004; HILL et al., 2016).

Beyond the filtration problems, CKD patients undergoing hemodialysis (HD) have been shown to present higher levels of stress, anxiety, and depression, also leading to poor sleep quality (CUKOR et al., 2007; BOSSOLA et al., 2010).

The golden standard solution for CKD is the kidney transplantation (KTx) (MEIER-KRIESCHE; KAPLAN, 2002; KDOQI, 2007; KDIGO, 2013). This procedure has been shown kidney, cardiovascular, social and cognitive benefits when compared to CKD patients in HD and it is currently the final gold standard procedure for HD patients (KDOQI, 2007; KDIGO, 2013).

In both HD and KTx cases, exercise training has been used as a non-pharmacological tool for reducing risks of cardiovascular events in CKD during HD and after the KTx surgery, mainly improving the cardiac autonomic modulation and kidney function, all of which had been investigated in our research group (MORAES DIAS et al., 2015; BARROSO et al., 2016; DIAS et al., 2017).

However, to this date, no study has ever described the benefits of exercise training among

HD and KTx patients. Furthermore, the investigation of this topic is of utmost importance, seeing that before and after the KTx surgery, sedentary individuals with CKD present a higher risk for cardiovascular events and present worse mood state and poor sleep quality (BARROSO et al., 2016).

Seen this, we aimed to analyze the effect of an exercise training program in both HD and KTx patients, regarding cardiovascular autonomic modulation and, exercise tolerance.

Methods

Sample

The sample was constituted of CKD patients from a reference hospital in São Luís, Brazil. The control groups (HD and KTx) was composed of routine patients at the same reference hospital. The exercised groups (HD+Ex and KTx+Ex) were already enrolled in an institutional exercise program inside the hospital at the beginning of the study and were evaluated for later comparison with the control groups.

For the KTx+Ex group, after a public call, 13 patients were eligible according to the inclusion criteria, but three subjects left the study for changes in the treatment (n=2) and graft rejection (n=1). For the HD + Ex group, 30 patients were eligible for the study according to our inclusion criteria (see above), but only seven remained in the study. The other 23 left the study for transplantation (n=2), changes in the pharmacological treatment (n=2), cardiac catheterism (n=1), zika virus infection (n=4), atrial fibrillation (n=1), anemia (n=3) and abandon (n=10).

For the transplanted groups (KTx and KTx+Ex), all patients older than 18 years-of-age, who underwent kidney transplantation at least six months before the start of the study joined the study. Also, for the inclusion in the KTx group, stable blood pressure and diabetes mellitus variables were required for eligibility. Participants were included in a physical evaluation routine, consisting of anamnesis, laboratory tests, anthropometric evaluation, and an electrocardiogram.

For the hemodialysis group (HD and HD+Ex), subjects were regularly undergoing hemodialysis in a reference hospital in São Luís, Brazil joined the study. All subjects must have met the following criteria: over 18 years-of-age, at least three months of continuous hemodialysis, stable pharmacological treatment for at least three months, and declared ability for exercise

execution.

Patients who smoked or with myopathies, heart disease, cardiac arrhythmias, pacemaker, atrial fibrillation, or any other symptom or illnesses which could jeopardize the analysis of heart rate variability (HRV) were excluded from the study.

Study design

Initially, a public call for the participants was made in the hospital. All patients who were eligible for the study underwent a series of anamnesis and evaluations, as can be seen in the results session (Table 1 and 2).

All subjects were submitted to a physical examination protocol which included an anamnesis, a resting electrocardiogram (4-lead ECG), to blood tests (Table 2), and an anthropometric evaluation (weight and height were measured using a digital scale with a stadiometer [Balmak, São Paulo, Brazil]), body composition was evaluated using a tetrapolar bioimpedance device (BF 906; Maltron, Rayleigh, UK).

Estimated glomerular filtration rate

Glomerular filtration rate (eGFR) was calculated using Levey et al. (LEVEY et al., 2006) formula for adult black males and females. This an alteration from the original formula, adding Creatinine and a 1.73 m2 body surface, used in Modification of Diet in Kidney Disease (MDRD) study.

The Six-Minute Walk Test (6MWT) and Peak of Oxygen Consumption

All subjects underwent a 6MWT, conducted following the established guidelines from the

American Thoracic Society (ENRIGHT, 2003). The test was performed at screening and habituation visit considering a possible learning effect, (14).

Heart rate variability

RR interval was continuously recorded for 10 min in individuals sitting, using an electrocardiogram device (Micromed Wincardio 600hz, Brasilia, DF, Brazil) to power spectral analyses of HRV. The spectrum resulting from the Fast Fourier Transforms modeling is derived from all the data present in a minimum five-minute window from the recorded signal; it includes the entire signal variance, regardless of whether its frequency components appear as specific spectral peaks or as nonpeak broadband powers. The frequency bands used for the spectral analysis are low-frequency (LF, 0.04-0.15Hz), and high-frequency (0.15-0.4Hz).

The symbolic analysis was calculated to provide a quantification of the complexity of the pattern distribution. All possible patterns (i. e., 216) were grouped without any loss into three families referred to as (1) patterns with no variation. The sequences are spread across six levels, and all possible patterns are divided into four groups, consisting of patterns with: 1) no variations (0V, three symbols equal, associated with sympathetic modulation); 2) one variation (1V, two symbols equal and one different associated with sympathetic and parasympathetic modulation); 3) two like variations (2LV and associated with parasympathetic modulation); and 4) two unlike variations (2UV and associated with parasympathetic modulation).

Exercise program

The sequence of exercises was: 1, unilateral knee flexion in standing position; 2, shoulder abduction in standing position; 3, leg abduction in the lateral position; 4, scapular retraction in sitting position; 5, elbow flexion in standing position; 6, unilateral knee extension in sitting position;

7, leg adduction in the lateral position; 8, elbow extension in the supine position.

The Borg scale was used to determine exercise intensity, with the range proposed of 12–13 (slightly tiring). The anklets and dumbbells calibrated in 0.5 kg were used to add resistance during movement and with intervals of 60s between sets.

All participants were already enrolled in a three-times-per-week exercise program, supervised by the hospital's exercise professionals. All groups performed a combined exercise training protocol, where aerobic exercise was divided into three stages: warm-up, conditioning, and cool-down. Strength training was composed of a total of eight exercises.

The aerobic exercise protocol was performed in a horizontal cycle ergometer (Athletic, Active, 50 BH), where exercise intensity was controlled by the participant's rate of perceived exertion, through Borg scale (moderate levels, slightly tiring). The conditioning session included local muscular endurance exercises, with three sets of fifteen repetitions with isotonic contractions, with 2-s duration for each type of contraction (concentric and eccentric) using the alternating segment method.

Anxiety, depression and sleep quality assessments

The quality of sleep and the presence of sleep disturbances were evaluated using the Pittsburgh Sleep Quality Index as initially described by de Buysse (BUYSSE et al., 1989; BERTOLAZI et al., 2011). To evaluate the quality of sleep of the subjects, the SQ was used. It is a questionnaire that evaluates the SQ and sleep disorders. The SQ used seven components: (1) quality subjective sleep, (2) sleep latency, (3) duration of sleep, (4) habitual sleep efficiency, (5) sleep disorders, (6) use of medication to sleep, and (7) daytime sleepiness and disorders during the day.

The score of each component was added to give an overall score ranging from 0 to 21 points.

Each component was individually determined. The higher the value obtained, the worse the quality of sleep (global score is between 6 and 21). For good sleep quality, the sum of the scores is only 5. The Beck Anxiety Inventory and the Beck Depression Inventory were used to evaluate anxiety and depression levels as initially described by Beck (BECK; STEER; BROWN, 1996; GOMES-OLIVEIRA et al., 2012).

Statistical analysis

Initially, a Shapiro-Wilk normality test was used to determine the normality of the sample data. A Two-way ANOVA was conducted to evaluate the difference between groups. A $p<0.05$ was considered significant. Also, the Student's T-test was made for comparisons between the time of treatment (Table 1). The clinical significance (effect size) was computed using Cohen's d formula, as described elsewhere (COHEN, 1988). Briefly, Cohen's d value of 0.8 or higher was considered with very strong clinical significance; values between 0.6 to 0.8 were considered with strong clinical significance; values ranging from 0.4-0.8 were considered with moderate clinical significance, and values lower than 0.4 were considered with weak clinical significance (COHEN, 1988).

Ethical considerations

This study was approved by the Institutional Ethical Board Committee and follows all national and international ethical standards, such as the Helsinki declaration. All subjects signed the Informed Consent before the study beginning. This study followed the STROBE recommendations for reporting observational (case-control) studies ("STROBE statement - Checklist of items that should be included in reports of observational studies (© STROBE Initiative)", 2008). Also, the study followed the Standards for Ethics in Sport and Exercise Science

Research (HARRISS; MACSWEEN; ATKINSON, 2017).

Results

Biochemical tests

Table 1 shows the general characteristics of the sample. No statistical difference was found in the Glycemia in the HD groups (Tukey's $p>0.05$; $d = -0.26$), and KTx groups, but, a clinical significance was achieved (Tukey's $p>0.05$; $d = -1.22$). When comparing the control groups, a significant and clinical significance was found (Tukey's $p<0.05$; $d = 2.40$), with the same pattern present in the KTx+Ex versus HD groups, with no difference, but with clinical significance (Table 3; Tukey's $p>0.05$; $d = 1.53$).

The HDL showed no significant difference but presented clinical significance in the HD groups (Tukey's $p<0.05$; $d = 1.00$). However, no clinical or statistical significance was found in the KTx groups (Tukey's $p>0.05$; $d = -0.03$). Also, a clinical significance was achieved in the comparison of the control groups (Tukey's $p>0.05$; $d = 2.40$), and, as well as in the KTx+Ex versus HD comparison, but with lower values (Tukey's $p>0.05$; $d = 0.71$).

The LDL showed no significant difference but presented clinical significance in the HD (Tukey's $p>0.05$; $d = -0.52$) and the KTx groups (Tukey's $p>0.05$; $d = 0.64$). Also, a clinical significance was achieved in the comparison of the control groups (Tukey's $p<0.05$; $d = -1.19$). Also, a clinical significance was found in the KTx+Ex versus HD comparison (Tukey's $p>0.05$; $d = -1.01$).

The Phosphorus showed no significant difference in the HD groups but achieved a clinical significance (Tukey's $p>0.05$; $d = 0.89$). In the KTx groups, neither statistical difference nor clinical significance was achieved (Tukey's $p>0.05$; $d = 0.11$). When comparing the control groups, a significant difference and a clinical significance were found (Tukey's $p<0.05$; $d = -2.38$). In KTx+Ex versus HD comparison, a statistical difference was found, and clinically relevant effect size was found (Tukey's $p<0.05$; $d = -2.16$).

The Potassium showed neither statistical nor clinical significance in the HD groups

comparison, as well as in the KTx groups comparison (Tukey's $p>0.05$; $d = 0.05$). However, in the control groups comparison, both statistical and clinical significance were found (Tukey's $p<0.05$; $d = -1.28$), as well as in the KTx+Ex versus HD comparison (Tukey's $p<0.05$; $d = -1.16$).

The Calcium showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = 0.94$), as well as in the KTx groups comparison (Tukey's $p>0.05$; $d = 0.64$). However, in the control groups comparison, both statistical and clinical significance were found (Tukey's $p<0.05$; $d = 1.72$).

The Urea showed no statistical difference and, no clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = 0.42$). Despite no statistical difference, a strong clinical significance was found in the KTx groups comparison (Tukey's $p>0.05$; $d = -1.56$). Also, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p<0.05$; $d = -2.55$).

The Hemoglobin showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = 1.15$). Despite no statistical difference, a moderate clinical significance was found in the KTx groups comparison (Tukey's $p>0.05$; $d = 0.63$). However, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p<0.05$; $d = 1.08$).

The Creatinine showed a statistical difference and, a strong clinical significance in the HD groups comparison was achieved (Tukey's $p<0.05$; $d = -1.20$). Despite no statistical difference, a strong clinical significance was found in the KTx groups comparison (Tukey's $p>0.05$; $d = -1.64$). However, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p<0.05$; $d = -8.70$).

The Glomerular filtration rate showed no statistical difference, but a clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = 2.96$). Both statistical difference

and a strong clinical significance were found in the KTx groups comparison (Tukey's $p<0.05$; $d = 4.46$). Also, in the control groups comparison, both statistical and a very strong clinical significance were found (Tukey's $p<0.05$; $d = 36.37$).

Exercise tolerance

The 6MWT distance showed a statistical difference, and a clinical significance in the HD groups comparison was achieved (Tukey's $p<0.05$; $d = 1.78$). Also, significant statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p>0.05$; $d = 1.13$). However, in the control groups comparison, both statistical and clinical significance were not achieved (Tukey's $p>0.05$; $d = -0.29$).

The expected distance achieved in the 6MWT distance showed a statistical difference, and a clinical significance in the HD groups comparison (Tukey's $p<0.05$; $d = 3.88$). Also, significant statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p<0.05$; $d = 3.33$). Also, in the control groups comparison, both statistical and clinical significance were achieved (Tukey's $p<0.05$; $d = -1.27$).

Autonomic modulation

Concerning autonomic modulation, results can be seen in Table 4 and 5. The Total variability showed no statistical difference, but a clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = 1.13$). However, a statistically higher value in the exercised group and, a strong clinical significance was found in the KTx groups comparison (Tukey's $p<0.05$; $d = 4.63$). Also, in the control groups comparison, both statistically higher values in the exercised group and, a strong clinical significance were found (Tukey's $p<0.05$; $d = 3.16$).

The RR showed no statistical difference, and, no clinical significance in the HD groups

comparison was achieved (Tukey's $p>0.05$; $d = 0.30$). Also, no statistical difference was found in the KTx groups, but, a strong clinical significance was found (Tukey's $p>0.05$; $d = 1.15$).

The SDNN showed neither statistical difference nor clinical significance in the HD groups comparison (Tukey's $p>0.05$; $d = -0.43$). Also, no statistical were found in the KTx group but, a strong clinical significance was found in the KTx groups comparison (Tukey's $p>0.05$; $d = 1.62$). Also, in the control groups comparison, no statistical difference was found, but, a strong clinical significance was found (Tukey's $p>0.05$; $d = 1.17$).

The absolute values of LF and HF showed no statistical difference, but a moderate clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = -0.43$ and 0.66, respectively). However, statistically significant higher values and, strong clinical significance were found in the KTx groups comparison (Tukey's $p<0.05$; $d = 1.32$ and 2.58, respectively). Also, in the control groups comparison, both statistically significant higher values in the KTx+Ex group and, strong clinical significance were found (Tukey's $p<0.05$; $d = 2.37$ and 3.02, respectively).

The normalized values of LF and HF showed a statistical difference with a strong clinical significance in the HD groups comparison (Tukey's $p<0.05$; $d = -1.29$ and 1.25, respectively). Also, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's $p<0.05$; $d = -2.58$ and 2.58, respectively). Although, in the control groups comparison, no significant values were found, but a strong clinical significance were found (Tukey's $p>0.05$; $d = -0.99$ and 0.99, respectively).

The LF/HF showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = -1.15$). However, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's $p<0.05$; $d = -2.02$). Although, in the control groups comparison, no significant values were found, but, a strong clinical significance was found (Tukey's $p>0.05$; $d = 1.83$).

The 0V showed no statistical difference, and a moderate clinical significance in the HD groups comparison was achieved (Tukey's $p>0.05$; $d = -0.55$). However, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's $p<0.05$; $d = -3.39$). Although, in the control groups comparison, no significant values were found, but, a moderate clinical significance was found (Tukey's $p>0.05$; $d = 0.71$).

The 1V showed no statistical difference and no clinically relevant in none of the case, except for the KTx groups comparison, which showed a moderate effect size ($d = 0.66$). In the 2LV, no significant difference was found in none of the comparisons. Although, a moderate effect size was found in the HD comparison ($d = 0.69$). However, a strong clinical relevance in the KTx groups comparison was achieved ($d = 4.24$), as well as in the control groups comparison ($d = -0.84$).

In the 2UV, significant differences were found in HD and KTx groups comparison (Tukey's $p<0.05$), with strong effect sizes ($d = 1.26$ and 2.91, respectively). However, no statistical differences were found in the control and KTx+Ex versus HD comparisons ($p<0.05$), but, a moderate effect size was found in the control groups comparison ($d = -0.43$).

Sleep, anxiety and depression inventories

The Sleep, anxiety and depression inventories results are described in Table 6 and 7.

Discussion

This study aimed to analyze the effect of an exercise training program on cardiovascular autonomic modulation and, exercise capacity of HD and KTx patients. Our data display improvements in cardiovascular autonomic modulation and exercise tolerance in both groups. Also, our data shows the HD+Ex group demonstrated lower values in important cardiovascular risk markers such as systolic blood pressure, diastolic blood pressure, LDL cholesterol, Urea, and, increases in HDL cholesterol, Hemoglobin, 6MWT distance and % of predicted. These changes are clinically relevant, seeing that the HD+Ex was able to enter normal reference values for blood pressure, LDL, HDL and, Hemoglobin (Table 2).

To the best of our knowledge, this is the first study to describe the effect of exercise training on autonomic modulation and kidney function of HD and KTx patients comparatively. Our group has been investigating the effects of exercise in CKD patients and had observed its positive effects on autonomic modulation, kidney function, anxiety, depression and sleep quality (MORAES DIAS et al., 2015; BARROSO et al., 2016).

CKD it has been recognized as an independent risk factor for cardiovascular diseases (HILL et al., 2016), with a marked cardiovascular autonomic imbalance (MORAES DIAS et al., 2015; SALMAN, 2015). Exercise has been used as an intervention for promoting a better quality of life and increased cardiac function (PETRAKI et al., 2008; OUZOUNI et al., 2009; BARROSO et al., 2016). Our results show improvements in essential markers of kidney function in both groups after training, such as phosphorus and creatinine (Table 2). As expected, the KTx + Ex group showed higher improvements in those biochemical markers than the HD + Ex group. The management of the biochemical markers are essential, seeing that usually, CKD patients under hemodialysis suffer from parathyroid problems, that can cause hypercalcemia and, hyperphosphatemia (GROUP, 2009),

complications that can further lead to vascular problems like artery calcification and even graft failure (MOE et al., 2004; EGBUNA et al., 2007; GROUP, 2009). Exercise can also be impaired by alterations in sodium and potassium availability in the skeletal muscle (PETERSEN et al., 2012), an activity that is profoundly impaired in patients with CKD. Other studies from our group had demonstrated that exercised CKD patients tend to have lower values of creatinine, phosphorus, and potassium (MORAES DIAS et al., 2015; BARROSO et al., 2016).

Also, the KTx+Ex group showed improved cardiac autonomic modulation, but with far more benefits and improvements than the HD+Ex group (Table 4 and 5). This improvement in the KTx group is remarkable because our data show decreased overall heart rate variability in the HD+Ex group. The KTx+Ex group also shows a reduction in the sympathetic modulation, as expressed by the LF (n.u. and ms2), and increases in vagal modulation, as expressed by HF (n.u. and ms2).

Other studies have shown the beneficial effect of exercise in the autonomic modulation of CKD patients. Kouidi et al. had shown not only benefits in cardiovascular autonomic modulation (similar to those we found), but also baroreflex sensitivity improvements in patients with end-stage kidney disease, with a significant correlation between baroreflex sensitivity indexes and VO2max, an important index of exercise capacity (KOUIDI, 2001). From the same group, Konstantinidou et al. as well showed the benefits of exercise in patients with CKD undergoing hemodialysis, with the same baroreflex and VO2max benefits cited before (KONSTANTINIDOU et al., 2002). Our data corroborate with these two studies, seen that we analyzed trained patients undergoing hemodialysis and after kidney transplantation.

Nonetheless, the autonomic imbalance is correlated with increased risk for cardiovascular diseases and re-hospitalization in subjects with CKD (BROTMAN et al., 2010). This data highlights the importance of effective interventions (such as exercise) to reduce the autonomic

imbalance in these patients, thus reducing the risk of cardiovascular diseases and re-hospitalization among CKD and kidney transplanted patients.

We did not assess the baroreflex sensitivity, but, we may suggest based on the increase of overall variability and changes the sympathovagal balance that these positive changes may have also occurred. Furthermore, we assessed baroreflex sensitivity after an acute session of exercise in CKD patients undergoing hemodialysis and found significant differences in response to exercise stimuli (DIAS et al., 2017).

Both HD+Ex and KTx+Ex groups showed improved exercise capacity, as can be seen by the significant elevations of the 6MWT distance (Table 2). The increases in exercise capacity have been correlated with increased life expectancy and better kidney function in patients with CKD (STACK et al., 2005; KOHL et al., 2012). Also, increased exercise capacity is correlated with increased overall autonomic modulation and reduced risk for cardiovascular diseases (LA ROVERE et al., 2003; STACK et al., 2005).

The most important finding of this study shows that HD+Ex patients show significant clinical improvements in important markers of cardiovascular disease such as blood pressure, lipid profile, hemoglobin and 6MWT distance. Other studies had been shown the benefits of exercise for HD patients, with reductions in blood pressure and increases in exercise capacity (KOUIDI, 2001; PETRAKI et al., 2008; OUZOUNI et al., 2009). This finding in comparison with the KTx patients highlights the increased risk for cardiovascular disease of the HD patients and gives a pathway leading to the use of exercise as a tool inside the hospital, focusing primarily in the HD patients instead of KTx patients.

In conclusion, our data show that an exercise program combined with the kidney transplantation procedure is capable of increasing autonomic modulation and, exercise tolerance of CKD patients. However, the patients undergoing hemodialysis that were also submitted to an

exercise program showed better prognosis in important cardiovascular risk factors, and as well, increased autonomic modulation.

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ANEXO I: TABELAS

Table 1. General characteristics between groups

	HD (n=7)	**HD+Ex (n=7)**	**KTx (n=10)**	**KTx+Ex (n = 10)**
Sex (Male/Female)	4/3	4/3	8/2	8/2
Age (years)	43 ± 7	38 ± 13	37 ± 9	43 ± 13
Hemodialysis time (months)	41 ± 87	44 ± 66	31 ± 28	35 ± 31
Chronic kidney disease time (months)	103 ± 29	97± 36	127 ± 54	132 ± 60
Transplant time (months)	-	-	69 ± 42	72 ± 39
Height (cm)	159 ± 10	164 ± 5	159 ± 8	165 ± 8
Weight (kg)	58 ± 6	52 ± 4	64 ± 11	69 ± 14#
Hospitalizations				
0	2	4	4	4
1-2	3	2	3	3
2-4	1	0	0	1
4 or more	1	1	3	2
Mycophenolate Sodium	-	-	7	8
Tacrolimus	-	-	10	10
Azathioprine	-	-	-	1
Prednisone	2	2	6	7
ACE inhibitors	1	1	7	6
Beta-blockers	2	3	8	6
Calcium channel blockers	1	1	4	5
Furosemide	1	2	-	-
Erythropoietin	4	4	-	-
Sevelamer	1	3	-	-
Calcitriol	2	1	1	1

# $p < 0.05$ same condition (control or exercise) versus Hemodialysis group (mean ± standard deviation)

Table 2. Mean and standard deviations of biochemical tests between groups

	Reference values	HD (n=7)	HD + Ex (n = 7)	KTx (n=10)	KTx + Ex (n=10)
Systolic arterial pressure (mm/Hg)	<130	136.50 ± 3.87	121.20 ± 14.27	114.22 ± 10.99	118.5 ± 9.23
Diastolic arterial pressure (mm/Hg)	<90	83 ± 5.13	75 ± 8.69	69.89 ± 8.52	75 ± 6.51
Glycemia (mg/dL)	60-99	84.5 ± 7.14	82.25 ± 10.01	103 ± 8.23#	94.2 ± 5.9□†
HDL cholesterol (mg/dL)	>60; Low <40	40.33 ± 3.21	58 ± 24.70	46 ± 9.88	45.7 ± 10.1
LDL cholesterol (mg/dL)	<100; High >160	124 ± 45.08	105.3 ± 22.69	85 ± 10#	91 ± 8.48
Phosphorus (mg/dL)	2.5-4.5	4.42 ± 0.66	4.94 ± 0.49	3.12 ± 0.40#	3.17 ± 0.48#
Potassium (mg/dL)	3.5-5.1	4.88 ± 0.74	4.6 ± 0.48	4.15 ± 0.33#	4.17 ± 0.44
Urea (mg/dL)	2.5-7.8	112 ± 30	96.4 ± 42	51.3 ± 15#	30.20 ± 11.76
Calcium (mg/dL)	8.6-10.2	8.76 ± 0.53	9.34 ± 0.69	9.57 ± 0.40#	10.06 ± 1†
Hemoglobin (g/dL)	13-18	10.8 ± 2.27	12.78 ± 0.83*	13.09 ± 1.93	14.15 ± 1.33#
Serum creatinine (mg/dL)	0.4-1.40	9.98 ± 1.39	7.66 ± 2.35*	1.32 ± 0.22	1.01 ± 0.15#
Glomerular filtration rate (mL/min)	>90	5.3 ± 0.6	7.4 ± 0.8*	59 ± 2#	82 ± 7*†#
Kt/V	>1.3	1.29 ± 0.33	1.51 ± 1.51	-	-
6MWT distance (meters)	-	450 ± 62	612 ± 77*	433 ± 55	607 ± 69*
6MWT (% of predicted)	-	78 ± 6	108 ± 10*	69 ± 8	103 ± 12*#

*p< 0.05 versus same condition without exercise; #p <0.05 versus Hemodialysis group; † versus HD + Ex group (mean ± standard deviation)

Table 3. Mean difference and effect size between groups

	(KTx control – HD control)		HD (exercise – control)		KTx (exercise – control)	
	Δ (CI)	**d**	**Δ (CI)**	**d**	**Δ (CI)**	**d**
Systolic arterial pressure (mm/Hg)	-22.28 (-36.04/-8.51)	-2.70	-15.30 (-30.22/-0.37)	-1.47	4.28 (-8.21/16.77)	0.42
Diastolic arterial pressure (mm/Hg)	-13.11 (-22.79/-3.42)	-1.87	-8.00 (-18.50/2.50)	-1.12	-5.11 (-3.68/13.90)	-0.67
Glycemia (mg/dL)	18.5 (8.03/28.94)	2.40	-2.25 (-9.10/13.6)	-0.26	-8.80 (-18.3/0.69)	-1.22
HDL cholesterol (mg/dL)	5.67 (-12.50/23.84)	0.77	17.67 (-37.38/2.04)	1.00	-0.30 (-16.79/16.19)	-0.03
LDL cholesterol (mg/dL)	-39 (-71.12/-6.89)	-1.19	-18.70 (-53.53/16.12)	-0.52	6.00 (-23.13/35.13)	0.64
Phosphorus (mg/dL)	-1.3 (-1.97/-0.62)	-2.38	0.52 (-0.20/1.25)	0.89	0.05 (-0.56/0.66)	0.11
Potassium (mg/dL)	-0.73 (-1.39/-0.06)	-1.28	-0.28 (-1.00/0.44)	-0.44	0.02 (-0.58/0.62)	0.05
Calcium (mg/dL)	0.81 (0.22/1.39)	1.72	0.58 (-0.05/1.21)	0.94	0.49 (-0.04/1.02)	0.64
Urea (mg/dL)	-60.7 (-94.64/-26.75)	-2.55	-15.6 (-52.41/21.21)	-0.42	-21.10 (-51.9/9.70)	-1.56
Hemoglobin (g/dL)	2.29 (0.04/4.53)	1.08	1.98 (-0.45/4.41)	1.15	1.06 (-0.98/3.10)	0.63
Serum creatinine (mg/dL)	-8.66 (-10.30/7.01)	-8.70	-2.32 (-4.10/-0.53)	-1.20	-0.31 (-1.80/1.18)	-1.64
Glomerular filtration rate (mL/min)	53.7 (48.32/59.07)	36.37	2.10 (-3.73/7.93)	2.96	23.00 (18.12/27.88)	4.46
Kt/V	-	-	0.22 (-1.49/1.05)	0.20	-	-
6MWT distance (meters)	-17.00 (-104/70.76)	-0.29	162 (66.80/257)	2.31	174 (94.35/254)	2.78
6MWT (% of predicted)	-9.00 (-21.68/3.68)	-1.27	30.00 (16.24/43.75)	3.88	34.00 (22.49/45.50)	3.33

Δ (CI), mean difference and 95% confidence interval; d, Cohen's d for effect size (negative numbers favours control group; positive numbers favours experimental group); Kt/V, indicator of hemodialysis adequacy (K, urea clearance by the dialyzer; t, treatment time; V, urea distribution volume)

Table 4. Mean and standard deviations of heart rate variability indexes between groups

	HD (n=7)	**HD + Ex (n=7)**	**KTx (n=10)**	**KTx + Ex (n=10)**
		Time domain		
Total variability (ms^2)	231 ± 76	312 ± 66*	488 ± 86#	923 ± 101*#
RR (ms)	777 ± 108	810 ± 105	750 ± 40	794 ± 36
SDNN (ms)	14 ± 9	18 ± 8*	22 ± 3.5	30 ± 6#
		Frequency domain		
LF (ms^2)	51 ± 53	33 ± 26	170 ± 30#	307 ± 143*#
HF (ms^2)	39 ± 34	108 ± 143	77 ± 16#	237 ± 86*
LF (nu)	56 ± 21	30 ± 19*	72 ± 9	54 ± 4*#
HF (nu)	44 ± 21	69 ± 19*	28 ± 9	46 ± 4*#
LF/HF	1.3 ± 1	0.45 ± 0.3	2.7 ± 0.4#	1.16 ± 1*#
		Symbolic analysis		
0V (%)	25 ± 19	16 ± 13	35 ± 5	21 ± 3*
1V (%)	45 ± 12	41 ± 17	43 ± 5	46 ± 4
2LV (%)	11 ± 10	17 ± 7	5 ± 0.8	8 ± 0.6#
2UV (%)	19 ± 6	26 ± 5*	17 ± 2.5	23 ± 1.5*

* $p < 0.05$ versus Control; # $p < 0.05$ same condition (control or exercise) versus Hemodialysis group (mean ± standard deviation);

Table 5. Difference between groups and moments for heart rate variability

	(KTx control – HD control)		**HD (exercise – control)**		**KTx (exercise – control)**	
	Δ (CI)	**d**	**Δ (CI)**	**d**	**Δ (CI)**	**d**
Total variability (ms^2)	257 (142/371)	3.16	81 (-43/205)	1.13	435 (331/538)	4.63
RR (ms)	-27 (-125/71.51)	-0.33	33 (-79/139)	0.30	44 (-45.4/133)	1.15
SDNN (ms)	8 (-0.83/16.83)	1.17	4 (-5.58/13.58)	0.46	8 (-0.02/16.01)	1.62
LF (ms^2)	119 (6.08/231)	2.76	-18 (-140/104)	-0.43	137 (34.53/239)	1.32
HF (ms^2)	38 (70/7147)	1.43	69 (-49.21/187)	0.66	160 (61.09/259)	2.58
LF (nu)	16 (-2.44/34.44)	-0.99	-26 (-46.00/-5.99)	-1.29	-18 (-1.26/-34.73)	-2.58
HF (nu)	-16 (-34.44/2.44)	0.99	25 (4.99/45.06)	1.25	18 (1.26/34.73)	2.58
LF/HF	1.4 (0.39/2.40)	1.83	-0.85 (-1.94/0.24)	-1.15	-1.54 (-2.45/-0.62)	-2.02
0V (%)	10 (-4.44/24.44)	0.71	-9 (-24.66/6.66)	-0.55	-14 (-27.10/-0.89)	-3.39
1V (%)	-2 (-15.32/11.32)	-0.21	-4 (-18.45/10.45)	-0.27	3 (-9.09/15.1)	0.66
2LV (%)	-6 (-13.35/1.35)	-0.84	6 (-1.97/13.97)	0.69	3 (-3.67/9.67)	4.24
2UV (%)	-2 (-7.14/3.14)	-0.43	7 (1.41/12.58)	1.26	6 (1.33/10.67)	2.91

Δ (CI), mean difference and 95% confidence interval; d, Cohen's d for effect size (negative numbers favours control group; positive numbers favours experimental group);

Table 6. Sleep, anxiety and depression scores in both groups

	HD (n=7)	HD+Ex (n=7)	KTx (n=10)	KTx+Ex (n=10)
Pittsburgh Sleep Quality Index	6.5 ± 2	4.5 ± 2	7 ± 2	5 ± 1.5
Beck Depression Index	9 ± 5	5 ± 4	5 ± 3	9 ± 5
Beck Anxiety Index	10 ± 7	5.5 ± 3	7 ± 4	6 ± 4

Table 7. Difference and effect sizes of the sleep quality, anxiety and depression inventories

	(KTx control – HD control)		HD (exercise – control)		KTx (exercise – control)	
	Δ (CI)	**d**	**Δ (CI)**	**d**	**Δ (CI)**	**d**
Pittsburgh Sleep Quality Index	0.5 (-1.99/2.99)	0.25	-2.00 (-4.70/0.70)	-1.00	-2.00 (-4.26/0.26)	-1.13
Beck Depression Index	-4.00 (-9.74/1.74)	-0.97	-4.00 (-10.23/2.23)	-0.88	4.00 (-1.21/9.21)	0.97
Beck Anxiety Index	-3.00 (-9.16/3.16)	-0.52	-4.50 (-11.19/2.19)	-0.83	-1.00 (-6.59/4.59)	-0.25

Δ (CI), mean difference and 95% confidence interval; d, Cohen's d for effect size

ANEXO II: ARTIGO PUBLICADO

A Case-control Study of Exercise and Kidney Disease: Hemodialysis and Transplantation

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A Case-control Study of Exercise and Kidney Disease: Hemodialysis and Transplantation

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exercise, chronic kidney disease, kidney replacement therapy, heart rate variability

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ABSTRACT

We aimed to analyze the effect of an exercise training program in autonomic modulation, and exercise tolerance of hemodialysis and kidney-transplanted patients. 4 groups of exercised and non-exercised patients undergoing hemodialysis and kidney-transplanted subjects had their biochemical tests, and heart rate variability evaluations analyzed. Also, sleep quality, anxiety and depression questionnaires were evaluated. Both exercised groups showed improvements in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance after the exercise training program. The exercised kidney-transplanted patients group showed better improvements in cardiovascular autonomic modulation, biochemical markers, and exercise tolerance when compared to the exercised hemodialysis patients group. Both groups showed improvements in sleep quality, anxiety, and depression. The group of kidney-transplanted patients show better results in the cardiovascular autonomic modulation than subjects undergoing hemodialysis. However, the patients undergoing hemodialysis showed improvements in blood pressure, HDL, hemoglobin and phosphorus, changes not observed in the kidney-transplanted group. Exercise is beneficial for both hemodialysis and kidney-transplanted patients groups. However, exercise programs should be focused mainly in improving cardiovascular risk factors in the HD patients.

Introduction

Chronic kidney disease (CKD) is a multifactorial disease with a prevalence of 11–13 % in the general population around the world [14]. The leading causes of CKD development are hypertension, diabetes, obesity and other kidney-related diseases like glomerulonephritis and other upper urinary tract infections [14]. CKD has a strong relationship with other cardiovascular diseases such as hypertension and autonomic imbalance, a substantial risk factor for sudden death and short survival [28, 29]. The decreased kidney function is associated with increased levels of hospitalization, cognitive dysfunction and poor quality of life [11, 14].

Beyond the filtration problems, CKD patients undergoing hemodialysis (HD) have been shown to present higher levels of stress, anxiety, and depression, also leading to poor sleep quality [3, 7].

The golden standard solution for CKD is kidney transplantation (KTx) [15, 16, 21]. This procedure has shown kidney, cardiovascular, social and cognitive benefits when compared to CKD patients in HD and it is currently the final gold standard procedure for HD patients [15, 16].

In both HD and KTx cases, exercise training has been used as a non-pharmacological tool for reducing risks of cardiovascular events in CKD during HD and after the KTx surgery, mainly improving the cardiac autonomic modulation and kidney function, all of which had been investigated in our research group [1, 8, 23].

However, to this date, no study has ever described the benefits of exercise training among HD and KTx patients. Furthermore, the investigation of this topic is of utmost importance, seeing that before and after the KTx surgery, sedentary individuals with CKD present a higher risk for cardiovascular events and present worse mood state and poor sleep quality [1].

With this in mind, we aimed to analyze the effect of an exercise training program in both HD and KTx patients, regarding cardiovascular autonomic modulation and, exercise tolerance.

Materials and Methods

Sample

The sample was constituted of CKD patients from a reference hospital in São Luís, Brazil. The control groups (HD and KTx) was composed of routine patients at the same reference hospital. The exercised groups (HD + Ex and KTx + Ex) were already enrolled in an institutional exercise program inside the hospital at the beginning of the study and were evaluated for later comparison with the control groups.

For the KTx + Ex group, after a public call, 13 patients were eligible according to the inclusion criteria, but 3 subjects left the study for changes in the treatment (n = 2) and graft rejection (n = 1). For the HD + Ex group, 30 patients were eligible for the study according to our inclusion criteria (see above), but only 7 remained in the study. The other 23 left the study for transplantation (n = 2), changes in the pharmacological treatment (n = 2), cardiac catheterism (n = 1), zika virus infection (n = 4), atrial fibrillation (n = 1), anemia (n = 3) and abandon (n = 10).

For the transplanted groups (KTx and KTx + Ex), all patients older than 18 years of age, who underwent kidney transplantation at least 6 months before the start of the study joined the study. Also, for the inclusion in the KTx group, stable blood pressure and diabetes mellitus variables were required for eligibility. Participants were included in a physical evaluation routine, consisting of anamnesis, laboratory tests, anthropometric evaluation, and an electrocardiogram.

For the hemodialysis group (HD and HD + Ex), subjects were regularly undergoing hemodialysis in a reference hospital in São Luís, Brazil joined the study. All subjects must have met the following criteria: over 18 years-of-age, at least 3 months of continuous hemodialysis, stable pharmacological treatment for at least 3 months, and declared ability for exercise execution.

Patients who smoked or with myopathies, heart disease, cardiac arrhythmias, pacemaker, atrial fibrillation, or any other symptom or illnesses which could jeopardize the analysis of heart rate variability (HRV) were excluded from the study.

Study design

Initially, a public call for the participants was made in the hospital. All patients who were eligible for the study underwent a series of anamnesis and evaluations, as can be seen in the results session (▶ **Table 1**, **2**).

All subjects were submitted to a physical examination protocol which included an anamnesis, a resting electrocardiogram (4-lead ECG), to blood tests (▶ **Table 2**), and an anthropometric evaluation (weight and height were measured using a digital scale with a stadiometer [Balmak, São Paulo, Brazil]), body composition was evaluated using a tetrapolar bioimpedance device (BF 906; Maltron, Rayleigh, UK).

Estimated glomerular filtration rate

Glomerular filtration rate (eGFR) was calculated using Levey et al. [20] formula for adult black males and females. This an alteration from the original formula, adding Creatinine and a 1.73 m^2 body surface, used in Modification of Diet in Kidney Disease (MDRD) study.

The 6-Min Walk Test (6 MWT) and Peak of oxygen consumption

All subjects underwent a 6 MWT, conducted following the established guidelines from the American Thoracic Society [10]. The test was performed at screening and habituation visit considering a possible learning effect, (14).

Heart rate variability

RR interval was continuously recorded for 10 min in individuals sitting, using an electrocardiogram device (Micromed Wincardio 600 hz, Brasilia, DF, Brazil) to power spectral analyses of HRV. The spectrum resulting from the Fast Fourier Transforms modeling is derived from all the data present in a minimum 5-min window from the recorded signal; it includes the entire signal variance, regardless of whether its frequency components appear as specific spectral peaks or as nonpeak broadband powers. The frequency bands used for the spectral analysis are low-frequency (LF, 0.04–0.15 Hz), and high-frequency (0.15–0.4 Hz).

The symbolic analysis was calculated to provide a quantification of the complexity of the pattern distribution. All possible patterns (i. e., 216) were grouped without any loss into 3 families referred

▶ **Table 1** General characteristics between groups.

	HD (n = 7)	HD + Ex (n = 7)	KTx (n = 10)	KTx + EX (n = 10)
Sex (Male/Female)	4/3	4/3	8/2	8/2
Age (years)	43 ± 7	38 ± 13	37 ± 9	43 ± 13
Hemodialysis time (months)	41 ± 87	44 ± 66	31 ± 28	35 ± 31
Chronic kidney disease time (months)	103 ± 29	97 ± 36	127 ± 54	132 ± 60
Transplant time (months)	-	-	69 ± 42	72 ± 39
Height (cm)	159 ± 10	164 ± 5	159 ± 8	165 ± 8
Weight (kg)	58 ± 6	52 ± 4	64 ± 11	69 ± 14#
Hospitalizations				
0	2	4	4	4
1–2	3	2	3	3
2–4	1	0	0	1
4 or more	1	1	3	2
Mycophenolate sodium	-	-	7	8
Tacrolimus	-	-	10	10
Azathioprine	-	-	-	1
Prednisone	2	2	6	7
ACE inhibitors	1	1	7	6
Beta-blockers	2	3	8	6
Calcium channel blockers	1	1	4	5
Furosemide	1	2	-	-
Erythropoietin	4	4	-	-
Sevelamer	1	3	-	-
Calcitriol	2	1	1	1

# p < 0.05 same condition (control or exercise) vs. Hemodialysis group (mean ± standard deviation)

▶ **Table 2** Mean and standard deviations of biochemical tests between groups.

	Reference values	HD (n = 7)	HD + Ex (n = 7)	KTx (n = 10)	KTx + Ex (n = 10)
Systolic arterial pressure (mm/Hg)	< 130	136.50 ± 3.87	121.20 ± 14.27	114.22 ± 10.99	118.5 ± 9.23
Diastolic arterial pressure (mm/Hg)	< 90	83 ± 5.13	75 ± 8.69	69.89 ± 8.52	75 ± 6.51
Glycemia (mg/dL)	60–99	84.5 ± 7.14	82.25 ± 10.01	103 ± 8.23#	94.2 ± 5.9†
HDL cholesterol (mg/dL)	> 60; Low < 40	40.33 ± 3.21	58 ± 24.70	46 ± 9.88	45.7 ± 10.1
LDL cholesterol (mg/dL)	< 100; High > 160	124 ± 45.08	105.3 ± 22.69	85 ± 10#	91 ± 8.48
Phosphorus (mg/dL)	2.5–4.5	4.42 ± 0.66	4.94 ± 0.49	3.12 ± 0.40#	3.17 ± 0.48#
Potassium (mg/dL)	3.5–5.1	4.88 ± 0.74	4.6 ± 0.48	4.15 ± 0.33#	4.17 ± 0.44
Urea (mg/dL)	2.5–7.8	112 ± 30	96.4 ± 42	51.3 ± 15#	30.20 ± 11.76
Calcium (mg/dL)	8.6–10.2	8.76 ± 0.53	9.34 ± 0.69	9.57 ± 0.40#	10.06 ± 1†
Hemoglobin (g/dL)	13–18	10.8 ± 2.27	12.78 ± 0.83*	13.09 ± 1.93	14.15 ± 1.33#
Serum creatinine (mg/dL)	0.4–1.40	9.98 ± 1.39	7.66 ± 2.35*	1.32 ± 0.22	1.01 ± 0.15#
Glomerular filtration rate (mL/min)	> 90	5.3 ± 0.6	7.4 ± 0.8*	59 ± 2#	82 ± 7* †#
Kt/V	> 1.3	1.29 ± 0.33	1.51 ± 1.51	-	-
6 MWT distance (meters)	-	450 ± 62	612 ± 77*	433 ± 55	607 ± 69*
6 MWT (% of predicted)	-	78 ± 6	108 ± 10*	69 ± 8	103 ± 12* #

* p < 0.05 vs. same condition without exercise; #p < 0.05 vs. Hemodialysis group; † vs. HD + Ex group (mean ± standard deviation)

to as (1) patterns with no variation. The sequences are spread across 6 levels, and all possible patterns are divided into 4 groups, consisting of patterns with:

1) no variations (0 V, 3 symbols equal, associated with sympathetic modulation); 2) one variation (1 V, 2 symbols equal and one different associated with sympathetic and parasympathetic modulation); 3) 2 like variations (2 LV and associated with parasympathetic modulation); and 4) 2 unlike variations (2 UV and associated with parasympathetic modulation).

Exercise program

The sequence of exercises was: 1, unilateral knee flexion in standing position; 2, shoulder abduction in standing position; 3, leg abduction in the lateral position; 4, scapular retraction in sitting position; 5, elbow flexion in standing position; 6, unilateral knee extension in sitting position; 7, leg adduction in the lateral position; 8, elbow extension in the supine position.

The Borg scale was used to determine exercise intensity, with the range proposed of 12–13 (slightly tiring). Anklets and dumbbells calibrated in 0.5 kg were used to add resistance during movement and with intervals of 60 s between sets.

All participants were already enrolled in a 3-times-per-week exercise program, supervised by the hospital's exercise professionals. All groups performed a combined exercise training protocol, where aerobic exercise was divided into 3 stages: warm-up, conditioning, and cool-down. Strength training was composed of a total of 8 exercises.

The aerobic exercise protocol was performed in a horizontal cycle ergometer (Athletic, Active, 50 BH), where exercise intensity was controlled by the participant's rate of perceived exertion, through Borg scale (moderate levels, slightly tiring). The conditioning session included local muscular endurance exercises, with 3 sets of fifteen repetitions with isotonic contractions, with 2-s duration for each type of contraction (concentric and eccentric) using the alternating segment method.

Anxiety, depression and sleep quality assessments

The quality of sleep and the presence of sleep disturbances were evaluated using the Pittsburgh Sleep Quality Index as initially described by de Buysse [5]. To evaluate the quality of sleep of the subjects, the SQ was used. It is a questionnaire that evaluates the SQ and sleep disorders. The SQ used 7 components: (1) quality subjective sleep, (2) sleep latency, (3) duration of sleep, (4) habitual sleep efficiency, (5) sleep disorders, (6) use of medication to sleep, and (7) daytime sleepiness and disorders during the day.

The score of each component was added to give an overall score ranging from 0 to 21 points. Each component was individually determined. The higher the value obtained, the worse the quality of sleep (global score is between 6 and 21). For good sleep quality, the sum of the scores is only 5. The Beck Anxiety Inventory and the Beck Depression Inventory were used to evaluate anxiety and depression levels as initially described by Beck [2].

Statistical analysis

Initially, a Shapiro-Wilk normality test was used to determine the normality of the sample data. A 2-way ANOVA was conducted to evaluate the difference between groups. A $p < 0.05$ was considered significant. Also, the Student's t-test was made for comparisons between the time of treatment (▶ **Table 1**). The clinical significance (effect size) was computed using Cohen's d formula, as described elsewhere [6]. Briefly, Cohen's d value of 0.8 or higher was considered with very strong clinical significance; values between 0.6 to 0.8 were considered with strong clinical significance; values ranging from 0.4–0.8 were considered to have moderate clinical significance, and values lower than 0.4 were considered to have weak clinical significance [6].

Ethical considerations

This study was approved by the Institutional Ethical Board Committee and follows all national and international ethical standards, such as the Helsinki declaration. All subjects signed the Informed Consent before the study beginning. This study followed the STROBE recommendations for reporting observational (case-control) studies [31]. Also, the study followed the Standards for Ethics in Sport and Exercise Science Research [13] as well as those of this journal.

Results

Biochemical tests

▶ **Table 1** shows the general characteristics of the sample. No statistical difference was found in the Glycemia in the HD groups (Tukey's $p > 0.05$; $d = -0.26$), and KTx groups, but, a clinical significance was achieved (Tukey's $p > 0.05$; $d = -1.22$). When comparing the control groups, a significant and clinical significance was found (Tukey's $p < 0.05$; $d = 2.40$), with the same pattern present in the KTx + Ex vs. HD groups, with no difference, but with clinical significance (▶ **Table 3**; Tukey's $p > 0.05$; $d = 1.53$).

The HDL showed no significant difference but presented clinical significance in the HD groups (Tukey's $p < 0.05$; $d = 1.00$). However, no clinical or statistical significance was found in the KTx groups (Tukey's $p > 0.05$; $d = -0.03$). Also, a clinical significance was achieved in the comparison of the control groups (Tukey's $p > 0.05$; $d = 2.40$), and, as well as in the KTx + Ex vs. HD comparison, but with lower values (Tukey's $p > 0.05$; $d = 0.71$).

LDL showed no significant difference but presented clinical significance in the HD (Tukey's $p > 0.05$; $d = -0.52$) and the KTx groups (Tukey's $p > 0.05$; $d = 0.64$). Also, a clinical significance was achieved in the comparison of the control groups (Tukey's $p < 0.05$; $d = -1.19$). Also, a clinical significance was found in the KTx + Ex vs. HD comparison (Tukey's $p > 0.05$; $d = -1.01$).

Phosphorus showed no significant difference in the HD groups but achieved a clinical significance (Tukey's $p > 0.05$; $d = 0.89$). In the KTx groups, neither statistical difference nor clinical significance was achieved (Tukey's $p > 0.05$; $d = 0.11$). When comparing the control groups, a significant difference and a clinical significance were found (Tukey's $p < 0.05$; $d = -2.38$). In KTx + Ex vs. HD comparison, a statistical difference was found, and clinically relevant effect size was found (Tukey's $p < 0.05$; $d = -2.16$).

Potassium showed neither statistical nor clinical significance in the HD groups comparison, as well as in the KTx groups comparison (Tukey's $p > 0.05$; $d = 0.05$). However, in the control groups comparison, both statistical and clinical significance were found (Tukey's $p < 0.05$; $d = -1.28$), as well as in the KTx + Ex vs. HD comparison (Tukey's $p < 0.05$; $d = -1.16$).

Calcium showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 0.94$), as well as in the KTx groups comparison (Tukey's $p > 0.05$; $d = 0.64$). However, in the control groups comparison, both statistical and clinical significance were found (Tukey's $p < 0.05$; $d = 1.72$).

Urea showed no statistical difference and, no clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 0.42$). Despite no statistical difference, a strong clinical signifi-

▶ **Table 3** Mean difference and effect size between groups.

	(KTx control – HD control)		HD (exercise – control)		KTx (exercise – control)	
	Δ (CI)	d	Δ (CI)	d	Δ (CI)	d
Systolic arterial pressure (mm/Hg)	−22.28 (−36.04/−8.51)	−2.70	−15.30 (−30.22/−0.37)	−1.47	4.28 (−8.21/16.77)	0.42
Diastolic arterial pressure (mm/Hg)	−13.11 (−22.79/−3.42)	−1.87	−8.00 (−18.50/2.50)	−1.12	−5.11 (−3.68/13.90)	−0.67
Glycemia (mg/dL)	18.5 (8.03/28.94)	2.40	−2.25 (−9.10/13.6)	−0.26	−8.80 (−18.3/0.69)	−1.22
HDL cholesterol (mg/dL)	5.67 (−12.50/23.84)	0.77	17.67 (−37.38/2.04)	1.00	−0.30 (−16.79/16.19)	−0.03
LDL cholesterol (mg/dL)	−39 (−71.12/−6.89)	−1.19	−18.70 (−53.53/16.12)	−0.52	6.00 (−23.13/35.13)	0.64
Phosphorus (mg/dL)	−1.3 (−1.97/−0.62)	−2.38	0.52 (−0.20/1.25)	0.89	0.05 (−0.56/0.66)	0.11
Potassium (mg/dL)	−0.73 (−1.39/−0.06)	−1.28	−0.28 (−1.00/0.44)	−0.44	0.02 (−0.58/0.62)	0.05
Calcium (mg/dL)	0.81 (0.22/1.39)	1.72	0.58 (−0.05/1.21)	0.94	0.49 (−0.04/1.02)	0.64
Urea (mg/dL)	−60.7 (−94.64/−26.75)	−2.55	−15.6 (−52.41/21.21)	−0.42	−21.10 (−51.9/9.70)	−1.56
Hemoglobin (g/dL)	2.29 (0.04/4.53)	1.08	1.98 (−0.45/4.41)	1.15	1.06 (−0.98/3.10)	0.63
Serum creatinine (mg/dL)	−8.66 (−10.30/7.01)	−8.70	−2.32 (−4.10/−0.53)	−1.20	−0.31 (−1.80/1.18)	−1.64
Glomerular filtration rate (mL/min)	53.7 (48.32/59.07)	36.37	2.10 (−3.73/7.93)	2.96	23.00 (18.12/27.88)	4.46
Kt/V	-	-	0.22 (−1.49/1.05)	0.20	-	-
6 MWT distance (meters)	−17.00 (−104/70.76)	−0.29	162 (66.80/257)	2.31	174 (94.35/254)	2.78
6 MWT (% of predicted)	−9.00 (−21.68/3.68)	−1.27	30.00 (16.24/43.75)	3.88	34.00 (22.49/45.50)	3.33

Negative numbers indicate higher values in the Control group; Positive numbers indicate higher values in the Experimental group; Δ (CI), mean difference and 95 % confidence interval; d, Cohen's d for effect size (negative numbers favours control group; positive numbers favour experimental group); Kt/V, indicator of hemodialysis adequacy (K, urea clearance by the dialyzer; t, treatment time; V, urea distribution volume)

cance was found in the KTx groups comparison (Tukey's $p > 0.05$; $d = -1.56$). Also, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p < 0.05$; $d = -2.55$).

Hemoglobin showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 1.15$). Despite no statistical difference, a moderate clinical significance was found in the KTx groups comparison (Tukey's $p > 0.05$; $d = 0.63$). However, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p < 0.05$; $d = 1.08$).

Creatinine showed a statistical difference and, a strong clinical significance in the HD groups comparison was achieved (Tukey's $p < 0.05$; $d = -1.20$). Despite no statistical difference, a strong clinical significance was found in the KTx groups comparison (Tukey's $p > 0.05$; $d = -1.64$). However, in the control groups comparison, both statistical and strong clinical significance were found (Tukey's $p < 0.05$; $d = -8.70$).

The Glomerular filtration rate showed no statistical difference, but a clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 2.96$). Both statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; $d = 4.46$). Also, in the control groups comparison, both statistical and a very strong clinical significance were found (Tukey's $p < 0.05$; $d = 36.37$).

Exercise tolerance

The 6 MWT distance showed a statistical difference, and a clinical significance in the HD groups comparison was achieved (Tukey's $p < 0.05$; $d = 1.78$). Also, significant statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p > 0.05$; $d = 1.13$). However, in the control groups comparison, both statistical and clinical significance were not achieved (Tukey's $p > 0.05$; $d = -0.29$).

The expected distance achieved in the 6 MWT distance showed a statistical difference, and a clinical significance in the HD groups comparison (Tukey's $p < 0.05$; $d = 3.88$). Also, significant statistical difference and a strong clinical significance were found in the KTx groups comparison (Tukey's $p < 0.05$; $d = 3.33$). Also, in the control groups comparison, both statistical and clinical significance were achieved (Tukey's $p < 0.05$; $d = -1.27$).

Autonomic modulation

Concerning autonomic modulation, results can be seen in ▶**Table 4**, **5**. The total variability showed no statistical difference, but a clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 1.13$). However, a statistically higher value in the exercised group and, a strong clinical significance was found in the KTx groups comparison (Tukey's $p < 0.05$; $d = 4.63$). Also, in the control groups comparison, both statistically higher values in the exercised group and, a strong clinical significance were found (Tukey's $p < 0.05$; $d = 3.16$).

RR showed no statistical difference, and, no clinical significance in the HD groups comparison was achieved (Tukey's $p > 0.05$; $d = 0.30$). Also, no statistical difference was found in the KTx groups, but, a strong clinical significance was found (Tukey's $p > 0.05$; $d = 1.15$).

SDNN showed neither statistical difference nor clinical significance in the HD groups comparison (Tukey's $p > 0.05$; $d = -0.43$). Also, no statistical were found in the KTx group but, a strong clini-

▶ **Table 4** Mean and standard deviations of heart rate variability indexes between groups.

	HD (n = 7)	HD + Ex (n = 7)	KTx (n = 10)	KTx + Ex (n = 10)
Time domain				
Total variability (ms^2)	231 ± 76	312 ± 66*	488 ± 86#	923 ± 101* #
RR (ms)	777 ± 108	810 ± 105	750 ± 40	794 ± 36
SDNN (ms)	14 ± 9	18 ± 8*	22 ± 3.5	30 ± 6#
Frequency domain				
LF (ms^2)	51 ± 53	33 ± 26	170 ± 30#	307 ± 143* #
HF (ms^2)	39 ± 34	108 ± 143	77 ± 16#	237 ± 86*
LF (nu)	56 ± 21	30 ± 19*	72 ± 9	54 ± 4* #
HF (nu)	44 ± 21	69 ± 19*	28 ± 9	46 ± 4* #
LF/HF	1.3 ± 1	0.45 ± 0.3	2.7 ± 0.4#	1.16 ± 1* #
Symbolic analysis				
0 V (%)	25 ± 19	16 ± 13	35 ± 5	21 ± 3*
1 V (%)	45 ± 12	41 ± 17	43 ± 5	46 ± 4
2 LV (%)	11 ± 10	17 ± 7	5 ± 0.8	8 ± 0.6#
2 UV (%)	19 ± 6	26 ± 5*	17 ± 2.5	23 ± 1.5*

*p < 0.05 vs. Control; # p < 0.05 same condition (control or exercise) vs. Hemodialysis group (mean ± standard deviation);

▶ **Table 5** Difference between groups and moments for heart rate variability.

	(KTx control – HD control)		HD (exercise – control)		KTx (exercise – control)	
	Δ (CI)	d	Δ (CI)	d	Δ (CI)	d
Total variability (ms^2)	257 (142/371)	3.16	81 (−43/205)	1.13	435 (331/538)	4.63
RR (ms)	−27 (−125/71.51)	−0.33	33 (−79/139)	0.30	44 (−45.4/133)	1.15
SDNN (ms)	8 (−0.83/16.83)	1.17	4 (−5.58/13.58)	0.46	8 (−0.02/16.01)	1.62
LF (ms^2)	119 (6.08/231)	2.76	−18 (−140/104)	−0.43	137 (34.53/239)	1.32
HF (ms^2)	38 (70/7147)	1.43	69 (−49.21/187)	0.66	160 (61.09/259)	2.58
LF (nu)	16 (−2.44/34.44)	−0.99	−26 (−46.00/−5.99)	−1.29	−18 (−1.26/−34.73)	−2.58
HF (nu)	−16 (−34.44/2.44)	0.99	25 (4.99/45.06)	1.25	18 (1.26/34.73)	2.58
LF/HF	1.4 (0.39/2.40)	1.83	−0.85 (−1.94/0.24)	−1.15	−1.54 (−2.45/−0.62)	−2.02
0 V (%)	10 (−4.44/24.44)	0.71	−9 (−24.66/6.66)	−0.55	−14 (−27.10/−0.89)	−3.39
1 V (%)	−2 (−15.32/11.32)	−0.21	−4 (−18.45/10.45)	−0.27	3 (−9.09/15.1)	0.66
2 LV (%)	−6 (−13.35/1.35)	−0.84	6 (−1.97/13.97)	0.69	3 (−3.67/9.67)	4.24
2 UV (%)	−2 (−7.14/3.14)	−0.43	7 (1.41/12.58)	1.26	6 (1.33/10.67)	2.91

Negative numbers indicate higher values in the Control group; Positive numbers indicate higher values in the Experimental group; Δ (CI), mean difference and 95 % confidence interval; d, Cohen's d for effect size (negative numbers favour control group; positive numbers favours experimental group);

cal significance was found in the KTx groups comparison (Tukey's p > 0.05; d = 1.62). Also, in the control groups comparison, no statistical difference was found, but, a strong clinical significance was found (Tukey's p > 0.05; d = 1.17).

The absolute values of LF and HF showed no statistical difference, but a moderate clinical significance in the HD groups comparison was achieved (Tukey's p > 0.05; d = −0.43 and 0.66, respectively). However, statistically significant higher values and, strong clinical significance were found in the KTx groups comparison (Tukey's p < 0.05; d = 1.32 and 2.58, respectively). Also, in the control groups comparison, both statistically significant higher values in the KTx + Ex group and, strong clinical significance were found (Tukey's p < 0.05; d = 2.37 and 3.02, respectively).

The normalized values of LF and HF showed a statistical difference with a strong clinical significance in the HD groups comparison (Tukey's p < 0.05; d = −1.29 and 1.25, respectively). Also, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's p < 0.05; d = −2.58 and 2.58, respectively). Although, in the control groups comparison, no significant values were found, but a strong clinical significance were found (Tukey's p > 0.05; d = −0.99 and 0.99, respectively).

The LF/HF showed no statistical difference, but a strong clinical significance in the HD groups comparison was achieved (Tukey's p > 0.05; d = −1.15). However, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's p < 0.05; d = −2.02). Although, in the control groups comparison, no significant values were found, but, a strong clinical significance was found (Tukey's p > 0.05; d = 1.83).

The 0 V showed no statistical difference, and a moderate clinical significance in the HD groups comparison was achieved (Tukey's

p > 0.05; d = − 0.55). However, statistically significant difference and strong clinical significance were found in the KTx groups comparison (Tukey's p < 0.05; d = − 3.39). Although, in the control groups comparison, no significant values were found, but, a moderate clinical significance was found (Tukey's p > 0.05; d = 0.71).

The 1 V showed no statistical difference and no clinically relevant in none of the case, except for the KTx groups comparison, which showed a moderate effect size (d = 0.66). In the 2 LV, no significant difference was found in none of the comparisons. Although, a moderate effect size was found in the HD comparison (d = 0.69). However, a strong clinical relevance in the KTx groups comparison was achieved (d = 4.24), as well as in the control groups comparison (d = − 0.84).

In the 2 UV, significant differences were found in HD and KTx groups comparison (Tukey's p < 0.05), with strong effect sizes (d = 1.26 and 2.91, respectively). However, no statistical differences were found in the control and KTx + Ex vs. HD comparisons (p < 0.05), but, a moderate effect size was found in the control groups comparison (d = − 0.43).

Sleep, anxiety and depression inventories

The sleep, anxiety and depression inventories results are described in ▶ **Table 6**, **7**.

Discussion

This study aimed to analyze the effect of an exercise training program on cardiovascular autonomic modulation and, exercise capacity of HD and KTx patients. Our data display improvements in cardiovascular autonomic modulation and exercise tolerance in both groups. Also, our data shows the HD + Ex group demonstrated lower values in important cardiovascular risk markers such as systolic blood pressure, diastolic blood pressure, LDL cholesterol, urea, and, increases in HDL cholesterol, hemoglobin, 6 MWT distance and % of predicted. These changes are clinically relevant, seeing that the HD + Ex was able to enter normal reference values for blood pressure, LDL, HDL and, Hemoglobin (▶ **Table 2**).

▶ **Table 6** Sleep, anxiety and depression scores in both groups.

	HD (n = 7)	HD + Ex (n = 7)	KTx (n = 10)	KTx + Ex (n = 10)
Pittsburgh Sleep Quality Index	6.5 ± 2	4.5 ± 2	7 ± 2	5 ± 1.5
Beck Depression Index	9 ± 5	5 ± 4	5 ± 3	9 ± 5
Beck Anxiety Index	10 ± 7	5.5 ± 3	7 ± 4	6 ± 4

To the best of our knowledge, this is the first study to describe the effect of exercise training on autonomic modulation and kidney function of HD and KTx patients comparatively. Our group has been investigating the effects of exercise in CKD patients and had observed its positive effects on autonomic modulation, kidney function, anxiety, depression and sleep quality [1, 23].

CKD it has been recognized as an independent risk factor for cardiovascular diseases [14], with a marked cardiovascular autonomic imbalance [23, 28]. Exercise has been used as an intervention for promoting a better quality of life and increased cardiac function [1, 24, 26]. Our results show improvements in essential markers of kidney function in both groups after training, such as phosphorus and creatinine (▶ **Table 2**). As expected, the KTx + Ex group showed higher improvements in those biochemical markers than the HD + Ex group. The management of the biochemical markers are essential, seeing that usually, CKD patients under hemodialysis suffer from parathyroid problems, that can cause hypercalcemia and, hyperphosphatemia [12], complications that can further lead to vascular problems like artery calcification and even graft failure [9, 12, 22]. Exercise can also be impaired by alterations in sodium and potassium availability in the skeletal muscle [25], an activity that is profoundly impaired in patients with CKD. Other studies from our group had demonstrated that exercised CKD patients tend to have lower values of creatinine, phosphorus, and potassium [1, 23].

Also, the KTx + Ex group showed improved cardiac autonomic modulation, but with far more benefits and improvements than the HD + Ex group (▶ **Table 4**, **5**). This improvement in the KTx group is remarkable because our data show decreased overall heart rate variability in the HD + Ex group. The KTx + Ex group also shows a reduction in sympathetic modulation, as expressed by the LF (n.u. and ms^2), and increases in vagal modulation, as expressed by HF (n.u. and ms^2).

Other studies have shown the beneficial effect of exercise in the autonomic modulation of CKD patients. Kouidi et al. had shown not only benefits in cardiovascular autonomic modulation (similar to those we found), but also baroreflex sensitivity improvements in patients with end-stage kidney disease, with a significant correlation between baroreflex sensitivity indexes and VO_2max, an important index of exercise capacity [19]. From the same group, Konstantinidou et al. as well showed the benefits of exercise in patients with CKD undergoing hemodialysis, with the same baroreflex and VO_2max benefits cited before [18]. Our data corroborate with these 2 studies, taking into account that we analyzed trained patients undergoing hemodialysis and after kidney transplantation.

Nonetheless, the autonomic imbalance is correlated with increased risk for cardiovascular diseases and re-hospitalization in subjects with CKD [4]. These data highlight the importance of

▶ **Table 7** Difference and effect sizes of the sleep quality, anxiety and depression inventories.

	(KTx control – HD control)		HD (exercise – control)		KTx (exercise – control)	
	Δ (CI)	d	Δ (CI)	d	Δ (CI)	d
Pittsburgh Sleep Quality Index	0.5 (− 1.99/2.99)	0.25	− 2.00 (− 4.70/0.70)	− 1.00	− 2.00 (− 4.26/0.26)	− 1.13
Beck Depression Index	− 4.00 (− 9.74/1.74)	− 0.97	− 4.00 (− 10.23/2.23)	− 0.88	4.00 (− 1.21/9.21)	0.97
Beck Anxiety Index	− 3.00 (− 9.16/3.16)	− 0.52	− 4.50 (− 11.19/2.19)	− 0.83	− 1.00 (− 6.59/4.59)	− 0.25
Δ (CI), mean difference and 95 % confidence interval; d, Cohen's d for effect size						

effective interventions (such as exercise) to reduce the autonomic imbalance in these patients, thus reducing the risk of cardiovascular diseases and re-hospitalization among CKD and kidney transplanted patients.

We did not assess the baroreflex sensitivity, but, we may suggest based on the increase of overall variability and changes the sympathovagal balance that these positive changes may have also occurred. Furthermore, we assessed baroreflex sensitivity after an acute session of exercise in CKD patients undergoing hemodialysis and found significant differences in response to exercise stimuli [8].

Both HD + Ex and KTx + Ex groups showed improved exercise capacity, as can be seen by the significant elevations of the 6 MWT distance (▶ **Table 2**). The increases in exercise capacity have been correlated with increased life expectancy and better kidney function in patients with CKD [17, 30]. Also, increased exercise capacity is correlated with increased overall autonomic modulation and reduced risk for cardiovascular diseases [27, 30].

The most important finding of this study shows that HD + Ex patients show significant clinical improvements in important markers of cardiovascular disease such as blood pressure, lipid profile, hemoglobin and 6 MWT distance. Other studies had been shown the benefits of exercise for HD patients, with reductions in blood pressure and increases in exercise capacity [19, 24, 26]. This finding in comparison with the KTx patients highlights the increased risk for cardiovascular disease of the HD patients and gives a pathway leading to the use of exercise as a tool inside the hospital, focusing primarily in the HD patients instead of KTx patients.

In conclusion, our data show that an exercise program combined with the kidney transplantation procedure is capable of increasing autonomic modulation and, exercise tolerance of CKD patients. However, the patients undergoing hemodialysis that were also submitted to an exercise program showed better prognosis in important cardiovascular risk factors, and as well, increased autonomic modulation.

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Conflict of Interest

The authors declare no conflict of interest.

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