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TARCISIO SANTANA GOMES

SAÚDE MUSCULAR EM PACIENTES PORTADORES DE DOENÇA RENAL CRÔNICA NÃO DIALÍTICA: MARCADORES CLÍNICOS NUTRICIONAIS E DE QUALIDADE DE VIDA.

Salvador

2024

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Tese apresentada à Pós-graduação em Alimentos, Nutrição e Saúde, Escola de Nutrição, Universidade Federal da Bahia, como requisito para obtenção do Título de Doutor em Nutrição.

Orientadora: Profª. Drª. Jairza M Barreto Medeiros

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Dedico minha tese à minha amada filha,

Chloe Espirito Santo Santana.

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LISTA DE ABREVIATURAS E SIGLAS

DRC – ND: Doença renal crônica em tratamento não dialítico

SRAA: Renina-angiotensina-aldosterona

TFG: Taxa de filtração glomerular

DM2: Diabetes Mellitus tipo 2

TRS: Terapia renal substitutiva

IMC: Índice de massa corporal

PEW: Desgaste energético proteico

UPS: Sistemas ubiquitina-proteassoma

IGF-1: Fator de crescimento insulínico

HD: Hemodiálise

OR: odds ratio

BIA: impedância bioelétrica

DEXA: raios X de dupla energia

TC: tomografia computadorizada

RM: ressonância magnética

AWGS: Grupo de Trabalho Asiático para Sarcopenia;

EWGSOP: Grupo de Trabalho Europeu sobre Sarcopenia em Pessoas Idosas;

FNIH: Fundação dos Institutos Nacionais de Sarcopenia em Saúde

FPM: Força de Preensão Manual

SPPB: bateria curta de desempenho físico

OMS: Organização Mundial da Saúde

QV: Qualidade de vida

QRVS: Qualidade de vida relacionada à saúde

SF-36: Study Short Form 36

EQ5D: European Quality of life (Euroqol)

LASAs: Linear analogue self-assessment

KDQOL-36: Kidney Disease Quality of Life

KDQ: Kidney Disease Questionnaire

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APRESENTAÇÃO

APRESENTAÇÃO

Este trabalho foi realizado no Ambulatório de Nutrição e Nefrologia do Complexo Hospitalar Universitário Professor Edgard Santos, sob orientação da Profª Jairza Barrreto Medeiros e coorientação da Profª Maria Helena Lima Gusmão, ambas docentes da Universidade Federal da Bahia (UFBA). Este trabalho faz parte de um projeto ampliado intitulado "Aspectos nutricionais e fatores associados em pacientes portadores de DRC em tratamento conservador" que contou com o apoio financeiro do Fundação Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) e da Fundação de Amparo à Pesquisa da Bahia (Fapesb).

A temática desta tese surgiu dos resultados de trabalhos científicos e da experiência das atividades de extensão realizadas no Ambulatório de Nutrição e Nefrologia do Complexo Hospitalar Universitário Professor Edgard Santos que mostram aumento importante de alterações nutricionais em indivíduos com DRC em tratamento não-dialítico (DRC-ND). Dessa forma, identificar de forma precoce essas alterações pode ser a chave para um avanço nessa temática, além de possibilitar o uso de novos indicadores na prática clínica.

O objetivo desta tese justifica-se da necessidade de determinar a associação dos marcadores de saúde muscular com alterações nutricionais e de qualidade de vida em pacientes com DRC-ND. Da mesma forma, busca-se também identificar precocemente alterações da composição corporal que possam predizer estágios iniciais de sarcopenia e dinapenia nestes pacientes.

Para atender este objetivo, esta tese está estruturada em três seções. A primeira apresenta o artigo de revisão sistemática e metanálise intitulado "Sarcopenia and mortality in patients with chronic non-dialytic renal disease: systematic review and meta-analysis", com objetivo de analisar os resultados de estudos prospectivos sobre a presença de sarcopenia e sua associação com mortalidade em pacientes com doença renal crônica não dependente de diálise.

A segunda seção apresenta os resultados do artigo 2, intitulado "Association of phase angle, sarcopenia and dynapenia in Non-Dialysis CKD patients", que avaliou a associação entre os valores de ângulo de fase com dinapenia e sarcopenia em pacientes com DRC-ND. E a terceira, os resultados do artigo 3, intitulado “Dinapenia and phase angle as markers of quality of life in Non-Dialytic Chronic Kidney patients” que avaliou a associação do ângulo de fase e força de preensão palmar com qualidade de vida em pacientes com DRC-ND.

Ao final do trabalho são apresentadas as conclusões gerais e perspectivas futuras com base nas evidências científicas disponíveis, para o melhor conhecimento da sarcopenia e dinapenia em pacientes com DRC-ND.

RESUMO

RESUMO

A progressão da doença renal crônica é acompanhada por múltiplas anormalidades nutricionais e metabólicas, as quais podem comprometer a função renal, afetando o quadro clínico e nutricional desses pacientes. Entre as alterações nutricionais, destacam-se a sarcopenia e a dinapenia, termos utilizados para designar redução da massa muscular, da força muscular e do desempenho físico. **OBJETIVOS:** Identificar a associação entre marcadores de qualidade muscular com aspectos clínicos nutricionais e de qualidade de vida em pacientes com doença renal crônica não-dialítica. **MÉTODOS**: Trata-se de um estudo transversal realizado no período de janeiro a setembro de 2012 com pacientes com diagnóstico de DRC, estágios 3 a 5 (estágio 5 não-dialítica), acompanhados no ambulatório de Nutrição e Nefropatias do Ambulatório Professor Francisco de Magalhães Neto. Participaram deste estudo pacientes adultos (20 e < 60 anos) e idosos (≥ 60anos), de ambos os sexos, que possuíam Clearance de Creatinina entre 89 a 15 ml/min/1,73m2. Foram avaliados indicadores antropométricos, de composição corporal, de força muscular, bioquímicos e de qualidade de vida. **RESULTADOS**: Os resultados apresentados permitem concluir que a sarcopenia e dinapenia são prevalentes em pacientes com DRC-ND e que, de acordo com a revisão realizada, são prognóstico de gravidade, incluindo a mortalidade. Vale ressaltar, que os indicadores de saúde muscular foram associados com domínios de qualidade de vida relacionados à saúde física nesta população. Além disso, observou-se que o ângulo de fase e a medida de FPM podem ser indicadores para avaliar a qualidade muscular nesses pacientes. C**ONCLUSÃO**: nossos estudos reforçam a importância do acompanhamento dos indicadores nutricionais associados a qualidade muscular com o objetivo de reduzir possíveis complicações clínicas, nutricionais e do impacto em qualidade de vida em pacientes com doença renal crônica não dependente de diálise.

Palavras chaves: doença renal crônica, sarcopenia, dinapenia

ABSTRACT

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The progression of chronic kidney disease is accompanied by multiple nutritional and metabolic abnormalities, which can compromise renal function, affecting the clinical and nutritional status of these patients. Among the nutritional alterations, sarcopenia and dynapenia stand out, terms used to designate a reduction in muscle mass, muscle strength and physical performance. **OBJECTIVES:** To identify the association of muscle quality markers with clinical, nutritional and quality of life aspects in patients with non-dialytic chronic kidney disease. **METHODS:** This is a cross-sectional study conducted from January to September 2012 with patients with CKD stages 3 to 5 (stage 5 non-dialysis) who were followed at the Nutrition and Nephropathy Outpatient Clinic of the Professor Francisco de Magalhães Neto Outpatient Clinic. Adult patients (20 and <60 years) and elderly patients (≥60 years), of both sexes, with creatinine clearance between 89 and 15 ml/min/1.73m^2, participated in this study. Anthropometric, body composition, muscle strength, biochemical and quality of life indicators were evaluated. **RESULTS:** The results presented allow us to conclude that sarcopenia and dynapenia are prevalent in patients with CKD-ND and that, according to the review performed, they are prognostic of severity, including mortality. It is worth noting that muscle health indicators were associated with quality of life domains related to physical health in this population. In addition, it was observed that the phase angle and HGS measurement can be indicators to assess muscle quality in these patients. **CONCLUSION:** our studies reinforce the importance of monitoring nutritional indicators associated with muscle quality in order to reduce possible clinical and nutritional complications and the impact on quality of life in patients with non-dialysis-dependent chronic kidney disease.

Key words: chronic kidney disease, sarcopenia, dynapenia

INTRODUÇÃO

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A progressão da doença renal crônica (DRC) é acompanhada por múltiplas anormalidades nutricionais e metabólicas. A etiologia subjacente inclui, mas não está limitada, a acidose metabólica, disbiose intestinal, inflamação sistêmica com ativação de complementos, eixo endotelina-1 e renina-angiotensina-aldosterona (SRAA), resistência aos hormônios anabólicos, elevação do gasto energético e acúmulo de toxinas urêmicas[1,2]. Todos esses distúrbios podem agravar a função renal, afetando o quadro clínico e nutricional desses pacientes[2].

A gênese que envolve as alterações nutricionais e metabólicas vem despertando interesse entre os pesquisadores, visto que muitos destes distúrbios relacionados com a DRC podem ser prevenidos e substancialmente revertidos, representando uma área de grande potencial para melhorar o tratamento da DRC e da doença renal terminal[3]. Desta forma, o uso de técnicas que possibilitem a identificação precoce dessas alterações é essencial para ter compreensão dos princípios nutricionais aplicáveis para tratar deficiências e distúrbios nutricionais potenciais ou contínuos[4].

Entre os distúrbios nutricionais associados a qualidade muscular, destacam-se a sarcopenia e a dinapenia, termos utilizados para designar redução da massa muscular, da força muscular e do desempenho físico[4,5]. Os mecanismos envolvidos são muitos e ainda não totalmente esclarecidos, mas é certo que todos convergem para um processo final de aumento da degradação proteica e redução da síntese proteica, levando a um balanço negativo de nitrogênio[5]. Essas condições levam a um risco aumentado de hospitalização e mortalidade e, por este motivo, podem ser consideradas um fator prognóstico negativo em pacientes com DRC[5].

Além disso, a DRC e suas implicações podem impactar negativamente a qualidade de vida desta população[6]. Existem evidências na literatura científica que demonstram que o paciente com DRC apresentam menores escores de qualidade de vida quando comparado a população geral, sendo que o grau dessas alterações está relacionado negativamente com à taxa de filtração glomerular[6].

A sarcopenia é uma doença musculoesquelética que envolve perda de massa muscular associada a redução da força muscular e/ou do desempenho físico[7]. No geral, a prevalência da sarcopenia em todo o espectro da DRC varia de 4% a 42%, estando associada a múltiplos resultados clínicos adversos, incluindo mortalidade[7,8]. Já a dinapenia é definida como uma perda de força e potência muscular em relação à qualidade muscular. Nesse caso, a massa muscular reduz significativamente mais lentamente do que a força muscular, sugerindo que a dinapenia pode ter um mecanismo fisiopatológico diferente da sarcopenia[9,10].

Os diagnósticos de sarcopenia e dinapenia podem associar-se com impacto na qualidade de vida dos pacientes com doença renal crônica, independente do estágio da doença. O estudo de Yokomachi et al, 2023, demostram que esses pacientes apresentam menor qualidade de vida, mais sintomas e maior sofrimento psicológico, e o grau dessas alterações está negativamente relacionado à taxa de filtração glomerular[11].

A principal limitação dos estudos para identificação da sarcopenia e dinapenia está associada a heterogeneidade de métodos, principalmente no que diz respeito ao método de análise da composição corporal, a funcionalidade muscular no diagnóstico da sarcopenia e ao ajuste da quantidade de massa muscular pelo peso corporal ou pela altura do indivíduo. Desta forma, para avaliação desses diagnósticos e prognóstico de gravidade, o ângulo de fase tem sido estudado como indicador em diversas patologias, incluindo a doença renal crônica, uma vez que menores valores de ângulo de fase se correlaciona com reduzida massa muscular esquelética e baixa força de preensão manual[12].

Portanto, fica evidente a importância da identificação de alterações na qualidade muscular de forma precoce uma vez que possibilita intervenção nutricional eficaz, proporcionando resultados promissores no tratamento desta condição patológica.

REFERENCIAL TEÓRICO

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Doença Renal Crônica (DRC) e Estado Nutricional

A DRC é definida pela presença de anormalidade estrutural e funcional dos rins presentes por um período superior a três meses, com implicações para saúde[13,14]. O declínio da função renal está relacionado à idade, presença de hipertensão, diabetes, obesidade e distúrbios renais primários[13]. A diminuição da função renal é um preditor de hospitalização, disfunção cognitiva e baixa qualidade de vida. A doença renal crônica apresenta uma prevalência global estimada, nos estágios de 1 a 5, de 13,4% (11,7–15,1%) e uma média global de 10,6% (9,2–12,2%) nos estágios 3–5, com a maioria no estágio 3 (7,6%)[14].

É classificada em estadios de acordo com a taxa de filtração glomerular e com a presença de albuminúria. O estágio 1 corresponde à fase inicial da lesão renal, mas com taxa de filtração glomerular (TFG) preservada ou aumentada (≥ 90 ml/min/1,73m^2). No estágio 2 já se observa redução da função renal, porém os rins ainda conseguem manter a equilíbrio fisiológico (TFG 60-89 ml/min/1,73m^2). No estágio 3A, a redução da filtração glomerular varia de levemente a moderadamente diminuída (TFG 45-59 ml/min/1,73m^2) e no estadio 3B varia de moderadamente a severamente diminuída (TFG 30-44 ml/min/1,73m^2). No estágio 4, as alterações laboratoriais são mais evidentes e já é possível observar a presença de sintomatologia urêmica (TFG 15-29 ml/min/1,73m^2). O estágio 5, também conhecido como insuficiência renal em estágio terminal ou fase dialítica, é aquele em que a função renal não é mais capaz de manter a homeostase corporal (TFG < 15 ml/min/1,73m^2). Nessa fase, a sintomatologia urêmica se torna evidente e faz-se necessário o início da terapia substitutiva da função renal por meio da diálise ou transplante renal[14,15].

A DRC é uma doença complexa, envolvendo fatores de risco não modificáveis, por exemplo, idade avançada, história familiar e etnia, e modificáveis, como diabetes mellitus tipo 2 (DM2), hipertensão e dislipidemia, que são responsáveis pelo início da DRC precoce, pela progressão (estágio 3-5) e estágio final, culminando com Terapia renal substitutiva (TRS). Nos estágios iniciais (estágio 1–2), fatores como hipertensão, obesidade e DM2 podem desencadear comprometimento da função renal, causando danos glomerulares/intersticiais e resultando em comprometimento da filtração glomerular, com diminuição da TFGe e ao aumento da albuminúria[14,15].

Conforme a DRC progride, a excreção de substâncias tóxicas sintetizadas pelo organismo reduz gradualmente, ocasionando um acúmulo na concentração sérica de várias moléculas[1]. Consequentemente, os pacientes passam a apresentar uma série de alterações sistêmicas, metabólicas e hormonais que podem afetar de maneira adversa o equilíbrio fisiológico de vários sistemas e órgãos, contribuindo para o desenvolvimento de complicações como a anemia, acidose metabólica, deficiência de vitamina D entre outras que aumentam a morbidade e a mortalidade desta população[2].

Nas últimas duas décadas, muitos artigos foram publicados demosntrando que a obesidade ou o índice de massa corporal (IMC) estão relacionados ao risco de DRC. Na coorte do estudo *Framingham Offspring*, incluindo participantes sem doença renal pré-existente, no período médio de acompanhamento de 18,5 anos, um IMC mais elevado foi associado a um maior risco de desenvolver DRC[16].

A obesidade é um achado comum nos pacientes com DRC e essa tendência é notória no cenário mundial. A prevalência global de sobrepeso e obesidade, avaliados pelo IMC é de aproximadamente de 50% a 60% dos pacientes na fase pré-dialítica, 40% a 60% dos pacientes em diálise peritoneal e em 20% a 30% nos pacientes em hemodiálise (HD) [17]. Estudos recentes, porém, mostram que a obesidade central e não o IMC elevado se associa com maior risco de eventos cardiovasculares e de morte em pacientes na fase não-dialítica da DRC, sugerindo, portanto, que o acúmulo de gordura visceral pode ser um dos mediadores dessa associação[18].

Por outro lado, o desgaste energético-proteico (*PEW*) foi historicamente introduzido pela primeira vez em 2007 pela Sociedade Internacional de Nutrição Renal e Metabolismo. A definição codificada foi que *PEW* é considerada como presença de distúrbios nutricionais e metabólicos em pacientes com doença renal crônica e doença renal em estágio terminal, caracterizado pela perda simultânea de proteínas corporais sistêmicas e reservas de energia[19]. A razão pela qual isso ocorre está relacionada ao estado hipercatabólico induzido pela uremia, anorexia, inflamação por condições sistêmicas (Diabetes) e autoimunes, que geralmente levam à DRC[20]. As evidências tendem a sugerir que isso se desenvolve mais em pacientes com DRC estágio 3b (taxa de filtração glomerular estimada <45 mL/min), conforme definido pelo estadiamento *Kidney Disease Improving Global Outcomes of CKD*. Embora a *PEW* e a desnutrição possam resultar num fenótipo de paciente semelhante, devem ser distinguidas uma da outra, uma vez que os fatores relacionados com a DRC são exclusivos do desenvolvimento da *PEW* em pacientes com doença renal[21].

Os fatores etiológicos dos distúrbios musculares que levam à perda muscular na DRC são diversos e podem estar relacionados a diversas condições, incluindo a própria doença renal, o procedimento de diálise e a típica inflamação crônica de baixo grau presente nesses pacientes que, juntos, aumentam a degradação proteica, diminuem a síntese de proteína e levam a um balanço proteico negativo[3]. Os fatores não inflamatórios relacionados à perda da função renal incluem o desenvolvimento de acidose metabólica, resistência à insulina e deficiência de vitamina D que atuam como promotores do catabolismo proteico e diminuição da síntese proteica. A deficiência de vitamina D pode reduzir a secreção de insulina e diminuir o estímulo para a síntese de proteínas, diminuindo os receptores de vitamina D presentes no músculo e reduzindo o influxo de cálcio das membranas celulares[22].

A acidose metabólica atua como um potente estimulador do catabolismo proteico, desencadeando dois sistemas responsáveis pela degradação intracelular de proteínas, a acaspase-3 e os sistemas ubiquitina-proteassoma (UPS)), promovendo a resistência à insulina. Além disso, fatores adicionais como distúrbios hormonais relacionados a testosterona, fator de crescimento insulínico (IGF-1) e resistência ao hormônio do crescimento) também podem induzir o catabolismo. Além disso, perda substancial de aminoácidos durante o procedimento de hemodiálise e a redução da ingestão de energia e proteína, também podem levar a um estado de equilíbrio negativo[23].

Mais recentemente, um efeito importante foi atribuído ao trato gastrointestinal no desenvolvimento de inflamação como consequência da disbiose e ruptura da barreira intestinal, resultando em um ambiente urêmico. Além disso, a obesidade em pacientes com DRC também pode atuar como fator pró-inflamatório devido à disfunção dos adipócitos, caracterizada pelo aumento da síntese de citocinas e quimiocinas (adipocinas) que ocorre independentemente da infiltração de macrófagos no tecido adiposo. Finalmente, a baixa atividade física, frequentemente encontrada em pacientes em HD, resulta em "desuso muscular", que é outra causa importante, mas subestimada, de perda muscular e sarcopenia nesta população[24].

Doença Renal Crônica (DRC) e Sarcopenia

O termo sarcopenia foi proposto por Irwin Rosenberg[25] em 1988, para descrever a redução da massa muscular relacionada à idade a partir do termo grego sarx que significa “carne/músculo” e penia que significa “redução”. Foi reconhecida como um problema de saúde quando Evans e Campbell[26] publicaram uma revisão que destacou a perda de músculo associada à idade, resultando em redução da força, taxa metabólica, capacidade aeróbica e estado funcional. A sarcopenia constitui um importante problema de saúde pública e terá ainda mais importância no futuro dado o envelhecimento da população. Dependendo da definição utilizada, estima-se que sua prevalência aumente entre 63,8 e 72,4% de 2016 a 2045[27].

De acordo com o Consenso Europeu[28], Sarcopenia: revised European consensus on definition and diagnosis, a sarcopenia é uma síndrome caracterizada pela perda progressiva e generalizada de força e massa muscular esquelética com risco de resultados adversos, como incapacidade física, má qualidade de vida e morte. A suspeita de sarcopenia é identificada por meio da baixa força muscular e confirmada quando adicionada a baixa quantidade ou qualidade muscular. Por fim, quando apresentar baixa força muscular, baixa quantidade ou qualidade muscular e baixo desempenho físico ela é considerada sarcopenia grave.

Embora a definição inicial de sarcopenia esteja relacionada aos idosos, a perda muscular esquelética também pode ocorrer por desuso em consequência à imobilidade, inatividade física, repouso prolongado, ou devido a inflamação por ativação de vias pró-inflamatórias e resistência à insulina. A sarcopenia também pode ser consequente a ingestão inadequada de macro e micronutrientes associados a doença aguda e crônica, sendo reconhecida neste caso, como “sarcopenia secundária”[29].

A etiologia da sarcopenia na DRC é complexa e multifatorial, com comorbidades relacionadas à DRC, diabetes, obesidade, doença cardiovascular, complicações, uremia, acidose metabólica, inflamação, estresse oxidativo, e terapia dialítica, todos impactando a perda de músculo esquelético. Juntos, esses fatores podem aumentar a degradação proteica e diminuir a síntese proteica muscular, levando a um balanço proteico negativo, comprometimento da regeneração muscular e atrofia muscular[30]. Além disso, a sarcopenia e suas características têm sido associadas à mortalidade, hospitalização, inflamação, eventos cardiovasculares e baixa qualidade de vida nesta população. A prevalência global de sarcopenia entre a população com DRC é de 25%, sem diferenças significativas entre os estágios e terapias renais substitutivas, já a sarcopenia grave é de 21%, sendo 3% em pacientes não dialíticos[5].

De acordo com a metanálise de Marvery P. Duarte et al.[5], publicada recentemente (2024), foram avaliados 140 estudos (42.041 pacientes) em 25 países, com o objetivo de investigar a prevalência global da sarcopenia e suas características em todo o amplo espectro da DRC. Encontraram uma variação na prevalência de sarcopenia, de acordo com a definição de consenso, de 11% a 30%, sem diferença significativa (p = 0,42). Uma prevalência de sarcopenia grave de 21,0%, com taxas mais altas para pacientes em diálise (26,2%) em comparação com pacientes sem diálise (3,0%). Em relação aos traços de sarcopenia, foi encontrada baixa força muscular em 43,4%, baixa massa muscular em 29,1% e baixo desempenho físico em 38,6%, para DRC geral. Na tabela 1 destacamos as publicações com os dados associados aos pacientes com DRC-ND, em que apresentaram uma prevalência absoluta de 16,7%.

A revisão sistemática realizada por Ribeiro et al.[31], com o objetivo de avaliar a associação entre sarcopenia e desfechos clínicos em pacientes com DRC, sendo desfecho primário a mortalidade, secundário a hospitalização e o terciário a progressão da doença, em 50 estudos incluídos, com um total de 72.34, encontrou que quinze estudos mostraram que a baixa força muscular está associada a um risco de mortalidade duas vezes maior (OR:1,99; IC95%:1,65–2,41), vinte estudos demonstraram que a baixa massa muscular está associada a um risco aumentado de mortalidade de 51% (OR: 1,51; IC 95%: 1,36–1,68), cinco estudos avaliaram que o baixo desempenho físico está associado a um aumento duas vezes maior no risco de mortalidade (OR: 2,09; IC 95%: 1,68–2,59) e, por fim, oito estudos demonstraram que a sarcopenia diagnosticada está associada a um risco de mortalidade 87% maior em pacientes em diálise (OR: 1,87; IC 95%: 1,35–2,59). Com relação a hospitalização, os estudos não mostraram uma medida de associação significativa (RR: 1,81; IC 95%: 0,78–4,22). Já com relação a progressão da doença, descobriram que a baixa força muscular está significativamente associada a um risco 108% maior, e o baixo desempenho físico por tempo determinado, não está significativamente associado à progressão da DRC. Na tabela 2 apresentamos os dados associados aos pacientes em DRC-ND.

Um dos desafios que determinam o diagnóstico de sarcopenia em pacientes com DRC é a grande variedade de métodos utilizados para quantificar a massa muscular em estudos publicados e os diferentes pontos de corte adotados. Esses métodos incluem antropometria, biópsia muscular, análise de impedância bioelétrica (BIA), absorciometria de raios X de dupla energia (DEXA), tomografia computadorizada (TC) e ressonância magnética (RM), variando amplamente em precisão e confiabilidade, podendo ser afetado por flutuações no estado de hidratação[32]. Juntos, o uso de diversas técnicas, medidas, equações e algoritmos usados para estimar a massa muscular esquelética torna um desafio determinar a magnitude da atrofia muscular esquelética na DRC. Por outro lado, o baixo número de evidências em pacientes não dialíticos e transplantados mostra que são necessários mais estudos de rastreio da sarcopenia[33].

O ângulo de fase vem sendo utilizado como marcador na avaliação da qualidade muscular e associação com diagnóstico de sarcopenia em pacientes com doenças crônicas, incluindo a doença renal. É o ângulo do vetor, derivado da análise de impedância bioelétrica (BIA), determinado pela resistência e reatância do corpo, indicando a integridade celular e o estado de hidratação desses indivíduos[12].

Shin et al[26], investigaram a utilização do ângulo de fase para estimar a saúde muscular e a qualidade de vida em 149 pacientes com DRC. Os resultados demostraram que o ângulo de fase foi associado aos critérios de baixa massa muscular e baixa força muscular (ambos $P < 0,001$) e previu a presença de sarcopenia ($P = 0,001$). Além disso, foi relacionado a vários aspectos do questionário de qualidade de vida, incluindo funcionamento físico, saúde geral, saúde mental, escala de componente físico, escala de componente mental, status de trabalho, qualidade da interação social, função sexual e suporte social.

Tabela 1. Prevalência de sarcopenia em pacientes com doença renal crônica não dialítica.

Autor	Ano	País	Desenho do estudo	Pacientes (n)	Sexo Masculino (n)	Idade (anos)	Prevalência de Sarcopenia*		Consenso
							Absoluto (n)	Relativo (%)	
Amorim et al.[34]	2022	Brasil	Transversal	139	65	57	29	20,9	EWGSOP2
Caldiroli et al.[35]	2021	Italia	Transversal	99	66	81	23	23,2	EWGSOP2
Chen et al.[36]	2022	China	Transversal	233	82	69.32	43	18,5	AWGS2
D'Alessandro et al.[37]	2018	Italia	Transversal	80	80	73.7	54	67,5	EWGSOP
Fernandes et al.[38]	2018	Brasil	Transversal	73	42	62.88	9	12,3	EWGSOP
Guida et al.[6]	2020	Italia	Transversal	85	55	65	6	7,1	EWGSOP2
Ishikawa et al.[39]	2018	Japão	Transversal	260	169	76	65	25,0	AWGS
An et al.[40]	2021	Coreia	Coorte Prospectiva	892	523	66	189	21,2	AWGS2
Kusunoki et al.[41]	2020	Japão	Transversal	225	79	75.8	24	10,7	AWGS2
Lee et al.[42]	2020	Coreia	Transversal	150	96	65	14	9,3	AWGS2
Montenegro et al.[43]	2022	Brasil	Transversal	257	148	64.8	2	0,8	EWGSOP2
Moreno-Gonzalez et al.[44]	2020	Multicêntrico	Transversal	494	–	–	56	11,3	EWGSOP2
Ran-hui Cha. et al [45]	2021	Coreia	Transversal	150	97	65	24	16,0	AWGS2
Rao et al.[46]	2022	India	Transversal	117	88	55.7	34	29,1	AWGS2
Shin et al.[47]	2022	Coreia	Transversal	149	97	65	14	9,4	AWGS2
Souza et al.[48]	2017	Brasil	Transversal	100	41	73.59	29	29,0	FNIH
Wilkinson et al.[49]	2021	Reino Unido	Coorte Prospectiva	8740	4055	62.8	66	0,8	FNIH
Yoshimura et al.[50]	2021	Japão	Coorte Retrospectiva	333	203	73.5	152	45,6	AWGS2
Lin YL et al.[51]	2022	Taiwan	Transversal	297	169	68.8	60	20,2	AWGS2

* A sarcopenia foi definida conforme recomendado pelos consensos como baixa função física assocada a baixa massa muscular.

AWGS, Grupo de Trabalho Asiático para Sarcopenia; EWGSOP, Grupo de Trabalho Europeu sobre Sarcopenia em Pessoas Idosas; FNIH, Fundação dos Institutos Nacionais de Sarcopenia em Saúde

Tabela 2. Sarcopenia e DRC-ND e prognóstico de gravidade.

Autor, ano	País	Participantes	Diagnóstico	Resultados	Risco ajustado (IC 95%)
Androga et al.[52] 2017	EUA	GE: n=138 GC: n=348 n=1.101 Idade: ≥20 anos não institucionalizados TFGe 15 - 60 mL/min/1.73m^2	Índice de massa muscular esquelética apendicular <7,26 kg/m² para homens e <5,45 kg/m² para mulheres	Mortalidade durante um seguimento médio de 56 meses	OR = 1.24 (0.98-1.58)
Bichels et al.[53] 2021	Brasil	GE: n=58 GC: n=165 n=223 Idade Média = 60 (11) anos DRC-ND	Baixa massa muscular na terceira vértebra lombar (<138 cm² para homens e <98 cm² para mulheres)	Mortalidade por todas as causas durante um seguimento de 49 meses	OR = 2.15 (1.21 – 3.84)
Brar et al.[54] 2021	Canada	GE: n=138 GC: n=348 n=603 Idade Média = 64 (54-73) e 73 (65-82) anos DRC-ND	FPM ≤30 kg para homens e ≤20 kg para mulheres Velocidade da marcha <0.8 m/s SPPB escore <10	Mortalidade por todas as causas durante um seguimento médio de 48 meses	OR = 1.61 (1.20-2.18) OR = 1.99 (1.49-2.65) OR = 1.96 (1.42–2.70)
Kruse et al.[55] 2020	EUA	n=1,036 Idade Média =58 (13) anos DRC-ND	Índice de massa esquelética ≤8,5 kg/m² para homens e ≤5,75 kg/m² para mulheres	Mortalidade por todas as causas durante um acompanhamento de 2005 a 2014	OR = 1.20 (0.82-1.74) para homens e 0.98 (0.69-1.38) para mulheres
Jung et al.[56] 2021	Coreia	GE: n=627 GC: n=1713 n=2,340 Idade ≥ 65 anos DRC-ND estádio 4	Timed-up and Go 10,0 a 14,9 segundos	Doença renal em estágio terminal durante um seguimento médio de 60 meses	OR não apresentado
Lin et al.[57] 2018	Taiwan	GE: n=163 GC: n=163 n=326 Idade media = 66 (13) years DRC-ND	Mediana do Índice de Massa Magra (<15.1 kg/m^2)	Mortalidade por todas as causas durante um seguimento médio de 55 meses	OR = 0.34 (0.15–0.78)
Pereira et al.[58]		GE: n=17 GC: n=270	Índice de massa muscular esquelética <10,76 kg/m² para homens e <6,76 kg/m²	Mortalidade por todas as	

2015	Brasil	n=287 Idade Média=60 (11) years DRC-ND	para mulheres e FPM <percentil 30 de uma população de referência	causas durante um seguimento de até 40 meses	OR = 3.02 (1.30–7.05)
Roshanravan et al.[59] 2013	EUA	EG: n=86 CG: n=295	FPM por sexo e IMC	Mortalidade por todas as causas durante um seguimento médio de 36 meses	OR = 1.30 (0.71–2.37)
		GE: n=122 GC: n=240	Timed-Up and Go ≥12 segundos	Mortalidade por todas as causas durante um seguimento médio de 36 meses	OR = 1.30 (0.71–2.37)
		GE: n=100 GC: n=222	Velocidade de marcha ≤0,8 m/s		OR = 2.45(1.09–5.54)
		GE: n=86 GC: n=223 n=322 Idade média =61 (13) anos DRC-ND	Teste de caminhada de 6 minutos <350 m		OR = 2.82 (1.17–6.92)
Weng et al.[60] 2021	Taiwan	GE: n=153 GC: n=178	FPM ≤20.4 kg para homens e ≤15.435 kg para mulheres	Mortalidade por todas as causas durante um seguimento médio de 37 meses	
		GE:n=91 GC:n=240 n=331 Idade Média =81 (7) anos DRC-ND	Teste Timed-up and go ≥24 segundos		OR = 3.47 (1.15–10.42)
Wilkinson et al.[49] 2021	Reino Unido	GE: n=844 GC: n=7,923 n=8,767 Idade Média =63 (6) anos DRC-ND	FPM <27 kg em homens e <16 kg em mulheres	Mortalidade por todas as causas e doença renal terminal durante um seguimento médio de 108 meses	OR = 1.33 (1.07-1.66)

GC = grupo controle; GE = grupo exposição; TFGe = taxa de filtração glomerular estimada; FPM = Força de Preensão Manual; SPPB = bateria curta de desempenho físico; IC: Intervalo de Confiança; OR : Razão de chance

Doença Renal Crônica (DRC) e Dinapenia

A dinapenia, definida como uma perda de força e potência muscular em relação à qualidade muscular, tem como descrição "*dina*" referindo-se a "poder ou força" e "*penia*" a "pobreza"[61]. Neste contexto, à dinapenia abrange os aspectos mais amplos do desempenho da força muscular esquelética e inclui força (isto é, força voluntária máxima) e/ou potência mecânica (um produto de força x velocidade)[62].

Evidências recentes sugerem que a perda de força muscular é o principal fator prognóstico negativo na DRC, no qual está associada com maior mortalidade, menor tempo para doença renal terminal e concentrações plasmáticas mais baixas de albumina sérica[63]. Há, portanto, um grande interesse em diagnosticar corretamente a sarcopenia e dinapenia – isto é, redução isolada da força muscular sem mudança na massa muscular - para investigar fatores causais que ligam essas condições à progressão e gravidade da doença[64]. O Consenso Europeu sobre Definição e Diagnóstico de Sarcopenia[28] apresentou uma mudança importante recomendando como suspeita para diagnóstico de sarcopenia à perda de força muscular. O consenso também afirma que a única demonstração de uma força muscular subnormal é suficiente para iniciar o tratamento.

A força muscular geral é convenientemente avaliada medindo a FPM com um dinamômetro de preensão manual. Dado o custo relativamente baixo e a facilidade de avaliação, as medidas são utilizadas em ambientes clínicos e epidemiológicos para determinar a capacidade de força[65]. No entanto, alguns pesquisadores recomendam que a FPM por si só não pode ser considerada um substituto para a força muscular geral e que outras medidas físicas, como a força de extensão do joelho, podem fornecer valor adicional nas avaliações da capacidade de força. A diminuição da força está particularmente associada a gravidade de doenças, como mortalidade, estando relacionada com a presença de doenças cardiometabólicas crônicas (por exemplo, diabetes mellitus) e neurodegenerativas (por exemplo, comprometimento cognitivo)[66].

O mecanismo de associação entre DRC e dinapenia pode ser explicado de diversas maneiras. Primeiro, a resistência à insulina pode ter afetado a perda muscular em pacientes com DRC[67]. Em segundo lugar, um aumento nos níveis de IL-6 devido ao estresse oxidativo e à inflamação crônica pode diminuir a força muscular e funcionar como um resultado prejudicial da DRC. Terceiro, o músculo esquelético sofre apoptose em resposta à estimulação do sistema renina-angiotensina, e a miostatina e a apoptose influenciam fortemente a expressão gênica. Desta forma, alterações fisiopatológicas nos níveis celular e do sistema orgânico da DRC interferem nos processos de bioenergia celular, inibem a recuperação muscular e as vias de síntese proteica e aumentam a degradação proteica[9,10].

Pacientes com DRC normalmente apresentam medidas de desempenho físico mais baixas do que a população em geral. Um estilo de vida sedentário geralmente começa nos estágios iniciais da DRC, o que, por sua vez, leva a uma diminuição no desempenho físico, acompanhada por um declínio na taxa de filtração glomerular[63]. Além disso, a DRC tem efeitos sistêmicos, como perda de apetite, inflamação crônica, anemia, acidose metabólica, todos os quais contribuem para a perda de massa muscular e declínio no desempenho físico[64].

Estudos realizados em pacientes com DRC, incluindo estudos de base populacional, vem demonstrando uma associação negativa, independente, de força muscular e progressão da DRC[9,10,63,64,65,66,67]. No entanto, observamos poucos estudos que analisaram separadamente sarcopenia e dinapenia em pacientes com DRC.

Guida et al.[67] em um estudo com 85 pacientes com DRC pré-diálise clinicamente estáveis (92,9% nos estágios 3-5), com idade mediana de 65,0 (52,5-72,0) anos identificou uma prevalência de sarcopenia e dinapenia, respectivamente, 7,1% e 17,6%. Além disso, não foi identificada diferença em nenhum dos parâmetros citados entre pacientes dinapênicos e pacientes com massa e força muscular preservadas.

Um estudo de base populacional com 7.029 idosos coreanos, participantes da Pesquisa Nacional Coreana de Exame de Saúde e Nutrição (KNHANES) de 2014-2019, com idade ≥65 anos, encontraram, após ajuste para todas as covariáveis, associação significativa entre DRC e dinapenia, OR = 1,207 (IC 95%: 1,056-1,379) no estágio de DRC 2 e OR = 1,790 (IC 95%: 1,427-2,246) na DRC estágio 3a-5. Além disso, a prevalência de dinapenia aumentou significativamente em relação a progressão da DRC. Assim, concluíram que a DRC está significativamente relacionada à dinapenia, principalmente em mulheres, quando estratificada por sexo[10].

Hayashi et al[64]. investigaram a prevalência de dinapenia em pacientes dialíticos, classificando-os em grupos de dinapenia e não-dinapenia. Entre 150 pacientes sem sarcopenia, 46 foram diagnosticados com dinapenia (30,6%). Na análise de Kaplan-Meier, a taxa de eventos cardiovasculares foi significativamente diferente entre os grupos de forma estratificada, com a maior taxa no grupo sarcopenia. Ambos os pacientes com sarcopenia e dinapenia tiveram eventos cardiovasculares significativamente aumentados em comparação com aqueles sem (OR 8,00; IC 95% 2,73-34,1; p < 0,0001 vs. OR 4,85; IC 95% 1,28-23,0; p < 0,02). Yoshikoshi et al.[65], estudo clínico que avaliou 616 pacientes idosos com total de 616 pacientes (65,4 ± 12,2 anos) com diagnóstico de DRC, sendo a maioria homens (61%), diagnosticou a dinapenia quando o paciente apresentava redução da FPM e força do quadríceps baixa. Durante o acompanhamento (mediana, 3,0 anos), ocorreram um total de 163 mortes e 288 hospitalizações por problemas cardiovasculares. Pacientes com dinapenia apresentaram um risco maior de mortalidade (OR, 2,80; IC 95%, 2,49-3,14) e hospitalização por eventos cardiovasculares (OR: 2,04, IC 95%: 1,44-2,89). Na tabela 3 exploramos os demais artigos que avaliaram essa relação.

Tabela 3: Dinapenia em pacientes com doença renal crônica.

Autor, ano	País	Participantes	Idade	Diagnóstico	Resultados	Risco ajustado (IC 95%)
Yildirim et al.[9] 2022	Turquia	120 receptores de transplante renal; 60 pacientes com DRC; 60 indivíduos controle com função renal normal	idade média: 40,4 ± 10,5 anos idade média: 41,9 ± 11,4 anos idade média: 38,8 ± 9,9 anos	força de preensão manual (FPM <26 kg em homens e <16 kg em mulheres), análise de impedância bioelétrica (índice de massa muscular <0,789 em homens e <0,512 em mulheres), teste de caminhada de 6 minutos (<0,8 m/Segundo)	12,5% dos pacientes no grupo de transplante renal (13,3% com sobrepeso, 20% de obesidade), 11,6% no grupo de DRC e 1,6% no grupo de controle apresentaram dinapenia (P = 0,015)	-
Souza et al.[66] 2023	Brasil	940 indivíduos em hemodiálise	idade média de 54,74 ± 14,71 anos	FPM 27 kg para homens e 16 kg para mulheres	39,92% dos indivíduos apresentavam FPM depletada (p < 0,001)	a preservação da massa muscular pela HSG (p < 0,001; OR = 0,524; IC 95%: 0,384–0,715) apresentou redução das chances de presença de obesidade abdominal dinapênica
Do-Youn Lee et al.[10] 2023	Coreia	7.029 participantes da Pesquisa Nacional Coreana de Exame de Saúde e Nutrição (KNHANES) de 2014–2019	Idade media de 74,44±0,34 anos para homens e 75,89±0,32 anos para mulheres	FPM <28 kg para homens, <18 kg para mulheres	20,8% estágio 2 e 32,3% estágio 3-5 em homens; 34,4% estágio 2 e 46,1% estágio 3-5 em mulheres	OR = 1,207 (IC 95%: 1,056–1,379) no estágio de DRC 2 e OR = 1,790 (IC 95%: 1,427–2,246) na DRC estágio 3a–5
Corrêa et al.[63] 2020	Brasil	257 pacientes em hemodiálise	Idade media de 64,9±3,8 anos	FPM ≤18 kgf	25,9% apresentavam dinapenia	-

Guida et al.[67] 2020	Italia	85 (55 homens) pacientes com DRC pré-diálise clinicamente estáveis (92,9% nos estágios 3–5)	Idade mediana de 65,0 (52,5–72,0) anos	FPM inferior a 27 kg (homens) ou 16 kg (mulheres)	A prevalência de dinapenia foi de 17,6%.	-
Yoshikoshi et al.[65] 2022	Japão	616 pacientes em hemodiálise	Idade média 65,4 ± 12,2 anos; homens, 61%	FPM <28 kg para homens e <18 kg para mulheres + força isométrica do quadríceps <40% seco peso	211 (34,3%) foram classificados como tendo dinapenia	Dinapenia apresentou risco maior de mortalidade(OR = 2,80; IC 95%, 2,49-3,14) e de incidentes de hospitalizações cardiovasculares (OR = 2,04, IC 95%: 1,44-2,89).
Hayashi et al.[64] 2022	Japão	244 pacientes em Hemodiálise	Idade media 66,6±11,8 anos	< 28 kg para homens e < 18 kg para mulheres e/ou caminhada de 6 m < 1,0 m/s	Entre 150 pacientes sem sarcopenia, 46 (30.6%) foram diagnosticados com dinapenia	Pacientes com dinapenia tiveram eventos cardiovasculares significativamente aumentados (OR = 8,00; IC 95% 2,73–34,1; p < 0,0001).

IC: Intervalo de Confiança; OR: Razão de chance

Doença Renal Crônica (DRC) e Qualidade de Vida (QV)

Nas últimas décadas, com as mudanças dos conceitos de saúde e doença, o campo da saúde está cada vez mais dando atenção à qualidade de vida (QV)[68]. Segundo a Organização Mundial da Saúde (OMS)[68], não existe uma definição unânime sobre QV, sendo a mesma definida pela OMS como "as percepções dos indívíduos sobre sua posição na vida no contexto da cultura e dos sistemas de valores em que vivem e em relação aos seus objetivos, expectativas, padrões e preocupações". Desta forma, as principais preocupações com à saúde mudaram da doença em si para o estado de saúde e bem-estar. Essa mudança de paradigma possibilita o surgimento de um novo termo "qualidade de vida relacionada à saúde (QRVS) " que pode ser muito apropriado em doenças crônicas, como por exemplo a DRC, na qual não há cura definitiva e o paciente terá que conviver com essa condição de saúde[68,69].

A QRVS de pacientes com DRC tem um impacto considerável no bem-estar do indivíduo relacionado ao exercício da sua cidadania, na progressão da DRC e na escolha entre a modalidade de TRS ou tratamento conservador[70,71]. Muitas evidências demostraram que pacientes com DRC têm QRVS menor do que a população em geral[72,73,74] e que quanto pior a função renal, menor a QRVS e vice-versa[75,76], mesmo uma redução moderada na TFG está associada negativamente à QRVS, particularmente entre os idosos[77]. Uma menor QRVS entre DRC se estenderia para afetar negativamente o paciente em termos de adesão a medicamentos e acompanhamento médico regular ou atividade física, hábitos alimentares e mortalidade por todas as causas[78].

Diversos instrumentos foram utilizados para avaliar a QRVS em muitos estudos com pacientes com DRC. Os instrumentos mais utilizados foram o *Study Short Form 36 (SF-36)*, *Medical Outcomes Kidney Disease Quality Of Life (KDQOL)*, *linear analogue self-assessment (LASAs)*, *Kidney Disease Questionnarie (KDQ)* e o *European Quality of life (Euroqol) EQ5D* (Tabela 4). Vale ressaltar que o instrumento mais utilizado para avaliação da QRSV em pacientes com DRC é o SF-36[6].

O SF-36 foi criado originalmente na língua inglesa por Ware and Sherbourne (1992)[79], sendo um instrumento do tipo genérico de avaliação da saúde, pois não foi criado para uma determinada faixa etária ou enfermidade[80,81]. No Brasil, teve sua tradução e validação cultural realizada por Ciconelli et al. (1999)[81]. O questionário é formado por

36 questıes que abrange 8 dimensões: capacidade funcional, limitações por aspectos físicos, dor, estado geral de saúde, vitalidade, aspectos sociais, limitações por aspectos emocionais e saúde mental. Ao final, cada dimensãoo apresenta uma pontuação que varia de 0 a 100, sendo o 0 representado pelo pior estado de saúde do indivíduo e 100 pelo melhor estado de saúde[79].

Tabela 4. Instrumentos utilizados para avaliar qualidade de vida de pacientes com DRC

Instrumentos	
Instrumentos genéricos utilizados em pacientes com DRC	SF-36[79]
	European quality of life (Euroqol) – EQ5D[82]
	Linear analogue self-assessment (LASAs)[83]
Instrumentos específicos para pacientes com DRC	Medical outcomes kidney disease quality of life (KDQOL – 36)[84]
	Kidney Disease Questionnaire (KDQ)[85]

OBJETIVOS

OBJETIVOS

GERAL

Identificar a associação de marcadores de saúde muscular com aspectos clínico nutricionais e de qualidade de vida em pacientes com doença renal crônica não-dialítica.

ESPECÍFICOS

1. Revisar a associação entre sarcopenia e mortalidade em pacientes com doença renal crônica não-dialítica;

2. Avaliar se existe associação entre ângulo de fase, sarcopenia e dinapenia em pacientes com doença renal crônica não-dialítica;

3.Avaliar a associação entre dinapenia e ângulo de fase com marcadores de qualidade de vida em pacientes com doença renal crônica não-dialítica.

METODOLOGIA, RESULTADOS E DISCUSSÃO

METODOLOGIA, RESULTADOS E DISCUSSÃO

A metodologia, os resultados e discussão desta tese serão apresentados na forma de artigos científicos intitulados:

Artigo 1: Sarcopenia and mortality in patients with chronic non-dialytic renal disease: systematic review and meta-analysis. Publicado na Journal of Renal Nutrition

Artigo 2: Association of phase angle, sarcopenia and dynapenia in Non-Dialysis CKD patients.

Artigo 3: Dinapenia and phase angle as markers of quality of life in Non-Dialytic Chronic Kidney patients.

ARTIGO 1

ARTIGO 1

https://www.jrnjournal.org/article/S1051-2276(21)00064-9/abstract[1]

SARCOPENIA AND MORTALITY IN PATIENTS WITH CHRONIC NON-DIALYTIC RENAL DISEASE: SYSTEMATIC REVIEW AND META-ANALYSIS

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Objective: To analyze the results of prospective studies on the presence of sarcopenia and its association with cardiovascular events and mortality in patients with non-dialysis-dependent chronic renal disease.

Methods: This study used the PRISMA protocol for systematic review. The systematic review and meta-analysis protocol was re- corded in the prospective record of systematic reviews by PROSPERO International: CRD42019120391. Data sources: MEDLINE via PubMed, Embase, Cochrane Library, CINAHL, Scopus, Web of Science and LILACS from December 2018 to April 20, 2019, with the survey results updated in January 2021. Data analysis: Random effect models were calculated to compare the results due to high het- erogeneity identified.

Results: The survey identified 951 studies. Of these, 392 were removed by duplicates and 559 references were selected for analysis. In the stage of evaluating titles and abstracts, 555 articles were excluded because they did not include inclusion criteria related to the population and study design, leaving 4 articles that were included in the systematic review and meta-analysis. A meta-analysis identified that the presence of sarcopenia increased the risk of mortality by 143%.

Conclusion (s): The meta-analysis identified the influence of sarcopenia on mortality in non-dialysis-dependent chronic renal disease.

Introduction

[1]Link do artigo publicado no Journal of Renal Nutrition

Sarcopenia is considered a syndrome charac- terized by progressive decline in muscle mass and func- tion, associated with fragility, disability and increased risk of mortality.[1,2] Although originally known as an aging condi- tion, several international societies now recognize the important role of catabolic diseases, such as chronic kidney disease (CKD), in the etiology of sarcopenia.[3]

In fact, loss of skeletal muscle mass is a prevalent compli- cation in CKD, regardless of its etiology, and is associated with poor prognosis.[3,4] This may be associated with several factors, such as the negative balance of protein homeostasis, reduction of cellular activation and expression of myogenic regulatory factors associated with increased myostatin levels, as well as accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, vitamin D deficiency, oxidative stress and increased ubiqui- tination.[4,5] Therefore, sarcopenia becomes a risk factor for several adverse outcomes, including death.[5]

In addition, several studies have proposed sarcopenia as a new prognostic factor for cardiovascular disease in patients with CKD, since inflammation and skeletal muscle mass loss are factors associated with atherosclerosis.[6,7] However, in light of these studies, a clear conclusion is needed on the prognosis of sarcopenia in these patients, in order to outline tools for nutritional prevention and treatment. This study used the PRISMA protocol for systematic review having as a starting question whether the presence of sarcopenia is associated with a higher risk of cardiovascular events and mortality in patients with non-dialysis-dependent chronic renal disease (NDD-CKD).

Methods

<u>Data Sources and Searches</u>

A systematic review and meta-analysis was performed with studies evaluating sarcopenia, cardiovascular events, and mortality in patients with non-dialysis-dependent chronic renal disease. We used the recommendations of the Preferred Items statement for Systematic Review Reports and Meta-Analysis (PRISMA). The systematic re- view and meta-analysis protocol was recorded in the prospective registry of PROSPERO International systematic reviews.

<u>Search Strategy</u>

In order to conduct a comprehensive and systematic literature review, the following databases were searched from December 2018 to April 20, 2019, with the survey re- sults updated in January 2021: MEDLINE via PubMed, Embase, Cochrane Library, CINAHL, Scopus, Web of Sci- ence and LILACS. The reference list of the included studies was also evaluated.

There was no language restriction or publication period. The search strategy was developed with the MeSH descrip- tors, following the PICOS question (Table 1). The terms for exposure (Sarcopenia) and population (chronic non- dialytic renal disease) and their respective synonyms were used in the search strategy to include all relevant studies on this topic. The Boolean operators ‘‘AND’’ and ‘‘OR’’ were adopted to search the databases. Specific descriptors by controlled vocabulary for exposure, outcome and pop- ulation in MEDLINE/PubMed lation are available in Supplementary Table S1. For the search in the LILACS database, the descriptors were selected from the Health Sci- ences Descriptors of the Virtual Health Library. Finally, the vocabulary descriptors controlled by Embase subject head- ings were used to construct Boolean word expressions (discovered by results) to search articles indexed in this data-base. Rayyan software, developed at the Qatar Computing Research Institute (Data Analytics), was used to store man- uscripts and evaluate duplicates.

Inclusion and Exclusion Criteria

The studies were included in the systematic review when the following inclusion criteria were met (Table 1): (1) prospective observation; (2) the population consisting of adults and older adults with non-dialysis-dependent chronic renal disease (glomerular filtration rate, 60 mL/min/1,73 m2, stage 3-5); (3) exposure as the presence of sarcopenia; (4) outcomes related to cardiovascular events and mortality;

(4) provide at least Relative Risk (RR) or Hazard Ratio (HR Ratio) with their confidence intervals (CIs) for cate- gorical risk and continuous risk estimates. There was no re- striction on sample size, study location, time of study, length of follow-up, and language. We excluded studies in which individuals were selected by high risk group; research on animals, retrospective, cross-sectional, review and/or case reports; and those that provided only a risk es- timate with no means to calculate 95% confidence intervals or without adjusting RR or HR.

Study Selection

The studies obtained through the search strategy were independently assessed by two authors, who met the study's eligibility criteria. Titles and abstracts were read and those that did not meet the selection criteria were excluded. All studies that were selected in the previous phase had their eligibility confirmed by reading the full article. At this stage, the primary reason for exclusion was recorded to make up the study selection flow. A third reviewer was available to resolve any disagreement between the authors. The research team jointly concluded which studies were finally selected for data synthesis.

Extraction of Data and Evaluation of Quality

The following variables were independently extracted by two reviewers: author, year of publication, country, study design and purpose, sample size, characteristics of participants (age, gender), sarcopenia evaluation methods, sarco- penia diagnosis, prevalence of sarcopenia in the population, prevalence of sarcopenic obesity, follow-up time, number of deaths, number of complications due to cardiovascular diseases, RR and HR adjusted with their confidence intervals. In the absence of data, contact was made with the author and/or search for publications by the author, who used the same population to collect the information.

The evaluation of the methodological quality was per- formed by two independent researchers, using the Check- list Downs and Black for randomized and non-randomized studies, consisting of five scales: external validity, bias, con- founding variable/selection bias and power of the study. To assess the methodological quality of the studies included in this review, only the questions applicable to observational studies (22 items after adaptation) were used.8 The quality score of each article corresponds to the total sum of the items analyzed as positive, with a maximum score of 23 points. Based on the score received, three categories were established for quality assessment: A - when the study meets more than 80% of the established criteria; B - when 50%- 80% of the criteria are met and C - when less than 50% of the criteria are met.[9]

Risk Assessment of Bias

The risk of bias was evaluated according to the Bank of Items of the Research Triangle Institute (RTI)[10] items composed of 13 questions related to observational studies. Based on the responses of the evaluated items, the quality of evidence/risk of bias was categorized into three levels: low, moderate and high quality. The chosen cut score was determined based on previous systematic reviews and meta-analyzes: 0% to 40% of positive responses: high risk of bias; 41% to 70% of positive responses: moderate risk of bias; 71% to 100% positive responses: low risk of bias.[11-13]

Meta-Analysis

Analyzing the absence of information related to cardio- vascular events, it was only possible to perform a meta- analysis of mortality data from studies included in the systematic review. For the meta-analysis we excluded the study by Androga et al,[14] since its population is included in the Ziolkowsky et al[15] manuscript. The coefficients of the Cox regression models were extracted, estimating the log of the HR and their respective confidence intervals (CI 95%), adjusted for age and sex. For the meta-analysis, the HR log was used, considering that the scales of the ratio estimates are not symmetric, with the lowest value being zero (0) and the highest value 1N. Random-effects models were calculated to compare the results between the sarcopenia group and the non-sarcopenia group, due to the high heterogeneity identified, presented in a Forest Plot.16 The standard errors, required for HR meta- analysis, were estimated from the confidence intervals of the Cox model estimates.[16]

The assumption of the homogeneity of the studies was tested by the Cochran Q test and the extent of heterogene- ity was interpreted by the total percentage of variation among the included studies as measured by the I2 statistic.[16] The inconsistency test (I2. 50%) was used as an indicator of moderate heterogeneity. It was not possible to assess the sources of heterogeneity identified among the studies, considering the low number of eligible articles included in the meta-analysis.[16] All statistical tests were bi-caudal, adopting the level of significance 0.05. The analyzes were conducted in the statistical package STATA v.12.0 (StataCorp, LLC, College Station, TX USA).

Results

Study Selection

The detailed steps of the search and selection of the studies, carried out between December 2018 and April 2019, with the survey results updated in January 2021, are presented in flow chart below (Figure 1). During the search phase, 951 studies were identified in the electronic data- bases. Of these, 392 were removed by duplicates and 559 references were selected for analysis. In the stage of evaluating titles and abstracts, 555 articles were excluded because they did not include inclusion criteria related to the population and study design, leaving 4 articles that were included in the systematic review. For the meta- analysis, 3 manuscripts were used due to the exclusion of Androga et al[14] because its population is included in the study by Ziolkowski et al.[15] According to Cochrane Hand- book for Systematic Reviews of Interventions, it is possible to make a meta-analysis based on two combinable articles.[16]

Quality of Studies

According to the Downs and Black checklist, all studies were classified as of medium quality (B) with values ranging from 63.6% to 77.3%.14,15,17,18 In the sections related to external validity, most of the articles (75%) had average quality (66.6%) and, in relation to the power of the study, all reached a maximum score, showing excellent quality. Limitations of the studies were concentrated on the lack of data related to loss of follow-up or adjustment for follow-up, with only one study[18] describing the number of losses. In addition, the item representativeness of the population was also limited by the studies[14,15,17,18] (Table 2).

Risk Assessment of Bias

Considering the 4 studies evaluated, 100% presented low risk of bias, ranging from 76.9 to 84.6% (71% to 100% pos- itive responses: low risk of bias) considering the Item Bank scale (RIT) (Table 3).

Characteristics of Selected Studies

The main features of the studies included in this review are provided in Table 4. The selected articles were pub- lished in the United States, Japan and Brazil between 2015 and 2019. All studies presented prospective cohort design with a total of 4,496 patients diagnosed with chronic kidney disease with mean follow-up of 72.5 months (SD 5 47.22). The mean age of the subjects in the studies was 57.97 years with a standard deviation of 10.65, that is, mostly adult individuals. Data on number of patients with NDD-CKD and sarcopenia by sex was a limiting factor in all studies.

All 4 articles of the systematic review and meta-analysis aimed to evaluate the prognosis of mortality in patients with sarcopenia and NDD-CKD.[14,15,17,18] Of these, 1 article also evaluated the risk of mortality in patients with a diagnosis of sarcopenic obesity and 1 evaluated a higher r isk ratio for cardiovascular events in patients with sarcopenia.[14,17]

O analyze the outcome (mortality and cardiovascular disease events) and exposure (sarcopenia), the variables of interest presented discrete and categorical characteristics. All studies performed statistical analysis by Cox Regression with adjustments of sex, age and race variables for HR or RR.

Diagnostic Methods for Sarcopenia

Regarding the methods used for the diagnosis of sarco- penia, two studies used the X-ray dual-density densitom- etry (DEXA) for the evaluation of skeletal muscle mass[14,15]; a study evaluated by the muscular mass given by the bioelectrical impedance (BIA) associated with hand- grip strength (HGS)[18] and a simple screening trial for sarco- penia using age, HGS, and calf circumference.[17] In the study by Androga et al,[14] muscle mass was quantified using the appendicular skeletal muscle mass index (ASMI), where sarcopenia was defined as ASMI 5.45 kg/m2 in women and 7.26 kg/m2 in men. Ziolkowski et al[15] also used the DEXA tool, but adopted different statistical measures for the diagnosis of sarcopenia. The three-dimensional ra- diofrequency derived appendicular lean mass index (ALMI, kg/m2) and fat mass index (FMI, kg/m2) were used for the diagnosis of sarcopenia using standard devia- tion scores for sex and race/ethnicity compared to young adults (T scores), T score of ALMI score # 2 and sarcopenia relative to T scores of ALMI FMI # 2.[19]

In the study by Pereira et al[18] the method used for the diagnosis of sarcopenia was the association of skeletal mus- cle mass index (10.76 kg/m^2 for men; 6.76 kg/m^2 for women) estimated by BIA with reduced muscle function assessed by handgrip strength (HGS ,30th percentile of a population-adjusted reference for gender and age). Finally, the study by Hanatai et al[17] used a new method for the diagnosis of sarcopenia, the sarcopenia screening score, calculated by means of a scoring chart for the estimated probability of sarcopenia advocated by Ishii et al. (2014),[20] which uses handgrip strength and calf circumfer- ence. In this study, a high sarcopenia score was defined as a screening score $105 for men and $120 for women.

Prevalence of Sarcopenia

Data from sarcopenia prevalence studies in patients with chronic kidney disease with an estimated glomerular filtra- tion rate #60 mL/min/1.73 m^2 ranged from 5.9 to 62.6%. The study by Pereira et al[18] carried out with 287 patients in Brazil found the lowest prevalence of sarcopenia (only 17 individuals). The study by Hanatai et al[16] in Japan found the highest prevalence of sarcopenia in their population in 166 of 256 patients with chronic kidney disease. This variation in prevalence may be associated with the methods used for its diagnosis.

Prognostic Assessment

All studies evaluated mortality as a clinical outcome in patients with NDD-CKD and without sarcopenia. The mean follow-up time also varied between the studies, with the study by Hanatai et al[17] showing the shortest follow-up (24 months), while those of Androga et al[14] and Ziolkowski et al[15] followed for 113 months. The risk of mortality ranged from 1.33 in the study of Androga et al[14] to 3.58 in the study by Pereira et al,[18] with all adjusted for age and sex. Regarding the increased risk of cardiovas- cular complications, only the study by Hanatai et al[17] eval- uated this event, in which the risk of individuals with chronic renal disease and sarcopenia was HR 1.97 when compared to non-sarcopenic individuals.

Meta-Analysis Results

Meta-analysis identified the influence of sarcopenia on mortality in patients with chronic kidney disease not dependent on dialysis (Figure 2). There was a 143% increase in the risk of dying in patients with sarcopenia, compared to those without sarcopenia (HR: 2.43; 95% CI: 1.64-3.60).

Discussion

The results of this meta-analysis indicate that patient's non-dialysis-dependent chronic renal disease have a 143% increase in the risk of dying when compared to patients without sarcopenic.

The etiology of the loss of skeletal muscle mass in chronic renal disease is multifactorial, involving inflammation, reduction of food intake, physical inactivity, excess of angiotensin II; abnormalities in insulin/insulin-like growth factor-1 (IGF-1) signaling and myostatin expression; reduced function of satellite cells and myocellular changes.[21] The inflammatory state resulting from CKD and uremia are related to metabolic acidosis, increased pro- tein catabolism and oxidative stress, and decreased antioxi- dant capacity. These factors, together with the action of inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-a), promote muscle loss in the patient.[22,23]

Oxidative stress can lead to atrophy by the activation of autophagy pathways and may affect skeletal muscle through the myostatin pathway. Myostatin regulates muscle atrophy through the activation of proteolytic pathways and impaired muscle regeneration.[24] Muscle regeneration is an organized process that, in response to a noxious stimulus, activates quiescent satellite cells to differentiate and form myotubes and subsequent myofibers. Some studies have shown that impaired function is associated with satellite cell proliferation and differentiation due to myogenic expression changes.[24,25]

Skeletal muscle loss in these patients may be induced by vitamin D deficiency via the ubiquitin-proteasome pathway. In addition, in NDD-CKD, hypogonadism is common and may be exacerbated by other common co- morbidities of the disease.[26] Serum levels of testosterone were associated with reduced muscle mass and strength in CKD. The renin-angiotensin-aldosterone system is over- regulated in CKD. Increased expression of Angiotensin II reduces the pool of satellite cells and muscle regeneration capacity, in addition to positively regulating caspase-3 and the proteolytic pathways of the proteasome ubiquitin.[4]

Finally, NDD-CKD is associated with resistance to growth hormone and is considered a potential cause of increased protein catabolism and loss of skeletal muscle due to the resistance of IGF-1 anabolic hormone to protein turnover in skeletal muscle.[4,23] All these mechanisms lead to the diagnosis of sarcopenia in this population.

Sarcopenia is a generalized and progressive skeletal mus- cle disorder involving accelerated loss of muscle mass and function with important clinical consequences, including frailty and mortality. Once understanding that NDD- CKD per se leads to increased mortality, the association of the disease with the development of sarcopenia may in- crease the risk of death in these patients.[3]

Studies have shown a prevalence of up to 60% of sarco- penia in patients with non-dialysis-dependent chronic renal disease. This difference may vary depending on the method used for diagnosis. According to the European Consensus for the Definition and Diagnosis of Sarcopenia (2019)[3], the diagnosis should be made by the association of low mus- cle strength given by handgrip strength, reduced physical performance and low skeletal muscle mass by the standard- ized methods of computed tomography, DEXA, magnetic resonance imaging, or BIA. However, none of the studies in this meta-analysis covered all recommended methods, which could have under or overestimated the prevalences found.[14,15,17,18]

A higher mortality risk was associated with sarcopenia in each of the studies included in this meta-analysis, regardless of the method used for the diagnosis of sarcopenia (HR 1.33-3.58).[14,15,17,18] Therefore the risk of mortality caused by sarcopenia in these patients is independent of the methods used and the cutting points adopted in clinical practice and the need for this evaluation to be performed early in order to establish nutritional barriers that avoid or minimize installation.

It should be noted that all the studies included in this meta-analysis presented medium quality, with low scores only on the items external validity (associated to sample representativeness in the population), reporting (related to follow-up data) and bias (with limitation of the analysis adjusted by time follow-up). In addition, all studies had a low risk of bias, which made the findings more robust.

As a limitation, this meta-analysis did not present the evaluation of the sources of heterogeneity identified among the studies, due to the low number of eligible articles included in the meta-analysis. In addition, it was not possible to evaluate the prognosis of cardiovascular events due to the limitation of published articles. In summary, findings from this meta-analysis indicate higher mortality in patients with non-dialysis-dependent chronic renal dis- ease with sarcopenia, suggesting that the routine evaluation of the diagnosis of sarcopenia in these patients may be a protective event of morbidity and mortality in this group, since muscle complications in this phase may still be reversible.

Practical Application

This systematic meta-analysis review concluded that pa- tients with non-dialysis chronic kidney disease and sarcope- nia are at increased risk of mortality. Therefore, we believe that our study can not only contribute to knowledge, but also stimulate conducts for the prevention and/or treatment of this clinical and nutritional alteration, however, further studies are necessary.

CRediT authorship contribution statement Tarcisio Santana Gomes: Conceptualization, Meth- odology, Investigation, Writing - original draft. Dannieli do Espirito Santo Silva: Conceptualization, Methodol- ogy, Investigation. Gesner Francisco Xavier Junior:

Conceptualization. Priscila Ribas de Farias Costa: Formal analysis, Writing - review & editing. Maria Helena Lima Gusm~ao Sena: Writing - review & editing

Jairza Maria Barreto Medeiros: Investigation, Writing - review & editing.

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Supplementary Data

Supplementary data related to this article can be found at https://doi.org/10.1053/j.jrn.2021.02.004.

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Table 01: PICOS criteria for inclusion of studies

Parameter	Inclusion criteria
Population	Adults and older adult with chronic kidney disease under conservative treatment
Intervention or exposure	The presence of sarcopenia
Comparison	Absence of sarcopenia
Outcomes	Related to cardiovascular events and mortality
Study design	prospective observation

Table 02. Methodological quality assessment according to Checklist Downs and Black.

Reporting	Androga L et al.[15]	Hanatani S et al.[16]	Ziolkowski S et al.[17]	Pereira R et al.[18]
1.Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1
2.Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1

3. Are the characteristics of the patients included in the study clearly described?	1	1	1	1
4. Are the interventions of interest clearly described?	1	1	1	1
5.Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	2	1	0
6.Are the main findings of the study clearly described?	1	1	1	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	0	0	0	0
9. Have the characteristics of patients lost to follow-up been described?	0	0	0	0

10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1	1	1	1
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	0	1	0
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	0	1	1
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	0	0	1	1

14. If any of the results of the study were based on “data dredging”, was this made clear?	0	0	0	0
15. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0	0	0	1
16. Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1
17. Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1
18. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	0	1	0	1

19. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	1	1	1
20.Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	1	0	1
21.Were losses of patients to follow-up taken into account?	0	0	0	1
22. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	1	1	1
Punctuation %	63,6	68,2	68,2	77,3
Quality Methodological	B	B	B	B

Table 03. Evaluation of the bias risk of the articles included in the Systematic Review

Study	Selection bias	Performance bias	Detection bias	Confusion bias	Risk of bias
[15]	+++	+	++++	+++	Low risk
[16]	+++	+	++++	+++	Low risk
[17]	+++	+	+++	++	Low risk
[18]	+++	+	++++	+++	Low risk

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Possible answers to each question (Presence, Absence, Uncertain); +: absence; Maximum selection bias of +++; Maximum performance bias of +, Maximum detection bias of +++++++; Plus confusing bias of +++.

Table 04: Characteristics of selected studies investigating the prognosis of Sarcopenia in patients with chronic kidney disease.

Study	Country	Design	Age*	Gender n(%)	Number of patients	eGFR (mean mL/min/ $1.73m^2$ or %)	Statistical analysis	Instrument used to evaluate Sarcopenia	Cutting Points	Follow-up time (months)	Sarcopenia n(%)	Mortality	OR (95% IC)	Sarcopenic Obesity n(%)	OR (95% IC)	Events CD	OR (95% IC)	Methodological quality
[15]	USA	Cohort	50.75 ± 0.5	-	1101	-	Cox regression models	DEXA	<5.45 kg/m^2 Woman and <7.26 kg/m^2 Men	113	138 (12.5)	2402	1.33 (1.05-1.68)	106 (9.7)	1.83 (1.34–2.48)	-	-	B
[16]	Japan	Cohort	72.3 ± 9.8	Male 184 (69)	256	43,1±17,2	Cox regression models	Sarcopenia Screening Score (CC + Handgrip Strength)	≥105 Men and ≥120 Woman	24	166 (62.6)	23	3.04 (1.45-6.38)	-	-	23	1.97(1.12-3.48)	B
[17]	USA	Cohort	54.9 (43.9-68.2)	-	2852	-	Cox regression models	DEXA	ALMI T score ≤2.0	113	172 (6.03)	2402	1.97 (1.36 – 2.87)	-	-	-	-	B

[18]	Brazil	Cohort	59.9 ± 10.5	Male 178 (62)	287	State 3:33 State 4:38 State 5:29	Cox regression models	BIA + Handgrip Strength (HGS)	<6.76 kg/m² Woman and <10.76 kg/m² Men; HGS < P30	40	17 (5.92)	51	3.58 (1.54-8.31)	-	-	-	-	B

* Mean and standard deviation or median and interquatile range; eGRF: Estimated glomerular filtration rate; CD: cardiovascular disease; OR: odds ratio; CI: Confidence Interval; USA: United States of America; DEXA: dual-energy X-ray absorptiometry; CC: calf circumference; BIA: bioelectrical impedance; HGS: Handgrip Strength; Score ALMI: appendicular lean mass index.

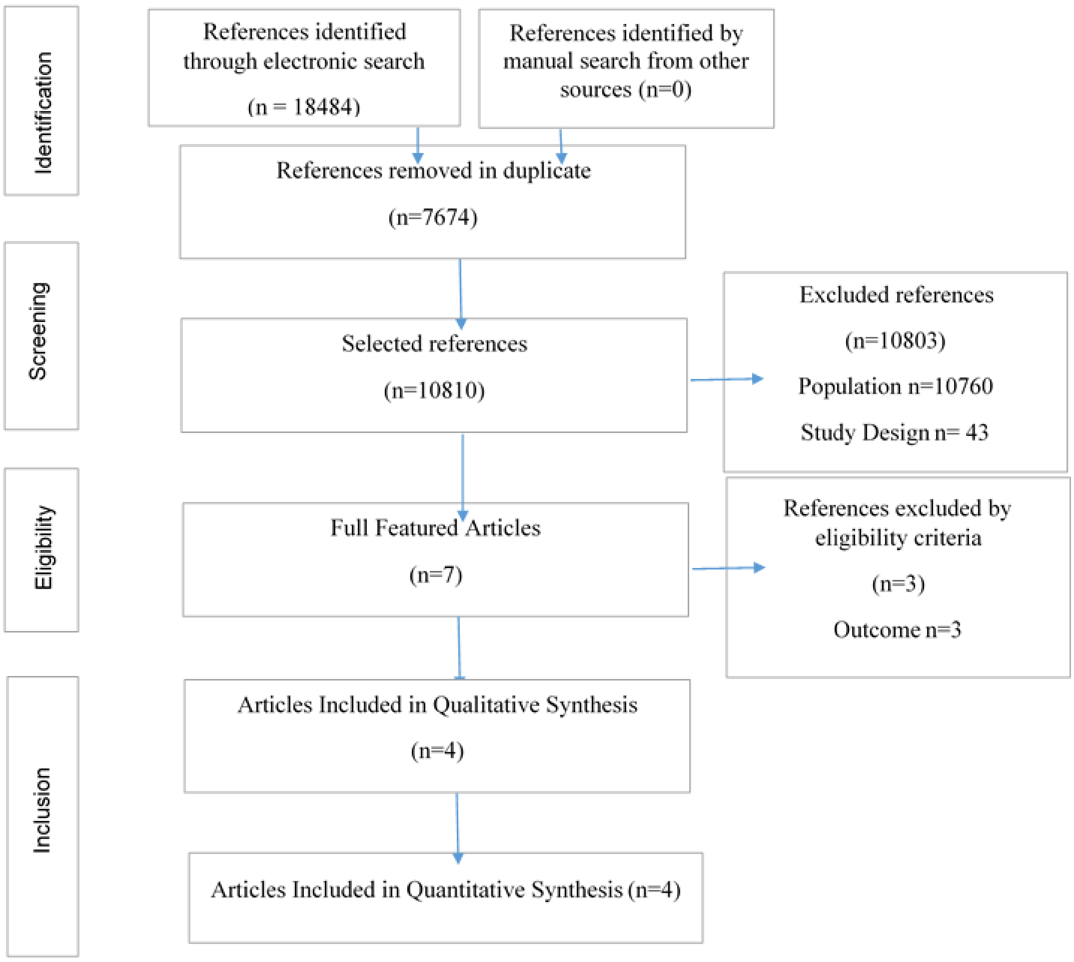

Figure 1. Flow of article selection from systematic review.

ARTIGO 2

ARTIGO 2

ASSOCIATION OF PHASE ANGLE, SARCOPENIA AND DYNAPENIA IN NON-DIALYSIS CKD PATIENTS

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ABSTRACT

Background: Sarcopenic is an important problem for patients with chronic kidney disease non-dialysis (CKD-ND), leading to morbidity and mortality. Phase angle (PA) is a marker of cell integrity and has been associated with muscle mass and handgrip strength. However, the usefulness of this parameter as a sarcopenia marker as not yet been evaluated. The aim of the present study was to evaluate the association between PA values with dynapenia and sarcopenia in patients with ND-CKD. **Methods**: After performing electrical bioimpedance, patients with CKD-ND (n = 85) were grouped according to their PA values (> 5.45° or ≤ 5.45°), dynapenia (HGS ≤10kg female and male with HGS ≤12.5kg) and sarcopenia. Pearson's correlation coefficient was used to examine the association between clinical/nutritional variables and PA and handgrip strength values. Poisson's regression multivariate model evaluated the prevalence ratio between PA, dynapenia and sarcopenia. The area of the ROC curve was calculated to identify the power of PA values to predict sarcopenia, as well as HGS. In addition, the area of the ROC curve was identified for diagnosis of low HGS through the phase angle. **Results**:

PA values ≤ 5.45º were directly correlated with low HGS values ($p = 0.000$) and sarcopenia ($p = 0.009$). Patients with reduced dynapenia had lower values of PA (5.20 vs. 6.09; $p = 0.001$) and albumin (3.95 vs. 4.4; $p = 0.009$). **Conclusion:** PA values ≤ 5.45° and HSG ≤ 12, 25kg were able to predict the diagnosis of sarcopenia. PA ≤ 5.35º identified low HSG in the population studied.

Key Words: Phase Angle, Sarcopenia, Dynapenia, Handgrip strength, Chronic Kidney Disease

INTRODUCTION

Sarcopenia is defined as a syndrome characterized by loss of muscle mass, strength, and / or functional capacity that comprises a risk factor for several adverse outcomes, including death[1,2]. Some factors can affect the nutritional and metabolic status of CKD patients requiring a combination of therapeutic maneuvers to prevent or reverse protein and energy depletion. These include optimizing dietary nutrient intake, appropriate treatment of metabolic disturbances such as metabolic acidosis, systemic inflammation and hormonal deficiencies[3,4]. Therefore, it can be hypothesized that CKD patients are prone to develop sarcopenia and in this context, early detection of sarcopenia is thought to be essential.[5,6]

Handgrip strength is widely used as a functional test of general strength, being associated with a high prevalence of sarcopenia and malnutrition and strongly associated with mortality. According to the Consensus European consensus on definition and diagnosis the sarcopenia[1], muscle strength is the main parameter of sarcopenia, being diagnosed as probable when low muscle strength is detected. In addition, some studies are associated with an effective predictor of different clinical outcomes[2,7,8].

In recent years, attention has been focused on the condition termed "dynapenia", condition in which a person has reduced walking speed and/or handgrip strength;

however, the skeletal mass index (SMI) remains unaltered. Dynapenia increase the risk of physical disability, poor physical performance, and even death[9].

The PA derived from the bioelectrical impedance analysis (BIA) is a parameter obtained from the value of the arc tangent between the resistance and reactance values[9]. PA has gained attention in the clinical assessment of nutritional status because it is thought to be marker of water distribution and body cell mass, reflecting cell vitality and integrity[9-11]. The relationship between phase angle measurements and disease prognosis can be understood by the inflammation and prolonged malnutrition that negatively affect the electrical properties of tissues, resulting in cell death[4,11].

In patients with CKD, fluid imbalances can limit the performance of BIA in estimating skeletal muscle mass for the diagnosis of sarcopenia[10]. Nonetheless, several studies have demonstrated Low PA values have been correlated with reduced skeletal muscle mass and low handgrip strength (HGS) in some clinical populations[9,10,12,13,14]. However, the association between low PA values, dynapenia and sarcopenia in ND-CKD remains to be tested. Therefore, our objective was to associate PA, dynapenia and sarcopenia in patients with CKD-ND.

METODS

Subjects

The present cross-sectional study was conducted in a university hospital nutrition and nephropathy outpatient clinic, between September 2012 and November 2013. The study included clinically stable, from both genders, adult (≥ 20 and < 60 years old) and elderly adult (≥ 60 years old) outpatients with glomerular filtration rates (GFRs) between 15 and 89 ml/min/1.73 m². The exclusion criteria were as follows: admission to a hospital within the past month, limb amputation, malignant disease, chronic infectious disease, muscular and neurological disease, acquired immunodeficiency syndrome, history of dialysis or transplantation, use of immunosuppressant drugs, acute kidney failure, severe liver failure, leukocytosis (defined as total leukocit count higher than 10.000 cells/mm³) and terminal CKD. The study protocol approval by the local Ethical Committee (104761/12)

Demographic and clinical/nutritional data

The following demographic and clinical/nutritional data were collected: age, gender, CKD Stages 2 and 4 (estimated glomerular filtration rate [eGFR] of 15-89 mL/minute/1.73m²), presence of diabetes mellitus (DM), physical activity, body weight and height, and body mass index (BMI). The biochemical tests evaluated were hemoglobin, serum levels of albumin, creatinine, CPR levels. Body weight was measured with the participant standing in the center of a single electronic weighing platform (PDA; BOD POD TM BC system; Life Measurement Instruments, Concord, CA, USA), barefoot and wearing only light clothing. Body height was measured using a single stadiometer (Sanny, São Paulo, SP, Brazil) with the individual standing barefoot, heels together, straight back and arms extended at the side of the body. BMI was calculated as the weight divided by the squared height (kg/m²)[15].

Physical Activity Level

The short version of International Physical Activity Questionnaires (IPAQ) was applied to determine the physical activity level[16]. The questionnaire was validated for Brazilian population and was applied referring to the last week information, which consisted in evaluating the frequency, duration, and vigorousness of the physical activities.

Handgrip strength and Dynapenia

Muscle strength was assessed in the dominant hand using a dynamometer (Bulb Dynamometer®). Patients were first familiarized with the device and were then examined standing with both arms extended sideways from the body with the dynamometer facing away from the body. Patients were instructed to grip the dynamometer with the maximum strength in response to a voice command, and the highest value of three measurements was considered for the study[17].

Participants were classified as having high or low handgrip strength after taking the quartile measurement, adjusted for sex. For females, dynapenia was considered when HGS ≤10kg and for males HGS ≤12.5kg.

Bioelectrical impedance analysis

BIA was assessed by a tetrapolar device (Biodynamics® BIA450 Bioimpedance Analyzer, Seattle,WA, USA). The measurements were made with the patient in the supine position, with the arms lying parallel and separated from the trunk and with the legs separated so that the thighs were not touching. Two electrodes were placed on the hand and wrist and another two were positioned on the foot and ankle of the non-dominant side of the body. An electrical current of 800 A at 50 kHz was introduced into the subject, and resistance and reactance were measured. The Fluid & Nutrition software, version 3.0, was used to calculate the total body water, fat-free mass, fat mass, body cell mass and phase angle. The following skeletal muscle mass equation developed by Janssen et al. and recommended by the EWSOP was used in the present study[1,18].

$$\text{SMM} = \left[\left(\frac{(heigth)^2}{resistance}\ x\ 0.401\right) + (sex\ x\ 3.825) + \left(age\ x\ (-0.071)\right)\right] + 5.102$$

SMM = skeletal muscle mass; height in centimeters; resistance in ohms; sex: women = 0, men = 1; age in years.

Then, the absolute muscle mass (kg) was normalized for squared height and defined as skeletal muscle mass index (SMMI). The cutoff to establish reduced muscle mass was SMMI of <7,29 kg/m² for women and <8,1 kg/m² for men[1,19].

Phase angle measuring

PA evaluation were performed using Biodynamics 450 bioimpedance (Biodynamics, Seattle, WA). The participants were asked to perform 12-hour overnight fast before the test. In addition, the individuals should avoid intense physical activity and intake of caffeine and alcoholic beverages during the day before the test to ensure the adequate hydration. For childbearing-aged women, the evaluation was performed outside the menstrual period. Participants were advised to empty their urinary bladders 30 minutes before the evaluation[18]. PA values were calculated as PA = tangent arc Xc / R × 180 / π. Patients were grouped according to the value of PA (high: PA > 5,45° or low: PA ≤ 5,45°).

Sarcopenia diagnosis

Diagnosis of sarcopenia was based on the simultaneous presence of low appendix skeletal muscle index and low muscle strength[1].

Statistical analysis

Data were expressed as mean, standard deviation, median, interquartile ranges (IQRs, 25°-75° percentiles), or percentages, depending on the normality of distribution and the type of variable. Differences in the studied variables were analyzed using the t-Student or Chi-square test, as appropriate. Pearson's correlation test was applied for PA evaluation with demographic and clinical/nutritional markers. Poisson regression model was created to examine factors related to low PA values, where demographic and clinical / nutritional variables were considered dependent. The area of the ROC curve was calculated to identify the diagnostic power of PA for sarcopenia and dynapenia, through sensitivity and specificity analysis. All analyzes were performed with the SPSS software version 20.0 (SPSS Inc, Chicago, IL, USA) under the significance level of 5%.

RESULTS

Among 85 patients evaluated, 45 (52.9%) were male, age (60 ± 11.66 years), 35 (41.2%) were diagnosis DM, eGFR = 38.67 (23.91 – 52.78) mL/min/1.73 m², CKD stage 73% stage 3-4. From the total patients, 31 presented PA values ≤ 5.45º (mean = 5.7º ± 1.05°) and 11 (12,9%) were diagnosed as sarcopenic. When comparing patients with PA values ≤ 5.45º to patients with PA values > 5.45°, the first had lower HGS (11.3 *vs*. 13.71; p = 0.000) and diagnosis sarcopenia (7 *vs*. 3; p = 0.009) (Table 1). When comparing sarcopenic to non-sarcopenic patients (Table 1), the first had higher age (66.6 vs.57; p = 0.014), low HGS (10,92 *vs*. 13.11; p = 0,003); PA value (4,97 vs. 6.04, p = 0.001 and SSMI (6,97 vs. 9.70, p = 0.000). Patients with reduced dynapenia had lower values of PA (5.20 vs. 6.09; p = 0.001) and albumin (3.95 vs. 4.4; p = 0.009).

PA values were inversely correlated with age (r -0.538; p = 0.000) and were directly correlated with com HGS (r 0.466; p = 0,000), LBM (r 0.355; p = 0.001), BMI (r 0,294; p = 0,006), SSMI (r 0.318; p = 0,003), albumin (r 0.314; p = 0.003) and hemoglobin (r 0.407; p = 0,000), but not with any inflammatory marker or eGFR (Table 2). HGS values were inversely correlated with age (r -2.55; p = 0.019) and were directly correlated with FA (r 0.544; p = 0.000), SSMI (r 0.618; p = 0.000) and albumin (r 0.314; p = 0.007) (Table 2).

The ROC curve area (0.79; Fig. 1, A) identified PA ≤ 5.45° as a cutoff value with 72,7% sensitivity, 68,9% specificity to diagnose sarcopenia (p = 0,002, 95% CI 0.694 - 0.895). HGS ≤ 12.25kg (ROC curve area 0.74; Fig 1, B) as cut-off value with sensitivity of 81.8%, specificity of 60.8% for diagnosis of sarcopenia ($p = 0.010$, 95% CI 0.620 - 0.866) and PA ≤ 5.35º with sensitivity of 66.7%, specificity of 79.1% to identify dynapenia (ROC curve area 0.73, p = 0,003; Fig 1, C).

In the Poisson Multivariate Model, the variables that remained significantly associated with the lowest phase angle value were sarcopenia ($p < 0.009$) and dynapenia ($p = 0.000$) when adjusted for age (Table 3). The multivariate model demonstrates that the absence of sarcopenia was related to a 55% [prevalence ratio (PR) = 0.457] reduction in PR for a lower phase angle, while a 0.23kg reduction in HGS increases PR by 21%. (RP = 0.787) for lower phase angle (table 3).

DISCUSSION

The main finding of the present study was that a correlation of low PA values (≤ 5.45°) with clinical/nutritional depletions in patients with CKD-ND. Furthermore, we showed for the first time that this correlation also occurs for sarcopenia and highlighted a ≤ 5.45° PA cutoff as a good marker for the diagnosis of this nutritional complication in CKD-ND. These findings suggest that early alterations in body composition as measured using BIA may be markers of risk in this population.

PA values have been shown to be highly predictive of clinical progression in various diseases, including a prognostic value for mortality associated with malnutrition in CKD-ND[12-15]. The relationship between PA values and diseases prognosis can be understood by the picture of inflammation and prolonged malnutrition that negatively affect the integrity of tissues, resulting in cell death[21-23]. In this context, the CKD physiopathology may explain the prognostic value of PA on the disease. In fact, metabolic disorders inherent in CKD lead to an increase in protein catabolism, resulting in decreased muscle mass and function, contributing to the progression of CKD and the emergence of malnutrition in this clinical setting.[24,25].

In this study, individuals with lower PA were more likely to have dynapenia, which corroborates Reis et al[26] in that BP was associated only with handgrip strength, and not with the diagnosis of sarcopenia or its components in kidney transplant recipients. However, another study (Kosoku et al)[27] revealed that BP was negatively correlated with sarcopenia in kidney transplant recipients. The difference found in the studies may be associated with the cutoff points of the adopted AP, in which Reis's work used 5.8 ° for women and 6.2 ° for men and in the study of 4.46° PA was adapted for both the sexes. In this study, the PA value of 5.45° was used. In addition, other factors may justify this difference in the findings, the study population and diagnosis of sarcopenia by different criteria, in addition to the average age.

Although, PA has been associated with HGS in several populations, it should not be used as a handgrip evaluation substitute, but it can be useful as an additional evaluation for CKD-ND patient in clinical practice. The mechanism that explains the association between PA and HGS is still unknown, but it is possible to suggest that because PA is a predictor of cell membrane integrity, individuals with lower PA would present higher muscle cell damage, which can induce to strength impairment[26,28]. However, further studies are needed to verify the exact mechanism that explains the association between PA and HGS.

According to the European Consensus for the diagnosis of sarcopenia, low muscle strength is an important factor in the diagnosis of probable sarcopenia[1]. Some studies in patients with CKD-DN point to a greater importance in the assessment of muscle strength to the detriment of muscle mass, such as the study by Isoyama et al.[29], who reported that among dialysis patients, those with low muscle mass alone do not present increased risk of mortality, whereas those with reduced muscle strength, defined by HGS, presented.

Yae Lim Lee et al.[30], demonstrated a positive relationship between low HGS and renal function.

In the current study, albumin an was associated with lower HGS. In general, chronic disease with malnutrition is related to poor prognosis. While hypoalbuminemia is not a synonym for malnutrition, it is associated with morbidity and mortality[24,31,32]. Malnutrition in CKD-ND patients can be multifactorial and complicated. This is a difficult issue in monitoring and treating malnourished patients. In patients CKD-ND, it is unclear whether hypoalbuminemia is simply secondary to poor nutrition itself or is associated with other complex conditions such as chronic systemic inflammation, fluid overload, underlying comorbidities, and impaired compensatory hepatic synthesis of albumin[24].

The altered homeostasis in CKD negatively affects skeletal muscle mass. In our study low PA values correlated with sarcopenia and dynapenia. Studies have now showed that mechanisms contributing to the development of sarcopenia in patients with CKD-ND include to increase the myostatin levels, a negative regulator of skeletal muscle mass[33,34]. In addition to impaired regeneration, increased catabolism is common in CKD and attributed to a number of factors: accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, malnutrition, dietary restrictions, low protein diet, physical inactivity, vitamin D deficiency, oxidative stress and increased ubiquitination[35]. These alterations may induce muscle catabolism and decreased synthesis of muscle, which can be potentially reflected by low PA values[24].

Studies in different clinical populations have analyzed the association of PA and sarcopenia. Espirito Santo Silva et al[13] demonstrated that in male patients with cirrhosis, low PA values may reflect disease prognosis by correlating to sarcopenia among other clinical/nutritional. Similarly Blasio et al[35] found an association between PA with severe sarcopenia and cachexia in patients with chronic obstructive pulmonary disease. So far, we did not find studies in patients with CKD, but it was previously showed that in patients kidney transplant recipients PA ≤ 4.46° PA increased the chance the diagnosis of sarcopenia[27]. These data and the present study show that is possible to suggest that PA can predict sarcopenia independently of the disease and the population that was evaluated.

In this study, we found that 38,2% of patients with sarcopenia exhibited a PA value ≤ 5.45 °and this cutoff point was able to predict the syndrome with good specificity and high sensitivity. In addition, it demonstrates a correlation between low PA values and low HGS (components of sarcopenia), with a PA cut-off point ≤ 5.35º, which may justify the use of this indicator as a diagnosis of sarcopenia in patients with CKD-ND.

This study has some limitations. First, this study was performed in a single center in Brazil, and these results should not be generalized to subjects of other races or nationalities. Another important factor there are several definitions for the diagnosis of sarcopenia, but all of these include low skeletal muscle mass, alone or combined with low muscle strength and/or performance[1]. Here we combined the values of the appendicular muscle of the skeletal muscle measured by BIA and the HGS measured by dynamometry with the sample itself. However, there is a lack of complementary data on muscle performance and an unreferenced cutoff point for other populations.

We conclude that PA can be used as a viable marker for sarcopenia, since it is a good predictor of nutritional changes in CKD-ND.

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Table 1: Clinical and nutritional data associated with phase angle, sarcopenia and handgrip strength in patients with CKD-ND.

Characteristics	Phase angle		P value	Handgrip strength		P value	Sarcopenia		P value
	≤ 5,45º (n = 31)	> 5,45º (n = 54)		Low (n=18)	High (n=67)		Yes (n = 11)	No (n = 74)	
Sex									
Male	18 (40)	27 (60)	0,506	11 (24,4)	34 (75,6)	0,596	7 (15,6)	38 (84,4)	0,443
Female	13 (32,5)	27 (67,5)		7 (17,5)	33 (82,5)		4 (10)	36 (90)	
Age (years)	60,09 (9,7)	58,44 (12,68)	0,533	62,72 (9,47)	58,05 (12,05)	0,091	66,6 (9,31)	57,9 (11,60)	0,014*
Serum Creatinine (mg/dL)	1,7 (1,2 – 2,0)	1,55 (1,0 – 2,92)	0,802	1,75 (1,35 -2,12)	1,5 (1,1 – 2,8)	0,914	1,9 (1,4 – 2,1)	1,55 (1,10 – 2,65)	0,665
eGFR (ml/min/1.73 m²)	38,76 (27,84 – 46,61)	37,13 (22,35 – 60)	0,715	40,21 (31,01 – 44,9)	38,4 (22,89 – 55,20)	0,931	33 (23,23 – 43,82)	38,81 (25,14 – 55,38)	0,236
CKD Stage									
2	3 (33,3)	6 (66,7)	0,603	2 (22,2)	7 (77,8)	0,987	2 (22,2)	7 (77,8)	0,395
3	19 (42,2)	26 (57,8)		10 (22,2)	35 (77,8)		7 (15,6)	38 (84,4)	
4	9 (31)	20 (69)		6 (20,7)	23 (73,3)		2 (6,9)	27 (93,1)	
DM									
Yes	13 (37,1)	22 (62,9)	0,914	10 (20)	40 (80)	0,751	6 (17,1)	29 (82,9)	0,348
No	18 (36)	32 (64)		8 (22,9)	27 (77,1)		5 (10)	45 (90)	
Physical Activity									
Yes	6 (31,6)	13 (68,4)	0,612	3 (15,8)	16 (84,2)	0,514	3 (15,8)	16 (84,2)	0,675
No	25 (37,9)	41 (62,1)		15 (22,7)	51 (77,3)		8 (12,1)	58 (87,1)	
BMI (kg/m²)	24,81 (5,97)	25,53 (4,47)	0,527	24,89 (5,01)	25,10 (5,08)	0,556	24,5 (6,28)	25,38 (4,88)	0,663
HGS (Kg)	11,30 (2,17)	13,71 (2,79)	0,000*	-	-	-	10,92 (1,78)	13,11 (2,85)	0,003*
Phase angle (º)	-	-	-	5,20 (1,17)	6,09 (0,95)	0,001*	4,97 (0,81)	6,04 (1,02)	0,001*
Sarcopenia	8 (72,7)	3 (27,3)	0,009***	3 (27,3)	8 (72,7)	0,424	-	-	-
LBM (kg) BIA	47,7 (40,5 – 54,2)	48,75 (42,47 – 59,80)	0,383	50,25 (45,2 – 51,1)	48,10 (40,5 – 58,6)	0,536	48,6 (38,70 – 58,10)	48,4 (41,15 – 58,22)	0,623
FBM (kg) BIA	16,70 (6,99)	17,51 (6,49)	0,591	18,07 (7,31)	16,98 (6,49)	0,571	16,26 (7,83)	17,36 (6,50)	0,613
ICW (%)	52,4 (47,90 – 55,80)	52,45 (48,2 – 56,25)	0,841	51,7 (46,5 – 57,2)	52,4 (48,3 – 55,5)	0,805	50,7 (47,8 – 56,1)	52,7 (48,37 – 55,87)	0,560

SSMI (kg/m^2)	8,83 (1,76)	9,65 (2,32)	0,074	8,68 (1,44)	9,53 (2,29)	0,062	6,97 (0,64)	9,70 (2,08)	0,000*
Hemoglobin (g/dL)	12,11 (1,74)	11,85 (2,03)	0,550	11,92 (2,03)	11,95 (1,91)	0,949	12,68 (2,15)	11,84 (1,88)	0,243
CRP (mg/dL)	1,0 (0,10 – 4,5)	4,0 (1,0 – 8,0)	0,019**	2,0 (0,1 – 7,0)	3,0 (0,1 – 8,0)	0,323	1,5 (0,10 – 6,5)	3,00 (0,10 – 7,75)	0,735
Albumin (g/dL)	4,25 (3,97 - 4,52)	4,3 (4,10 - 4,57)	0,581	3,95 (3,62 – 4,35)	4,4 (4,1 – 4,6)	0,009**	4,1 (3,80-4,42)	4,3 (4,10-4,60)	0,204

*CKD-ND: non-dialysis chronic kidney disease; eGRF: Estimated glomerular filtration rate; DM Diabetes mellitus; BMI: Body mass index; HGS: Handgrip strength; LBM: lean body mass; BIA: Electrical Bioimpedance; FBM: Fat body mass; ICW: intracellular water; SSMI: Skeletal muscle mass index; CRP: C-Reactive Protein.; *Test t-student **Mann-Whiteny ***Chi-Square*

Table 2: Pearson's correlation coefficient between phase angle, dynapenia and clinical and nutritional data in patients with CKD-ND.

Characteristics	**Phase angle**		**Dynapenia**	
	r	**p**	**r**	**P**
Age (years)	-0,538	0,000	-2,55	0,019
Serum Creatinine (mg/dL)	0,081	0,463	0,102	0,352
eGFR (ml/min/1.73 m²)	0,139	0,203	0,023	0,831
HGS (Kg)	0,466	0,000	-	-
Phase angle(º)	-	-	0,554	0,000
LBM (kg) BIA	0,355	0,001	0,192	0,078
FBM (kg) BIA	0,108	0,327	-0,118	0,282
BMI (kg/m²)	0,294	0,006	0,004	0,972
SSMI (kg/m²)	0,318	0,003	0,618	0,000
Albumin (g/dL)	0,314	0,003	0,311	0,007
Hemoglobina (g/dL)	0,407	0,000	0,068	0,536
CRP (mg/dL)	-0,003	0,979	0,140	0,222

CKD-ND: non-dialysis chronic kidney disease*; eGRF: Estimated glomerular filtration rate; HGS: Handgrip strength; LBM: Lean body mass; BIA: Electrical Bioimpedance; FBM: Fat body mass; BMI: Body mass index; SSMI: Skeletal muscle mass index CRP:C-Reactive Protein.*

Table 3: Multivariate Poisson model derived prevalence ratio for phase angle by sarcopenia and Handgrip strength in patients with CKD-ND.

Factor	PR	CI (95%)	p-value
Sarcopenia	0,457	0,253 – 0,825	0,009
HGS (kg)	0,787	0,711 – 0,871	0,000

*HGS: Handgrip strength; PR: prevalence ratio. CI: confidence interval. *p < 0.05.*

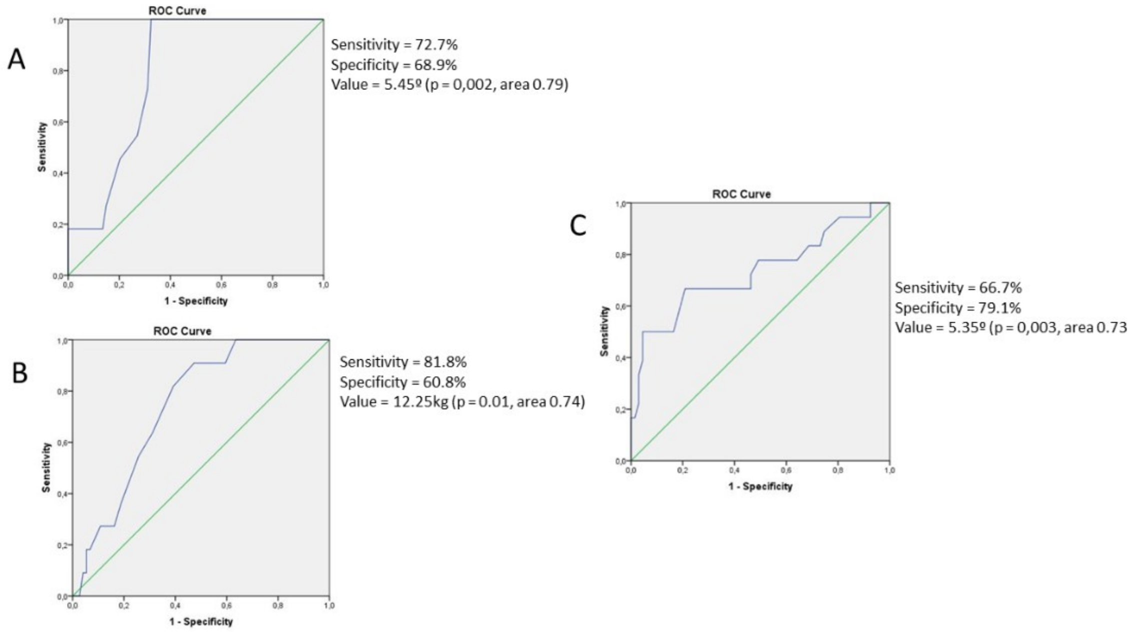

Figure 1. ROC curve for the association between phase angle and sarcopenia (A); dynapenia and sarcopenia (B); phase angle and dynapenia (C) in patients with chronic kidney disease undergoing non-dialysis treatment.

ARTIGO 3

ARTIGO 3

DINAPENIA AND PHASE ANGLE AS MARKERS OF QUALITY OF LIFE IN NON-DIALYTIC CHRONIC KIDNEY PATIENTS

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ABSTRACT

Introduction: The metabolic changes caused by chronic kidney disease have an impact on muscle mass, favoring the emergence of physical, emotional and psychosocial health problems. Dynapenia, measured by handgrip strength (HGS), and phase angle (FA) have been used to evaluate muscle quality in patients with non-dialysis chronic kidney disease (CKD-ND) and its reduction can influence the quality of lives of these patients. **Objective:** to evaluate the association of PA and dynapenia with quality of life in patients with CKD-ND. **Methodology:** study carried out in patients with non-dialysis chronic kidney disease who met the eligibility criteria. AF was derived from bioelectrical impedance (BIA) data and HGS was measured with a dynamometer. Health-related quality of life was assessed by the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36). **Results:** The study included 93 patients. Of these, 55.9% were male and the average age of the sample was 58.95 ± 12.46 years. Of the total number of patients, 34 had a phase angle < 5.45º (average of 5.96º ± 1.20) and 23 (26.9%) were diagnosed with dynapenia. Patients with PA < 5.45º had lower scores in the functional capacity domains (55.0 vs. 85.0; p = 0.000), limitation due to physical aspect (37.5 vs. 100.0; p = 0.008) and aggregate physical component (34.86 vs. 46.83; p = 0.004), while those with dynapenia had lower functional capacity scores (35.0 vs. 80.0; p = 0.002) and aggregate physical component (36.31 vs. 46.51; p = 0.015). In the correlation analysis with the SF-36 domains, it is noted that phase angle and dynapenia were positively associated with functional capacity (r = 0.438 p = 0.000; r = 0.419 p = 0.000), limitation due to physical aspect (r = 0.354 p = 0.000; r = 0.267 p = 0.000) and aggregate physical component (r =

0.365 p = 0.000; r = 0.369 p = 0.000). The multivariate regression analysis of factors potentially associated with the aggregate physical component of the SF-36 showed that PA adjusted for age (r = 0.257; p = 0.020) was the significant factor for the aggregate physical component ($r^2 = 0.157$). **Conclusion**: PA and HGS are reliable markers to assess quality of life in patients with CKD-ND.

Keywords: Phase angle, handgrip strength, dynapenia, quality of life, chronic kidney disease.

Introduction

Patients with chronic kidney disease (CKD) suffer from uremia and this clinical condition has been associated with changes in body composition, mainly related to muscle mass[1,2]. These changes have a multifactorial pathophysiology, including chronic systemic inflammation, decrease in anabolic hormones such as insulin growth factor type 1 (IGF-1), testosterone and active vitamin D, increased levels of myostatin and angiotensin 2 (AT2), as well as occurrence metabolic acidosis, in addition to sedentary lifestyle and malnutrition[3-5]. The pathophysiological mechanisms by which the elevation of inflammatory markers promotes changes in muscle mass are probably linked to an imbalance in muscle protein renewal, with activation of the ubiquitin-proteasome system, stimulation of cell death and apoptosis, which compromises the capacity for muscle regeneration[4, 6].

Assessing the body composition of patients with CKD is a major challenge in clinical practice. A wide variety of methods have been used to assess muscle mass, including bioelectrical impedance (BIA). BIA analysis is a practical, fast and non-invasive method for estimating body composition[1,7], and its derivatives have also been used for the diagnosis of sarcopenia and malnutrition[8-10]. Phase angle (FA), a BIA-derived parameter, has been demonstrated as an indicator of nutritional status and inflammation and a predictor of mortality in individuals with various diseases, including CKD[11-14]. Furthermore, lower PA values have been related to low muscle strength and changes in quality of life[15,16]. In this context, continuous efforts are needed to monitor muscle quantity and quality, especially in vulnerable individuals, such as patients with CKD.

In addition, dynapenia, characterized by loss of muscle strength, is identified through low handgrip strength (HGS), which has been used as an indicator of protein-energy status and functional status in patients with CKD[17-18]. Furthermore, HGS has been shown to be a useful tool for identifying risk of early mortality in patients with CKD [17]. Therefore, there is strong evidence that HGS, diagnosing dynapenia, can be a useful indicator of nutritional and functional status, including in kidney patients.

Furthermore, dynapenia can impact the quality of life of patients with chronic kidney disease, regardless of the stage of the disease. Some studies show that these patients have a lower quality of life, more symptoms and greater psychological suffering, with the degree of these changes negatively related to the glomerular filtration rate[19,20].

It is already known that the advancement of CKD and the diagnosis of sarcopenia significantly impacts the functional capacity of patients. However, few studies available in the literature use PA and dynapenia associated with these quality of life indicators. As low muscle strength is associated with poor quality of life and phase angle has emerged as an indicator of poor muscle health, we propose to evaluate the association of PA and dynapenia with quality of life in patients with CKD-ND.

Method

Participants

Cross-sectional study for convenience carried out in a university hospital, between 2012 and 2013. Clinically stable patients of both sexes, adults (≥ 20 and < 60 years) and elderly (≥ 60 years) with glomerular filtration rates (GFR) between 15 and 89 ml/min/1.73 m². Non-inclusion criteria were hospital admission in the last month, muscular and neurological disease and CKD in other stages of the disease. Approval of the study protocol by the local Ethics Committee (104761/12).

Demographic and clinical/nutritional data

Demographic and clinical/nutritional data were collected to characterize the population. They are: age, sex, degree of CKD, presence of diabetes mellitus (DM), body weight and height, as well as biochemical markers, such as hemoglobin and albumin.

Handgrip strength and dynapenia

Muscle strength was assessed in the dominant hand using a dynamometer (Bulb Dynamometer®), according to the technique described by Hillman et al. (2005)[21]. Participants were classified as having dynapenia after taking the quartile measurement, at the 25th percentile, adjusted for sex. Females were considered dynapenic when HGS ≤10kg and males were considered HGS ≤12.5kg

Bioelectrical impedance analysis

BIA was assessed using a Biodynamics® BIA450 tetrapolar device (Bioimpedance Analyzer, Seattle, WA, USA). Fluid and Nutrition software, version 3.0, was used to calculate total body water, fat-free mass, fat mass, body cell mass and phase angle. The following skeletal muscle mass equation developed by Janssen et al. (2000)[22] and recommended by EWGSOP [22] was used in the present study.

$$\text{MME} = \left[\left(\frac{(height)^2}{resistance}\ x\ 0.401\right) + (sex\ x\ 3.825) + \left(age\ x\ (-0.071)\right)\right] + 5.102$$

SMM = skeletal muscle mass; height in centimeters; resistance in ohms; sex: women = 0, men = 1; age in years.

Then, absolute muscle mass (kg) was normalized to height squared and defined as skeletal muscle mass index (SMI). The threshold for establishing reduced muscle mass was IMMA <7.29 kg/m² for women and <8.1 kg/m² for men[23,24].

Phase angle measurement

AF values were calculated as PA = arctangent Xc/R × 180/π. Patients were grouped according to the AF value, after performing the quartile measurement, in the 25th percentile (high: > 5.45° or low: AF ≤ 5.45°).

Assessment of health-related quality of life

To assess health-related quality of life (HRQoL), the generic instrument Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) translated and validated in Brazil by Ciconelli et al.[25]. The SF-36 consists of 36 questions, distributed across eight dimensions: 1- Functional capacity; 2- Limitations due to physical aspects; 3- Pain; 4- General health status; 5- Vitality; 6- Social aspects; 7- Limitations due to emotional aspects; and 8- Mental health. The 8 domains and two summary measures of the SF-36: Aggregate Physical Component (CFA) and the Aggregate Mental Component (CMA) were examined. The dimensions are quantitative and were evaluated with a final score ranging from 0 to 100, the higher the score the better the health status.

Statistical analysis

Data were expressed as mean, standard deviation, median, interquartile ranges (IQRs, 25th-75th percentiles) or percentages, depending on the normality of the distribution and the type of variable. Differences in the studied variables were analyzed using the t-Student/Mann-Whitney test or Chi-square/Fischer's exact test, as appropriate. The assessment of the normality of the variables was examined using analytical methods (Kolmogorov-Smirnov test). To evaluate the association between PA and dynapenia with the SF-36 domains, the Pearson correlation test was applied. In multiple regression analysis to determine which variables correlated best with the CFA, maintaining the distribution of residual variables. A significance level of 5% was considered. All analyzes were performed using the Statistical Package for the Social Science version 21.0 softwares (SPSS Inc; Chicago, IL, USA; Series: 10101121364; Authorization Code: d94a40fad9135460c4fb).

Results

Patients 93 with CKD-ND were evaluated, 52 male patients (55.9%), with a mean age of 58.95 ± 12.46 years, 41 (41.4%) had a diagnosis of DM and 85 % were in stages 3-4 of CKD. Of the total number of patients, 34 had a phase angle < 5.45º (mean 5.96 ± 1.20) and 23 (26.9%) were diagnosed with dynapenia. When comparing patients with AF values < 5.45º with those with AF ≥ 5.45º, it is noted that patients with AF < 5.45º had lower HGS (11.24 vs. 13.65; p = 0.000), MCC (19.24 vs. 24.78; p = 0.000), MM (46.52 vs. 51.98; p = 0.026), FFM (19.24 vs. 24.78; p = 0.000), IMMA (7.25 vs. 9.19; p = 0.000), Hemoglobin (10.98 vs. 12.3; p = 0.001) and albumin (4.09 vs. 4.36; p = 0.010), in addition, patients with AF < 5.45º had a higher mean age (65.5 vs. 54.6; p = 0.000) (Table 1). In relation to patients with dynapenia, it was noted that they were older (65.2 vs. 56.12; p = 0.000) and had lower eGFR (31.88 vs. 39.46; p = 0.030), phase angle (5.52 vs. 6.15; p = 0.024), MCC (19.79 vs. 23.81; p = 0.006), MM (44.9 vs. 51.66; p = 0.016), FFM (25. 23 vs. 27.84; p = 0.018) and IMMA (7.59 vs. 8.80; p = 0.015) (Table 1).

Patients with PA < 5.45º had lower scores in the following domains: functional capacity (55.0 vs. 85.0; p = 0.000), limitation due to physical aspect (37.5 vs. 100.0; p = 0.008) and of the aggregate physical component (34.86 vs. 46.83; p = 0.004) (Table 2). While those with dynapenia had lower scores in the domains: functional capacity (35.0 vs. 80.0; p = 0.002) and aggregate physical component (36.31 vs. 46.51; p = 0.015) (Table 2). In the correlation analysis with the SF-36 domains, it is noted that phase angle and dynapenia were positively associated with functional capacity ($r = 0.438$ $p = 0.000$; $r = 0.419$ $p = 0.000$), limitation due to physical aspect ($r = 0.354$ $p = 0.000$; $r = 0.267$ $p = 0.000$) and aggregate physical component ($r = 0.365$ $p = 0.000$; $r = 0.369$ $p = 0.000$) (Table 3).

Multivariate regression analysis of factors potentially associated with the aggregated physical component of the SF-36 showed that the phase angle adjusted for age ($r = 0.257$; $p = 0.020$) was the significant factor for the aggregated physical component ($r^2 = 0.157$) (Table 4).

Discussion

This study investigated the relationships between PA and dynapenia with quality of life in patients with CKD-ND. We observed that these indicators had a significant association with age and body composition markers, in addition to showing a significant positive association with SF-36 domains. Although there have been reports investigating the relationship between quality of life and phase angle in patients with CKD-ND and on hemodialysis[26,27], To our knowledge, this is the first report involving phase angle and dynapenia with quality of life.

PA values have been shown to be highly predictive of progression in several diseases, including prognostic value for mortality associated with malnutrition in CKD-ND [28,29]. Low phase angle values have been attributed to increased resistance due to increased body fat and decreased water content, as well as decreased reactance due to decreased muscle mass and impaired cellular integrity.[30]. In this context, AF can be considered an index of muscle quality[31] and its use in clinical practice in patients with CKD should be encouraged. In the present study, we found that individuals with lower PA had lower values of body composition markers associated with muscle mass. Similar results can be observed in other studies with CKD at different stages of the disease, including CKD stage 5 patients on hemodialysis and peritoneal dialysis and post-transplant[32-34].

In our study we observed that low FA values were associated with older age, this is due to the fact that older individuals present an increase in the volume of extracellular water and a decrease in the volume of intracellular water associated with aging[22]. Furthermore, it is worth mentioning that CKD interferes with the balance of body fluids[35], therefore, the presence of CKD together with older age may contribute to more significant outcomes of changes in this marker. Han et al[28] observed a negative correlation of phase angle with age in both groups of patients in the study (patients with non-dialysis end-stage CKD and patients on peritoneal dialysis). In this same study, a negative association between PA and overhydration was observed, with the non-dialysis CKD group being more likely to present overhydration when compared to the peritoneal dialysis group.

Low PA values have been correlated with poor muscle function, including the diagnosis of sarcopenia in patients with CKD[36]. However, we do not have much evidence about the association of PA with markers of quality of life in patients with CKD. In our study we observed a positive correlation between PA and SF-36 domains related to physical capacity. In multivariate regression analysis, age-adjusted FA was significantly related to SF-36 CFA, therefore, we can hypothesize that lower FA values are related to worse cell viability and thus worse vitality and physical capacity of our patients with CKD.

Study carried out by Pawlaczyk et al[37] with 3 groups of patients (CKD-ND, CKD hemodialysis and post-transplant) using the mini nutritional assessment (MNA) as a marker of nutritional status and the KDQoL-SF™ questionnaire observed that in the comparative analysis of quality of life of patients in the three groups study showed no statistically significant differences in overall KDQoL scores. However, in regression analysis, group assignment significantly affected KDQoL scores, with the kidney transplant patient group having a higher mean score and the dialysis patient group having a lower score, indicating lower quality of life scores in this group. Shin et al[26] in a study with 149 patients with CKD-ND, a positive association was observed between PA and the following domains of the SF-36: general health, mental health, CFA and CMA. Furthermore, in this same study it was observed in the longitudinal follow-up that in the group that presented a reduction in the phase angle (< -0.2º/year) there was a negative impact in the domain related to limitations due to physical health problems.

The mechanism that explains the association between PA and dynapenia is still unknown, but it is possible to suggest that, as PA is a predictor of cell membrane integrity, individuals with lower PA would present greater damage to muscle cells, which can induce impairment of strength. In the present study, we observed a linear association between PA and dynapenia, just as PA was associated with criteria of low muscle mass and low muscle strength. Shin et al[26] found a similar result related to PA and HGS, in addition, in the longitudinal analysis, a reduction of 0.2º in PA was associated with a reduction in muscle strength.

In our study, patients with dynapenia had lower scores in the domains: functional capacity and aggregate physical component. Furthermore, dynapenia was positively associated with functional capacity, limitation by physical aspect and aggregate physical component. Recent studies have suggested that the impairment of muscle-protein status caused by sarcopenia and dynapenia has a negative impact on functional capacity and quality of life[38]. HGS is an easy-to-use, low-cost marker associated with severity prognosis, the authors suggest its use in the care of patients with CKD-ND[26,38].

Some limitations of our study must be recognized. Firstly, the study is cross-sectional; correlations cannot differentiate cause and effect. However, it is biologically plausible that chronic inflammation, uremia, comorbidities or inactivity contribute to a smaller quantity of muscles and consequently to worse physical performance. Second, the study is only performed on a small sample; therefore, we cannot generalize the data to all CKD-ND patients. Third, we did not perform any tests to assess physical function, such as the gait speed test.

In conclusion, data from our study showed that PA and dynapenia were associated with the SF-36 domains related to the physical component. A better understanding of the use of these indicators of muscle mass and strength is relevant, since body composition and muscle performance in patients with CKD are related to unfavorable outcomes[4,29]. However, more prospective studies are needed to determine the clinical significance of these indicators on the quality of life of patients with CKD-ND.

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Table 1: Clinical and nutritional aspects associated with phase angle and dynapenia in patients with CKD-ND.

	Phase Angle		p value	Dynapenia		P value
	Low (n=34)	**High (n=59)**		**yes (25)**	**No (68)**	
Sex						
Men	15 (31,2)	33 (68,8)		12 (25,5)	35 (74,5)	0,717
Women	19 (42,2)	26 (57,8)	0,272	13 (28,9)	32 (71,1)	
Age (years)	65,5 (9,4)	54,6 (11,7)	0,000*	65,2 (9,20)	56,12 (12,2)	0,000*
Serum creatinine (mg/dL)	1,4 (1,1 – 3,0)	1,8 (1,15 – 2,70)	0,756	1,65 (1,32 – 2,72)	1,70 (1,1 – 2,8)	0,739
eGFR (ml/min/1.73 m²)	35,27 (21,19 – 50,64)	38,41 (28,55 – 51,46)	0,341	31,88 (22,20 – 40,96)	39,46 (27,98 – 55,12)	0,030**
CKD						
2	3 (9,9)	9 (92.3)		1 (8,3)	11 (91,7)	
3	15 (44,1)	32 (55,9)	0.178***	12 (27,3)	34 (72,7)	0,178
4	16 (47,0)	18 (53,0)		12 (36,4)	23 (63,6)	
Diabetes Mellitus						
Yes	20 (51,3)	19 (48,7)	0.015***	12 (31,6)	26 (68,4)	
No	14 (26,4)	39 (73,6)		13 (24,5)	40 (75,5)	0,457
Physical activity						
Yes	6 (27,3)	16 (72,7)	0,301	2 (9,1)	20 (20,9)	
No	28 (39,4)	43 (60,6)		23 (32,9)	48 (67,1)	0,023***
BMI (kg/m²)	24,2 (5,08)	26,12 (4,67)	0,088			
HGS	11,24 (2,08)	13,65 (2,93)	0,000*	9,8 (1,61)	13,89 (2,44)	0,000*
Phase Angle	4,86 (0,59)	6,59 (0,98)	0,000*	5,52 (1,6)	6,15 (0,96)	0,024*
Body Cell Mass (kg)	19,24 (4.47)	24.78 (6,98)	0,000*	19,79 (5,72)	23,81 (6,80)	0,006*

Lean mass (kg)	46,52 (10,31)	51,98 (12,45)	0,026*	44,9 (8,48)	51,66 (12,58)	0,016*
Fat Mass (kg)	19,24 (4,47)	24.78 (6.98)	0,000*	25,23 (3,75)	27,84 (6,35)	0,018*
IMMA (kg/m2)	7,25 (1,37)	9,19 (2,01)	0,000*	7,59 (2,08)	8,80 (1,94)	0,015*
Urea (mg/dL)	78,0 (50,0 – 118,30)	67,5 (46,25 – 102,25)	0,341	77,0 (57,25 – 128,0)	65,5 (46,0 – 107,5)	0,223
Hemoglobin (g/dL)	10,98 (1,70)	12,3 (1,85)	0.001*	11,33 (1,88)	12,03 (1,89)	0,135
CRP (mg/dL)	3.5 (0,77 – 7,35)	2,0 (0,10 – 7,00)	0.545	3,0 (1,0 – 8,37)	2,0 (0,1 – 7,0)	0,339
Albumin (g/dL)	4,09 (0,51)	4,36 (0,40)	0.010*	4,21 (0,70)	4,28 (0,31)	0,633

*CKD-ND: Non-Dialysis Chronic Kidney Disease; eGFR: Estimated Glomerular Filtration Rate; DM Diabetes mellitus; BMI: Body Mass Index; FPP: Handgrip strength; IMMA: Appendicular Muscle Mass Index; CRP: C-reactive protein; *Student t-test; **Mann-Whitney; ***Chi-Square or Fischer Test*

Table 2: Association of SF-36 score domains and PA and dynapenia in patients with CKD-ND

	Phase Angle		**p value**	**Dynapenia**		**P value**
	Low (n=34)	**High (n=59)**		**Yes (25)**	**No (68)**	
Functional capacity	55,0 (20 – 76,25)	85,0 (50,0 – 95,0)	0,000*	35,0 (20,0 – 85,0)	80,0 (55,0 – 90,0)	0,002*
Limitation due to physical aspects	37,5 (0,0 – 100,0)	100 (25,0 – 100,0)	0,008*	50,0 (0,0 – 100,0)	75,0 (25,0 – 100,0)	0,108
Pain	61,0 (32,0 – 100,0)	61,0 (44,0 – 72,0)	0,853	61,0 (31,0 – 86,0)	61,0 (42,0 – 76,5)	0,574
General Health Status	53,0 (19,21)	61,6 (21,41)	0,050	59,2 (22,76)	58,82 (19,85)	0,942
Vitality	60,0 (48,75 – 75,62)	70,0 (45,0 – 80,0)	0,457	70,0 (50,0 – 77,5)	60,0 (45,0 – 80,0)	0,944
Social aspects	62,5 (50,0 – 100,0)	87,5 (50,0 – 100,0)	0,137	87,5 (50,0 – 100,0)	75,0 (50,0 – 100,0)	0,598
Emotional Aspects	100,0 (33,3 – 100,0)	100,0 (33,3 – 100,0)	0,651	100,0 (0,0 – 100,0)	100,0 (33,0 – 100,0)	0,488
Mental health	66,0 (56,0 – 80,0)	72,0 (54,0 – 88,0)	0,235	76,0 (60,0 – 86,0)	68,0 (56,0 – 84,0)	0,379
Aggregate Physical Component	34,86 (28,57 – 47,54)	46,83 (37,47 – 51,64)	0,004*	36,31 (25,5 – 47,56)	46,51 (34,44 – 51,48)	0,015*
Aggregate Mental Component	50,34 (40,24 – 57,97)	51,68 (42,2 – 57,74)	0,959	51,68 (43,94 – 62,21)	50,83 (40,37 – 57,18)	0,296

Table 3: Correlation Analysis between PA and dynapenia and SF-36 in patients with CKD-ND.

Parameters	**Phase Angle**		**Dynapenia**	
	r	**p**	**r**	**p**
Functional capacity	0.438	0,000*	0.419	0,000*
Limitation due to physical aspects	0.354	0,000*	0.267	0,000*
Pain	0.101	0.334	0.150	0,140
General Health Status	0.192	0.065	0.051	0,618
Vitality	0.111	0.289	0.158	0,119
Social aspects	0.244	0.018	0.149	0,142
Emotional Aspects	0.165	0.114	0.119	0,244
Mental health	0.156	0.136	-0.018	0,861
Aggregate Physical Component	0.365	0,000*	0.369	0,000*
Aggregate Mental Component	0.090	0,391	-0.034	0,742

Table 4: Multivariate regression analysis of factors associated with the SF-36 Aggregate Physical Component in patients with CKD-ND.

Factor	**Regression coefficient (r)**	**CI (95%)**	**p-value**
Adjusted Aggregate Physical Component R^2 = 0.157 (p=0,000)			
Constant	39,95	20,22 – 59,68	0,000
Age	-0,231	-0,40 – -0,014	0,035
Phase Angle	0,257	0,38 – 4,26	0,020

*eGRF: Estimated glomerular filtration rate; PR: prevalence ratio. CI: confidence interval. *p < 0.05.*

CONSIDERAÇÕES FINAIS

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Os resultados apresentados permitem concluir que a sarcopenia e dinapenia são prevalentes em pacientes com DRC-ND e que, de acordo com a revisão realizada, são prognóstico de gravidade, incluindo a mortalidade. Além disso, observou-se que o ângulo de fase e a medida de FPM podem ser indicadores para avaliar a qualidade muscular nesses pacientes. Detsa forma, nossos estudos reforçam a importância da utilização de medidas de baixo custo e fácil utilização na prática clínica no atendimento a esses pacientes, com o objetivo de promover prevenção e tratamento da perda da qualidade muscular desenvolvida pela doença.

Diante dos resultados apresentados, propõe-se como futuros estudos:

1. Avaliar a prevalência de sarcopenia e dinapenia utilizando, também, os indicadores de desempenho físico e sua associação com os marcadores clínicos e nutricionais em uma pesquisa multicêntrica;

2. Realizar estudo de coorte prospectiva com objetivo de avaliar a associação de dinapenia e sarcopenia com complicações associadas à doença e mortalidade.

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ANEXOS

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ORIGINAL RESEARCH

Sarcopenia and Mortality in Patients With Chronic Non-dialytic Renal Disease: Systematic Review and Meta-Analysis

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Objective: To analyze the results of prospective studies on the presence of sarcopenia and its association with cardiovascular events and mortality in patients with non-dialysis-dependent chronic renal disease.

Methods: This study used the PRISMA protocol for systematic review. The systematic review and meta-analysis protocol was recorded in the prospective record of systematic reviews by PROSPERO International: CRD42019120391. Data sources: MEDLINE via PubMed, Embase, Cochrane Library, CINAHL, Scopus, Web of Science and LILACS from December 2018 to April 20, 2019, with the survey results updated in January 2021. Data analysis: Random effect models were calculated to compare the results due to high heterogeneity identified.

Results: The survey identified 951 studies. Of these, 392 were removed by duplicates and 559 references were selected for analysis. In the stage of evaluating titles and abstracts, 555 articles were excluded because they did not include inclusion criteria related to the population and study design, leaving 4 articles that were included in the systematic review and meta-analysis. A meta-analysis identified that the presence of sarcopenia increased the risk of mortality by 143%.

Conclusion(s): The meta-analysis identified the influence of sarcopenia on mortality in non-dialysis-dependent chronic renal disease.

Introduction

SARCOPENIA IS CONSIDERED a syndrome characterized by progressive decline in muscle mass and function, associated with fragility, disability and increased risk of mortality.[1,2] Although originally known as an aging condition, several international societies now recognize the important role of catabolic diseases, such as chronic kidney disease (CKD), in the etiology of sarcopenia.[3]

In fact, loss of skeletal muscle mass is a prevalent complication in CKD, regardless of its etiology, and is associated with poor prognosis.[3,4] This may be associated with several factors, such as the negative balance of protein homeostasis, reduction of cellular activation and expression of myogenic regulatory factors associated with increased myostatin levels, as well as accumulation of uremic toxins, chronic inflammation, insulin resistance, hormonal imbalance, vitamin D deficiency, oxidative stress and increased ubiquitination.[4,5] Therefore, sarcopenia becomes a risk factor for several adverse outcomes, including death.[5]

In addition, several studies have proposed sarcopenia as a new prognostic factor for cardiovascular disease in patients with CKD, since inflammation and skeletal muscle mass loss are factors associated with atherosclerosis.[6,7] However, in light of these studies, a clear conclusion is needed on the prognosis of sarcopenia in these patients, in order to outline tools for nutritional prevention and treatment. This study used the PRISMA protocol for systematic review having as a starting question whether the presence of sarcopenia is associated with a higher risk of cardiovascular events and mortality in patients with non-dialysis-dependent chronic renal disease (NDD-CKD).

Methods

Data Sources and Searches

A systematic review and meta-analysis was performed with studies evaluating sarcopenia, cardiovascular events, and mortality in patients with non-dialysis-dependent chronic renal disease. We used the recommendations of the Preferred Items statement for Systematic Review Reports and Meta-Analysis (PRISMA). The systematic review and meta-analysis protocol was recorded in the prospective registry of PROSPERO International systematic reviews.

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Search Strategy

In order to conduct a comprehensive and systematic literature review, the following databases were searched from December 2018 to April 20, 2019, with the survey results updated in January 2021: MEDLINE via PubMed, Embase, Cochrane Library, CINAHL, Scopus, Web of Science and LILACS. The reference list of the included studies was also evaluated.

There was no language restriction or publication period. The search strategy was developed with the MeSH descriptors, following the PICOS question (Table 1). The terms for exposure (Sarcopenia) and population (chronic non-dialytic renal disease) and their respective synonyms were used in the search strategy to include all relevant studies on this topic. The Boolean operators "AND" and "OR" were adopted to search the databases. Specific descriptors by controlled vocabulary for exposure, outcome and population in MEDLINE/PubMed lation are available in Supplementary Table S1. For the search in the LILACS database, the descriptors were selected from the Health Sciences Descriptors of the Virtual Health Library. Finally, the vocabulary descriptors controlled by Embase subject headings were used to construct Boolean word expressions (discovered by results) to search articles indexed in this database. Rayyan software, developed at the Qatar Computing Research Institute (Data Analytics), was used to store manuscripts and evaluate duplicates.

Inclusion and Exclusion Criteria

The studies were included in the systematic review when the following inclusion criteria were met (Table 1): (1) prospective observation; (2) the population consisting of adults and older adults with non-dialysis-dependent chronic renal disease (glomerular filtration rate < 60 mL/min/1,73 m^2, stage 3–5); (3) exposure as the presence of sarcopenia; (4) outcomes related to cardiovascular events and mortality; (4) provide at least Relative Risk (RR) or Hazard Ratio (HR Ratio) with their confidence intervals (CIs) for categorical risk and continuous risk estimates. There was no restriction on sample size, study location, time of study, length of follow-up, and language. We excluded studies in which individuals were selected by high risk group; research on animals, retrospective, cross-sectional, review and/or case reports; and those that provided only a risk estimate with no means to calculate 95% confidence intervals or without adjusting RR or HR.

Study Selection

The studies obtained through the search strategy were independently assessed by two authors, who met the study's eligibility criteria. Titles and abstracts were read and those that did not meet the selection criteria were excluded. All studies that were selected in the previous phase had their eligibility confirmed by reading the full article. At this stage, the primary reason for exclusion was recorded to make up the study selection flow. A third reviewer was available to resolve any disagreement between the authors. The research team jointly concluded which studies were finally selected for data synthesis.

Extraction of Data and Evaluation of Quality

The following variables were independently extracted by two reviewers: author, year of publication, country, study design and purpose, sample size, characteristics of participants (age, gender), sarcopenia evaluation methods, sarcopenia diagnosis, prevalence of sarcopenia in the population, prevalence of sarcopenic obesity, follow-up time, number of deaths, number of complications due to cardiovascular diseases, RR and HR adjusted with their confidence intervals. In the absence of data, contact was made with the author and/or search for publications by the author, who used the same population to collect the information.

The evaluation of the methodological quality was performed by two independent researchers, using the Checklist Downs and Black for randomized and non-randomized studies, consisting of five scales: external validity, bias, confounding variable/selection bias and power of the study. To assess the methodological quality of the studies included in this review, only the questions applicable to observational studies (22 items after adaptation) were used.[8] The quality score of each article corresponds to the total sum of the items analyzed as positive, with a maximum score of 23 points. Based on the score received, three categories were established for quality assessment: A – when the study meets more than 80% of the established criteria; B – when 50%-80% of the criteria are met and C – when less than 50% of the criteria are met.[9]

Risk Assessment of Bias

The risk of bias was evaluated according to the Bank of Items of the Research Triangle Institute (RTI)[10] items composed of 13 questions related to observational studies. Based on the responses of the evaluated items, the quality of evidence/risk of bias was categorized into three levels: low, moderate and high quality. The chosen cut score was determined based on previous systematic reviews and meta-analyses: 0% to 40% of positive responses: high risk of bias; 41% to 70% of positive responses: moderate risk of bias; 71% to 100% positive responses: low risk of bias.[11-13]

Meta-Analysis

Analyzing the absence of information related to cardiovascular events, it was only possible to perform a meta-analysis of mortality data from studies included in the systematic review. For the meta-analysis we excluded the study by Androga et al,[14] since its population is included in the Ziolkowsky et al[15] manuscript. The coefficients of the Cox regression models were extracted, estimating the log of the HR and their respective confidence intervals

Table 1. PICOS Criteria for Inclusion of Studies

Parameter	Inclusion Criteria
Population	Adults and older adult with chronic kidney disease under conservative treatment
Intervention or exposure	The presence of sarcopenia
Comparison	Absence of sarcopenia
Outcomes	Related to cardiovascular events and mortality
Study design	prospective observation

(CI 95%), adjusted for age and sex. For the meta-analysis, the HR log was used, considering that the scales of the ratio estimates are not symmetric, with the lowest value being zero (0) and the highest value +∞. Random-effects models were calculated to compare the results between the sarcopenia group and the non-sarcopenia group, due to the high heterogeneity identified, presented in a *Forest Plot*.[16] The standard errors, required for HR meta-analysis, were estimated from the confidence intervals of the Cox model estimates.[16]

The assumption of the homogeneity of the studies was tested by the Cochran Q test and the extent of heterogeneity was interpreted by the total percentage of variation among the included studies as measured by the I^2 statistic.[16] The inconsistency test ($I^2 > 50\%$) was used as an indicator of moderate heterogeneity. It was not possible to assess the sources of heterogeneity identified among the studies, considering the low number of eligible articles included in the meta-analysis.[16] All statistical tests were bi-caudal, adopting the level of significance <0.05. The analyses were conducted in the statistical package STATA v.12.0 (StataCorp, LLC, College Station, TX USA).

Results

Study Selection

The detailed steps of the search and selection of the studies, carried out between December 2018 and April 2019, with the survey results updated in January 2021, are presented in flow chart below (Figure 1). During the search phase, 951 studies were identified in the electronic databases. Of these, 392 were removed by duplicates and 559 references were selected for analysis. In the stage of

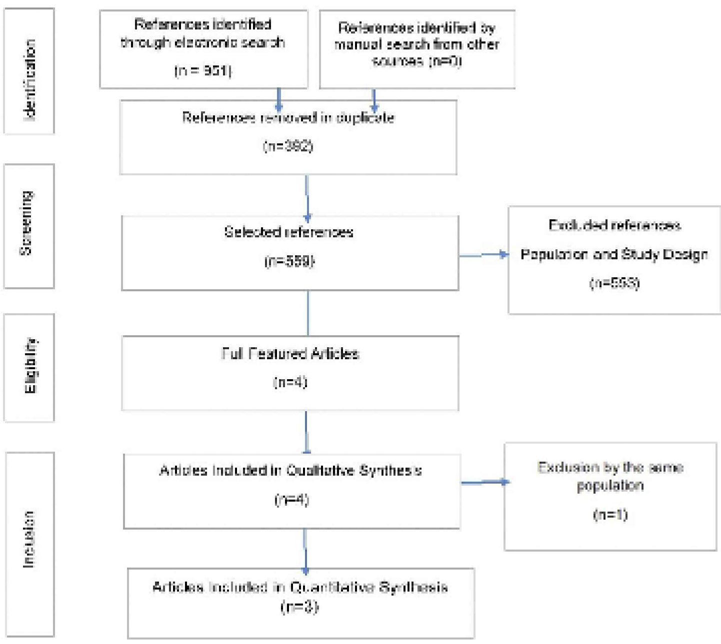

Figure 1. Flow of article selection from systematic review.

Table 2. Methodological Quality Assessment According to Checklist Downs and Black

Reporting	Andrega L et al.[14]	Hanstad S et al.[17]	Zieliowski S et al.[18]	Pereira R et al.[14]
1. Is the hypothesis/aim/objective of the study clearly described?	1	1	1	1
2. Are the main outcomes to be measured clearly described in the Introduction or Methods section?	1	1	1	1
3. Are the characteristics of the patients included in the study clearly described?	1	1	1	1
4. Are the interventions of interest clearly described?	1	1	1	1
5. Are the distributions of principal confounders in each group of subjects to be compared clearly described?	1	2	1	0
6. Are the main findings of the study clearly described?	1	1	1	1
7. Does the study provide estimates of the random variability in the data for the main outcomes?	1	1	1	1
8. Have all important adverse events that may be a consequence of the intervention been reported?	0	0	0	0
9. Have the characteristics of patients lost to follow-up been described?	0	0	0	0
10. Have actual probability values been reported (e.g. 0.035 rather than <0.05) for the main outcomes except where the probability value is less than 0.001?	1	1	1	1
11. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?	1	0	1	0
12. Were those subjects who were prepared to participate representative of the entire population from which they were recruited?	1	0	1	1
13. Were the staff, places, and facilities where the patients were treated, representative of the treatment the majority of patients receive?	0	0	1	1
14. If any of the results of the study were based on "data dredging", was this made clear?	0	0	0	0
15. In trials and cohort studies, do the analyses adjust for different lengths of follow-up of patients, or in case-control studies, is the time period between the intervention and outcome the same for cases and controls?	0	0	0	1
16. Were the statistical tests used to assess the main outcomes appropriate?	1	1	1	1
17. Were the main outcome measures used accurate (valid and reliable)?	1	1	1	1
18. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?	0	1	0	1

(Continued)

Table 2. Methodological Quality Assessment According to Checklist Downs and Black (Continued)

Reporting	Andrade L et al.[14]	Hanatani S et al.[17]	Ziolkowski S et al.[15]	Pereira R et al.[18]
19. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?	1	1	1	1
20. Was there adequate adjustment for confounding in the analyses from which the main findings were drawn?	0	1	0	1
21. Were losses of patients to follow up taken into account?	0	0	0	1
22. Did the study have sufficient power to detect a clinically important effect where the probability value for a difference being due to chance is less than 5%?	1	1	1	1
Punctuation %	63,6	68,2	68,2	77,3
Quality Methodological	B	B	B	B

evaluating titles and abstracts, 555 articles were excluded because they did not include inclusion criteria related to the population and study design, leaving 4 articles that were included in the systematic review. For the meta-analysis, 3 manuscripts were used due to the exclusion of Andrade et al[14] because its population is included in the study by Ziolkowski et al.[15] According to Cochrane Handbook for Systematic Reviews of Interventions, it is possible to make a meta-analysis based on two combinable articles.[16]

Quality of Studies

According to the Downs and Black checklist, all studies were classified as of medium quality (B) with values ranging from 63.6% to 77.3%.[14,15,17,18] In the sections related to external validity, most of the articles (75%) had average quality (66.6%) and, in relation to the power of the study, all reached a maximum score, showing excellent quality. Limitations of the studies were concentrated on the lack of data related to loss of follow-up or adjustment for follow-up, with only one study[18] describing the number of losses. In addition, the item representativeness of the population was also limited by the studies[14,15,17,18] (Table 2).

Risk Assessment of Bias

Considering the 4 studies evaluated, 100% presented low risk of bias, ranging from 76.9 to 84.6% (71% to 100% positive responses: low risk of bias) considering the Item Bank scale (RTI) (Table 3).

Characteristics of Selected Studies

The main features of the studies included in this review are provided in Table 4. The selected articles were published in the United States, Japan and Brazil between 2015 and 2019. All studies presented prospective cohort design with a total of 4,496 patients diagnosed with chronic kidney disease with mean follow-up of 72.5 months (SD = 47.22). The mean age of the subjects in the studies was 57.97 years with a standard deviation of 10.65, that is, mostly adult individuals. Data on number of patients with NDD-CKD and sarcopenia by sex was a limiting factor in all studies.

All 4 articles of the systematic review and meta-analysis aimed to evaluate the prognosis of mortality in patients with sarcopenia and NDD-CKD.[14,15,17,18] Of these, 1 article also evaluated the risk of mortality in patients with a diagnosis of sarcopenic obesity and 1 evaluated a higher

Table 3. Evaluation of the Bias Risk of the Articles Included in the Systematic Review

Study	Selection Bias	Performance Bias	Detection Bias	Confusion Bias	Risk of Bias
14	+++	+	++++	+++	Low risk
17	+++	+	++++	+++	Low risk
15	+++	+	+++	++	Low risk
18	+++	+	++++	+++	Low risk

Research Triangle Institute (RTI)

Possible answers to each question (Presence, Absence, Uncertain); +: absence; Maximum selection bias of +++; Maximum performance bias of +, Maximum detection bias of +++++++; Plus confusing bias of +++.

Table 4. Characteristics of Selected studies Investigating the Prognosis of Sarcopenia in Patients With Chronic Kidney Disease

Study	Country	Design	Age (Years)*	Gender n (%)	Number of patients	eGFR (mean mL/min/ 1.73 m² or IQ)	Statistical analysis	Instrument used to evaluate sarcopenia	Cutting Points	Follow-up time (months)	Sarcopenia n (%)	Mortality	OR (95% IC)	Sarcopenic Obesity n (%)	OR (95% IC)	Events CD	OR (95% IC)	Methodological quality
14	USA	Cohort	60.75 ± 8.5	-	1,18[illegible]	-	Cox regression models	DEXA	<5.45 kg/m² Women and <7.26 kg/m² Men	119	130 (12.[illegible])	[illegible]	1.[illegible] (1.0[illegible]-1.[illegible])	[illegible] (8.7)	1.[illegible] (1.24-2.4[illegible])	-	-	■
17	Japan	Cohort	72.4 ± 8.8	Male 164 (64)	256	48.1 ± 17.2	Cox regression models	Sarcopenia Screening Score (CC + Handgrip Strength)	≥105 Men and ≥120 Women	24	166 (62.6)	29	3.04 ([illegible])	-	-	33	1.87 (1.13-3.0[illegible])	■
15	USA	Cohort	65.14 (54.2-75.4)	-	2,852	-	Cox regression models	DEXA	ALMI T score ≤2.0	119	172 (6.0[illegible])	2,4[illegible]	1.27 ([illegible])	-	-	-	-	■
18	Brazil	Cohort	56.6 ± 16.5	Male 170 (59)	287	Stage 3 [illegible] Stage 4 [illegible] Stage 5 [illegible]	Cox regression models	BIA + Handgrip Strength (HGS)	<6.76 kg/m² Women and <10.76 kg/m² Men HGS < P30	40	17 (5.9)	51	3.[illegible] (1.54-[illegible])	-	-	-	-	■

BIA, bioelectrical impedance; CC, calf circumference; CD, cardiovascular disease; CI, Confidence interval; DEXA, dual-energy X-ray absorptiometry; eGFR, Estimated glomerular filtration rate; HGS, Handgrip Strength; OR, odds ratio; Score ALMI, appendicular lean mass index; USA, United States of America.
*Mean and standard deviation or median and interquartile range in years.

risk ratio for cardiovascular events in patients with sarcopenia.[14,17]

To analyze the outcome (mortality and cardiovascular disease events) and exposure (sarcopenia), the variables of interest presented discrete and categorical characteristics. All studies performed statistical analysis by Cox Regression with adjustments of sex, age and race variables for HR or RR.

Diagnostic Methods for Sarcopenia

Regarding the methods used for the diagnosis of sarcopenia, two studies used the X-ray dual-density densitometry (DEXA) for the evaluation of skeletal muscle mass[14,15]; a study evaluated by the muscular mass given by the bioelectrical impedance (BIA) associated with handgrip strength (HGS)[18] and a simple screening trial for sarcopenia using age, HGS, and calf circumference.[17] In the study by Androga et al,[14] muscle mass was quantified using the appendicular skeletal muscle mass index (ASMI), where sarcopenia was defined as ASMI <5.45 kg/m² in women and <7.26 kg/m² in men. Zielkowski et al[15] also used the DEXA tool, but adopted different statistical measures for the diagnosis of sarcopenia. The three-dimensional radiofrequency derived appendicular lean mass index (ALMI, kg/m2) and fat mass index (FMI, kg/m²) were used for the diagnosis of sarcopenia using standard deviation scores for sex and race/ethnicity compared to young adults (T scores), T score of ALMI score ≤ 2 and sarcopenia relative to T scores of ALMI FMI ≤ 2.[19]

In the study by Pereira et al[18] the method used for the diagnosis of sarcopenia was the association of skeletal muscle mass index (<10.76 kg/m² for men; <6.76 kg/m² for women) estimated by BIA with reduced muscle function assessed by handgrip strength (HGS <30th percentile of a population-adjusted reference for gender and age). Finally, the study by Hanatani et al[17] used a new method for the diagnosis of sarcopenia, the sarcopenia screening score, calculated by means of a scoring chart for the estimated probability of sarcopenia advocated by Ishii et al. (2014),[20] which uses handgrip strength and calf circumference. In this study, a high sarcopenia score was defined as a screening score ≥105 for men and ≥120 for women.

Prevalence of Sarcopenia

Data from sarcopenia prevalence studies in patients with chronic kidney disease with an estimated glomerular filtration rate ≤60 mL/min/1.73 m² ranged from 5.9 to 62.6%. The study by Pereira et al18 carried out with 287 patients in Brazil found the lowest prevalence of sarcopenia (only 17 individuals). The study by Hanatani et al16 in Japan found the highest prevalence of sarcopenia in their population in 166 of 256 patients with chronic kidney disease. This variation in prevalence may be associated with the methods used for its diagnosis.

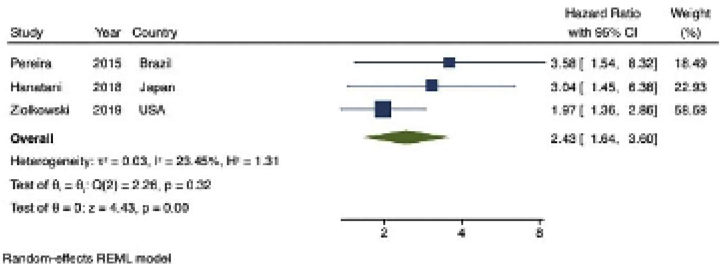

Figure 2. Hazard Ratio difference between mortality and sarcopenia in individuals with chronic renal disease on conservative treatment.

Prognostic Assessment

All studies evaluated mortality as a clinical outcome in patients with NDD-CKD and without sarcopenia. The mean follow-up time also varied between the studies, with the study by Hanatai et al[17] showing the shortest follow-up (24 months), while those of Andrega et al[14] and Zinlkowski et al[15] followed for 113 months. The risk of mortality ranged from 1.33 in the study of Andrega et al[14] to 3.58 in the study by Pereira et al,[18] with all adjusted for age and sex. Regarding the increased risk of cardiovascular complications, only the study by Hanatai et al[17] evaluated this event, in which the risk of individuals with chronic renal disease and sarcopenia was HR 1.97 when compared to non-sarcopenic individuals.

Meta-Analysis Results

Meta-analysis identified the influence of sarcopenia on mortality in patients with chronic kidney disease not dependent on dialysis (Figure 2). There was a 143% increase in the risk of dying in patients with sarcopenia, compared to those without sarcopenia (HR: 2.43; 95% CI: 1.64–3.60).

Discussion

The results of this meta-analysis indicate that patient's non-dialysis–dependent chronic renal disease have a 143% increase in the risk of dying when compared to patients without sarcopenia.

The etiology of the loss of skeletal muscle mass in chronic renal disease is multifactorial, involving inflammation, reduction of food intake, physical inactivity, excess of angiotensin II; abnormalities in insulin/insulin-like growth factor-1 (IGF-1) signaling and myostatin expression; reduced function of satellite cells and myocellular changes.[21] The inflammatory state resulting from CKD and uremia are related to metabolic acidosis, increased protein catabolism and oxidative stress, and decreased antioxidant capacity. These factors, together with the action of inflammatory cytokines such as C-reactive protein (CRP), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α), promote muscle loss in the patient.[22,23]

Oxidative stress can lead to atrophy by the activation of autophagy pathways and may affect skeletal muscle through the myostatin pathway. Myostatin regulates muscle atrophy through the activation of proteolytic pathways and impaired muscle regeneration.[24] Muscle regeneration is an organized process that, in response to a noxious stimulus, activates quiescent satellite cells to differentiate and form myotubes and subsequent myofibers. Some studies have shown that impaired function is associated with satellite cell proliferation and differentiation due to myogenic expression changes.[24,25]

Skeletal muscle loss in these patients may be induced by vitamin D deficiency via the ubiquitin-proteasome pathway. In addition, in NDD-CKD, hypogonadism is common and may be exacerbated by other common comorbidities of the disease.[26] Serum levels of testosterone were associated with reduced muscle mass and strength in CKD. The renin-angiotensin-aldosterone system is overregulated in CKD. Increased expression of Angiotensin II reduces the pool of satellite cells and muscle regeneration capacity, in addition to positively regulating caspase-3 and the proteolytic pathways of the proteasome ubiquitin.[4]

Finally, NDD-CKD is associated with resistance to growth hormone and is considered a potential cause of increased protein catabolism and loss of skeletal muscle due to the resistance of IGF-1 anabolic hormone to protein turnover in skeletal muscle.[4,27] All these mechanisms lead to the diagnosis of sarcopenia in this population.

Sarcopenia is a generalized and progressive skeletal muscle disorder involving accelerated loss of muscle mass and function with important clinical consequences, including frailty and mortality. Once understanding that NDD-CKD per se leads to increased mortality, the association of the disease with the development of sarcopenia may increase the risk of death in these patients.[3]

Studies have shown a prevalence of up to 60% of sarcopenia in patients with non-dialysis–dependent chronic renal disease. This difference may vary depending on the method used for diagnosis. According to the European Consensus for the Definition and Diagnosis of Sarcopenia (2019)[3], the diagnosis should be made by the association of low muscle strength given by handgrip strength, reduced physical performance and low skeletal muscle mass by the standardized methods of computed tomography, DEXA, magnetic resonance imaging, or BIA. However, none of the studies in this meta-analysis covered all recommended methods, which could have under or overestimated the prevalences found.[14,15,17,18]

A higher mortality risk was associated with sarcopenia in each of the studies included in this meta-analysis, regardless of the method used for the diagnosis of sarcopenia (HR 1.33–3.58).[14,15,17,18] Therefore the risk of mortality caused by sarcopenia in these patients is independent of the methods used and the cutting points adopted in clinical practice and the need for this evaluation to be performed early in order to establish nutritional barriers that avoid or minimize installation.

It should be noted that all the studies included in this meta-analysis presented medium quality, with low scores only on the items external validity (associated to sample representativeness in the population), reporting (related to follow-up data) and bias (with limitation of the analysis adjusted by time follow-up). In addition, all studies had a low risk of bias, which made the findings more robust.

As a limitation, this meta-analysis did not present the evaluation of the sources of heterogeneity identified among the studies, due to the low number of eligible articles included in the meta-analysis. In addition, it was not possible to evaluate the prognosis of cardiovascular events due to the limitation of published articles. In summary, findings from this meta-analysis indicate higher mortality in patients with non-dialysis-dependent chronic renal disease with sarcopenia, suggesting that the routine evaluation of the diagnosis of sarcopenia in these patients may be a protective event of morbidity and mortality in this group, since muscle complications in this phase may still be reversible.

Practical Application

This systematic meta-analysis review concluded that patients with non-dialysis chronic kidney disease and sarcopenia are at increased risk of mortality. Therefore, we believe that our study can not only contribute to knowledge, but also stimulate conducts for the prevention and/or treatment of this clinical and nutritional alteration, however, further studies are necessary.

CRediT authorship contribution statement

Tarcisio Santana Gomes: Conceptualization, Methodology, Investigation, Writing – original draft. **Danniell do Espírito Santo Silva:** Conceptualization, Methodology, Investigation. **Gesner Francisco Xavier Junior:** Conceptualization. **Priscila Ribas de Farias Costa:** Formal analysis, Writing – review & editing. **Maria Helena Lima Gusmão Sena:** Writing – review & editing. **Jairza Maria Barreto Medeiros:** Investigation, Writing – review & editing.

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Table S1. Specific Descriptors by Controlled Vocabulary for Exposure, Outcome and Population in MEDLINE/PubMed

Search	Strategy	Results
#1	"Sarcopenia"[Mesh] OR Sarcopen*	11,482
#2	"Renal Insufficiency, Chronic"[Mesh] OR "Chronic Renal Insufficiencies" OR "Chronic Renal Insufficiency" OR"Kidney Insufficiency, Chronic" OR "Chronic Kidney Insufficiency" OR "Chronic Kidney Diseases" OR "Chronic Kidney Disease" OR "Disease, Chronic Kidney" OR "Diseases, Chronic Kidney" OR "Kidney Disease, Chronic" OR "Kidney Diseases, Chronic" OR "Chronic Renal Diseases" OR "Chronic Renal Disease" OR "Disease, Chronic Renal" OR "Diseases, Chronic Renal" OR "Renal Disease, Chronic" OR "Renal Diseases, Chronic"	149,818
#3	"Kidney Failure, Chronic"[Mesh] OR "End-Stage Kidney Disease" OR "Disease, End-Stage Kidney" OR "End Stage Kidney Disease" OR "Kidney Disease, End-Stage" OR "Chronic Kidney Failure" OR "End-Stage Renal Disease" OR "Disease, End-Stage Renal" OR "End Stage Renal Disease" OR "Renal Disease, End-Stage" OR "Renal Disease, End Stage" OR "Renal Failure, End-Stage" OR "End-Stage Renal Failure" OR "Renal Failure, End Stage" OR "Renal Failure, Chronic" OR "Chronic Renal Failure"	125,728
#4	#2 OR #3	173,842
#5	#1 AND #4	348

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Plataforma Brasil

PROJETO DE PESQUISA

Título: ASPECTOS NUTRICIONAIS E FATORES ASSOCIADOS EM PACIENTES PORTADORES DE DOENÇA RENAL CRÔNICA EM TRATAMENTO CONSERVADOR

Área Temática:

Versão: 1

CAAE: 05806812.6.0000.0049

Pesquisador: Maria Helena Gusmão

Instituição: Hospital Universitário Prof. Edgard Santos-UFBA

PARECER CONSUBSTANCIADO DO CEP

Número do Parecer: 104.761

Data da Relatoria: 20/09/2012

Apresentação do Projeto:

Trata-se de um estudo transversal e observacional a ser desenvolvido com 75 indivíduos portadores de Doença Renal Crônica em tratamento conservador acompanhados no Ambulatório de Nutrição e Nefropatias, Complexo Hospitalar Universitário Professor Edgard Santos, Salvador-BA, para que sejam avaliados suas características nutricionais, clínicas, alimentares, sociais e econômicas.

Objetivo da Pesquisa:

GERAL
Identificar o estado nutricional e alguns aspectos envolvidos em pacientes portadores de doença renal crônica (DRC) em tratamento conservador.

ESPECÍFICOS
- Caracterizar a população estudada;
- Identificar o estado nutricional de indivíduos adultos e idosos portadores de DRC segundo os dados antropométricos e exames bioquímicos;
- Estudar a função muscular dos pacientes através da dinamometria;
- Avaliar a composição corporal através da bioimpedância elétrica;
- Identificar o estado nutricional de pacientes portadores de DRC através da Avaliação Subjetiva Global (ASG) e do Índice de Desnutrição-Inflamação (MIS);
- Determinar os fatores sociais, econômicos, ambientais, comportamentais, clínicos, alimentares e nível de qualidade de vida que se associam ao déficit ou excesso nutricional.

Avaliação dos Riscos e Benefícios:

Riscos associados com a coleta de sangue incluem: dor, hematoma ou desconforto no local da coleta. Raramente podem ocorrer desmaio ou infecções do local de punção. A bioimpedância pode gerar leve desconforto em pessoas mais sensíveis.

Não há benefício direto para o participante desse estudo. Espera-se que o conhecimento das características nutricionais, clínicos, alimentares, sociais e econômicos destes pacientes possa favorecer ações da Secretaria de Saúde no que diz respeito ao estado nutricional e condições de

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saúde dos doentes renais crônicos em tratamento conservador, podendo melhorar consequentemente sua qualidade de vida no futuro.

Comentários e Considerações sobre a Pesquisa:

A solicitação para o cumprimento das pendências, listadas em parecer versão impressa pelo CEP/HUPES em 20/08/2012, foi satisfatoriamente atendida.

Considerações sobre os Termos de apresentação obrigatória:

Satisfatórios.

Recomendações:

Aprovar.

Conclusões ou Pendências e Lista de Inadequações:

Sem pendências.

Situação do Parecer:

Aprovado

Necessita Apreciação da CONEP:

Não

Considerações Finais a critério do CEP:

Projeto Aprovado.

SALVADOR, 24 de Setembro de 2012

Assinado por:
Roberto José da Silva Badaró

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