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Efeito do treinamento resistido combinado com dietas cetogênicas: uma revisão sistemática e metanálise

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Só é digno da liberdade, como da vida,
aquele que se empenha em conquistá-la.
Johann Goethe

Resumo

SINNOTT, Luis Roberto. Efeito do treinamento resistido combinado com dietas cetogênicas: uma revisão sistemática e metanálise. Orientador: Carlos Castilho de Barros. 2021. 85f. Dissertação (Mestrado em Nutrição e Alimentos). Faculdade de Nutrição, Universidade Federal de Pelotas, Pelotas, 2021.

Dietas que causam cetose (DC), ricas em gorduras e restritas em carboidratos, têm sido propostas como alternativa para o tratamento da obesidade. Dentre as várias críticas que são levantadas pelos opositores ao seu uso para perda de peso, a perda de massa livre de gordura (MLG) que essas dietas podem causar, tem sido relatada como um efeito indesejável, pois pode reduzir a taxa metabólica basal e causar outras consequências relacionadas à saúde dos pacientes. Uma vez que o treinamento resistido (TR) pode promover hipertrofia muscular, sua prática acompanhada de DC poderia ajudar na manutenção da MLG. No presente estudo, revisou-se sistematicamente a literatura e comparou-se o efeito do TR em dietas com ou sem restrição de carboidratos. Embora uma pequena redução na massa magra tenha sido identificada na metanálise (-0,347 IC 95%: -0,549, 0,144), alguns autores relatam que não houve perda de desempenho físico. Outros sugerem que essa diferença na massa magra está associada à perda de água nos pacientes, fenômeno típico causado por dietas com restrição de carboidratos. Concluiu-se que o treinamento resistidoo é uma ferramenta importante na manutenção da massa magra em indivíduos submetidos a dietas restritivas de carboidratos que causam cetose. Estudos específicos comparando indivíduos submetidos a DC, associados ou não ao TR, ainda são raros na literatura.

Palavras-chave: Dieta Cetogênica. Obesidade. Metabolismo. Exercício. Dietas Restritivas.

Abstract

SINNOTT, Luis Roberto. Effect of resistance training combined with ketogenic diets: a systematic review and meta-analysis. Advisor: Carlos Castilho de Barros. 2021. 85f. Dissertation (Master in Nutrition and Food). Faculty of Nutrition, Federal University of Pelotas, Pelotas, 2021.

Diets that cause ketosis (DCK), high in fat and restricted in carbohydrates, have been proposed as an alternative for the treatment of obesity. Among several criticisms that are raised by opponents of its use for weight loss, the loss of free fat mass (FFM) that these diets can cause, has been reported as an undesirable effect because it can reduce basal metabolic rate and cause other consequences related to health of patients. Since resistance training (RT) can promote muscle hypertrophy, its practice accompanied by DCK could help to maintain FFM. In the present study, the literature was systematically reviewed and the effect of RT in diets with or without carbohydrate restriction was compared. Although a small reduction in lean mass was identified in the meta-analysis (-0.347 CI 95%: -0.549, 0.144), some authors report that there was no loss of physical performance. Others suggest that this difference in lean mass is associated with loss of water in patients, typical phenomenon caused by carbohydrate-restricted diets. It was concluded that resistance trainingis an important tool in maintaining lean mass in relation to restrictive carbohydrate diets that cause ketosis. Specific comparing studies related to DCK, associated or not with RT, are still rare in the literature.

Keywords: KD. Obesity. Metabolism. Exercise. Restrictive Diets. Ketogenic Diet.

Lista de abreviaturas e siglas

Acetil-Coa	Acetilcoenzima A
AKT	Proteína quinase B
ATP	Adenosina trifosfato
CC	Corpos cetônicos
CF	Cetose fisiológica
DC	Dieta cetogênica
GDF8	Miostatina (growth differentiation factor 8)
GH	Hormônio do crescimento (growth hormone)
IGF-1	Somatomedina C (insulin-like growth factor-1)
IL-5	Interleucina 5
IL-6	Interleucina 6
IMC	Índice de massa corporal
INS	Instituto Nacional de Saúde
LIF	Fator inibidor de leucemia (Leukemia inhibitory fator)
MAPK	Proteína quinase ativada por mitogênio (mitogen-activated protein kinase)
Myf5	Fator de regulação miogênica
MyoD	Fator de regulação miogênica
miRNA	MicroRNA
MRF4	Fator regulador miogênico 4
mRNA	Ácido ribonucleico mensageiro
mTOR	Alvo mamífero da rapamicina (mammalian target of rapamycin)

OMS	Organização Mundial de Saúde
RNA	Ácido ribonucleico
TMB	Taxa metabólica basal
TR	Treinamento resistido
VCT	Valor calórico total
VET	Valor energético total

Sumário

1 Introdução

O treinamento resistido (TR) é uma das principais estratégias utilizadas para o aumento de massa muscular através da hipertrofia(SCHOENFELD *et al.*, 2019). Além disso, existem várias evidências dos benefícios do TR em relação a reversão de perda de massa muscular, impacto no metabolismo de repouso, redução de gordura corporal, aumento de mobilidade física, regulação metabólica hormonal (insulínica), melhora do sistema cardiovascular através da normalização dos níveis de pressão arterial, regulação dos níveis de lipoproteínas circulantes, aumento de densidade mineral óssea, melhora de saúde mental e reversão da degradação mitocondrial muscular, típica do envelhecimento(WESTCOTT, 2012). Além dos benefícios à saúde, a prática do TR estimula o aumento da síntese de proteína muscular e da taxa metabólica basal, auxiliando no emagrecimento(WESTCOTT, 2012; DONG *et al.*, 2020).

A hipertrofia muscular é mediada pelos microRNAs (miRNAs) que são uma classe de moléculas de ácido ribonucleico (RNA) não codificantes que atuam como reguladores pós-transcricionais da expressão gênica(LU TX, 2018). A regulação ocorre através da degradação ou repressão da tradução de moléculas-alvo de RNA mensageiro (RNAm). Os miRNAs têm sido implicados na maioria das principais funções celulares, como proliferação, diferenciação, apoptose, resposta ao estresse e regulação transcricional(LU TX, 2018).

A hipertrofia no músculo esquelético, aguda ou crônica, pode ocorrer tanto quando há aumento no número de células musculares quanto quando há aumento no tamanho das fibras musculares, sendo este último denominado de hiperplasia muscular(WACKERHAGE *et al.*, 2019;KRZYSZTOFIK *et al.*, 2019). A hipertrofia é um processo metabólico influenciado por uma série de variáveis como o programa de treinamento, memória muscular (em treinados), sexo, predisposição genética, dieta e estado nutricional(WERNBOM M, AUGUSTSSON J, 2007;MORTON RW, MCGLORY C, 2015;SLATER *et al.*, 2019;MOORE, 2019;HAGSTROM AD, MARSHALL PW, HALAKI M, 2020).

As estratégias nutricionais mais utilizadas para hipertrofia muscular costumam controlar com mais rigor os níveis de proteínas ingeridas e/ou prescrição de suplementos alimentares específicos a fim de criar reservas de

energia suficientes para preservar a massa muscular prévia e os tecidos musculares em (re)construção(SLATER *et al.*, 2019).

O uso das dietas indutoras de cetose, também conhecidas como dietas cetogênicas(DC), é uma estratégia bastante utilizada quando o objetivo é a perda de peso ou emagrecimento em curto espaço de tempo(KIM, J. Y., 2020), promovendo, em alguns casos, um aumento significativo da definição muscular(CHOLEWA; NEWMIRE; ZANCHI, 2019). Principalmente por esse motivo são muito utilizadas por atletas que necessitam reduzir seu peso corporal no intuito de obter vantagens em seu desempenho esportivo(GREENE DA, VARLEY BJ, HARTWIG TB, CHAPMAN P, 2018;KASPAR *et al.*, 2019). Ainda não há consenso se as DC podem ou não ser prejudiciais ao desempenho esportivo em atletas de resistência(MURPHY; CARRIGAN; MARGOLIS, 2021). Em exercícios com intensidades submáximas elas demonstraram melhoras significativas na performance enquanto que em intensidades mais altas reduziram e prejudicaram o desempenho(BURKE, 2021;HARVEY; HOLCOMB; KOLWICZ, 2019).

Por serem ricas em gorduras e restritas em proteínas e carboidratos, as DC simulam, em alguns aspectos, o estado de jejum aumentando a produção de corpos cetônicos (CC) a partir da utilização das reservas corporais de gordura para manutenção da homeostase(VIDALI *et al.*, 2015). A produção dos CC em condições ideais para emagrecimento costuma ocorrer com o consumo dietético de até 50g de carboidratos por dia ou valores calóricos de carboidratos que representem até 10% do valor calórico total (VCT) da dieta(WESTMAN *et al.*, 2018). Embora o consumo máximo de carboidratos seja restrito, a quantidade de energia ingerida pode ser controlada ou livre (*ad libitum)* sem qualquer prejuízo durante o emagrecimento(JOHNSTONE, A. M. *et al.*, 2008).

A sensível redução da carga glicêmica circulante causada pelas DC estimula a produção de CC(DĄBEK *et al.*, 2020) os quais são sintetizados na matriz mitocondrial dos hepatócitos em razão do excesso de acetil-coA produzido na lipólise. Neste estado metabólico, denominado de cetose fisiológica, há uma perda rápida de peso inicial devido à diurese aumentada em resposta à redução dos níveis hormonais insulínicos e aumento nos níveis de glucagon e produção de CC(MILLER; VILLAMENA; VOLEK, 2020). Estabilizada

a perda de líquidos, a redução de peso permanece constante pois o VCT de carboidratos continua em níveis restritos(IGAWA; TAKAMURA, 2017).

Apesar da DC apresentar uma série de benefícios para a saúde, ela também pode provocar alguns efeitos adversos como desidratação, hipoglicemia, letargia, halitose, distúrbios gastrointestinais, hiperuricemia, hipoproteinemia, hipocalcemia, dano ósseo, alterações no perfil lipídico, urolitíases, cálculos biliares ou queda de cabelo(O'NEILL; RAGGI, 2020).

Além disso, mesmo que a redução de peso seja uma condição fundamental para o restabelecimento da saúde, seus benefícios podem estar relacionados a perdas de massa corporal magra elevando o risco de sarcopenia(CAVA; YEAT; MITTENDORFER, 2017).

Alguns achados na literatura mostram que pessoas obesas possuem proporcionalmente mais massa magra do que pessoas não-obesas, porém, a presença maior de células lipídicas nas células musculares tem um efeito prejudicial na contração e na força muscular(CARTER; JUSTICE; THOMPSON, 2019).

A redução de peso contribui para melhor função física global pois quando induzida por dieta não afeta significativamente a força muscular mesmo em situações em que haja discreta redução de massa muscular(CAVA; YEAT; MITTENDORFER, 2017). Entretanto, por muito tempo, a redução de massa muscular foi considerada um fator conflitante para o emagrecimento já que reduziria também o gasto energético basal(JOHANNSEN *et al.*, 2012). A análise estatística comparativa de estudos com redução de peso gradual revelou estabilidade da taxa metabólica basal(TMB) e redução de TMB quando a redução de peso foi rápida(ASHTARY-LARKY *et al.*, 2020). Contudo, ainda não existe uma definição das implicações na massa muscular em situações em que é utilizado o TR simultaneamente a DC.

2 Revisão da literatura

2.1 Treinamento resistido

O treinamento resistido (TR), também conhecido como treinamento de força ou treinamento com pesos, é um método reconhecido entre várias organizações de saúde como estratégia de prevenção e reabilitação de diversos tipos de doenças(DONNELLY *et al.*, 2009). Além disso, é muito utilizado para o desenvolvimento da aptidão musculoesquelética já que existe uma forte relação entre a área de secção transversal muscular e força muscular(SUCHOMEL *et al.*, 2018;TALLIS; JAMES; SEEBACHER, 2018).

Tanto a manutenção quanto o aumento gradativo de massa muscular atuam positivamente na saúde de diversas populações sendo um indicativo associado à melhoria de qualidade de vida(TIELAND; TROUWBORST; CLARK, 2018). O estímulo do TR resulta em fadiga muscular com duração variável de horas a dias após a execução do exercício(SCHOENFELD; OGBORN; KRIEGER, 2015). Em condições ideais, a tensão mecânica gerada pelo TR sob as fibras musculares ativadas rompe estruturalmente alguns elementos contráteis(KRZYSZTOFIK *et al.*, 2019). Devido aos danos celulares causados pelo uso de sobrecarga mecânica, há uma resposta inflamatória incluindo a degradação de proteínas danificadas, síntese de fatores de crescimento e citocinas, interações hormonais e síntese de novas proteínas promovendo a remodelação muscular(FRANCAUX; DELDICQUE, 2019). Desta forma, os sistemas imunológico e endócrino, restauram a homeostase e auxiliam na adaptação aos estímulos externos(KIRK B, FEEHAN J, LOMBARDI G, 2020).

Indivíduos não-treinados e em estágios iniciais de TR apresentam, em geral, ganhos de força em razão de novas adaptações neurais e não necessariamente através da hipertrofia/hiperplasia muscular(SIDDIQUE *et al.*, 2020). O aumento volumétrico da massa muscular é melhor estimado após alguns meses de estímulos aplicados de forma crônica e periódica e é influenciado por vários fatores como protocolo de treinamento, memória muscular, sexo, predisposição genética, dieta e estado nutricional(COFFEY; HAWLEY, 2017).

Os efeitos da frequência do TR já foram investigados em uma revisão sistemática que demonstrou que os principais grupos musculares devem ser

treinados pelo menos duas vezes por semana havendo a possibilidade de ganhos hipertróficos maiores com três vezes por semana(SCHOENFELD; OGBORN; KRIEGER, 2016).

2.1.1 Efeitos fisiológicos do treinamento resistido

O tecido musculoesquelético tem o seu metabolismo regulado pelo equilíbrio dinâmico entre síntese e degradação de proteína muscular. Sendo assim, a hipertrofia muscular ocorre quando há maior síntese (em número e/ou em tamanho) do que degradação de proteína muscular(MCGLORY; DEVRIES; PHILLIPS, 2017;SCHIAFFINO *et al.*, 2013).

As células satélites, também conhecidas como células-tronco musculares, são capazes de realizar mitose celular e contribuem na hipertrofia doando núcleos extras para fibras musculares aumentando a síntese de novas proteínas contráteis já que o conteúdo nuclear de uma fibra muscular permanece constante durante todo o processo(SHAMIM; HAWLEY; CAMERA, 2018). Os núcleos celulares da fibra muscular atuam como reguladores da produção do ácido ribonucleico mensageiro(mRNA) pois existe um limite no volume sarcoplasmático. Portanto, as células satélites são fundamentais no auxílio da expressão de outros fatores de transcrição regulatórios presentes na reparação, regeneração e crescimento muscular(Myf5, MyoD, miogenina e MRF4) ao ligarem-se ao ácido desoxirribonucléico(DNA) específico da miogênese(SHAMIM; HAWLEY; CAMERA, 2018).

Várias vias de sinalização celular são ativadas em resposta ao estímulo hipertrófico(WACKERHAGE *et al.*, 2019). As vias de proteína quinase B e *mammalian target of rapamycin* (Akt/mTOR), proteína quinase ativada por mitógenos (MAPK) e vias dependentes de cálcio (Ca2 +) constituem o conjunto de vias metabólicas que ativam a síntese de moléculas a partir de unidades menores(SAXTON; SABATINI, 2017).

A via Akt/mTOR é o mecanismo molecular responsável pela sinalização anabólica no músculo esquelético. A regulação da expressão gênica realizada por MAPK em resposta à sobrecarga mecânica, promove adaptações na célula muscular modulando seu crescimento e diferenciação(BODINE *et al.*, 2001;SCHIAFFINO *et al.*, 2013).

Por fim, o íon cálcio é um elemento fundamental para o aumento de miócitos de segunda ordem, sinalização de células endoteliais e fator nuclear de células T ativadas(MICHEL; DUNN; CHIN, 2004).

As modificações celulares geradas pelo estímulo hipertrófico também são mediadas pelas variações nos níveis hormonais e pelo sistema regulatório imunológico(KRAEMER *et al.*, 2020). O metabolismo de crescimento, proliferação e diferenciação celular também é regulado pela ação das interleucinas 5 e 6 (IL-5, IL-6), do fator 8 de crescimento e diferenciação (GDF8) e do fator inibidor de leucemia (LIF)(WACKERHAGE *et al.*, 2019;SANDRI, 2008).

Além disso, a síntese de insulina auxilia na atenuação da proteólise podendo induzir mitose e diferenciação de células satélite. O fator de crescimento semelhante à insulina (IGF-1) é encontrado nas células satélite ativadas, miócitos adultos e em células de Schwann(FINK; SCHOENFELD; NAKAZATO, 2018).

O TR também induz maior síntese hormonal de testosterona e de hormônio do crescimento (GH), essenciais no estágio anabólico. Ambos auxiliam na hipertrofia/hiperplasia muscular de diversas formas como, por exemplo, no aumento de neurotransmissores liberados e na regeneração de terminações nervosas(KRAEMER *et al.*, 2020). A síntese aguda de testosterona também auxilia na replicação e ativação de células satélites comprometidas na miogênese(LUK HY, LEVITT DE, BOYETT JC, ROJAS S, FLADER SM, MCFARLIN BK, 2019).

Sujeito a ação da testosterona, o hormônio GH possui tanto propriedades anabólicas quanto catabólicas que auxiliam no metabolismo da gordura (mobilização de triglicerídeos), estimulação da captação celular e incorporação de aminoácidos em várias proteínas. Também atua na regulação da função imunológica, modelagem óssea e volume de fluído extracelular(FINK; SCHOENFELD; NAKAZATO, 2018).

A prática crônica do TR estimula uma série de alterações metabólicas benéficas para os obesos já que melhora o desempenho físico, controle de movimento, velocidade de caminhada, independência funcional, habilidades cognitivas e auto-estima. Além disso, pode prevenir/controlar o diabetes tipo 2, reduzir a gordura visceral, reduzir os níveis séricos de hemoglobina glicada

(HbA1c), aumentar a densidade do transportador de glicose 4 (Glut4) e melhorar a sensibilidade à insulina, melhorar o sistema cardiovascular, reduzir a pressão arterial em repouso, reduzir os níveis séricos de colesterol e triglicerídeos e aumentar a densidade mineral óssea(WESTCOTT, 2012). Todos estes benefícios tornam o TR um excelente recurso que pode ser utilizado no tratamento da obesidade(SWIFT *et al.*, 2018).

2.1.2 Obesidade e estratégias dietéticas para o emagrecimento

A Organização Mundial da Saúde (OMS), órgão dedicado à saúde pública, demonstrou através de dados estatísticos robustos que a obesidade é uma doença de alta prevalência mundial e que eleva consideravelmente os custos com saúde em todas as esferas(SPIEKER; PYZOCHA, 2016;CABALLERO, 2019; ASSOCIAÇÃO BRASILEIRA PARA O ESTUDO DA OBESIDADE E DA SÍNDROME METABÓLICA (ABESO), 2016). Em 2013, a Associação Médica Americana (AMA) passou a reconhecer a obesidade como sendo uma doença crônica complexa e que demanda atenção médica(KYLE; DHURANDHAR; ALLISON, 2016; RAMANATHAN *et al.*, 2020).

Embora já exista uma série de métodos desenvolvidos para a redução de peso, ainda não há um tratamento definitivo para a obesidade(CAMILLERI; ACOSTA, 2018;FREIRE, 2020). Por este motivo, a obesidade ainda é uma doença de difícil manejo pois sua evolução está relacionada a diversos fatores que tornam o tratamento pouco eficaz na redução e estabilização do peso corporal em médio e longo prazo(JOHNSTONE, A., 2015).

Entretanto, é recomendada a intervenção precoce no estilo de vida já em ambientes de atenção primária focando a avaliação de risco à saúde e não apenas as dimensões corporais. Outra recomendação fundamental é o destaque à relevância da abordagem abrangente a fatores como dieta, atividade física e comportamentos(RYAN; KAHAN, 2018).

A obesidade é uma condição caracterizada pelo excesso de depósito de gordura corporal que aumenta a chance do desenvolvimento de doenças. Pode ser resultante da interação entre influências genéticas, socioeconômicas e culturais além de ser um fator de risco para morte prematura(BLÜHER, 2019; KIM, T. N., 2021).

A gordura corporal pode ser estimada de diversas formas(LEE, S. Y., & GALLAGHER, 2008). Contudo, os métodos considerados mais precisos ou “padrão ouro” são a Pletismografia de deslocamento aéreo(Bod Pod), Absorciometria de raios-x de dupla energia(DXA) e Impedância bioelétrica multi-frequência(MF-BIA)(GOMEZ-ARBELAEZ *et al.*, 2017;SHEPHERD *et al.*, 2018;NICKERSON *et al.*, 2020).

Um dos fatores mais importantes para o emagrecimento é o déficit energético estabelecido na recomendação de dieta de baixa caloria com baixo teor de gorduras ou carboidratos. Além disso, deve haver controle da quantidade de comida ingerida, tipo de comida e horário das refeições. Ainda existem situações em que é necessária a realização aguda de dieta de muito poucas calorias por um curto período(KIM, J. Y., 2020).

Alguns estudos demonstraram que a perda de peso está associada a uma redução no gasto energético diário em até 15% tendo o efeito oposto em situações de sobrealimentação(LEIBEL RL, ROSENBAUM M, 1996;BRAY *et al.*, 2015). Tais dados evidenciam a mudança desproporcional no gasto energético durante a fase dinâmica da mudança de peso, fenômeno conhecido como adaptação metabólica ou termogênese adaptativa(MÜLLER, M. J.; BOSY-WESTPHAL, 2013).

A termogênese adaptativa, resultante da adaptação metabólica às alterações na composição corporal durante o emagrecimento, ocorre de forma independente em relação às variações tanto em massa livre de gordura quanto na composição da massa livre de gordura(MÜLLER, Manfred J.; ENDERLE; BOSY-WESTPHAL, 2016).

Quando o balanço energético é negativo, a termogênese adaptativa visa a economia energética. Após a redução de peso, sua maior contribuição é em relação a manutenção do peso corporal. Estabelecida a fase inicial do emagrecimento, a termogênese adaptativa age principalmente para garantir suprimento energético ao cérebro em resposta ao esgotamento das reservas de glicogênio associadas à queda na secreção hormonal de insulina. Contudo, durante a manutenção da redução de peso, a termogênese adaptativa mantém o gasto energético em níveis baixos tendo sua função influenciada pelos baixos

níveis hormonais de leptina preservando os estoques de triglicerídeos(MÜLLER, Manfred J.; ENDERLE; BOSY-WESTPHAL, 2016).

Outros fatores importantes, além do gasto energético proporcional à massa muscular e massa gorda, são o gasto energético resultante de atividade física com a massa corporal alterada e a variação alimentar que usa diferentes quantidades de energia no processo de assimilação de nutrientes(SPEAKMAN; SELMAN, 2003).

Com o objetivo de controlar o avanço da obesidade nas últimas cinco décadas, a OMS elaborou uma série de diretrizes voltadas ao manejo do sobrepeso e da obesidade. As recomendações de perda de peso com benefícios à saúde estimam uma meta de redução que varia entre apenas 5 e 10% do peso corporal(YUMUK *et al.*, 2015;RYAN; KAHAN, 2018;JENSEN *et al.*, 2014).

2.1.3 Metabolismo energético e emagrecimento

O metabolismo energético pode ser definido como o conjunto de reações químicas que possibilita a transformação de aproximadamente 90% do total de energia ingerida diariamente. Admite-se que a energia restante seja perdida nas excreções(EM, 1955).

Tais reações químicas são reguladas por mecanismos que agem tanto na manutenção da homeostase energética celular através da utilização dos principais macronutrientes advindos da dieta (carboidratos, proteínas e gorduras) quanto no armazenamento de energia na forma de glicogênio ou tecido adiposo visando o aporte glicolítico constante para a corrente sanguínea(EMADIAN *et al.*, 2015).

Os níveis glicêmicos são controlados através de uma complexa rede composta pelo pâncreas, fígado, tecido adiposo, músculos e cérebro sendo a sua interação mediada através de uma série de sinais hormonais. A manutenção dos níveis glicêmicos seja no período absortivo, pós-absortivo ou em jejum, é fundamental,principalmente para o sistema nervoso, medula renal e hemácias, pois dependem exclusivamente da glicose para seus requerimentos energéticos (LAM, 2010).

O fígado é o principal órgão regulador dos níveis glicêmicos pois participa ativamente no fornecimento de glicose livre para a corrente sanguínea a partir

de estoques de glicogênio (glicogenólise). Também possui a capacidade de sintetizar glicogênio a partir de resíduos desaminados de aminoácidos, glicerol e lactato (neoglicogênese). A glicogenólise e a neoglicogênese são processos fundamentais para prevenção de hipoglicemia durante períodos de jejum, exercício prolongado e emagrecimento(WAHREN; EKBERG, 2007;HARGREAVES, 2004).

Durante o período absortivo os níveis glicêmicos aumentam pois os nutrientes da dieta são absorvidos pelo trato gastrointestinal e lançados na circulação sanguínea. Esta condição ativa inicialmente a via da oxidação da glicose (glicólise) que entra na célula dando origem a duas moléculas de piruvato, e posteriormente em Acetil-CoA, destinando-se ao Ciclo de Krebs, para a liberação de ATP´s e hidrogênios de alto valor energético que serão levados à cadeia transportadora de elétrons, para produção de energia. A oxidação da glicose acontece em todos os tecidos para obtenção de energia. Além da ativação desta via em estado alimentado, existe também a estimulação das vias anabólicas armazenadoras de glicose reserva. As vias envolvidas no armazenamento de glicose são a glicogênese (transformação da glicose em glicogênio a ser armazenado no fígado e no músculo) e a lipogênese (síntese de triacilgliceróis no tecido adiposo)(MULUKUTLA *et al.*, 2016).

A insulina, secretada pelas células beta pancreáticas, é o hormônio predominante nesta via metabólica quando há altos níveis de glicose sanguínea sendo também inibida a sua síntese quando os níveis glicêmicos estão abaixo dos níveis considerados normais. A insulina é um hormônio anabólico e controla as vias envolvidas na síntese da glicose através da ativação das enzimas-chave destas vias metabólicas(TOKARZ; MACDONALD; KLIP, 2018).

Em períodos de severa privação calórica (jejum) ou de restrito acesso a alimentos (dietas), outros mecanismos metabólicos podem ser ativados a fim de normalizar os níveis glicêmicos na circulação sanguínea que, naturalmente, apresenta uma leve redução após as primeiras horas de jejum(LAEGER; METGES; KUHLA, 2010).

Vários mecanismos regulatórios são ativados para possibilitar a obtenção de glicose a partir de fontes de energia armazenadas. As principais vias de degradação envolvidas neste processo são a via da glicogenólise (degradação

hepática do glicogênio armazenado durante o estado alimentado) e a neoglicogênese (síntese de novo de glicose a partir de compostos carbonados não glicídicos, como glicerol, que é proveniente de degradação lipídica, e resíduos desaminados de aminoácidos, além de piruvato e lactato)(RUI, 2014). Durante o jejum, diversos hormônios hiperglicemiantes agem no controle desses mecanismos, principalmente o glucagon, secretado pelas células alfa das ilhotas pancreáticas, os glicocorticóides (cortisol e cortiscoterona), catecolaminas (adrenalina e noradrenalina) e o hormônio de crescimento (GH) que estimulam as vias catabólicas (glicogenólise, lipólise, proteólise) e a neoglicogênese, sendo a ativação destas vias essenciais no processo de emagrecimento(HALL, 2017).

2.1.4 Dietas cetogênicas

A maioria das dietas para emagrecimento é restritiva em algum aspecto(FREIRE, 2020). Além de estimular o consumo de alimentos naturais e minimamente processados(KATZ; MELLER, 2014), têm a sua elaboração voltada para que o indivíduo consiga aderir às recomendações estabelecidas garantindo que a restrição energética seja suficiente para causar emagrecimento(LARSEN *et al.*, 2010). As dietas clássicas para redução de peso visam a restrição do valor de energético total (VET) diário além de incentivar a reeducação alimentar, independente do conteúdo energético(EBBELING *et al.*, 2012).

Todavia, a restrição dietética também pode enfatizar um macronutriente específico como, por exemplo, nas dietas com baixa ingestão de gordura, proteína ou carboidrato(SACKS *et al.*, 2009). Este tipo de abordagem é capaz de auxiliar no controle da hipertensão(OZEMEK *et al.*, 2018), diabetes(CHESTER *et al.*, 2019) e síndrome metabólica(DE LA IGLESIA *et al.*, 2016) além de outras doenças para as quais, eventualmente, os tratamentos tradicionais não sejam eficazes(MARTIN *et al.*, 2016);CASTRO-BARQUERO *et al.*, 2020).

Sendo assim, as dietas hipocalóricas são elaboradas com a finalidade de causar balanço energético negativo estimulando a utilização de reservas de gordura para realizar a manutenção energética do metabolismo reduzindo os depósitos corporais de gordura(YUMUK *et al.*, 2015).

As DC são caracterizadas pelo alto teor de gorduras e baixo teor de carboidratos e proteínas que estimulam o estado metabólico conhecido como cetose fisiológica. Em geral, as proporções de macronutrientes utilizadas para estabelecer a cetose fisiológica admitem valores entre 20g/d e 50g/d (ou até 10% do VET) de carboidratos, 15 a 20% do VET de proteínas e até 80% do VET de gorduras(O'NEILL; RAGGI, 2020).

Durante a cetose fisiológica, grande parte do aporte energético é resultante da síntese hepática de gorduras e do aumento da oxidação dos CC potencializados pela restrição dos carboidratos na dieta(ADAM-PERROT; CLIFTON; BROUNS, 2006).

Os CC são produzidos a partir da oxidação de ácidos graxos, mas também admitem uma rota alternativa através do catabolismo de alguns aminoácidos. A metabolização do acetil-CoA é alavancada durante a cetogênese na matriz mitocondrial dos hepatócitos quando os carboidratos estão tão escassos que a energia deve ser obtida através da quebra dos ácidos graxos(ABDUL KADIR; CLARKE; EVANS, 2020; EVANS; COGAN; EGAN, 2017).

As cetonas são formadas a partir da descarboxilação espontânea do acetoacetato. Os níveis de cetonas são muito menores do que os níveis dos outros dois tipos de corpos cetônicos. A cetona não pode ser convertida de volta a acetil-CoA, portanto deverá ser excretada na urina(ABDUL KADIR; CLARKE; EVANS, 2020).

Analogamente, a cetose fisiológica também ocorre durante situações de jejum prolongado permitindo que as DC sejam utilizadas para simular o estado de jejum(SHERRIER; LI, 2019).

A redução dos níveis glicêmicos provocada pela restrição dos carboidratos faz com que o pâncreas reduza a síntese de insulina e aumente a síntese de glucagon com o objetivo de utilizar as fontes armazenadas de gordura como fonte de energia a serem metabolizadas no fígado como já foi abordado anteriormente(IQBAL; HELLER, 2016).

A soma desta série de ajustes metabólicos provocados pela DC auxilia na redução de gordura visceral(CUNHA *et al.*, 2020), melhora a densidade do transportador de glicose(BOLLA AM, CARETTO A, LAURENZI A, SCAVINI M, 2019) além de impactar também na normalização do perfil lipídico(DASHTI;

MATHEW; AL-ZAID, 2020) reduzindo a chance de acometimento por síndrome metabólica(HA; JOUNG; SONG, 2018) e redução drástica de fatores de risco cardiovasculares(GE *et al.*, 2020).

Segundo o Instituto Nacional para Orientação de Excelência em Saúde e Cuidados, as DC devem ser consideradas como parte multiestratégica de controle do peso em pessoas obesas com indicação clínica de redução de peso rápida(STEGENGA *et al.*, 2014). Porém, as DC costumavam ser estigmatizadas em virtude da ocorrência de alguns efeitos colaterais e principalmente por causa da alta proporção de lipídios ignorando a considerável restrição feita aos carboidratos e proteínas(MUSCOGIURI *et al.*, 2019).

Apesar das DC apresentarem um grau de restrição alto, a elaboração de planos alimentares deve seguir os princípios gerais da nutrição oferecendo energia, proteínas, minerais e vitaminas, a fim de promover a manutenção da saúde. Em geral, durante as DC é recomendada a suplementação de minerais e vitaminas pois os alimentos utilizados na dieta não são capazes de fornecer os valores mínimos diários recomendados(KENIG *et al.*, 2019).

2.1.5 Associação entre treinamento resistido e dietas cetogênicas

A atividade física é comprovadamente benéfica à saúde(WARBURTON; BREDIN, 2018;WARBURTON; BREDIN, 2017; WARBURTON; BREDIN, 2016). Da mesma forma, o TR estimula uma série de efeitos metabólicos regulatórios além de ser muito eficaz para o emagrecimento. Aplicável a obesos, o TR promove o aumento do gasto energético através do acréscimo no estímulo da lipólise do tecido adiposo em situações de restrição dietética, especialmente quando utilizado simultaneamente a DC(HUNTER *et al.*, 2015; CHATZINIKOLAOU *et al.*, 2008).

Além disso, um dos efeitos mais importantes causado pelo TR em conjunto com o emagrecimento é a capacidade de auxiliar na manutenção da taxa metabólica de repouso, à medida em que minimiza o catabolismo da massa magra, característico das situações em que o balanço energético é negativo(DELMONICO; LOFGREN, 2010).

Ainda não existe um consenso sobre o resultado da combinação simultânea entre TR e DC pois existem poucas evidências científicas além de os resultados descritos serem conflitantes(JABEKK *et al.*, 2010;WOOD *et al.*, 2012).

3 Artigo

Effect of Resistance Training Combined with Ketogenic Diets: A Systematic Review and Meta-Analysis

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Abstract

Diets that cause ketosis (DCK), high in fat and restricted in carbohydrates, have been proposed as an alternative for the treatment of obesity. Among several criticisms that are raised against its use for weight loss, the loss of free fat mass (FFM), has been reported as an undesirable effect because it can reduce basal metabolic rate and cause other consequences related to patients health. Since resistance training (RT) can promote muscle hypertrophy, its practice accompanying DCK could help to maintain FFM. In the present study, we systematically reviewed the literature and compared the effect of RT while diets with or without carbohydrate restriction. Although a small reduction in lean mass was identified in the meta-analysis (-0.347 CI 95%: -0.549, 0.144), some authors report that there was no loss of physical performance. Others suggest that this difference in lean mass is associated with loss of water in patients, a typical phenomenon caused by carbohydrate-restricted diets. We conclude that physical exercise is an important tool in maintaining lean mass in individuals undergoing carbohydrate-restrictive diets that cause ketosis. Specific studies comparing individuals submitted to a DCK, associated or not with RT, are still rare in the literature.

Keywords: KD, Obesity, Metabolism, Exercise, Restrictive Diets, Ketogenic Diet

Introduction

Resistance training (RT) is mainly used to gain muscle mass by stimulating muscle hypertrophy(SCHOENFELD *et al.*, 2019),(KRZYSZTOFIK *et al.*, 2019). RT also promotes a number of other health benefits by lowering blood pressure(DE SOUSA *et al.*, 2017),(CORNELISSEN; SMART, 2013), lowering glycaemia(ISHIGURO *et al.*, 2016; LEE; KIM; KIM, 2017; TAKENAMI *et al.*, 2019), increasing basal metabolic rate(ARISTIZABAL *et al.*, 2015a), aiding in the treatment of weight loss(GOLDFIELD *et al.*, 2017) and promotes the reduction of mortality associated with cardiovascular risk(SAEIDIFARD *et al.*, 2019). The induction of the increase in total energy expenditure obtained with the practice of resistance exercise, as well as the increase in the BMR, are consequences of the metabolic effects promoted by exercise and of the gain of lean mass(ARISTIZABAL *et al.*, 2015b),(MACKENZIE-SHALDERS *et al.*, 2020). These effects consequently favor weight loss(HUNTER *et al.*, 2015),(MACKENZIE-SHALDERS *et al.*, 2020).

Much is already known about the molecular mechanisms involved in the hypertrophy of skeletal muscle associated with RT. The amount of muscle mass depends on the balance between signaling pathways related to hypertrophy and hypotrophy of muscle fibers. Some hyperplastic effect has been described and is related to the activation of satellite cells in skeletal muscle, but their percentage participation in muscle mass gain seems small, although there are still controversies between studies(JORGENSON; PHILLIPS; HORNBERGER, 2020),(MURACH *et al.*, 2018). Satellite cells also participate in hypertrophy by increasing the components of existing fibers involving the calcineurin/ nuclear factor of activated T cells (NFAT) pathway and myostatin regulation(SCHULZ; YUTZEY, 2004), (RODRIGUEZ *et al.*, 2014). TR stimulates the protein synthesis of muscle fibers, among other mechanisms, by activating the signaling pathways of the serine/ threonine kinase protein “protein-kinase-B/ mammalian-target-of-rapamycin” (Akt/ mTOR) blocking the activation of adenosine mono phosphate kinase proteins (AMPK) antagonistic to the stimulus of Akt/mTOR(SCHIAFFINO *et al.*, 2013),(YOON, 2017). Simultaneously, the hypertrophic response induces the blocking of several processes such as muscle proteolysis (regulated by cathepsin proteases, calcium-dependent calpains and caspases), muscle

catabolism via ubiquitin ATP-dependent proteasome (UPS), activation of specific gene expression via forkhead box protein O (FoxO), apoptosis via tumor necrosis factor alpha (TNFα), transcriptional activation of inflammatory mediators via nuclear factor kappa B (NFkB) and regulation of glucocorticoid-induced gene transcription(YOSHIDA; DELAFONTAINE, 2020).

There is a consensus that the most common treatment for weight loss consists mainly of diet and exercise(MOZAFFARIAN *et al.*, 2011). Any of these weight loss diets is restrictive in some way(VAN HORN, 2014),(SACKS *et al.*, 2009). In general, dietary restriction is based on energy deficit (regardless of the proportion of macronutrients)(DE SOUZA *et al.*, 2012) or in the composition of macronutrients (regardless of caloric value)(BUENO *et al.*, 2013). The quality of the diet can also be important, as proposed by the consumption of unprocessed foods(LOCKE; SCHNEIDERHAN; ZICK, 2018),(RICHI *et al.*, 2015),(SROUR *et al.*, 2019). Therefore, they can be conventional hypocaloric (low energy density)(FOCK; KHOO, 2013), low-fat diets(RAZAVI ZADE *et al.*, 2016), (TOBIAS *et al.*, 2015), low-carb diets(CARE; SUPPL, 2020), (KELLY; UNWIN; FINUCANE, 2020) or high-protein diets(LARSEN *et al.*, 2010), (ZHAO *et al.*, 2018).

Among restrictive diets, the ketogenic diet (KD) has gained attention as it is a very efficient solution in the short term, making a severe restriction on carbohydrate intake, but not restricting, in principle, the total amount of energy ingested, which can be indicated with *ad libitum* intake of the recommended foods in the diet(JOHNSTONE, A. M. *et al.*, 2008), (KANG *et al.*, 2020). KD is characterized by being rich in lipids, moderate in proteins and low in carbohydrates(GIUGLIANO *et al.*, 2018). Limiting ingested carbohydrates to less than 50g/day(MUSCOGIURI *et al.*, 2019), or caloric value of carbohydrates less than 10% of the total energy value (TEV), simulates in some aspects the state of fasting, stimulating the production of ketone bodies, which can be used as an energy source for the maintenance of metabolism. Physiological ketosis promotes rapid initial weight loss due to increased diuresis in response to reduced glycogen levels in tissues, mainly because of hormonal changes such as reduced insulin release and stimulated gluconeogenesis. After stabilizing fluid loss, weight reduction remain constant if the TEV is maintained at levels below

energy expenditure, which will depend on a patient's adaptive process(MUSCOGIURI *et al.*, 2019). Although KD has a number of benefits, it can also cause adverse effects such as dehydration, hypoglycemia, lethargy, halitosis, gastrointestinal disorders, hyperuricemia, hypoproteinemia, hypocalcemia, bone damage, changes in lipid profile, urolithiasis, gallstones or hair loss(O'NEILL; RAGGI, 2020). These effects are usually moderate and can be overcome with patient monitoring. Despite the adverse effects, this type of diet can be used to treat diseases such as type 2 diabetes(DASHTI; MATHEW; AL-ZAID, 2020) and hypercholesterolemia making drug treatment unnecessary(KIRKPATRICK *et al.*, 2019).

A criticism, in relation to diets that cause ketosis, that has become important in recent years is the effect on the amount of free fat mass (FFM). Many studies point to the loss of FFM as the central problem, even claim that this would be deleterious to health, harming the relationship between fat mass and FFM, and thus harming the weight loss treatment as a whole(NOAKES *et al.*, 2006),(JOHNSTONE, A. M. *et al.*, 2008),(BREHM *et al.*, 2005),(BRINKWORTH *et al.*, 2009), (RUTH *et al.*, 2013), (WOOD *et al.*, 2007). In this hypothesis, the reduction of FFM caused by restrictive diets would lead to a reduction in energy expenditure and deleterious effects on the metabolism, which would also be associated with changes in body composition.

Despite this, some studies became famous at the beginning of the century, showing that even with an 80% consumption of energy from fats, cholesterol levels were rapidly reduced in obese patients, both in those with or without dyslipidemia(DASHTI HM, MATHEW TC, HUSSEIN T, ASFAR SK, BEHBAHANI A, KHOURSHEED MA, AL-SAYER HM, BO-ABBAS YY, 2004). It was later shown that low insulin levels reduced the synthesis of endogenous cholesterol due to a lack of activation of the enzyme 3-hydroxy-3-methyl-glutaryl-CoA reductase. Even so, many authors remain concerned about the deleterious effects that loss of lean mass may cause.

The hypothesis of this study is that RT is an important tool in maintaining FFM during dietary treatment using DCK. Therefore, we reviewed the literature searching for articles that combine DCK and RT. To prove our hypothesis, we

performed a meta-analysis of the existing literature searching for articles that combine KD with RT.

Methods

This systematic review followed a pre-established protocol and was registered at the PROSPERO platform (CRD42018116655) in addition to the PRISMA guidelines(LIBERATI *et al.*, 2009) designed for systematic reviews and meta-analyzes. Eligibility criteria were established including articles containing experimental studies involving diets that cause ketosis and resistance exercise, in humans and animals into our study.

The systematic search for scientific works was carried out using three databases (PUBMED, Embase and Sportdiscus, choosing articles) published until 2020-10-06. The search algorithm is described in supplementary materials as Figure S1. In general, for the search "ORs" were made between several terms that identify diets that can cause ketosis and between terms that can identify resistance exercise. An “AND” was used between the two groups of terms. Adjustments to the algorithms were made to work in the different databases. With the result of the electronic search, we performed the reading of the title and summary to exclude those that did not fit the determined criteria. After the search, duplicates, articles in languages other than English and Portuguese, reviews, incomplete articles that presented only abstracts, case studies, articles that did not report ketosis in the participants, who did not present lean mass values, who had treatment duration of less than 4 weeks or who did not have a control group were excluded. The remaining articles were red by two authors before defining the final selection.

The sample number and changes in FFM (mean ± standart deviation) were extracted for meta-analysis. When the data were presented exclusively in graphs, we used the GetData Graph Digitizer program to extract them. The meta-analysis was performed using STATA software using the random method. The selected studies were submitted to bias assessment using the RoB 2.0 tool(THE COCHRANE COLLABORATION, 2019).

Two hundred ninety-five articles were found in EMBASE, 199 in PubMed and 73 in SPORTDiscus in a total of 567. Of these, 92 were removed because they were duplicates. Of the remaining 475 articles, 389 were excluded after

reading the title and abstract. Of the 86 articles read in full, 76 were excluded for various reasons (2 case studies, 3 studies in experimental animal models, 58 studies with diets that did not cause ketosis, 1 study with aerobic exercise, 3 studies with incomplete data on muscle mass, 6 clinical studies lasting less than 4 weeks, 1 congress summary, 1 non-clinical and randomized study and 1 congress annals). Ten studies were selected to perform the meta-analysis.

Inclusion criteria

Randomized controlled clinical trials assessing the impact of resistance training associated with consumption of ketosis-inducing diets (KD) on men or women (with or without chronic disease), trained or untrained aged> 18 years, were included in the current analysis. Dietary carbohydrates must be <50 g / d (up to 10% TEV) or ketosis was confirmed by circulating β-hydroxybutyrate (βHB) ≥ 0.5 mmol / L. weeks. Resistance training and diet must have been applied for ≥at least 4 weeks. Reading body composition data at the beginning and end of the study using gold standard methods.

Exclusion criteria

Studies in children / adolescents (<18 years) and animal models and cross-sectional studies were excluded. Studies were excluded if the RT intervention was ≤ 2 times a week and KD was> 50 g carbohydrate / d or ketosis was not confirmed using circulating βHB> 0.5 mmol / L, administered for <14 d, replenished with carbohydrate before exercise, or had no corresponding control. Studies were excluded if food intake was not reported or ketosis was not confirmed. Studies with body composition data collected only at the beginning or at the end of the study were excluded. If data were missing from a manuscript, the corresponding authors were contacted.

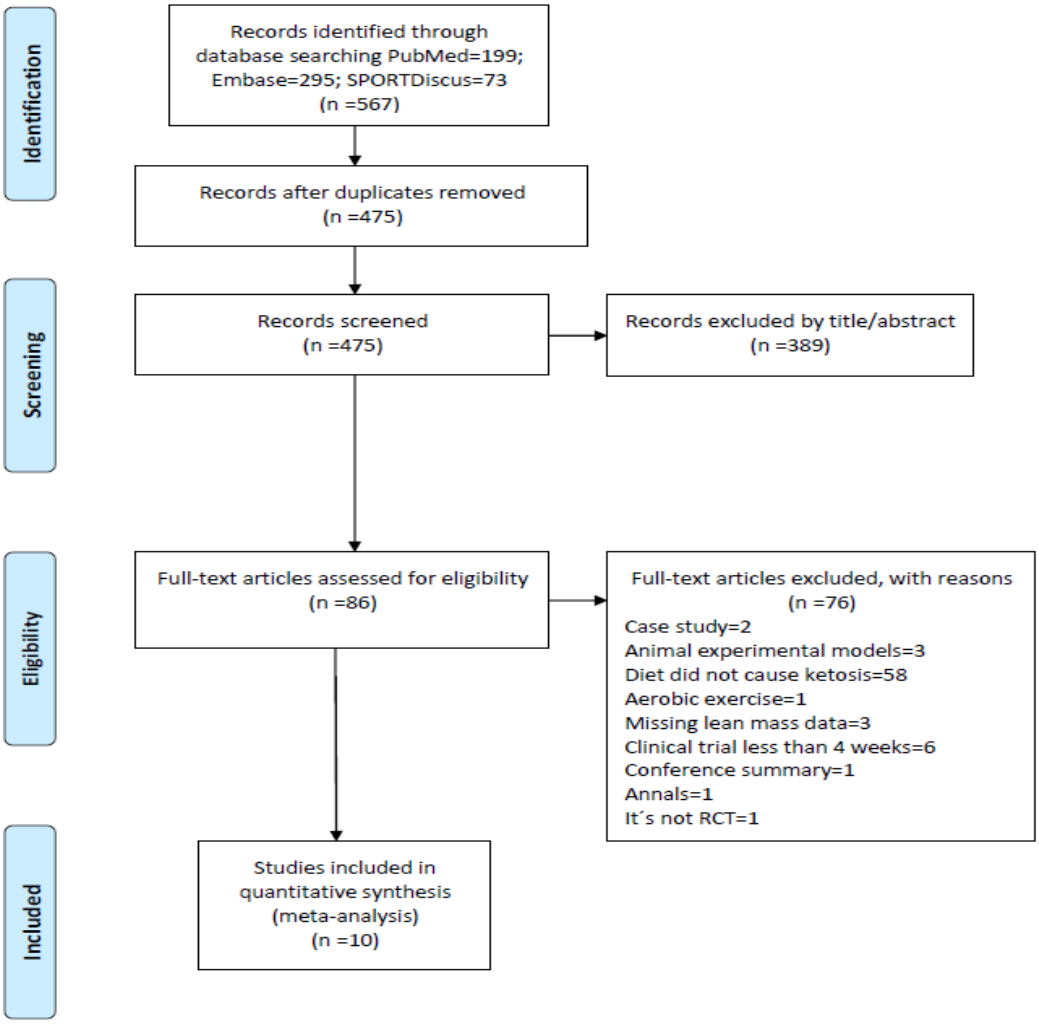

Figure 1: Articles search and exclusion protocol

Effect of resistance exercise on the preservation of lean mass in humans

The initial intention of this study was to verify whether RT is an effective tool for maintaining lean mass during weight loss treatment using diets that cause ketosis. To answer this question, the ideal studies would be those whose experimental design would allow the comparison of subjects submitted to a ketogenic diet with and without resistance exercise. Unfortunately, studies with this experimental design have been rare in the literature, giving rise mainly to studies that present only trained groups submitted to different diets. Therefore, we use these studies to compare changes in FFM between diets. Ten of these studies were selected for the meta-analytical synthesis. The details of these studies, such as sample population, diet and exercise interventions, sample size, intervention time and observed main results, are shown in Table 1. Despite the

heterogeneity of the studies, the meta-analysis gave us a weighted analysis of the changes in the FFM of patients showing a small reduction (Figure 2). The effect represented by grouped D + L of SMD was -0.347 with a 95% confidence interval between -0.549 and -0.144. This analysis showed 29.48 (d.f. = 10), p = 0.001, I-squared (variation in SMD attributable to heterogeneity) = 66.1% and estimate of between-study variance Tau-squared = 0.1252. Test of SMD = 0: z = 3.36, p <0.001

The detailed results of the analysis are shown in Table 2.

Table 1: Details from selected studies.

Study	Population	Diet	Exercise protocol	Time	n	Main results	Obs.
Greene, D.A.; 2018	Intermediate competitive lifting athletes (age 34 6 10.5, n = 5 female)	*Ad libitum* usual diet (UD) (.250 g daily intake of carbohydrates) and an *ad libitum* LCKD (#50 g or #10% daily intake of carbohydrates) in random order, each for 3 months in a crossover design.	Subjects were instructed to maintain their normal training during both dietary phases.	Three months plus 3 months.	12 plus 12 weeks pareated.	Lean mass changes: -2.26, SE 0.64; 95% CI -4.10 to -0.42 .	Without reduction in physic performance.
Kerksick, C.M.; 2010	One hundred forty-one sedentary, obese women (38.7 ± 8.0 yrs, 163.3 ± 6.9 cm, 93.2 ± 16.5 kg, 35.0 ±6.2 kg•m-2, 44.8 ± 4.2% fat).	No diet + no exercise control group (CON), no diet + exercise control (ND), or one of four diet + exercise groups (high-energy diet [HED], very low carbohydrate, high protein diet [VLCHP], low carbohydrate, moderate protein diet [LCMP] and high carbohydrate, low protein [HCLP]).	Three times week, supervised resistance training program.	14 weeks	43 and 39	FFM 48, SE 6 x 48, SE 7 kg total	No differences in lean mass.
Tay, J.; 2015	One hundred and fifteen obese adults with T2D [mean +- SD age: 58 +- 7 y; body mass index (in kg/m2): 34.6 .	Hypocaloric LC diet [14% of energy as carbohydrate, 28% of energy as protein, and 58% of energy as fat or an energy matched HC diet [53% of energy as carbohydrate, 17% of energy as protein, and 30% of energy as fat.	Supervised aerobic and resistance exercise (60 min; 3 d/wk)	52 weeks	37 and 41	Changes in Free Fat Mass FFM: LC-1.8 sd 0.28 and HC -1.6 sd 0.3.	Mixed Exercise.
Vargas-Molina, S.; 2020	Twenty-one strength-trained women (27.6 ± 4.0 years; 162.1 ± 6.6 cm; 62.3 ± 7.8 kg; 23.7 ± 2.9 kg·m− 2).	Non-KD group (n = 11, NKD) or a KD group (n = 10, KD)	Four training sessions per week (divided into 2 4-week cycles) for 8 weeks.	8 weeks	11 and 10	NKD (0.7 ± 1.1 kg; P = 0.074; d = 0.2) KD(− 0.7 ± 1.7 kg; P = 0.202; d = − 0.1) or	
Vargas, S.; 2018	Twenty-four healthy men (age 30 ± 4.7 years; weight 76.7 ± 8.2 kg; height 174.3 ± 19.7 cm).	KD group (n = 9), non-KD group (n = 10, NKD), and control group (n = 5, CG).	Four sessions per week of a hypertrophy training protocol, organized into a 2-days upper- and 2-days lower-limb, with 72 h of rest between sessions.	8 weeks	10 and 9	Changes in muscle mass: NKD (1.3[0.5,2.2] kg; p < 0,05; ES = 0.31, respectively), KD (− 0.1 [− 1.1,1.0]; p > 0,05; ES = − 0.04).	
McSwiney, F.T.; 2018	Twenty male endurance-trained athletes (age 33 ± 11 y, body mass 80 ± 11 kg; BMI 24.7 ± 3.1 kg/m2)	High-carbohydrate (HC) group (n = 11, %"carbohydrate:protein:fat" = 65:14:20), or a LCKD group (n = 9, 6:17:77).	Mixed training: endurance, strength and high intensity interval training (HIIT).	12 weeks	11 and 9	Lean mass: HC +01 e LCKD +0.3.	Without reduction in physic performance.
Wood, R.J.; 2012	Fourty two men (59 – 7 years) were matched [body mass index (BMI)] and randomized to LFD, LFD&PRE, CRD, and CRD&PRE.	The % of "carbohydrate:fat:protein" was: LFD = 55:24:18, LFD&PRE = 57:20:20, CRD= 16:54:28, and CRD&PRE = 12:56:31.	Supervised strength training three times per week.	12 weeks	8, 9, 8 and 7	Reduction in FFM was: LFD LFD&PRE , CRD, and CRD&PRE = 27.5%, 15.9%, 15.7%, and 17.3% with SD 21, 8, 8, e 7.	Possibility to compare KD with and without exercise.
Jabekk, P.T.; 2010	Eighteen untrained women between 20 and 40 years with BMI ≥ 25 kg*m-2.	Low carb with less that 20g carbo.	60-100 min of varied resistance exercise twice weekly.	10 weeks	8 and 8	Change in FFM :normal diet 1.6 ± 1.8, low carb 0.1 ± 1.7.	
Perissiou, M.; 2020	Male and female participants in the experimental (EX-LC; sexercise + low-carbohydrate meals; n = 33; 35.3 years) and control (EX-CO; exercise + standard dietary advice; n = 31; 34.2 years).	The low-carbohydrate group pre-prepared meals did not exceed in total 50 g of CHO per day.	Four sessions per week/45 min per session). The exercise sessions involved a combination of aerobic and resistance exercise.	8 weeks	33 and 31	Muscle size measurements .	
Wilson, J.M.; 2017	Twenty-five college aged men divided into a KD or traditional WD from weeks 1-10, with a reintroduction of carbohydrates from weeks 10-11.	The KD consisted of 20% calories from protein, 5% from carbohydrate including fiber, and 75% from fat.	Resistance training.	10 weeks	WD 12 and KD 13	Lean body mass: KD 1.4 + 1.9 e WD 2.6 + 1.3 KD and WD groups (2.4% and 4.4%, p<0.01) at week 10.	Only KD group get more LBM after carbo reloaded at the end.

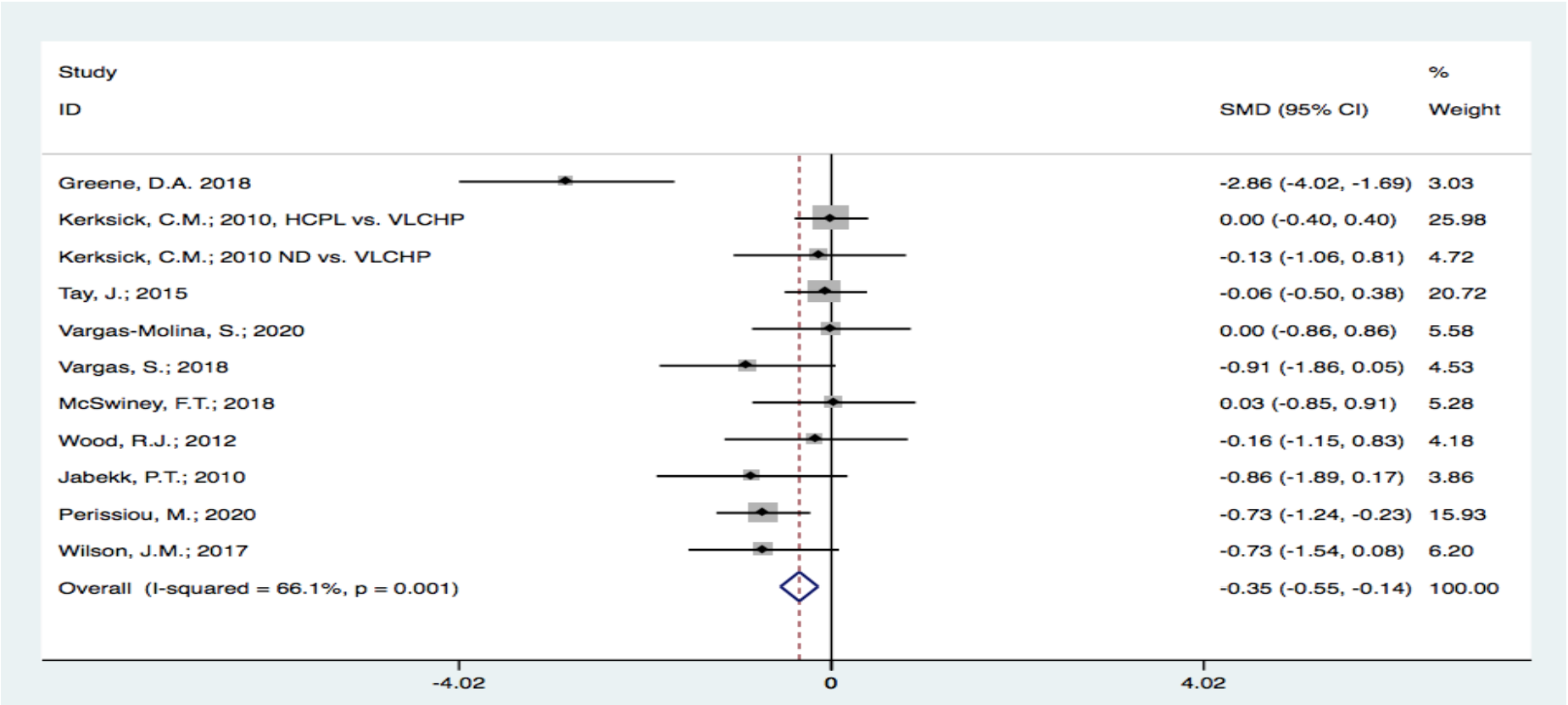

Figure 2: Plot of meta-analysis showing compare of RT group and Control group. Heterogeneity chi-squared = 29.48 (d.f. = 10) p = 0.001 I-squared (variation in SMD attributable to heterogeneity) = 66.1% and estimate of between-study variance Tau-squared = 0.1252. Test of SMD=0: z = 3.36, p < 0.001.

Table 2: Meta-analysis detailed results

Study	SMD	[95% Conf.	Interval]	% Weight
Greene, D.A. 2018	-2.858	-4.022	-1.695	3.03
Kerksick, C.M.; 2010	0.000	-0.397	0.397	25.98
Kerksick, C.M.; 2010	-0.126	-1.057	0.806	4.72
Tay, J.; 2015	-0.060	-0.505	0.384	20.72
Vargas-Molina, S.; 2	0.000	-0.856	0.856	5.58
Vargas, S.; 2018	-0.906	-1.856	0.045	4.53
McSwiney, F.T.; 2018	0.027	-0.854	0.908	5.28
Wood, R.J.; 2012	-0.164	-1.154	0.825	4.18
Jabekk, P.T.; 2010	-0.857	-1.887	0.173	3.86
Perissiou, M.; 2020	-0.735	-1.242	-0.228	15.93
Wilson, J.M.; 2017	-0.731	-1.544	0.081	6.20
I-V pooled SMD	-0.347	-0.549	-0.144	100.00

Changes in mass, water retention and sports performance

In view of the result obtained in the meta-analysis, we verified how the authors discussed the causes of reduced FFM, when it was observed in the study, and also if this loss was reflected in reduction of sports performance, when this feature was analyzed in the study. In Table 3 we present a summary of the effects observed from 10 selected articles, highlighting whether there was a reintroduction of carbohydrates at the end of the experiment, whether a reduction in FFM was observed, when the latter occurred, if the authors related this reduction to the reduction of water in the body due to characteristic of low carb diets, if there was a reduction in athletic performance when the experimental design foresaw this analysis, and finally if the diet that caused ketosis had a greater effect in reducing body mass and fat mass in individuals compared to the control diet. The two articles in which there was replacement of carbohydrates in the diet at the end of the experiment, for at least a week, reported a small loss of FFM or gain after replacement of the carbohydrate(KERKSICK *et al.*, 2010), (WILSON *et al.*, 2017). Two other studies report that there was no reduction in FFM before and after KD, despite being different from the control diet where there was a gain in FFM attributed to(VARGAS-MOLINA *et al.*, 2020) resistance training. Another 4 articles report that there was no significant difference between FFM of the groups with different diet(TAY *et al.*, 2015), (VARGAS-MOLINA *et al.*, 2020), (MCSWINEY *et al.*, 2018), (WOOD *et al.*, 2012). Of the articles where a significant reduction in FFM was observed, both refer in the

discussion that this reduction would be compatible with the water reduction in the body, a phenomenon that has been well described and known to be caused by diuresis in patients with carbohydrate restriction in the diet(GREENE DA, VARLEY BJ, HARTWIG TB, CHAPMAN P, 2018), (PERISSIOU M, BORKOLES E, KOBAYASHI K, 2020). Finally, seven studies report that in the groups with KD there was a greater reduction in BW and Fat, although when there was carbohydrate replacement this difference was reversed at least in one study(WILSON *et al.*, 2017).

Table 3: Changes in free fat mass and exercise performance

Study	Carbohydrate reintroduction	Reduction in FFM	Blame water	Performance	Weight loss	Fat mass
Greene, D.A.; 2018	No	Yes	Yes	Keep	Reduced	Reduced
kerksick, C.M.; 2010	Yes	Very small	No	Not evaluated	Reduced	Reduced
Tay, J.; 2015	No	No	NA	Not evaluated	Similar	Similar
Vargas-Molina, S.; 2020	No	No	NA	Keep	Reduced	Reduced
Vargas, S.; 2018	No	No difference inside group, but reduced comparing to NKD group.	Not discussed	Not evaluated	Reduced	Reduced
McSwiney, F.T.; 2018	No	No	NA	Keep	Reduced	Reduced
Wood, R.J.; 2012	No	No	NA	Keep	Reduced	Reduced
Jabekk, P.T.; 2010	No	No difference betweengroup, but reduced comparing groups.	Do not discuss water content.	Not evaluated	Reduced	Reduced
Perissiou, M.; 2020	No	Yes	Yes	Not evaluated	Reduced	Similar reduction
Wilson, J.M.; 2017	Yes	Increase muscle mass in KD.	NA	Increased performance	Similar after reload carbo	Similar

Mechanisms proposed for maintaining lean mass through exercise

Among the selected studies, some of them researched evidence related to the mechanisms involved in the effect of the ketogenic diet and resistive exercise on variations in FFM. Since insulin activation via the AKT pathway has often been linked to muscle hypertrophy, reduced insulin release in diets low in carbohydrates should be the main cause of muscle wasting. Although this hypothesis seems evident, work on humans and animal models has failed to show this process, and more data is needed to verify this connection. Other compensatory mechanisms are also stimulated by exercise. A study in rats showed that basal levels of gastrocnemius phosphorylated (p-rps6, p-4EBP1,

and p-AMPKα were similar between diets, although serum insulin, serum glucose, and several essential amino acid levels were lower in Low Carbohydrate Ketogenic Diet-fed(LCKD) rats(ROBERTS *et al.*, 2016). In addition, LCKD- and Western Diet-fed(WD) rats exhibited increased postexercise muscle protein synthesis levels, but no diet effect was observed(ROBERTS *et al.*, 2016). Constantly exercise-trained, LCKD- and WD-fed rats also presented similar increases in relative hind limb muscle masses compared with their sedentary counterparts, but there was no difference between-diet(ROBERTS *et al.*, 2016). On a very good described review, Paoli A. and colegues tryed to elucidate the possible mechanisms related to the maintenance of muscle mass in subjects submitted to KD. They described the overloaded regulatory systems controlling muscle hypertrophy as exercise effects that reflect in changes in protein synthesis and protein degradation, and several stimuli that lead to protein synthesis and subsequent muscle hypertrophy. They also discussed the diet carbo restriction involving reduction of some hormones and their signaling, concluding in the end that data provided by scientific literature suggest only a negligible or no effect of KD on muscle mass with concomitant resistance training(PAOLI *et al.*, 2019). The results in the present study corroborate with that hypothesis.

Conclusion

The present study systematically reviewed the literature to see if RT is an efficient tool in maintaining FFM in people who undergo carbohydrate-restricted diets that cause ketosis. Although there is not an expressive number of studies comparing groups under ketogenic diets with or without exercise, we were able to compare people submitted to resistance exercise with or without diets that cause ketosis. This meta-analysis indicated a small reduction in the lean mass of people submitted to ketogenic diets, a reduction that was reversed by carbohydrate reload or was described as a possible effect of water loss due to the characteristic of diets with low carbohydrate content. In addition, no work has

shown loss of muscle strength. These results strongly suggest that resistance physical exercise is an efficient tool in the preservation of lean mass in patients submitted to diets that cause ketosis. Works comparing people with or without exercise and submitted to carbohydrate-restricted diets are necessary to confirm this conclusion.

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4 Considerações finais

A presente dissertação resultou em uma revisão sistemática de trabalhos científicos baseados na investigação dos efeitos, sob a massa muscular livre de gordura, do treinamento resistido associado simultaneamente a dietas que causam cetose, em humanos. Para tal, foi desenvolvido um protocolo de pesquisa de trabalhos que foi utilizado em três bases mundiais de dados em saúde.

O resultado da pesquisa evidenciou que ainda existe um número bastante limitado de ensaios clínicos nos quais o objetivo era observar os efeitos sob a massa muscular livre de gordura da combinação entre dieta cetogênica e de treinamento resistido. Além disso, reforçando a necessidade da realização de mais estudos, ainda não há consenso sobre os resultados desta associação de fatores entre os autores. Contudo, apesar de escasso o número de estudos, foi possível realizar a comparação estatística entre pessoas submetidas a exercícios resistidos com ou sem dieta que causasse cetose.

O resultado conclusivo da metanálise indicou uma pequena redução na massa magra de pessoas submetidas a dietas cetogênicas. Entretanto, esta variação foi revertida pela recarga de carboidratos sendo descrita também como um possível efeito da perda de água devido à característica de dietas com baixo teor de carboidratos. Além disso, nenhum trabalho mostrou perda de força muscular provando que dietas cetogênicas podem ser utilizadas sem prejudicar o desempenho mecânico da força.

Sendo assim, os resultados sugerem fortemente que o exercício físico resistido é uma ferramenta eficiente na preservação da massa magra em pacientes submetidos a dietas que causam cetose.

Sendo a revisão sistemática uma ferramenta para a prática baseada em evidências, a conclusão deste trabalho pode auxiliar na tomada de decisão em situações em que haja possibilidade da utilização de treinamento resistido e dieta cetogênica simultaneamente a fim de reduzir possíveis riscos associados à redução de massa magra durante o emagrecimento.

Da mesma forma, o artigo resultante desta dissertação tem como objetivo fornecer subsídios para futuras reflexões de sua aplicação em situações concretas no cenário profissional.

Também é importante existirem mais trabalhos comparando pessoas com ou sem exercícios e submetidas a dietas restritas em carboidratos para confirmar definitivamente esta conclusão.

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