UNIVERSIDADE FEDERAL DE ALAGOAS
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INFLUÊNCIA DA RESTRIÇÃO DO PERÍODO ALIMENTAR E DIETA HIPOCALÓRICA SOBRE O PERFIL METABÓLICO E COMPOSIÇÃO CORPORAL DE MULHERES COM OBESIDADE EM VULNERABILIDADE SOCIAL

ISABELE REJANE DE OLIVEIRA MARANHÃO PUREZA

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Dissertação apresentada à Faculdade de Nutrição da Universidade Federal de Alagoas como requisito à obtenção do título de Mestre em Nutrição.

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por

ISABELE REJANE DE OLIVEIRA MARANHÃO PUREZA

A Banca Examinadora, reunida aos 06/09/2019, considera a candidata **APROVADA**.

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Dedico ao meu marido e companheiro Renato, aos meus pais, Rosa e Isnaldo, e à minha irmã Isadora, meus maiores incentivadores.

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RESUMO

Diante da prevalência de obesidade na população em vulnerabilidade social e a busca crescente por estratégias que facilitem adesão ao tratamento da obesidade, foi desenvolvida essa dissertação, a partir da realização de um ensaio clínico aleatório, no qual foram produzidos dois artigos de resultados. O primeiro artigo trata-se de um estudo observacional desenvolvido a partir dos dados da linha de base do ensaio clínico, intitulado como "*Agreement between equations-estimated resting metabolic rate and indirect calorimetry-estimated resting metabolic rate in low-income obese women*", teve por objetivo determinar a equação preditiva da taxa metabólica de repouso que mostra a maior concordância com a taxa metabólica de repouso obtida por calorimetria indireta em mulheres brasileiras obesas que vivem em vulnerabilidade social. Dentre as equações analisadas, nenhuma estimou satisfatoriamente a taxa metabólica de repouso por calorimetria indireta, no entanto, a equação a de Harris-Benedict apresentou maior concordância e a de Henry-Rees maior precisão, as quais podem ser consideradas na ausência de equações específicas. O segundo artigo trata-se do ensaio clínico intitulado como "*Acute effects of time-restricted feeding in low-income women with obesity submitted to hypoenergetic diets: randomized trial*", que tem como objetivo avaliar os efeitos agudos da restrição do período alimentar em mulheres com obesidade em vulnerabilidade social submetidas à dieta com um mesmo déficit energético. A perda de peso foi considerada como desfecho primário, enquanto os desfechos secundários envolviam: composição corporal (bioimpedância), sinais vitais (temperatura, pressão arterial e frequência cardíaca), apetite, dosagem de hormônios do eixo tireoidiano, leptina, insulina e glicemia, sendo estas últimas utilizadas para determinar sensibilidade a insulina, antes e após 21 dias de intervenção. Por ANOVA mista foram observadas interações significativas grupo x tempo apenas na temperatura axilar (-0,4°C; IC95% [-0,7 – -0,1]°C; p = 0,01) e no percentual de gordura corporal (0,75%; IC95% [0,0 – 1,4]%; p < 0,05), onde a restrição do período alimentar induziu a manutenção da temperatura axilar e à redução no percentual de gordura corporal em comparação a dieta hipoenergética, e pode ser considerada uma estratégia coadjuvante no tratamento da obesidade em mulheres em vulnerabilidade social. Diante do exposto, destacamos a dificuldade em determinar o gasto energético por meio de equações preditivas para população com obesidade e a relevância do presente estudo para auxiliar em intervenções nutricionais de forma eficiente. Assim como também consideramos que a restrição do período alimentar apresentou ser uma estratégia que pode contribuir para o tratamento da obesidade de mulheres em vulnerabilidade social ao contribuir no tratamento sem implicar em maiores custos pela inserção de novos alimentos que não correspondam ao padrão alimentar dessa população.

Palavras-chave: Obesidade. Peso corporal. Comportamento alimentar.

ABSTRACT

Given the prevalence of obesity in the socially vulnerable population and the growing search for strategies that facilitate adherence to obesity treatment, this dissertation was developed based on a randomized clinical trial in which two results articles were produced. The first article is an observational study based on baseline data from the clinical trial entitled “Agreement between equations-estimated resting metabolic rate and indirect calorimetry-estimated resting metabolic rate in low-income obese women”, the objective of this study was to determine the predictive equation of resting metabolic rate that shows the highest agreement with the resting metabolic rate obtained by indirect calorimetry in obese Brazilian women living in social vulnerability. Among the analyzed equations, none satisfactorily estimated the resting metabolic rate by indirect calorimetry; however, the Harris-Benedict equation presented greater agreement and the Henry-Rees equation had higher precision, which can be considered in the absence of specific equations. The second article deals with the clinical trial entitled as “Acute effects of time-restricted feeding in low-income women with obesity submitted to hypoenergetic diets: a randomized trial”, the objective of this study was to evaluate the acute effects of dietary restriction in obese women in social vulnerability submitted to the same energy deficit diet. Weight loss was considered as the primary outcome, while secondary outcomes involved: body composition (bioimpedance), vital signs (temperature, blood pressure, and heart rate), appetite, thyroid hormone dosage, leptin, insulin, and glycemia. The latter is used to determine insulin sensitivity before and after 21 days of intervention. Through a mixed ANOVA, significant group x time interactions were observed only at the axillary temperature (-0,4°C; IC95% [-0,7 – -0,1]°C; p = 0,01) and in body fat percentage (0,75%; IC95% [0,0 – 1,4]%; p < 0,05), where the time restricted-feeding induced the maintenance of axillary temperature and the reduction in body fat percentage compared to the hypoenergetic diet, and may be considered a supporting strategy in the treatment of obesity in socially vulnerable women. Given the above, we highlight the difficulty in determining energy expenditure through predictive equations for the obese population and the relevance of the present study to assist in nutritional interventions efficiently. As we also consider that the time-restricted feeding was a strategy that can contribute to the treatment of obesity of women in social vulnerability by contributing to treatment without implying higher costs for the insertion of new foods that do not correspond to the dietary pattern of this population.

Keywords: Obesity. Body weight. Eating behavior.

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LISTA DE ABREVIATURAS

ANOVA - Analysis of variance

BIA – Biompedância elétrica

BMI – Body mass index

BMR - Basal metabolic rate

CC – Circunferência da cintura

CCC - Correlation concordance coefficient

CCEB - Critério de Classificação Econômica Brasil

CI – Calorimetria indireta

CONSORT - Consolidated Standards of Reporting Trials

CREN - Centro de Recuperação e Educação Nutricional

DEXA - Absorciometria radiológica de dupla energia

EE – Energy expenditure

GC - Gordura corporal

GET - Gasto energético total

HD + TRF - Hypoenergetic diet with TRF

HDI - Human Development Index

HPT - Hipotálamo-pituitária-tireoide

IC - Indirect calorimetry

IMC – Índice de massa corporal

LEPR - Leptina receptors

LL - Lower limit

MET - Metabolic equivalent of task

MLG – Massa livre de gordura

MPE - Maximum Positive Error

MNE - Maximum Negative Error

OMS – Organização Mundial de Saúde

RCQ – Relação cintura-quadril

ReBEC - Registro Brasileiro de Ensaios Clínicos

RMR - Resting metabolic rate

RMSE - Root mean square error

SD – Standard deviation

SNC – Sistema nervosa central

TEE - Total energy expenditure

TMR – Taxa metabólica de repouso

TRF - Time-restricted feeding

UCPs - Uncoupling proteins

UL - Upper limit

WC – Waist circumference

WHO – World Health Organization

SUMÁRIO

1 INTRODUÇÃO GERAL

A obesidade é um problema de saúde pública a nível global, e pelas estimativas, a maioria da população mundial vive em locais em que causas relacionadas com a obesidade matam mais do que a subnutrição (WORLD HEALTH ORGANIZATION, 2018). Segundo dados publicados pelo Ministério da Saúde do Brasil (2019), o grupo populacional com maior prevalência de obesidade no país é o de mulheres de baixa escolaridade, correspondente a 27,8%, enquanto este valor é de apenas 14,4% nas mulheres no mais alto estrato de escolaridade. Em comparação com países da Organização para Cooperação e Desenvolvimento Econômico, tal grupo populacional ficaria na 8ª maior colocação em termos de prevalência de obesidade (THE ORGANIZATION FOR ECONOMIC CO-OPERATION AND DEVELOPMENT, 2017)

Investigações sobre estratégias alimentares simples e eficientes que facilitem a adesão dos pacientes ao tratamento para perda de peso se torna um campo frutífero para pesquisa (PAGOTO et al., 2013). Principalmente em indivíduos que apresentam um padrão de consumo alimentar monótono, condição comum em populações de baixa renda, que exibem baixa diversidade alimentar, com ingestão elevada de alimentos de alto índice glicêmico e alto teor lipídico, por comumente ser os alimentos de menor custo (FLORÊNCIO et al., 2015).

Uma estratégia que vem atraindo atenção de clínicos e pacientes é o jejum intermitente, que pode assumir várias formas, dentre elas a de promover períodos de jejum diários mais longos que o convencional jejum noturno, começando a partir de um período de jejum de 12 horas por dia, denominada restrição do período alimentar. Restringir o período de ingestão alimentar a poucas horas sem uma tentativa explícita de reduzir a ingestão calórica pode desencadear a fisiologia do jejum após algumas horas de cessação da alimentação (LONGO; PANDA, 2016). Esses efeitos do jejum em células humanas podem promover mudanças potentes nas vias metabólicas e nos processos celulares, como resistência ao estresse, lipólise, e estimulação da autofagia (MATTSON, 2014). Se realizado frequentemente, o jejum periódico diário ou alternativo pode exercer efeitos pleiotrópicos e se tornar uma estratégia de tratamento eficaz para várias doenças crônicas (LONGO; PANDA, 2016).

Acredita-se que a eficácia das intervenções com o jejum intermitente dependa não apenas da perda de peso, mas também o ajuste no período de consumo alimentar pode promover melhora nos marcadores associados à saúde cardiometabólica e na regulação do apetite (SUTTON et al., 2018). Em humanos, os estudos com restrição do período alimentar são mais escassos e os existentes não apresentam um grupo controle com restrição energética igual ao do grupo experimental visto que não se pode inferir que esses efeitos são determinados pela restrição energética global/perda de peso ou um efeito específico do regime de jejum intermitente (MATTSON et al., 2017).

Portanto, pretende-se com a realização desta investigação responder à seguinte questão: o período alimentar (com restrição versus sem restrição de horário) influencia no peso, composição corporal, taxa metabólica de repouso, apetite, sensibilidade à insulina, leptinemia e função tireoidiana de mulheres obesas, em vulnerabilidade social, submetidas a dietas com um mesmo déficit energético? Com a hipótese de que a restrição do período alimentar com restrição energética induziria uma maior perda de peso em relação a dieta, apenas, com restrição energética em mulheres com obesidade em vulnerabilidade social. Visto que, em modelos animais, existem evidências de que a restrição do período alimentar, pode contribuir para o controle e prevenção do diabetes, resistência à insulina e hipertensão arterial, envolvendo mecanismos de modulação hormonal e do gasto energético.

No entanto, há uma escassez de estudos com humanos obesos, atribuída ao receio de que a sensação de fome, comum nos diferentes tipos de jejum intermitente, seja uma limitação para o uso dessa intervenção nestes indivíduos (MATTSON et al., 2017). Além disso, a restrição do período alimentar para a população com obesidade que se encontra em vulnerabilidade social pode ser uma estratégia para o tratamento da obesidade, pois não implica na aquisição de gêneros alimentícios e, se apenas a modificação do horário de ingestão alimentar (em conjunto com as possíveis, porém limitadas, modificações qualitativas) promover benefícios na composição corporal e no perfil metabólico, já contribuirá positivamente como mais um recurso terapêutico.

Sendo assim, o presente estudo tem como objetivo identificar a influência da restrição do período alimentar e dieta hipocalórica sobre o perfil metabólico e composição corporal de mulheres com obesidade em vulnerabilidade social.

Esta dissertação está dividida em: (a) um capítulo de revisão da literatura, em que serão abordados os aspectos epidemiológicos e metabólicos da obesidade e do jejum intermitente, mais especificamente da restrição do período alimentar, como coadjuvante no tratamento da obesidade; b) dois artigos de resultados: i) *Agreement between equations-estimated resting metabolic rate and indirect calorimetry-estimated resting metabolic rate in low-income obese women*.e ii) *Acute effects of time-restricted feeding in low-income women with obesity submitted to hypoenergetic diets: randomized trial.*

2 REVISÃO DA LITERATURA

2.1 Obesidade

2.1.1 Definição e aspectos epidemiológicos

O excesso de peso, sobrepeso e obesidade, é definido pela Organização Mundial de Saúde (OMS) (2018) como o acúmulo anormal ou excessivo de gordura, que implica em efeitos deletérios à saúde. No ano de 2016, os dados mundiais apontavam que 39% dos adultos acima de 18 anos (39% dos homens e 40% das mulheres) se encontravam acima do peso, e no geral, cerca de 13% da população adulta (11% dos homens e 15% das mulheres) apresentavam a condição de obesidade (OMS, 2018). Se a tendência de crescimento na prevalência de obesidade se mantiver, estima-se que em 2025, a prevalência global de obesidade nas mulheres ultrapassará 21% (DI CESARE et al., 2016). No Brasil, dados recentes de uma pesquisa nacional (MINISTÉRIO DA SAÚDE, 2019), revela que a frequência de adultos obesos é de 19,8%, em ambos os sexos, com uma menor frequência nos adultos com até 34 anos de idade e ligeiramente maior entre as mulheres (20,7%) do que entre os homens (18,7%). Além disso, entre as mulheres, a frequência de obesidade diminui de forma acentuada com o aumento da escolaridade, em que 27,8% das mulheres que se encontram no menor estrato de escolaridade são classificadas com obesidade.

Considerada uma epidemia e, consequentemente um problema de saúde pública, a obesidade gera impactos negativos na economia ativa do país pelo fato de estar diretamente associada as doenças crônicas e agravos não transmissíveis, tais como: diabetes mellitus, hipertensão arterial, doença arterial coronariana, acidente vascular encefálico, alguns tipos de câncer, apneia obstrutiva do sono e osteoartrite. Situações estas que geram aposentadorias precoces por invalidez e afastamentos temporários, especialmente em decorrência de doenças cardiovasculares (GRAY et al., 2018) e implica em maiores custos para o sistema único de saúde (BAHIA et al., 2012).

A etiologia da obesidade é multifatorial e resulta de interações entre fatores genéticos, metabólicos, comportamental e ambiental (AMUNA; ZOTOR, 2008). Esses fatores podem ser classificados como: não modificáveis (genética e história familiar) e modificáveis (ingestão alimentar e atividade física). Além dessa classificação, as circunstâncias socioeconômicas como a pobreza também contribuem para a etiologia da obesidade (GRAY et al., 2018). O aumento dramático na prevalência dessa condição sugere que os componentes comportamentais e ambientais sejam os principais fatores responsáveis pelo surgimento da obesidade, com ênfase na alimentação e no exercício (AMUNA; ZOTOR, 2008).

A alimentação da sociedade moderna converge para o padrão alimentar denominado ocidental, a qual é caracterizada por ingestão de alimentos com alta densidade energética derivada de níveis elevados de lipídeos e carboidrato (SWINBURN et al., 2011; VANDERVIJERE et al., 2015). Embora multifatorial, devido à complexidade dos diversos mecanismos fisiológicos e fenômenos sociais que influenciam no estabelecimento da obesidade, a maioria deles culminam na maior ingestão energética em relação ao gasto energético, o que tem sido determinante para seu surgimento (RICHARDSON et al., 2015; SMITH; SMITH, 2016). Além disso, a inatividade física também é vista como um dos principais contribuintes para a epidemia da obesidade devido ao aumento da motorização e mecanização, maior tempo gasto em frente às telas e a diminuição do transporte e da atividade física ocupacional (MCCORMARCK; VIRK, 2014).

2.1.2 Diagnóstico nutricional

A massa corporal relacionada a distribuição de gordura é mais preditiva de saúde do que somente a massa corporal relacionada ao peso. De fato, a combinação de massa corporal e distribuição de gordura é, provavelmente, a melhor alternativa para uma avaliação clínica completa. No entanto, não há avaliação única para sobrepeso e obesidade, pelo fato da variação presente está associada aos fatores étnicos e genéticos (ABESO, 2016).

2.1.2.1 Indicadores antropométricos

O índice de massa corporal (IMC) é um índice simples de peso-por-altura, comumente utilizado para classificar sobrepeso e obesidade em adultos e em nível populacional. É definido como o peso de um indivíduo em quilogramas dividido pelo quadrado da sua altura em metros (kg/m^2), e determina obesidade quando assume um valor maior ou igual a 30. No entanto, deve ser considerado um guia aproximado, por não corresponder ao mesmo grau de adiposidade em diferentes indivíduos (WORLD HEALTH ORGANIZATION, 2000). Essa medida foi descrita pela primeira vez por Adolphe Quetelet em meados do século XIX, baseado em observações de que o peso corporal era proporcional ao quadrado da estatura em adultos com estruturas corporais normais (KHOSLA; LOWE, 1967).

Outras medidas que compõem a avaliação antropométrica são as mensurações das circunferências: circunferência abdominal e circunferência do quadril. A medida da circunferência abdominal reflete melhor o conteúdo de gordura visceral e total, e de acordo com o *National Cholesterol Education Program (NCEP) – Adult Treatment Panel III* (ATP-III), o ponto de corte deve ser de 102 cm para homens e 88 cm para mulheres (LIPSY, 2003). A relação circunferência cintura/quadril (RCQ) foi inicialmente, a medida mais comum para avaliação da obesidade central (POLIOUT et al., 1994). Tipicamente correlacionada com risco cardiometabólico, mas, há aproximadamente 20 anos se reconheceu sua menor validade como medida relativa (MYINT et al., 2014; KONING et al., 2007).

Outra mensuração, como a relação cintura-estatura vem sendo considerada nos últimos anos como um melhor preditor de risco de mortalidade para ambos os sexos quando comparada ao IMC, ao assumir que a circunferência abdominal deve ser menor que a metade da estatura, com o ponto de corte delimitado em 0,5. No qual, a relação cintura-estatura se torna uma medida simples para avaliação do risco associado ao estilo de vida e excesso de peso em adultos (ASHWELL et al., 2012; ASHWELL et al., 2014; ASHWELL; GIBSON, 2016).

As avaliações antropométricas são simples e baratas, mas não são fáceis de realizar nem confiáveis o suficiente para serem usadas em pacientes gravemente obesos, por exemplo, o que limita sua aplicabilidade (DAS, 2005).

2.1.2.2 Composição corporal

Em obesos, a avaliação da composição corporal é cercada de limitações devido ao seu tamanho físico e as variações na composição corporal em relação ao peso normal, o que repercute na dificuldade em utilizar alguns equipamentos e nas características dos métodos (DAS, 2005). Apesar da boa correlação entre IMC e percentual de gordura corporal (GC), a acurácia do IMC para diagnosticar obesidade é limitada, particularmente para indivíduos nos intervalos intermediários de IMC. Medidas diretas, mas simples, de massa gorda corporal e medidas de distribuição de gordura corporal, podem ser úteis nesses indivíduos para estratificá-los ainda mais de acordo com seu nível de gordura corporal (ROMERO-CORRAL, 2008).

Embora, a avaliação do percentual de gordura por meio de dobras cutâneas seja utilizada como uma técnica indireta de avaliação da composição corporal e apresente um menor custo financeiro, não é aconselhável para aferir o grau de adiposidade em indivíduos obesos, pelo fato da gordura subcutânea não ser facilmente separada do músculo, além da amplitude limitada do adipômetro nessa população, o que compromete a exatidão da medida e subestima o total de gordura (JACKSON; POLLOCK, 1985; LUTOSLAWSKA et al., 2014). Além da influência de outros fatores, como a habilidade do avaliador, o material e a técnica utilizada, assim como o nível de hidratação do paciente (MARTIN et al., 1992).

O padrão-ouro para medidas de composição corporal em pessoas obesas tem considerado a absorciometria radiológica de dupla energia (DEXA). No entanto, é um métodoaltamente dispendioso, o que dificulta sua utilização para mensurar composição corporal. Como alternativa, a análise por impedância biolétrica (BIA) é uma técnica comumente aplicada para este fim, por ser um método não invasivo, barato, simples, rápido e portátil (NATIONAL INSTITUTES OF HEALTH, 1996).

A BIA envolve o uso de eletrodos em diferentes partes do corpo humano, geralmente na mão e no pé, abrangendo todo o corpo. O instrumento de impedância envia uma alternância inofensiva e imperceptível corrente elétrica através de um par de eletrodos e mede como o corpo impede o fluxo de corrente através de um segundo par de eletrodos. A oposição (impedância Z) ao fluxo de corrente varia de tecido para tecido; em que se observa baixa impedância nos tecidos com maior teor de líquidos e eletrólitos, devido a sua alta condutividade, enquanto gordura e osso pela sua baixa condutividade apresentam alta impedância. O dispositivo mede essa impedância ao fluxo da corrente quando passa pelo corpo, com base nessas medidas, a BIA usa equações de predição que fornecem estimativas dos parâmetros de composição corporal. Apesar de uma ampla variedade de dispositivos de medição de BIA comercialmente disponíveis, eles são todos baseados nos mesmos princípios físicos (KYLE et al., 2004).

Ainda assim, esse método também pode ter seus resultados comprometidos em indivíduos obesos, pela quantidade relativamente elevada de água extracelular e água corporal total, o que pode superestimar a massa livre de gordura e subestimar a massa gorda, por esse motivo deve ser usada com cautela (COPPINI et al., 2005; ROMERO-CORRAL, 2008).

2.1.3 Regulação hormonal e gasto energético na obesidade

O peso corporal é regulado no sistema nervoso central (SNC), principalmente no hipotálamo, através de sinais hormonais periféricos liberados do trato gastrointestinal, pâncreas e tecido adiposo, todos esses integrados a fim de regular a ingestão de alimentos e o gasto de energia (SCHWARTZ et al., 2000).

O hormônio tireoidiano é um importante determinante do gasto energético e contribui para a regulação do apetite, no entanto, pode ser influenciado pelos produtos secretados pelo tecido adiposo que atuam no SNC, o que pode ter impacto na atividade do eixo hipotálamo-pituitária-tireoide (HPT) (BIONDI, 2010). É conhecido que os níveis de TSH aumentam com o acúmulo de adiposidade em sujeitos eutireoidanos, abrangendo uma vasta gama de IMC (DE MOURA; SICHIERI, 2011). O envolvimento da adiposidade com os hormônios tireoidianos repercute nas baixas concentrações de T4 livre e valores normais ou elevados de T3 livre, associado ao aumento do IMC (MARZULLO et al., 2016). Todavia, um déficit calórico, tanto em indivíduos magros quanto obesos, é caracterizado por uma redução no T3 e um aumento concomitante no T3 reverso na circulação, em que estes efeitos aparecem relacionados tanto ao conteúdo calórico quanto à composição da dieta. Os mecanismos responsáveis ainda são desconhecidos, embora o principal sinal neuroendócrino que rege a resposta do eixo HPT à adiposidade envolve ações da leptina na atividade do hormônio tireotrófico no encéfalo e no rombencéfalo (SANTINI et al., 2014).

O tecido adiposo tem um papel fundamental que se estende além do peso corporal para abranger interações com o eixo endócrino hipotálamo-hipófise (FIELD, 2014). Dentre as adipocinas secretadas pelo tecido adiposo, a leptina é produzida predominantemente pelos adipócitos em proporção à massa gorda corporal, seus níveis transmitem informações sobre as reservas de energia aos centros que regulam a homeostase energética. Depósitos adiposos elevados estão associados a balanço energético positivo, que normalmente induzem uma resposta para reduzir a alimentação e promover o gasto energético (FRIEDMAN; HALAAS, 1998). Baixos níveis de leptina aumentam a ingestão de alimentos e suprimem o gasto de energia, ambos os quais tendem a restaurar os estoques de energia esgotados. Como a obesidade é definida pela massa adiposa elevada, as concentrações de leptina aumentam, esse evento acontece por uma série de mecanismos potenciais que limitam a sinalização de leptina com seu receptor (LEPR) (por exemplo, inibidores da via de sinalização de receptores de leptina, a ativação de vias de sinalização inflamatórias e citocinas ou estresse do retículo endoplasmático no hipotálamo, ou gliose hipotalâmica), que têm sido associado a prejuízos na sinalização de LEPR na obesidade e, assim, permitir balanço energético positivo (PAN; MYERS JR, 2018).

Assim como a leptina, os níveis de insulina são proporcionais a adiposidade e atua por meio de ação central no hipotálamo, em que é secretada pelas células beta das ilhotas de Langerhans na porção endócrina do pâncreas e participa da homeostase energética e da glicose no metabolismo periférico (SCHWARTZ, 2000). O aumento agudo da insulina circulante é induzido pela ingestão de alimentos, visto que a insulina desempenha um papel regulador no acúmulo lipídico de adipócitos brancos, promovendo o armazenamento de nutrientes nos tecidos alvos periféricos, por atuar inibindo a lipólise e promovendo a síntese de ácidos graxos e triglicerídeos (lipogênese) e estimulando a expressão de genes envolvidos na captação e armazenamento de lipídios (CZECH et al., 2013; TEMPLEMAN et al., 2017).

Os níveis elevados de insulina estão associados com a obesidade, caracterizando o quadro de resistência à insulina, que pode resultar do comprometimento das suas vias de sinalização (KONNER; BRUNNING, 2012). A obesidade é considerada uma inflamação de baixo grau que envolve a ativação do NFκB, que quando livre se transloca para o núcleo da célula e se liga a genes alvo, estimulando mediadores inflamatórios (TNFα, IL-1B, IL-6, PKC) envolvidos na aterogênese, essas citocinas causam fosforilação da serina no IRS-1 e inibe a sinalização da insulina, causando resistência à insulina (ROGERO; CALDER, 2018).

Estabelecer uma avaliação adequada do gasto energético inclui determinar as necessidades individuais a partir da Taxa Metabólica de Repouso (TMR) calculada por equações preditivas ou determinada por calorimetria indireta (CI), que combinadas com o nível de atividade física e a ingestão habitual avaliada, contribui para intervenção nutricional mais adequada (PSOTA, CHEN, 2013). A calorimetria indireta é considerada padrão ouro para estimar TMR, a partir da determinação do volume de oxigênio e dióxido de carbono, com a suposição de que a energia química de um substrato é obtida após sua completa oxidação com o consequente consumo de oxigênio e liberação de dióxido de carbono e água (REDONDO, 2015).

A TMR está bem estabelecida como o principal componente do gasto energético total (GET) diário, representando 50-75% do total do gasto energético (WEIGLE, 1994). Um dos principais determinantes para a TMR é a composição corporal, mais especificamente o que se entende por massa livre de gordura (MLG), que envolve osso, massa muscular esquelética e demais órgãos metabolicamente ativos, como cérebro, coração, fígado, rim e trato gastrointestinal (HEYMSFIELD et al., 2002). Portanto, qualquer diferença na composição corporal pode afetar diretamente os valores do gasto energético (JOHNSTONE et al., 2005).

O tecido adiposo é consideravelmente um tecido com menor atividade metabólica em relação a MLG, embora não seja metabolicamente inerte (GALLAGHER et al., 2006). Na obesidade, o ganho de peso se deve principalmente ao tecido adiposo, que minimamente contribui para elevação global do gasto energético (KAIYALA et al., 2010). A MLG aumenta concomitantemente com o aumento da massa gorda (para suportar o excesso de peso corporal), contribuindo assim para o aumento dos requerimentos energéticos (HORGAN;

STURBBS, 2003). Em contrapartida, a intervenção com restrição energética reduz drasticamente o gasto energético em repouso, tanto de indivíduos magros quanto em obesos, como consequência de perdas iniciais na MLG e progredindo para perda de fase tardia na massa gorda (CAMPS; VERHOEF; WESTERTERP, 2013).

2.2 Intervenção nutricional na obesidade

2.2.1 Restrição energética

A restrição de energia é implementada com o intuito de alcançar e manter um peso corporal saudável, sendo determinada como pedra angular no tratamento da obesidade e dos fatores de risco cardiometabólicos concomitantes, vários dos quais fazem parte da síndrome metabólica, como níveis lipídicos, glicêmicos e pressóricos (PÉREZ-MARTINEZ et al., 2017). As recomendações, em sua maioria, apoiam a intervenção por meio de restrição energética contínua, caracterizada pela redução diária consistente no consumo de energia, geralmente envolvendo reduções de 30 a 40% (ANSON et al., 2003). No entanto, a restrição energética e o processo de perda de peso corporal estão associados a um declínio na taxa metabólica de repouso, em que essas mudanças nas vias neurobiológicas favorecem a resistência na perda de peso e a recuperação do peso, o que implica na dificuldade dos pacientes em aderir a esse tipo de intervenção (GREENWAY, 2015). Mesmo após o aumento nas intervenções nutricionais de baixo teor calórico, o insucesso persiste pela dificuldade significativa em aderir, principalmente por longos períodos de tempo (HEYMSFIELD et al., 2007; SCHEEN, 2008).

2.2.2 Jejum intermitente

Ultimamente, o jejum intermitente ganhou popularidade como uma alternativa à restrição calórica, em contraste com os paradigmas tradicionais, ao envolver uma abordagem dietética que requer jejum por períodos variados de tempo, normalmente por 12 horas ou mais (LONGO; PANDA, 2016). É importante ressaltar que a evolução nos sistemas metabólico, endócrino e nervoso permitiu altos níveis de desempenho físico e mental durante o estado de jejum (LONGO; MATTSON, 2014).

Os efeitos metabólicos proporcionados pelo estado de jejum, que inicia tipicamente 12 horas após cessação da ingestão de alimentos, impulsiona as respostas fisiológicas dos principais sistemas orgânicos, incluindo o sistema musculoesquelético no início da mudança metabólica: o ponto de balanço energético negativo promove depleção dos estoques de glicogênio hepático e após esgotamento dessas reservas, os ácidos graxos são mobilizados, levam ao aumento na produção de cetonas e preservam massa muscular e sua função. Assim, os regimes de jejum intermitente que induzem a troca metabólica têm o potencial de melhorar a composição corporal em indivíduos com excesso de peso (ANTON et al., 2018).

Isto pode ser observado em estudos de jejum intermitente, incluindo indivíduos eutróficos e com excesso de peso, ao exibirem resultados satisfatórios na perda de peso e melhorias em múltiplos indicadores de saúde, abrangendo resistência à insulina e redução nos fatores de risco cardiovascular (MATTSON; LONGO; HARVIE, 2017; SUNDFOR; SVENDSEN; TONSTAD, 2018; SUTTON et al., 2018).

No entanto, ensaios clínicos avaliando o impacto dos vários protocolos de jejum na saúde metabólica são extremamente limitados (HUTCHINSON; HEIBRONN, 2016; TEMPLEMAN et al., 2018). O padrão alimentar envolvendo restrição energética intermitente tem sido usado por razões de saúde e religião por milhares de anos (FARIAS et al., 2012). Entretanto, o jejum intermitente é um termo "guarda-chuva" usado para descrever diferentes formas de jejum, incluindo jejum de dias alternados, jejum periódico, restrição do período alimentar e jejum Ramadã (HORNE; MUHLESTEIN; ANDERSON, 2015).

O jejum de dias alternados (*Alternate day fasting – ADF)*, consiste em consumir nenhuma caloria nos dias de jejum e alternar dias de jejum com dias de ingestão alimentar *ad libitum*. Esse regime apresenta uma variação denominada jejum modificado em dias alternados (*Alternate-day modified fasting - ADMF*), que envolve o consumo de menos de 25% das necessidades energéticas nos dias de "jejum" alternada a ingestão alimentar sem restrições. Outra forma é o jejum periódico ou 5:2, padrão alimentar que consiste em jejuar apenas 1 a 2 dias por semana e permite o consumo *ad libitum* em 5 a 6 dias por semana (ANTON et al., 2018). Já o Ramadã, é uma prática religiosa no qual se realiza o jejum com aproximadamente 12 horas de duração, ao consumir uma grande refeição após o pôr do sol e uma refeição mais leve antes do amanhecer durante o mês sagrado do Ramadã. Enquanto a restrição do período alimentar (*Time-restricted feeding -TRF*) permite a ingestão de energia dentro de prazos específicos, induzindo intervalos de jejum regulares e prolongados (PATTERSON; SEARS, 2017).

2.2.2.1 Restrição do período alimentar

A restrição do período alimentar implica restringir a ingestão de alimentos a períodos de tempo específicos do dia, normalmente entre 8 e 12 horas por dia, rotineiramente (ANTON et al., 2017). Estudos de menos de três refeições por dia são exames indiretos de períodos prolongados de jejum diários ou noturnos (PATTERSON et al., 2015). Dentre os regimes de jejum intermitente, a restrição do período alimentar é uma nova alternativa que permite a alimentação *ad libitum* dentro de uma grande janela de tempo por dia e não requer qualquer contagem de calorias (CHAIX et al., 2014; LONGO; PANDA, 2016).

Muitos dos estudos publicados envolvem modelos animais, mais especificamente experimentos com camundongos, submetidos a alimentação com restrição do período em que foram observadas reduções no peso corporal, nos níveis de colesterol total, triglicerídeos, glicose, insulina, interleucina-6 (IL-6) e TNF-α, além de melhorias na sensibilidade à insulina (PATTERSON et al., 2015). Em humanos, as evidências acumuladas sugerem que a restrição do período alimentar é um meio eficaz para o déficit de peso corporal, mantendo a massa magra em peso normal, com relatos também em indivíduos com excesso de peso (GIL; PANDA, 2015, MORO et al., 2016; TINSLEY et al., 2017). Mais recentemente, foi demonstrado que a restrição do período alimentar também pode ser eficaz para perda de peso em adultos com obesidade, sendo mais uma estratégia no combate à obesidade (GABEL, 2017).

3 COLETÂNEA DE ARTIGOS

3.1 ARTIGO DE RESULTADOS 1

PUREZA, IROM; MACENA, ML; SILVA JUNIOR, AE; PRAXEDES, DRS; VASCONCELOS, LGL; FLORÊNCIO, TMMT; BUENO, NB**. Agreement between equations-estimated resting metabolic rate and indirect calorimetry-estimated resting metabolic rate in low-income obese women.** Submetido ao periódico *Archives of endocrinology and metabolism* (Classificação B1, segundo os critérios do sistema Qualis da CAPES/Área de Nutrição).

AGREEMENT BETWEEN EQUATIONS-ESTIMATED RESTING METABOLIC RATE AND INDIRECT CALORIMETRY-ESTIMATED RESTING METABOLIC RATE IN LOW-INCOME OBESE WOMEN

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AGREEMENT BETWEEN EQUATIONS-ESTIMATED RESTING METABOLIC RATE AND INDIRECT CALORIMETRY-ESTIMATED RESTING METABOLIC RATE IN LOW-INCOME OBESE WOMEN

Abstract

Background: Indirect calorimetry is established as a gold standard to determine the resting metabolic rate (RMR), however, its clinical use is limited, especially in low-income settings. Thus, the use of predictive equations appear as an alternative to estimate the RMR, but its precision is debatable, especially in obese individuals and in populations without specifically developed equations. Objectives: To evaluate the agreement between the RMR estimated by equations and by indirect calorimetry in low-income obese women. Method: A cross-sectional study with adult and obese women, which estimated the RMR by indirect calorimetry and compared with 13 predictive equations using the concordance correlation coefficient, root mean square error (RMSE) and Bland-Altman methods. The maximum allowed differences were predefined as 10%. Results: no equation presented its confidence intervals for the Bland-Altman limits of agreement inside the predefined acceptable range. The Harris-Benedict equation achieved better agreement (bias of 2.9% and RMSE of 274.3kcal) whereas the Henry-Rees equation achieved better precision (42.3% of the sample within the 10% maximum allowed difference). Conclusion: none of the studied equations satisfactorily estimated the RMR estimated by indirect calorimetry. In the absence of specific equations for this population, the use of the Harris-Benedict and Henry-Rees equations could be considered.

Introduction

Obesity is a worldwide public health problem and is associated with increased morbidity and mortality (1). In Brazil, data from a national survey revealed that the prevalence of obesity in women with up to 8 years of schooling is 27.8%, while in those with 12 or more years of schooling it is 14.4%, highlighting that women in the lowest stratum of schooling, and presumably income, are the most vulnerable group for the development of obesity (2). When compared to countries from the Organization for Economic Cooperation and Development, the obesity prevalence of 25.5% in low-income Brazilian women would be ranked as the 8th highest (3).

Despite the complexity of the various physiological mechanisms and social phenomena that influence the establishment of obesity, most of them culminate in the greater individual energy intake in relation to the energy expenditure (EE) (4). Hence, for the prevention or treatment of obesity, it is important to adequately determine both energy intake and energy expenditure. Energy expenditure involves basal metabolic rate, thermic effect of food or diet-induced thermogenesis and physical activity, which may be influenced by several factors, including age, body composition, body and ambient temperature, health condition, use of medications, thyroid hormones and catecholamines (5). In addition, the environment in which the individual is inserted may influence his EE, as some studies have reported an inverse association between socioeconomic status and sympathetic nervous system activity, by increasing the circulating catecholamine and cortisol levels (6). Furthermore, it was recently reported that lower socioeconomic status, alongside with higher psychosocial stress and systemic inflammation, induces a greater activity of the cerebellar tonsils, which is considered a measure of stress associated with neural activity (7). Another factor that may influence the resting metabolic rate (RMR) in this population is a possible perinatal malnutrition, which can lead to important metabolic adaptations in adulthood, manifested as short stature, which is common in many developing countries that have experienced nutritional transition, and is associated with obesity, especially in low-income populations (8). Early malnutrition is believed to influence energy homeostasis, leading to a reduction in energy requirements and central nervous system modifications that may facilitate fat accumulation (9).

An adequate evaluation of the individual energy expenditure is usually achieved by estimating the RMR, which may be calculated through the use predictive equations or determined by indirect calorimetry (IC), which must be combined with the physical activity level to determine the total energy expenditure of the individual (5). Although IC is established as the gold standard for the determination of RMR, its clinical use is limited, especially in low-income settings, because it is a costly method, in addition to the limitations related to the qualification of the personnel and logistic issues (10), turning its use almost impossible in socially vulnerable populations. In this way, the use of predictive equations appears like a feasible alternative to estimate RMR, considering that it commonly demands trivial parameters of the individuals such as age, weight, and height. However, the choice of a predictive equation that is accurate, especially in individuals with obesity, is still debatable. Equations developed for individuals with obesity prove to be inadequate to adequately predict their RMR as its results become less accurate as body mass index (BMI) increases (11). In addition, the heterogeneity between the studied populations used to derive the equations and the populations that need the most to use predictive equations, such as the low-income ones, may further increase the imprecision found in these equations.

Therefore, the present study aimed to determine the predictive equation of RMR that shows the highest agreement with RMR obtained by indirect calorimetry in Brazilian obese women living in social vulnerability.

Materials and Methods

The research was approved by the Research Ethics Committee of the Federal University of Alagoas (number 2 535.99). All participants were informed about the procedures and signed written informed consent form before starting the study, making their formal participation. The present study is a substudy of a randomized clinical trial still in progress, registered in the Registro Brasileiro de Ensaios Clínicos (ReBEC) under number RBR-387v6v.

POPULATION AND SAMPLE

Women with obesity, aged 19-44 years and classified as economic class “C” and “D-E”, as determined by the Critério de Classificação Econômica Brasil (CCEB), Brazil's economic classification criteria, were included (12). The CCEB is an instrument consisting of questions about assets, household employees, housing data, head of household instruction, access to piped water and paved street, where each item yields a different score. According to the achieved score, individuals are classified into 6 classes that vary from "A", the highest one, to "D-E", the lowest one. Also, data on ethnicity were collected and participants self-reported whether they considered their skin color to be white (Caucasian), black (African descent), brown, yellow (oriental) or indigenous. Obesity was defined by the presence of two of the following criteria: BMI ≥ 30 kg/m^2 and < 45 kg/m^2, waist circumference (WC) $\geq$ 88cm, body fat percentage $\geq 35\%$). Women who were on chronic (anti-diabetic, antihypertensive, antiretroviral, immunosuppressive, anti-depressant) medications who were at menopause, pregnant or breastfeeding, or had undergone any surgical intervention for weight loss were not included. Sampling was non-probabilistic for convenience and recruitment occurred through advertisements in the community or direct invitation to women who had some link with the Center for Recovery and Nutritional Education (CREN-AL), which treats malnourished children, located in the 7th administrative region of the municipality of Maceió-AL and has the lowest Human Development Index (HDI) of the municipality (0.65).

ANTHROPOMETRIC EVALUATION AND BODY COMPOSITION

An anthropometric evaluation was performed with weight and height data collection. The participants' weight was measured on a digital scale and the height was measured by means of a standardized wall stadiometer. The BMI was calculated and classified according to the World Health Organization. The percentage of body fat was estimated by means of four-pole electric bioimpedance Sanny BI 1010 (Sanny, São Paulo, SP). For the test, 4 electrodes were fixed in the right hemibody of the patients who were lying in the supine position, using light clothes, barefoot and without metallic props (13). Participants were instructed not to perform any physical activity and to abstain from drinking in the 24 hours prior to the test and to perform a 10-hour fast.

ESTIMATION OF THE RMR BY INDIRECT CALORIMETRY

RMR was estimated using a gas analyzer (Quark, Cosmed, Rome, Italy). The participants were taken by car to the Federal University of Alagoas Laboratory of Applied Sports Sciences, the collection took place in the morning (between 07:00 and 09:00 hours), in a quiet environment, with low light and comfortable temperature for participants (22-26 °C), following the same preparation for bioimpedance, since the measurements were performed in the same moment. The equipment was calibrated before each test session according to the manufacturer's specifications, with gases in the concentration of 20.9% O2 and 5% CO2, and a 3 L syringe, with the secondary pressure gauge adjustable between 40 and 60 psi.

On this occasion, measurements of axillary temperature using a digital thermometer and heart rate using a tensiometer were collected to avoid calorimeter measurements in individuals with signs of hyperthermia (> 37.5ºC) or tachycardia (> 100bpm). Participants were asked to wear the equipment's silicone mask, and thus the inspired volumes of expired oxygen and carbon dioxide were counted for 15 minutes. The first five minutes were discarded to avoid discrepancies due to the location and use of the silicone mask and data were collected every 1 minute (14). After measuring the oxygen and carbon dioxide volumes in liters per minute, the equation proposed by Weir was used to estimate the RMR.

ESTIMATION OF THE RMR BY PREDICTIVE EQUATIONS

The studied equations were selected based on the clinical practice use for obese women and also those specifically developed for the Brazilian public. Thirteen equations were included: Anjos et al (15), Bernstein et al (16), FAO/WHO/UNU (17), Harris-Benedict (18), Henry-Rees (19), Horie et al (20), Mifflin et al (21), Owen et al (22), Oxford (23), Rodrigues et al (24), Schofield (25), Siervo et al (26) e Weijs & Vansant (27). In the present study, we used equations that estimate the basal metabolic rate (BMR) or the RMR, since these are used for the same purpose in clinical practice and often used interchangeably in scientific studies (5). Information on equation formulas is given in Table 1.

PHYSICAL ACTIVITY

The physical activity level was measured using a triaxial accelerometer (ActivPAL®, Glasgow, UK), which was placed in the frontal area of the thigh of the participants, in the medium point between the inguinal line and the upper edge of the patella, with two transparent, hypoallergenic medical dressings (VitaMedical®, Minas Gerais Brazil) to avoid contact of the device with the skin of the participants. The women used the accelerometers for 3 consecutive days without removal for any activity. The data was transferred to the ActivPAL3 ™ software version 7.2.32 to yield the intensity and duration of each activity performed by the individuals. The system estimates the physical activity for the period in which the device was used and the calculation is based on acceleration from three body axes: anteroposterior, lateral and vertical, by means of computing the periods that the individual spent lying down/sitting down, standing, walking and running at every tenth of a second. The activPAL software provides an indirect estimate of METs based on default values for sitting/lying (1.25 MET), standing (1.40 MET) and stepping at 120 steps per minute (4 MET).

For cadences that differ from 120 steps per minute, the following equation is used to calculate the MET estimate: MET.h = (1.4 x *d*) + (4 - 1.4) x (*c* / 120) x *d*, where *c* is the cadence (steps per minute) and *d* is the duration of the activity (in hours). Software analysis of accelerometer data provides the MET value for the entire period that individuals used, multiplying the MET value for each activity by the duration of the activity. MET is defined as an amount of oxygen consumed while at rest, which corresponds to 3.5 ml of O_2 per kg of body weight x min or as 1 kcal/kg/hour and is roughly equal to the cost of sitting quietly. This concept, while simple, can express the energy expenditure of physical activity as a multiple of RMR, regardless of the individual's characteristics and type of activity.

STATISTICAL ANALYSIS

The methods for assessing the agreement between the equations-RMR and the IC-RMR were: (a) the method proposed by Bland and Altman (28), where the percentage differences were used in order to reduce the proportionality bias. Concordance limits and their 95% confidence intervals were calculated and the maximum allowed difference was predefined as an acceptable limit of agreement of ± 10% (29,30), which was also used to determine the precision, i.e. the percentage of participants with the equation-RMR result with a bias lower than 10% compared to the IC-RMR. In addition, in order to evaluate which equation-RMR presented no significant bias in relation to the IC-RMR, a “t” test for paired samples was performed; (b) the correlation concordance coefficient (CCC), obtained by multiplying the Pearson's correlation coefficient by the accuracy (deviation between the 45º line and the best fit line) for each pair was calculated. The CCC is generally classified as poor (≤ 0.20), fair (0.21 - 0.40), moderate (0.41 - 0.60), good (0.61 - 0.80) and very good (0.81 - 1.0); (c) the root mean square error (RMSE) between the IC-RMR and each equation-RMR, with the interpretation that the lower values show better agreement between the methods. In addition, to explore the influence of ethnicity, BMI and met.hour on the bias of each equation, we performed Kruskal-Wallis test, Pearson correlations, and Spearman correlations. To observe the influence on weight-adjusted RMR, multivariable linear regression was performed. All analyses were performed using the statistical package MedCalc Statistical Software v. 16.4 (MedCalc Software bvba, Oostende, Belgium) and an alpha value of 5% was adopted.

In regards to sample size, as this is study uses the baseline data of a randomized clinical trial, the sample size calculation was not delineated considering the present analyses. An *a posteriori* calculation, based on the equation with the lowest RMSE in the present study, and that considered the mean and the standard deviation of the differences between the estimated-RMR and the IC-RMR, a power of 80%, an alpha of 5% and the present sample size of 59 was conducted to estimate the maximum allowed difference of the limit of agreement that should be considered in the present study.

Results and Discussion

Fifty-eight obese women were included and their characteristics are present in Table 2. The assessment of the agreement between the RMR by the predictive equations and the RMR measured by the IC of the women is presented in Table 3. Among the 13 equations analyzed, it was observed significant bias in five: Anjos et al (15), Bernstein et al (16), Horie et al (20), Owen et al (22), Rodrigues et al (24). In addition, it was observed that no equation presented its limits of agreement within the predefined acceptable range of ± 10%. The equations that showed non-significant bias were those proposed by FAO/WHO/UNU (17), Harris-Benedict (18), Henry-Rees (19), Mifflin et al (21), Oxford (23), Schofield (25), Siervo et al (26) e Weijs & Vansant (27). The equation proposed by Henry-Rees (19) presented the lowest bias (0.8%) and the highest precision (42.3%) but also presented the lowest CCC. The other equations presented a reasonable CCC, being that of Weijs & Vansant (27) the highest (0.27). The Harris-Benedict equation (18) presented the lowest RMSE values. Using the data obtained with this equation in the *a posteriori* calculations of the maximum allowed difference, a value of 750 kcal was found, which is roughly 50% of the IC-RMR of the sample, whereas it was pre-defined a maximum allowed difference of 10%. The Bland-Altman scatter plots can be found in Figure 1.

The present study demonstrated that among the 13 equations analyzed to estimate RMR, seven showed no significant bias when compared to IC-RMR. The Henry-Rees (19) equation showed the lowest bias and the Harris-Benedict (18) equation showed the highest agreement when evaluated by the RMSE. However, none of the equations showed its limits of agreement narrower than the predefined acceptable range of 10%, indicating that no equation satisfactorily estimates the IC-RMR in the present sample. It is worth mentioning that all the equations developed for the Brazilian population analyzed in this study (Anjos et al (15), Horie et al (20) and Rodrigues et al (24)) presented significant bias, which indicates poor agreement with the IC-RMR.

The Henry-Rees (19) equation was not analyzed in any of the RMR concordance assessment studies in obese women of our knowledge, which prevents the comparability of our finding that this equation present the lowest bias among all equations (11,29,30). A study with Brazilian obese women (29) also showed that the Harris-Benedict equation (18) and the Mifflin (21) equation showed non-significant bias compared to the IC-RMR, being the Harris-Benedict equation (18) the most accurate (40%) among the analyzed equations. In a systematic review, which analyzed the most accurate predictive equations of rest and total energy expenditure in overweight adults, it was shown that the equation of Mifflin et al (21) showed the lowest bias in the BMI subgroup of 30-39.9 kg / m² (-0.5%), while the Harris-Benedict equation (18) provided a more precise prediction (62.7% predicted at 10% of the measure) for the subgroup with BMI ≥ 30 kg / m² (31). Horie et al (20), when comparing it with the IC-RMR also observed good precision and accuracy of the Harris-Benedict equation

(18), while developing a new equation to estimate RMR in severe obesity. In a study carried out in northern Spain with 86 obese individuals, it was observed that the Harris-Benedict equation (18) presented one of the lowest RMSE (152kcal/d) among the analyzed equations (31), similar to the present study, in which this equation showed the lowest RMSE.

This evidence suggests that the Harris-Benedict equation (18) is acceptable in individuals with a wide weight range and in several studies with obese individuals (30). This is one of the most used equations in clinical practice and, because it is the oldest one, it has already undergone extensive validation (16), although some studies support the use of the Mifflin (21) equation for extremely obese men and women, especially for the American population (30,31). Although the Harris-Benedict equation (18) was not developed for obese individuals, it has been reported in other studies that the equations developed for eutrophic individuals are more precise when applied to obese individuals, when compared to those equations developed specifically for individuals with obesity (5,29). In the present study, equations developed specifically for the individuals with obesity, such as the Weijs & Vansant (27) and Horie et al (20) did not perform better than the other equations, despite the former presenting the highest CCC in the present study. Furthermore, equations that included body composition data, such as free fat mass and body fat, did not show greater precision when compared to equations without the use of these variables, as one would expect. This is possibly due to the possible inaccuracy in obtaining these variables of body composition in the obese population, especially with the use of bioimpedance (29). Hence, the equations based on simple anthropometric parameters, such as weight and height, are more feasible in the outpatient routine, especially in a context of social vulnerability, when compared to the equations based on body composition, since it does not generate additional costs for its application.

The environmental conditions may influence the biological factors of women living in socially vulnerable conditions, a fact that is corroborated by studies with women from the same community of the present research group (32), who evaluated the association between height and total energy expenditure, concluding that women with short stature, possibly due to perinatal malnutrition, presenting the same energy consumption and a higher level of physical activity, showed a lower total energy expenditure when compared to women with higher stature. It is noteworthy that the mean height of the women included in the present study was 1.55m, which is below the expected median height for adult women. In the present study, there was no association between self-reported ethnicity, BMI, met.hour and the bias presented by the studied equations, as shown in table 4. There was also no interaction between weight-adjusted RMR and ethnicity ($p = 0.47$), BMI ($p = 0.52$) and MET.hour ($p = 0.13$). Sharp et al. (33) assessed whether there were ethnic and gender differences in RMR in a group of young American adults. The authors concluded that there are differences in RMR between African Americans and white women, but these differences are unlikely to be the main reason for the high rate of obesity in African American women. It is possible that the method of self-report adopted in the present study to define ethnicity may induce some bias in the analysis, however, it is the method recommended to be used by the Brazilian Institute of Geography and Statistics. Also, the heterogeneous genetic profile of the Brazilian population has an important contribution from European, African and Amerindian ancestry, and this process of miscegenation makes it difficult to observe ethnic/racial patterns (34). Regarding BMI, we recognize that the sample is composed by obese individuals including participants in a wide range of BMI by covering the 3 groups defined by WHO to classify the degree of obesity. However, in our study, BMI did not influence either bias or weight-adjusted RMR, a finding corroborated by a study conducted in Brazil with a sample composed of obese but hospitalized individuals, which aimed to define the best RMR value in kcal/kg, considering the class and/or the BMI range of the patients and observed that there was no difference in RMR values between the different BMI class in the fasting state (35).

A major limitation of the present study is due to the absence of an *a priori* sample size calculation. Considering the sample size of this study, the maximum allowed difference that should be considered was 750kcal, or roughly 50% of the IC-RMR, while we assumed a pre-defined maximum allowed difference of 10%. It means that with the present sample, an estimated-RMR that showed its limits of agreement within a range of 50% of the IC-RMR, would still be considered to agree with the IC-RMR, indicating the low precision yielded by the present sample size. However, as our goal was to show wich equation would perform better, considering that there is no gold-standard equation for this population, we believe that the present study may still provide useful information for clinicians and researchers working with populations similar to ours.

In conclusion, none of the studied equations satisfactorily estimated the IC-RMR, which would indicate that these equations are not sufficiently precise in the context of this study. However, the Harris-Benedict (18) equation presented the highest agreement and the Henry-Rees (19) equation the highest precision and lowest bias. Therefore, in the absence of specific equations for this population, the use of the Harris-Benedict (18) and Henry-Rees (19) equations could be considered.

Authorship

All authors collected and analyzed the data; wrote the draft of the manuscript; critically reviewed the manuscript; read and approved the final version of the manuscript.

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Disclosure Statement

The authors have no conflicts of interest to declare.

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Table 1. Predictive equations used to estimate the Resting Metabolic Rate in obese women found in the literature (n = 13)

Equation	Year	Formula
Anjos et al. (15)	2014	(37.46 x Weight (kg)) + (37.13 x Height (cm)) – (2.92 x Age (years)) – 3407.09
Bernstein et al. (16)	1983	(7.48 × Weight (kg)) – (0.42 × Height (cm)) – (3 × Age (years)) + 844
FAO/WHO/UNU (17)	2001	a.18 – 30 years: (14.818 x Weight (kg)) + 486.6 b.31 – 60 years: (8.16 × Weight (kg)) + 845.6
Harris-Benedict (18)	1919	655.0955 + (9.5634 × Weight) + (1.8496 × Height (cm)) – (4.6756 × Age (years))
Henrry-Rees (19)	1991	a.18 – 30 years: (0.048 × Weight (kg)) + (2.562 × 239) b.31 – 60 years: (0.048 × Weight (kg)) + (2.448 × 239)
Horie et al. (20)	2011	560.43 + (5.39 × Weight (kg)) + (14.14 × Free Fat Mass (kg))
Mifflin et al. (21)	1990	(9.99 × Weight (kg)) + (6.25 × Height (cm)) – (4.92 × Age (years)) – 161
Owen et al. (22)	1986	795 + (7.18 × Weight (kg))
Oxford (23)	2005	a. 18 – 30 years: (10.4 × Weight (kg)) + (615 × Height (m)) - 282 b. 31 – 60 years: (8.18 × Weight (kg)) + (502 × Height (m)) – 11.6
Rodrigues et al. (24)	2010	a. IMC<35 kg/m²: 407.57 + (9.58 × Weight) + (2.05 × Height (cm)) – (1.74 × Age (years)) b. IMC>35 kg/m²: 172.19 + (10.93 × Weight) + (3.10 × Height (cm)) – (2.55 × Age (years))
Schofield (25)	1985	a. 18 – 30 years: (0.062 × Weight (kg) + 2.036) × 239 b. 31 – 60 years: (0.034 × Weight (kg) + 3.538) × 239
Siervo et al. (26)	2003	(11.5 × Weight (kg)) + 542.2
Weijs & Vansant (27)	2010	(Weight (kg) × 14.038) + (Height (cm) × 4.498) – (Age (years) × 0.977) − 221.631

Table 2. Characteristics of included women (n = 58)

Variables	**Mean**	**Standard deviation**
Age (years)	31.57	7.01
Weight (kg)	80.86	11.60
Height (m)	1.55	0.06
BMI (kg/m²)	32.86	5.94
Free Fat Mass (kg)	45.02	4.77
Body fat (%)	42.78	5.45
Resting Metabolic Rate (kcal)	1543.93	290.92
MET.hour (24h-multiple of RMR)	1.45	0.06
	n	%
Ethnicity		
White	10	16.9
Black	14	23.7
Brown	35	59.3

BMI: Body Mass Index

Table 3. Evaluation of the concordance between resting metabolic rates by equations and resting metabolic rates measured by indirect calorimetry in obese women with social vulnerability (n = 58)

Equation	RMR (kcal)[a]		RMSE[b]	Bias[c]	T-test	Limits of Agreement [LL – UL][e]	LoA Lower Limit	LoA Upper Limit	CCC[f]	MPE[g]	MNE[h]	Precision[i]
	Mean	SD	Kcal	(%)	P[d]	(%)	[CI 95%]	[CI 95%]		(%)	(%)	(%)
RMR-CI	1543.9	290.9	-	-	-	-	-	-	-	-	-	
Anjos et al. (15)	1268.9	138.8	394.7	-18.2	<0.01	[-54.0 – 17.4]	[-62.1– -45.8]	[9.3 – 25.6]	0.12	12.2	-41.0	32.2
Bernstein et al. (16)	1288.8	90.1	372.0	-16.4	<0.01	[-49.9 – 17.1]	[-57.6 – -43.3]	[9.4 – 24.7]	0.11	15.2	-40.5	33.8
FAO/WHO/UNU (17)	1593.97	167.5	296.7	4.3	0.07	[-32.1 – 40.8]	[-40.4 – -23.7]	[32.4 – 49.1]	0.22	45.1	-27.5	33.8
Harris-Benedict (18)	1568.4	125.4	274.7	2.9	0.19	[-31.1 – 37.0]	[-38.9 – -23.3]	[29.2 – 44.8]	0.23	40.9	-26.7	35.5
Henrry-Rees (19)	1511.3	137.5	303.2	-0.8	0.74	[-38.1 – 36.5]	[-46.7 – -29.6]	[28.0 – 45.0]	0.10	49.3	-32.2	42.3
Horie et al. (20)	1656.6	119.3	292.4	8.4	<0.01	[-25.1 – 42.0]	[-32.8 – -17.4]	[34.3 – 49.7]	0.22	48.3	-24.0	35.5
Mifflin et al. (21)	1463.4	148.3	292.3	-4.1	0.08	[-9.3 – 31.1]	[-47.3 – 31.2]	[23.0 – 39.1]	0.23	31.9	-30.6	33.8

Owen et al. (22)	1375.6	83.3	303.2	-9.9	<0.01	[-43.7 – 23.8]	[-51.4 – -36.0]	[16.1 – 31.6]	0.13	21.7	-38.3	37.2
Oxford (23)	1486.2	134.2	294.3	-2.5	0.30	[-38.6 – 33.7]	[-46.9 – -30.3]	[25.4 – 41.9]	0.16	36.4	-32.1	38.9
Rodrigues et al. (24)	1409	94.4	326.0	7.5	<0.01	[-44.7 – 29.6]	[-53.2 – -36.2]	[21.1 – 38.1]	0.03	41.5	-37.4	35.5
Schofield (25)	1593.9	169.0	296.7	4.3	0.07	[-31.1 – 40.8]	[-40.4 – -23.7]	[32.4 – 49.1]	0.22	45.1	-27.5	33.3
Siervo et al. (26)	1472.1	133.4	284.0	-3.4	0.13	[-37.6 – 30.7]	[-45.4 – -29.7]	[22.9 – 38.5]	0.23	27.6	-32.1	35.5
Weijs & Vansant (27)	1582.2	178.5	289.4	3.5	0.13	[-31.7 – 38.8]	[-39.8 – -23.6]	[30.5 – 46.8]	0.27	40.2	-25.4	28.8

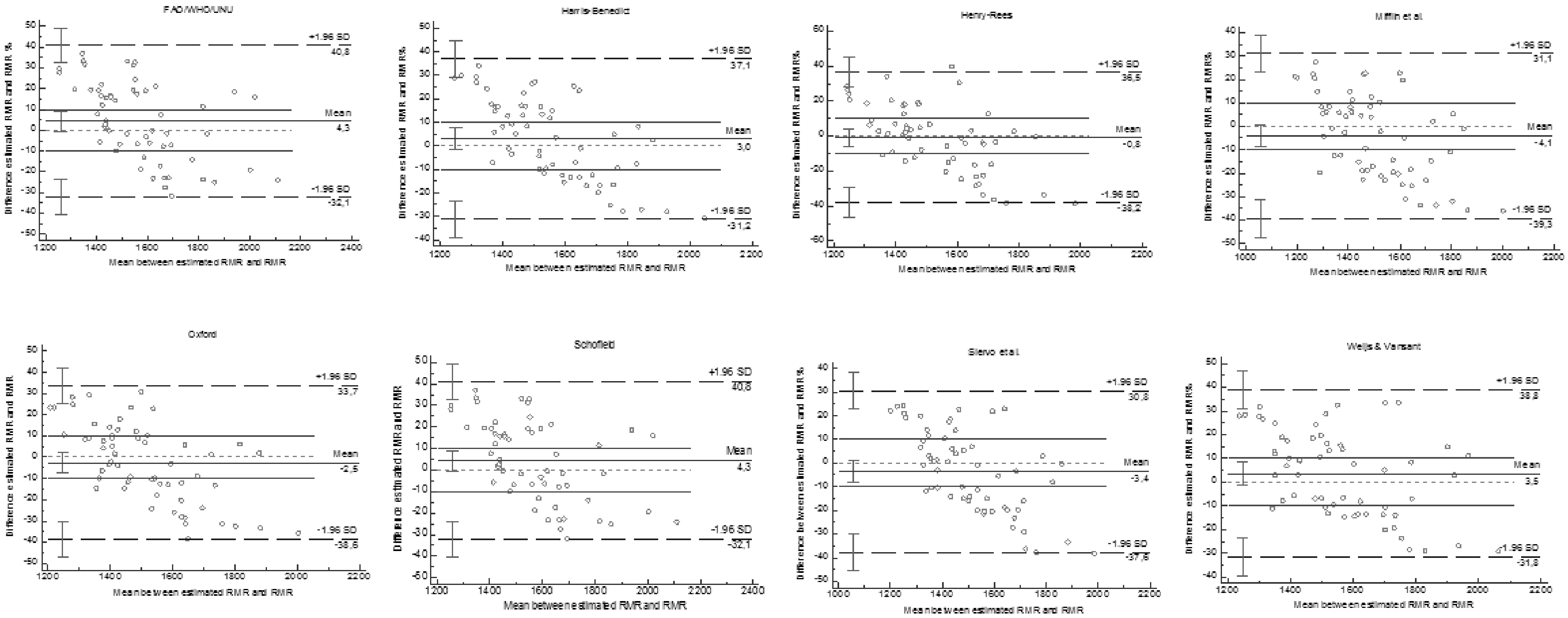
[a] Mean estimated RMR.
[b]Root mean square error.
[c]Bland-Altman percentage mean differences. Calculated by dividing the difference between the estimated-RMR and RMR-CI by the mean between the estimated RMR and RMR-CI. multiplied by 100.
[d]P-value for a "t" test for paired samples, comparing the mean estimated-RMR to the mean RMR-CI.
[e]Lower limit and upper limit of the Bland-Altman Limits of Agreement, where 95% of the differences is expected to lie between.
[f]Concordance Correlation Coefficient.
[g]Maximum Positive Error.
[h]Maximum Negative Error.
[i]Percentage of participants with predicted resting metabolic rate within 10% of IC measured values.

Table 4. Interaction analyzes between the bias of each equation, in %, and MET.hour, ethnicity and BMI (n = 58)

	MET.hour	**Ethnicity**	**BMI**
Equation (bias in %)	**p-value***	**p-value‡**	**p-value†**
Anjos et al. (15)	0.26	0.63	0.95
Bernstein et al. (16)	0.37	0.39	0.65
FAO/WHO/UNU (17)	0.27	0.55	0.20
Harris-Benedict (18)	0.33	0.42	0.70
Henrry-Rees (19)	0.21	0.49	0.06
Horie et al. (20)	0.47	0.39	0.37
Mifflin et al. (21)	0.12	0.68	0.78
Owen et al. (22)	0.38	0.39	0.53
Oxford (23)	0.22	0.62	0.07
Rodrigues et al. (24)	0.94	0.23	0.09
Schofield (25)	0.27	0.55	0.30
Siervo et al. (26)	0.30	0.45	0.66
Weijs & Vansant (27)	0.18	0.58	0.45

BMI: Body Mass Index
***** p-value for the Spearman correlations
‡ p-value for the Kruskal Wallis test
† p-value for the Pearson correlations

Figure 1. Bland–Altman plots of differences in resting metabolic rate (RMR), measured using indirect calorimetry and calculated using predictive equations that presented no significant bias



3.2 ARTIGO DE RESULTADOS 2

PUREZA, IROM; BUENO, NB**. Acute effects of time-restricted feeding in low-income women with obesity submitted to hypoenergetic diets: randomized trial.** A ser submetido a revista *Metabolism clinical and experimenal* (Classificação A1, segundo os critérios do sistema Qualis da CAPES/Área de Nutrição).

Acute effects of time-restricted feeding in low-income women with obesity submitted to hypoenergetic diets: randomized trial

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Abstract

Objective. To evaluate the acute effects of time-restricted feeding in obese women living in social vulnerability, submitted to diets with the same energy deficit.

Methods. Fifty-eight obese women (19-44 years) were randomized either to a group with hypoenergetic diet and 12 hours daily of fasting or to a group with only hypoenergetic diet for 21 days. The determination of the individual's energy content of the diets was based on their resting metabolic rate (by indirect calorimetry) and physical activity level (by triaxial accelerometers). Body composition, temperature, blood pressure, appetite, adhesion difficulty, thyroid axis hormones, leptin, glycemia and insulin were measured before and after 21 days of intervention. A mixed ANOVA test was performed.

Results. Women had a mean age of 31 years and mean BMI of 33 kg/m². Significant interaction between Group x Time was observed only in axillary temperature (-0.4°C, CI 95% [-0.7 - -0.1] °C), decreased in the control group, and in body fat percentage (0.75%, CI 95% [0.0 - 1.4] %), decreased in the experimental group. There were no differences in hormonal profile, resting metabolic rate, reported appetite, and adhesion difficulty.

Conclusion. Time-restricted feeding may be considered an alternative strategy for treating obesity in socially vulnerable women.

Trial registration. www.rebec.gov.br/RBR-387v6v

Key Words: Fasting; Body composition; Obesity treatment.

1. Introduction

Obesity is a global public health problem, and by estimates, the majority of the world's population lives in places where obesity-related causes kill more than malnutrition [1]. In Brazil, the population with the highest prevalence of obesity in the country are women with low levels of schooling, whose obesity prevalence is 27.8%, whereas it is only 14.4% in women in the highest stratum of schooling [2]. Compared with countries of the Organization for Economic Co-operation and Development, such a population group would be ranked 8th in terms of obesity prevalence [3].

It is a consensus that the negative energy balance is an adequate strategy to promote weight loss [4]. However, the most significant limitation of the success of any dietary intervention involves adherence to treatment by the patient, which drives the development of efficient and straitgh forward dietary strategies [5]. This development is even more necessary in low-income individuals, who commonly present a monotonous food consumption pattern, with high intake of foods with a high glycemic index and lipid content, as they are usually the lowest-cost foods and consequently more accessible to this population [6]. Thus, interventions that require the acquisition of foodstuffs different from those commonly obtained by this population, implying higher costs, may constitute a limiting factor for adherence to the dietary treatment [7].

One strategy that has gained considerable scientific and popular appeal is intermittent fasting, which can assume many forms, including the one that promotes daily fasting periods longer than the regular overnight fasting, starting from a 12-hour fasting period per day, referred to as the time-restricted feeding (TRF) [8,9]. Restricting the period of food intake to a few hours without an explicit attempt to decrease energy intake triggers the fasting physiology [9], adaptive mechanism of the human body developed in the face of periods of food shortage and prolonged fasting, and is determinant for species survival [8].

This mechanism would be driven by the metabolic changes required to meet energy demands, in which hepatic glycogen stores are depleted after 10 hours of fasting, promoting β-oxidation of fatty acids in adipocytes and production of Acetyl-CoA and ketones in hepatocytes for ATP production [8]. The levels of adiponectin and AMPK, which is inhibited by feedback, regulates this process [10]. In humans, the effects result in resistance to stress, lipolysis, and autophagy stimulation [8]. If performed frequently, daily or alternate periodic fasting may exert pleiotropic effects and become an effective treatment strategy for chronic diseases as well [9].

It is believed that the effects of intermittent fasting depend not only on weight loss but also on the period of food consumption [11]. However, there are not enough studies involving TRF, and clinical trials usually do not present a control group with identical energy restriction to that of the experimental group, which does not allow to affirm if the effects observed are due to the differences in energy intake or to the fasting itself. Besides, the results are even scarcer in obese individuals, probably because of the idea that the hunger sensation, prevalent in different types of intermittent fasting, would be a limitation for using such intervention in these individuals [12]. Considering the studies investigating the effects of TRF [11,13-19], few assessed thyroid hormones [19] and energy expenditure [17-19] on humans, factors that may be mediators of the supposed beneficial effects of intermittent fasting.

Thus, the present study aims to evaluate the acute effects of a TRF regimen in obese women in social vulnerability submitted to diets with the same energy deficit.

2. Methods

The present research was approved by the Ethics in Research Committee of the Federal University of Alagoas with an opinion number 253599. All participants provided written informed consent before their inclusion. This study was registered as a clinical trial.

There was no financial compensation to participate in the study. This paper is reported following the Consolidated Standards of Reporting Trials (CONSORT) [20].

2.1. Study Design

This study is a randomized, parallel trial with two research groups and 21 days duration. Due to the nature of the intervention, it can neither be double-blind nor placebo-controlled.

2.2. Participants

The research was carried out at the obesity outpatient clinic of the Centro de Recuperação e Educação Nutricional (CREN), linked to the Universidade Federal de Alagoas. CREN is a center for the treatment of undernourished children in a day-hospital system. It is located in the seventh administrative region of the municipality of Maceió-AL, a region of high social vulnerability.

Sampling was conducted in a non-probabilistic way, by convenience, and recruitment was done through announcements in the community, direct invitations to women attending CREN activities, or directly to those women who went to CREN on the days of screening for nutritional care.

Adult women (19-44 years old) living in social vulnerability, classified as economic class "C" or "D-E", as determined by the Brazilian Economic Classification Criterion (CCEB, 2015) [21], were included. The CCEB is an instrument consisting of questions about assets, household employees, housing data, head of household instruction, access to piped water and paved street, where each item yields a different score. According to the achieved score, individuals are classified into six classes that vary from "A", the highest one, to "D-E", the lowest one.

Obesity was defined by the presence of two of the following three criteria: Body Mass Index (BMI) ≥ 30 kg / m² and <45 kg/m²; waist circumference ≥ 88cm; and body fa percentage ≥ 35% [22] determined by bioimpedance). Only women who wished to lose weight but who were weight stable for at least one month were included. Women in chronic use of medicines (anti-diabetic, antihypertensive, antiretroviral, immunosuppressive, anti-depressants and diet pills), menopausal, pregnant, nursing, engaged on shift work or who have already undergone any surgical intervention for weight loss were not included. Participants who became pregnant during follow-up, those who needed to perform any surgical procedure, or those who requested a decline in the study were excluded.

2.3. Intervention

Two interventions were compared: one composed of a hypoenergetic diet with TRF (HD + TRF) and another intervention composed by a diet with the same energy restriction but without TRF. In the TRF diet, women were instructed to eat only in a 12-hour period and kept fasting in the other 12 hours, from the time of the last meal, determined by the participant. The determination of the energy content of the diets was performed in an individualized way; that is, each woman had their estimated energy requirements based on their total energy expenditure (TEE). Resting metabolic rate (RMR) was estimated by indirect calorimetry through a gas analyzer (Quark, Cosmed, Rome, Italy), and the physical activity level (PAL) was estimated by triaxial accelerometers (ActivPAL, Glasgow, UK), which yield an estimated metabolic equivalent of task (MET) for each participant. To determine the TEE the factorial approach (i.e., TEE = RMR × PAL) [23] was used, and it was subtracted 500-1000 kcal to determine the energy content of the proposed hypoenergetic diet plan for each woman, the interval used is proposed by the Brazilian obesity guideline [24] and aimed to ensure a proportional reduction in the total energy value of the diet according to the participant's measured energy expenditure avoiding bids below RMR. As well, the macronutrient distribution was distributed as: which contained 45-55% carbohydrates, 25-30% lipids and 15-25% proteins [24]. Thus, the only difference between the investigated groups was the restriction or not of the feeding period. The women had individual weekly follow-up up to 21 days, and during the follow-up, a nutritionist made the necessary adjustments in the diet to maintain weight loss during the period.

2.4. Outcomes

Outcomes were measured before and after 21 days of intervention, with women fasted for 10 hours, with preparation by the participants that included abstinence from alcoholic beverage and physical activity in the last 24 hours and emptying of the bladder 30 minutes before the procedures.

2.4.1. Vital signs

Axillary temperature was measured by a clinical digital thermometer (Techline, São Paulo, Brazil), while systolic blood pressure, diastolic blood pressure and heart rate were measured using a tensiometer (HEM-4030, OMRON, Japan), before performing indirect calorimetry and electrical bioimpedance tests.

2.4.2. Body composition

BMI was calculated and classified according to the World Health Organization [25]. The waist circumference was measured using an inelastic tape measure, in the largest perimeter between the last rib and the iliac crest [24]. Body fat was estimated from four-electrode electrical bioimpedance Sanny BI 1010 (Sanny, São Paulo, SP), with participants in a supine position, using light clothes, barefoot and without metallic props, in the right hemicorp of the evaluated ones and four electrodes were fixed as proposed by Kyle et al [26]. The data of resistance and reactance, obtained in the evaluation, were interpreted in the software Bio Tectronic Sanny version 1.2.2, defining the percentage of body fat.

2.4.3. Resting metabolic rate

A gas analyzer was used to estimate the RMR. The participants were taken by car to the place, and the collection took place in the morning (between 07 am to 09 am), in a quiet environment, with low light and temperature between 22 to 26 °C. Before each test session, the equipment was calibrated with gases at a concentration of 20.9% O_2 and 5% CO_2, and a 3 L syringe with a secondary manometer adjustable between 40 and 60 psi. Before starting the test, axillary temperature, blood pressure levels, and heart rate were measured to avoid calorimetric measurements in individuals with signs of hyperthermia (> 37.5ºC) or tachycardia (> 100bpm). Participants were asked to wear the equipment's silicone mask, so that inspired oxygen and expired carbon dioxide volumes were counted for 15 minutes. The first five minutes of measurement were discarded to avoid discrepancies due to the location and use of the silicone mask, and data were collected every 1 minute [27]. Oxygen and carbon dioxide volumes collected in liters per minute were used to estimate the RMR in the Weir equation.

2.4.4. Hunger

Hunger was measured using a visual analog scale, based on the Canty et al. study scale [28] where 0 means "I am not hungry" and ten means "I am starving"; the participants were instructed to mark at the point where their sense of hunger approached the referred extremity.

2.4.5. Adhesion difficulty

The evaluation of the degree of difficulty in adhering to the proposed dietary plan was evaluated by a visual analog scale of 0 to ten to predict difficulty, where 0 was classified as very easy and ten very difficult.

2.4.6. Biochemical tests

The blood levels of glucose, insulin, leptin and thyroid hormones (TSH, free T3 and free T4) were measured from blood samples collected by peripheral venous puncture in the left or right cubital fossa, withdrawing 20 mL of blood, on average, and transferred for separator gel tube, procedure performed by qualified local laboratory accredited contracted as provider of such services. The GOD-trinder technique (Glucose-PP Analisa® kit) was used for serum glucose levels, and the immunoassay method ELISA (Linco Research®, St. Charles-MI, USA) was used for leptin, and the chemiluminescence method (Unissel DxI 800 from Beckman Coulter®) was used for insulin, TSH, free T3, and free T4 hormones. From the plasma levels of insulin and fasting glucose, the sensitivity to insulin was quantified by calculating the homeostatic model of insulin resistance (HOMA-IR) by the equation developed by Matthews et al [29].

2.4.7. Complementary data

A triaxial accelerometer was used to measure the level of physical activity. The device was fixed in the frontal thigh of the participants, at the midpoint between the inguinal line and the upper edge of the patella. Two transparent and hypoallergenic dressings (VitaMedical®, Minas Gerais Brazil) were used to avoid the contact of the device with the participant's skin, keeping the device isolated. The women used the accelerometers for three consecutive days and were told not to remove it for any activity. Data captured by the device was transferred to ActivPAL3 ™ version 7.2.32 software, which provides the intensity and duration of each activity performed by the individual. The system computes the periods in which the individual spent lying/sitting, standing, walking and running every tenth of a second, for the entire period in which the device was used, based on the acceleration of three-body axis: anteroposterior, lateral and vertical. It provides the MET value for the entire period that individuals used the device, by multiplying the MET value for each activity by the duration of the activity, based on default values for sitting/lying (1.25 MET), standing (1.40 MET) and stepping at 120 steps per minute (4 MET). For cadences that differ from 120 steps per minute, the following equation is used to calculate the MET estimate: MET.h = (1.4 xd) + (4 - 1.4) x (c / 120) x d, where c is the cadence (steps per minute), and d is the duration of the activity (in hours) [30]. MET is determined as the amount of oxygen consumed at rest, corresponding to 3.5 ml O_2 per kg body weight x min or 1 kcal/kg/ hour. The MET value expresses the energy expenditure of physical activity as a multiple of RMR, regardless of the individuals' characteristics and type of activity. According to what recommends the Food and Agriculture Organization joint report (2001) [31], the total MET value is divided by the total amount of hours that the individuals used the accelerometer, yielding the estimated MET.hour, which is a proxy of the individual's PAL.

2.5. Sample size

Assuming a 5% alpha and 80% statistical power that the difference in weight loss between interventions would be 1.5 ± 2.0 kg, 28 individuals per group was needed.

2.6. Randomization

Based on a random sequence of numbers generated using the RUNIF command of the software R v 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria) [32], women were allocated to the group receiving the HD + TRF intervention or to the group receiving HD intervention. The random sequence was guarded by a researcher who had no initial contact with the participants, to ensure the allocation concealment.

2.7. Statistical method

Data were presented as mean and standard deviation for continuous variables and relative and absolute frequencies for categorical variables. A mixed analysis of variance (ANOVA) was conducted to verify if treatment effect existed over the intervention period, where the independent factor was the designated group (HD *vs*. HD + TRF), and the dependent factor was the moment of measurement (before and after the intervention). In addition, mixed analysis of covariance was performed to evaluate the intrasubject variation of the RMR adjusted by the body weight variation. A t-test was performed for independent samples for the data collected only after the intervention. An alpha value of 5% was adopted. Intention-to-treat analyses were performed using the last observation carried forward method to minimize the risk of bias from follow-up losses. All the analyses were conducted using the R software v 3.6.1[32], with the "Rcmdr" [33] and "RcmdrPlugin.aRnova"[34] packages.

Results

Participants were recruited between July 2018 and January 2019. The mean age of participants was 31.03 years (±7.06) and 31.80 years (±6.96), in the HD group and HD + TRF, respectively. The sample composition and dropouts during follow-up can be observed through the flowchart of the participants in Figure 1. The baseline characteristics of the participants are described in Table 1. After 21 days of intervention, there were no significant changes in weight loss, hormonal profile, and RMR between groups, even in the analysis adjusting RMR by bodyweight variation ($p = 0.14$). Significant changes were observed only in axillary temperature (-0.4 ° C, 95% CI [-0.7 - -0.1] °C, $p < 0.01$), which lowered in the control group when compared to the experimental group, and in the percentage of body fat (0.75%, 95% CI [0.0 - 1.4] %, $p < 0.05$) which lowered in the experimental group when compared to the control group, as presented in Table 2.

3. Discussion

In the present study, at 21 days of follow-up, there was a maintenance in axillary temperature and a decrease in the percentage of body fat in women submitted to HD + TRF intervention, when compared to those submitted only to HD. However, no significant change was observed in weight loss, thyroid hormones, insulin sensitivity, leptin, and RMR between groups after 21 days of TRF.

Different from our findings, a greater weight loss in TRF intervention compared to control interventions had already been documented in several other studies involving from trained to overweight individuals [13, 14, 19]. The small decrease in body weight observed in our study may be due to the short intervention period and probably because no important changes in RMR were observed. However, our results are consistent with a trial involving 10-

hour TRF with overweight men and women, where no change was found in the percentage of weight loss either in the short term (after 16 weeks of intervention) or long term (after one year of intervention) [14]. Besides, the percentage of weight loss observed in our study showed a similar result to other studies with TRF ranging from 16 to 20 hours during eight weeks, which resulted in a decrease of 1-3% of body weight [13,19] with trained men. Several systematic reviews, including those with and without meta-analysis, point out that excess body weight losses in subjects doing intermittent fasting are equivalent to those produced by continuous energy restriction [35].

To our knowledge, only one study involving TRF reported body fat reduction; however, it consisted of a sample of resistance-trained men followed for eight weeks with 16h dietary restriction [19]. In other investigations with individuals in TRF, no significant changes in body composition were found, and in those studies, the intervention group was not submitted to energy restriction in addition to TRF [13-15]. The purpose of nutritional interventions for weight loss is to promote the reduction of adipose tissue and, as far as possible, preserve fat-free mass to maintain functional capacity and to mitigate the decline of RMR, thus contributing to avoiding weight regain [36], although a recent study conducted with 54 obese adults undergoing a very low energy diet, observed that changes in RMR do not predict long-term weight recovery [37]. Although only the control group showed decreases in RMR and RMR adjusted by body weight values, no statistical differences were observed between groups, which is similar to that found in a randomized, crossover, isocaloric, controlled feeding trial, with overweight American subjects undergoing TRF for four days [18]. Relative changes in RMR during weight loss, regardless of the type of intervention, lasting less than six weeks have significantly higher decreases in RMR compared to longer-lasting studies [38]. On the other hand, persistent deviations of energy balance, even small ones, would be to attribute to alter energy expenditure and energy misalignment, resulting in changes in body energy stocks and consequent changes in body weight over time [39]. Although it is not clear whether RMR is related to weight loss success, a lower RMR may be a predisposing risk factor for the development of obesity, because with a low RMR an energy imbalance is expected to lead to excessive fat accumulation and eventually to obesity as it equates to lower basic maintenance costs in conditions of higher energy consumption and lower energy expenditure with physical activity [40]. We believe that the fact that there was no statistically or clinically significant change in RMR also did not affect significant weight change.

To our knowledge, none of the studies involving TRF found in the literature analyzed body temperature as an outcome [11,13-19]. In our study, maintenance in axillary temperature in the TRF group was observed, with no detectable increase in the levels of TSH, free-T3, free-T4, and the RMR values. However, fat depletion alone is also considered a determinant factor for adaptive thermogenesis [41]. Thus, this increase in body temperature may likely be associated with fasting lipolysis, which promotes intense stimulation of uncoupling proteins (UCPs) in adipose tissue through interaction with peroxisome proliferator-activated receptors, by the action of adiponectin. UCPs play an essential role in cell energy homeostasis by decoupling proton transport into mitochondria by generating heat rather than ATP [42,43]. Energy restriction (or adequate feeding/fasting cycles) will likely promote bioenergetic adaptation, which could explain some of the beneficial effects associated with the energy restriction during fasting [43]. This fact can be evidenced by the higher body fat percentage decrease in the TRF group in the present study. The glycemic and hormone levels collected remained unchanged after the intervention, which has also been observed in other trials with similar intervention, in which no significant changes in glucose levels [11,15,19], insulin [15-17], HOMA-IR [11,15,19], leptin [11], and T3 [19] were found.

In addition, TRF did not promote changes in hunger between the groups in the present study, a different result than that found in a study with obese subjects submitted to fasting on alternate days, who reported a greater sensation of hunger when compared to the continuous energy restriction group, in all intermediate measurements (3 months, 6 months) during 1-year follow-up [44]. On the other hand, Ravussin et al [18] reported that participants undergoing early TRF (eating from 8 am to 2 pm) had a lower sense of hunger when compared to the control group (eating from 8 am to 8 pm). Similar to our findings Hutchinson et al [17] reported no differences in subjective appetite classifications, including hunger, when assessing the effects of an early TRF or delayed TRF, on glucose tolerance in men at risk for type 2 diabetes, a result also found by Coutinho et al [45] in individuals with obesity but undergoing alternate day modified fasting.

At the end of the intervention, no statistical difference was observed in the adherence difficulty to the protocol, and on average, the participants reported being moderately challenging to adhere to both protocols. These results resemble those of a cross-controlled clinical trial involving overweight and pre-diabetic men undergoing 18-hour fasting for five weeks, reporting that it was not challenging or only moderately challenging to adhere to the protocol, using a visual analog scale [11]. Such findings can be attributed to the fact that the participants were able to choose when it was appropriate to begin the fasting period each day, as long as the period of targeted dietary restriction of 12 hours was respected, in a similar way to our study, which may have facilitated adherence.

The present study has some limitations, such as not considering the phase of the menstrual cycle to perform the electrical bioimpedance test, because of changes in the state of hydration present in this phase compromise the results of body composition. To minimize this influence, it was ensured that the data were not collected during the menstrual period. In addition, it is noteworthy that the findings of axillary temperature maintenance were not our primary outcome; hence, it may be only seen as hypothesis-generating findings. Also, we were not able to determine if the women effectively followed the proposed dietary energy deficit, since this study was not conducted in a strictly controlled environment; however, participants had weekly consultations with a nutritionist to adjust the dietary consumption and maintain weight loss throughout the study. Furthermore, one may consider that the fasting period proposed in the present study would not be long enough to induce the metabolic changes associated with TRF regimens. Nevertheless, it is acknowledged that 12 hours is the minimum period required for an intervention to be considered as TRF [9]. Also, considering that our sample was composed of individuals with low levels of education and high levels of non-adherence to weight loss regimens [46], we believed that the 12 hour regimen would be a feasible approach in this population and, possibly, more extreme regimens would importantly decrease the adherence of the participants and the external validity of the study. At last, despite the short follow-up period, the 21-day period is relatively longer compared to other studies [17,18] and should be enough to witness changes, especially in the hormonal profile and RMR.

On the other hand, our investigation also show some strengths, such as the use of a homogenous sample of obese adult women living in social vulnerability, a population with high levels of obesity worldwide; the fact that the individuals were free-living, which enhances the external validity of the study; and the dietary energy restriction that was applied to both groups, which may isolate the effects of the TRF itself.

4. Conclusion

TRF associated with HD did not induce significant different weight loss in 21 days of intervention when compared to HD alone, but induced a decrease in the percentage of body fat and maintained the body temperature, whereas the HD group showed a decrease in body temperature, but there were no differences in RMR, thyroid hormones, insulin or leptin between groups. The findings indicate that the TRF can be considered a support strategy in the treatment of obesity in women in social vulnerability. Effects of TRF in body temperature deserves further investigation.

Author Contributions

All authors collected and analyzed the data; wrote the draft of the manuscript; critically reviewed the manuscript; read and approved the final version of the manuscript.

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Conflicts of Interest

The authors declared no conflict of interest.

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Table 1. Characteristics of the participants at the beginning of the intervention (n = 58)

Variables	HD n = 27		HD+TRF n = 31	
Sociodemographic	**n**	**%**	**n**	**%**
Have biological child				
No	5	18.5	6	19.4
Yes	22	81.5	25	80.6
Alcohol user				
Yes	10	37	14	45.2
No	17	63	17	54.8
Smoker				
Yes	2	7.4	4	12.9
No	25	92.6	27	87.1
	Mean	**SD**	**Mean**	**SD**
Anthropometric				
Weight (kg)	80.25	9.40	81.25	13.51
Height (m)	1.55	0.06	1.55	0.05
BMI(Kg/m²)	33.12	3.63	33.53	4.53
WC (cm)	98.86	9.61	102.51	10.75
Vital signs				
Temperature (ºC)	36.06	0.40	35.86	0.48
SBP (mmHg)	124.03	11.28	126.87	15.29
DBP (mmHg)	86.51	10.08	86.03	13.20
HR (bpm)	71.85	9.48	75.70	8.79
Body Composition				
% Body fat	43.55	4.70	44.03	5.47

Biochemical tests				
Glycemia (mg/dL)	78.37	9.14	79.74	9.89
Insulin (µUI/mL)	15.29	8.70	13.98	6.41
HOMA-IR	3.02	1.90	2.78	1.38
Leptin (ng/mL)	50.75	28.02	40.78	22.38
TSH (µUI/mL)	1.96	1.16	1.94	1.27
Free T3 (pg/mL)	2.74	0.52	2.88	0.51
Free T4 (ng/dL)	0.93	0.13	0.92	0.14
Indirect calorimetry				
RMR (kcal)	1,598.11	301.23	1 486,64	275.10
RQ	0.84	0.05	0.84	0.06
MET.hour (24h-multiple of RMR)	1.45	0.06	1.43	0.06
Hunger (likert scale score)	4.48	2.81	5.00	2.51

HD: Hypoenergetic Diet; TRF: Time-restricted feeding; HD+TRF: Hypoenergetic Diet + Time-restricted feeding; BMI: Body mass index; WC: waist circumference; SBP: Systolic blood pressure; DBP: Diastolic Blood Pressure; HR: Heart rate; TSH: thyroid stimulating hormone; RMR: Resting metabolic rate; RQ: Respiratory quotient;

Table 2. Final values and changes (final values - initial) of the anthropometric variables, vital signs, body composition, biochemical tests, calorimetry, appetite and difficulty of adherence to the protocol of both groups after 21 days of intervention

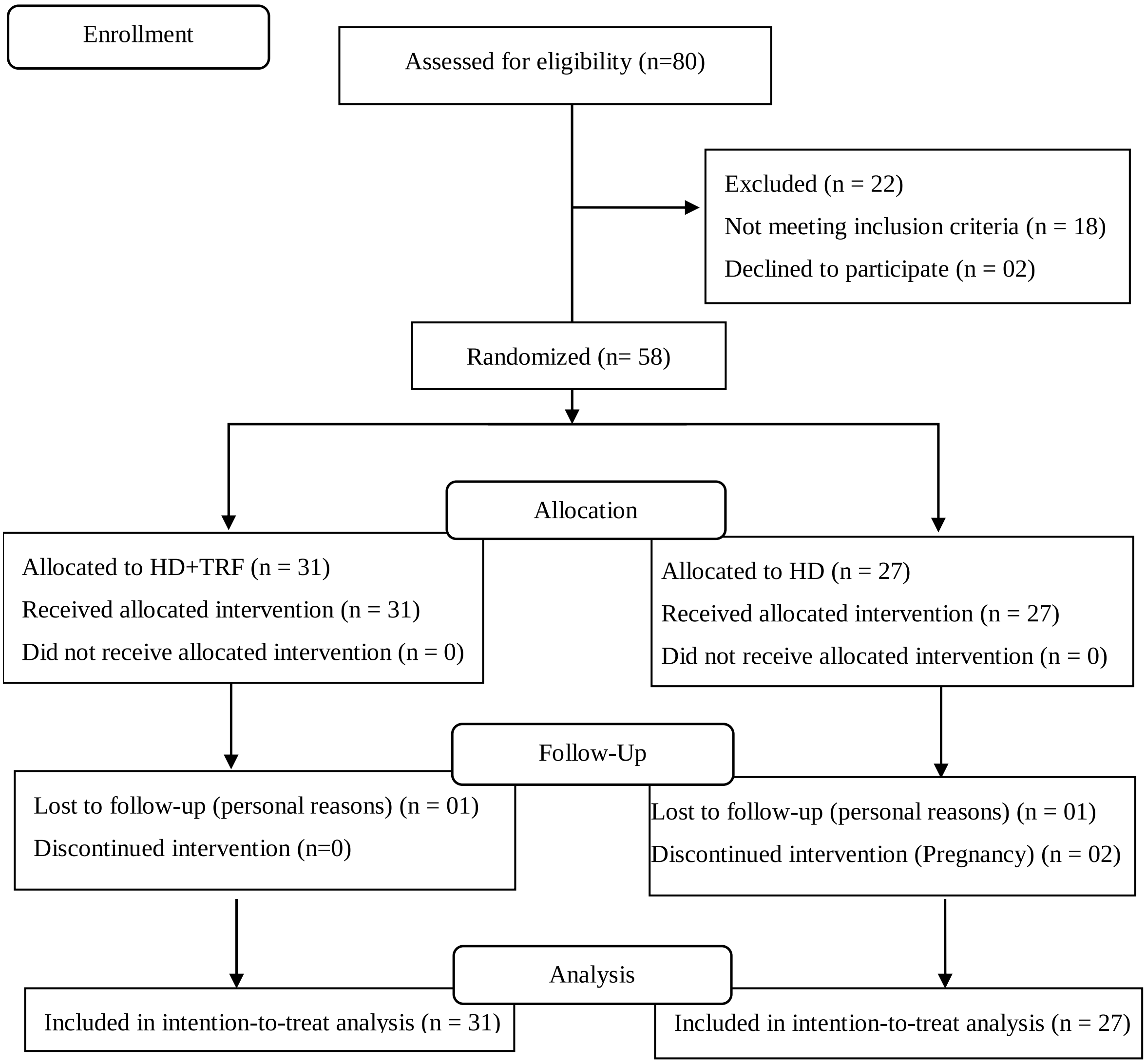
Outcomes	HD (n = 27)		ΔHD		HD+TRF (n= 31)		ΔHD+TRF		Effect size		p*
	MEAN	**SD**	**MEAN**	**SD**	**MEAN**	**SD**	**MEAN**	**SD**	**MEAN**	**CI 95%**	
Anthropometric											
Weight loss (%)	-	-	-1.1	1.5	-	-	-1.6	1.3	0.5	[-0.1– 1.3]	0.14
BMI (Kg/m²)	32.7	3.8	-0.3	0.4	32.9	4.4	-0.5	0.4	0.2	[-0.2 – 0.4]	0.08
WC (cm)	97.7	9.8	-1.1	2.6	100.2	11.3	-2.3	3.8	1.1	[-0.5 – 2.9]	0.18
Vital signs											
Temperature (ºC)	35.6	0.4	-0.3	0.4	35.9	0.3	0.0	0.5	-0.4	[-0.7 – -0.1]	< 0.01
SBP (mmHg)	117.9	9.7	-6.0	7.7	122.2	16.0	-4.6	8.4	-1.4	[-5.7 – 2.8]	0.50
DBP (mmHg)	80.5	11.1	-5.9	7.7	82.8	12.5	-3.2	7.6	-2.7	[-6.8 – 1.3]	0.18
HR (bpm)	70.6	10.9	-1.1	7.9	73.6	8.3	-2.0	7.9	0.9	[-3.2 – 5.1]	0.66
Body Composition											
% Body fat	43.8	4.7	0.3	1.6	43.5	5.5	-0.4	0.8	0.75	[0.0 – 1.4]	0.02
Biochemical tests											
Glycemia (mg/dL)	79.8	8.2	0.8	9.1	80.3	8.2	-2.0	14.7	2.8	[-3.7 – 9.3]	0.39

Insulin (µUI/mL)	14.8	12.4	-0.4	8.8	13.0	4.5	-1.4	5.4	0.9	[-2.8 – 4.7]	0.61
HOMA-IR	2.9	2.5	-0.1	1.9	2.5	0.9	-0.2	1.0	0.1	[-0.6 – 0.9]	0.78
Leptin (ng/mL)	38.5	18.6	-12.1	20.1	36.8	21.1	-3.9	19.4	-8.1	[-18.6 – 2.2]	0.12
TSH (µUI/mL)	1.7	0.9	-0.2	1.0	2.1	1.6	0.1	0.9	-0.4	[-0.9 – 0.0]	0.10
Free T3 (pg/mL)	2.8	0.4	0.0	0.4	2.9	0.4	0.0	0.4	0.0	[-0.2 – 0.2]	0.73
Free T4 (ng/dL)	0.9	0.1	-0.0	0.1	0.9	0.1	0.0	0.0	-0.0	[-0.0 – 0.0]	0.10
Indirect calorimetry											
RMR (kcal)	1 529.2	372.9	-68.8	221.9	1 494.3	287.3	7.6	215.0	-76.5	[-191.6 – 38.5]	0.18
RQ	0.8	0.0	-0.0	0.0	0.8	0.0	-0.0	0.0	-0.0	[-0.0 – 0.0]	0.60
Appetite (likert scale score)	3.9	2.7	-0.5	3.1	4.0	3.5	-0.8	3.6	0.7	[-1.1 – 2.6]	0.70
Difficulty of adhesion (likert scale score)	6.2	3.0	-	-	5.1	3.1	-	-	1.0	[-0.5 – 2.78]	0.19

HD: Hypoenergetic Diet; TRF: Time-restricted feeding; HD+TRF: Hypoenergetic Diet + Time-restricted feeding; Δ: Difference between final and initial measures; BMI: Body mass index; WC: waist circumference; SBP: Systolic blood pressure; DBP: Diastolic Blood Pressure; HR: Heart rate; TSH: thyroid stimulating hormone; RMR: Resting metabolic rate; RQ: Respiratory quotient.

* P values for interaction between group (DH x DH + TRF) x moment (beginning and end) using Mixed ANOVA. Except for the variables "weight loss (%)" and "difficulty of adhesion" because they do not present initial data, only final data, and were compared using an independent sample t-test.

Figure 1. Participant recruitment and study flow diagram.



Subtitle: HD: Hypoenergetic Diet; TRF: Time-restricted feeding; HD+TRF: Hypoenergetic Diet + Time-restricted feeding.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	54
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	55
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	56
	2b	Specific objectives or hypotheses	57
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	57
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	58
	4b	Settings and locations where the data were collected	58
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	59
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	59
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	63
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	63
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	63
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	63
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	63
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	

	11b	If relevant, description of the similarity of interventions	
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	63
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	80
	13b	For each group, losses and exclusions after randomisation, together with reasons	80
Recruitment	14a	Dates defining the periods of recruitment and follow-up	64
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	76
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	80
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	64
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	67
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	67
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	64 – 67
Other information			
Registration	23	Registration number and name of trial registry	55
Protocol	24	Where the full trial protocol can be accessed, if available	55
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	69

4 CONSIDERAÇÕES FINAIS

Diante do cenário nutricional atual, com o número crescente de indivíduos acometidos pela obesidade, principalmente na população em vulnerabilidade social, a presente dissertação buscou contribuir com estratégias efetivas que auxiliem no combate a este quadro. Destacamos a dificuldade em determinar o gasto energético por meio de equações preditivas para população com obesidade e evidenciamos a relevância do presente estudo para auxiliar na aplicação de uma intervenção nutricional eficiente, visto que a determinação adequada do gasto energético é fundamental nesse processo.

Assim como também consideramos a relevância do estudo realizado por meio de ensaio clínico aleatório, em que se percebe que a restrição do período alimentar apresentou ser uma estratégia que pode contribuir para o tratamento da obesidade de mulheres que vivem em vulnerabilidade social, por ser uma estratégia simples que pode contribuir no tratamento dietético, sem a necessidade de implicar em maiores custos com a aquisição de gêneros alimentícios que não correspondam ao padrão alimentar dessa população.

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ANEXOS

A – Parecer Consubstanciado do Comitê de Ética em Pesquisa

UNIVERSIDADE FEDERAL DE ALAGOAS

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: Influência do período alimentar (com restrição versus sem restrição de horário) na perda de peso, taxa metabólica basal, apetite e controle glicêmico e lipidêmico de mulheres com excesso de peso, submetidas a dietas com um mesmo déficit energético

Pesquisador: Nassib Bezerra Bueno
Área Temática:
Versão: 4
CAAE: 60931416.4.0000.5013
Instituição Proponente: Faculdade de Nutrição - UFAL
Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 2.535.991

Apresentação do Projeto:
A obesidade é um problema de saúde pública de dimensões mundiais. No Brasil, estimativas mostram que 50% dos homens e 48% das mulheres apresentam sobrepeso, sendo 12% e 16%, respectivamente, já obesos. É consenso que o balanço energético negativo é a estratégia mais adequada para promover perda de peso. No entanto, apesar da miríade de dietas disponíveis e já testadas nenhuma parece ser claramente superior. De fato, a maior limitação do sucesso de qualquer intervenção alimentar é a aderência ao tratamento por parte do paciente. Assim o campo de investigação sobre estratégias alimentares simples e eficientes que facilitem a aderência dos pacientes ao tratamento é frutífero. Uma estratégia que vem atraindo atenção de clínicos e pacientes é a que envolve restrição do período alimentar, ou alimentação com restrição de horário,popularmente conhecida como "jejum intermitente", que pode assumir várias formas, dentre elas a de promover períodos de jejum diários mais
longos que o convencional jejum noturno, começando a partir de um período de jejum de 12 horas por dia. A ideia de que o jejum traz efeitos
benéficos para os mais variados organismos já é longamente conhecida e bem estabelecida em formas de vidas inferiores, como em procariontes e fungos. Em modelos animais de doenças humanas, existem evidências de que a restrição do período alimentar pode contribuir para o

controle e prevenção do diabetes, resistência à insulina e hipertensão arterial. Logo, o objetivo geral desta pesquisa é determinar se o período alimentar (com restrição versus sem restrição de horário) influencia na perda de peso, na taxa metabólica basal, no apetite e no controle glicêmico e lipidêmico de mulheres com excesso de peso, submetidas a dietas com um mesmo déficit energético. Trata-se de um ensaio clínico aleatório, paralelo, com dois grupos de investigação e 2 meses de duração. O estudo será realizado no ambulatório de obesidade do Centro de Recuperação e Educação Nutricional (CREN), vinculado à Faculdade de Nutrição da UFAL. Serão incluídas mulheres adultas (19-44 anos), com excesso de peso. Não serão incluídas mulheres em uso de medicamentos crônicos; grávidas ou lactantes. As mulheres serão alocadas aleatoriamente para uma de duas intervenções: Uma composta por uma dieta hipoenergética com restrição do horário de consumo alimentar (12 horas de jejum versus 12 horas período alimentar) e outra composta por uma dieta com a mesma restrição energética, porém sem restrição de período alimentar. A determinação do

conteúdo energético das dietas será feita de maneira individualizada, estimadas com auxílio de um calorímetro. As dietas conterão 45-50% de carboidratos, 30-35% de lipídios e 15-25% de proteínas. As mulheres serão acompanhadas individualmente e semanalmente por um nutricionista, que fará os ajustes necessários na dieta. As variáveis analisadas serão: Massa corporal (Kg), Índice de Massa Corporal (Kg/m²); taxa metabólica basal; percentual de gordura; sensação subjetiva de fome, por meio de uma escala análoga visual; atividade física, com o questionário internacional de atividade física (IPAQ); níveis glicêmicos, insulinêmicos e lipidêmicos dos indivíduos. Todas as medidas serão tomadas anteriormente ao início da intervenção e após seu término. Assumindo-se 95% de confiança e 80% de poder estatístico de que a diferença na perda de peso entre as intervenções será menor que 1,5 ± 3,0 kg, isto é, uma intervenção não induzirá uma perda de peso clinicamente mais importante que a outra, serão necessários 28 indivíduos por grupo. Com uma adição de 20% considerando as perdas, serão necessários 68 indivíduos ao todo. Com os achados,

espera-se gerar uma forte evidência que pode ser usada para guiar condutas de nutricionistas no combate à obesidade.

Objetivo da Pesquisa:

Objetivo Primário:

O objetivo geral da pesquisa é determinar se o período alimentar (com restrição versus sem restrição de horário) influencia na perda de peso, na taxa metabólica basal, no apetite e no controle glicêmico e lipidêmico de mulheres com excesso de peso, submetidas a dietas com um mesmo déficit energético.

Avaliação dos Riscos e Benefícios:

Riscos:

Os riscos para os participantes com a realização desta pesquisa são pequenos. Espera-se um desconforto durante o procedimento de punção venosa para obtenção de sangue e posterior dosagem de marcadores bioquímicos. Além disso, espera-se um certo desconforto e possível
sensação de fome no início da intervenção dietética, especialmente para o grupo com restrição de horário nas refeições. Entretanto, essas sensações são passageiras e perfeitamente toleráveis por adultos saudáveis.

Benefícios:

Com os resultados deste ensaio clínico, espera-se afirmar que não existem diferenças clinicamente significativas entre seguir uma dieta com 3 refeições ao dia ou uma dieta com 6 refeições ao dia. Com isso, será possível flexibilizar os planos alimentares prescritos na prática clínica, que normalmente pregam uma alta frequência alimentar que pode contribuir para a baixa adesão de pacientes aos tratamentos dietéticos. Ademais, os
participantes receberão aconselhamento dietético para perda de peso durante toda a execução do projeto.

Comentários e Considerações sobre a Pesquisa:

Trata-se de solicitação de emenda a projeto já aprovado por este CEP. A mudança principal consistiu no efeito da mudança do período das refeições ao invés do número de refeições diárias nos desfechos. Foram feitas mudanças no título, no objetivo e na metodologia.

Considerações sobre os Termos de apresentação obrigatória:

Adequadamente refeitos para se adequar às mudanças no projeto.

Conclusões ou Pendências e Lista de Inadequações:

Por estar de acordo cpm as recomendações da resolução 466/12 sugerimos sua aprovação

Considerações Finais a critério do CEP:

Protocolo Aprovado

Prezado (a) Pesquisador (a), lembre-se que, segundo a Res. CNS 466/12 e sua complementar 510/2016:

O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado e deve receber cópia do TCLE, na íntegra, por ele assinado, a não ser em estudo com

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Telefone: (82)3214-1041 **E-mail:** comitedeeticaufal@gmail.com

autorização de declínio;

V.Sª. deve desenvolver a pesquisa conforme delineada no protocolo aprovado e descontinuar o estudo somente após análise das razões da descontinuidade por este CEP, exceto quando perceber risco ou dano não previsto ao sujeito participante ou quando constatar a superioridade de regime oferecido a um dos grupos da pesquisa que requeiram ação imediata;

O CEP deve ser imediatamente informado de todos os fatos relevantes que alterem o curso normal do estudo. É responsabilidade do pesquisador assegurar medidas imediatas adequadas a evento adverso ocorrido e enviar notificação a este CEP e, em casos pertinentes, à ANVISA;

Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas. Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial;

Seus relatórios parciais e final devem ser apresentados a este CEP, inicialmente após o prazo determinado no seu cronograma e ao término do estudo. A falta de envio de, pelo menos, o relatório final da pesquisa implicará em não recebimento de um próximo protocolo de pesquisa de vossa autoria.

O cronograma previsto para a pesquisa será executado caso o projeto seja APROVADO pelo Sistema CEP/CONEP, conforme Carta Circular nº. 061/2012/CONEP/CNS/GB/MS (Brasília-DF, 04 de maio de 2012).

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1080850_E1.pdf	28/02/2018 11:10:23		Aceito
Outros	Solicitacao_emenda.pdf	28/02/2018 11:09:50	Nassib Bezerra Bueno	Aceito
Projeto Detalhado / Brochura Investigador	Projeto_Frequencia_alimentar_PLATBR_ALTERADO.docx	27/02/2018 09:30:56	Nassib Bezerra Bueno	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_NOVO.pdf	23/02/2018 15:04:21	Nassib Bezerra Bueno	Aceito

Folha de Rosto	folhaDeRosto_NOVA.pdf	23/02/2018 14:39:10	Nassib Bezerra Bueno	Aceito
Declaração de Pesquisadores	declaracao.pdf	13/10/2016 00:25:20	Nassib Bezerra Bueno	Aceito
Declaração de Instituição e Infraestrutura	CREN.pdf	13/10/2016 00:25:03	Nassib Bezerra Bueno	Aceito

Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

MACEIO, 09 de Março de 2018

Assinado por:
Luciana Santana
(Coordenador)

B – Registro Brasileiro de Ensaios Clínicos

Ensaios Clínicos

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Influência do período alimentar (com restrição versus sem restrição de horário) na composição corporal, taxa metabólica de repouso, sensação de fome, insulinemia, leptinemia e função tireoidiana de mulheres obesas submetidas a dietas com um mesmo déficit energético.

Data de registro: 9 de Out. de 2017 às 09:13

Last Update: 10 de Julho de 2018 às 09:37

Tipo do estudo:

Intervenções

Título científico:

PT-BR	EN
Influência do período alimentar (com restrição versus sem restrição de horário) na composição corporal, taxa metabólica de repouso, sensação de fome, insulinemia, leptinemia e função tireoidiana de mulheres obesas submetidas a dietas com um mesmo déficit energético.	Influence of the dietary period (with restriction versus time restriction) on body composition, resting metabolic rate, hunger sensation, insulinemia, leptinemia and thyroid function of obese women submitted to diets with the same energy deficit.

Identificação do ensaio

Número do UTN: U1111-1203-4610

Título público:

PT-BR	EN
Influência do período alimentar (com restrição versus sem restrição de horário) na composição corporal, taxa metabólica de repouso, sensação de fome, insulinemia, leptinemia e função tireoidiana de mulheres obesas submetidas a dietas com um mesmo déficit energético.	Influence of the dietary period (with restriction versus time restriction) on body composition, resting metabolic rate, hunger sensation, insulinemia, leptinemia and thyroid function of obese women submitted to diets with the same energy deficit.

Acrônimo científico:

PT-BR

ERAPT.

Acrônimo público:

PT-BR

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