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REPERCUSSÕES DO JEJUM INTERMITENTE SOBRE A MICROBIOTA INTESTINAL E CONTROLE DO PESO CORPORAL: UMA REVISÃO SISTEMÁTICA

Recife
2021

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Área de concentração: Bases Experimentais da Nutrição.

Orientador: Profa. Dra. Sandra Lopes de Souza.

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À Deus, porque para Ele são todas as coisas.

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“A imaginação é mais importante que a ciência, porque a ciência é limitada, ao passo que a imaginação abrange o mundo inteiro”.

(EINSTEIN, 1931, p. 97)

RESUMO

Dentro do problema multifatorial da obesidade, a interação cérebro-intestino-microbiota alcançou grande evidência. Diversas terapias têm sido testadas para combater a obesidade, entre elas o interesse pelo jejum intermitente tem crescido muito. Jejum intermitente (IF) é usado é um termo genérico que se refere a vários métodos de jejum que restringem a ingestão calórica, como jejum em dias alternados (ADF) e restrição de temporal do alimento (TRF). Tipos de protocolos de jejum restritivo são cada vez mais comuns, configurando diversos desenhos metodológicos. A ritmicidade circadiana afeta o comportamento alimentar e as funções intestinais múltiplas, bem como a composição e as interações do microbioma com o intestino. Foram relatados profundos efeitos pré-clínicos do jejum intermitente e da alimentação com restrição de tempo no microbioma intestinal e no metabolismo do hospedeiro, principalmente demonstrados em modelos animais e em um número limitado de ensaios controlados em humanos. O objetivo desta revisão é fornecer ao leitor uma pesquisa atual dos protocolos de jejum intermitente (FI) e compreender os resultados encontrados no perfil da microbiota em organismos obesos. Identificamos 82 artigos com dados originais adequados para inclusão de acordo com nossos objetivos. Os dados foram obtidos em três bancos de dados (PUBmed, SCOPUS, LILLACs e Web of Science) em abril. Foram identificados 82 artigos nas bases de dados, 35 foram eliminados por duplicação. 47 estudos foram elegíveis para análise e seguiram os critérios de inclusão. Com essa análise, 28 publicações foram excluídas. Após a análise dos textos completos 4 estudos foram excluídos por envolverem outros tipos de jejum, não apresentarem dados sobre a microbiota e utilizarem indivíduos jovens, e somando mais 2 artigos encontrados em uma nova busca, um total de 17 estudos foram incluídos nesta Reveja. Dentre os protocolos, o jejum em dias alternados (ADF) e a restrição de temporal do alimento (TRF) são os mais comuns e possuem mecanismos distintos de sinalização metabólica. O TRF influencia o controle de peso e parâmetros bioquímicos, regulando os sinais do sistema circadiano, melhorando os sistemas de controle da saciedade, atuando na secreção de leptina. Enquanto o ADF, leva a uma redução de ± 75% de todo o consumo de energia independente da composição da dieta além de promover ajustes hormonais que promovem o controle do peso e melhora glicêmica. Além disso, ambos os protocolos mostraram a capacidade de remodelar o MI a fim de melhorar a relação entre

Firmicutes/Bacteroidetes e aumentar a abundância de cepas como *Lactobacillus* spp. e *Akkermansia m*. que têm um efeito protetor sobre o metabolismo contra os efeitos do ganho de peso. Em suma, os protocolos ADF e TRF têm um efeito positivo na remodelação do MI tanto em humanos quanto em modelos animais, e podem ser usados para controlar a adiposidade corporal e melhorar a sensibilidade à insulina.

Palavras-chave: jejum intermitente; disbiose; resistência à insulina; ganho de peso.

ABSTRACT

Within the multifactorial problem of obesity, the brain-gut-microbiota interaction has reached great evidence. Several therapies have been tested to combat obesity, among them the interest in intermittent fasting has grown a lot. Intermittent fasting (IF) is used is an umbrella term referring to various fasting methods restricting caloric intake, such as alternate-day fasting (ADF) and time-restricted feeding (TRF). Types of restrictive fasting protocols are increasingly common, configuring several methodological designs. Circadian rhythmicity affects both eating behavior and multiple gut functions, as well as the composition and interactions of the microbiome with the gut. Profound preclinical effects of intermittent fasting and time restricted eating on the gut microbiome and on host metabolism, mostly demonstrated in animal models and in a limited number of controlled human trials, have been reported. The purpose of this review is to provide the reader with a current survey of intermittent fasting (IF) protocols and to understand the outcomes found in the profile of the microbiota in obese organisms. We identified 82 papers with original data suitable for inclusion according to our aims. The data were obtained from three databases (PUBmed, SCOPUS, LILLACs and Web of Science) in April. 82 articles were identified in the databases, 35 were eliminated by duplication. 47 studies were eligible for analysis and followed the inclusion criteria. With this analysis, 28 publications were excluded. After analyzing the full texts 4 studies were excluded because they involved other types of fasting, didn't present data on the microbiota and used young individuals, and adding 2 more articles found in a new search, a total of 17 studies were included in this review. Among the protocols, alternate-day fasting (ADF) and time-restricted feeding (TRF) are the most common and have different mechanisms in metabolic signaling. TRF influences weight control and biochemical parameters by regulating circadian system signals, improving satiety control systems, acting on leptin secretion. While the ADF, it leads to a reduction of ±75% of all energy consumption regardless of dietary composition in addition to promoting hormonal adjustments that promote weight control and glycemic improvement. Furthermore, both protocols showed the ability to remodel IM in order to improve the relationship between Firmicutes/Bacteroidetes and increasing the abundance of strains such as *Lactobacillus* spp. and *Akkermansia m*. that have a protective effect on metabolism against the effects of weight gain. In short, the ADF and TRF protocols have a positive effect on the remodeling of the IM in both humans

and animal models, and can possibly be used to control body adiposity and improve insulin sensitivity.

Keywords: intermittent fasting; dysbiosis; insulin resistance; weight gain.

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LISTA DE ABREVIATURAS E SIGLAS

5-HT	5-hidroxitriptamina
A	Altura
ADF	Alternate-day fasting (Jejum de dias alternados)
ADL	*Ad libitum*
AKT	Proteína quinase B
CC	Circunferência da cintura
CLD	Claudina
DCNT	Doença crônica não transmissível
DHGNA	Doença hepática gordurosa alcoólica
DNA	Deoxyribonucleic *acid*
DSS	Sulfato de dextrano sódico
FIAF	*Fasting-induced adipose factor*
FMD	Fasting mimicking diet
GLUT-4	Transportador de glicose 4
HDL	*High density lipoprotein*
HFD	Dieta hiperlipídica
HOMA-IR	*Homeostatic model assessment for insulin resistance*
IBGE	Instituto brasileiro de geografia e estatística
IF	Intermittent fasting (Jejum intermitente)
IGF-1	Fator de crescimento semelhante à insulina tipo 1
IKK	*IKappa Kinase*
IKKβ	Inibidor da subunidade beta do NF-kβ
IL-1β	Interleucina 1 beta
IL-6	Interleucina 6
IMC	Índice de massa corpórea
JNK	*C-jun N-terminal Kinase*
LDL	*Low density lipoprotein*
LPS	Lipopolissacarídeo
MADF	Modified alternate-day fasting (Jejum modificado de dias alternados)
MI	Microbiota intestinal
ND	Dieta normal

NF-Kβ	Fator nuclear Kappa β
OMS	Organização mundial de saúde
PA	Pressão arterial
PAMP	Padrões moleculares associado a patógenos
PC	Peso corporal
PYY	Peptídeo YY
RC	Restrição calórica
REC	Restrição energética contínua
RIE	Restrição intermitente de energia
SCFA	*Short-chain fatty acid* (ácido graxo de cadeia curta)
SM	Síndrome metabólica
TG	Triglicerídeos
TGI	Trato gastrointestinal
TLR	receptor *toll-like*
TLR-4	receptor *toll-like 4*
TNF-α	Fator de necrose tumoral alfa
TRF	Time-restricted feeding (Restrição temporal do alimento)
TRFc	Restrição do alimento cedo
TRFt	Restrição do alimento tarde

SUMÁRIO

1 INTRODUÇÃO

Nas últimas décadas, a humanidade passou pelas mudanças mais complexas, entre as quais uma das mais marcantes aconteceu na alimentação. Houve mudanças no comportamento alimentar e nas atividades diárias, trazendo consigo o crescimento de distúrbios metabólicos, principalmente aqueles relacionados ao ganho excessivo de peso corporal (AL-ASSAL et al., 2018; BARBOSA et al., 2019; TASNIM et al., 2017). No Brasil, segundo o Instituto Brasileiro de Geografia e Estatística (IBGE, 2020), a prevalência de sobrepeso (60,3%) e obesidade (25,9%) em 2019 entre os maiores de 18 anos foi alarmante. Sabe-se que a obesidade atua como fator relevante no desenvolvimento de doenças crônicas não transmissíveis (DCNT) e até mesmo no agravamento do quadro clínico pré-existente (IBGE, 2020). Como forma de minimizar os efeitos da obesidade na saúde do indivíduo, recomenda-se a perda de peso com ajustes na dieta e atividade física (DOMBROWSKI et al., 2014; KHAN et al., 2016; KUNATH et al., 2019).

Além disso, estratégias nutricionais baseadas na restrição do tempo de alimentação têm demonstrado potencial efeito no controle do ganho de peso corporal e na melhor adaptação à rotina alimentar dos indivíduos. Assim, os protocolos de jejum intermitente (*intermittent fasting* - IF) têm se mostrado uma das ferramentas emergentes no manejo nutricional atual (ANSON et al., 2003; DE CABO; MATTSON, 2019; MATTSON; WAN, 2005). Pesquisa animal (BELI et al., 2018; CATTERSON et al., 2018; CHUNG et al., 2016) e humana (CAI et al., 2019; CIENFUEGOS et al., 2020; HUTCHISON et al., 2019) que utilizam IF têm demonstrado potenciais efeitos benéficos no controle do peso corporal e distúrbios metabólicos. O IF é uma estratégia nutricional que se baseia em um conjunto de protocolos para restringir o tempo de alimentação nos mais variados horários. E esses protocolos de jejum têm demonstrado efeito positivo no ambiente intestinal, especificamente na qualidade de sua microbiota intestinal (*intestinal microbiota* - IM), que por sua vez tem sido associada à melhora de diversas doenças, como doenças inflamatórias intestinais e alterações eixo intestino-cérebro (AL-ASSAL et al., 2018; MILANI et al., 2017).

O ambiente intestinal é colonizado por várias espécies de microrganismos que compõem a microbiota. Entre os quais podemos encontrar bactérias, vírus e fungos, que quando em simbiose com o hospedeiro influenciam na manutenção da

homeostase corporal (AL-ASSAL et al., 2018; BATTSON et al., 2018). Nessa relação, o organismo humano é beneficiado pelo fornecimento de nutrientes, proteção contra patógenos e/ou agentes físicos e químicos (CANI, 2018; GENTON; CANI; SCHRENZEL, 2015; RASTELLI; CANI; KNAUF, 2019). Entre os filos bacterianos presentes no IM, *Firmicutes* (gram-positivos) e *Bacteroidetes* (gram-negativos) (AL-ASSAL et al., 2018; KARL et al., 2018) são equivalentes a cerca de 90% de toda a bactéria intestinal comunidade (MILANI et al., 2017; MITEV; TALESKI, 2019). Essas populações têm funções metabólicas importantes, quando em equilíbrio com o hospedeiro, e são capazes de gerar metabólitos como os ácidos graxos de cadeia curta (*short-chain fatty acid* - SCFAs) por meio da fermentação de substratos alimentares e componentes derivados não digeríveis, como os frutooligossacarídeos, pectina e inulina, entre outros (AL-ASSAL et al., 2018). Assim, os nutrientes não absorvidos nas porções intestinais superiores, atuam como substrato para o IM que sintetiza produtos capazes de modular a expressão de genes que atuam na produção/liberação de hormônios intestinais, tecido adiposo e sistema nervoso, como a grelina, leptina, peptídeo semelhante ao glucagon 1 (GLP-1) e peptídeo YY (PYY), atuando no controle do apetite (MITEV; TALESKI, 2019; RASTELLI; CANI; KNAUF, 2019).

Entre os fatores reguladores da flora intestinal estão a alimentação, a atividade física, o meio social e fatores genéticos (MILANI et al., 2017). Esses fatores juntos produzem uma série de elementos, que definem como cada variedade taxonômica se desenvolverá no ambiente intestinal (NAKAYAMA et al., 2017; TASNIM et al., 2017). Destes fatores, a alimentação inadequada juntamente com a herança genética, leva ao desenvolvimento desordenado de microrganismos patogênicos no ambiente intestinal, levando à “disbiose intestinal” (RASTELLI; CANI; KNAUF, 2019). Este é o principal fator no desenvolvimento de doenças no hospedeiro e está frequentemente associado a um aumento na relação entre os dois filos predominantes (KHAN et al., 2016; MEROPOL; EDWARDS, 2015; RASTELLI; CANI; KNAUF, 2019). Tal evento leva à ruptura do equilíbrio do meio intestinal, da relação simbiótica e redução da diversidade, que por sua vez está associada a uma série de doenças crônicas como obesidade, diabetes e doenças inflamatórias (BATTSON et al., 2018; MILANI et al., 2017; MITEV; TALESKI, 2019). Por exemplo, na obesidade há redução na proporção e diversidade de frações do filo *Bacteroidetes* em relação ao filo *Firmicutes*

(BATTSON et al., 2018). Possivelmente associado ao excesso de produção de SCFAs e endotoxinas, aumentando a disponibilidade de substratos energéticos e o estado inflamatório, consequentemente levando ao acúmulo de tecido adiposo e outras alterações metabólicas (CANI et al., 2008; KHAN et al., 2016; TASNIM et al., 2017). Os mecanismos relevantes para essa relação entre o IM e seu hospedeiro advêm principalmente de a capacidade de seus metabólitos reagirem com receptores de células intestinais, induzindo a expressão ou supressão de genes moduladores de funções orgânicas (KHAN et al., 2016; RASTELLI; CANI; KNAUF, 2019). Em suma, pode-se dizer que o alimento modula como cada cepa da microbiota se desenvolverá no ambiente intestinal (CANI et al., 2008; HU et al., 2018).

Além disso, existem diversos protocolos de IF nas pesquisas que acabam levantando dúvidas, quais são os protocolos mais eficazes em promover resultados benéficos ao indivíduo. Por outro lado, quando aplicado de forma adequada, auxilia na resposta glicêmica, aumento da termogênese (DE CABO; MATTSON, 2019; FABBIANO et al., 2018; MATTSON; WAN, 2005), controle do peso corporal (CAI et al., 2019; CATTERSON et al., 2018; RYNDERS et al., 2019), na saúde da microbiota (BELI et al., 2018; FABBIANO et al., 2018) e na prevenção de doenças cardiovasculares e do sistema nervoso (ANSON et al., 2003; MATTSON; WAN, 2005; SUTTON et al., 2018).

Diante disso, torna-se cada vez mais relevante investigar as possíveis aplicações e variações do jejum intermitente, bem como as repercussões dessa estratégia na promoção da saúde intestinal (microbiota) e metabólica.

2 OBJETIVO

Verificar os efeitos do jejum intermitente sobre a microbiota intestinal e na manutenção do peso corporal em indivíduos obesos.

3 REFERENCIAL TEÓRICO

3.1 OBESIDADE

A crescente prevalência de obesidade no mundo alcançou níveis epidêmicos nas últimas décadas, estando relacionada principalmente a alterações na distribuição de gordura e o seu diagnóstico é obtido a partir de ferramentas como o índice de massa corpórea (IMC). Essa escala é feita a partir da formula: *IMC = P / (A²)* e diagnostica indivíduos cujo resultado desse cálculo seja acima de 24,9kg/m² com excesso de peso e como obesos acima de 29,9kg/m² (**tabela 1)** (BLÜHER, 2019; VECCHIÉ et al., 2018). Este quadro clinico é visto em todo mundo, entre indivíduos de todas idades e classes econômicas, dados epidemiológicos relatam que entre 1975 a 2014 foi observado o aumento da prevalência de obesidade entre indivíduos adultos (3,2% para 10,8% em homens e de 6,4% para 14,9% em mulheres) além da alta prevalência de homens e mulheres obesos mórbidos (respectivamente, 0,64% e 1,6%) (BLÜHER, 2019). Do mesmo modo no Brasil a prevalência de obesidade entre adultos ultrapassa os 25% em 2019 (IBGE, 2020) e segundo a Organização Mundial de Saúde (OMS), dados sugerem que em 2025 haverá cerca de 2,3 bilhões de adultos obesos em todo mundo.

Tabela 1 - Definição de obesidade pela OMS.

Parâmetro	Valor de referencia	Classificação
IMC	< 18,5kg/m²	Abaixo do peso
	18,5 – 24,9kg/m²	Eutrófico
	25 – 29,9kg/m²	Sobrepeso
	30 – 34,9kg/m²	Obesidade grau I
	35 – 39,9kg/m²	Obesidade grau II
	> 39,9kg/m²	Obesidade grau III
Circunferência da cintura		
Homem	> 102 cm	-
Mulher	> 88 cm	-
Relação cintura/quadril		
Homem	> 0,9	-
Mulher	> 0,85	

Fonte: adaptado de Vecchié et al. (2018). IMC – índice de massa corpórea.

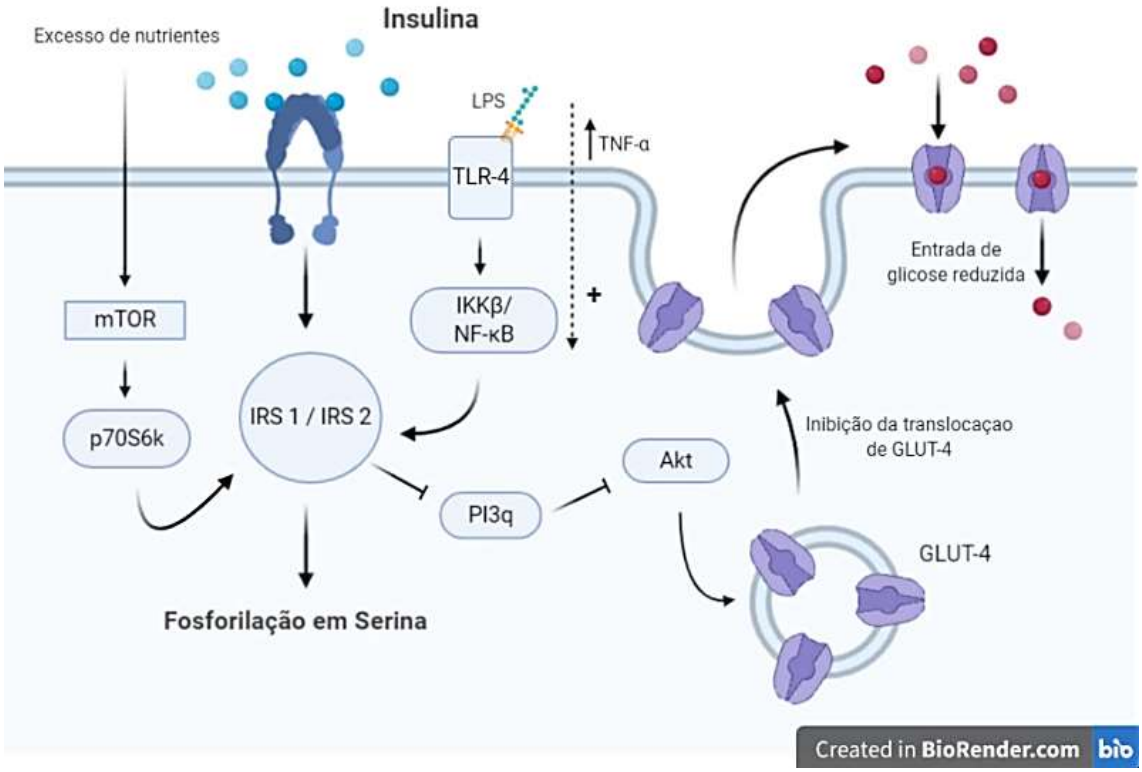
De etiologia multifatorial, seus principais precursores são a alimentação inadequada, a inatividade física, predisposição genética dentre outros (BARBOSA et al., 2019; KHAN et al., 2016; MOREIRA et al., 2012a; SWINBURN; SACKS; RAVUSSIN, 2009). A obesidade é caracterizada principalmente pelo acúmulo excessivo de gordura corporal e o aumento da atividade inflamatória, concomitantemente há uma diminuição da responsividade dos sistemas de controle da saciedade e glicemia (BARBOSA et al., 2019; KHAN et al., 2016). A alimentação figura-se como uma das mais relevantes causas da obesidade, a sua composição é importante para a instalação da obesidade, principalmente quando baseada no alto consumo de produtos industrializados característico da alimentação “ocidentalizada” (DEMIGNÉ et al., 2006; HOWIE et al., 2009; NAKAYAMA et al., 2017).

Essa alimentação ocidental ou ocidentalizada, está cada vez mais rica em produtos hiperenergéticos (fonte de altas concentrações de açúcares simples e gordura saturada), pobre em compostos bioativos e fibras, é comum na sociedade moderna e relaciona-se às alterações bioquímicas no desenvolvimento de doenças crônicas não transmissíveis (DCNT) (BARBOSA et al., 2019; DAVIS et al., 2017; NAKAYAMA et al., 2017; SWINBURN; SACKS; RAVUSSIN, 2009; WAN et al., 2019). Tal cultura alimentar somado a inatividade física e outros fatores influenciam em adaptações fisiológicas que elevam o armazenamento de gordura nos adipócitos e consequentemente alterando toda bioquímica do indivíduo além disso, essas modificações presentes na obesidade, elevam consideravelmente o risco para outras alterações metabólicas e DCNTs (BLÜHER, 2019).

Entre as DCNTs, a obesidade tem se configurado como um problema grave de saúde pública, com diversas alterações metabólicas, dentre elas a resistência insulínica (GAO et al., 2019) e de acordo com a *International Diabetes Federation* em 2019 há cerca de 463 milhões de pacientes com diabete mellitus tipo 2 (DMT2) em todo o mundo (SAEEDI et al., 2019). Esta por sua vez ocorre devido a redução da capacidade da insulina em ativar múltiplas vias e cascatas de fosforilação intracelular que levam a captação de glicose do meio extracelular (GUO, 2014; MOREIRA et al., 2012b). O mecanismo proposto como possível causa da resistência à insulina, na obesidade é a produção/secreção de citocinas inflamatórias pelo tecido adiposo, em especial a interleucina 6 (IL-6) e o fator de necrose tumoral alfa (TNF-α) (CANI et al., 2007; MOREIRA et al., 2012b; WEI et al., 2008). Essas citocinas estão envolvidas em

várias alterações metabólicas e na resistência à insulina, atuando através da ativação das vias c-jun N-terminal quinase (JNK), Ikappa kinase (IkK) e fator nuclear kappa-β (NF-kβ) (**figura 1**) (GUO, 2014; MOREIRA et al., 2012b). A ativação destes mecanismos, induzem a fosforilação dos substratos de receptores de insulina (IRS) em serina e suprimindo a via PI3q/Akt, reduzindo a captação de glicose (GUO, 2014; ZAULKFFALI et al., 2019).

Figura 1 - Obesidade e microbiota intestinal: possíveis mecanismos fisiológicos envolvidos no desenvolvimento da resistência à insulina.



Fonte: elaborado pelo pesquisador. A ativação dos receptores *toll-like* pela interação do LPS, com a ativação da via IKK/Nf-kβ induzindo a fosforilação dos IRS 1 e 2 em serina ou o acumulo de nutrientes através da via mTOR induz a fosforilação dos IRS 1 e 2 com consequente inativação da via PI3q/Akt, causando a redução da translocação do transportador de glicose 4 e consequentemente a hiperglicemia. Legendas: AKT – proteína quinase B; GLUT-4 – transportador de glicose 4; IKKβ – inibidor da subunidade beta do fator nuclear kappa-β quinase; IRS – substrato do receptor de insulina; LPS – Lipopolissacarídeo; mTOR – *mammalian target of rapamycin*; NF-kβ - fator nuclear kappa-β; p70S6k – proteína ribossômica S6 quinase; PI3q - fosfoinositídeo 3-quinase; TLR-4 – receptor *toll like*; TNF-α – fator de necrose tumoral alfa.

Outras vias podem estar relacionadas a indução da produção/secreção de citocinas pró-inflamatórias, uma delas é através da ativação dos receptores *toll-like 4* (TLR-4) pelo lipopolissacarídeo (LPS) bacteriano. Essa via é o principal meio através do qual a IM induz o processo inflamatório e a ativação excessiva dessa via leva ao

desenvolvimento da resistência à insulina (CANI et al., 2007; KHAN et al., 2016; MOREIRA et al., 2012a). Por fim, o ganho de peso e os distúrbios da massa gorda causam resistência à insulina (levando a redução de seu efeito) provocando hiperglicemia. A glicemia elevada é a principal responsável por boa parte da lesão tecidual característica, o aumento da glicação e estresse oxidativo com favorecimento do aumento do perfil inflamatório (MOREIRA et al., 2012a).

3.2 PRINCIPAIS PROTOCOLOS DE JEJUM INTERMITENTE E REPERCUSSÕES METABÓLICAS

A busca constante de formas mais eficazes de controle do peso e manutenção das funções metabólicas é crescente. Nos últimos anos, estudos demonstram que estratégias nutricionais de restrição exercem uma importante atividade na melhora da qualidade de vida dos indivíduos (MATTSON; WAN, 2005). A utilização de protocolos de IF para o controle de peso e a melhora do metabolismo, com destaque para o controle/prevenção de comorbidades relacionadas a obesidade, estão mais comuns e esse interesse é crescente (DE CABO; MATTSON, 2019; MATTSON; LONGO; HARVIE, 2017; RYNDERS et al., 2019; TINSLEY; LA BOUNTY, 2015). Além disso os protocolos de IF apresentam melhor adaptação a rotina e hábitos alimentares dos praticantes, promovendo maior adesão e o uso por longos períodos (HU et al., 2020). O fato dos protocolos de IF influenciarem no estado energético e metabólico da célula, promove alterações em nível molecular com fins de proteção celular e minimização de processos inflamatórios (HATORI et al., 2012; MORO et al., 2016; TREPANOWSKI et al., 2017; VAN DER MERWE et al., 2020; ZHENG; WANG; JIA, 2018). Sua continuidade modifica não apenas o perfil inflamatório, mas também, a distribuição de gordura, podendo também levar ao aumento da gordura marrom, ditando o percurso de boa parte das adaptações metabólicas e da microbiota durante o jejum (FABBIANO et al., 2018; LI et al., 2017).

Segundo Van Der Merwe et. al., (2020) os tipos de IF podem ser classificados em dois grandes tipos: restrição temporal do alimento (TRF) e o jejum de dias alternados (*alternate-day fasting* - ADF). O jejum do tipo TRF trata-se de um protocolo de regime diário, em que o indivíduo permanece em períodos de jejum e alimentação. Geralmente os períodos de jejum baseados em TRF variam entre 12, 14 e 16 horas por dia (**tabela 2**), limitando em média os períodos de alimentação a uma janela de

<10h/dia podendo haver restrições na composição das refeições (CIENFUEGOS et al., 2020; HU et al., 2019; RYNDERS et al., 2019; VAN DER MERWE et al., 2020; ZEB et al., 2020a). Enquanto que os protocolos baseados em jejum ADF, refere-se a um jejum de 24h seguido por 24h de alimentação (**tabela 2**) (ANSON et al., 2003; VAN DER MERWE et al., 2020; ZHANG et al., 2020).

Tabela 2 - Protocolos de Jejum Intermitente.

Protocolos	**DIA 1**	**DIA 2**	**DIA 3**	**DIA 4**	**DIA 5**	**DIA 6**	**DIA 7**
TRF (12:12)	12h de jejum	12h de jejum	12h de jejum	12h de jejum	12h de jejum	12h de jejum	12h de jejum
TRF (14:10)	14h de jejum	14h de jejum	14h de jejum	14h de jejum	14h de jejum	14h de jejum	14h de jejum
TRF (16:8)	16h de jejum	16h de jejum	16h de jejum	16h de jejum	16h de jejum	16h de jejum	16h de jejum
ADF	24h de jejum	Livre	24h de jejum	Livre	24h de jejum	Livre	24h de jejum

Fonte: adaptado de Tinsley e La Bounty (2015). TRF – restrição temporal do alimento; ADF – Jejum de Dias Alternados.

Os protocolos do tipo TRF apresentam variações no tempo da oferta de alimento (**tabela 2**) por uma janela igual ou menor que 12h de alimentação (CAI et al., 2019; RYNDERS et al., 2019; TINSLEY; LA BOUNTY, 2015). Os protocolos de TRF com variações do início do período alimentar, caracterizam–se em comer no início do dia, ou seja, seguindo os padrões do sistema circadiano, denominado como restrição temporal do alimento no início do dia (TRFc) (SUTTON et al., 2018). Já os protocolos baseados em jejum ADF, são estruturados em períodos de jejum de 24h seguido por 24h de alimentação promovendo a redução de até 75% do consumo energético total (**tabela 2**) (ANSON et al., 2003; CAI et al., 2019; VAN DER MERWE et al., 2020; ZHANG et al., 2020). Além disso, o ADF também pode sofrer pequenas mudanças na programação dos períodos de jejum, podendo haver consumo de até 37% das necessidades energéticas diárias nos dias de jejum (RYNDERS et al., 2019), definido como jejum modificado de dias alternados (MADF).

Sabe-se que estudos que fazem uso de protocolos de IF apresentam benefícios semelhantes tanto em humanos (CIENFUEGOS et al., 2020; HUTCHISON et al., 2019) como em animais (CHUNG et al., 2016). Atuando principalmente na redução o peso corporal e/ou gordura corporal (MORO et al., 2016; RYNDERS et al., 2019; SUTTON et al., 2018), na redução dos níveis de glicose e/ou insulina, na melhora da sensibilidade à insulina (CHUNG et al., 2016), do perfil lipídico (CAI et al., 2019) e reduzindo os marcadores de inflamação e estresse oxidativo (HU et al., 2020; MATTSON; WAN, 2005; MORO et al., 2016; SUTTON et al., 2018; TINSLEY; LA BOUNTY, 2015; ZEB et al., 2020b). Esses benefícios podem até ser relacionados a diminuição da ingestão de macronutrientes e/ou densidade energética diária.

3.3 MICROBIOTA INTESTINAL, DISBIOSE E RESISTÊNCIA À INSULINA

O trato gastrointestinal (TGI) tem o papel de degradar o alimento e absorver os nutrientes para posterior utilização pelo organismo. O TGI vem se destacando nas últimas décadas, visto que sua funcionalidade não se restringe apenas a digestão de alimentos (MOREIRA et al., 2012b). Hoje, sabe-se que TGI exerce muito mais influência na fisiologia humana. Nele, os alimentos são digeridos por enzimas e outras substâncias que irão promover a produção de moléculas menores e posterior passagem para a corrente sanguínea. Porém, esse processo não ocorre com todos os substratos alimentares e a existência de moléculas com baixa ou nenhuma digestão/absorção requer a participação de outras estruturas, como a IM (GENTON; CANI; SCHRENZEL, 2015).

O ambiente intestinal é colonizado por diversas espécies de microrganismos que compõem a IM e entre esses encontram-se: bactérias, vírus e fungos, que quando em simbiose com o hospedeiro influenciam na manutenção da homeostase (AL-ASSAL et al., 2018; BATTSON et al., 2018). Nessa relação, ambos os grupos são beneficiados, tanto pelo fornecimento de nutrientes, quanto pela proteção contra patógenos e/ou agentes físicos e químicos (CANI, 2018; GENTON; CANI; SCHRENZEL, 2015; RASTELLI; CANI; KNAUF, 2019). Entretanto essas populações microbianas são constituídas predominantemente de bactérias, como as dos filos *Firmicutes* (gram-positivas) e *Bacteroidetes* (gram-negativas) (AL-ASSAL et al., 2018; KARL et al., 2018). A diversidade de filos, principalmente os bacterianos, que compõem a IM e o estudo dessas espécimes tem ganhado destaque em anos

recentes (RINNINELLA et al., 2020). Dentre os filos bacterianos presentes na IM, os *Firmicutes* e *Bacteroidetes* equivalem a cerca de 90% de toda comunidade bacteriana intestinal e o restante composto por *Actinobacteria*, *Fusobacteria*, *Proteobacteria* e outras (MILANI et al., 2017; MITEV; TALESKI, 2019). Estas populações microbiológicas exercem funções metabólicas importantes, quando em equilíbrio com o hospedeiro e são capazes de gerar metabólitos através da fermentação de substratos alimentares e componentes derivados não digeríveis, como polissacarídeos dentre outros (AL-ASSAL et al., 2018). Deste modo, os nutrientes não absorvidos nas porções intestinais superiores, atuam como substrato para a microbiota sintetizando produtos capazes de modular a expressão de genes reverberando na produção/liberação de hormônios intestinais, no tecido adiposo e a nível do sistema nervoso, como grelina, leptina, peptídeo semelhante ao glucagon 1 e peptídeo YY (PYY), atuando no controle do apetite (MITEV; TALESKI, 2019; RASTELLI; CANI; KNAUF, 2019).

A IM residente apresenta forte participação no metabolismo humano desde o nascimento. Logo nos primeiros dias de vida, o tipo de parto indica inicialmente como o intestino perderá sua característica estéril, no momento em que o recém-nascido tem contato oral-anal ou oral-abdômen sendo rapidamente colonizado pela microbiota materna (VIDAL-SANTOS et al., 2017), adquirindo as mesmas características e assim provendo os primeiros traços de desenvolvimento do sistema imune inato (AL-ASSAL et al., 2018; CANI, 2018; MEROPOL; EDWARDS, 2015; RASTELLI; CANI; KNAUF, 2019). Após a instalação da IM residente, esta passa a auxiliar na produção de nutrientes e compostos energéticos, bem como a participação na produção e excreção de hormônios (RASTELLI; CANI; KNAUF, 2019). Sendo a IM um “órgão complementar” ao sistema gastrointestinal (GENTON; CANI; SCHRENZEL, 2015; KHAN et al., 2016) e sistema nervoso (KHAN et al., 2016; MATTSON; WAN, 2005; MEROPOL; EDWARDS, 2015).

Entre os fatores reguladores e intervenientes da flora intestinal tem-se a alimentação, a atividade física, o ambiente social, e os fatores genéticos (MILANI et al., 2017). O conjunto desses fatores produzem uma série de elementos, que definem como cada variedade taxonômica irá se desenvolver no ambiente intestinal (NAKAYAMA et al., 2017; TASNIM et al., 2017). Destes fatores que podem intervir na estruturação da comunidade microbiana, os relacionados com a alimentação

apresentam maior potencial modulatório e destacando-se a frequência e a qualidade dos nutrientes (FABERSANI et al., 2019; RANGAN et al., 2019). Um ambiente favorável a IM residente permite uma relação simbiótica com o hospedeiro, contribuindo para a manutenção homeostática (BAUER; HAMR; DUCA, 2016; FETISSOV, 2017; TASNIM et al., 2017).

Em contrapartida, a alimentação inadequada em conjunto com outros fatores, a exemplo da herança genética, leva ao desenvolvimento desordenado de microrganismos patogênicos no ambiente intestinal, ocasionando na “disbiose intestinal” (rompimento dessa relação simbiótica entre a microbiota e o hospedeiro) que constitui o principal fator no desenvolvimento de doenças no hospedeiro e é frequentemente associada ao aumento da relação entre os dois filos predominantes (KHAN et al., 2016; MEROPOL; EDWARDS, 2015; RASTELLI; CANI; KNAUF, 2019). A disbiose intestinal é caracterizada como uma perturbação quantitativa e/ou qualitativa que ocorre no balanceamento entre populações de micróbios protetores e patogênicos no hospedeiro. Tal evento leva a uma ruptura no equilíbrio do ambiente intestinal, da relação simbiótica e a redução da diversidade, que por sua vez é associada a uma série de doenças crônicas como obesidade, diabetes e doenças inflamatórias (BATTSON et al., 2018; MILANI et al., 2017; MITEV; TALESKI, 2019). Por exemplo, na obesidade ocorre a redução da proporção e diversidade de frações do filo Bacteroidetes em relação ao filo *Firmicutes* (BATTSON et al., 2018). Este desequilíbrio possivelmente está associado a um excesso na produção de ácidos graxos de cadeia curta (*short-chain fatty acids* - SCFAs) e de endotoxinas, elevando a disponibilidade de substratos energéticos e do estado inflamatório, o que consequentemente pode levar ao acúmulo de tecido adiposo além de outras alterações no metabolismo (CANI et al., 2008; KHAN et al., 2016; TASNIM et al., 2017).

A composição dietética é um fator alimentar importante a ser considerado na modulação da IM, no caso de dietas com baixo teor de fibras e elevadas concentrações de gorduras, por exemplo. Em estudos com humanos, o aumento da gordura dietética induz o maior desenvolvimento *Bacteroides* spp. do filo Bacteroidetes e prevalentes em dietas “hiperenergéticas” bem como a redução de *Bifidobacterium* spp. (DAVIS et al., 2017; MOREIRA et al., 2012b; NAKAYAMA et al., 2017; WAN et al., 2019). Do mesmo modo, pode-se observar que estudos de restrição

calórica e/ou tempo de alimentação aplicados em camundongos obesos, promoveram um rearranjo no IM e apresentando uma similaridade com a microbiota de animais saudáveis (eutróficos) (FABBIANO et al., 2018; GENTON; CANI; SCHRENZEL, 2015). Além disso, existem grupos bacterianos que apresentam um efeito protetor ao metabolismo, como é o caso das *Bifidobacterium* spp. (gram-positivas), *Lactobacillus* spp. (gram-positivas) e as do gênero *Akkermansia* spp. (gram-negativas) (**tabela 3)** (CANI; DE VOS, 2017). Esses filos são responsáveis pela metabolização dos carboidratos complexos não digeridos atuando como probióticos e produzindo metabolitos como SCFAs essenciais em várias vias de regulação do metabolismo, promovendo a manutenção de sistemas fisiológicos (AL-ASSAL et al., 2018; KOH et al., 2016). Os mecanismos pertinentes a essa relação entre a IM e seu hospedeiro advém principalmente da capacidade de seus metabolitos reagirem com receptores das células intestinais, induzindo a expressão ou supressão de genes moduladores de funções orgânicas (KHAN et al., 2016; RASTELLI; CANI; KNAUF, 2019). Em suma, pode-se dizer que a alimentação modula como cada cepa irá se desenvolver no ambiente intestinal (CANI et al., 2008; HU et al., 2018).

Tabela 3 - Associação entre microbiota intestinal e sua influência no desenvolvimento de doenças crônicas.

Bactéria/Filo	Obesidade	Diabetes Mellitus	DII
Firmicutes	-		-
Clostridiales	-	-	-
Ruminococcaceae	-	-	-
Lachnospiraceae	-	-	-
Bacteroidetes	+	+	+
Actinobacteria	+		+
Lactobacillus	-	-	-
Staphylococcus	+		+
Roseburia		-	
Bifidobacteriaceae	-	-	-
Akkermansia m.	-	-	-

(+), aumenta o risco de desenvolver a doença; (-), reduz o risco de desenvolver a doença; DII – doença inflamatória intestinal. Fonte: adaptado de Hu *et al.,* (2018); Cani e De Vos, (2017).

A influência da IM não se limita a ação dos SCFAs visto que existem outras moléculas capazes de atuar na sinalização sistêmica. Uma destas moléculas é o lipopolissacarídeo (LPS), presentes na camada externa das bactérias gram-negativas. Os LPS atuam na maturação do sistema imune e linfoide, através de sinais, como os padrões moleculares associados a patógenos (PAMPs) que levam a ativação dos receptores *toll-like* (TLRs) promovendo a resposta inflamatória (LEE; ZHAO; HWANG, 2010; TASNIM et al., 2017). A ativação excessiva destes receptores apresenta um papel bem definido no aumento da produção/secreção de citocinas e quimiocinas relevantes na indução do processo inflamatório sistêmico fundamental na instalação e manutenção da obesidade (CANI et al., 2008). Além de conexo com a diminuição da barreira intestinal, o processo inflamatório intenso promove o aumento da permeabilidade intestinal permitindo maior passagem de LPS e outras grandes moléculas para a circulação sistêmica e essa ascensão de LPS induz a endotoxemia. Este fenômeno está relacionado à elevação dos processos inflamatórios no tecido adiposo, a diminuição a sensibilidade à insulina e a leptina (BAUER; HAMR; DUCA, 2016; CANI; DELZENNE, 2011; MOREIRA et al., 2012a).

O termo endotoxina é ocasionalmente usado para referir-se a qualquer “toxina” associada a células microbianas (flagelina, DNA, peptidoglicano, ácido lipoteicoico) e à sua atividade biológica (HURLEY, 1995). A atuação do LPS é fundamental na maturação do sistema imune inato como estímulo a mobilização dos mecanismos de defesa (FABBIANO et al., 2018; MOREIRA et al., 2012a). O problema pode surgir quando essa resposta é exagerada, como na sepse, ou de baixo grau, porém crônico, como é o caso da obesidade e do DMT2. O LPS funciona como agonista dos receptores TLR4 que após a sua ativação, induz o processo inflamatório ao estimular a produção e liberação de citocinas (SHI et al., 2006) em virtude da ativação da transcrição gênica via NF-Kβ. As citocinas liberadas mediante estímulo com LPS, particularmente o TNF-α e IL-6, levam ao aumento da fosforilação da serina dos IRS (**figura 1**), resultando em um desestímulo na via sinalização da insulina (VAN DER MERWE et al., 2020; WEI et al., 2008). Em suma, a ativação excessiva dos TLRs devido ao aumento dos níveis de LPS, pode levar a uma inflamação severa sistêmica e resistência à insulina, culminando numa série de complicações na saúde do indivíduo, principalmente obesidade (AL-ASSAL et al., 2018; KHAN et al., 2016;

MITEV; TALESKI, 2019), doenças cardiovasculares (BATTSON et al., 2018; RINNINELLA et al., 2020), dentre outras DCNTs.

Alterações metabólicas em decorrência da obesidade e de alterações na IM podem ser relacionadas a vários mecanismos. O LPS é uma das vias mais relevantes no processo de resistência à insulina, outra via relevante, é o acumulo de gordura que vem sendo relacionado a ativação da via *mammalian target of rapamycin* (mTOR) (CANI et al., 2019; RASTELLI; CANI; KNAUF, 2019) e a alterações no perfil inflamatório (MOREIRA et al., 2012b), induzindo a fosforilação do IRS em serina impedindo a translocação do transportador de glicose 4 (GLUT-4) e reduzindo a entrada da glicose para o interior da célula (**figura 1**) (CANI et al., 2019; RASTELLI; CANI; KNAUF, 2019; ZAULKFFALI et al., 2019). Contudo, o envolvimento do LPS é somente uma das variáveis por trás da influência da microbiota no metabolismo do hospedeiro. Um dos modelos propostos é de que a disbiose intestinal está associada com a obesidade nutricional (especialmente dieta rica em gordura) e genética (CANI et al., 2007; CANI; DELZENNE, 2011; MOREIRA et al., 2012a).

Em suma, vários mecanismos podem associar a microbiota, o desenvolvimento da obesidade e resistência à insulina. De fato, a alimentação e a inatividade física convergem com outros fatores, levando a alterações na composição da microbiota (DAVIS et al., 2017; KARL et al., 2018; KHAN et al., 2016; MOREIRA et al., 2012b; WAN et al., 2019). Que por fim, induz ao aumento da adiposidade e dos níveis de citocinas pró-inflamatórias, culminando na resistência à insulina e outras modificações metabólicas (CANI et al., 2007, 2019; CANI; DELZENNE, 2011; FABBIANO et al., 2018; MOREIRA et al., 2012a).

4 METODOLOGIA

4.1 DESENHO DE ESTUDO

A pesquisa da literatura foi conduzida utilizando o programa START (gerenciador de revisão sistemática de bibliografia) (FABBRI et al., 2016) a partir do protocolo previamente elaborado. Para triagem dos dados foi utilizado as recomendações propostas pelo PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). Foram selecionados estudos publicados sobre a aplicação do jejum de dias alternados e/ou da restrição temporal do alimento sobre a microbiota intestinal na obesidade. Para a realização dessa revisão sistemática foi utilizada a seguinte pergunta: Protocolos de jejum intermitente podem auxiliar na melhora da saúde metabólica através do remodelamento da microbiota intestinal e na manutenção do peso corporal?

4.2 BASES DE DADOS

Foi realizada uma busca de estudos que avaliaram os desfechos das estratégias de jejum intermitente nas bases de dados PubMed, MEDLINE, Scopus, Web of Science e LILACS em abril de 2021. Para a busca foram utilizados os filtros, com os seguintes descritores, pesquisados nos termos DeCS, foram usados as equações: AB (("intermittent fasting") OR ("time-restricted feeding") OR ("alternate-day fasting")) AND AB (("gut microbiota") OR (microbiota)) AND A obesity. Nós limitamos a pesquisa por seguir os critérios: a) publicações entre os anos de 2016 e 2021 (para permitir um foco mais estreito e obter um estado mais relevante da arte), b)dados publicados em periódicos científicos; C) Estudos publicados em inglês; d) artigos com os três descritores avaliados e) estudos realizados em humanos e animais. Associados a conectores booleanos “AND” para associação entre termos ou “OR” entre sinônimos.

4.3 CRITÉRIOS DE ELEGIBILIDADE

Foram incluídos na revisão sistemática, estudos que atendiam aos seguintes critérios:

População: humanos, ratos e/ou camundongos adultos de ambos os sexos;

Intervenção: jejum de dias alternados, restrição temporal do alimento e variações;

Comparador: indivíduos sem intervenção (controle);

Outcomes **(Desfechos):** reestruturação para uma microbiota intestinal saudável.

Tipos de estudos: avaliação das estratégias de jejum intermitente sobre o remodelamento da microbiota intestinal.

Além de estudos utilizando animais geneticamente modificados, animais alimentados com dietas experimentais, uso conjunto de outras estratégias nutricionais e que tenham sido publicados nos últimos 5 anos em inglês, espanhol ou em português.

Não foram selecionados estudos com outros animais e não adultos, que não avaliem a composição da microbiota intestinal e em indivíduos não obesos, que avaliem o efeito do jejum na atividade física e em outros idiomas.

4.4 EXTRAÇÃO DOS DADOS

Dois revisores extraíram os dados dos estudos seguindo os critérios de elegibilidade, e selecionaram títulos e resumos de forma independente, logo em seguida, a avaliação do texto completo dos estudos potencialmente elegíveis. Em caso de desacordos, as decisões foram tomadas por um consenso ou com auxílio de um terceiro revisor. Foi elaborada uma tabela com o objetivo de agrupar os dados e facilitar a análise comparativa da pesquisa. De acordo com o tipo de informação fornecida pela análise, a tabela é dividida em quatro partes:

- Seção A- Informações gerais sobre as análises selecionadas;
- Seção B – Informações sobre o tipo de intervenção e comparador e a população incluída na análise e informações sobre a perspectiva analisada no estudo;
- Seção C – Desfechos por estratégias avaliados nas análises;
- Seção D – Discussão, financiamento e conflito de interesse;
- Seção E – Fontes dos dados utilizados no estudo.

4.5 AVALIAÇÃO DA QUALIDADE DOS ESTUDOS

Dois revisores avaliaram a qualidade das evidencias dos estudos e o risco de viés de cada estudo utilizando a ferramenta *“The Cochrane Collaboration’s”* (HIGGINS et al., 2011). Neste estudo, a aplicação dessa ferramenta de qualidade foi organizada de forma independente por dois revisores, e as diferenças foram resolvidas por consenso e, caso necessário um terceiro revisor foi consultado. A lista estabelece três níveis de classificação para cada item: "Sim" informações relatadas, "Desconhecido" informações parcialmente relatadas ou incompletas e "Não" para as informações não relatadas. Os ensaios foram considerados de baixo risco de viés se os autores apresentassem informações sobre a ocultação de alocação, cegamento dos participantes e avaliadores, se uma avaliação de conformidade fosse realizada e o número de desistências e os motivos para desistência fossem relatados; caso contrário, os ensaios foram considerados de alto risco de viés. Se o risco de viés não pudesse ser determinado em qualquer um dos segmentos, o risco de viés foi classificado como desconhecido.

4.6 ANÁLISE E INTERPRETAÇÃO DOS DADOS

O desenho do estudo e suas características foram descritos em planilha com auxílio do Microsoft Excel® versão 1908 de forma a comparar os parâmetros e pressupostos selecionados, bem como os seguintes: tipo de análise, intervenção e comparador, tempo de intervenção, características das medidas de intervenção, população, métodos de modelagem, opiniões analíticas e resultados clínicos. As comparações de pesquisa são agrupadas de acordo com os resultados e os comparadores usados.

5 RESULTADOS E DISCUSSÃO

O resultado dessa dissertação está apresentado na forma de artigo.

Special Article

Repercussions of intermittent fasting on the intestinal microbiota community and body composition: a systematic review

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Context: *Several therapies have been tested for combating weight gain and obesity-related metabolic diseases, and among these therapies, intermittent fasting (IF) has gained a great deal of interest.* ***Objective:*** *The aim of this study was to provide the reader with a current survey of IF protocols and an understanding of the outcomes found to date in terms of the profile of the intestinal microbiota (IM) in obese organisms.* ***Data Sources:*** *Data were obtained from 4 databases: PubMed, SCOPUS, LILACs, and Web of Science.* ***Data Extraction:*** *Data from studies relating IF protocols to the microbiota and weight loss were extracted using a protocol in START program.* ***Data Analysis:*** *Of the 82 original articles identified from the databases, 35 were eliminated due to duplication, and 32 were excluded due to not meeting the inclusion criteria. Two additional articles found in a new search were added, yielding a total of 17 studies to be included in this review. Among the protocols, alternate-day fasting (ADF) and time-restricted feeding (TRF) were the most common, and they were shown to have different mechanisms of metabolic signaling. TRF influences weight control and biochemical parameters by regulating the circadian system, and improving satiety control systems by acting on leptin secretion. On the other hand, ADF leads to a reduction of ±75% of all energy consumption regardless of dietary composition in addition to promoting hormonal adjustments that promote weight control. Furthermore, both protocols showed the ability to remodel the IM by changing the Firmicutes/Bacteroidetes ratio and increasing the abundance of strains such as* Lactobacillus *spp. and* Akkermansia m. *that have a protective effect on metabolism against the effects of weight gain.* ***Conclusion:*** *In short, the ADF and TRF protocols have a positive effect on the remodeling of the IM and can possibly be used to control body adiposity, improve insulin sensitivity, and achieve other obesity-related metabolic changes.*

INTRODUCTION

In recent decades, humanity has gone through the most complex changes, among which, one of the most striking has happened in food. There have been changes in eating behavior and daily activities, bringing with these changes an increase in metabolic disorders, especially those related to excessive body weight gain.[1–3] In

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Brazil, according to the Instituto Brasileiro de Geografia e Estatística (IBGE, 2020),[4] the prevalence of overweight (60.3%) and obesity (25.9%) in 2019 among individuals over 18 years was alarming. It is known that obesity acts as a relevant factor in the development of noncommunicable diseases (NCDs) and even in the worsening of the pre-existing clinical conditions.[4] As a way to minimize the effects of obesity on the health of the individual, weight loss with adjustments in diet and physical activity are recommended.[5–7]

Nutritional strategies based on restricted feeding time have been shown to have a potential effect on the control of body weight gain and are easier to work into an individuals's dietary routine than some approaches. Thus, intermittent fasting (IF) protocols have been shown to be one of the emerging tools for weight management.[8–10] Animal[11–13] and human[14–16] research with IF has shown potential beneficial effects in the control of body weight and metabolic disorders. IF is a nutritional strategy that is based on a group of protocols to restrict feeding time in a variety of ways. These fasting protocols have demonstrated a positive effect on the intestinal environment, specifically, on the quality of its intestinal microbiota (IM), which in turn has been associated with the amelioration of several diseases, such as inflammatory bowel diseases, and changes in the gut–brain axis.3

The intestinal environment is colonized by several species of microorganisms that compose the microbiota. Among the microbiota are bacteria, viruses, and fungi, which when in symbiosis with the host influence the maintenance of body homeostasis.[3,18] In this relationship, the human organism benefits from the supply of nutrients, and by protection against pathogens and/or physical and chemical agents.[19–21] Among the bacterial phyla present in the IM, Firmicutes (gram-positive) and Bacteroidetes (gram-negative)[3,22] represent 90% of the intestinal community.[17,23] These populations have important metabolic functions, when in balance with the host, and are capable of generating metabolites such as short-chain fatty acids (SCFAs) through the fermentation of food substrates and nondigestible derived components, such as fructooligosaccharides, pectin, inulin, among others.[3] Thus, the nutrients not absorbed in the upper intestinal tract, act as a substrate for the IM that synthesizes products capable of modulating the expression of genes that act in the production/release of intestinal hormones, adipose tissue, and the nervous system, such as ghrelin, leptin, glucagon-like peptide 1 (GLP-1), and peptide YY (PYY), that act on appetite control.[20,23]

Among the factors regulating the intestinal flora are food, physical activity, the social environment, and genetic factors.[17] These factors together produce a series of elements, which define how each taxonomic variety will develop in the intestinal environment.[1,24] Of these factors, inadequate feeding together with genetic inheritance, leads to the disordered development of pathogenic microorganisms in the intestinal environment, leading to "intestinal dysbiosis".[20] This is one of the main factor in the development of NCDs related to the inflammatory profile (such as type 2 diabetes mellitus [T2DM], cardiovascular diseases, inflammatory bowel disease, cancer, among others) in the host and is often associated with an increase in the relationship between the 2 predominant phyla.[5,20,25] Dysbiosis leads to a rupture in the balance of the intestinal environment, the symbiotic relationship, and a reduction in diversity, which in turn is associated with a series of chronic diseases related to obesity.[17,18,23] For example, in obesity there is a reduction in the proportion and diversity of the phylum Bacteroidetes in relation to the phylum Firmicutes.[18] This is possibly associated with an excess in the production of SCFAs and endotoxins, increasing the availability of energetic substrates and the inflammatory state, consequently leading to the accumulation of adipose tissue and other metabolic changes.[1,5,26] The mechanisms relevant to this relationship between the IM and its host are mainly related to the ability of its metabolites to react with receptors of intestinal cells, inducing the expression or suppression of genes modulating organic functions.[5,20] In short, it can be said that food modulates how each strain of the microbiota will develop in the intestinal environment.[26,27]

In addition, there are several protocols of IF in the research literature, which results in doubts about which protocols are the most effective in promoting beneficial outcomes to the individual. On the other hand, when applied properly, IF assists in the glycemic response, in increased thermogenesis,[8,10,28] in body weight control,[11,15,29] in the microbiota health,[12,28] and in the prevention of cardiovascular diseases and diseases of the nervous system.[8,9,30] In view of this, it is becoming increasingly relevant to investigate the possible applications and variations of IF, as well as the repercussions of this strategy for the promotion of intestinal (microbiota) and metabolic health. Thus, this review aims to verify the effects of IF on the intestinal microbiota and body weight maintenance.

METHODS

Literature search strategy

The literature search was conducted using the START program (systematic bibliographic review manager).[31] To sort the data, the recommendations proposed by

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[32] were used. Two independent and concurrent reviewers were consulted, who conducted the study using a predefined protocol. A third reviewer was used when there were disagreements between the other 2 reviewers. The data were obtained from 4 databases (PubMed, SCOPUS, LILACs, and Web of Science) in April 2021. Filters were used with the following descriptors, searched under the terms DeCS, with the following equations: (["intermittent fasting"] OR ["time-restricted feeding"] OR ["alternate-day fasting"]) AND (["gut microbiota"] OR [microbiota]) AND "obesity".

Eligibility criteria

The research was limited by following the criteria: (a) publications between the years 2016 and 2021, (b) data published in scientific journals; (c) studies published in English; (d) articles with the 3 descriptors evaluated, and (e) studies carried out in humans and animals. In the first step, the articles were selected by title and abstract, by 2 independent researchers to reduce errors in classification.

Studies were eligible for analysis if they followed the inclusion criteria based on the PICOS[32] strategy (Table 1): used and described IF protocols; used the IF protocols in the restructuring of the IM, in obese individuals; used genetically modified animals and/or used experimental diets; reports published and available in full in the scientific databases used; articles published in the last 5 years. Works were excluded that did not use IF and IM; that used non–mice/rat experimental models or non-adult individuals; literature reviews; and studies that did not present data on IM strains. The results of the analyses were compared. Disagreements among reviewers were discussed and decisions were made by consensus.

Extraction and synthesis of data

The two authors (F.C.S.P. and S.L.S.) extracted the data. The START[31] program was used to group the data and facilitate a comparative analysis of the research. The data extracted from each study were as follows: (a) general information about the selected analyses; (b) information on the type of intervention, the comparator, the population included in the analysis, and the perspective analyzed in the study; (c) policy outcomes formulated in the analyses; (d) discussion of financing and conflicts of interest, and (e) sources of data used in the study.

Assessing the quality of trials

Two reviewers assessed the quality of the evidence from the studies and the risk of bias in each study using the the Cochrane Collaboration's tool.[33] In this study, this quality tool was independently applied by 2 reviewers, and differences in findings were resolved by consensus; if necessary, a third reviewer was consulted. The list established 3 levels of classification for each item: "Yes" for reported information, "Unknown" for partially reported or incomplete information, and "No" for unreported information. The trials were considered to be of low risk of bias if the authors presented information about the allocation concealment, blinding of the participants and evaluators, whether a conformity assessment was carried out, and the number of dropouts and the reasons for dropping out; otherwise, the trials were considered to be at high risk of bias. If the risk of bias could not be determined in any of the segments, the risk of bias was classified as unknown.

RESULTS

Study identification and selection

A Systematic Literature Review of studies was carried out that evaluated the application of different IF protocols in humans and in obese adult rats/mice and their effects on the IM, body weight, and metabolism. Studies published in the years 2016–2021 were collected and indexed in the databases (PubMed, LILACS, Web of Science, and Scopus), and 82 references were found. In a manual search, 2 more studies were found that met the inclusion and exclusion criteria, totaling 84 references. After removing the duplicates (35), 49 articles remained. Of these 32 were excluded after reading the title and summary because they failed to meet the inclusion criteria. The 17 studies remaining studies are included in this review (Fig. 1).[32] Their characteristics are described in Tables 2[12,27,34–42] and 3,[43–48] and below.

Corresponding authors' countries

Of the corresponding authors of the selected studies, 9 were in China,[27,35,36,38,40,41,44,45,48] 6 were in the United States,[12,34,37,39,42,43] and 2 were in Turkey.[46,47]

Risk of bias and quality of evidence

The risk-of-bias assessment was conducted by 2 reviewers individually using the Cochrane Collaboration's tool.[33] The risk of bias in the studies was variable. In the randomized studies in animal

Table 1 **PICOS criteria for inclusion and exclusion of studies**

Parameter	Inclusion criterion	Exclusion criterion
Population	Adult (aged > 18 y), rats and/or mice	Children and adolescents (aged < 18 y); non-mice or rat design
Intervention	Following intermittent fasting protocols	Following others dietary restriction protocols
Comparators	Following any form of a nonrestrictive diet	Following any specific supplementation protocol
Outcomes	Restructuring for a healthy gut microbiota	No gut microbiota data
Study design	Any study design, observation or experimental	None

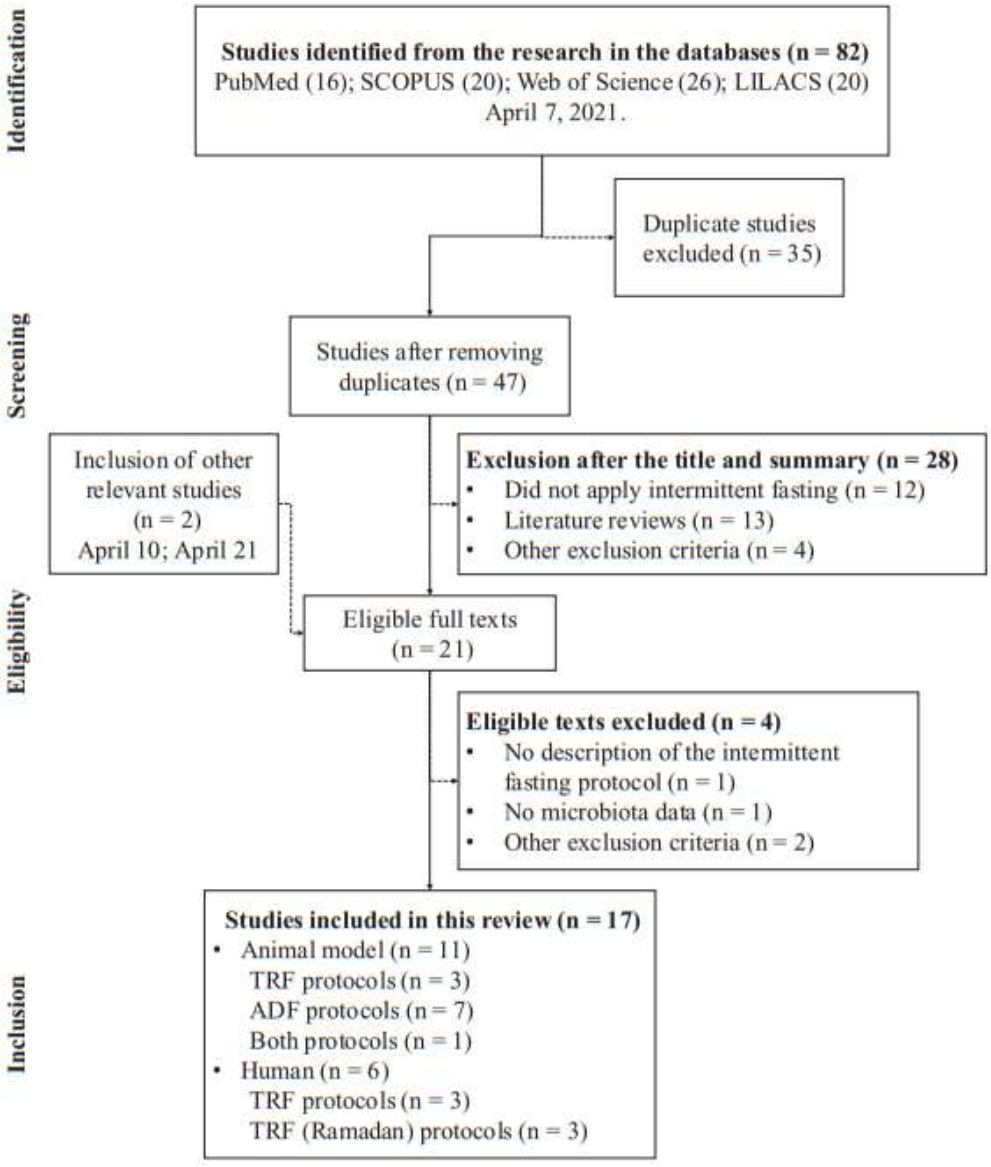

Figure 1 **PRISMA flowchart of studies included in this review.** *Abbreviations:* ADF, alternate-day fasting; TRF, time-restricted feeding

Table 2 **Main characteristics of the animal model studies included in the systematic literature review**

Reference	Intermittent fasting protocols	Methods	Population	Control	Outcomes
			Time-restricted feeding protocols		
Hu et al. (2018)[27]	ND + TRF (16:8) 8 wk	8-wk-old male Kunming mice (n = 10/group)	TRF/TRF TRF/ADL ADL/TRF	ADL/ADL	TRF led to increased diversity in the phylum Firmicutes, in the class Clostridia, in the family Ruminococcus and in the genus *Roseburia*, which are generally associated with a healthier IM, while the harmful flora was suppressed.
Li et al. (2020)[35]	ND + TRF (12:12); (16:8); (20:4) 4 wk	6-wk-old male C57BL/6JLivr mice Diet-induced obesity model (n = 15/group)	TRF12 TRF16 TRF20	ADL	16-h fasting led to and increased level of *Akkermansia* and a decreased level of *Alistipes*. Also, cumulative food intake was significantly decreased in the 16 h and 20 h fasting groups, but had not significantly changed after 12 h daily fasting.
Ye et al. (2020)[36]	HFD + TRF (16:8) 8 wk	6-wk-old male Kunming mice Diet-induced obesity model (n − 20/group)	HFD/TRF	ND/ADL HFD/ADL	The HFD/TRF group showed greater abundance of Bacteroidetes and Firmicutes, less weight gain, and reduced liver steatosis and hepatic levels of triglycerides.
van der Merwe et al. (2020)[37]	HFD + ADF HFD + TRF (18:6) 8 wk	6-wk-old male C57BL/6 mice Diet-induced obesity model (n = 8–9/group)	HFD/ADF HFD/TRF	HFD/ADL	The HFD/TRF group showed an increase in α-diversity, but had no difference at phylum level. Furthermore, all restricted dietary protocols promoted a reduction in body weight and attenuated the metabolic effects caused by HFD.
			Alternate-day fasting protocols		
Beli et al. (2018)[12]	ND + ADF 7 mo	4-mo-old male B6.BKS(D)-Lepr (db)/J mice Diabetes model (n = 10/group)	db/m ADF db/db ADF	db/m ADL db/db ADL	IF promotes an increase in gut mucin, goblet cell number, and villi length, and reductions in plasma peptidoglycan. Consistent with microbiome analysis that revealed increased levels of Firmicutes and decreased Bacteroidetes and Verrucomicrobia in db/db mice.
Deng et al. (2020)[38]	HFD + ADF 4 wk	3-wk-old male C57BL/6J mice Diet-induced obesity model (n = 15/group)	ND/ADF HFD/ADF	ND/ADL HFD/ADL	IF did not change the IM richness, but tended to increase community diversity in the intestinal flora. Furthermore, IF significantly reduced the proportion of Firmicutes to Bacteroidetes and increased the relative abundance of *Allobaculum*. In addition to showing greater weight loss, there was reduced endotoxemia, and improved lipid metabolism, mainly reflected in lower serum lipid levels and improved liver steatosis.
Li et al. (2017)[39]	HFD + ADF 4 wk	8-wk-old male C57BL/6N mice Diet-induced obesity model (n = 14–16/group)	HFD/ADF	HFD/ADL	The ADF protocol increased OTU abundance of the phylum Firmicutes and reduced Bacteroidetes and Actinobacteria. In addition, it selectively stimulated the development of beige fat in white adipose tissue, associated with a significant improvement in obesity, insulin resistance, and hepatic steatosis.
Liu et al. (2020)[40]	ND + ADF 4 wk	4-wk-old male BKS.Cg-Dock7m$^{+/+}$ Lepr (db)/J mice (n = 15/group)	db/db-ADF	db/m db/db	The IF restructured the IM, increasing alpha diversity, but the total number of OTUs remained unchanged. Furthermore, IF increased the *Lactobacillus* and the butyrate-producing *Odoribacter* genus, while it reduced the *Enterococcus* and *Streptococcus*, improving the microbial metabolites. Also, it increased mitochondrial biogenesis and gene expression for energy metabolism in the hippocampus.

(continued)

Table 2 **Continued**

Reference	Intermittent fasting protocols	Methods	Population	Control	Outcomes
Wei et al. (2018)[41]	ND + MADF (70% restriction) 8 wk (obs.: alternating weeks between MADF and ADL)	8-wk-old male C57BL/ksj-db mice (n = 8/group)	MADF	ADL	Intermittent MADF led to an increase in *Parabacteroides* and *Blautia* genera, while reducing Prevotellaceae, *Alistipes* and Ruminococcaceae, as well as normalizing blood glucose levels, with significant improvements in insulin sensitivity. In addition, it attenuated hepatic steatosis, pancreatic islet deterioration, and β-cell loss in db/db mice.
Cignarella et al. (2018)[42]	ND + ADF 4 wk	7-wk-old female C57BL/6J mice MS model (n = 10/group)	ND/ADF	ND/ADL	IF increased the richness of intestinal bacteria, with an increase in the Lactobacillaceae, Bacteroidaceae, and Prevotellaceae families and in the antioxidant microbial metabolic pathways.
Rangan et al. (2019)[34]	ND + MADF 2 cycles of 4 d (70% restriction) 8 wk	8-wk-old female C57BL/6 mice DSS-induced inflammatory bowel disease model (n = 11–19/group)	MADF DSS/MADF	ND DSS/ND	MADF cycles reduced intestinal inflammation, increased stem cell numbers, and stimulated protective gut microbiota. A significant increase in the bacterial families Lactobacillaceae, Erysipelotrichaceae, and Bifidobacteriacea occurred, along with an increase in the percentage of splenic $CD3^+CD4^+$ and $CD3^+CD8^+$ T cells that are central memory T cells in the DSS/MADF group.

Abbreviations: ADF, alternate-day fasting; ADL, ad libitum; DSS, dextran sodium sulfate; HFD, high-fat diet; IF, intermittent fasting; IM, intestinal microbiota; MADF, modified alternate-day fasting; MS, multiple sclerosis; ND, normal-chow diet/standard diet; OTU, operational taxonomic unit; TRF, time-restricted feeding.

models, it was observed that all studies presented the variables, the randomization data and the sample losses in a clear and complete way, so were classified as having low to medium risk of bias, due mainly to the non-blinding of the evaluators.[12,27,34–42] On the other hand, in studies with a human model, a medium to high risk of bias was identified, due mainly to the nature of the interventions in relation to: (1) impossibility of blinding the participants and evaluators; (2) potentially incomplete recalls[43–48]; (3) loss of samples/participants; (4) absence of groups without intervention; and (5) heterogeneous and/or small groups.[43,46,47]

Interventions, population, comparators, and effects on intestinal microbiota

In general, the strategies used as a comparison for fasting protocols were mainly untreated groups. Some studies used a high-fat diet (HFD) for obese groups and a normal-chow diet/standard diet (ND) for the control group. Of the included studies, 11 were carried out using wild-type (2) and genetically modified (9) mice, 2 applied alternate-day fasting (ADF), and 3 applied the ADF protocol in conjunction with a HFD; for the control group, a ND and/or HFD was applied without the fasting protocol. In a study using a ND, Beli et al. (2018)[12] applied the ADF for a period of 7 months in diabetic mice (db/db) and evaluated the repercussions of fasting on the microbiota and biochemicals parameters (Table 2).[12,27,34–42] In their study, they observed that the mice subjected to ADF showed an improvement in the relative abundance of the bacterial community associated with a change in the ratio of Firmicutes to Bacteroidetes, and changes in specific phyla (specifically, the db/m-IF mice showed an increase in abundance of the phylum Verrucomicrobia, while the db/db-IF animals showed significantly reduced abundance of Verrucomicrobia ($P < 0.001$), compared with the untreated db/db group (Table 3).[12,27,34–42] In addition, there was an expansion of genera such as *Lactobacillus* and a reduction in *Bifidobacterium* and *Clostridium* in both treated groups, as well as a reduction in bacterial metabolites such as serum peptidoglycan, indicative of improved intestinal permeability, as well as an increase in the production of bile acids compatible with improvement of the hepatic lipid profile.[12]

The study by Liu et al. (2020)[40] evaluated the effect of ADF over 4 weeks in diabetic mice (db/db). They found improvement in insulin sensitivity and remodeling of the IM with the increase of *Lactobacillus* and *Odoribacter* and the reduction of *Enterococcus*, *Streptococcus*, and strains of the Enterococcaceae family ($P < 0.05$), as well as weight reduction and stimulus for the production of intestinal neurotransmitters and

Table 3 **Effects of intermittent fasting protocols on intestinal microbiota, body weight, and intestinal permeability in the animal model**

Reference	Protocol	BW	BFM	IBP	Rf/B	Variations between the main phyla of the intestinal microbiota			
						Firmicutes	Bacteroidetes	Actinobacterias	Verrucomicrobia
Time-restricted Feeding protocols									
Hu et al. (2018)[27]	TRF/TRF	↓	NE	↓	↑	↑ *Ruminococcus* ↑ *Lactobacillus* ↑ *Lachnospira* ↓ *Staphylococcus*	↓ *Bacteroidetes*	↓ *Actinobacteria*	NS
	TRF/ADL	↓	NE	↓	↑	↑ *Ruminococcus* ↑ *Lactobacillus* ↑ *Lachnospira* ↓ *Staphylococcus*	↓ *Bacteroidetes*	↓ *Actinobacteria*	NS
	ADL/TRF	↓	NE	NS	↓	↑ *Staphylococcus*	↑ *Bacteroidetes*	↑ *Actinobacteria*	NS
Li et al. (2020)[35]	TRF12	NS	NS	NE	NE	NS	NS	NS	NS
	TRF16	↓	↓	NE	NE	↑ *Lactobacillus* ↓ *Enterococcus* ↓ *Streptococcus* ↓ *Alistipes*	NS	NS	↑
		Akkermansia							
TRF20	↓	↓	NE	NE	NS	NS	NS	NS	
Ye et al. (2020)[36]	HFD/TRF	↓	NE	NE	NS	↓ *Firmicutes*	↑ *Bacteroidetes*	NS	NS
van der Merwe et al. (2020)[37]	HFD/TRF	↓	NE	NE	↑	↑ *Lactococcus* ↑ *Clostridiales* ↑ *Ruminococcus* ↑ Christensenellaceae ↓ *Enterococcus*	NS	NS	NS
	HFD/ADF	↓	NE	NE	↑	↑ *Lactococcus* ↓ *Enterococcus*	NS	↑ *Bifidobacterium*	NS
Alternate-day fasting protocols									
Beli et al. (2018)[12]	db/m ADF	NE	↓	↓	NS	↑ *Lactobacillus* ↑ *Oscillospira* ↑ *Ruminococcus* ↓ *Clostridium*	↓ *Bacteroides*	↓ *Bifidobacterium*	↑
		Akkermansia							
db/db ADF	NE	↓	↓	↑	↑	*Lactobacillus* ↑ *Oscillospira* ↑ *Ruminococcus* ↓ *Clostridium* ↓ *Allobaculum*	↓ *Bacteroides*	↓ *Bifidobacterium*	↓
Akkermansia									
Deng et al. (2020)[38]	ND/ADF	↓	NE	↓	↑	↑ *Lactobacillus*	NS	NS	NS
	HFD/ADF	↓	NE	↓	↑	↑ *Allobaculum* ↑ *Bifidobacterium* ↓ Enterobactereaiaceae	↑ *Alloprevotella*	NS	NS
Li et al. (2017)[39]	HFD/ADF	↓	NE	NE	↑	↑ Firmicutes	↓ *Bacteroides*	NS	NS

(continued)

Table 3 **Continued**

Reference	Protocol	BW	BFM	IBP	Rf/B	Variations between the main phyla of the intestinal microbiota			
						Firmicutes	Bacteroidetes	Actinobacterias	Verrucomicrobia
Liu et al. (2020)[40]	ADF	↓	↓	↓	↑	↑ *Lactobacillus* ↑ *Odoribacter* ↓ *Enterococcus* ↓ *Streptococcus*	*NS*	*NS*	*NS*
Wei et al. (2018)[41]	MADF	↓	↓	NE	↑	↓ Firmicutes ↑ *Blautia* ↓ Ruminococcaceae	↑ Bacteroidetes ↑ Parabacteroides ↓ Prevotellaceae ↓ *Alistipes*	NS	NS
Cignarella et al. (2018)[42]	ND/ADF	↓	NA	↓	↑	↑ Lactobacillaceae	↑ Bacteroidaceae ↑ Prevotellaceae	↑ *Bifidobacterium p.*	NS
Rangan et al. (2019)[34]	DSS/MADF	↓	↓	↓	NE	↑ Lactobacillaceae ↑ *Allobaculum*	NS	↑ Bifidobacteriaceae	NS

↑—increased/improved; ↓—reduced. *Abbreviations*: ADF, alternate-day fasting; ADL, ad libitum; BFM, body fat mass; BW, body weight; DSS, dextran sodium sulfate; HFD, high-fat diet; IBP, intestinal barrier permeability; MADF, modified alternate-day fasting; NE, not evaluated; NS, not significant and/or unchanged; RF/B, Firmicutes/Bacteroidetes ratio; TRF, time-restricted feeding.

hormones compared with db/m and db/db ad libitum (ADL) mice. Cignarella et al. (2018)[42] had previously evaluated the application of ADF in a multiple sclerosis (MS) model and evaluated the repercussions on cognitive, inflammatory aspects, and on the composition of the IM, where they observed enrichment of the families Lactobacillaceae, Bacteroidaceae and Prevotellaceae ($P < 0.05$) compared with animals fed ad libitum. The 2 studies above applied a HFD/ADF over a 4-week period in obese C57BL/6J mice and evaluated the repercussions of fasting on weight control and the lipid profile through the IM. There was a reduction in the body weight of the animals, and an improvement in the biochemical and inflammatory parameters, concomitant with the reduction in the level of serum lipopolysaccharides (LPSs).[38,39] The authors used non-obese and obese ADL mice as a comparator and identified an beneficial increase in the Firmicutes/Bacteriodetes ratio, as well as a reduction in the relative abundance of the Enterobacteriaceae family ($P < 0.05$), an increase in the genera *Allobaculum* ($P < 0.01$),[38] a reduction in fat mass gain, and an increase in the production of bacterial metabolites consistent with the increase in the diversity and richness of the IM.[38,39]

Of the studies that evaluated the application of time-restricted feeding (TRF), Hu et al. (2018)[27] evaluated the application of different duration periods of ND/TRF. Following the scheme: TRF-TRF (2 mo of intervention), TRF-ADL – (first month of TRF and the second free feeding), ADL-TRF (first month of free feeding and the second restriction), compared with the ADL-ADL group (2 mo of free feeding). During the 2 months of these experiments, reduced body weight, improved lipid profile, and amelioration of inflammatory bowel disease were observed.

Three studies evaluated TRF combined with HFD to induce obesity and insulin resistance. The study of Li et al. (2020)[35] evaluated the use of different periods of TRF fasting:eating (12:12), (16:8), and (20:4) (Table 2), combined with a HFD in weight gain and IM; as a comparator, the control group HFD ad libitum was used. They found that food intake was significantly decreased in the 16 h and 20 h fasting groups. The composition of the gut microbiota was altered by all these types of IF (Table 3). Ye et al. (2020)[36] applied TRF (16:8) combined with HFD for 8 weeks and evaluated the repercussions on body weight, biochemical parameters, and IM in obese Kunming mice compared with ADL non-obese mice (ND/ADL) and obese mice (HFD/ADL). Mice that received HFD/TRF had less weight gain, milder liver steatosis, and lower hepatic levels of triglycerides than mice that received a HFD/ADL.[36] The numbers of Bacteroidetes and Firmicutes differed between mice

that received HFD/TRF and mice that received a HFD/ADL.[36]

Van der Merwe et al. (2020)[37] who assessed the effects of the HFD/TRF protocols (18:6 – active phase) and HFD/ADF for 8 weeks, assessed the repercussions of the protocols in obese mice compared with ADL obese animals, on weight gain, body fat distribution and IM. Body mass gain was reduced with all restricted dietary groups. HFD-fed microbiota displayed lower α-diversity, along with reduced phylum levels of Bacteroidetes and increased Firmicutes.[37] Animals switched from a HFD to ADF demonstrated a rapid transition in bacterial taxonomic composition, α and β-diversity that initially resembled that of a HFD, but was distinct after 4 and 8 weeks of HDF feeding.[37] In addition, 2 studies evaluated the effects of a variation of the ADF on the Modified Alternate-Day Fasting (MADF)[49] known as the Fasting-Mimicking Diet (FMD). The first study verified the effect of intermittent application of MADF with a 70% restriction of daily calorie intake for 8 weeks in db/db mice.[41] It assessed body weight gain, insulin sensitivity, liver lipid profile, and IM compared with ADL mice.[41] Rangan et al. (2019),[34] on the other hand, evaluated the effects of two 4-day cycles of MADF (70% restriction/d) in female mice with inflammatory bowel disease induced by Sodium Dextran Sulfate (DSS) and evaluated mainly the repercussions of fasting on inflammation, intestinal permeability, and on the composition of the IM compared with the DSS/ADL (Table 2). These MADF cycles reduced intestinal inflammation, increased stem cell number, stimulated protective gut microbiota, and reversed intestinal pathology caused by DSS, whereas water-only fasting increased regenerative and reduced inflammatory markers without reversing pathology.[34]

Gabel et al. (2020)[43] evaluated the effects of TRF (16:8) in obese adult individuals for 12 weeks (Table 4)[43–48] (without making any other restrictions on the type, quality, or quantity of the food) on body composition, biochemical parameters and IM compared with individuals without restriction on feeding time. Body weight decreased.[43] Gut microbiota phylogenetic diversity remained unchanged.[43] Three studies evaluated body composition, biochemical and inflammatory parameters, and the composition of the IM in healthy individuals practicing Ramadan (restriction of food and calorie drinks from 16–17 h during the day for 29 d), comparing the IM before and after Ramadan.[46–48] Microbial richness was significantly increased after Ramadan. No significant difference was found in terms of phylogenetic diversity. However, microbial community structure was significantly different between baseline and after Ramadan. The *Butyricicoccus*, *Bacteroides*, *Faecalibacterium*, *Roseburia*, *Allobaculum*, *Eubacterium*, *Dialister*, and *Erysipelotrichi*[46,47] were significantly enriched genera, and there was an increase in butyric acid–producing Lachnospiraceae and Ruminococcaceae[48] after the end of Ramadan fasting (Table 5).[43–48]

Moreover, pilot studies with a limited sample size on the effects of Ramadan by Ozkul et al. (2019, 2020)[46,47] reported that Ramadan fasting, which represents an IF regime, leads to compositional changes in the gut microbiota.[46,47] Zeb et al. (2020)[44,45] evaluated the effects of TRF (16:8) in healthy adult men for 25 days on body composition, circadian rhythm, biochemical parameters, and on the composition of the IM in comparison with ADL individuals. They showed that TRF reduced serum lipids and ameliorated liver dysfunction by altering enzymatic markers such as alanine-aminotransferase (ALT) and albumin levels related to nonalcoholic steatosis.[44,45] In the TRF group, gut microbial richness was significantly enhanced, with enrichment of Prevotellaceae and Bacteroideaceae. Cluster analysis revealed that *Prevotella_9*, *Faecalibacterium*, and *Dialister* were the most abundant species in the TRF group (Table 5), whereas *Prevotella_7*, *Alloprevotella*, and *Prevotella_2* were less abundant in the non-TRF group.[44,45] At the genus level, the gut microbiota of the TRF group was significantly changed compared with that of the non-TRF group. Moreover, bar plot analysis revealed that Bacteroidetes was the most abundant phylum in TRF group, followed by Firmicutes.[44,45]

Efficacy outcomes and other effects

Most studies in both animal models[12,27,34–42] and human models[44–48] reported that, although to a limited degree, the fasting protocols had positive effects on most of the parameters evaluated, including body weight and serum lipid control. In the study by Li et al. (2020),[35] in which TRF mice were subjected to 12 h and 20 h of daily fasting, the TRF did not result in lasting positive effects on the IM. In addition, the animals showed high feed intake and body weight gain 4 weeks after the end of the experiment. Similarly, Gabel et al. (2020)[43] also demonstrated no significant effects on the IM. In addition to the effects observed on the IM and body weight, these 2 studies also evaluated other biochemical parameters such as: body fat distribution, lipid profile, inflammatory profile, liver and bile function, circadian rhythm, oxidative stress/damage, and cognitive function.

Of the included studies, only 9 investigated other biochemical and histological parameters, and most of these investigated the effect of IF on the distribution of body fat[36,38–40,45] and the serum lipid profile.[36,38,40,41,45]

Table 4 **Main characteristics of the human model studies included in the systematic literature review**

Reference	Intermittent fasting protocols	Methods	Population	Control	Outcomes
Time-restricted feeding protocols					
Gabel et al. (2020)[43]	TRF (16:8) 12 wk	Obese adults (n = 14)	Before TRF	After TRF	The TRF did not significantly alter the phylogenetic diversity of the IM; however, a reduction in body weight and in other metabolic parameters was observed.
Ozkul et al. (2019)[46]	TRF (17:7) (Ramadan) 29 d	Healthy adults Usual free food (n = 9)	Before TRF	After TRF	After Ramadan, an increase in *Akkermansia m.* and *Bacteroides fragilis* was observed, along with a reduction in fasting serum glucose and total cholesterol levels in all individuals.
Ozkul et al. (2020)[47]	TRF (17:7) (Ramadan) 29 d	Healthy adults Usual free food (n = 9)	Before TRF	After TRF	Ramadan fasting did not significantly alter alpha diversity. However, the microbial community structure was significantly different between baseline samples according to unweighted UniFrac analysis. There was an increase in *Butyricicoccus*, *Bacteroides*, *Faecalibacterium*, *Roseburia*, *Allobaculum*, *Eubacterium*, and *Dialister* genera, and *Butyricicoccus pullicaecorum* was the bacterial species most affected by fasting.
Zeb et al. (2020)[45]	TRF (16:8) 25 d	Health male students Usual free food (n = 15/group)	TRF	ADL	TRF induced enrichment of Bacteroidetes in relation to the phylum Firmicutes, which was the second-most abundant. In addition, it significantly altered the microbiota at the genus level, as well as increased the *Prevotella_9*, *Faecalibacterium*, and *Dialister* species in relation to the non-fasting group.
Zeb et al. (2020)[44]	TRF (16:8) 25 d	Healthy adult male students Usual free food (TRF, n = 56; ADL, n = 24)	TRF	ADL	TRF altered the IM with enrichment of Prevotellaceae and Bacteroideaceae. It also ameliorated the serum lipid and liver profiles, and enhanced circadian gene expression, probably by activation of sirtuin-1, which is positively associated with the gut microbiome richness of individuals.
Su et al. (2021)[48]	TRF (16:8) (Ramadan) 30 d	Healthy young-adult and middle-aged males Usual free food (n = 30 and 37, respectively)	Young group Before TRF Middle-aged group TRF	Young group After TRF Middle-aged group Non-TRF	TRF remodeled the intestinal microbiome, increasing the population of Lachnospiraceae. Because this species is linked to the intestinal production of butyrate, it may be related to improved metabolic health.

Abbreviations: ADL, ad libitum; TRF, time-restricted feeding.

For example, Deng et al. (2020)[38] and Li et al. (2017)[39] reported that mice subjected to ADF showed a significant ($P < 0.05$) reduction in body fat, while also showing the beiging of white adipose tissue (in the form of an increase in multilocular adipocytes); thus, an association with increased thermogenic capacity is suggested. Concomitantly, a reduction in serum lipids (such as triglycerides [TGs] and low density lipoprotein [LDL]) was found in the study using Kunming mice by Ye et al. (2020).[36] Also in humans under TRF, Zeb et al. (2020),[45] found a significant difference between the IF group and the untreated group ($P < 0.05$), and they also

Table 5 **Effects of intermittent fasting protocols on intestinal microbiota, body weight, and intestinal permeability in the human model**

Reference	Protocol	BW	BFM	IBP	Rf/B	Variations between the main phyla of the intestinal microbiota			
						Firmicutes	Bacteroidetes	Actinobacterias	Verrucomicrobia
Time-restricted feeding protocols									
Gabel et al. (2020)[43]	TRF	↓	NS	NE	NS	NS	NS	NS	NS
Ozkul et al. (2019)[46]	TRF (Ramadan)	↓	↓	↓	↑	↑ *Lactobacillus* ↓ *Faecalibacterium p.* ↓ Enterobacteriaceae	↑ *Bacteroides f.*	↓ *Bifidobacterium*	↑ *Akkermansia m.*
Ozkul et al. (2020)[47]	TRF (Ramadan)	↓	↓	↓	↑	↑ *Butyricicoccus p.* ↑ *Faecalibacterium p.* ↑ *Roseburia* ↓ *Lactobacillus* ↓ *Clostridium* ↓ *Escherichia*	↑ *Bacteroides*	NS	↑ *Akkermansia m.*
Zeb et al. (2020)[45]	TRF	↓	↓	NE	↑	NS	↑ Bacteroidetes ↑ Prevotellaceae	NS	NS
Zeb et al. (2020)[44]	TRF	↓	↓	NE	NE	↓ Firmicutes ↑ *Feacalibacterium* ↑ *Dialister*	↑ Bacteroidetes ↑ *Prevotella* ↓ *Alloprevotella*	NS	NS
Su et al. (2021)[48]	TRF Young (Ramadan)	↓	NE	NE	↑	↑ Ruminococcaceae	↓ *Prevotellaceae*	NS	NS
	TRF Middle-aged (Ramadan)	↓	↓	NE	↑	↑ Lachnospiraceae ↑ Ruminococcaceae	↓ Prevotellaceae	NS	NS

↑—increased/improved; ↓—reduced. *Abbreviations:* BW, body weight; BFM, body fat mass; IBP, intestinal barrier permeability; NE, not evaluated; NS, not significant and/or unchanged; RF/B, Firmicutes/Bacteroidetes ratio; TRF, time-restricted feeding.

identified a significant increase in high-density lipoprotein (HDL) levels ($P < 0.0001$).

Furthermore, in the study by Ye et al. (2020),[36] the histological liver samples from animals subjected to IF were shown to have metabolic alterations in obesity and fat accumulation,[36,41] in accordance with the improvement in the previously mentioned serum parameters. This indicated an ability to reduce and/or prevent the progression of the liver injury characteristic of nonalcoholic liver steatosis, and possible improvement in lipid oxidation due to a reduction in the liver enzymes alkaline phosphatase/gamma-glutamyl transferase (AKP/GGT, $P < 0.0009$), aspartate aminotransferase (AST, $P < 0.05$), and alanine aminotransferase (ALT, $P = 0.0003$), an effect also seen in another study.[41] In addition, it was observed by Wei et al. (2018)[41] that the MADF had a protective effect on insulin levels by preventing the loss of the islets of Langerhans in diabetic db/db mice.

Other effects observed during the IF protocols were the regulation of inflammatory cytokines,[12,34,42,45] of the genes of the circadian system,[36,45] and of the production of bile acids.[12] As an example, Rangan et al. (2019)[34] in their study verifying the effects of MADF in mice subjected to the model of inflammatory disease induced by DSS managed to observe an attenuation of the effects of DSS applications during the period of fasting, in addition to effects on serum levels of white blood cells, and they reported that there was a reduction in the count of splenic $CD3^+CD4^+$ T cells ($P < 0.0001$) and an increase in granulocytes and neutrophils ($P < 0.05$) in the group DSS/MADF, compared with the DSS group, together with a reduction in intestinal permeability. This relationship between improvement in the intestinal barrier and the inflammatory response can be seen in the study assessing serum endotoxin levels – the application of the IF protocol also led to a reduction in peptidoglycan[12] and LPSs ($P < 0.001$, for both endotoxins)[38] and an increase in SCFAs such as 3-hydroxybutyrate ($P < 0.0005$), acetate and propionate ($P < 0.05$, for acetate and propionate).[40,42] In the regulation of circadian genes, increased expression of the genes *BMAL1* and *CLOCK* ($P < 0.05$) has been reported in conjunction with the activation of Sirt1, among other genes responsible for the synchronization of the circadian rhythm.[36,45] In addition, the study by Beli et al. (2018)[12] reported effects on the production of bile acids, more precisely an increase in deoxycholate and taurochenodeoxycholate (TCDCA) ($P < 0.05$).[40]

Limitations

Most studies had a few limitations, the main ones reported being small samples,[35,46,47] exposure period, and oversimplified diet composition, especially in the human studies. Some authors reported that the lack of pronounced effects in certain populations may have been related to the participants' freedom to define the quality/quantity of food eaten daily, errors in filling in the recalls,[43,46,47] possible noncompliance with fasting times, errors and/or methodological limitations[38,42,44,45] and results that were incomplete and/or susceptible to bias.[43–47] Authors of the remaining studies did not declare limitations.[12,27,34–37,39–41]

DISCUSSION

Effects on the Firmicutes/Bacteroidetes ratio and intestinal microbiota communities

In the current systematic review on the effects of the IF protocols on IM metabolism, weight control, and other obesity-related factors, we observed that the IM is directly affected by the quantity and quality of food, as well as the duration of the feeding time. As reported by other authors, the IM is mainly affected by factors associated with food,[27,50,51] and the "obesogenic" diet induces the IM to acquire dysbiosis characteristics.[52,53] This behavior of the IM is still poorly described, and there is controversy over how microbial populations behave in the face of fasting. Interestingly, some authors report significant changes in IM composition during periods of food restriction, but they do not relate these changes to the amount of energy ingested.[9,12,28,34,54]

One of the potential factors leading to these changes could be a greater availability of certain nutrients, such as lipids, which are strongly related to an increase in the development of bacterial populations that have greater inflammatory potential, and that consequently increase the fat deposition and the dysregulation of glucose metabolism present in obesity.[20,55–57] This microbiota restructuring was observed in db/db mice (genetically modified animals for studies of obesity and insulin resistance) subjected to the protocol of ADF for 7 months and a high-fat diet (HFD) (Table 3): in the HFD/ADL animals that were fasted, in addition to a reduction in the permeability of the intestinal barrier seen in the animals, the regimen resulted in the enrichment of Firmicutes and the reduction of Bacteroidetes.[12] This improvement in the intestinal barrier has a positive relationship with improved metabolic state and greater efficiency in the production of SCFAs.[19,53] It is also associated with a reduction in endotoxemia due to less translocation of LPSs into the bloodstream.[26,58]

A similar trend was observed in a study with a caloric restriction protocol (40%)[28] for 30 days: Fabbiano et al observed changes in the diversity of the bacterial community, including an increase in the families Lactobacillaceae and Erysipelotrichaceae, a decrease in

the Firmicutes phylum, and an increase in Bacteroidaceae and *Akkermansia muciniphila*. This increase in *Lactobacillus* spp. and *Akkermansia m.* is frequently associated with the most diverse metabolic benefits. *Lactobacillus* spp., belonging to the Lactobacillaceae family, are considered a probiotic,[59–61] and *Akkermansia m.*, although only a recently studied bacterium, has already been associated with improvement of insulin resistance, lipid profile, and other benefits for metabolism and the control of diseases related to excess fat.[21,28,62–65]

Fasting exposure time was also relevant in IM remodeling. The application of three TRF variations (12:12; 16:8 and 20:4) (Table 2) under a ND[35] in C57BL/6J germ-free mice for a period of 30 days induced different changes and chronicity, since although there was an improvement in abundance in all groups, they were only significant in the group submitted to 16 h fasting. However, these changes disappeared weeks after the interruption of the fast.[35] This reversal may be associated with the short period of exposure to fasting leading to only a transient change in IM, and lacking the necessary chronicity to allow remodeling of the resident IM. In another case, animals submitted to 2 months of TRF had larger populations of families of 3-hydroxybutyrate-producing bacteria, including Lachnospiraceae and Ruminococcaceae (Table 3), which are less frequent in animals with T2DM, but the authors did not assess the effects after the interruption of the fast.[12]

The fact that IM plays a role in health and disease opens up the tempting possibility of using dietary means to maintain optimal health. Furthermore, there is a strong link between the Firmicutes/Bacteroidetes ratio, body weight, and metabolic changes; for example, a relative increase in certain classes within Firmicutes and Bacteroidetes is seen in obese individuals, and a decrease in these classes associated with IF is associated with reduced weight.[20,23,47] IF protocols appear to be strategies that positively modulate how the resident IM will behave. This positive stimulus in the enrichment of the population of Firmicutes has been reported by several authors,[5,27,29,57,66] mainly an increase in the population of *Lactobacillus* spp. and other strains producing 3-hydroxybutyrate and other SCFAs. This feature has potential in the control of diseases related to weight gain,[9,27,67] through the stimulation of leptin secretion related to the improvement of satiety control systems.[23] In addition, the production of SCFAs leads to an improvement in the intestinal barrier,[19,68] reducing the translocation of LPSs into the bloodstream. This effect is linked to a reduction in Toll-like receptor 4 (TLR4) activation and, consequently, less stimulation of the secretion of tumor necrosis factor alfa (TNF-α) and interleukin 6 (IL-6),[20,56] pertaining to insulin desensitization. Therefore, although limited, the available biomarker data suggests that the IF leads to considerable changes in most obesity-related metabolic disease risk biomarkers, with possible application in treating insulin resistance and controlling inflammation through IM remodeling.

Effects on body composition and metabolic regulation

Obesity is mainly characterized by the excessive accumulation of body fat and an increase in inflammatory activity, concomitant with a decrease in satiety and glycemic control systems.[2,5] Food is one of the most relevant causes of obesity, and its composition is important in relation to the onset of obesity, especially when based on high consumption of the industrialized products characteristic of "westernized" food.[24,69,70] In the current study, the relationship between the intestinal bacterial community and body composition during the IF protocols was verified. When interpreting this data, it is important to consider the strength of the evidence. The animal studies included in this review generally had a higher level of evidence than the human trials. For example, when using obese mice subjected to ADF or TRF, the authors identified in both groups a significant reduction in body weight associated with a reduction in epididymal white adipose tissue, when compared with animals without food restriction.[37] This change in body composition mainly relates to the amount and type of adipose tissue. In the human studies, these changes were not so evident.

Unfortunately, some studies had limitations in the assessment of obesity, as observed in the study by Gabel et al. (2020)[43] who noted a reduction in body weight, but did not provide initial data on lean and fat mass, which makes understanding of the possible effect on body fat difficult. On the other hand, a clear "anti-obesogenic" effect was observed in the study by Li et al. (2017),[39] in which ADF, in addition to reducing body weight, presented a "beiging" of white subcutaneous adipose tissue; this phenomenon is associated with an increased thermogenic effect.[71] It is interesting that IF protocols influence the energetic and metabolic state of the cell, and promote changes at the molecular level for the purpose of cellular protection and the minimization of inflammatory processes.[37,72–75] This further reinforces the idea that the continuation of fasting modifies not only the inflammatory profile, but also the distribution of fat, which can lead to an increase in brown fat, thus dictating the course of a major part of the metabolic adaptations of the IM during fasting.[28,39]

It was also possible to identify an improvement in glycemic levels after IF, which, by modulating the IM and its metabolites, acts through two possible mechanisms. The first mechanism is related to the ability to reduce low-grade inflammation, common in obesity,

which leads to better signaling/induction of phosphorylation cascades that precede GLUT-4 translocation to the cell's outer membrane.[21,76] The second mechanism is related to the ability to reduce pancreatic wasting and to restore the pancreatic β cells responsible for insulin production, as seen in mice subjected to MADF.[41] Thus, fasting can be effective against hyperglycemia by improving insulin sensitization and/or by avoiding the reduction of its secretion.[28,40,66] This effect is linked to the reduction of TLR4 activation and, consequently, less stimulation of TNF-α and IL-6 secretion.[20,56] ADF also demonstrated the ability to inactivate the mTOR pathway, positively regulating energy metabolism and improving central and peripheral insulin sensitivity,[40] reinforcing the participation of fasting in the control/prevention of T2DM.

As seen, IF regardless of the configuration of the protocol, leads to significant improvement in biochemical parameters, body composition and IM.[36,38,45] These findings have demonstrated that even after a short term (studies with 25–30 days of intervention)[45] the TRF has a positive effect, mainly on the lipid profile, with a reduction in TG and LDL levels, along with an increase in HDL in accordance with a reduction in the size of adipocytes. In addition, modulating the IM to a healthier shape has the ability to regulate the release of fasting-induced adipose factor (Fiaf) from intestinal cells, acting as a lipoprotein lipase (LPL) inhibitor, regulating the accumulation of TGs in adipocytes.[5,23,77] These metabolic changes are associated with amelioration of dyslipidemias and cardiovascular diseases, and possibly with reduction of liver lesions associated with nonalcoholic hepatic steatosis.[15,36,41,78,79]

Another interesting consequence of the IM and IF was the positive regulation of transcriptional activators such as BMAL1 and CLOCK, as well as Sirtuins expression, which is linked to circadian control.[36,45,57] Within this context, food frequency and energy density are 2 of the environmental factors that interfere in the expression of clock genes, desynchronizing the circadian rhythm.[80] Finally, the TRF reproduced feeding/fasting cycles similar to natural feeding rhythms, affecting the amplitude of the oscillations of these genes, translating to healthier phenotypes.[36,57] With this in mind, the IM is also altered by food, and the effect of IF on the regulation of circadian genes may be not only by the host's lifestyle, but also mediated by changes in the microbiota.[57,80] In addition, it has also been observed that fasting protocols can prevent diabetic retinopathy, prolong survival in db/db mice,[12,40] and lead to increased levels of 5-hydroxytryptamine (5-HT), and an anxiolytic effect in db/db mice.[40] This effect may be related to the increased abundance of *Lactobacillus* spp.[59]

Is intermittent fasting an anti-inflammatory factor?

Improvement in the inflammatory profile is commonly associated with the profile of the microbiota and the linked reduction in TLR4 activation by LPSs.[20,56] For example, there is a difference between the microbiota populations present in overweight and eutrophic individuals, and the IF protocols influence metabolic functioning, directly or indirectly, mainly in the control of weight and inflammation.[19,27,57,58] This suggests that IF protocols are able to regulate the secretion/production of inflammatory cytokines through IM metabolites,[12,34,42,45] mainly the secretion of TNF-α and IL-6, as described by other authors.[20,28,53,78] As well as fasting, IM metabolites have the ability to regulate the immune response, through a reduction in the count of splenic $CD3^+CD4^+$ T cells, as seen in animals submitted to TRF after being treated with DSS, and which was associated with improved permeability of the intestinal barrier.[34] These findings are in agreement with the findings of Zhang et al. (2020)[54] in which, after the administration of DSS, the mice were subjected to TRF or intermittent energy restriction, and the animals showed improvement in intestinal permeability, through the greater expression of Claudine-1, Ocludine, and ZO-1 proteins present in the tight junction. This change led to less translocation of LPSs into the bloodstream and consequently less expression of TNF-α and IL-1β, controlling inflammation and helping to reverse ulcerative colitis.[54] This evidence supports the hypothesis that IF protocols can be used to treat inflammatory bowel diseases.

Limitations

Fasting, like any other nutritional management tool, has certain limitations. Among them are the adequacy of the dietary routine, the age of the individual, and the culture within which the individual lives. Nutritional management always presents problems in its implementation, and in the case of IF protocols it is no different. The biggest limitation found in the analysis of the studies was the difference between the composition of the diets in the studies, especially those using the animal model.[36–39] The consequences of this lack of standardization in the distribution and quality of macronutrients was possibly the determining factor in the different responses found.[36–39,44–48] Furthermore, daily habits such as work routine and food culture have a strong impact on adherence to protocols.[29] For example, in a study with adult individuals under different dietary restriction protocols, they reported less adherence to the IF of the ADF type than to caloric restriction (CR).[73] Such an event is believed to be due to the fact that few

individuals are used to spending long periods without eating.

Moreover, although IF is beneficial in metabolic regulation, even with good adaptation to the patient's routine, in certain cases its application may pose risks to the individual's development. In young mice, for example, TRF (16:8) induces a reduction in body weight and serum glucose levels; however, after the end of the intervention, they become obese and hyperglycemic.[81] This trend can be explained by low levels of leptin and PYY increasing the food consumption[23] of animals submitted to TRF. In addition, a tendency towards fatty liver disease and a reduction in the speed of sexual maturation and the size of the islets of Langerhans are also reported. This is linked to the low insulin levels[81] and reduced diversity of the phylum Firmicutes, the order Clostridiales, and the family Ruminococcaceae, which are associated with the more protective profile of the metabolism.[19,27,57,81] Therefore, the most appropriate time/age to initiate such protocols should be carefully evaluated in order to avoid damage to development, especially in sexual maturation and the immune system, as has been reported.

CONCLUSIONS

Literature on this subject is scarce, and there are no studies that evaluate the long-term effects of IF; however, this approach has shown promise for improving weight loss through the remodeling of the IM. In conclusion, the IF protocols can be considered as an alternative method for the reduction of body weight of overweight individuals, in particular for those individuals who are unable to follow a conventional food prescription in a regulated way.

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Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

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6 CONSIDERAÇÕES FINAIS

Atualmente, o jejum de dias alternados (ADF) e a restrição temporal do alimento (TRF) tem se tornado cada vez mais comuns como estratégias para perder peso e melhorar a saúde em indivíduos adultos. No entanto, também deve ser adotado um estilo de vida saudável, que deve incluir também a prática de exercícios físicos regulares, pois eles têm um efeito sinérgico na saúde do indivíduo.

A literatura existente sobre o assunto ainda é escassa e não há estudos que avaliem seus efeitos em longo prazo, porém esse método tem se mostrado promissor na melhora do peso (fator determinante na resistência à insulina) e no remodelamento da IM. Podendo ser considerado como um método alternativo para aqueles indivíduos que não conseguem seguir uma prescrição alimentar convencional de forma regrada. Em contrapartida, a participação do IF como uma estratégia moduladora da IM, ainda existem controvérsias em relação a como a microbiota se comporta. E seu uso deve ser avaliado com cautela, principalmente quando se refere ao estágio de vida em que é utilizado, podendo ocasionar em um “dismetabolismo” irreversível como visto no estudo de Hu *et al*., (2019a) ao avaliar a exposição ao TRF em animais pré-púberes.

Como visto, estes métodos de restrição do alimento apresentaram a capacidade de estimular o desenvolvimento das famílias *Lachnospiraceae, Ruminococcaceae, Lactobacillaceae, Verrucomicrobiaceae* e outras responsáveis pela produção de SCFAs, frequentemente associadas à saúde metabólica, além da redução da abundância de cepas associadas à disfunção metabólica. Além disso, esses protocolos de IF quando aplicado na fase adulta é bem tolerado e a taxa de redução glicêmica dentro do esperado. Portanto, ao melhorar os níveis de açúcar no sangue e promover a reestruturação da microbiota para um formato mais saudável, representa um enorme ônus econômico, ao auxiliar na prevenção das complicações decorrentes do ganho de peso excessivo e ao reduzir a morbimortalidade dos indivíduos.

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