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LUIZA SCALCON DE OLIVEIRA

INTOLERÂNCIA À LACTOSE E O MANEJO DOS SINTOMAS COM PROBIÓTICOS E PREBIÓTICOS: UMA REVISÃO SISTEMÁTICA

FRANCISCO BELTRÃO – PR
AGOSTO, 2022

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LISTA DE ABREVIATURAS E SIGLAS

AGCC - ácidos graxos de cadeia curta

FAO - *Food and Agriculture Organization of the United Nations*

FOS - fruto-oligossacarídeos

EFSA - European Food Safety Authority

GRADE - *Grading of Recommendation, Assessment, Development and Evaluation*

GOS - galacto-oligossacarídeos

HBT - *Hydrogen Breath Test*

IL – Intolerância à Lactose

ISAPP - *International Scientific Association for Probiotics and Prebiotics*

RCT - Randomized Controled trials

RevMan - Review Manager

RoB 2.0 - *Risk-of-bias tool for Randomized trials* version 2.0

RS – Revisão Sistemática

TOS - trans-galacto-oligossacarídeos

WHO - World Health Organization.

Intolerância à lactose e o manejo dos sintomas com probióticos e prebióticos: uma revisão sistemática

Resumo

A intolerância à lactose (IL) é caracterizada pela diminuição ou incapacidade de digerir a lactose, por consequência alguns sintomas como diarreia, flatulência, distensão abdominal, entre outros, podem do aparecer. O aparecimento dos sintomas da IL é multifatorial, depende da quantidade de lactose que o indivíduo ingeriu e da quantidade de lactase que o organismo produz. O tratamento da IL, consiste inicialmente na remoção das fontes de lactose, posteriormente faz-se a reintrodução gradual de produtos lácteos, acompanhando a tolerância do indivíduo. A reposição enzimática também é uma conduta utilizada para a melhora dos sintomas. Abordagens com o uso probióticos e/ou prebióticos vêm sendo avaliadas, para auxiliar no manejo da condição. Os probióticos são microrganismos benéficos que podem proporcionar melhoria da saúde por meio do equilíbrio da microbiota gastrointestinal. Já os prebióticos são oligossacarídeos que estimulam o crescimento e/ou a atividade de um grupo de microrganismos no trato gastrointestinal, promovendo benefícios à saúde do indivíduo. A presença desta microbiota, favorece o metabolismo da lactose, proporcionando melhoria dos sintomas da IL. Apesar da existência de dados envolvendo a IL e o uso de probióticos ou prebióticos, há uma dificuldade em encontrar na literatura, especificamente, estudos que reavaliem os sintomas da IL com produtos contendo lactose ao término do uso de microrganismos e/ou oligossacarídeos. Logo, a presente pesquisa tem como objetivo, investigar por meio de uma revisão sistemática a eficiência da aplicação clínica dos suplementos probióticos ou prebióticos na diminuição dos sintomas da IL, com vistas a reunir evidências úteis para os profissionais de saúde na recomendação e manejo dos sintomas em pessoas com IL. Para a realização da pesquisa, foram utilizadas as diretrizes do PRISMA 2020. Os estudos foram recuperados nas seguintes bases de dados: SciElo, PubMed, LILACS, ScienceDirect e também na literatura cinza. Para o

risco de viés adotou-se a ferramenta RoB 2.0, e para a análise de certeza dos achados foi utilizada a ferramenta GRADE. Foram encontrados 830 estudos, 5 foram incluídos nesta revisão, os demais não se adequavam aos critérios de inclusão. Dois estudos abordaram um prebiótico e três estudos abordaram probióticos diversos. Destacaram-se os probióticos *Lactobacillus reuteri* e o DDS-1 de *Lactobacillus acidophilus,* e o prebióticos GOS RP-G28. No pós-tratamento, o prebiótico pareceu ser mais efetivo na diminuição dos sintomas. O risco de viés para estudos sobre probióticos apresentou preocupações em todos os estudos avaliados, já para prebióticos apenas um dos estudos apresentou alguma preocupação. A certeza de evidência foi alta para o prebiótico GOS RP-G28, em contrapartida, se apresentou baixa para os probióticos pelos vieses metodológicos e baixo número de indivíduos incluídos. Sabe-se que os alimentos não são usados como tratamento, entretanto, esta RS apresenta uma abordagem alternativa para auxiliar na diminuição dos sintomas da IL. Dentre as limitações, a hetererogeneidade e a falta de dados impossibilitou a realização de uma análise de sensibilidade. As evidências de alegações funcionais para probióticos demonstraram ser muito baixas, e para prebióticos os dados são limitados. Novos estudos são necessários, adotando metodologias robustas, sobretudo na divulgação completa dos dados.

Palavras-chave: Intolerância à lactose; microbiota intestinal; oligossacarídeos; probióticos.

Lactose intolerance and symptom management with probiotics and prebiotics: a systematic review

Abstract

Lactose intolerance (IL) is characterized by the decrease or inability to digest lactose, therefore some symptoms such as diarrhea, flatulence, abdominal distension, among others, may appear. The appearance of IL symptoms is multifactorial, depending on the amount of lactose that the individual ingested and the amount of lactase that the body produces. The treatment of IL initially consists of removing the sources of lactose, followed by the gradual reintroduction of dairy products, following the individual's tolerance. Enzyme replacement is also a procedure used to improve symptoms. Approaches using probiotics and/or prebiotics have been evaluated to help manage the condition. Probiotics are beneficial microorganisms that can provide improved health through the balance of the gastrointestinal microbiota. Prebiotics are oligosaccharides that stimulate the growth and/or activity of a group of microorganisms in the gastrointestinal tract, promoting benefits to the health of the individual. The presence of this microbiota favors the metabolism of lactose, providing improvement in the symptoms of IL. Despite the existence of data involving IL and the use of probiotics or prebiotics, it is difficult to find in the literature, specifically, studies that reassess the symptoms of IL with products containing lactose at the end of the use of microorganisms and/or oligosaccharides. Therefore, the present research aims to investigate, through a systematic review, the efficiency of the clinical application of probiotic and prebiotic supplements in reducing the symptoms of IL, in order to gather useful evidence for health professionals in the recommendation and management of symptoms. in people with IL. The PRISMA 2020 guidelines were used to carry out the research. The studies were retrieved from the following databases: SciElo, PubMed, LILACS, ScienceDirect, and the gray literature. For the risk of bias, the RoB 2.0 tool was adopted, and for the certainty analysis of the findings, the GRADE tool was used. A total of 830 studies were found, 5 were included in this review, and the others did not meet the inclusion criteria. Two studies addressed a

prebiotic and three studies addressed several probiotics. The probiotics *Lactobacillus reuteri* and the DDS-1 of *Lactobacillus acidophilus*, and the prebiotics GOS RP-G28, stood out. Post-treatment, the prebiotic appeared to be more effective in reducing symptoms. The risk of bias for studies on probiotics presented concerns in all studies evaluated, whereas for prebiotics only one of the studies presented any concerns. The certainty of evidence was high for the prebiotic GOS RP-G28, on the other hand, it was low for the probiotics due to methodological biases and the low number of individuals included. It is known that food is not used as a treatment, however, this RS presents an alternative approach to help reduce IL symptoms. Among the limitations, heterogeneity and lack of data made it impossible to carry out a sensitivity analysis. Evidence for functional claims for probiotics has been shown to be very low, and for prebiotics data are limited. New studies are needed, adopting robust methodologies, especially in the full disclosure of data.

Keywords: Lactose intolerance; intestinal microbiota; oligosaccharides, probiotics.

SUMÁRIO

1 INTRODUÇÃO GERAL

Historicamente, os relatos referentes à intolerância à lactose (IL) têm início com Hipócrates (460–370 aC) e Galeno (129–200 dC), ambos observaram que algumas pessoas experimentaram problemas intestinais após beber leite (MATTHEWS *et al.,* 2005). Entretanto, somente em 1960 a intolerância à lactose foi reconhecida e investigada cientificamente, pelos estudos de Holzel, Schwarz e Sutcliffe (1959) e Durand (1960), que reportam os primeiros estudos sobre a condição.

Posteriormente, em 1963, a IL foi finalmente bem compreendida por meio do uso de métodos confiáveis. Tais métodos foram criados justamente para a detecção da atividade da lactase intestinal, sendo então difundida como intolerância à lactose, termo como é conhecido atualmente (DAHLQVIST *et al.,* 1963; DAHLQVIST, 1964; MONTGOMERY *et al.*, 1991).

Com a possibilidade de detectar essa condição, estimativas mundiais sobre a IL foram realizadas. Dados da última década apontam que aproximadamente 65% da população mundial tenha IL (VUORISALO *et al.,* 2012) e entre 68% e 75% da população mundial, tenha algum nível de deficiência da enzima lactase (BRANCO *et al.,* 2017; STORHAUG; FOSSE; FADNES, 2017).

Caracteriza-se como IL a diminuição da capacidade de digerir o carboidrato do leite (lactose). Consequentemente, há o aparecimento de sintomas decorrentes da má absorção da lactose como a diarreia, flatulência, distensão e dor abdominal entre outros sintomas (MATTAR; DE CAMPOS MAZO; CARRILHO, 2012).

Sabe-se que diarreias infecciosas (ZUCKERMMAN *et al.,* 1993) ou provenientes da síndrome do intestino irritável (SII) (BARBARA *et al*., 2012) alteram a microbiota e podem provocar lesões no epitélio intestinal, contribuindo para o aumento da permeabilidade de grandes moléculas. Com a permeabilidade aumentada, facilita-se a penetração de antígenos, endotoxinas, patógenos e outros agentes pró-inflamatórios no corpo humano, o que pode desencadear inflamação, doença local ou sistêmica e demais consequências como a baixa absorção de nutrientes (FUKUI, 2016).

Quando o manejo do indivíduo com IL não é adequado, podem ocorrer

alterações bioquímicas e de comportamento alimentar, prejudicando, por exemplo, o consumo de cálcio pela exclusão do leite e derivados ou por más escolhas alimentares (BOUCHOUCHA *et al.,* 2020; OLIVEIRA; CASARIL; TRECO, 2022). Logo, uma restrição de lácteos sem as devidas substituições, pode, no longo prazo, causar deficiência de cálcio, um mineral responsável por várias funções biológicas, e que impactam na qualidade de vida dos intolerantes à lactose (SANTO*S et al.*, 2014; FRANÇA, MARTINI, 2014; MISSELWITZ *et al.,* 2019).

Assim, o manejo adequado dos sintomas da IL torna-se importante para a saúde e qualidade de vida do indivíduo. Uma das primeiras alternativas pensadas para esta finalidade foi o uso da enzima lactase exógena (beta-galactosidase). Quando a enzima lactase é ingerida antes do consumo de alimentos contendo lactose, diminui-se as chances do aparecimento de sintomas ou ao menos amenizam-no (OJETTI *et al.,* 2010).

Entretanto, a lactase nem sempre supre a necessidade do indivíduo, uma vez que o consumo de lactose pode ser superior ao que a enzima é capaz de digerir, possibilitando o aparecimento dos sintomas. Portanto, uma forma alternativa que vem ganhando espaço é a modulação da microbiota intestinal, com o uso de probióticos e/ou prebióticos, pois ambos são capazes de contribuir com a proliferação de microrganismos digestores da lactose e ainda melhorar a permeabilidade intestinal, amenizando os sintomas da IL e contribuindo para a saúde geral (LEIS *et al.,* 2020).

Os probióticos são definidos como “microrganismos vivos que, quando administrados em quantidades adequadas, conferem um benefício à saúde do hospedeiro” (FAO/OMS, 2001; HILL *et al.*, 2014, p. 507). Já o termo prebiótico é atribuído à “um substrato que é utilizado seletivamente por microrganismos hospedeiros, conferindo um benefício à saúde” (GIBSON *et al.,* 2017, p. 494). Entretanto, ambos podem também atuar em conjunto, como simbióticos, para contribuir com o equilíbrio da microbiota intestinal (SWANSON *et al.,* 2020).

Apesar da existência de estudos abordando o uso de probióticos e prebióticos na sintomatologia da IL, verificou-se na literatura uma dificuldade em encontrar microrganismos e oligossacarídeos específicos com efeitos claros na IL e especialmente de estudos que buscassem especificamente a eficiência na

diminuição dos sintomas após o período de uso dos probióticos e dos prebióticos. Portanto, essa pesquisa teve como objetivo geral investigar, por meio de uma revisão sistemática (RS), a eficiência da aplicação clínica dos suplementos probióticos e prebióticos na diminuição dos sintomas da IL, de modo a apresentar evidências que possam ser úteis para os profissionais de saúde na recomendação e condução do manejo dos sintomas em pessoas com IL. Em suma, traz-se como problema de pesquisa o seguinte questionamento: quais microrganismos e/ou oligossacarídeos são mais eficientes para a diminuição dos sintomas da intolerância à lactose?

1.1 Intolerância à lactose e a ação da enzima lactase

A lactose é um dissacarídeo formado por glicose e galactose (beta-galactosil-1-4-glicose), presente principalmente em produtos lácteos. Para sua absorção, é necessário a ação de uma enzima especializada, a β-D-galactosidase (1-4), também conhecida por lactase, produzida nos enterócitos nas microvilosidades do intestino delgado e expressa ao máximo no jejuno médio. O processo de hidrólise dessa molécula permite que os monossacarídeos adentrem as células da mucosa intestinal (no intestino delgado) através de transporte ativo, dependente de sódio e mediado por carreador (GUYTON, 2006; VOET *et al.,* 2008; MAHAN *et al.,* 2012; FASSIO; FACIONI; GUAGNINI, 2018).

Estudos da mesma década da descoberta da IL mostraram que a enzima lactase tem o início da sua produção ainda na 10ª semana de gestação (DOELL; KRETCHMER, 1962; ANTONOWICZ, 1974). A lactase é composta por 1927 aminoácidos, codificada no gene da lactase (LCT) na fita curta do cromossomo 2 (2q.21-22). Todavia, a atividade da lactase passa a diminuir na maioria dos seres humanos logo após os primeiros meses de vida – não persistência da lactase - podendo diminuir exponencialmente para cerca de 10% do valor neonatal após o desmame (VESA, 2000; MAHAN *et al.,* 2012).

Conforme observam Deng *et al.* (2015), quando a atividade da lactase está abaixo de 50% da produção neonatal, ocorre ineficiência no processo de digestão da lactose, culminando na má absorção da lactose devido a hipolactasia. Nessa condição, alguns sintomas podem começar a surgir, caracterizando assim a IL (FASSIO; FACIONI; GUAGNINI, 2018).

Uma revisão sistemática realizada por Storhaug, Fosse e Fadnes (2017) levantou estudos de todo o mundo e encontrou uma prevalência global estimada de 68% para má absorção de lactose. Estima-se ainda que pelo menos 75% da população mundial tenha algum nível de hipolactasia (BRANCO *et al.,* 2017).

De acordo com Mattar *et al.* (2009), em estudo de genotipagem realizado com 567 indivíduos (brasileiros), há diferenças na prevalência de IL primária em adultos de diferentes raças, sendo que em algumas a atividade da lactase pode persistir até a idade adulta. Neste mesmo estudo, estimaram que a IL primária (genótipo CC) estaria prevalente em aproximadamente 62,8% dos brasileiros e a persistência de lactase (genótipo TC e TT) presente em 37,2%.

A IL é caracterizada pelo aparecimento de sintomas ao consumir produtos contendo lactose. Os sintomas ocorrem justamente pela má digestão da lactose devido à baixa produção/produção insuficiente de lactase (hipolactasia) e consequente má absorção da lactose (FASSIO; FACIONI; GUAGNINI, 2018).

Logo, com a lactose presente no intestino delgado, há um aumento da retenção osmótica de água e sódio, provocando assim a aceleração dos movimentos peristálticos que conduzem o quimo para o cólon. Nesta região do intestino (cólon), a microbiota metaboliza a lactose, e tem como produtos da fermentação, os ácidos graxos de cadeia curta, principalmente ácido acético, ácido láctico, propiônico e butiríco, e a produção de gases como o dióxido de carbono, o gás metano e o gás hidrogênio (PRETTO *et al.,* 2002; BAIJAL; TANDON, 2020). Com a produção desse conjunto de substâncias o indivíduo passa a apresentar tanto sintomas intestinais quanto sintomas sistêmicos (MATTHEWS *et al.,* 2005).

Uma revisão realizada por Misselwitz *et al.* (2019) envolvendo 95 estudos sobre a temática da IL, esclareceu que a probabilidade do desenvolvimento de sintomas após a ingestão de lactose é multifatorial, envolvendo fatores extrínsecos e intrínsecos. Entre os fatores extrínsecos estão a quantidade de lactose ingerida e se os produtos lácteos são ingeridos com outros alimentos que podem afetar o trânsito intestinal e a taxa de entrega de lactose ao cólon. Entre os fatores intrínsecos, estão a expressão da lactase na borda em escova do intestino delgado, história de distúrbios gastrointestinais e a composição do microbiota intestinal (MISSELWITZ *et al.,* 2019; BOUCHOUCHA *et al.,* 2021).

Outros fatores que podem não estar diretamente relacionados à digestão da lactose são a presença de transtornos de ansiedade, altos níveis de estresse e a presença de transtornos gastrointestinais funcionais, como a SII. Ademais, a IL e a SII também podem estar associadas (DENG *et al.,* 2015; MISSELWITZ *et al.,* 2019; BOUCHOUCHA *et al.,* 2021). Dentre os sintomas mais comuns da IL, encontram-se: a) **sintomas em nível local/intestinal:** dor abdominal, distensão abdominal, flatulência, borborigmo, diarreia, constipação, náusea e vômito e b) **sintomas em nível sistêmico:** dor de cabeça e tontura, perda de concentração e falta de memória de curto prazo, cansaço severo de longo prazo, dor muscular, dores articulares ou inchaço e rigidez, arritmia cardíaca, úlceras bucais, maior frequência de micção e dor de garganta (MATTHEWS *et al.* 2005; BAIJAL; TANDON, 2020).

Há uma importância na existência dos sintomas, pois são eles que caracterizam e diferenciam a IL de uma má absorção de lactose. A má absorção da lactose se dá pela diminuição da produção da enzima lactase, ou seja, uma hipolactasia, sem a presença de sintomas ao consumir lactose (BOUCHOUCHA *et al.,* 2021). O tipo de hipolactasia que o indivíduo apresenta varia de acordo com as causas e podem ser classificados como: intolerância congênita à lactose, hipolactasia primária e secundária do tipo adulto (DENG *et al.,* 2015).

A deficiência congênita de lactase, é permanente e extremamente rara (FASSIO; FACIONI; GUAGNINI, 2018) e decorrente de um defeito genético (autossômico recessivo), devendo-se à herança de 2 alelos defeituosos do gene LCT (ENATTAH *et al*., 2002). Os sintomas de diarreia líquida aparecem no neonato logo em suas primeiras mamadas, e, caso não seja diagnosticada precocemente, pode evoluir e levar a óbito. (GASPARIN; TELES; ARAÚJO, 2010; MATTAR; DE CAMPOS MAZO; CARRILHO, 2012; WORTMANN, 2013; BRANCO *et al.,* 2017). Entretanto, estudos recentes sobre esta condição congênita, parecem escassos na literatura atual.

A hipolactasia primária do tipo adulto, é a forma mais comum de má absorção da lactose ou da intolerância à lactose (MISSELWITZ *et al.,* 2019). Segundo Mattar *et al.* (2009), a hipolactasia primária tem prevalência de 57% em brancos e mulatos, em 80% em negros e 100% em japoneses.

A hipolactasia primária é determinada geneticamente e se caracteriza pela

deficiência da enzima lactase que ocorre por um polimorfismo de alelo variante $C/T_{-13910a}$ montante do gene da lactase (ENATTAH *et al.,* 2002). Fisiologicamente, a atividade da lactase diminui na maioria das populações a partir dos primeiros anos de vida. Com o avanço da idade, ocorre uma perda programada da atividade de lactase, por alterações nos genes codificadores de lactase, cujo mecanismo é desconhecido, porém, resultante de fatores hereditários (GASPARIN; TELES; ARAÚJO, 2010; BRANCO *et al.,* 2017).

Diferente da hipolactasia primária do tipo adulto e da intolerância congênita, a hipolactasia secundária é transitória e reversível mediante tratamento adequado (MATTAR; DE CAMPOS MAZO, 2010; MISSELWITZ *et al.,* 2019;). A hipolactasia secundária é a mais comum, e sua causa pode ser em função de alterações gastrointestinais, decorrente de algumas condições pós-cirúrgicas, como síndrome da alça estagnada ou síndrome do intestino curto, infecção por protozoários (G*iardia lambia*, *Amoeba*, *Ascaris lumbricoides,* criptosporidiose) enterite regional, entre outros*.*

As irritações causadas pela desnutrição severa, doença celíaca, doença inflamatória intestinal (especialmente doença de Crohn), enterites bacterianas ou virais (por exemplo, rotavírus), enterite actínica ou induzidas por drogas ou radiação, doença diverticular do cólon, induzida por alguns tratamentos farmacológicos (canamicina, neomicina, polimicina, tetraciclina, colchicina e outros medicamentos quimioterápicos) e anemia, também podem estar associadas à IL secundária, bem como a SII e os fatores psicológicos (DENG *et al.,* 2015; BRANCO *et al.,* 2017; FASSIO; FACIONI; GUAGNINI, 2018; BOUCHOUCHA *et al.*, 2021).

Devido a enzima ser encontrada no ápice das vilosidades duodenais, todas as condições patológicas que envolvem estas microvilosidades podem resultar na redução da lactase. Assim que a causa da agressão às microvilosidades for resolvido, os produtos que contêm lactose podem ser consumidos normalmente, sendo assim, torna-se uma IL transitória (FASSIO; FACIONI; GUAGNINI, 2018). Entretanto, para saber qual o tipo de IL o indivíduo apresenta, é necessário proceder uma investigação.

1.2 Diagnóstico e tratamento convencional para a intolerância à lactose

A forma mais difundida para diagnóstico da intolerância à lactose é o teste de hidrogênio expirado, ou, do inglês *Hydrogen Breath Test* (HBT) (BRANCO *et al.,* 2017). O HBT é um exame respiratório que utiliza a medida do hidrogênio expirado após a ingestão de doses de lactose. O gás hidrogênio produzido pelas bactérias ao fermentar a lactose livre no intestino, entra para a corrente sanguínea e é eliminado pelos pulmões, o que permite a sua detecção por exame respiratório, tornando-o um exame simples e não invasivo (BRANCO *et al.,* 2017; MISSELWITZ *et al.,* 2019).

Apesar de ser amplamente utilizado, a confiabilidade do HBT depende da atividade da flora bacteriana, da lealdade do indivíduo em seguir as orientações antecedentes ao teste, e, ainda, da avaliação pré-teste. Pois, se o indivíduo estiver fazendo uso de antibióticos, o resultado pode ser um falso positivo (MATTAR *et al.,* 2012). Dentre outros testes para detecção da intolerância à lactose estão: o teste respiratório com carbono marcado (CO_2), exame do pH fecal, exame de glicose nas fezes, exame de curva glicêmica e galactosêmica do sangue, biópsia jejunal/duodenal e teste genético, sendo que, com exceção deste último, os demais todos dependem do consumo prévio de uma dose específica de lactose (VESA *et al.*, 2000; DENG *et al.,* 2013). Testes genéticos mais sofisticados podem identificar polimorfismos do nucleotídeo único $C/T_{-13910a}$, presente no gene LCT, (responsável pela produção da lactase) (MATTAR *et al*., 2008). Este polimorfismo no gene LCT foi associado à hipolactasia do tipo adulto (MATTAR *et al*., 2008; MISSELWITZ *et al.,* 2019). Um recente estudo propôs o uso de um teste simples e viável por meio da análise sintomatológica da IL (ROCCO *et al.,* 2021). O estudo diagnosticou a IL por meio dos sintomas relatados e, posteriormente com o uso de um exame, como o HBT. Segundo Rocco *et al.* (2021), caso os dados sejam confirmados em um estudo multicêntrico, o uso na prática clínica de um questionário validado poderá ser recomendado para diagnóstico em indivíduos com IL autorreferida. Este questionário precisará mais ainda a identificação dos pacientes que provavelmente se beneficiarão de uma alimentação sem lactose (ROCCO *et al.,* 2021). O manejo dietético para a IL varia de acordo com o tipo de hipolactasia.

Para o manejo da IL deve considerar a sua etiologia (SANTOS *et al.,*

2019), objetivando a remissão dos sintomas gastrointestinais (MAHAN *et al.,* 2012). Segundo Santos *et al.* (2019), o manejo adequado, considerando as etiologias da intolerância à lactose, são: **a) hipolactasia congênita:** excluir a lactose da dieta permanentemente; **b) hipolactasia primária do adulto:** o consumo de lactose deve ser inicialmente evitado, para que os sintomas sejam amenizados, posteriormente, a reintrodução pode ser conduzida, considerando a tolerância do indivíduo e **c) hipolactasia secundária do adulto:** evitar ou excluir os alimentos que contenham lactose, até que a causa subjacente seja controlada, posteriormente, a lactose pode ser reintroduzida, também respeitando a tolerância do indivíduo.

Entretanto, a tarefa de reduzir e até mesmo excluir o consumo de lactose pode ser dificultada pela presença de alimentos com lactose não identificada na sua composição, e ainda trazer riscos à saúde dos intolerantes à lactose (MATTAR; DE CAMPOS MAZO; CARRILHO, 2012). Evitar leite e produtos lácteos pode causar estados de deficiência de cálcio, vitamina D e riboflavina, diminuir a qualidade de vida, levar à osteoporose e à depressão (BAIJAL; TANDON, 2020).

De acordo com Santos *et al*. (2019), algumas pessoas possuem a capacidade de se adaptar e tolerar (sem apresentar sintomas), até 12g ou mais de lactose, o que seria equivalente a uma porção de leite de 240 ml. Porém, em estado de IL primária ou secundária, a reintrodução da lactose deve ser contínua e gradual, durante várias semanas (SANTOS *et al*., 2019). A prática da reintrodução gradual do consumo de leite pode provocar alterações benéficas da microbiota intestinal, como o aumento de microrganismos produtores de beta-galactosidase, que contribuem para a digestão da lactose diminuindo o limiar para aparecimento dos sintomas (KATO *et al.*, 2018).

Ressalta-se ainda que produtos fermentados possuem menor quantidade de lactose, como, por exemplo, queijos curados e iogurtes, sendo mais bem aceitos pelos portadores da hipolactasia primária e secundária do adulto (MAHAN *et al.*, 2012). Atualmente, é possível encontrar no varejo uma ampla gama de produtos “sem lactose” ou “zero lactose” pois estes produtos alimentares são pré-tratados com lactase e podem fazer parte do tratamento dietéticos para pacientes intolerantes à lactose (BAIJAL; TANDON, 2020). A exclusão total e definitiva da

lactose da dieta deve ser evitada, pois, conforme já apresentado, pode acarretar prejuízo nutricional e predispor à doenças (MAHAN *et al.*, 2012; SANTOS *et al.,* 2019; BAIJAL; TANDON, 2020).

A enzima lactase externa/exógena também pode compor parte do tratamento dietético na IL (BAIJAL; TANDON, 2020). De acordo com um estudo randomizado realizado por Ojetti *et al*. (2010), a reposição enzimática de lactase representa uma estratégia terapêutica válida com eficácia para a redução de sintomas e sem efeitos colaterais. Segundo uma revisão sistemática realizada por Barbosa *et al.* (2020), ainda não há um consenso da quantidade da enzima lactase a ser ingerida, sendo que pode ser encontrada nas doses de 300 mg/1500 UI, 500 mg/2500 UI, 750 mg/3700 UI e 1000 mg/5000 UI. As fontes comerciais de β-galactosidases (lactases) incluem as espécies de leveduras *Kluyveromyces marxianus, Kluyveromyces lactis e Candida kefyr, Aspergillus niger* e *Aspergillus oryzae,* e mais recentemente células de *Streptococcus thermophilus* e de *Lactococcus lactis* permeabilizadas por nisina podem hidrolisar a lactose de forma eficiente (GARCIA-GARIBAY; GÓMEZ-RUIZ, 1996; WANG et al. 2020). Entretanto, no Brasil, a Resolução RDC nº 205/2006 especifica que a lactase deve ter como origem os seguintes microrganismos, aprovados pelo FDA (*Food and Drugs Administration*), consideradas como seguros para aplicação em alimentos: *Aspergillus niger, Aspergillus oryzae, Candida pseudotropicalis, Kluyveromyces lactis, Kluyveromyces marxianus, Kluyveromyces fragilis* e *Saccharomyces sp*. (BRASIL, 2006).

Outra estratégia de tratamento para melhora dos sintomas da IL, envolve o uso de probióticos e mais recentemente também os prebióticos. Ambos (probióticos e prebióticos) demonstraram capacidade de beneficiar a microbiota intestinal, melhorando a digestão da lactose e contribuindo também com a saúde geral dos indivíduos (LEIS *et al.,* 2020).

1.3 Microbiota intestinal e a intolerância à lactose

Durante o desenvolvimento uterino, os humanos são abrigados em um ambiente estéril. Entretanto, com o rompimento das membranas para o nascimento, os bebês ficam expostos a um mundo colonizado por

microrganismos, e, o trato gastrointestinal, em especial o cólon, é o ambiente de maior colonização microbiana (TIIHONEN; OUWEHAND; RAUTONEN, 2010).

As grandes mudanças da microbiota intestinal ocorrem na infância e se estabilizam durante a amamentação ou uso de fórmulas (TIIHONEN; OUWEHAND; RAUTONEN, 2010). Posteriormente, outras alterações significativas da microbiota intestinal acontecem com a introdução de alimentos sólidos e o desmame. Durante a vida adulta, a composição da microbiota intestinal é relativamente estável, todavia, variações substanciais podem ocorrer em um curto período com o uso de medicações, principalmente com antibióticos (TIIHONEN; OUWEHAND; RAUTONEN, 2010).

Considerando a alteração da microbiota pela ingestão alimentar, um estudo realizado por Hertzler e Savaiano (1996) demonstrou que a microbiota intestinal se adapta para facilitar a ingestão de laticínios. Os autores apontaram que, embora a expressão da lactase não seja regulada positivamente pela ingestão de lactose, o consumo regular de lactose pareceu reduzir a excreção de hidrogênio no ar expirado e reduzir os sintomas de intolerância à lactose (HERTZLER; SAVAIANO, 1996).

Estudo realizado com 1068 japoneses saudáveis mostrou que a abundância de Bifidobactérias é positivamente correlacionada com a ingestão de laticínios na dieta ($r = 0,164$, $p<0,01$) (KATO *et al.*, 2018). Entretanto, os autores ainda observaram que a lactose não é um substrato de crescimento seletivo para *Bifidobacterium* no intestino, então deve-se considerar outros possíveis fatores contribuintes para a abundância de *Bifidobacterium*, como por exemplo, os vários tipos de fibras solúveis na dieta japonesa (KATO *et al.*, 2018). Em discussão sobre o artigo de Kato *et al.* (2018), Misselwitz *et al*. (2019) lembram que, a população japonesa população é predominantemente má absorvedora de lactose (90% a 100%), e a ocorrência do aumento de Bifidobactérias pode ser reflexo do efeito da ingestão regular de lactose sobre a microbiota, assim como o inverso não pode ser excluído.

Estimulado pelo progresso global na compreensão do papel da microbiota humana na saúde e na doença, também surgiu a necessidade de definir estratégias eficazes para moldar uma microbiota mais saudável. Portanto, ensaios de intervenção controlados, revisões sistemáticas e meta-análises fornecem

evidências convincentes dos benefícios dos probióticos e prebióticos em diferentes necessidades da saúde humana, incluindo na digestão da lactose (HILL *et al.*, 2014; GIBSON *et al.,* 2017). No caso dos indivíduos com IL, a fermentação da lactose por bactérias sacarolíticas (digestoras de açúcar) pode também, trazer benefícios para a saúde geral, visto que os ácidos graxos de cadeia curta liberados na fermentação beneficiam a saúde do cólon (MISSELWITZ *et al*., 2019).

Um estudo clínico randomizado realizado por Almeida *et al*. (2012) propôs o consumo de uma combinação de *Lactobacillus casei Shirota* e *Bifidobacterium breve Yakult* durante quatro semanas. Como resultado, melhorou os sintomas e diminuiu a produção de hidrogênio em indivíduos intolerantes à lactose. Esses efeitos pareceram persistir por pelo menos três meses após a suspensão do consumo dos probióticos.

Em geral, estudos randomizados têm demostrado que as bifidobactérias e os lactobacilos são capazes de digerir a lactose em intolerantes, diminuindo a sintomatologia sem apresentar efeitos adversos (MUSTAPHA; JIANG; SAVAIANO, 1997; SALTZMAN *et al.*,1999; RIZKALLA *et al.,* 2000; OJETTI *et al.,* 2010; PAKDAMAN *et al.*, 2016; VITELLIO *et al.,* 2019). Sendo assim, o uso de alguns microrganismos parece promissor para o manejo dos sintomas em intolerantes à lactose, ainda mais se considerado o tempo de atividade mesmo após cessar o consumo dos probióticos, uma vez que a efetividade na melhora dos sintomas pode permanecer por alguns meses conforme apresentado no estudo de Almeida *et al*., (2012).

1.4 Probióticos

Os probióticos são estudados há muitos anos. O termo probiótico (do grego "*para a vida"*) foi descrito pela primeira vez em 1965 por Lilly e Stillwell, que adotaram o termo para descrever substâncias produzidas por um microrganismo que atuavam como fatores promotores de crescimento. Durante os anos, outras modificações nas definições foram acontecendo. Todavia, a definição mais difundida foi estabelecida pela FAO/OMS, em 2001, e, posteriormente adaptada pela *International Scientific Association for Probiotics and Prebiotics (ISAPP)*, em

uma conferência que definiu como probióticos os “microrganismos vivos que, quando administrados em quantidades adequadas, conferem um benefício à saúde do hospedeiro” (FAO/OMS, 2001; HILL *et al.*, 2014, p. 507).

No Brasil, a legislação segue a mesma definição da ISAPP. A Resolução da Diretoria Colegiada RDC Nº 241, DE 26 DE JULHO DE 2018 dispõe sobre os requisitos para comprovação da segurança e dos benefícios à saúde dos probióticos para uso em alimentos (BRASIL, 2018).

Os produtos probióticos podem conter bactérias liofilizadas ou leveduras, mais comumente dos gêneros *Lactobacillus* e *Bifidobacterium* (FAO/OMS, 2001; HILL *et al.*, 2014). As primeiras definições de probióticos incluíam alimentos fermentados tradicionais, como iogurte (variedades não medicinais), chucrute e kefir, embora sejam atualmente considerados fontes de alimento de “culturas vivas e ativas”. Para um microrganismo ser considerado probiótico, precisa cumprir com os requisitos mínimos definidos pela FAO/OMS (2001, 2002):

- Passar por avaliação da identidade da cepa (gênero, espécie, nível de cepa);
- Apresentar resistência à acidez gástrica, ácido biliar e enzimas digestivas, assim como atividade antimicrobiana contra bactérias potencialmente patogênicas;
- Passar por avaliação de segurança: requisitos para a prova de que uma cepa probiótica é segura e sem contaminação em sua forma de entrega;
- Ter estudos *in vivo* para comprovação dos efeitos na saúde do hospedeiro alvo.

Sendo assim, os probióticos que satisfaçam os requisitos elencados pela FAO/OMS (2001, 2002) podem ser inoculados em produtos alimentícios em quantidade suficiente para promover benefícios à saúde como podem ser encontrados como suplementos nutricionais, em forma de cápsulas ou comprimidos (BINNS, 2013). Com efeito, sabe-se que microrganismos probióticos atuam de várias formas para beneficiar a saúde humana, através da competição dos probióticos com bactérias patogênicas, da produção de subprodutos imunorreguladores e neurogênicos da fermentação em alimentos ou da fermentação em nível intestinal (DIMIDI *et al.,* 2019).

Os microrganismos probióticos podem metabolizar carboidratos e fibras

alimentares como os polissacarídeos, açúcares (lactulose, lactose não absorvida e frutose não absorvida), polióis e oligossacarídeos. Os metabólitos derivados da fermentação das bactérias geram peptídeos bioativos e poliaminas com efeitos potenciais na saúde cardiovascular, imunológica e metabólica (BINNS, 2013). Como exemplo de metabólitos estão os ácidos graxos de cadeia curta (AGCC) (DAVANI-DAVARI *et al.,* 2019), que são absorvidos e melhoram a captação de água e sais minerais (BINNS, 2013). O ácido butírico por sua vez pode influenciar no crescimento e na diferenciação celular, pois é esta a principal fonte de energia das células epiteliais que revestem o cólon (BINNS, 2013). Os gases hidrogênio, metano e dióxido de carbono também são produzidos e podem contribuir para o equilíbrio da microbiota e saúde intestinal (BINNS, 2013; MISSELWITZ *et al*., 2019).

Um substrato que pode ser metabolizado e estimular o desenvolvimento dos microrganismos do intestino são os prebióticos. Atualmente, os prebióticos são estudados devido à capacidade de auxiliar na manutenção da saúde (DAVANI-DAVARI *et al.,* 2019).

1.5 Prebióticos

Segundo um documento da ISAPP (2017), o conceito prebiótico foi definido pela primeira vez em 1995, inicialmente reconhecido como um ingrediente alimentar não digerível, que deveria afetar beneficamente o hospedeiro e assim, estimular de modo seletivo o crescimento e/ou atividade de uma bactéria ou de algumas de bactérias já residentes no cólon (GIBSON; ROBERFROID, 1995; GIBSON *et al.,* 2017). A FAO/WHO, em 2001, também reconheceu os benefícios potenciais dos prebióticos em relação aos probióticos, e sua capacidade de estimular bactérias benéficas autóctones ao hospedeiro.

Ao longo do tempo, outras definições foram propostas e, atualmente, a mais adotada em estudos sobre prebióticos é a estabelecida pela convenção da ISAPP em 2017. Sendo assim, ficou estabelecido como prebiótico “um substrato que é utilizado seletivamente por microrganismos hospedeiros, conferindo um benefício à saúde” (GIBSON *et al.,* 2017, p. 494).

Entre os prebióticos mais estudados e que conferem benefícios à saúde

estão os fruto-oligossacarídeos (FOS), galacto-oligossacarídeos (GOS) e trans-galacto-oligossacarídeos (TOS). Estes prebióticos são utilizados como fonte de energia para os microrganismos residentes no intestino. Conforme comentado anteriormente, os produtos da fermentação dos prebióticos são liberados no intestino, os AGCC como o ácido lático, butírico e propiônico, e promovem benefícios à saúde (DAVANI-DAVARI *et al.,* 2019).

Os AGCC são cruciais para a saúde intestinal e suas atividades podem subsequentemente influenciar locais distantes ao intestino, ou seja, podem atuar sobre toda a saúde do indivíduo. Os AGCC podem modular certos aspectos da atividade metabólica, incluindo a função dos colonócitos, homeostase intestinal, ganho de energia, o sistema imunológico, lipídios do sangue, apetite e fisiologia renal (GIBSON *et al.,* 2017).

A descoberta dos prebióticos possibilitou que as mais variadas doenças fossem beneficiadas com a ação desses carboidratos não digeríveis, como, por exemplo, no transtorno do espectro do autista, melhorando o comportamento antissocial das crianças (GRIMALDI *et al.*, 2018). Também, os indicadores imunológicos séricos foram melhorados com o consumo de prebióticos realizado sete dias antes da operação de pacientes com câncer colorretal (XIE *et al.,* 2019).

No Brasil, são reconhecidos como prebióticos funcionais a ingestão de alimentos que forneçam uma porção diária de 3g em alimento sólido ou de 1,5g em alimento líquido contendo inulina ou FOS, estes podem conter a alegação de alimento funcional: “Contribui para o equilíbrio da flora intestinal. Seu consumo deve estar associado a uma alimentação equilibrada e hábitos de vida saudáveis”. (BRASIL,2008).

O uso dos probióticos associado aos prebióticos também pode ser realizado e a união deles é conhecida pelo termo simbiótico. A definição de simbiótico se deu em 2020, pela ISAPP que estabeleceu como: “uma mistura compreendendo microrganismos vivos e substrato(s) seletivamente utilizados por microrganismos hospedeiros que conferem um benefício à saúde do hospedeiro” (SWANSON *et al.,* 2020, p. 698).

Conforme exposto, os prebióticos parecem benéficos em várias doenças e podem contribuir com a saúde como um todo, bem como auxiliar na melhora dos sintomas da IL. Um ensaio clínico duplo-cego e randomizado realizado por

Savaiano *et al.* (2013) avaliou um novo GOS, o RP-G28, em 57 indivíduos com IL. Os resultados mostraram uma diminuição significativa no hidrogênio expirado e diminuição nos sintomas da IL após o 36º dia de consumo de GOS, trazendo uma expectativa de melhora da tolerância geral da IL, que pode ser um benefício significativo para os indivíduos com intolerância à lactose.

Em razão das evidências encontradas que sugerem benefícios à saúde humana tanto dos probióticos (BINNS, 2013 DIMIDI *et al.,* 2019; DAVANI-DAVARI *et al.,* 2019; VITELLIO *et al.,* 2019) como dos prebióticos (GRIMALDI *et al.*, 2018; XIE *et al.,* 2019), o presente estudo buscou avaliar estudos envolvendo ambos sobre a temática da IL. Para tanto, uma RS foi conduzida, de modo a obter, com segurança e precisão, evidências científicas atualizadas.

2 OBJETIVOS

2.1 Geral

Investigar, por meio de uma revisão sistemática, a eficiência da aplicação clínica dos suplementos probióticos e prebióticos na diminuição dos sintomas da intolerância à lactose.

2.2 Específicos

- Encontrar na literatura quais microrganismos e oligossacarídeos que melhor atuam sobre a diminuição dos sintomas da intolerância à lactose;
- Verificar a segurança do uso de probióticos e prebióticos em intolerância à lactose;
- Examinar as evidências científicas quanto tempo de uso necessário de prebióticos e probióticos para obtenção de melhoria nos sintomas da intolerância à lactose.

3 METODOLOGIA

Trata-se de uma pesquisa do tipo Revisão Sistemática (RS) e que se baseou nas recentes diretrizes da *Preferred Reporting Items for Systematic Reviews and Meta-Analyses* - PRISMA 2020 (PAGE *et al.,* 2021). Para nortear o trabalho, levantou-se o seguinte questionamento: “quais probióticos e prebióticos são mais eficientes para a diminuição dos sintomas da IL?”. Ademais, para auxiliar na construção da pergunta de pesquisa elaborou-se o anagrama *Population, Intervention, Comparator, Outcomes* (PICO), igualmente recomendado para estudos de RS (PAGE *et al.,* 2021), que se encontra sumarizado no Quadro 1.

Quadro 1 - Anagrama PICO utilizado para o desenvolvimento da pergunta de pesquisa sobre a IL.

Anagrama	Definição	Descrição
P	População	Indivíduos intolerantes à lactose.
I	Intervenção	Probióticos ou prebióticos de qualquer natureza.
C	Controle/comparador	Indivíduos com ntolerância à lactose. consumindo placebo
O	Resultado	Melhora dos sintomas comuns da Intolerância à lactose.*.

Fonte: Elaborado pelo autor, Oliveira, L. S. (2022).

3.1 Estratégias de busca

Foram realizadas buscas por estudos clínicos randomizados e controlados, que tivessem a temática dos probióticos ou prebióticos na intolerância à lactose. Para tanto, nas bases de dados ScienceDirect, PubMed, SciELO e LILACS, foram utilizadas combinações de termos de busca que melhor especificavam o objetivo desse trabalho, como: 'probiotic' OR ‘*Bifidobacterium longum’* OR ‘*Lactobacillus rhamnosus’* OR *‘Lactobacillus acidophilus’* OR ‘*Lactobacillus reuteri’* OR ‘*Lactobacillus casei’* AND ‘prebiotic’ OR ‘fructo-oligosaccharides’ OR ‘galacto-oligosaccharides’, OR ‘trans-galacto-oligosaccharides’ AND 'lactose intolerance' OR ‘lactose malabsorption' AND 'randomized controlled trial'. Não foram restringidos os anos de publicação dos estudos. Foram usadas opções de refinamento para a pesquisa na base do PubMed (Free full text, Clinical Trial and Randomized Controlled Trial). O critério de ‘acesso aberto’ foi defido a fim de não

limitar o acesso dos artigos incluídos para os demais leitores. A identificação dos estudos em casa base de dados deu-se com as seguintes as combinações de termos descritos no quadro 2:

Quadro 2 - Combinações de termos para buscas nas bases de dados.

Base de dados:	Combinações de termos
LILACS:	(probiotic) OR (Bifidobacterium longum) OR (prebiotic) OR (galacto-oligosaccharides) AND (lactose intolerance) AND (randomized) Termos em português: (probiótico) OR (Bifidobacterium longum) OR (prebiótico) OR (galacto-oligosacarídeos) AND (intolerância à lactose) AND (randomizado)
SciELO:	(probiótico) OR (prebiótico) AND (intolerância à lactose) AND (randomizado) Termos em inglês: (probiotic) OR (prebiotic) AND (lactose intolerance) AND (randomized)
ScienceDirect:	'probiotic' AND ‘prebiotic’ AND 'lactose intolerance' OR ‘lactose malabsorption' AND 'randomized controlled trial'
PubMed:	'probiotic' OR ‘*Bifidobacterium longum’* OR ‘*Lactobacillus rhamnosus’* OR *‘Lactobacillus acidophilus’* OR ‘*Lactobacillus reuteri’* OR ‘*Lactobacillus casei’* AND ‘prebiotic’ OR ‘fructo-oligosaccharides’ OR ‘galacto-oligosaccharides’, OR ‘trans-galacto-oligosaccharides’ AND 'lactose intolerance' OR ‘lactose malabsorption' AND 'randomized controlled trial'

Fonte: Elaborado pelo autor L. S. O. (2022)

A busca nas bases de dados PubMed, SciELO e LILACS foi realizada no dia 07 de dezembro de 2021 e no ScienceDirect no dia 03 de janeiro de 2022. Uma busca manual foi realizada na literatura cinza das referências dos artigos, estudos já previamente conhecidos pelos autores e sugestões de leituras das bases de dados usadas. Todos os estudos encontrados foram igualmente avaliados com os critérios de inclusão e exclusão.

As bases de dados SciELO e LILACS foram escolhidas para que pudéssemos ter um parâmetro de como as pesquisas para a temática da IL estão na América Latina; já a base de dados PubMed traz um aspecto das ciências

médicas enquanto a ScienceDirect é um mais generalista e possui um mecanismo de pesquisa mais eficaz que as demais bases incluídas (TOBER, 2011; PEREIRA; GALVAO, 2014).

3.2 Critérios de inclusão

- Abordar o tema intolerância à lactose associado ao uso de probióticos e prebióticos de qualquer natureza;
- Ser um estudo com participantes humanos adultos >18 anos;
- Ser um estudo randomizado e controlado por placebo;
- Estar em formato de artigo científico, teses ou dissertações;
- Ter acesso livre para leitura;

3.3 Critérios de exclusão

- Abordar outro tema que não o de interesse deste trabalho;
- Ser um estudo no formato de vídeos, livros;
- Ser um estudo repetido;
- Ser um estudo com animais;
- Ser um estudo com gestantes ou crianças;
- Não ser um artigo de acesso livre;
- Incluir pacientes com doenças crônicas, infecciosas, ou outras doenças

Após as buscas nas bases de dados os artigos duplicados foram excluídos manualmente. Foram avaliados os títulos e resumos dos estudos aplicando os critérios de inclusão e de exclusão. Posteriormente, os estudos selecionados foram lidos na íntegra, e novamente aplicado critérios de elegibilidade. Todas as fases do estudo foram realizadas em duplicata.

3.4 Tipos de intervenção

Os estudos aceitos para avaliação foram aqueles envolvendo intervenções com probióticos ou prebióticos em população com mal absorção de lactose ou

intolerância à lactose, desde que avaliassem também, um grupo controle. Qualquer estudo que atendesse a essas características, independente da duração, intensidade ou tipo de suplementação (probiótico ou prebiótico), foi considerado para inclusão.

3.5 Seleção dos estudos

Com exceção da busca na literatura cinza, todas as etapas para o desenvolvimento desta revisão (busca em base de dados, exclusão de duplicatas, seleção dos estudos elegíveis, extração dos dados e avaliação do risco de viés), foram realizadas no mínimo em duplicata por dois juízes independentes. Em caso de dúvidas os autores dos trabalhos foram contatados. As discordâncias encontradas foram resolvidas em conversa com um terceiro juiz.

3.6 Extração e síntese de dados

Depois de selecionados, os artigos incluídos, foram compilados em duplicata em planilhas (Microsoft Excel 365®) e deles foram extraídos dados como autor e ano; local do estudo; número de incluídos para grupo intervenção e grupo controle; idade/sexo; delineamento/tempo de intervenção; diagnóstico de IL; meio da intervenção aplicado; probiótico ou prebiótico; tipo de controle; resultados sintomáticos; resultado do teste de hidrogênio expirado pós-tratamento; efeitos adversos e nos artigos aplicáveis, realizou-se a extração dos dados da análise dos pacientes após o término do tratamento. Na comparação dos resultados extraídos, em caso de divergência, foi buscado um consenso e/ou avaliação de um terceiro juiz. Dúvidas sobre o desvio padrão e intervalo interquartil dos resultados sintomáticos dos estudos de Savaiano *et al. (2013)* e de Chey *et al.* (2020), e dos resultados sobre o teste de hidrogênio, consumo de lactose no pós-tratamento e acompanhamento no período pós-tratamento do estudo de Aguilera *et al*. (2021), foram resolvidas entrando em contato via e-mail com os autores.

As medidas de efeito de cada estudo foram apresentadas de formas diferentes. Portanto, a síntese resultados para idade, sexo, sintomas, HBT, efeitos adversos se deu conforme a apresentação do estudo (por exemplo: desvio

padrão, odds ratio, diferença média, níveis de significância, porcentagens e valores médios).

Reunimos separadamente os estudos de acordo com as suas características formando o grupo dos prebióticos e o grupo dos probióticos. Os mesmos dados coletados nos estudos clínicos com probióticos também foram analisados para estudos envolvendo prebióticos. Os estudos sobre probióticos incluídos nesta RS não realizaram acompanhamento dos indivíduos após o término do tratamento, portanto, esses dados não foram compilados na tabela. Não realizamos uma meta-análise devido à falta de dados.

3.7 Avaliação de risco de Viés

Usando a ferramenta *Revised Cochrane risk-of-bias tool for randomized trials* (RoB 2.0) (STERNE *et al.,* 2019), dois pesquisadores avaliaram independentemente o risco de viés em cada estudo. Para cada estudo, cada um dos cinco domínios de viés da ferramenta foi avaliado: viés no processo de randomização, viés de desvios da intervenção pretendida, viés devido a dados faltantes, viés na aferição dos desfechos, viés no relato dos desfechos. Para cada estudo, o risco de cada tipo de viés foi classificado como “alto”, “baixo” ou, “algumas preocupações”, para os casos de dados insuficientes. Em casos de RCT com a maioria dos vieses altos, o artigo seria desconsiderado para o trabalho (STERNE *et al.,* 2019). Em caso de falta de consenso, um juiz atuou como árbitro.

3.8 Medidas de efeito

Devido as diferenças nas medidas de efeito de cada publicação, foram coletados dados das associações relatadas em cada estudo. Assim, por exemplo, dados disponíveis sobre razão de risco, razão de chances, risco relativo, razão de taxa de incidência, razão de incidência padronizada, coeficiente de correlação e seus intervalos de confiança correspondentes ou níveis de significâncias (p valor) foram relatados.

3.9 Meta-análise e viés de publicação

Apesar de ser um dos objetivos iniciais deste trabalho, a meta-análise não pôde ser conduzida, uma vez que os artigos selecionados para este fim (SAVAIANO *et al.,* 2013; CHEY *et al.,* 2020) não possuíam dados suficientes (desvio padrão e/ou intervalo interquartil) para serem submetidos à uma análise estatística. Os autores dessa RS entraram em contato via e-mail com os pesquisadores dos artigos em questão (SAVAIANO *et al.,* 2013; CHEY *et al.,* 2020) que afirmaram não terem mais os dados disponíveis, o que impediu a realização da meta-análise. Todavia, relatamos os efeitos encontrados em cada estudo bem como para os prebióticos, que, poderiam ter sido avaliados por meio de uma síntese, entretanto, a falta de dados reportados nos estudos e as diferentes medidas de efeito entre eles impediu a realização da meta-análise.

3.10 Avaliação da certeza das evidências

Um autor (O.S.L) avaliou a certeza das evidências e outro autor revisou a classificação (W.W.G). Utilizou-se a ferramenta GRADE (*Grading of Recommendation, Assessment, Development and Evaluation*) para avaliação dos desfechos primários (metodologia-quadro) (BALSHEM *et al.,* 2011) e baseado na abordagem para a classificação da certeza em evidência na ausência de uma única estimativa de efeito, proposta por Murad *et al.* (2017).

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5 ARTIGO CIENTÍFIO 1

The use of probiotics and prebiotics can enable the ingestion of dairy products by lactose intolerant individuals

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Abstract

Objective: To investigate, through a systematic review, the efficiency of the clinical application of probiotic and prebiotic supplements in reducing the symptoms of lactose intolerance (LI). **Methods:** This systematic review was conducted according to PRISMA 2020 guidelines and registered at the PROSPERO platform (CRD42022295691). The inclusion criteria were: studies addressing the issue of LI associated with the use of probiotics and prebiotics of any nature; studies performed with adults; randomized, placebo-controlled trials; and open access scientific articles, theses, or dissertations. The studies were retrieved from the following databases: SciELO, PubMed, LILACS, ScienceDirect, and gray literature. In order to avoid the risk of bias, the RoB 2.0 tool was adopted, and to assess the certainty of the evidence, the GRADE tool was used. **Results:** A total of 830 studies were found; however, after applying the inclusion and exclusion criteria, only five studies remained. Two studies used the prebiotic GOS (RP-G28) for the treatment of LI and, together, included 462 subjects. Three studies used the probiotics *Bifidobacterium bifidum* 900791, *Lactobacillus reuteri*, and *Lactobacillus acidophilus* DDS-1 to evaluate their effects on LI and comprised 117 subjects. The risk of bias for studies on probiotics suggested concerns in all studies, whereas the risk of bias was low in investigations evaluating prebiotics, with only one study classified as concerning. The certainty of evidence was high for the studies using the GOS (RP-G28) prebiotic and low

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for the probiotics. The heterogeneity and lack of data hindered the chances of performing both sensitivity analysis and meta-analysis. **Conclusion:** The probiotics *Lactobacillus reuteri* and *Lactobacillus acidophilus* DDS-1 showed the best results in the management of LI symptoms. The prebiotic GOS (RP-G28) appeared to be more efficient in reducing post-treatment symptoms. However, it is noteworthy that evidence regarding the use of probiotics for the management of LI is considerably scarce; as for prebiotics, data are limited. New studies adopting robust methodologies, especially regarding the complete reporting of data, are therefore warranted.

Keywords: Intestinal Microbiota; Lactose Intolerance; Lactose Malabsorption; Oligosaccharides; Probiotics; Prebiotics;

Introduction

It is estimated that between 68% and 75% of the world population has some level of lactase enzyme deficiency [1, 2]. Symptoms of deficiency or even lack of lactase production that characterize lactose intolerance (LI) include diarrhea, flatulence, and abdominal distention and pain [3].

When LI is not managed properly, biochemical alterations and changes in eating behavior can occur [4]. Avoiding milk and dairy products can lead to calcium, vitamin D, and riboflavin deficiency, underpinning diseases such as osteoporosis and decreased quality of life, which can lead to depression, for example [5, 6]. Also, avoiding lactose intake can be hampered by the existence of foods with unidentified levels of lactose in their composition [3, 7].

The management of LI symptoms is vital for the health and quality of life of these individuals. One of the first proposed methods for the improvement of LI symptoms was the use of the exogenous lactase enzyme (beta-galactosidase). When this enzyme is ingested prior to the consumption of foods containing lactose, there is a lower chance of the appearance of symptoms or even attenuation of them [8]. However, the enzyme lactase

does not always meet the individual's needs since the intake of lactose can be higher than what the enzyme is capable of digesting. Alternatives that have been proposed include the modulation of the intestinal microbiota with probiotics and prebiotics, as both are able to contribute to the proliferation of lactose-digesting microorganisms, alleviating LI symptoms, and improving intestinal permeability, in addition to contributing to general health [9].

Probiotics are live microorganisms that can generate health benefits for the host, if used properly [10, 11]. Prebiotics, on the other hand, are substrates used selectively by host microorganisms that also benefit health [12].

Probiotics and prebiotics are not considered medicinal drugs. Therefore, they are not intended for treatment, but for assisting in the symptomatic management of various conditions/diseases [11, 12, 13].

Scientific evidence regarding the role of microorganisms and specific oligosaccharides in the management of LI remains scarce, as well as data on their efficiency in post-treatment symptomatic improvement. Therefore, this systematic review sought to investigate the efficiency of the clinical application of probiotic and prebiotic supplements in reducing symptoms of LI to aid health professionals when they conduct symptom management in individuals with LI.

Methods

This systematic review (SR) of the literature was conducted based on PRISMA 2020 guidelines [14] and registered at the PROSPERO platform (CRD42022295691). To help formulate the research problem, the Population, Intervention, Comparator, Outcomes (PICO) model was adopted [14]. The population (P) was determined as "lactose intolerant individuals", the intervention (I) as "probiotics or prebiotics of any given nature", the

Control/comparator (C), as “individuals with LI consuming placebo”, and the outcome (O) as “improvement of common LI symptoms”.

Eligibility criteria

All studies found were equally evaluated according to the inclusion and exclusion criteria as shown in Table 1. Importantly, we did not apply a temporal criterion in selecting the investigations.

Table 1 – Inclusion and exclusion criteria used to evaluate the studies.

Inclusion criteria	**Exclusion criteria**
✓ Address the topic of lactose intolerance associated with the use of probiotics and prebiotics of any nature; ✓ Study with human participants adults >18 years; ✓ Randomized and placebo-controlled; ✓ Form of a scientific article, thesis, or dissertation; ✓ Study open access publication.	✓ Address a topic aside from the one of interest in this study; ✓ Study in the video or book format; ✓ Repeated study in more than one database; ✓ Study with animals; ✓ Study with pregnant women of children; ✓ Study with children and adolescents with lactose intolerance; ✓ Not be an open-access article; ✓ Include patients with chronic, infeccious, or other diseases.

Search strategies and sources of information

A search for randomized controlled clinical trials (RCT) focusing on the use of probiotics or prebiotics in LI was carried out. To that end, we conducted searches in four databases (ScienceDirect, PubMed, SciELO, and LILACS) using combinations of search terms that best specified the objective of this study: ‘probiotic’, OR ‘*Bifidobacterium*

longum', OR '*Lactobacillus rhamnosus*', OR '*Lactobacillus acidophilus*', OR '*Lactobacillus reuteri*', OR '*Lactobacillus casei*' AND 'prebiotic', OR 'fructo-oligosaccharides', OR 'galactooligosaccharides', OR 'trans-galactooligosaccharides' AND 'lactose intolerance', OR 'lactose malabsorption' AND 'randomized controlled trial'. Refinement options were used for the search in the PubMed database (open access full text, Clinical Trial, and Randomized Controlled Trial). We did not delimit an interval of years, all studies that appeared in the searches were evaluated. The identification of studies in each database was carried out using the following combinations of terms described in Supplementary Table 2.

The searches in the PubMed, SciELO, and LILACS databases were performed on December 07, 2021, and in ScienceDirect on January 03, 2022. A manual search was carried out in the gray literature of the articles references, including studies previously known to the authors and reading suggestions in the analyzed databases. After searching the databases, duplicate articles were manually excluded. The study titles and abstracts were evaluated by applying the inclusion and exclusion criteria (Table 1). Subsequently, the selected studies were read, and the eligibility criteria were again applied. All stages of this SR were performed in duplicate – involving two independent researchers –, with the exception of the gray literature search and the assessment of certainty of evidence. Any divergences found were discussed with a third judge.

Types of intervention and study selection

The studies accepted for analysis were those involving interventions with probiotics or prebiotics in a population with lactose malabsorption or LI, provided that they also evaluated a control group. Any study that met these characteristics – regardless of duration, intensity, or type of probiotic – was considered for inclusion.

Extraction of data and data items

Once selected, the included articles were compiled in duplicate in spreadsheets (Microsoft Excel 365®), and the following data were extracted: authors and year; study location; the number of participants included in both intervention and control groups; data on participants' age and sex; study design and intervention duration; diagnosis of LI; methods used in the intervention; probiotic or prebiotic investigated; type of control adopted; symptomatic results; post-treatment exhaled hydrogen test results and adverse effects. When applicable, data were also extracted from the analysis of patients after the end of treatment. Issues regarding the standard deviations (SD) and interquartile ranges (IR) of the symptomatic results from the studies by Savaiano *et al*. [15] and Chey *et al*. [16] and the results obtained in the hydrogen test, post-treatment lactose consumption, and follow-up in the post-treatment period of the study by Aguilera *et al*. [17] were resolved by contacting the authors via e-mail.

We gathered the studies separately according to their characteristics, thus forming two groups: prebiotics and probiotics. The data collected in the studies on prebiotics were the same as those gathered in the studies on probiotics, only varying in the type of material used for the intervention. In the studies on probiotics included in this SR, the original authors did not follow up the subjects after the end of treatment. Therefore, these data were not compiled in the characteristics displayed in Table 4. We were unable to perform a meta-analysis due to lack of data reported in the articles (i.e.., IR and SD).

Risk of bias assessment

Using the Revised Cochrane risk of bias tool for randomized trials (RoB 2.0) [18], two researchers independently evaluated the risk of bias. For each study, five domains were classified as "high", "low", or "some concerns", the latter in case of insufficient data.

The analyzed domains were: bias in the randomization process, bias in deviations from the intended intervention, bias due to missing data, bias in the assessment of outcomes, and bias in the reporting of outcomes. In cases of RCT with mostly high biases, the article would be disregarded for analysis [18]. Again, in cases of lack of consensus, a third judge acted as an arbitrator.

Measures of effect

Due to the differences in effect measures, data were collected according to the associations reported in each study; for example: hazard ratio, odds ratio, relative risk, incidence rate ratio, standardized incidence ratio, correlation coefficient, and their corresponding confidence intervals or significance levels (*p*-value).

Evaluation of the certainty of evidence

One author (L.S.O.) evaluated the certainty of the evidence, while another reviewed the classification (G. W.W.). The GRADE (Grading of Recommendation, Assessment, Development and Evaluation) tool was used to assess primary outcomes [19] based on the approach of classifying certainty of evidence in the absence of a single effect estimate as proposed by Murad *et al*. [20].

Results

Study selection

After searching the databases and gray literature, a total of 830 studies were found. Subsequently, a selection in duplicate was independently performed and 5 studies [15, 16, 8, 21, 17] were included in the present review (Figure 1). The SciELO and LILACS databases did not return studies using the selected terms; thus, in an attempt to find

possible articles, terms in the following languages were also used: English, Portuguese, and Spanish.

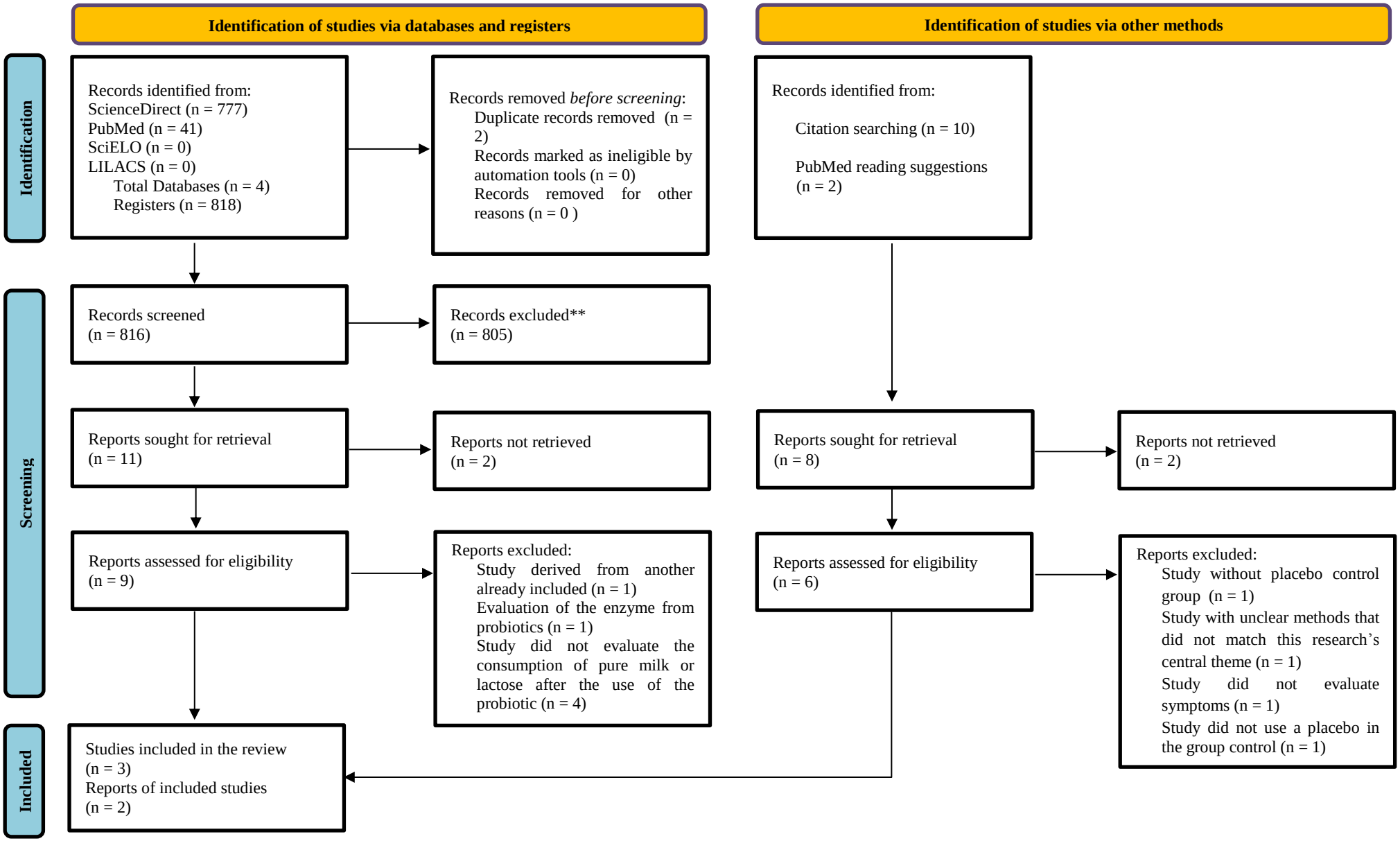
Despite seeming to meet most of the criteria, some studies were excluded due to: being derived from another already included study [22]; for evaluating the efficiency of enzymes produced by probiotics [23], for not being placebo-controlled or having a control group with proton pump inhibitors (omeprazole type) [24], or for having a control group (non-placebo) containing lactose-metabolizing microorganisms [25]. Others were excluded for having unclear study designs, inadequate intervention characteristics, or for failing to assess LI symptoms [26, 27, 28, 29].

Some studies were excluded because the objective of this SR was to investigate the efficiency of the clinical application of probiotic and prebiotic supplements in reducing the symptoms of lactose intolerance - with the intention of understanding if the symptoms would improve even after returning to the consumption of products containing lactose. Therefore, the effectiveness of supplements could only be confirmed if, in the period before and after the intervention, the symptoms with consumption of some product containing lactose were evaluated. Thus, studies that did not reassess the consumption of lactose-containing products or did not encourage the consumption of such products after the end of treatment were excluded from this SR [26, 28, 30, 31]. Since the date of publication of the other cited studies [26, 28, 30] was over 25 years old, we could only electronically contact Vitellio *et al*. [31] to confirm the non-adoption of the use of lactose after the administration of the probiotic supplement; however, no answer was obtained.

Furthermore, the study by Vitellio *et al.* [31], despite being included in other SRs [9, 32], used vitamin B6 together with the microorganisms, which may be a confounding factor to the study results since the low intake of vitamin B6 seems to be associated with symptoms of irritable bowel syndrome (IBS). Indeed, the consumption of vitamin B6

appears to improve symptoms/pain in IBS [33, 34], a factor which hindered comparison with the other studies that only included microorganisms in the analyses.

Figure 1 - Flowchart of the SR showing the literature search process.



Characteristics of the studies

In the five studies included, two (2) associated prebiotics to the treatment of LI symptoms, specifically the use of GOS (RP-G28); together, the two studies randomized 462 individuals with LI [15, 16]. The other three (3) studies used various probiotics to assess their effects on LI, and together they included 117 lactose intolerant individuals [8, 21, 17]. Among the evaluated microorganisms, none of them matched between studies: Pakdaman *et al*. [21] assessed a specific strain of *Lactobacillus acidophilus* DDS-1, while Ojetti *et al*. [8] and Aguilera *et al*. [17] used *Lactobacillus reuteri* and *Bifidobacterium bifidum* 900791, respectively; Ojetti *et al*. [8] did not specify which strain was used.

As for the probiotics studies, all of them performed the analysis of symptoms and the hydrogen breath test (HBT) after treatment. Regarding the HBT – used for the purpose of verifying the metabolism of lactose after the use of probiotics [8, 21, 17] –the doses of lactose were diluted in water, milk or lactose-containing ice cream [17]. Moreover, doses varied between 20g and 25g of lactose [8, 15, 21,17].

Meanwhile, the study by Chey *et al*. [16] adopted a personalized approach, with the administration of anhydrous lactose at 0.35g/kg of body weight to analyze the HBT and LI symptoms. For most studies, the cut-off point for determining whether patients had LI was hydrogen exhalation >20 ppm. All studies on probiotics reassessed symptoms and HBT after treatment, using the same dose of lactose as at baseline.

In the investigation from Savaiano *et al*. [15], the subjects underwent two additional challenges of 25 grams of lactose 30 days after treatment. The study by Chey *et al*. [16] did not perform lactose challenges; however, both studies on prebiotics carried out a follow-up of the patients after treatment, thus analyzing how long the prebiotic would be efficient even after ceasing its use [15, 16]. The studies on probiotics did not follow up the participants for some time after the end of treatment, hindering comparisons of the

effectiveness of the probiotics and prebiotics in the post-treatment period.

As post-treatment results, in the study by Savaiano *et al*. [15], the authors reported a lactose tolerance of 30% in the RP-G28 group (n = 40), as opposed to only 6% (n = 18) in the placebo group (p = 0.0389). Thirty days after the start of treatment, 64% of the group with abdominal pain did not present the symptom. Additionally, after 30 days of dairy reintroduction, 82% of that same group reported no abdominal pain.

In the study by Chey *et al*. [16], which involved more patients, both the lowest dose (15 g) and the highest dose (20 g) showed favorable results up to 30 days after treatment, when dairy reintroduction was allowed and encouraged.: Symptom relief was significantly (p = 0.042) greater in the RP-G28 group than in the placebo group; 82% of the treated patients reported symptoms cessation or mild symptoms. In addition, 66% of the patients receiving treatment reported being “very satisfied” or “extremely satisfied” compared to 52% in the placebo group (p = 0.030).

Risk of bias assessment

Savaiano *et al*. [15], in domain 5 (selection of the reported result), pointed out some concerns for not presenting all the intended results. The study by Chey *et al*. [16] obtained a low risk of bias for all domains. In Ojetti *et al*. [8], domains 1, 2, and 5 of the RoB 2.0 tool raised some concerns since the study does not clearly disclose its blinding, nor the deviation of intervention intent; we did not find a clinical intervention protocol record for that study. Meanwhile, Pakdman *et al*. [21], despite not presenting bias in the other domains, raised concerns regarding domain 5 due to the lack of a previously registered intervention protocol, thus changing the overall bias (see Figure Supplement 2).

The study by Aguilera *et al*. [17] raised some concerns regarding domains 1 and 2 of RoB 2.0, as they did not clearly describe the blinding of both parties and the random

sequencing (randomization). Furthermore, Aguilera *et al*. [17] presented a protocol record but did not measure all intended results, assuming some concerns for domain 5 (result selection). The authors were contacted via e-mail on the matter but did not respond. The crossover of this information led the algorithm of the RoB 2.0 tool to recommend "some concerns" to Aguilera *et al*. [17]. The judges found that the biases of the study by Aguilera *et al*. [17] did not benefit the results since the report pointed out the inefficiency of the studied microorganism, and even the results that lacked significance were reported. The information can be seen in Figure 2 in the Supporting Information section.

Results of individual studies

Supplementary Table 3 presents the characteristics and data of the studies on prebiotics, and Table 4 shows the characteristics and data of the studies on probiotics. Both tables can be visualized in the Supplementary online material (ie., Supplementary Table 3 and 4).

Certainty of evidence

The overall certainty of the studies using the prebiotic GOS RP-G28 was high (please see Supplementary Table 5). The samples were large and the risk of bias, low. The only limitation was the small difference in magnitude of effect for some symptoms, which may also have occurred due to the smaller number of individuals included in the study by Savaiano *et al*. [15]. The overall certainty of the probiotic studies was low since the available evidence was limited. There were concerns regarding methodological bias, indirect risk, risk of inaccuracy, and risk of inconsistency (please see Supplementary Table 6).

Discussion

The present SR aimed to verify the efficiency of the clinical application of probiotic and prebiotic supplements in reducing the symptoms of LI. Searches were carried out for studies that reassessed the consumption of products containing lactose after the end of interventions. This attempt might aid in the understanding the efficiency of probiotics and prebiotics in reducing the symptoms of LI since, as pointed out by past investigations, it is understood that individuals with LI will continue to consume products containing lactose, sometimes included in the ingredients of various foods [3, 7]. However, after treatment with probiotics and prebiotics, the aim is to reduce the aforementioned symptoms of LI, thus deliberately promoting the consumption of lactose-containing products.

Among the probiotics *Lactobacillus reuteri*, - at the doses proposed by Ojetti *et al*. [8] - was the one that, in the shortest time of intervention, was most successful regarding the results in symptoms and the HBT when compared to the other treatments. However, it should be noted that this study did not inform the strain of the microorganism in question and, currently, the indication of the strain is required in research involving microorganisms that have the purpose of treatment so they can be recognized as probiotics [11].

Although the results of the HBT were not significant in the study by Pakdaman *et al*. [21], there was a significant improvement in the relief of diarrhea, abdominal cramps, vomiting, and overall symptoms with the DDS-1 strain of *Lactobacillus acidophilus*, a fact not observed in other studies. This suggests that *Lactobacillus acidophilus* DDS-1 could promote relief on LI symptoms. The study by Kim and Gilliland [26], involving *Lactobacillus acidophilus* (without informing the strain) improved the HBT. On the other hand, other studies involving *Lactobacillus acidophilus* (BG2FO4 strain and other unreported strains) seemed to reduce some symptoms; however, significant changes in the HBT were not found, thus demonstrating that the effects of the microorganism on LI

depend on the strain under analysis [30, 24].

Indeed, the results from Aguilera *et al*. [17] clarify that not all microorganisms and strains are effective against the symptoms of LI. Aguilera *et al*. [17] pointed out that the chronic consumption of *Bifidobacterium bifidum* 900791 in one month did not result in improvements in the HBT or in the symptoms, in addition to causing a higher rate of acid regurgitation in the probiotic group detected during the fourth week, whereas acute consumption obtained good results in the HBT. These results may occur because the effects of probiotics may diminish over time, and could lose effectiveness weeks after ceasing the treatment as demonstrated in a study with probiotics for IBS [35].

Moreover, other microorganisms have been evaluated and appear to be of importance for the symptoms of LI. A recent study by Masoumi *et al*. [25], which used *Lactobacillus acidophilus* associated with *Bifidobacterium sp*., showed improvements in exhaled hydrogen in the second week of use in LI patients, in addition to improving flatulence and bloating. The role of *Bifidobacterium* is of interest in LI as it seems to assist in the metabolic activity of the colonic microbiota, such as in the reduction of the HBT, diarrhea, and swelling, as demonstrated in previous studies [28, 36, 31]. These results are due to the activity of β-galactosidase produced by probiotics, which end up contributing to the digestion of lactose, lowering the threshold for the appearance of symptoms and, consequently, for hydrogen exhalation [37]. Simultaneously, the metabolites of lactose fermentation carried out by these bacteria are associated with immune regulation, glucose and lipid homeostasis, and colonocyte differentiation, with implications for homeostasis and gut-brain modulation [5].

Efficient microorganisms and oligosaccharides against symptoms of LI

When observing the data on symptoms and hydrogen exhalation to assess the efficiency of the microorganisms found in the analyzed studies, the microorganisms that best acted against the symptoms of LI were: *Lactobacillus reuteri* (4×10^8 CFU/dose) and *Lactobacillus acidophilus* DDS-1 (1×10^{10} CFU/dose), from the studies by Ojetti *et al*. [8] and Pakdaman *et al*. [21], respectively.

Other SRs found *Bifidobacterium animalis* to be the most beneficial microorganism in relieving LI symptoms [38]. Similar to our results, Leis *et al*. [9] considered *L. acidophilus* and *L. reuteri* as effective in attenuating clinical signs, in addition to *L. rhamnosus*, *L. bulgaricus*, *S. thermophilus*, and *B. longum.*

The results obtained so far in this review are still preliminary regarding the efficacy of probiotics and the safety of using prebiotics for the treatment of LI. However, it presents data that substantiate the efficiency of the use of probiotics and prebiotics for the management of LI symptoms, corroborating the conclusions reported in other SRs [38, 9].

It should be noted that, even in recent publications, there was a lack of identification of the microbial strain [8, 25], a fact that limits the reproducibility of the study and the knowledge of their effects. Still, one study by the International Scientific Association for Probiotics and Prebiotics considers that even if randomized controlled trials are not conducted with specific strains, they can still be considered probiotics due to accumulated evidence on health benefits [11].

In the searches for prebiotics for LI, we found only two studies that used the same GOS RP-G28; thus, comparison with other prebiotics for LI is limited, a result also found previously [32]. Despite this limitation, the results provided by the reviewed studies seem promising and the low risk of bias associated with the GRADE assessment suggests high quality of evidence [19].

Verification of symptoms after discontinuing the use of probiotics and prebiotics

It is known that strain exerts an effect while it is being ingested, however, with the interruption of ingestion of microorganisms, they return to baseline, except when colonization in the gastrointestinal tract by the evaluated strain is proven. Although the studies with probiotics included in this SR did not follow up with the individuals after the end of treatment a randomized study (not included in this SR because it is a private access article) by Almeida et al. [17] involved the probiotics L. casei Shirota and B. breve Yakult, administered for four weeks to lactose intolerant individuals. After discontinuing the consumption of the probiotics, their effect persisted for three months, reducing digestive symptoms and hydrogen excretion, thus indicating that the effects of probiotics may continue after the treatment period. Hence, future studies on the subject could follow up with the individuals for a more extended period, aiming to clarify the duration of action of the used probiotics in the post-treatment period since, according to Aguilera et al. [17], the chronic consumption of probiotics may not have beneficial effects.

Although probiotics seem promising for the management of LI, the total decrease in symptoms was only reported in the treatment with the prebiotics. The side effects were mild or moderate for GOS RP-G28, which can be considered safe for consumption [15, 16].

Savaiano *et al*. [15] suggested that even after the end of treatment, the microbiota acquired with the consumption of GOS RP-G28 continues to act and improve the symptoms of lactose intolerance. In that study, the authors concluded that GOS RP-G28 has the potential to allow people to regularly consume dairy foods without experiencing LI symptoms [15]. This result is possible because GOS acts by improving the intestinal microbiome. Coincidentally, in the study by Chey *et al*. [16], the *Lactobacillus* and *Bifidobacterium* proliferated in greater numbers. In addition to improving LI, the

fermentation products of prebiotics released into the intestine promote health benefits as a whole [40].

Limitations

The high heterogeneity among the probiotic studies hindered our goal of performing statistical sensitivity analyses since the microorganisms and outcomes were different. As for the prebiotic GOS RP-G28, despite the similarities in the assessments and the use of the same symptom verification tool, basic data (i.e., standard deviations and/or interquartile range) were not reported in the text or in supplementary files. The authors were contacted via e-mail, but they no longer had the data.

The impossibility of carrying out a meta-analysis due to limited information available sheds light on the scientific gaps related to this topic. The first is that there is no uniformity in studies on probiotics related to LI. The second is related to the lack of data reported in the publications (on probiotics and prebiotics), which also compromises the quality of the scientific evidence [19], in addition to characterizing a lack of rigor in science regarding this topic. There was also very low certainty of evidence for the studies on probiotics, which may be related to the variety of studies, that is, there were no studies involving the same strain, seeking the same clinical effects and in the same target group.

Implications

This SR presents results evidencing that the symptoms of LI can be reduced with the use of probiotics and prebiotics, improving the quality of life of individuals by providing the consumption of lactose, since the symptoms seem to decrease with the consumption of lactose after these treatments [15, 16, 8, 21]. However, it also points out that the evidence for probiotics and prebiotics in LI is still weak, requiring further research

with complete data reporting (i.e., standard deviation and other effect size measures that should be presented in the body of the text or in supplementary tfiles. There is also a need for similar study designs, with the assessment of lactose consumption after treatment to better capture the real effectiveness of probiotics and prebiotics. These efforts could reduce heterogeneity, and then sensitivity assessments can be performed.

Conclusion

Changes in the intestinal microbiota caused by supplementation with probiotics and/or prebiotics seem to be factors that lead to a decrease in the LI symptoms. This study provides preliminary evidence of the possibility of managing LI with probiotics and prebiotics through the modulation of the intestinal microbiota, and evaluations after the use of *Lactobacillus reuteri*, *Lactobacillus acidophilus* DDS-1, and GOS RP-G28 may encourage the ingestion of products containing lactose by LI individuals.

Studies are underway to show that there are beneficial effects of probiotics and/or prebiotics in the management of LI symptoms, especially regarding GOS RP-G28. However, there is still a need for research that evaluates the probiotic and/or addresses other prebiotics that may be beneficial in the management of LI symptoms, so that there is robust evidence to support their use in clinical practice safely. This SR suggests that further studies be carried out with *Lactobacillus reuteri* (specifying the used strain), *Lactobacillus acidophilus* DDS-1, and with GOS RP-G28, since they were noteworthy in effectiveness, both regarding the symptoms and hydrogen excretion after treatment. Moreover, this SR did not evaluate non-dairy symbiotics for LI. Nevertheless, we did not find studies on symbiotics for LI in our searches. Therefore, in order to know the effects of non-dairy symbiotics for LI, clinical studies aiming at this theme need to be carried out.

To the best of our knowledge, this SR is the first study that considers the exclusive administration of probiotics or prebiotics for the management of LI symptoms without

combinations with other substances, using only placebos as a control group and focusing solely on studies that evaluated symptoms both before and after the administration of probiotics and/or prebiotics. We found no other SRs on probiotics and prebiotics that assessed the quality of the evidence.

Registration and protocol

The protocol of the current SR was registered on the PROSPERO platform under code CRD42022295691 and may be accessed through the link: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022295691. The only addition to the the protocol refers to the non-inclusion of studies that did not reassess the consumption of lactose-containing products or did not report encouraging the consumption of lactose-containing products after the end of treatment in the text. However, the same excluded studies that did not carry out this evaluation were also excluded for other reasons.

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Conflict of interest

There are no conflicts of interest to report.

Author contributions

OLIVEIRA, L. S.: Term, Conceptualization, Methodology, Validation, Formal analysis, Investigation and article selection, Data curation (analysis and interpretation of data), Writing – Original draft, Visualization, Project research administration. **WENDT, G. W.:**

Methodology, Validation, Formal analysis, Data curation, Writing – Original draft, Review and Editing, Supervision. **CRESTANI, A. P. J.:** Investigation and article selection. **CASARIL, K. B. P. B.:** Supervision, Review and Editing.

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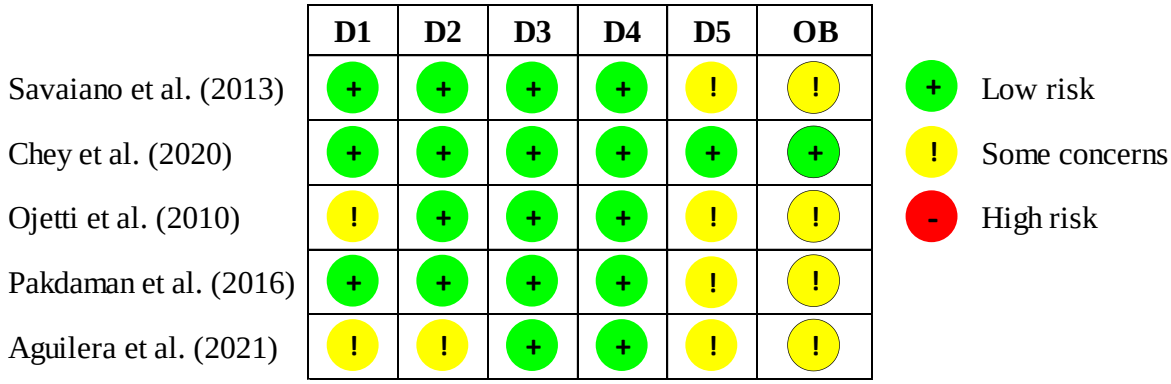
5.2 Supporting Information

Table 2 – Combinations of terms for database searches.

Database	Combination of terms
LILACS:	(probiotic) OR (Bifidobacterium longum) OR (prebiotic) OR (galacto-oligosaccharides) AND (lactose intolerance) AND (randomized) **Terms in portuguese:** (probiótico) OR (Bifidobacterium longum) OR (prebiótico) OR (galacto-(oligosacarídeos) AND (intolerância à lactose) AND (randomizado)
SciELO:	(probiotic) OR (prebiotic) AND (lactose intolerance) AND (randomized) **Terms in portuguese:** (probiótico) OR (prebiótico) AND (intolerância à lactose) AND (randomizado)
ScienceDirect:	'probiotic' AND ‘prebiotic’ AND 'lactose intolerance' OR ‘lactose malabsorption' AND 'randomized controlled trial'
PubMed:	'probiotic' OR ‘*Bifidobacterium longum’* OR ‘*Lactobacillus rhamnosus’* OR *‘Lactobacillus acidophilus’* OR ‘*Lactobacillus reuteri’* OR ‘*Lactobacillus casei’* AND ‘prebiotic’ OR ‘fructo-oligosaccharides’ OR ‘galacto-oligosaccharides’, OR ‘trans-galacto-oligosaccharides’ AND 'lactose intolerance' OR ‘lactose malabsorption' AND 'randomized controlled trial'

Figure 2 – Risk of bias assessment for the prebiotic and probiotic studies.



(D1) Randomization process; (D2) Deviations from the intended interventions; (D3) Missing outcome data; (D4) Measurement of the outcome; (D5) Selection of the reported result; (OB) Overall Bias.

Table 3 - Characteristics and data from the randomized clinical trials on prebiotics for the treatment of lactose intolerance, articles from 2013 to 2020.

Author and year	Study location	n, (IG/CG)	Age/sex	Study design/Intervention duration	Diagnosis of LI	Means of intervention	Prebiotic	Control	Symptomatic results	Post-treatment HBT results	Adverse effects	Patient analysis after the end of treatment
Savaiano *et al*. 2013	2 locations in the USA	n = 85 (IG = 57 / CG = 28)	Mean age: 41 years / Men: 42%, Women: 58%	RCT, Multicenter / 35 days	Moderate to severe symptom severity score and HBT result > 20 ppm (with 25g of lactose)	Liquid in polyethylene flasks which were to be added water before consumption	GOS RP-G28 gradual increase from 1.5g/day until 15g/day (administered as 7.5 grams twice a day)	Corn syrup in polyethylene flasks	72% of the subjects had a > 50% reduction in abdominal pain (p = 0.0288).	The HBT values decreased to a greater extent after treatment with RP-G28 compared to the CG; however, the difference was not significant (p = 0.1909)	The AEs were mild/moderate: headache, dizziness, nausea, upper respiratory tract infection, nasal congestion, and pain. There were no serious AEs.	50% of the patients on RP-G28 who reported abdominal pain at the beginning of the study did not report abdominal pain after 36 and 66 days.
Chey *et al.* 2020	15 locations in the USA	n = 377 (368 started, 344 ended), IG = 250 (127 LD, 123 HD) / CG= 127	18 - 74 / Men: 148, Women: 220	RCT / 30 days	Moderate to high symptom severity score and an HBT	Dilution sachet	GOS RP-G28 at LD: 5g 2x/day from days 1–10, 7.5g from days 11–30. For HD: 7.5g 2x/day from days 1–10 and 10g 2x/day from days 11–30	Powdered corn syrup	Reduced cramps (p = 0.026) and abdominal distension (p = 0.028). Abdominal pain (p = 0.105) and gas movement (p = 0.060)	NA	6.9% of the patients had some form of unspecified TEAE. No deaths.	After 30 days, the IG drank significantly more milk (mean = 1.5 tc/day) *versus* 0.2 tcs/day before treatment). The mean increase in ingestion was significantly higher in the IG than in the CG (0.7 tc/day) (p = 0.008).

Abbreviations: IG = Intervention group; CG = Control group; NA = Not available; HBT = Hydrogen Breath Test; H2 = Exhaled hydrogen; TEAE = Treatment-emergent adverse effects; LD = Low dose; HD = High dose; GOS =Galactooligosaccharides; AEs= Adverse effects; RCT = Randomized clinical trial; ppm = Parts per million; tc= Teacup.

Table 4 - Characteristics and data from the randomized clinical trials on probiotics in the treatment of lactose intolerance, articles from 2010 to 2021.

(continues)

Author and year	Study location	n, (IG/CG)	Age/sex	Study design/Intervention duration	Diagnosis of LI	Means of intervention	Probiotic	Control	Symptomatic results	Post-treatment HBT result	Adverse effects
Ojetti *et al*. 2010	Rome, Italy	n = 60 (IG, n = 20; Tilactase group, n = 20; CG, n = 20)	Mean age: 32 ± 5 years/Men = 6, Women = 54	RCT / 10 days	Presence of gastrointestinal symptoms after ingestion of lactose + HBT (>20 ppm) with 25g of lactose.	Capsules	*Lactobacillus reuteri* (4 × 10^8 CFU/dose) (Reuterin®, Noos, Rome, Italy), 2 pills for 10 days.	Unspecified pill composition.	Improvement in: Abdominal pain: IG 6.9 ± 1.07; CG 7.1 ± 0.72; Bloating: IG 9.95 ± 0.88; CG 7.1 ± 0.72; Diarrhea: IG 2.95 ± 2.07; CG 5.9 ± 0.85; Flatulence: IG 3.95 ± 1.35; CG: 5.15 ± 0.93; 6-hour symptoms for intestinal sounds and flatulence were not significantly different between groups.	Significant reduction in the mean peak of excretion of H2 was observed in the IG (23.1 ± 7.85 ppm) in relation to baseline values; no changes were observed in the placebo group (31.7 ± 8.3 ppm) ($p < 0.0001$)	IG: 2 presented with mild diarrhea and 1 with mild constipation.
Pakdaman *et al*. 2016	USA	n=28 (IG= 18 / CG = 20)	18 - 75 years / NA	RCT, Crossover / 4 weeks of intervention, followed by elimination and another 4 weeks of intervention	Analysis of overall symptoms every hour for 6 h + HBT with 25g of lactose dissolved in water.	Capsules	*Lactobacillus acidophilus* DDS-1 at 1 x 10^{10} CFU/dose	Maltodextrin	Improvement in: diarrhea (p = 0.033); abdominal cramps (p = 0.012), vomiting (p = 0.002), and overall (p = 0.037; 9.28 IG in comparison with 10.51 in the CG).	No statistically significant differences were observed between groups in the HBT.	No adverse effects were reported.

Table 4 – Characteristics and data from the randomized clinical trials on probiotics in the treatment of lactose intolerance, articles from 2010 to 2021.

(conclusion)

Author and year	Study location	n, (IG / CG)	Age/sex	Study design / Intervention duration	Diagnosis of LI	Means of intervention	Probiotic	Control	Symptomatic results	Post-treatment HBT result	Adverse effects
Aguilera *et al*. 2021	Chile	n = 29 (IG= 13, CG = 16)	21–50 years, mean age: 28 ± 7 / Men:* Women:*	RCT / 1 month	Report of digestive symptoms + HBT (>20 ppm) with 20g of lactose dissolved in 200mL of water.	Sorvete	*Bifidobacterium bifidum* 900791: low dose of 10^5 CFU/g or high dose of 10^7 CFU/g.	Ice cream containing 20 g of lactose, without probiotic.	In acute consumption, no significant differences were observed. In chronic consumption, for digestive symptoms and frequency / consistency of feces, the only alteration observed was an elevated rate of acid regurgitation in the IG compared to the CG ($p < 0.01$), which was detected on the fourth week of use of the probiotic.	During HBT3 (ice cream containing lactose + HD of probiotic), the plateau of excretion of H2 was of 19 ppm, and the H2 values were significantly lower than in HBT1 (ice cream containing lactose) in 150 and 180 min. The HBT at a HD and LD of probiotics was significantly reduced compared to those from HBT0 and HBT1. In chronic consumption, no significant differences were observed in the excretion of H2 between the IG and the CG.	Not evaluated, however, a higher rate of acid regurgitation was observed in the probiotic group ($p < 0.01$), detected during the fourth week.

* No information on the proportions of male and female participants was given.

Abbreviations: IG = Intervention group; CG = Control group; NA = Not available; HBT = Hydrogen Breath Test; H2 = Exhaled hydrogen; TEAE = Treatment-emergent adverse effects; LD = Low dose; HD = High dose; AEs = Adverse effects; CFU = colony-forming unit; RCT = Randomized clinical trial; ppm = Parts per million.

Table 5 - Evidence certainty classification of the studies on the prebiotic GOS RP-G28.

Result	Effect	Number of participants (studies)	Evidence certainty
Reduction in LI* symptoms using the prebiotic GOS RP-G28	The studies showed reductions in symptoms, mainly regarding abdominal pain, cramps, and abdominal distension.	462 participants (2 placebo-controlled, randomized clinical trials)	HIGH** ⊕⊕⊕⊕ (Despite the limitations for inconsistency, the magnitude of the effect should not change with studies involving many subjects)

* LI – Lactose Intolerance

**HIGH - Further research is very unlikely to change our confidence in the estimate of effect.

Table 6 - Evidence certainty classification of the studies on probiotics.

Result	Effect	Number of participants (studies)	Evidence certainty*
Reduction of LI* symptoms using probiotics	The studies showed a reduction in symptoms, mainly regarding diarrhea and cramps/abdominal pain.	177 (3 placebo-controlled randomized clinical trials)	VERY LOW** ⊕OOO (Due to the serious methodological risk of bias, indirect risk, risk of inaccuracy, and risk of inconsistency)

* LI – Lactose Intolerance

**VERY LOW - Any estimate of effect is very uncertain.

5.3 Registro no PROSPERO

PROSPERO
International prospective register of systematic reviews

Probiotics and prebiotics in the symptomatic treatment of lactose intolerance in adults: a systematic review and meta-analysis.

Luiza Scalcon de Oliveira, Kérley Braga Pereira Bento Casaril, Guilherme Welter Wendt

Review methods were amended after registration. Please see the revision notes and previous versions for detail.

Citation

Luiza Scalcon de Oliveira, Kérley Braga Pereira Bento Casaril, Guilherme Welter Wendt. Probiotics and prebiotics in the symptomatic treatment of lactose intolerance in adults: a systematic review and metaanalysis.. PROSPERO 2022 CRD42022295691 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022295691

Review question

Which strains of microorganisms are most effective in improving symptoms of LI in adults?

Searches [1 change]

We will search Randomised Controlled Trials (RCT) from electronic databases (Cochrane Library, ScienceDirect, PubMed, SciELO, and LILACS) from the beginning of publications until November 2021. Studies published in Portuguese, Spanish and English languages will be included. Also, we will check the reference lists of the included trials for additional eligible trials from grey literature.

For each platform, a combination of the following terms will be used: 'probiotic' OR 'Bifidobacterium longum' OR 'Lactobacillus rhamnosus' OR 'Lactobacillus acidophilus' OR 'Lactobacillus reuteri' OR 'Lactobacillus casei' AND 'prebiotic' OR 'fructo-oligosaccharides' OR 'galacto-oligosaccharides', OR 'trans-galactooligosaccharides' AND 'lactose intolerance' OR 'lactose malabsorption' AND 'randomised controlled trial'.

Types of study to be included [1 change]

The inclusion criteria are:

- being a randomised placebo-controlled clinical trial;
- addressing the issue of lactose intolerance associated with the use of probiotics of any kind;
- being a study with human participants;
- being performed with adults;
- being in scientific article format;
- having free access to read the full text;
- having good methodological quality assessed by RoB 2.0.

The exclusion criteria are:

- atudies with non-randomised designs;
- studies not reporting on the effect of probiotics and prebiotics in patients with lactose intolerance
- being a study in the form of videos, books;
- being a repeated study;
- being a study with animals;
- being a study with children;
- not being a free-access article for full reading;
- including patients with chronic, infectious, or other illnesses.

Condition or domain being studied

Lactose intolerance is a condition when occurred a decrease in the production of lactase enzyme. As a consequence of this, when consuming certain quantities of products containing lactose, the characteristic symptoms of this condition appear. Among the symptoms are diarrhoea, abdominal pain, flatulence, stomach pains, vomiting, and headaches. In this sense, probiotics and prebiotics have stood out as an alternative method of recomposing the intestinal microbiota, minimizing the symptoms caused by malabsorption of lactose.

Participants/population

Adults of all genders with a confirmed diagnosis of lactose intolerance, who have participated in a RCT that examined the effects of probiotics and prebiotics in this condition.

Intervention(s), exposure(s)

Supplementation of any probiotics and/or prebiotics as prevention, control or treatment of Lactose Intolerance symptoms. Interventions can be simultaneous or asynchronous.

Comparator(s)/control

Subgroup analyses should be conducted with a placebo group, with standard treatment with lactase enzymes or alternative supplementation or medicine.

The placebo group or control group must have similar characteristics to the intervention group.

Main outcome(s)

Improvement of clinical symptoms, measured either by self-reported measures and/or by biochemical or microbiological measures chosen and described in the RCT.

Measures of effect

Odds ratio (95% confidence intervals) for the association between being in the intervention group with prebiotics and probiotics and improvement in clinical symptoms;

Odds ratio (95% confidence intervals) for the association between being in the intervention group with prebiotics and probiotics and improvement in biochemical or microbiological measures;

Additional outcome(s)

Relief of abdominal pain, bowel distension, flatulence, diarrhoea, constipation, nausea, and vomiting; or other systemic symptoms, such as headaches,

dizziness, among others that may be reported in the RCT.

Data extraction (selection and coding)

Selection of studies and data extraction:

Two independent reviewers will screen the articles according to the inclusion and exclusion criteria. The two reviewers will not be aware of each other's decisions.

- Disagreements between individual judgments will be resolved by discussion between all authors.- Excel 360, version 2019, will be used individually by authors to record decisions and justifications for inclusion and exclusion, as well as data extraction, will be reported.

Data extraction:

- Two independent reviewers will extract the data;
- Information will be collected such as the name of the first author and year of publication, location (countryof origin), sample size/population, characteristics of the sample (including mean age, gender); diagnostic criteria for Lactose Intolerance; type of intervention, probiotics (strains of microorganisms) or type of prebiotics, time interval analysed, the number of participants in each group (cases and controls), main study results (mean values of the results, confidence interval reached and standard deviation).
- Disagreements in data extraction will be resolved by group discussion, and additional judges may beconsulted.
- Whenever necessary, we will contact the study investigators to verify missing or unpublished data relevantto the result of this research.
- Data extraction will be recorded in individual Excel spreadsheets.

Risk of bias (quality) assessment

We will assess the methods of randomisation and blinding at the study level. Two independent scholars will use the Revised Cochrane risk-of-bias tool for randomised trials (RoB 2.0) tool after the RCT survived the inclusion and exclusion criteria.

Disagreements will be resolved by asking a third, experienced scholar in systematic reviews. Results of the assessment of bias/quality will be informed when describing the potential studies and when drawing conclusions/implications for future studies.

Strategy for data synthesis

Each study will be summarised in terms of the sample included, institutions and countries involved, type of intervention, arms involved, and results on the improvement of clinical symptoms, measured either by selfreported measures and or by biochemical or microbiological measures between intervention vs standard care/placebo groups. RevMan v. 5.4 will be used to generate a combined odds ratio for the study outcomes with a fixed-effects model. Heterogeneity will be assessed with χ^2 test coupled with inconsistency analyses I^2 in Rev Man forest plots

Analysis of subgroups or subsets

Descriptive analyses will involve appropriate comparisons between control and/or placebo vs those undergoing intervention with probiotics and prebiotics.

If the data are sufficient, we will do a subgroup analysis by:

1) Doses of prebiotics;
2) Doses of probiotic agents;
3) Route of administration;4) Duration of treatment; 5) Follow-up period.

Contact details for further information

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Type and method of review

Meta-analysis, Systematic review

Anticipated or actual start date

02 December 2021

Anticipated completion date

31 March 2022

Funding sources/sponsors

CAPES - Coordination of Superior Level Staff Improvement

Conflicts of interest

None known

Language

English, Portuguese-Brazil, Spanish

Country

Brazil

Stage of review

Review

Ongoing

Subject index terms status

Subject indexing assigned by CRD

Subject index terms

MeSH headings have not been applied to this record

Date of registration in PROSPERO

01 January 2022

Date of first submission

01 December 2021

Stage of review at time of this submission

Stage	Started	/ Completed
Preliminary searches	Yes	No
Piloting of the study selection process	No	No
Formal screening of search results against eligibility criteria	No	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

01 January 2022
01 January 2022

5.4 Normas da Revista

Table of Contents

DESCRIPTION

CLINICAL NUTRITION, an official journal of ESPEN, The European Society for CLINICAL NUTRITION and Metabolism, is an international journal providing scientific information on nutritional and metabolic care and the relationship

between nutrition and disease both in the setting of basic science and clinical practice. Each issue combines original articles, reviews and other types of publications that will provide an invaluable reference for any specialist concerned with the field of interest.

Nutrition and nutritional care have gained wide clinical and scientific interest during the past decades. The increasing knowledge of metabolic disturbances and nutritional assessment in chronic and acute diseases has stimulated rapid advances in design, development and clinical application of nutritional support. The aims of ESPEN are to encourage the rapid diffusion of knowledge and its application in the field of clinical nutrition and metabolism.

Being an journal of ESPEN with members having various interest fields, either focused on basic research or clinical disciplines, the journal reflects the scientific nature of this multidisciplinary background and encourages the coordination of investigation and research from these disciplines. The journal publishes guidelines, consensus statements, review papers, original articles, short communications, and letters to the editor on those factors in acute and chronic diseases, which have metabolic and nutritional implications. It also publishes scientific works related to the development of new techniques and their application in the field of clinical nutrition.

The Clinical Nutrition ESPEN Journal is an electronic-only official publication of the European Society for CLINICAL NUTRITION and Metabolism (ESPEN). Each issue is published bimonthly, focusing on articles that highlight the relationship between nutrition and disease in the setting of basic science and clinical practice.
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All animal experiments should comply with the ARRIVE guidelines and should be carried out in accordance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978) and the authors should clearly indicate in the manuscript that such guidelines have been followed. The sex of animals must be indicated, and where appropriate, the influence (or association) of sex on the results of the study.

Conflict of interest

All authors must disclose any financial and personal relationships with other people or organizations that could inappropriately influence (bias) their work using the ICMJE

Form for Disclosure of Potential Conflicts of Interest http://icmje.org/conflicts-of-

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that are free of stereotyping (e.g.
'chairperson' instead of 'chairman' and 'flight attendant' instead of 'stewardess').

Author contributions

For transparency, we will request an author statement in the manuscript file outlining their individual contributions to the paper using the relevant CRediT roles: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation;
Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. Authorship statements should be formatted with the names of authors first and CRediT role(s) following. More details and an exampl e.

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Language (usage and editing services)

Please write your text in good English (American or British usage is accepted, but not a mixture of these). Authors who feel their English language manuscript may require editing to eliminate possible grammatical or spelling errors and to conform to correct scientific English may wish to use the English Language Editing service

available from Elsevier's Author Services.

Check this not to make common mistakes.

SUBMISSION

Prepare your submission

Choose an article type. Prepare your submission by following the specific article type Submission templates. Subsequently, our online submission system guides you stepwise through the process of entering your article details and uploading your files. The system converts your article files to a single PDF file used in the peer-review process. Editable files (e.g., Word, LaTeX) are required to typeset your article for final publication. All correspondence, including notification of the Editor's decision and requests for revision, is sent by e-mail.

Submit your article: Please submit your article via https://www.editorialmanager.com/yclnu/default.aspx/.

Peer review

This journal operates a single blind review process. All contributions are typically sent to a minimum of two independent expert reviewers to assess the scientific quality of the paper. The Editor is responsible for the final decision regarding acceptance or rejection of articles. The Editor's decision is final. More information on types of peer review.

CHOOSE AN ARTICLE TYPE

Full length Article

Original research and/or clinical studies. Please note, papers which only present data specific to a particular geographical area or country which are not novel or surprising from a worldwide perspective, are unlikely to be published. See further instructions for submission in the Full Length Article submission Template .

Narrative Review Article

Narrative Review Articles are publications that describe and discuss the state of the science of a specific topic or theme from a theoretical and contextual point of view. See further instructions for submission in the Narrative Review Article submission Template .

Randomized Control Trials

CLINICAL NUTRITION and CLINICAL NUTRITION ESPEN have adopted the proposal from the International Committee of Medical Journal Editors (ICMJE) which require, as a condition of consideration for publication of clinical trials, registration in a public trials registry. Clinical trials are defined as "biomedical or health related studies in human beings that follow a defined protocol." In addition to intervention studies, this definition encompasses observational, prevention, quality of life, diagnostic, and screening trials (www.clinicaltrials.gov).

Any clinical trial must be registered in one of the five ICMJE-approved public trials registries (i.e.,www.clinicaltrials.gov, www.isrctn.org, www.umin.ac.jp, www.trialregister.nl). Please report the study ID number and the website where the clinical trial is registered at the end of the abstract. See further instructions for submission in the Randomized Control Trials submission Template .

Meta-analyses

Meta-analyses (or systemic reviews) are considered original work because they are conducted using rigorous methodological approaches. We have adopted the definitions of systematic review and meta-analysis used by the Cochrane Collaboration. A systematic review is a review of a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise relevant research, and to collect and analyze data from the studies that are included in the review. Statistical methods (meta-analysis) may or may not be used to analyze and summarize the results of the included studies. Meta-analysis refers to the use of statistical techniques in a systematic review to integrate the results of included studies. See further instructions for submission in the Meta-analyses submission Template .

Letter to the editor

Comments on previously published articles in CLINICAL NUTRITION. When a letter refers to an article recently published in CLINICAL NUTRITION, the opportunity for reply will be given to the authors of the original article. Such a reply will be published along with the letter. The reply also needs to be submitted also

as a “Letter to the editor”. See further instructions for submission in the Letter to the Editor submission Template .

Editorial

Are submitted by members of the Editorial Board. See further instructions for submission in the Editorial submission Template .

Short Communication

Original research and /or clinical studies that do not require a full paper, but are completed studies, may be submitted as Short Communications. These papers may detail a smaller number of observations or may include a smaller number of patients. They may also add a small amount of new information but which is still considered important. Please note - CLINICAL NUTRITION does not accept case-studies and we suggest submitting case studies to CLINICAL NUTRITION ESPEN. See further instructions for submission in the Short Communication submission Template .

5.5 Opinion Paper

It reports original and personal views on a given subject. Authors should outline and craft selected arguments by bringing original and groundbreaking ideas and imaginative research solutions.The proposed structure of an opinion paper is:

- introduction to the topic;
- presentation of innovative and original hypotheses, and discussion of published data;
- analysis of the impact of the proposed hypotheses and of the target audience. Opinion papers should be based on published data, and should not expand on opinions by others, and should be written in a logical, professionally sound and convincing way. See further instructions for submission in the Opinion Paper submission Template .

ESPEN Guidelines

Are submitted in collaboration with the Editorial Office (espenjournals@espen.org). See further instructions for submission in the ESPEN Guidelines submission

Template.

ESPEN Endorsed Recommendation

Are submitted in collaboration with the Editorial Office (espenjournals@espen.org).See further instructions for submission in the ESPEN Endorsed Recommendation Template.

SUBMISSION TEMPLATES

Template: Full Length Article submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers			required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Abstract	required	required	Structure: Background&Aims - Methods - Results - Conclusion
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Introduction	required	required	1.5 page
	Material & Methods	required	required	
	Results	required	required	
	Discussion	required	required	Add titles to paragraphs, max 4 pages, 1200 words

	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	
	Figure legends	optional	optional	mandatory when Figures are submitted
	Imbedded figures and Tables	optional	optional	For peer review only
Figure		optional	optional	
Table		optional	optional	
Manuscript (including marked changes)			required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Narrative Review Article submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers			required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Abstract	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Introduction	required	required	
	Body Text	required	required	Add titles to paragraphs
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	
	Figure legends	optional	optional	Mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	

Figure		optional	optional	
Table		optional	optional	
Manuscript (including marked changes)			required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Randomized Control Trials submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers			required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Abstract	required	required	Structure: Background&Aims - Methods - Results - Conclusion
	Registration number of Clinical Trial	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Introduction	required	required	1.5 page
	Material & Methods	required	required	
	Results	required	required	

	Discussion	required	required	Add titles to paragraphs, max 4 pages, 1200 words
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	
	Figure legends	optional	optional	mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure (flow diagram)		required	required	
Figure		optional	optional	
Table		optional	optional	
CONSORT Agreement Checklist		required	required	
Manuscript (including marked changes)			required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Meta-analyses submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers		Not applicable	required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Abstract	required	required	Structure: Background&Aims - Methods - Results - Conclusion
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Introduction	required	required	1.5 page
	Material & Methods	required	required	
	Results	required	required	
	Discussion	required	required	Add titles to paragraphs, max 4 pages, 1200 words
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	

	Figure legends	optional	optional	mandatory When Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure (flow diagram)		required	required	
Figure		optional	optional	
Table		optional	optional	
PRISM checklist		required	required	
Manuscript (including marked changes)		Not applicable	required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Letter to the Editor submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		required	required	
Response to reviewers		Not applicable	required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Body Text	required	required	Add titles to paragraphs. Max 450 words
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	Max 5
	Figure legends	optional	optional	Mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure		optional	optional	
Table		optional	optional	

Manuscript (including marked changes)		Not applicable	required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Editorial submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		required	required	
Response to reviewers		Not applicable	required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Body Text	required	required	Add titles to paragraphs
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	

	Figure legends	optional	optional	Mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure		optional	optional	
Table		optional	optional	
Manuscript (including marked changes)		Not applicable	required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Short Communication submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers		Not applicable	required	
Manuscript		required	required	Format: double-spaced Introduction + Material & Methods + Results + Discussion: Max 1500 words
	Title Page	required	required	
	Abstract	required	required	Structure: Background&Aims - Methods - Results - Conclusion
	Key Words	required	required	Max 6

	Abbreviations	optional	optional	
	Introduction	required	required	
	Material & Methods	required	required	
	Results	required	required	
	Discussion	required	required	
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	Max. 10
	Figure legends	optional	optional	mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure		optional	optional	
Table		optional	optional	
Manuscript		Not	required	
(including marked changes)		applicable		
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: Opinion Paper submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		optional	optional	
Response to reviewers		Not applicable	required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Body Text	required	required	Add titles to paragraphs
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	
	Figure legends	optional	optional	Mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure		optional	optional	
Table		optional	optional	

Manuscript (including marked changes)		Not applicable	required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: ESPEN Guidelines submission

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		required	required	
Response to reviewers		Not applicable	required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Body Text	required	required	Add titles to paragraphs
	Conclusion	required	required	
	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	

	Figure legends	optional	optional	Mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure		optional	optional	
Table		optional	optional	
Manuscript (including marked changes)		Not applicable	required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

Template: ESPEN Endorsed Recommendation

SUMMARY				
Submission Files	**Manuscript elements (mandatory order)**	**NEW**	**REVISION**	**Remark**
Cover Letter		required	required	
Response to reviewers		Not applicable	required	
Manuscript		required	required	format: double-spaced
	Title Page	required	required	
	Key Words	required	required	Max 6
	Abbreviations	optional	optional	
	Body Text	required	required	Add titles to paragraphs
	Conclusion	required	required	

	Acknowledgement	optional	optional	
	Funding statement	required	required	
	Conflict of Interest	required	required	
	Author Contribution	required	required	
	References	required	required	
	Figure legends	optional	optional	Mandatory when Figures are submitted
	Imbedded figures and Tables (for review only)	optional	optional	
Figure		optional	optional	
Table		optional	optional	
Manuscript (including marked changes)		Not applicable	required	
Supporting Files		optional	optional	
ICMJE Conflict of Interest		required	required	for all authors

DESCRIPTION OF SUBMISSION TEMPLATE FILE TYPES

File type: Cover letter

In general the cover letter should explain to the editor why your work is perfect for CLINICAL NUTRITION or CLINICAL NUTRITION ESPEN why it will be of interest to the journal's readership.

<u>Mandatory for the following article types:</u>

- *Letter to the editor:* We will only consider “letter to the editor” in response to previously published articles in CLINICAL NUTRITION or CLINICAL NUTRITION ESPEN and provide the reference details of this article. In case it is a reply to a previous “letter to the editor”, provide the manuscript

code of the original “Letter to the editor”

- *Editorial, ESPEN Guidelines, ESPEN Endorsed Recommendation a*re submitted in collaboration with the Editorial Office (espenjournals@espen.org) . Therefore refer to this collaboration in the Cover Letter.

File type: Response to reviewers

A response to reviewers specifies how the authors addressed each comment the reviewers made. The response to reviewers is usually organized by presenting reviewers’ comments one by one, followed by the authors’ response. Authors should distinguish their responses from the reviewers’ comments by using phrases such as “author response” and/or a different font color or bold/italics. Then, each response should clearly explain the change made and where that change can be found in the revised manuscript (i.e., page number, paragraph, and/or line). If the authors did not make a suggested change, they should provide a rationale for their decision.

File type: Manuscript

General remarks

There are no strict formatting requirements but all manuscripts must been

1. 'spell checked' and 'grammar checked'
2. Manuscripts should be double-spaced (including references, tables, and figure legends).
3. The number of Figures and Tables should be in balance with the length of the manuscript, and carefully prepared to avoid duplication of data in the text.
   Embedded Figures (for peer review only) and Tables is an option.
   a. Please ensure when the figures and the tables are included in the manuscript file, that they are placed next to the relevant text in the manuscript, rather than at the bottom or the top of the file. The corresponding caption should be placed directly below the figure or table.
   b. **REMARK: High quality Figures should be submitted as separate**

files when the manuscript is submitted as a revision.

4. Regardless of the file format of the original submission, at revision you must provide us with an editable file of the entire article.
    a. Keep the layout of the text as simple as possible. Most formatting codes will be removed and replaced on processing the article.
    b. The electronic text should be prepared in a way very similar to that of conventional manuscripts (see also the Guide to Publishing with Elsevier).

THE ORDER OF THE FOLLOWING MANUSCRIPT ELEMENTS IS MANDATORY.

It is suggested to first check recent publications in the journal for structure and content of the manuscript.

Title page

- Title. Concise and informative. Titles are often used in information-retrieval systems. Do not include country or geographic region or brand names. Avoid abbreviations and formulae where possible.
- Author names and affiliations. Please clearly indicate the given name(s) and family name(s) of each author and check that all names are accurately spelled.
    - You can add your name between parentheses in your own script behind the English transliteration.
    - Present the authors' affiliation addresses (where the actual work was done) below the names. Indicate all affiliations with a lower-case superscript letter immediately after the author's name and in front of the appropriate address.
    - Provide the full postal address of each affiliation, including the country name and, if available, the e-mail address of each author.
- Corresponding author. Clearly indicate who will handle correspondence at all stages of refereeing and publication, also post-publication. This responsibility includes answering any future queries about Methodology and Materials. **Ensure that the e-mail address is given and that**

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by the corresponding author.

- Present/permanent address. If an author has moved since the work described in the article was done, or was visiting at the time, a 'Present address' (or 'Permanent address') may be indicated as a footnote to that author's name. The address at which the author actually did the work must be retained as the main, affiliation address. Superscript Arabic numerals are used for such footnotes.

Abstract

- A concise and factual abstract is required and should be structured according to:
  Background & Aims - Methods - Results - Conclusions.
- The abstract should state briefly the purpose of the research, the principal results and major conclusions.
- An abstract is often presented separately from the article, so it must be able to stand alone.
  - For this reason, References should be avoided, but if essential, then cite the author(s) and year(s). Also, non-standard or uncommon abbreviations should be avoided, but if essential they must be defined at their first mention in the abstract itself.

Registration number of Clinical Trial (for Randomized Controlled Trials only)

CLINICAL NUTRITION and CLINICAL NUTRITION ESPEN have adopted the proposal from the International Committee of Medical Journal Editors (ICMJE) which require, as a condition of consideration for publication of clinical trials, registration in a public trials registry.(www.clinicaltrials.gov). Any clinical trial must be registered in one of the five ICMJE-approved public trials registries (i.e.,www.clinicaltrials.gov, www.isrctn.org, www.umin.ac.jp, www.trialregister.nl). Please report the study ID number and the website where the clinical trial is registered at the end of the abstract of the article. CLINICAL NUTRITION and CLINICAL NUTRITION ESPEN require prospective registration of all trials.

Keywords

Provide a maximum of 6 keywords, using American spelling and avoiding general and plural terms and multiple concepts (avoid, for example, 'and', 'of'). Be sparing with abbreviations: only abbreviations firmly established in the field may be eligible. These keywords will be used for indexing purposes.

Abbreviations (optional)

Standard abbreviation may be used without definition, while non-standardized abbreviations should be explained in the text (as well as Tables and Figures) and should be listed. Ensure consistency of abbreviations throughout the article.

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Body Text

Only if the manuscript structure “Introduction - Material & Methods - Results- Discussion” is not applicable for your chosen article type. We recommend adding titles to paragraphs to enhance the readability.

Materials & Methods

The Materials and Methods section of the report gives a detailed account of the procedure that was followed in completing the experiment(s) discussed in the report. Such an account is very important, not only so that the reader has a clear understanding of the experiment, but a well written Materials and Methods section also serves as a set of instructions for anyone desiring to replicate the study in the future. Considering the importance of "reproducible results" in science, it is quite obvious why this is so vital.

Results

The results section summarizes the data that was collected and the statistical analyses that were performed. The goal of this section is to report the results without any type of subjective interpretation. The number of Figures and Tables should be in balance with the length of the manuscript, and carefully prepared to avoid duplication of data in the text. Important, ancillary information, which is relevant to the parent article but cannot

(and does not) appear in the print (or online) version of the journal can be referred

(clearly labeled as Supporting Information) in the result section, but need to be submitted as separate “Supporting Information” files.

Discussion

The purpose of the discussion is to interpret and describe the significance of your findings in light of what was already known about the research problem being investigated, and to explain any new understanding or fresh insights about the problem after you've taken the findings into consideration. We recommend adding titles to paragraphs to enhance the readability.

Conclusion

A conclusion is where you summarize the paper's findings and generalize their importance, discuss ambiguous data, and recommend further research. An effective conclusion should provide closure for a paper, leaving the reader feeling satisfied that the concepts have been fully explained.

Acknowledgements (optional)

List here those individuals who provided help during the research (e.g., providing language help, writing assistance or proof reading the article, etc.).

Funding statement

List funding sources in this standard way to facilitate compliance to funder's requirements:

Funding: This work was supported by the National Institutes of Health [grant numbers xxxx, yyyy]; the Bill & Melinda Gates Foundation, Seattle, WA [grant number zzzz]; and the United States Institutes of Peace [grant number aaaa].

It is not necessary to include detailed descriptions on the program or type of grants and awards. When funding is from a block grant or other resources available to a university, college, or other research institution, submit the name of the institute or organization that provided the funding.

If no funding has been provided for the research, please include the following sentence: “This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.”

Conflict of interest

All authors must disclose any financial and personal relationships with other

people or organizations that could inappropriately influence (bias) their work. Examples of potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding. If there are no conflicts of interest then please indicate this in this statement.

Author contributions

For transparency, we request the authors to submit an author statement file outlining their individual contributions to the paper using the relevant CRediT roles: Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation;

Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Roles/Writing - original draft; Writing - review & editing. Authorship statements should be formatted with the names of authors first and CRediT role(s) following. More details and an exampl e.

References

References have to be cited in the text by Arabic numerals and numbered in the order in which they are cited. The reference section should be typed double-spaced at the end of the text, following the sample format given below. Abbreviate journal titles according to the List of Journals Indexed in Index Medicus (available from the Superintendent of Documents, US Government Printing Office, Washington, D.C. 20402, USA, DHEW Publication No. (NIH) 91-267; ISSN 0093-3821. Provide all authors' names. Provide article titles and inclusive pages. 'Unpublished data' and 'personal communications' do not qualify as References and should be placed in parentheses in the text. Accuracy of reference data is the responsibility of the author. **Refer to the Vancouver style of citation with your reference manager program** or use the suggestions mentioned in ADDITIONAL INFORMATION section.

Figure legends/captions

Ensure that each illustration has a caption. A caption should comprise a brief title (**not** on the figure itself) and a description of the illustration. Keep text in the illustrations themselves to a minimum but explain all symbols and abbreviations used.

File type: Figure (flow diagram)

All Randomized controlled Trials submitted should include a Consolidated Standards of Reporting Trials (CONSORT) 2010 Flow diagram. Please refer to the CONSORT statement website at http://www.consort-statement.org for more information. An example flow diagram can also be downloaded from here. You will be asked to upload this flow diagram at the time of submission and this is file mandatory for submission.

All Meta-analyses submitted should include a completed uploaded PRISMA Flow Diagram. An example flow diagram can be downloaded from http://www.prisma-statement.org/. You will be asked to upload this flow diagram at the time of submission and this file is mandatory for submission.

File type : Figure

- *New submissions:* If illustrations/figures are submitted it can be embedded in the manuscript file only.
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All Randomized controlled Trials submitted for publication in CLINICAL

NUTRITION should include a completed Consolidated Standards of Reporting Trials (CONSORT)

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Sample References

Article in a journal

Oguro M, Imahiro S, Saito S, Nakashizuka T. Mortality data for Japanese oak wilt disease and surrounding forest compositions, Mendeley Data, v1; 2015. http://dx.doi.org/10.17632/xwj98nb39r.1.1.

Cummings J H, MacFarlane G T. Role of intestinal bacteria in nutrient metabolism. Clin Nutr 1997; 16: 3-11.

Book

1. McLaren D S, Meguid M M. Nutrition and its disorders, 4th edn. Edinburgh: Churchill Livingstone, 1988.

Chapter in a book

1. Goodwin S C, Liu S. Radiologic techniques for enteral access. In: Rombeau J L, Rolandelli R H, Eds. Enteral and tube feeding, 3rd edn. Philadelphia: W B Saunders, 1997: 193-206.

Website

1. U.S. positions on selected issues at the third negotiating session of the Framework

Convention on Tobacco Control. Washington, D.C.: Committee on Government Reform,

2002. (Accessed March 4, 2002, at

http://www.house.gov/reform/min/inves_tobacco/index_accord.htm.)

Online journal article

Tenesa A, Noble C, Satsangi J et al. Association of DLG 5 and inflammatory bowel disease across human populations. Eur Journal Hum Genet 2006: published online Jan 4. DOI:10.1038/sj.ejhg.5201516

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Gmail **Luiza Scalcon <scalcon.luiza@gmail.com>**

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5.7 Checklist do PRISMA 2020

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 4 -5
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 4-5
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 5-6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 6
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 6
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 6 - 7
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 7

Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	Page 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	-
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	-
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	-
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	-
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	-
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	-
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 7

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 8 -10
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 8 -10
Study characteristics	17	Cite each included study and present its characteristics.	Page 11
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Page 12
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Page 13 Table 3 and Table 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	-
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	-
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	-

	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	-
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	-
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 13 Table 5 and Table 6
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 14
	23b	Discuss any limitations of the evidence included in the review.	Page 18
	23c	Discuss any limitations of the review processes used.	Page 18
	23d	Discuss implications of the results for practice, policy, and future research.	Page 18 -19
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	Page 20
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	Page 20
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	Page 20
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Page 20
Competing interests	26	Declare any competing interests of review authors.	Page 20
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	-

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71

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