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ADESÃO À DIETA SEM GLÚTEN DE INDIVÍDUOS COM DOENÇA CELÍACA: UMA REVISÃO SISTEMÁTICA E METANÁLISE DE FERRAMENTAS COMPARADAS A TESTES LABORATORIAIS

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Dissertação apresentada ao Programa de Pós-Graduação em Nutrição Humana, da Universidade de Brasília, como requisito parcial à obtenção do grau de Mestre em Nutrição Humana. Área de concentração: Alimentos, Dietética e Bioquímica aplicada à Nutrição.

Orientadora: Profa. Dra. Renata Puppin Zandonadi

Coorientadora: Dra. Rosa Harumi Uenishi.

BRASÍLIA, DF

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RESUMO

Introdução: A doença celiaca (DC) é uma condição crônica multissistêmica desenvolvida em indivíduos geneticamente predispostos após o consumo do glúten. A DC causa sintomas intestinais e extraintestinais decorrentes da má absorção de nutrientes e danos histológicos na mucosa intestinal, que podem ser minimizados ou anulados com a adesão estrita à dieta sem glúten (DSG). A adesão à DSG é o único tratamento eficaz para a DC, por isso seu monitoramento é essencial. No entanto, há dificuldade em identificar com precisão a adesão à DSG devido à diversidade de métodos disponíveis, custos envolvidos para a realização de exames e divergências entre a ingestão de glúten e o tempo para a cicatrização completa da mucosa intestinal. **Objetivo:** Este estudo teve como objetivo avaliar a ferramenta que melhor prevê a adesão de indivíduos celíacos à DSG por meio de revisão sistemática. **Métodos:** A diretriz *Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis* (TRIPOD-SRMA) foi utilizada para a construção e coleta de dados a partir de oito bases de dados científicas (PubMed, EMBASE, LILACS, Web of Science, LIVIVO, SCOPUS, Google Scholar e Proquest). A busca nas bases de dados ocorreu em 16 de novembro de 2023. Os critérios de inclusão foram estudos envolvendo indivíduos com DC com mais de 18 anos, em tratamento para DC há pelo menos seis meses; estudos que utilizaram alguma ferramenta para prever a adesão à DSG e comparam-na com testes laboratoriais (testes sorológicos, peptídeo imunogênico do glúten - GIP, ou biópsia duodenal). Artigos de revisão, anais de congresso, capítulos de livros ou estudos sem dados suficientes foram excluídos. O *Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies* (CHARMS) foi usada para a coleta de dados dos estudos primários selecionados, e o risco de viés e qualidade foramavaliados usando a *Prediction Risk Of Bias Assessment Tool* (PROBAST). A associação entre a adesão à DSG pela ferramenta e pelos testes laboratoriais foi avaliada usando o coeficiente de contingência phi. **Resultados**: Foram selecionados 32 artigos para a revisão, sendo a maioria da Itália (n = 13) e estudos do tipo coorte (n = 31). Quatro ferramentas diferentes foram utilizadas para avaliar a adesão à DSG: pontuação BIAGI, *Celiac Dietary Adherence Test* (CDAT), perguntas de autorrelato e entrevistas. Os métodos de comparação mais usados foram biópsia (n = 19; 59,3%), seguidos por sorologia (n = 14; 43,7%) e peptídeos imunogênicos do glúten (GIP) (n = 4; 12,5%). Os métodos não invasivos são bons preditores para avaliar a DSG. Na análise por subgrupo, não houve diferenças significativas entre a entrevista, o autorrelato e as ferramentas BIAGI usadas para avaliar a DSG. Essas ferramentas foram melhor associadas à conformidade à DSG do que o CDAT. **Conclusão:** Considerando o custo, tempo de aplicação e capacidade de previsão, o autorrelato e o BIAGI foram as ferramentas preferidas para avaliar a adesão à DSG.Os instrumentos são métodos úteis para avaliar a adesão à DSG, porém são necessários mais estudos para uma padronização da ferramenta que seja aplicável em diferentes culturas.

Palavras-chave: Doença celíaca; Dieta sem glúten; Teste de Adesão; Pesquisas e questionários

ABSTRACT

Introduction: Celiac Disease (CD) is a chronic multisystemic condition that develops in genetically predisposed individuals after the consumption of gluten. CD causes both intestinal and extraintestinal symptoms resulting from poor nutrient absorption, which can be minimized or eliminated by strictly adhering to a gluten-free diet (GFD). Adherence to a GFD is the only effective treatment for CD, making its monitoring essential. However, there are challenges in accurately identifying adherence to a GFD due to the diversity of methods, the costs involved in conducting tests, and discrepancies between gluten intake and the time required for complete mucosal healing. **Objective: T**his systematic review aimed to evaluate the tool that best predicts celiac individuals' adherence to a gluten-free diet (GFD). **Methods:** The Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis (TRIPOD-SRMA) guideline was used for the construction and data collection from eight scientific databases (PubMed, EMBASE, LILACS, Web of Science, LIVIVO, SCOPUS, Google Scholar, and Proquest) on November 16, 2023. The inclusion criteria were studies involving celiac individuals over 18 years old, in treatment for CD for at least six months, using a questionnaire to predict adherence to a GFD and comparing it with laboratory tests (serological tests, gluten immunogenic peptide - GIP, or biopsy). Review articles, conference proceedings, book chapters, or studies without sufficient data were excluded. The Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) was used for data collection from the selected primary studies, and the risk of bias and quality was assessed using the Prediction Risk Of Bias Assessment Tool (PROBAST). The association between GFD compliance by the tool and laboratory test was assessed using the phi contingency coefficient. **Results:** Thirty-two articles were selected for review, mainly from Italy (n = 13) and cohort studies (n = 31). Four different tools were used to assess adherence to the DSG: BIAGI score, Coeliac Dietary Adherence Test (CDAT), self-report questions, and interviews. The comparison methods most used were biopsy (n = 19; 59.3%), followed by serology (n = 14; 43.7%), and gluten immunogenic peptides (GIP) (n = 4; 12.5%). Non-invasive methods are predictors for assessing DSG. In the subgroup analysis. There were no significant differences between the interview, self-report, and BIAGI tools used to evaluate GFD compliance. These tools were better associated with GFD compliance than the CDAT. **Conclusion:** Considering the cost, application time, and prediction capacity, the self-repost and BIAGI were the preferred tools for evaluating GFD compliance. The instruments are useful for assessing DSG adherence, but more studies are needed to standardize the tools and ensure their applicability across different cultures.

Keywords: Celiac Disease; Gluten-free Diet; Adherence Test; Surveys and Questionnaire.

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LISTA DE ABREVIATURAS E SIGLAS

AGA	Anticorpos-gliadina
ANP	Avaliação Nutricional Padronizada
CDAT	Celiac Dietary Adherence Test
CHARMS	*CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies*
DGP	Peptídeos de gliadina desaminados
DSG	Dieta Sem Glúten
EMA	Antiendomísio
GIP	Peptídeos Imunogênicos de Glúten
PROBAST	*Prediction model Risk Of Bias ASsessment Tool*
PROSPERO	*International Prospective Register of Systematic Reviews*
TRIPOD-SRMA	*Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis*
TTG	Teste de Transglutaminase Tecidual
PPGNH UnB	Programa de Pós Graduação em Nutrição Humana da Universidade de Brasília

SUMÁRIO

ESTRUTURA DA DISSERTAÇÃO

Esta dissertação está estruturada em três capítulos. O Capítulo 1 é composto de introdução, referencial teórico, objetivos e material e métodos. O Capítulo 2 apresenta os resultados e discussão em forma do artigo resultante desta pesquisa: "*Gluten-Free Diet Adherence Tools for Individuals with Celiac Disease : A Systematic Review and Meta-Analysis of Tools Compared to Laboratory Tests*" (RIBEIRO et al., 2024), publicado no periódico *Nutrients* (FI: 4,8) em 26 de julho de 2024. O Capítulo 3 expõe a conclusão e as considerações finais do estudo, as referências, apêndices e anexos.

CAPÍTULO 1

1. INTRODUÇÃO

A doença celíaca (DC) é uma condição crônica autoimune decorrente da ingestão do glúten por indivíduos geneticamente predispostos, que afeta o intestino delgado com atrofia vilositária, causando manifestações intestinais e extraintestinais (AL-TOMA et al., 2019; FASANO; CATASSI, 2012). Pode desencadear sintomas graves de má absorção e deficiências nutricionais como a anemia, diarreia, constipação, baixa estatura, atrofia muscular, dermatite herpetiforme, entre outros (AL-TOMA et al., 2019; ITZLINGER et al., 2018; LUDVIGSSON et al., 2013; SAHIN, 2021). Estima-se que a DC afete entre 0,7% e 1,4% da população mundial e seja predominante no sexo feminino, contudo é considerada uma condição negligenciada e subdiagnosticada (SAHIN, 2021; SINGH et al., 2018; TARAGHIKHAH et al., 2020).

O glúten é um complexo de proteínas que está naturalmente presente no trigo, centeio e cevada e seus derivados. A dieta sem glúten (DSG) é o único tratamento eficaz para a doença e tem a capacidade de reverter os danos causados à mucosa intestinal, agindo de forma primordial para reduzir a morbidade e melhorar a qualidade de vida de indivíduos com DC (BERNARDO; PEÑA, 2012; GALLI et al., 2014a; WIESER et al., 2021). A DSG consiste na restrição completa de alimentos contendo glúten.. Dada a ampla presença do glúten em produtos de confeitaria, de panificação, massas e produtos industrializados, a adesão à DSG pode se tornar um grande desafio para as pessoas acometidas pela DC (ELLI et al., 2024).

São diversos os fatores envolvidos na adesão à DSG, desde o nível de escolaridade, percepção do próprio paciente e autoeficácia sobre a dieta, conhecimento sobre a DC, duração da DSG, instrução fornecida por profissionais habilitados, consumo inconsciente devido à contaminação cruzada e até a rotulagem dos alimentos. Um dos principais motivos de transgressões à DSG são eventos sociais e mudanças no ambiente de consumo de alimentos (FERNÁNDEZ MIAJA et al., 2021; VILLAFUERTE-GALVEZ et al., 2015a). Porém, a avaliação da adesão à DSG por indivíduos com DC ainda é um desafio para pesquisadores e profissionais da saúde, visto que a resposta ao tratamento pode ser lenta, além disso existem

diversas barreiras para a adesão à DSG e poucas evidências sobre a forma mais adequada para o monitoramento da doença (ELLI et al., 2024).

Os métodos para a avaliação da adesão à DSG são variados e envolvem vantagens e desvantagens. A biópsia, apesar de essencial para o diagnóstico em adultos e padrão ouro para avaliar a recuperação da mucosa, é um método invasivo, e de alto custo para monitoramento da doença (PAGANIZZA et al., 2019). Dessa forma, estima-se ser possível utilizar métodos alternativos menos invasivos para avaliar a adesão à DSG, por exemplo, entrevistas por profissionais qualificados, uso de questionários, testes sorológicos ou rastreio de peptídeos imunogênicos de glúten (GIP) nas fezes ou na urina (GALLI et al., 2014; MUHAMMAD; REEVES; JEANES, 2019; SILVESTER et al., 2017)

Uma entrevista estruturada realizada por um profissional qualificado pode ser um método sensível para avaliar a adesão à DSG. Uma das formas de entrevista estruturada utilizada é a Avaliação Nutricional Padronizada (ANP) com autorrelato da alimentação pelos pacientes com DC (AL-TOMA et al., 2019; WIESER et al., 2021). A ANP consiste em uma ferramenta com perguntas estruturadas com registro alimentar de até três dias e a avaliação da capacidade do paciente em identificar o glúten em alimentos ou outros produtos como medicamentos e cosméticos. Esta forma de avaliação apresenta como desvantagens ser uma avaliação subjetiva e nem sempre haver um profissional especialista disponível nos serviços de saúde para a realização da mesma.

Os questionários se destacam por serem instrumentos simples, rápidos e fáceis de serem aplicados na prática clínica. Os mais utilizados são o *Celiac Dietary Adherence Test* (CDAT) (LEFFLER et al., 2009), e o chamado Pontuação de BIAGI (BIAGI et al., 2012), ambos já validados e amplamente utilizados nos estudos e com resultados de boa confiabilidade, mas até o momento sem validação para a população brasileira (MORENO et al., 2017).

Além das ferramentas mencionadas há também testes sorológicos recomendados para o diagnóstico da DC e posteriormente identificação de adesão à DSG. Os testes sorológicos utilizados são: anticorpos TTG (antitranglutaminase tecidual), EMA (antiendomísio), DGP (antipeptídeos de gliadina desamidados) da classe IgA e IgG. Os anticorpos diminuem em até 12 meses após o início da DSG e o IgA TTG é o mais recomendado para o monitoramento a longo prazo (ELLI et al., 2024; NACHMAN et al., 2011). Resultados positivos para estes testes indicam baixa

adesão à DSG ou contaminação pelo glúten, porém valores negativos podem não confirmar a adesão estrita à dieta se o consumo de glúten for muito recente. Além disso, estes testes podem ser inacessíveis na prática pela ausência do exame no serviço ou custos (AL-TOMA et al., 2019; ELLI et al., 2024; RODRIGO et al., 2018).

A dosagem de peptídeos imunogênicos de glúten (GIP) nas fezes e na urina é o método mais recentemente desenvolvido, por meio do qual é possível a identificação direta do consumo voluntário e involuntário do glúten (MARZAGALLI et al., 2020; RUSSELL et al., 2024b). Essa dosagem é recomendada para casos de DC não responsiva quando há suspeita de ingestão ou contaminação pelo glúten (ELLI et al., 2024). No entanto, ainda não está amplamente disponível, é suscetível à variabilidade individual no metabolismo do glúten, é influenciado pela quantidade de glúten ingerida para detecção, é de alto custo e ainda necessita de mais pesquisas para confirmação da possibilidade de marcador de adesão à DSG (COMINO et al., 2012, 2016a).

A adesão à DSG é essencial para a prevenção de sintomas e, recuperação histológica da mucosa, promove prevenção de complicações associadas à DC não tratada e melhora da qualidade de vida de indivíduos com DC, além de reduzir custos com saúde relacionados a essa condição (PAGANIZZA et al., 2019). Porém, a confirmação equivocada da adesão à DSG por um método não confiável pode representar riscos aos indivíduos com DC em relação à sua alimentação, na medida em que a confirmação incorreta da adesão pode levar à falsa percepção de tratamento adequado e expor o indivíduo prejuízos em sua saúde (WIESER et al., 2021). Até o momento, não há estudo para recomendação da melhor ferramenta para avaliar a adesão à DSG ou que melhor prediz a adesão à DSG por indivíduos com DC, por isso este trabalho se torna essencial para contribuição à literatura científica e monitoramento de pessoas com DC. Portanto, buscar uma ferramenta confiável, de baixo custo, fácil aplicação e menos invasiva, pode representar um ganho para os indivíduos com DC, para os profissionais de saúde que acompanham seu tratamento e para pesquisadores da área.

Diante disso, se faz necessário explorar a literatura sobre este tema, expor critérios para avaliar a adesão à DSG e consequentemente, contribuir para melhorar o monitoramento do tratamento dietético envolvido na DC e qualidade de vida dos pacientes.

2. REFERENCIAL TEÓRICO

2.1 Conceito e epidemiologia da doença celíaca

A doença celíaca (DC) é uma condição crônica autoimune e sistêmica, que afeta o intestino delgado causando atrofia das vilosidades de pessoas geneticamente predispostas. Ocorre após a ingestão contínua do glúten, causando sintomas intestinais e extraintestinais (AL-TOMA et al., 2019; SAHIN, 2021). Os danos à mucosa intestinal decorrentes da DC provocam a perda da superfície absortiva, consequentemente, diminuição da absorção de vitaminas e minerais. Dessa forma, pode produzir sintomas graves de má absorção e deficiências nutricionais, como diarreia, anemia, baixa estatura, atrofia muscular, defeitos do esmalte dentário, fadiga, osteoporose, além de dermatites, infertilidade, constipação, entre outros (AL-TOMA et al., 2019; ITZLINGER et al., 2018; LUDVIGSSON et al., 2013; SAHIN, 2021). A condição também pode ocorrer de forma assintomática, podendo ser identificada por meio de triagem sorológica (LEBWOHL; RUBIO-TAPIA, 2021; SAHIN, 2021).

A Itália foi pioneira na descrição epidemiológica da DC há cerca de 30 anos, quando houve uma testagem de 17201 escolares entre 6 e 15 anos de idade e 82 indivíduos foram diagnosticados com DC (7,5%), prevalência maior do que se imaginava e com amplo aspectos clínicos (CATASSI et al., 1996). Antes disso, a DC era considerada uma doença rara, acometendo principalmente crianças de ascendência europeia, pois era necessário apenas os sintomas gastrointestinais e biópsia duodenal para o diagnóstico. Porém, com o advento dos testes sorológicos, o rastreamento e identificação da prevalência ficaram mais acessíveis (CATASSI et al., 1996; LEFFLER; SCHUPPAN, 2010)

Os estudos mais recentes estimam que a DC afeta entre 0,7% e 1,4% da população mundial e varia entre sexo, idade e localização geográfica, sendo mais prevalente na Europa e Oceania (SAHIN, 2021; SINGH et al., 2018). Na América Latina, apesar de poucos estudos, a prevalência é semelhante à dos países europeus (PARRA-MEDINA et al., 2015). No Brasil, estudos em regiões específicas do Sul e Sudeste, corroboram com os dados da população mundial, sendo a prevalência maior em crianças e, menor em populações afrodescendentes, porém isso pode ser devido a uma condição subdiagnosticada (ALMEIDA et al., 2012;

MALTA ALMEIDA et al., 2013; MUNIZ; SDEPANIAN; FAGUNDES NETO, 2016). Em São Paulo, um estudo com quatro mil amostras de doadores de sangue avaliou marcadores sorológicos, EMA e TTG, para DC e detectou a DC em 1:286 adultos (ALENCAR et al., 2012). Em Brasília, um estudo mostrou que a DC atingiu 5,4 vezes mais crianças que idosos (0,1%) por meio de avaliação por testes sorológicos para TTG e EMA (MALTA ALMEIDA et al., 2013).

2.2 Diagnóstico

O diagnóstico precoce é fundamental para o manejo da DC e maior qualidade de vida. No entanto, um dos desafios é realizá-lo corretamente, tendo em vista a variedade e a não especificidade de sintomas. Devem-se levar em consideração fatores histológicos, sorológicos e clínicos, associados com a realização dos testes com o indivíduo ainda em consumo regular de glúten para evitar falsos negativos (AL-TOMA et al., 2019).

Inicialmente a identificação da DC era realizada apenas pelos sintomas gastrointestinais, como diarreia e esteatorreia,ou sintomas decorrentes da má absorção, como perda de peso e atraso no crescimento, com confirmação pela biópsia do intestino delgado.

Por muito tempo, o diagnóstico padrão-ouro foi a realização de três biópsias: a primeira, quando havia suspeita da doença (com atrofia vilositária); a segunda, após um ano de DSG estrita (melhora da anatomia vilositária); a terceira, ao reintroduzir o glúten por mais um ano e verificar a piora no padrão histológico.Em seguida, eram avaliados os anticorpos-gliadina (AGA) - teste atualmente não recomendado devido a baixa especificidade e sensibilidade. O teste sorológico AGA foi desenvolvido na década de 1980. Apesar do grande avanço para a época, o teste apresenta especificidade e sensibilidade razoáveis, com os falsos positivos maiores que os verdadeiros positivos. Por isso, o AGA não é mais recomendado como marcador para diagnosticar a DC. Existem sorologias mais precisas e superiores em especificidade e sensibilidades como o TTG, EMA e DGP (LEFFLER; SCHUPPAN, 2010).

Os anticorpos anti- EMA e TTG são testes sensíveis e específicos, especialmente para identificar formas silenciosas da doença, aumentando significativamente as taxas de detecção. Os testes sorológicos para DC devem ser priorizados em pessoas com sintomas sugestivos ou doenças associadas à DC.

Porém, mesmo em sorologias negativas a endoscopia duodenal é indicada em diarreia crônica, anemia ferropriva na ausência de outras causas, sintomas gastrointestinais com histórico familiar de DC, doença autoimune presente, deficiência de IgA e presença de dermatite herpetiforme devido a alta suspeita clínica (AL-TOMA et al., 2019; KASWALA et al., 2015; LIONETTI; CATASSI, 2011).

O EMA foi desenvolvido também na década de 1980, porém se mostrou mais específico e sensível que o AGA, chegando a mais de 90% em pacientes com atrofia de vilosidades. O EMA é baseado na imunoflorescência, ou seja, leitura no microscópio, e necessita de tecido de esôfago de macaco ou tecido de cordão umbilical humano como substrato, tornando o método dispendioso e com possível variabilidade do observador na predição do resultado (LEFFLER; SCHUPPAN, 2010).

O teste de TTG, desenvolvido no final na década de 1990, identificado como autoantígeno, utiliza o ELISA (*Enzyme Linked Immuno Sorbent Assay*) para detecção, por isso é mais acessível na prática. Além disso, foi observada maior sensibilidade do que a do EMA e especificidade semelhante. O TTG é o teste preferido para diagnóstico e monitorização de pacientes com DC em todas as idades, porque apresenta uma alta sensibilidade, menor custo e maior reprodutibilidade (AL-TOMA et al., 2019; LEFFLER; SCHUPPAN, 2010). Apesar de ser o autoanticorpo mais sensível, (sensibilidade de 96-98% e especificidade de 88-100%) para o diagnóstico, deve associá-lo à dosagem de IgA sérica total devido à possibilidade de deficiência de IgA, já que esta afeta até 3% dos pacientes com DC, o que pode levar a resultados falso negativos (TARAGHIKHAH et al., 2020).

O DGP é um marcador sensível e específico indica-se dosá-lo com o TTG para identificar pacientes com deficiência seletiva de IgA. No entanto, o custo é maior que a dosagem de TTG e os resultados são inferiores. Sozinho, o DGP não prediz o diagnóstico e nem adesão à dieta, por isso não é o teste mais recomendado (AL-TOMA et al., 2019; LEFFLER; SCHUPPAN, 2010).

Atualmente, as diretrizes recomendam testar, com sorologia TTG IgA, adultos com sinais e sintomas de má absorção, familiares de primeiro grau assintomáticos de indivíduos com DC e Diabetes Mellitus tipo 1 (AL-TOMA et al., 2019; RUBIO-TAPIA et al., 2023). O diagnóstico é definido com múltiplas biópsias de duodeno (um ou dois fragmentos do bulbo e quatro do duodeno distal) associadas a testes sorológicos (dosagem de TTG IgA e EMA) e dados clínicos.

A melhora dos sintomas após orientação feita por profissional qualificado acerca da DSG também é indicativo para o diagnóstico da DC. Em crianças, a biópsia pode ser dispensada na presença de sintomas e níveis de TTG dez vezes o valor de referência, EMA positivo em uma segunda amostra de sangue e na presença de HLA-DQ2 e/ou DQ8 associados à melhora dos sintomas e diminuição dos anticorpos após a DSG devidamente orientada por um profissional de nutrição com experiência em DC (AL-TOMA et al., 2019; RUBIO-TAPIA et al., 2023).

2.3 Adesão à dieta sem glúten

Os alimentos que contêm glúten são os derivados dos cereais trigo, centeio ou cevada como massas, pães, torradas, biscoitos e cerveja. Devido ao extenso grupo de alimentos que contêm glúten de forma intencional ou por meio de contaminação cruzada e à rotulagem inadequada dos alimentos, aderir à dieta é desafiador, pois exige conhecimento, habilidades culinárias e mudanças no comportamento (CRISTINE; OLIVEIRA, 2022).

A DSG rigorosa e permanente é o único tratamento eficaz para a DC e tem a capacidade de reverter os danos causados à mucosa intestinal, agindo de forma primordial para reduzir a morbidade e melhorar a qualidade de vida desses indivíduos (GALLI et al., 2014a; WIESER et al., 2021).

A adesão à DSG em nível populacional é difícil de mensurar devido à variedade de métodos utilizados. A única revisão sistemática sobre este assunto estima que a adesão à DSG seja entre 42% e 91% dependendo do método de avaliação utilizado (HALL; RUBIN; CHARNOCK, 2009). São diversos aspectos, facilitadores e barreiras envolvidos no processo de adesão à DSG que perpassam pelo individual (nível de educação e conhecimento, sintomas, autoconfiança, dificuldade com a dieta), interpessoal (família, amigos, atividades sociais, conhecer outras pessoas com DC), organizacional (disponibilidade de alimentos sem glúten, associações de DC), comunidade (barreiras culturais, viagens) e sistêmicos (qualidade de vida, conhecimento médico e da equipe de saúde, preparação dos serviços de saúde). Portanto, é preciso melhorar o conhecimento sobre a DC e a DSG, proporcionar contato entre pessoas com o mesmo diagnóstico, adequar a rotulagem de alimentos e melhorar habilidades e compreensão de profissionais de saúde sobre a doença e seu tratamento (ABU-JANB; JAANA, 2020).

A avaliação da adesão ao tratamento se torna primordial, uma vez que está associada a influências emocionais, socioculturais e cognitivas, diminuição de sintomas e melhora da qualidade de vida em adultos com DC (BURGER et al., 2017). Na avaliação de adesão à DSG, aspectos importantes a serem observados são o consumo inadvertido do glúten e a contaminação cruzada. Por isso, deve-se orientar a correta higienização dos utensílios de cozinha, uso de equipamentos, o consumo de alimentos em serviços de alimentação e a leitura de rótulos dos alimentos. Quando fornecidas instruções individualizadas, a chance do paciente com DC aderir à DSG é aumentada. Ainda, o acompanhamento próximo por profissional de saúde também permite identificar precocemente sintomas, outras doenças associadas e melhorar o manejo clínico. Não apenas a avaliação da adesão à DSG, mas o acompanhamento do estado nutricional é fundamental e precisa ser realizado periodicamente para evitar consequencias negativa à saúde (BURGER et al., 2017; WIESER et al., 2021).

Ademais, os custos com saúde podem impactar a adesão à DSG, pois são mais altos para indivíduos diagnosticados com DC em todas as faixas etárias e aumentam com o avançar da idade, mesmo naqueles com recuperação da mucosa. Simultaneamente, o custo de vida também é mais elevado e sobrecarrega principalmente pessoas de baixa renda devido ao custo mais alto de alimentos sem glúten e dificuldade de acesso aos serviços de alimentação específicos (MÅRILD et al., 2020; ROSTAMI et al., 2017).

2.4 Métodos para avaliar a adesão à dieta sem glúten

Existem diversas maneiras de avaliar o seguimento da DSG, por exemplo, consultas com um profissional especializado, questionários específicos, aferição de anticorpos séricos para DC, endoscopias com biópsias duodenais e determinação de peptídeos derivados do glúten nas fezes ou urina (RODRIGO et al., 2018). Apesar de a adesão à DSG poder ser avaliada por diferentes métodos, não há determinação de qual o melhor deles. (MUHAMMAD; REEVES; JEANES, 2019b).

2.4.1 Questionários

Existem na literatura científica apenas três questionários validados para a avaliação da adesão à DSG (BIAGI et al., 2012a; LEFFLER et al., 2009b;

ONTIVEROS et al., 2015). Antes da criação desses questionários específicos, os estudos utilizavam autorrelato, entrevista dietética com profissional especialista, registros alimentares, biópsia ou testes sorológicos que confirmassem que o indivíduo estava sem ingerir glúten (HALL; RUBIN; CHARNOCK, 2009).

O primeiro questionário foi criado em 2009 nos Estados Unidos da América (EUA) a partir da reunião de especialistas (gastroenterologistas, nutricionistas, psicólogos e indivíduos com DC) para avaliar especificamente a adesão à DSG, o *Celiac Dietary Adherence Test* (CDAT) (LEFFLER et al., 2009b). Após as reuniões, eles elegeram os cinco domínios mais importantes para a adesão à DSG, sendo eles: (1) sintomas relacionados à DC, (2) conhecimento específico da doença, (3) autoeficácia, (4) razões para manter uma DSG e (5) adesão percebida à DSG. Um banco de questões foi criado a partir destes domínios. Após as definições das questões que compunham o questionário, os voluntários com DC responderam ao questionário, fizeram teste sorológico TTG e foram submetidos à Avaliação Nutricional Padronizada (ANP) por um nutricionista experiente. Assim o CDAT foi validado para adultos.

O CDAT consiste em um questionário composto por sete itens em uma escala de um a cinco, a pontuação mínima é sete e máxima 35 pontos, sendo que menor que 13 pontos indica boa adesão (LEFFLER et al., 2009b). Este questionário já foi traduzido e validado na Espanha, Polônia e Suécia, corroborando sua utilidade e aplicabilidade (FUEYO DÍAZ et al., 2016; GŁADYŚ et al., 2020; JOHANSSON et al., 2019).

Ainda em 2009, o questionário chamado pontuação de BIAGI ou questionário de Pavia foi desenvolvido na Itália (BIAGI et al., 2009a). Posteriormente, em 2012, este foi validado em um estudo multicêntrico (BIAGI et al., 2012a). O instrumento consiste em quatro perguntas simples, as quais foram elaboradas a partir da experiência clínica dos pesquisadores e aplicadas a 141 pacientes adultos com DC para validação. A validade do questionário foi avaliada medindo a responsividade à condição clínica dos pacientes (persistência de EMA positivo e alterações típicas na biópsia). O EMA foi eleito para a validação, pois assim como o TTG, possui sensibilidade maior de 95%, no entanto o EMA, segundo estudo anterior do mesmo grupo, possui quase 100% especificidade (CPRAZZA, 2001). Uma das vantagens é que o instrumento pode ser aplicado mesmo por quem não tem experiência em DC

(BIAGI et al., 2012a). A literatura tem utilizado o questionário com resultados satisfatórios de reprodutibilidade (MORENO et al., 2017b; PAGANIZZA et al., 2019; SBRAVATI et al., 2020).

A classificação de pontos é de zero a quatro, sendo zero a um ponto: indivíduo não segue uma DSG estrita; dois pontos: segue uma DSG, mas com erros importantes que requerem correção; três a quatro pontos: segue uma DSG rigorosa. Os autores afirmam ser possível aplicar o instrumento em diferentes etnias. Porém, em alguns países pode não ser possível realizar a última pergunta (Você só come alimentos embalados garantidos pela Associação Celíaca?), já que as sociedades celíacas locais podem não fornecer essa informação ou não exigir listas de alimentos embalados sem glúten.

Em 2015, no México, um questionário foi desenvolvido para estimar a prevalência de sintomas relacionados ao glúten e adesão à DSG em adultos. O instrumento inclui dois questionários prévios: um de sintomas de distúrbios relacionados ao glúten e sensibilidade não celíaca (SGNC) da Itália e outro questionário foi uma versão em espanhol, utilizado devido ao idioma (ONTIVEROS et al., 2015). Nesse sentido, o instrumento não é específico para DC, foi desenvolvido a partir da população geral e envolvem a identificação de reações adversas ao glúten e alergia ao trigo, presença de DC, histórico familiar e sintomas autorreferidos. O instrumento foi validado também na Colômbia, El Salvador (CABRERA-CHÁVEZ et al., 2016) e Brasil (ARÁMBURO-GÁLVEZ et al., 2019)).

Os questionários são ferramentas úteis que apoiam a avaliação da adesão à DSG e possuem vantagens como o baixo custo, tempo e facilidade de aplicação. Contudo, podem ser subjetivos e o relato pode ser impreciso e mascarar o consumo inconsciente de glúten (AL-TOMA et al., 2019; MORENO et al., 2017b).

2.4.2 Entrevista estruturada

Uma entrevista bem estruturada feita por profissional de saúde pode até ser mais sensível que sorologias para pacientes não aderentes à DSG (LEFFLER et al., 2009b; WIESER et al., 2021). O principal objetivo do acompanhamento do paciente com DC com o profissional é, sobretudo, avaliar a presença e melhora dos sintomas, associado a exame físico e clínico e de adesão à DSG. A ANP é baseada em uma

entrevista detalhada para avaliar a conformidade à DSG, e deve ser feita por um nutricionista especialista e experiente.

A ANP busca identificar a exposição ao glúten em três partes: registro alimentar de pelo menos 24 horas ou três dias; avaliação da capacidade do paciente de identificar o glúten nos alimentos utilizando o questionário sobre rótulo de alimentos e avaliação de dúvidas sobre a leitura de rótulos de medicamentos, suplementos alimentares ou cosméticos. Os resultados podem ser registrados em escala *Likert* de seis pontos para avaliação, conforme Gladyz et al. (2020) realizou, sendo 1 a 6, da seguinte forma: 1 ponto — adesão perfeita à dieta sem glúten; 2 pontos — boa adesão à dieta sem glúten; 3 pontos — adesão razoável à dieta sem glúten; 4 pontos — adesão ruim à dieta sem glúten; 5 pontos — adesão muito ruim à dieta sem glúten e 6 pontos — nenhuma dieta sem glúten.

O nutricionista é o profissional mais preparado para avaliar o seguimento da DSG por meio da ANP, devendo participar ativamente do acompanhamento, orientação da DC e de seu tratamento (AL-TOMA et al., 2019; RODRIGO et al., 2018). No entanto, nem sempre os serviços de saúde dispõem de profissionais especialistas em DC, principalmente nutricionistas, ficando à cargo do médico gastroenterologista a avaliação da conformidade e orientação, uma limitação para a aplicação da ANP. Outra limitação é que a ANP é mais detalhada e trabalhosa que a os questionários, necessitando de mais tempo para a realização.

2.4.3 Testes sorológicos

Os testes sorológicos mais utilizados para detecção e acompanhamento da DC são TTG, EMA e DGP. Estes testes estão relacionados à quantidade de glúten consumido em longo prazo, sendo assim altos níveis sugerem a baixa adesão à DSG. A recomendação é que sejam realizados a cada seis meses até vinte e quatro meses após o diagnóstico. Após um ano do início da DSG, caso os níveis sorológicos ainda estejam altos, estes sugerem fortemente a contaminação por glúten dos alimentos ingeridos ou transgressões na dieta (AL-TOMA et al., 2019; RODRIGO et al., 2018).

A análise de anticorpos também é vantajosa para o monitoramento de indivíduos que não relatam a adesão à DSG precisamente, seja pelo conhecimento prévio deficiente sobre a DSG, pelo nível de instrução ou pela idade. Dessa forma, é bastante útil para avaliação em crianças e idosos. O

declínio nos níveis séricos dos testes sorológicos após a DSG é essencial na determinação da restrição ao glúten e identificação de pacientes que precisam de mais orientação e monitoramento, além de serem úteis para avaliar indivíduos com sintomas persistentes da DC (AL-TOMA et al., 2019; LEFFLER; SCHUPPAN, 2010).

Não obstante, a normalização dos níveis séricos de anticorpos é demorada e pode não identificar exposições ocasionais ao glúten e transgressões pontuais à DSG. Dessa forma, valores elevados podem ser limitados para avaliar a adesão estrita à DSG (WIESER et al., 2021). Resultados de Mehta et al. (2018) demonstraram que indicadores laboratoriais também podem ser imprecisos para avaliar a adesão à DSG quando comparados à avaliação em uma entrevista estruturada, mas o número de participantes (n=92) deste estudo pode ter sido pequeno para essa conclusão, indicando uma limitação (MEHTA et al., 2018).

2.4.4 Endoscopias com biópsias duodenais

A biópsia duodenal viabiliza a realização de lâminas histológicas que permitem a visualização da altura das vilosidades intestinais, de fissuras na mucosa e seu resultado permite classificação de acordo com a extensão da atrofia vilositária, do aumento de linfócitos intraepiteliais e hiperplasia de criptas intestinais. A recuperação completa da mucosa intestinal leva em média dois anos após o início da adesão à DSG. No entanto, existem diferenças significativas no grau de recuperação histológica, principalmente entre crianças e adultos, sendo que em crianças, podem ser necessários até dois anos e, em adultos, até cinco anos para cicatrização completa após a DSG (RODRIGO et al., 2018; WIESER et al., 2021).

O mais indicado é a realização de nova biópsia de um a dois anos após o início da DSG, principalmente em indivíduos maiores de 40 anos, pessoas que apresentam formas mais graves da DC ou aqueles com sorologias positivas, buscando confirmar a resposta à dieta (RODRIGO et al., 2018). Porém, a biópsia não é recomendada rotineiramente devido à variabilidade no monitoramento em indivíduos em DSG, ser um exame invasivo, tempo de cicatrização elevado e variação intra-observador da avaliação histológica (ELLI et al., 2024).

A biópsia, ao mesmo tempo em que avalia com segurança a cicatrização da mucosa intestinal e são importantes para avaliar a recuperação da mucosa em adultos com atrofia persistente da vilosidade,também pode demorar de dois a cinco

anos para recuperação completa e poucos estudos sustentam a indicação de rotina por ser um método que expõe a maiores riscos devido a necessidade de sedação e ser dispendioso (AL-TOMA et al., 2019; SADEGHI et al., 2020).

2.4.5 Peptídeos derivados do glúten

A quantificação de peptídeos imunogênicos de glúten (GIP) é um método inovador e recente para monitoramento da adesão à DSG, que pode ser realizado nas fezes ou na urina. Os peptídeos de glúten são pequenos fragmentos parcialmente resistentes à digestão, por isso podem ser identificados na excreção e indicar o consumo de alimentos com glúten. Na clínica, é um exame promissor como marcador de adesão à DSG. Com pesquisas iniciadas nos anos 2000 nos Estados Unidos, os peptídeos podem ser detectados entre o segundo e sétimo dia após ingestão em uma relação dose-dependente (COMINO et al., 2012; MORÓN et al., 2008). Comparado a questionários, sorologia e resposta clínica, foi identificado como um método preciso devido à alta sensibilidade, por ser menos invasivo e apresentar correlação positiva com o consumo de glúten e proporcional à quantidade ingerida (COMINO et al., 2012, 2016a). Na urina, foi descrito como um método sensível e específico para detectar a não adesão à DSG (MORENO et al., 2017a). No entanto, pode ser desconfortável para coleta e ainda não é um teste disponível na prática (MORENO et al., 2017b).

Estudos sugerem que o GIP pode ser incluído como uma avaliação para melhorar a conduta profissional e o descrevem como um importante marcador de monitoramento da adesão, sugerindo uma diminuição nos custos com endoscopias. Porém, ainda são necessárias mais pesquisas de validação, estudos de dose-resposta e dos fatores que influenciam no valor do biomarcador (ELLI et al., 2024; GERASIMIDIS et al., 2018).

Diante do exposto, é evidente a necessidade de identificação de métodos práticos, precisos e válidos para a verificação da adesão à DSG por parte dos indivíduos com DC.

3. OBJETIVOS

3.1 Objetivos geral

Determinar, por meio de revisão sistemática, a ferramenta que melhor prediz a adesão à DSG por indivíduos com DC, em no mínimo seis meses de tratamento.

3.2 Objetivos específicos

- Identificar as ferramentas disponíveis para predição da adesão à DSG por pessoas com DC;
- Avaliar a eficiência das ferramentas utilizadas para determinar a adesão à DSG;
- Comparar as ferramentas de avaliação de adesão à DSG com os testes laboratoriais em indivíduos com DC.

4. MÉTODOS

4.1. Delineamento do estudo

Trata-se de uma revisão sistemática de predição que utilizou a diretriz TRIPOD-SRMA (*Transparente Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis*) para sua construção. Este tipo de revisão busca reunir e resumir estudos para prever resultados de saúde e informar prognóstico ou diagnóstico (SNELL et al., 2023). A revisão foi cadastrada na plataforma de registros de revisão sistemática PROSPERO (*International Prospective Register of Systematic Reviews*), sob o número de parecer CRD42024518034.

As primeiras etapas do estudo consistiram em pesquisa geral sobre o tema, busca de revisão sistemática anterior e viabilidade. A pergunta de pesquisa norteadora foi: “Em adultos com doença celíaca em tratamento (dieta sem glúten) há mais de seis meses, qual ferramenta melhor prediz a adesão ao tratamento, comparado aos exames laboratoriais?”. Foi desenvolvida a estratégia de busca preliminar com as principais palavras-chave, seguindo o acrônimo PICOT (P: pessoa; I: intervenção; C: comparação; O: outcome/resultado e T: tempo), essencial para nortear a viabilidade da realização da revisão sistemática. A partir disso, houve a elaboração da estratégia de busca definitiva para cada base de dados, acrescida dos termos Mesh, DeCS e Emtree, conforme a Tabela de anotações no Apêndice 1, que contém os filtros utilizados na busca.

4.2 Critérios de elegibilidade

Foram incluídos estudos com indivíduos com DC, maiores de 18 anos, que estão em tratamento com DSG há pelo menos seis meses e que utilizaram algum método (questionário, autorrelato, entrevista, avaliação nutricional padronizada) para predizer a adesão à dieta e compararam com algum método laboratorial (TTG, EMA, AGA, GIP ou biópsia).

Os critérios de exclusão foram:

1) Estudos realizados com pessoas menores de 18 anos;
2) Estudos com pessoas com DC em tratamento há menos de seis meses;
3) Artigos de revisão, capítulos de livros e anais de congresso;
4) Estudos sem dados suficientes para extração;
5) Estudos que não avaliaram a adesão à DSG.

4.3 Estratégia de busca e extração de dados

Os estudos primários foram coletados simultaneamente e independentemente pelos Revisores 1 e 2 (R1 e R2) em oito bases científicas: PubMed, EMBASE, LILACS, Web of Science, LIVIVO, SCOPUS, Google Scholar e Proquest. A busca foi realizada usando os termos adequados para cada base de dados (listados no Apêndice 1) sem restrição de idioma e tempo de publicação.

4.4 Gerenciador de referências e seleção

O *software EndNote Web* foi utilizado para organização e primeira remoção de duplicados 100% iguais de forma automática. Em seguida, os trabalhos selecionados foram exportados para o *software* Rayyan (Ouzzani et al., 2016) para as etapas de organização dos dados e remoção dos duplicados de forma manual e para a Seleção Fase 1. As etapas de organização dos dados e remoção dos duplicados foram executadas pelo R1.

Dois revisores independentes (R1 e R2) selecionaram os artigos incluídos em duas fases. A Seleção Fase 1 tratou-se da leitura de títulos e resumos no *software* Rayyan de forma independente, aplicando-se os critérios de elegibilidade. Após isso, foi feita a conferência e julgamento das divergências. A Seleção Fase 2 consistiu na leitura completa dos artigos selecionados na Seleção Fase 1 e busca adicional nas listas de referências dos artigos lidos na íntegra, com intuito de encontrar estudos com potencial elegibilidade para serem incorporados à revisão sistemática em curso. Quando houve divergências, um terceiro revisor (R3) participou antes que uma decisão final fosse tomada em ambas as fases. Na fase de Seleção Fase 2, os critérios de exclusão foram numerados por ordem de importância e, para cada estudo excluído, foi atribuído o número do motivo de exclusão.

4.5 Coleta de dados e análise do risco de viés

Para realizar a coleta de dados dos estudos primários na seleção Fase 2, foi utilizado o *check list* CHARMS (*CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modelling Studies*) (MOONS et al., 2014). Os dados faltantes foram consultados via e-mail diretamente com os autores dos artigos por no máximo três tentativas. A coleta de dados também foi feita de forma independente pelos revisores R1 e R2.

Após a coleta de dados, dois revisores (R1 e R2) preencheram a lista PROBAST (*Predição Risk Of Bias ASsessment Tool*) também de forma independente. O PROAST é uma ferramenta específica para avaliar o risco de viés e a aplicabilidade de estudos de predição prognóstica (WOLFF et al., 2019). A ferramenta possui quatro domínios (participantes, preditores, resultado e análise), com um total de 20 questões conforme o Anexo 1.

Para a extração de dados e geração de tabelas e gráficos foi utilizado um modelo de *Microsoft Excel*® (versão Office 365) de forma independente pelos dois revisores, com uma reunião de consenso ao final. O R3 foi consultado quando houve divergências na decisão. O arquivo para preenchimento consistiu em duas planilhas denominadas template CHARMS e PROBAST, desenvolvida a partir dos estudos anteriores (FERNANDEZ-FELIX et al., 2023).

4.6 Análise estatística e metanálise

A associação entre a adesão à DSG pela ferramenta e o teste laboratorial foi avaliada usando o coeficiente de contingência phi. O coeficiente phi mede a associação entre duas variáveis binárias e assume valores entre -1 e 1, com phi<0 indicando uma associação negativa, phi>0 uma associação positiva e phi=0 indicando nenhuma associação (YULE, 1912). Foi realizada uma meta-análise dos estudos que abordaram a associação da adesão à DSG pela ferramenta e pelos testes laboratoriais. A medida meta-analítica de phi (valor agrupado) foi obtida usando um modelo de efeitos aleatórios.

As estimativas foram obtidas considerando um único agrupamento com todos os estudos e também por subgrupos de acordo com o instrumento adotado. A associação entre a adesão à DSG pela ferramenta e o teste laboratorial foi considerada significativa (em um nível de significância de 5%) quando o intervalo de confiança (IC) 95% não continha o valor zero. Além disso, as associações entre dois subgrupos foram consideradas significativamente diferentes quando seus respectivos ICs não se cruzavam. As análises foram realizadas usando o pacote metafor do programa R, versão 4.4.0 (VIECHTBAUER, 2010).

CAPÍTULO 2

1. RESULTADOS

Os resultados e discussão desta dissertação estão apresentados na forma de artigo científico. O artigo "*Gluten-Free Diet Adherence Tools for Individuals with Celiac disease: A Systematic Review and Metanalysis of tools compared to Laboratory tests*" (RIBEIRO et al., 2024), foi submetido em 21 de junho de 2024.

1.1 Artigo *"Gluten-Free Diet Adherence Tools for Individuals with Celiac Disease : A Systematic Review and Meta-Analysis of Tools Compared to Laboratory Tests"*

nutrients

MDPI

Review

Gluten-Free Diet Adherence Tools for Individuals with Celiac Disease: A Systematic Review and Meta-Analysis of Tools Compared to Laboratory Tests

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Abstract: This systematic review aimed to find the tool that best predicts celiac individuals' adherence to a gluten-free diet (GFD). The Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis (TRIPOD-SRMA) guideline was used for the construction and collection of data from eight scientific databases (PubMed, EMBASE, LILACS, Web of Science, LIVIVO, SCOPUS, Google Scholar, and Proquest) on 16 November 2023. The inclusion criteria were studies involving individuals with celiac disease (CD) who were over 18 years old and on a GFD for at least six months, using a questionnaire to predict adherence to a GFD, and comparing it with laboratory tests (serological tests, gluten immunogenic peptide—GIP, or biopsy). Review articles, book chapters, and studies without sufficient data were excluded. The Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies (CHARMS) was used for data collection from the selected primary studies, and their risk of bias and quality was assessed using the Prediction Risk of Bias Assessment Tool (PROBAST). The association between the GFD adherence determined by the tool and laboratory test was assessed using the phi contingency coefficient. The studies included in this review used four different tools to evaluate GFD adherence: BIAGI score, Coeliac Dietary Adherence Test (CDAT), self-report questions, and interviews. The comparison method most often used was biopsy (n = 19; 59.3%), followed by serology (n = 14; 43.7%) and gluten immunogenic peptides (GIPs) (n = 4; 12.5%). There were no significant differences between the interview, self-report, and BIAGI tools used to evaluate GFD adherence. These tools were better associated with GFD adherence than the CDAT. Considering their cost, application time, and prediction capacity, the self-report and BIAGI were the preferred tools for evaluating GFD adherence.

Keywords: gluten-free diet; celiac disease; treatment adherence; laboratory test

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1. Introduction

Celiac disease (CD) is a chronic autoimmune condition that affects the small intestine with villous atrophy, causing intestinal and extraintestinal symptoms, and is triggered by the ingestion of gluten in genetically predisposed individuals (AL-TOMA et al., 2019; FASANO; CATASSI, 2012). It can trigger severe symptoms of malabsorption and nutritional deficiencies, such as anemia, diarrhea, constipation, short stature, muscular atrophy, and dermatitis herpetiformis, among others (AL-TOMA et al., 2019; ITZLINGER et al., 2018; LUDVIGSSON et al., 2013; SAHIN, 2021). It is estimated that CD affects between 0.7% and 1.4% of the world population and is predominant in females; however, it is considered a neglected and underdiagnosed condition (SAHIN, 2021; SINGH et al., 2018; TARAGHIKHAH et al., 2020).

A gluten-free diet (GFD) is the only current treatment for the disease (BERNARDO; PEÑA, 2012; GALLI et al., 2014a; WIESER et al., 2021). It can reverse the damage caused to the intestinal mucosa, primarily reducing morbidity and improving the quality of life of individuals with CD. GFDs entail completely restricting the consumption of gluten, a protein complex in wheat, rye, and barley, and its derivatives. Given the widespread presence of gluten in confectionery, bakery, pasta, and other industrialized products, adherence to a GFD can become a critical challenge for people affected by CD (ELLI et al., 2024).

Several factors are involved in GFD adherence, such as the level of education received, the patient's own perception and self-efficacy regarding the diet, knowledge, the duration of the GFD, instruction from qualified professionals, social restrictions, and even food labeling. The main reasons for GFD transgression are social events and changes in the food consumption environment (FERNÁNDEZ MIAJA et al., 2021; VILLAFUERTE-GALVEZ et al., 2015a). However, assessing GFD adherence in individuals with CD is still challenging for researchers and health professionals, and how to monitor patients with CD is not well defined (ELLI et al., 2024).

The methods for assessing GFD adherence are diverse and may have advantages and disadvantages. Despite being essential for adult diagnoses and the gold standard for evaluating mucosal recovery, biopsy is an invasive and high-cost method for monitoring the disease (PAGANIZZA et al., 2019). It is believed that it is possible to use alternative and less invasive methods to assess GFD adherence, such as interviews conducted by qualified professionals, the use of questionnaires, serological tests, or screening for gluten-derived peptides (GIPs) in feces or urine (GALLI et al., 2014a; MUHAMMAD; REEVES; JEANES, 2019a; SILVESTER, J.A.; KURADA, S.; SZWAJCER, A.; KELLY, C.P.; LEFFER, D.A.; DUERKSEN, 2017). The serological tests recommended for predicting GFD adherence are tTG antibodies (tissue anti-transglutaminase), EMA (anti endomysium), and anti-DGPs (anti-deamidated gliadin peptides) of the IgA and IgG classes. Their high levels indicate low adherence, but negative values may not confirm strict adherence to the GFD and may be inaccessible in practice due to the lack of testing in healthcare services, patients refusing to have blood samples collected, and the cost (AL-TOMA et al., 2019; ELLI et al., 2024; RODRIGO et al., 2018). The measurement of GIPs in feces and urine is the most recently established method; therefore, it is not yet widely available. It is expensive and has been rejected by patients (ELLI et al., 2024).

GFD adherence must be guided and evaluated by health professionals with experience in CD, especially dietitians, through dietary interviews, food diaries, and questionnaires (ELLI et al., 2024). Questionnaires are simple, quick, and easy instruments that can be applied in clinical practice. Some of them are validated and widely used in studies, with good reliability (BIAGI et al., 2012a; ELLI et al., 2024; GŁADYŚ et al., 2020; LEFFLER et al., 2009a). However, there is no study that recommends the best tool to assess adherence to the DSG or which tool best predicts the GFD adherence of CD individuals, which is why this work is essential for contributing to the scientific literature and monitoring people with CD.

GFD adherence is essential in preventing symptoms, improving the quality of life of individuals with CD, and reducing health costs related to this condition (PAGANIZZA et al., 2019). However, confirming GFD adherence via an unreliable method may pose a risk to individuals with CD in terms of their diet (WIESER et al., 2021). Therefore, looking for a reliable, low-cost, and less invasive tool can

benefit CD individuals, the health professionals who monitor their treatment, and researchers in the field. It is necessary to explore the literature on this topic better, expose the criteria used to evaluate GFD adherence in CD individuals, and, consequently, contribute to improving the monitoring of the dietary treatments used in CD and the quality of life of CD individuals. In this sense, this systematic review aimed to evaluate the non-invasive method that best predicts the adherence of individuals with celiac disease to a gluten-free diet.

2. Materials and Methods

2.1. Study Design

This systematic prediction review used the Transparent Reporting of Multivariable Prediction Models for Individual Prognosis or Diagnosis (TRI-POD-SRMA) guidelines for its construction. This type of review seeks to gather and summarize studies to predict health outcomes and inform prognoses or diagnoses (SNELL et al., 2023). The review was registered on the systematic review registration platform PROSPERO (International Prospective Register of Systematic Reviews) and is being analyzed by it under opinion number CRD42024518034.

The first stages consisted of general research on the topic, a search for previous systematic reviews, and the study feasibility study. The search question was "In adults with celiac disease undergoing treatment (gluten-free diet) for more than six months, which tool best predicts treatment adherence, compared to laboratory tests?". A preliminary search strategy was carried out using the main keywords, following the acronym PICOT (P: person; I: intervention; C: comparison; O: outcome/result; and T: time), which is essential to guide the viability of a systematic review. A definitive search strategy was developed for each database, as well as the terms Mesh, DeCS, and Emtree (Table S1).

2.2. Eligibility Criteria

The following were included: (i) studies on adults older than 18 years old with a CD diagnosis and (ii) who have been undergoing treatment with a GFD for at least six months and (iii) studies which used questionnaires to predict adherence to the diet and compared it with a direct assessment method (tTG, EMA, DGP, GIP, or biopsy). The exclusion criteria were (i) studies carried out on people under 18 years old (ii) who had been on a GFD for less than six months (iii) and had no diagnosis of CD; (iv) review articles, book chapters, and conference proceedings; (v) studies without sufficient data for extraction; (vi) studies that did not evaluate adherence to a GFD.

2.3. Search and Data Extraction Strategy

Reviewers 1 and 2 (R1 and R2) collected the primary studies simultaneously and independently from eight scientific databases: PubMed, EMBASE, LILACS, Web of Science, LIVIVO, SCOPUS, Google Scholar, and Proquest. The search used the appropriate terms for each database (Table S1) without language or publication time restrictions.

2.4. Reference and Selection Manager

EndNote Web software was used to organize and remove 100% identical duplicates automatically. Then, the selected studies were exported to Rayyan software to organize the data and remove duplicates manually, before Phase 1 selection. The steps of organizing the data and duplicate removal were performed only by R1.

Two independent reviewers (R1 and R2) selected the articles to be included in two phases. Phase 1 selection involved independently reading the studies' titles and abstracts in Rayyan software and applying the eligibility criteria. After that, differences were discussed and judged. Phase 2 selection consisted of the complete reading of the articles selected in Phase 1 and an additional search within the reference lists of the articles read in full to find studies with potential eligibility for this review. If disagreements arose in either phase, a third reviewer (R3) evaluated them before making a final decision. During Phase 2 selection, the exclusion criteria were numbered in order of importance, and a numbered reason was assigned to each excluded study.

2.5. Data Collection and Risk of Bias Analysis

To collect data from the primary studies that were included in Phase 2 selection within this study, the CHARMS checklist (CHecklist for critical Appraisal and data extraction for systematic Reviews of prediction Modeling Studies) was used (MOONS et al., 2014). Missing studies were asked for directly by email to the authors, with a maximum of three attempts made. Data collection was also conducted independently by R1 and R2. After data collection, the two reviewers (R1 and R2) completed the PROBAST list (Prediction Risk Of Bias Assessment Tool), also independently (WOLFF et al., 2019).

To extract data and generate tables and graphs, a Microsoft Excel® (Office 365 version) model was independently used by the two reviewers and, at the end, a consensus meeting was held. R3 was consulted to solve divergencies. The file to be completed consisted of two spreadsheets, a template CHARMS and PROBAST, developed in previous studies (FERNANDEZ-FELIX et al., 2023).

2.6. Statistical Analysis and Meta-Analysis

The association between the GFD adherence calculated by the tool and laboratory test was assessed using the phi contingency coefficient. The phi coefficient measures the association between two binary variables and takes values between −1 and 1, with phi < 0 indicating a negative association, phi > 0 a positive association, and phi = 0 indicating no association. A meta-analysis of the studies that addressed the association between the GFD adherence calculated by the tool and laboratory tests was performed. Phi's meta-analytic measurement (grouped value) was obtained using a random effects model.

Point estimates of the grouped phi values and their respective 95% confidence intervals (95% CI) are presented. The estimates were obtained by considering a single grouping of all the studies and also by considering subgroups according to the instrument adopted. The association between the GFD adherence calculated by the tool and laboratory test was considered significant (at a significance level of 5%) when the 95% CI did not contain a zero value. Additionally, the associations between two subgroups were considered significantly different when their respective CIs did not intersect. The analyses were performed using the R program's metafor package , version 4.4.0 (R: A LANGUAGE AND ENVIRONMENT FOR STATISTICAL COMPUTING, [s.d.]).

3. Results

3.1. Study Selection

The database search resulted in 4883 articles, of which 2444 were duplicates. After Phase 1 selection, 2439 articles remained for the reading of their titles and abstracts, 114 of which were read in full and had their bibliographic references consulted (Phase 2 selection). The excluded studies and the reasons for their exclusion are presented in Table S2. Finally, 32 studies were eligible for this systematic review and 31 for a meta-analysis, as shown in the PRISMA flowchart (Figure 1).

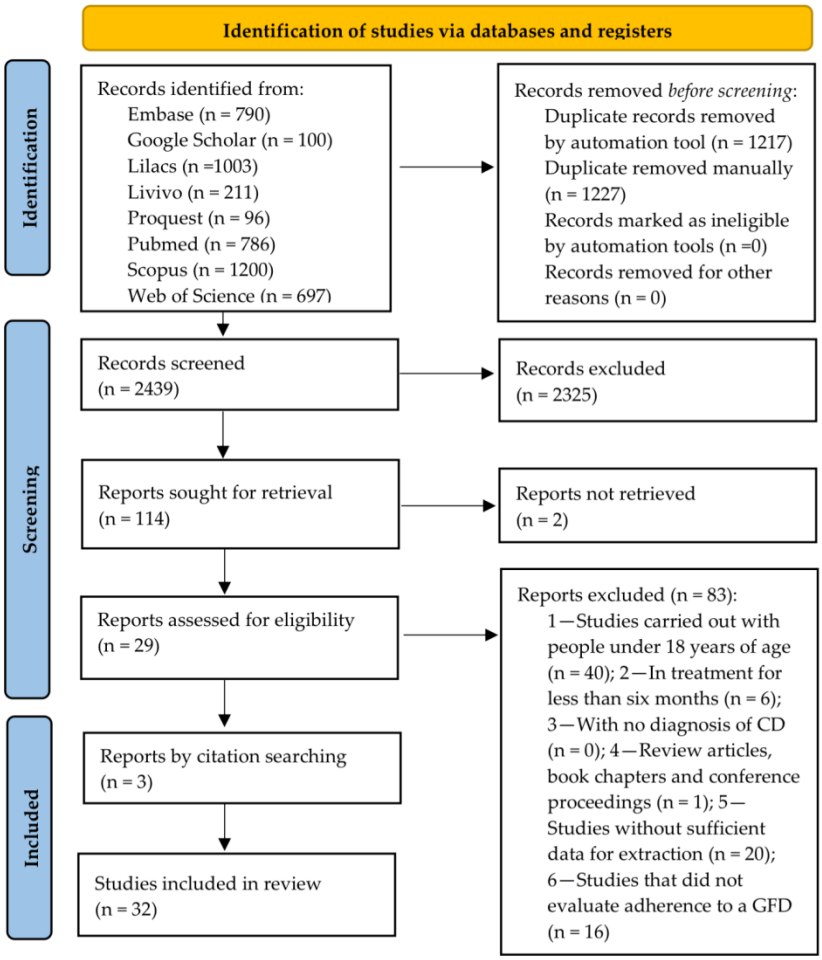

Figure 1. PRISMA flow diagram of literature search and selection criteria.

3.2. The Studies' Characteristics

The studies were performed from 1997 to 2024 and ranged from 18 to 694 (137.82 ± 145.24) participants. Thirty-one studies were characterized as cohort studies, and one was a randomized clinical trial study (Table 1). Most studies were performed in Italy (BIAGI et al., 2009b, 2012b; CIACCI et al., 2002; ELLI et al., 2020; GALLI et al., 2014b; LANZINI et al., 2009; LOMBARDO et al., 2023; MARSILIO et al., 2020; NORSA et al., 2018; SCHIEPATTI et al., 2023a; STASI et al., 2016; USAI et al., 2002) (n = 13; 40.6%), followed by Finland (KAUKINEN et al., 2002; METSO et al., 2012; PEKKI et al., 2017; VILJAMAA et al., 2005) (n = 4; 12.5%), the United Kingdom (COLEMAN et al., 2021; HUTCHINSON et al., 2010; SCHIEPATTI et al., 2023a), and the United States (GONG et al., 2023; SCHIEPATTI et al., 2023a; VILLAFUERTE-GALVEZ et al., 2015a) (n = 3, 9.3%), Argentina (BAI et al., 1997; NACHMAN et al., 2011), Australia (NEWNHAM et al., 2016; RUSSELL et al., 2024b), Canada (DUERKSEN et al., 2010; SILVESTER et al., 2020), Norway (HÆRE et al., 2016; SKODJE et al., 2022) (n = 2, 6.25%), while Paraguay, Poland, Romania, Spain, and Türkiye had one study each (FERREIRA et al., 2018; GŁADYŚ et al., 2020; NEMTEANU et al., 2023; SAYAR et al., 2021; SCHIEPATTI et al., 2023a).

The studies included in this review used four different tools to evaluate GFDs: BIAGI scores (BIAGI et al., 2009b), the Coeliac Dietary Adherence Test (CDAT) (LEFFLER et al., 2009b), self-report questionnaires, and interviews. Most of them used a biopsy (BIAGI et al., 2009b, 2012a; CIACCI et al., 2002; COLEMAN et al., 2021; DUERKSEN et al., 2010; GALLI et al., 2014a; GŁADYŚ et al., 2020; GONG et al., 2023; HÆRE et al., 2016; HUTCHINSON et al., 2010; KAUKINEN et al., 2002; LANZINI et al., 2009; METSO et al., 2012; NEMTEANU et al., 2023; NEWNHAM et al., 2016; NORSA et al., 2018; PEKKI et al., 2017; SCHIEPATTI et al., 2023a; STASI et al., 2016) (n = 19; 59.3%), followed by serology

(BAI et al., 1997; BIAGI et al., 2009a, 2012b; ELLI et al., 2020; FERREIRA et al., 2018; GALLI et al., 2014b; KAUKINEN et al., 2002; MARSILIO et al., 2020; NACHMAN et al., 2011; SAYAR et al., 2021; STASI et al., 2016; USAI et al., 2002; VILJAMAA et al., 2005; VILLAFUERTE-GALVEZ et al., 2015b) (n = 14; 43.7%) and GIPs (LOMBARDO et al., 2023; RUSSELL et al., 2024b; SILVESTER et al., 2020; SKODJE et al., 2022) (n = 4; 12.5%). Of the 32 studies, most (n = 45; 46.8%) used the self-report method to evaluate GFD adherence (BAI et al., 1997; DUERKSEN et al., 2010; ELLI et al., 2020; FERREIRA et al., 2018; HUTCHINSON et al., 2010; KAUKINEN et al., 2002; LANZINI et al., 2009; NACHMAN et al., 2011; NEMTEANU et al., 2023; NEWNHAM et al., 2016; NORSA et al., 2018; PEKKI et al., 2017; SAYAR et al., 2021; STASI et al., 2016; VILJAMAA et al., 2005), followed by the CDAT (COLEMAN et al., 2021; GŁADYŚ et al., 2020; HÆRE et al., 2016; LOMBARDO et al., 2023; RUSSELL et al., 2024b; SILVESTER et al., 2020; SKODJE et al., 2022; VILLAFUERTE-GALVEZ et al., 2015b) (n = 8; 25%), BIAGI (BIAGI et al., 2009b, 2012b; COLEMAN et al., 2021; GALLI et al., 2014b; MARSILIO et al., 2020) (n = 5; 15.6%), and interviews (CIACCI et al., 2002; GONG et al., 2023; METSO et al., 2012; USAI et al., 2002) (n = 4; 12.5%), while only one used the Standardized Dietitian Evaluation (SDE) (GŁADYŚ et al., 2020) and one of the studies used both the BIAGI and CDAT tools (SCHIEPATTI et al., 2023a).

Table 1. Baseline characteristics of the studies included.

Author, Year	Study Design	Enrolment Period	Country	n	Females (n)	Age	GFD Period (Month)	GFD Adherence Tool	%Adherence Using the Tool	Laboratory Test	%Adherence Using the Laboratory Test
Biagi et al., 2009 (BIAGI et al., 2009b)	Cohort	NI	Italy	168 162	126 NI	42.4 ± 13.9	82 (15–389)	BIAGI	79.7	Biopsy EMA	91 70.3
Biagi et al., 2012 (BIAGI et al., 2012b)	Cohort	2008–2011	Italy	141	108	34 ± 15	27 (6–298)	BIAGI	82.2	Biopsy EMA	85.8 73
Galli et al., 2014 (GALLI et al., 2014b)	Cohort	2009–2012	Italy	65 57	47 NI	38 (18–70)	12	BIAGI	81.5	Biopsy EMA/tTG	67.6 70
Marsilio et al., 2020 (MARSILIO et al., 2020)	Cohort	2020	Italy	100	86	39.73 ± 13.51	79.68 ± 76.68	BIAGI	90	tTG	85
Coleman et al., 2021 (COLEMAN et al., 2021)	Cohort	2013–2019	UK	201	136	50.3	>30	BIAGI	91	Biopsy	68.6
Villafuerte-Galvez et al., 2015 (VILLAFUERTE-GALVEZ et al., 2015a)	Cohort	2011–2012	USA	118	NI	53.6 ±1 15.4	118.8 ± 76.8	CDAT	73.7	tTG	82
Haere et al., 2016 (HÆRE et al., 2016)	Cohort	NI	Norway	127	79	55 ± 14	111.6 ± 60	CDAT	46.4	Biopsy	94.4
Gladys et al., 2020 (GŁADYŚ et al., 2020)	Cohort	2015–2018	Poland	44	38	40.8	78 ± 86.4	CDAT	47.7	Biopsy	56.8
Silvester et al., 2020 (SILVESTER et al., 2020)	Cohort	NI	Canada	18	12	41 (21–77)	24	CDAT	77.7	uGIPs fGIPs	33.3
Coleman et al., 2021 (COLEMAN et al., 2021)	Cohort	2013–2019	England	201	136	50.3	>30	CDAT	49.7	Biopsy	68.6
Skodje et al., 2022 (SKODJE et al., 2022)	Cohort	NI	Norway	70	59	45	12	CDAT	53	fGIPs	91.4
Lombardo et al., 2023 (LOMBARDO et al., 2023)	Cohort	2019–2020	Italy	280	232	42.9	133.2 ± 122.4	CDAT	69.2	uGIPs	88.5
Russell et al., 2024 (RUSSELL et al., 2024b)	RCT	2020–2021	Australia	51	36	55 (44–62)	120 (60–168)	CDAT	72.5	fGIPs	23.5
Schiepatti et al., 2023 (SCHIEPATTI et al., 2023a)	Cohort	2020–2022	Italy, Spain, UK, USA	694	491	>18	32 (15–61)	CDAT/BIAGI	83.5	Biopsy	77.3
Ciacci et al., 2002 (CIACCI et al., 2002)	Cohort	2002	Italy	390	299	27.9 ± 10.9	82.8 ± 90	Interview	42.5	Biopsy	76
Usai et al., 2002 (USAI et al., 2002)	Cohort	2002	Italy	66	66	46 (18–74)	>24	Interview	59	EMA/AGA	57.5
Metso et al., 2012 (METSO et al., 2012)	Cohort	2003–2006	Finland	26	22	>45	>12 meses	Interview	92.3	Biopsy	100

Gong et al., 2023 (GONG et al., 2023)	Cohort	2008–2019	USA	106	66	43.9	84	Interview	74.5	Biopsy	54.7
Gladys et al., 2020 (GŁADYŚ et al., 2020)	Cohort	2020	Italy	44	38	40.8	78 ± 86.4	SDE	75	Biopsy	56.8
Bai et al., 1997 (BAI et al., 1997)	Cohort	1997	Argentina	22	NI	44 (21–73)	47 (23–75)	Self-reported	59	EMA/tTG	95.4
Kaukinen et al., 2002 (KAUKINEN et al., 2002)	Cohort	2002	Finland	57 87 87	NI 63 63	49 (22–73)	12 (12–216)	Self-reported	80.7 87.3 87.3	Biopsy EMA tTG	52.6 87.3 73.3
Viljamaa et al., 2005 (VILJAMAA et al., 2005)	Cohort	NI	Finland	97	51	51	144	Self-reported	83	tTG	91.7
Lanzini et al., 2009 (LANZINI et al., 2009)	Cohort	2009	Italy	465	356	31 (18–81)	16 (13–222)	Self-reported	85.8	Biopsy	79.5
Duerksen et al., 2010 (DUERKSEN et al., 2010)	Cohort	NI	Canada	21	19	50.5	116.4	Self-reported	71.4	Biopsy	71.4
Hutchinson et al., 2010 (HUTCHINSON et al., 2010)	Cohort	2009	UK	234	202	>18	34.8	Self-reported	88	Biopsy	35
Nachman et al., 2011 (NACHMAN et al., 2011)	Cohort	2004–2005	Argentina	53	48	18–66	12 48 12 48	Self-reported	60.3 52.8 60.3 52.8	TTG TTG tTG/DGP tTG/DGP	62.2 49 79.2 71.7
Newnham et al., 2016 (NEWNHAM et al., 2016)	Cohort	NI	Australia	44	NI	40 (18–71)	60	Self-reported	97.7	Biopsy	16
Stasi et al., 2016 (STASI et al., 2016)	Cohort	NI	Italy	39 52	NI	40	66 (13–261)	Self-reported	53.8 86.5	Biopsy EMA	84.6 75
Pekki et al., 2017 (PEKKI et al., 2017)	Cohort	NI	Finland	476	NI	55	96	Self-reported	98.7	Biopsy	58
Ferreira et al., 2018 [53]	Cohort	2015–2017	Paraguay	72	55	35.6 ± 12.4	294	Self-reported	68	tTG	44.4
Norsa et al., 2018 (NORSA et al., 2018)	Cohort	2014–2015	Italy	63	NI	31.34	320 (1–432)	Self-reported	46	Biopsy	74.6
Elli et al., 2020 (ELLI et al., 2020)	Cohort	2017–2018	Italy	197	159	44.6	87 ± 74	Self-reported	75.6	tTG	94.4
Sayar et al., 2021 (SAYAR et al., 2021)	Cohort	2010	Türkiye	78	68	36.8 ± 7.7	31	Self-reported	78.2	EMA/tTG	59
Nemteanu et al., 2023 (NEMTEANU et al., 2023)	Cohort	2016–2021	Romania	102	79	39.54 ± 12.70	22.6	Self-reported	27.4	tTG	71.5

Abbreviation: BIAGI = Biagi score; CDAT = Coeliac Dietary Adherence Test; GFD = gluten-free diet; SDE = Standardized Dietician Evaluation; AGA = gliadin antibody; tTG = tissue anti-transglutaminase antibody; EMA = anti-endomysium antibody; DGP = anti-deamidated gliadin peptide; fGIPs = gluten-derived peptides in feces; uGIPs = gluten-derived peptides in urine; RCT = randomized clinical trial; NI = no information.

3.3. Meta-Analysis

The results of the meta-analysis of the association between the GFD adherence calculated by the tool and laboratory tests are shown in Table 2 and Figure 2.

One study was excluded from the subgroup analysis because it used two instruments simultaneously (CDAT and BIAGI) and it was impossible to separate the data (SCHIEPATTI et al., 2023a). There were no significant differences between the interview, self-report, and BIAGI tools used to evaluate GFD adherence. These tools were better associated with GFD adherence than the CDAT. The Standardized Assessment of Dietitians (SDE) did not demonstrate an association with adherence to a GFD. However, it was evaluated in only one study and did not show statistically significant differences from any other instrument.

Table 2. Meta-analysis results for the association between the GFD adherence calculated by tools and laboratory tests.

	Number of Studies	**Grouped Estimation Phi (CI 95%)**
TOTAL	42	0.297 (0.220; 0.372)
Tool used to evaluate GFD adherence *		
CDAT	8	0.112 (0.032; 0.192) ^{A}
SDE	1	0.238 (−0.051; 0.528) ^{AB}
BIAGI	8	0.242 (0.073; 0.410) ^{AB}
Self-report	21	0.308 (0.209; 0.406) ^{B}
Interview	3	0.641 (0.380; 0.903) ^{B}
Laboratory test used to evaluate GFD adherence		
GIP	4	0.088 (−0.031; 0.207) ^{A}
Biopsy	20	0.264 (0.163; 0.365) ^{AB}
Serological (TTG, EMA, AGA)	18	0.378 (0.256; 0.501) ^{B}
Tool X laboratory test *		
BIAGI and Serological	4	0.066 (−0.126; 0.258) ^{A}
CDAT and GIP	4	0.088 (−0.031; 0.207) ^{A}
Self-report and Biopsy	9	0.116 (0.016; 0.216) ^{A}
CDAT and Biopsy	3	0.126 (−0.053; 0.304) ^{AB}
CDAT and Serological	1	0.226 (0.027; 0.425) ^{ABC}
SDE and Biopsy	1	0.238 (−0.051; 0.528) ^{ABC}
BIAGI and Biopsy	4	0.410 (0.268; 0.551) ^{BC}
Self-report and Serological	12	0.467 (0.384; 0.551) ^{C}
Interview and Biopsy	2	0.489 (0.419; 0.559) ^{C}
Interview and Serological	1	0.903 (0.796; 1.000) ^{D}

* The study by Schiepatti et al. (2023) (SCHIEPATTI et al., 2023a) adopted the CDAT/BIAGI questionnaires; therefore, it does not fit (in isolation) into either instrument. Groups with the same letters do not differ significantly. Abbreviations: BIAGI = Biagi score; CDAT = Coeliac Dietary Adherence Test; GFD = gluten-free diet; SDE = Standardized Dietician Evaluation; AGA = gliadin antibody; TTG = tissue anti-transglutaminase antibody; EMA = anti-endomysium antibody;; GIP = gluten-derived peptide; CI = confidence interval.

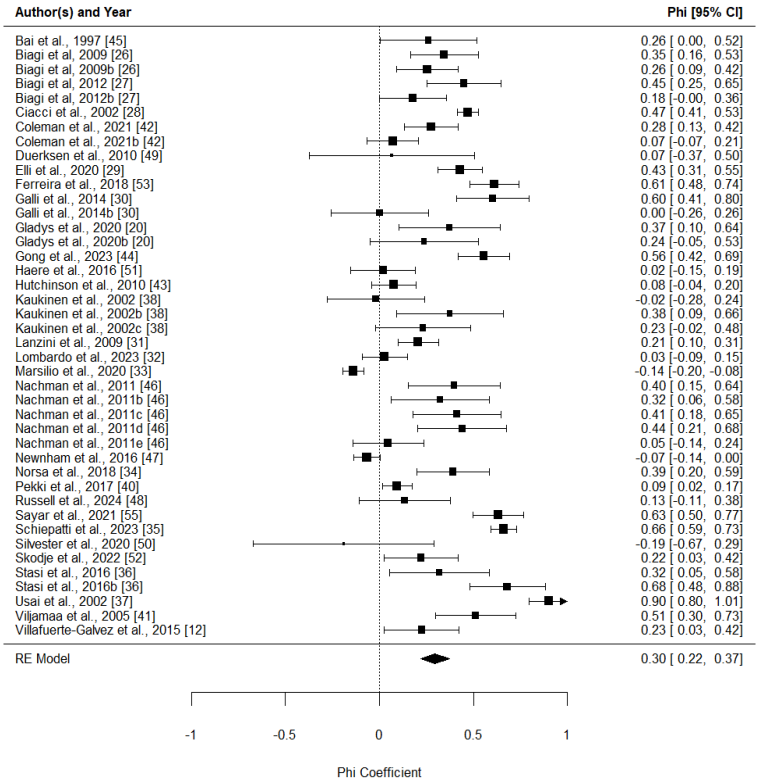

Figure 2. Forest plot of the phi coefficients of the association between the adherence measured with the tools and the adherence measured with the laboratory tests (42 studies).

3.4. Risk of Bias and Concern

Figures 3 and 4 present the analysis of the risk of bias and concern in the included studies, classified according to PROBAST (WOLFF et al., 2019). In total, 50% (n = 16) of the included studies demonstrated a low risk of bias (BAI et al., 1997; BIAGI et al., 2012a; COLEMAN et al., 2021; ELLI et al., 2020; FERREIRA et al., 2018; GŁADYŚ et al., 2020; HÆRE et al., 2016; LANZINI et al., 2009; LOMBARDO et al., 2023; NACHMAN et al., 2011; NEMTEANU et al., 2023; NORSA et al., 2018; RUSSELL et al., 2024a; SCHIEPATTI et al., 2023b; VILLAFUERTE-GALVEZ et al., 2015c). A high risk of bias was identified in four studies (METSO et al., 2012; SILVESTER et al., 2020; STASI et al., 2016; USAI et al., 2002), one of which used the self-report method (STASI et al., 2016), another an interview (USAI et al., 2002), and another the CDAT (SILVESTER et al., 2020).

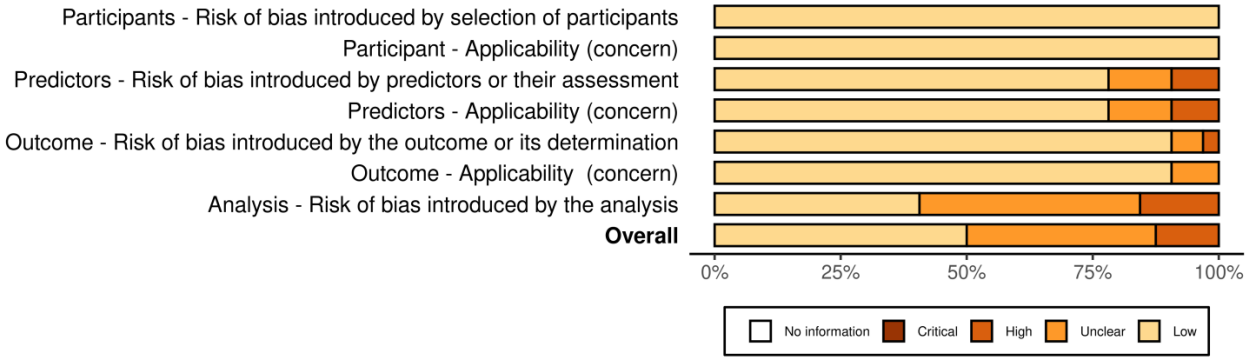

Figure 3. Risk of bias and concern in the included studies by domain, classified according to PROBAST.

Figure 4. Risk of bias and applicability of the included studies, classified according to PROBAST.

4. Discussion

This is the first systematic review with a meta-analysis to evaluate which non-invasive method best predicts the gluten-free diet adherence of individuals with celiac disease. Most studies were performed (n = 25; 78%) in Europe, and mainly in Italy (n = 12; 37.5%). Even though CD is considered a major worldwide public health problem and its prevalence varies by sex, age, and geographic location, the global estimates show that most of the population with CD is found in European countries (SAHIN, 2021; SINGH et al., 2018), which justifies the large number of studies in Europe. In addition, about twenty years ago, Italy was considered the birthland of CD epidemiology due to the serological screening of its population; therefore, several studies on CD have been performed in this country (LIONETTI et al., 2023; VOLTA et al., 2001).

Four methods were used in the studies and compared to laboratory tests: the CDAT, BIAGI, self-reports, and interviews. The self-report method was the most used tool to evaluate GFD adherence (BAI et al., 1997; DUERKSEN et al., 2010; ELLI et al., 2020; FERREIRA et al., 2018; HUTCHINSON et al., 2010; KAUKINEN et al., 2002; LANZINI et al., 2009; NACHMAN et al., 2011; NEMTEANU et al., 2023; NEWNHAM et al., 2016; NORSA et al., 2018; PEKKI et al., 2017; SAYAR et al., 2021; STASI et al., 2016; VILJAMAA et al., 2005). This method is characterized by an individual reporting whether or not they adhere to a GFD, in a dichotomous way (yes or no) or using a Likert scale (from never to always), or reporting their food intake through three-, four-, or seven-day food records to be analyzed or a dietary history. The dichotomous and Likert-scale methods used to evaluate GFD adherence are related to perceived adherence to the GFD, and their advantages are accessibility, quickness, and simplicity. However, records or dietary histories may take more time and be more complex, despite being helpful in evaluating food quality (BARONE et al., 2016). Although a food diary with a dietary interview was indicated by a study to adequately assess GFD adherence (ELLI et al., 2024), the lack of classification standardization, the need for an expert, and memory bias can become barriers in practice. Self-reported adherence was positively correlated with dietitian assessments but not with the CDAT, according to authors (ATSAWARUNGRUANGKIT et al., 2020). However, some authors consider a self-report method for assessing GFD adherence problematic, since individuals with CD can incorrectly report (intentionally or not) their level of GFD adherence, leading to an over- or underestimation of their adherence to a GFD (SILVESTER et al., 2016). A prospective comparative study comparing the predictive value of self-reported GFD adherence to serological tests and expert dietitian evaluations showed that self-reporting is less reliable than serological tests, biopsies, and dietitian evaluations (LEFFLER et al., 2007). Despite this, our systematic review showed that self-reported GFD adherence did not differ from the BIAGI score and interviews and presented better accuracy than the CDAT tool. A structured interview conducted by a qualified professional can be a sensitive method for assessing GFD adherence, either through an SDE or through the self-reporting of diet by individuals with CD (AL-TOMA et al., 2019; WIESER et al., 2021), as confirmed by our results. The SDE consists of a tool composed of structured questions, with food records lasting up to three days, assessing the patient's ability to identify gluten in foods or other products, such as medicines and cosmetics. The disadvantages are that the SDE is subjective, takes more time, and a specialist is not always available in health services.

The BIAGI score was developed and validated in Italy in 2012 by a multicenter study (BIAGI et al., 2009b, 2012a). Five studies included in this review used the BIAGI tool (BIAGI et al., 2009b, 2012b; COLEMAN et al., 2021; GALLI et al., 2014b; MARSILIO et al., 2020). Four simple questions were developed based on the researchers' clinical experience. One of the advantages is that the instrument can be applied even by those with no experience in CD and GFDs (BIAGI et al., 2012a). Studies have been using this tool with satisfactory reproducibility results (MORENO et al., 2017b; PAGANIZZA et al., 2019; SBRAVATI et al., 2020). Its classification varies from 0 to 4, with 0–1 points for those who do not follow a strict GFD; 2 points for those following a GFD but with important errors that require correction, and 3–4 points for those following a strict GFD. The authors state that it is possible to apply

this to different ethnicities, with the last question (Do you only eat packaged foods guaranteed by the Celiac Association?) able to be omitted without affecting the final result in some countries, as local celiac societies may not provide lists of gluten-free packaged foods. Therefore, when validating the BIAGI tool in each country it will be applied as necessary.

The CDAT was created in 2009 in the USA from a meeting of specialists (gastro-enterologists, dietitians, psychologists, and CD individuals) to assess GFD adherence specifically [19]. After the meeting, they chose the five most important domains for evaluating GFD adherence: (1) symptoms related to CD, (2) specific knowledge of the disease, (3) self-efficacy, (4) reasons for maintaining a GFD, and (5) perceived adherence to the GFD. The CDAT consists of a seven-item questionnaire on a scale of 1 to 5. The minimum score is seven, and the maximum score is 35 points, with less than 13 points indicating good adherence (LEFFLER et al., 2009a). This instrument has been translated into Spanish, Polish, and Norwegian (FUEYO DÍAZ et al., 2016; GŁADYŚ et al., 2020; HÆRE et al., 2016; JOHANSSON et al., 2019), which are important for comparing different populations. However, its application takes time due to the number of items it contains and, in this systematic review, the CDAT presented the lowest association with laboratory tests.

The guidelines for celiac disease highlight that monitoring must be carried out through clinical evaluation, laboratory tests, and serology (AL-TOMA et al., 2019; RAITERI et al., 2022; RUBIO-TAPIA et al., 2023). The normalization of laboratory tests indicates the remission of the disease, but the negativation of the tests is not immediate, and each test also has disadvantages that can limit its results. The quantification of antibodies, such as tTG, EMA, and DGP, is strongly recommended due to their high specificity and sensitivity (ELLI et al., 2024; LEFFLER; SCHUPPAN, 2010). Even though negative values cannot confirm a lack of exposure to gluten (ELLI et al., 2024), it is evident that antibody values gradually decrease after months of a GFD (NACHMAN et al., 2011). Therefore, serology alone is not indicated to determine strict adherence to a gluten-free diet, and normalization does not indicate mucosal recovery (ELLI et al., 2024; SILVESTER, J.A.; KURADA, S.; SZWAJCER, A.; KELLY, C.P.; LEFFER, D.A.; DUERKSEN, 2017).

Biopsy is considered the gold standard for evaluating mucosal healing; however, its invasive and high-cost nature means that the exam is not mandatory in monitoring CD, and the mucosal recovery time after a GFD is slow. Moreover, it varies for each individual. Studies differ on the indication period for biopsy, varying between repeating the biopsy after two years on a gluten-free diet or when symptoms and serological levels are altered (ELLI et al., 2024; LUDVIGSSON et al., 2014; RAITERI et al., 2022; RUBIO-TAPIA et al., 2023). In this systematic review, most of the studies performed a biopsy after a gluten-free diet was maintained for more than two years (CIACCI et al., 2002; COLEMAN et al., 2021; DUERKSEN et al., 2010; GŁADYŚ et al., 2020; GONG et al., 2023; HÆRE et al., 2016; HUTCHINSON et al., 2010; NEWNHAM et al., 2016; PEKKI et al., 2017), which minimized the bias in the results.

Quantifying GIPs in feces and urine is a promising test that has also detected involuntary gluten consumption (COMINO et al., 2016b; MONACHESI et al., 2021; RUSSELL et al., 2024a) and is recommended as a good direct approach to assessing adherence to a gluten-free diet and is helpful when available (AL-TOMA et al., 2019; ELLI et al., 2024); however, few studies used this comparator (LOMBARDO et al., 2023; RUSSELL et al., 2024a; SILVESTER et al., 2020; SKODJE et al., 2022). More studies are needed due to the individual variability in gluten metabolization and as their detectable time after ingestion is short (up to seven days) (ELLI et al., 2024). The consensus is that monitoring should be carried out frequently to assess the response to treatment and the adherence to a gluten-free diet (AL-TOMA et al., 2019; NACHMAN et al., 2011; RAITERI et al., 2022; RUBIO-TAPIA et al., 2023). Therefore, searching for less invasive, low-cost, and fast instruments to evaluate GFD adherence is essential.

This systematic review also has limitations. By including only studies on individuals over 18 years of age with celiac disease, many studies with the potential for analyzing the prediction of these instruments may have been excluded. Although biopsy is the gold standard for visualizing mucosal recovery, it can take up to five years for complete recovery in adults (RODRIGO et al., 2018; WIESER

et al., 2021), which may have been a barrier in articles that used biopsy as a comparator over a short period for adherence assessments. In addition, the use of different methods (biopsy, serological, and GIP tests) may be a potential limitation, since the studies did not use the same method to evaluate GFD adherence. In order to minimize this, the tests were analyzed separately (Table 2).

A high risk of bias was only identified in four studies (METSO et al., 2012; SILVESTER et al., 2020; STASI et al., 2016; USAI et al., 2002), and the concern was relatively low among the included studies. Accurately determining adherence to a GFD remains a challenge, particularly with respect to unintentional consumption. Both self-reports and tools rely on prior knowledge about the presence of gluten in foods, and this knowledge is not always accurate (SILVESTER et al., 2016). However, a standardized and straightforward tool facilitates the monitoring of individuals with celiac disease and guides professionals toward better management practices. Therefore, through this systematic review and meta-analysis, it is possible to emphasize the importance of using practical tools capable of predicting adherence to a GFD, thereby ensuring the effective monitoring of individuals with celiac disease.

5. Conclusions

There were no significant differences between the interview, self-report, and BIAGI tools used to evaluate GFD adherence. These tools were better associated with GFD adherence than the CDAT.

Considering their cost, application time, potential accuracy of the level of GFD adherence, and prediction capacity, the self-report and BIAGI tools were considered the preferred tools to evaluate GFD adherence. These instruments are questionnaires completed by individuals. The evaluated tools depend on the CD patient's responses in interviews or to questionnaires; therefore, it is necessary to raise awareness about the importance of accurately filling out these questionnaires and to expand patients' knowledge about foods and the gluten-free diet to obtain the most accurate responses. Furthermore, additional studies are required to create standardized methods for evaluating diet adherence in various regions. These methods should be easily translatable and validated in multiple languages. They should also be simple to implement and highly accurate.

Supplementary Materials: The following supporting information can be downloaded at www.mdpi.com/xxx/s1, Table S1: Database search strategy; Table S2: Excluded references and reasons.

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CAPÍTULO 3

1. CONCLUSÃO E CONSIDERAÇÕES FINAIS

Verificou-se que as ferramentas apresentadas são úteis para avaliar a adesão à DSG, sobretudo quando exames laboratorias não estão disponíveis. São consideradas métodos confiáveis, fáceis e de baixo custo que permitem melhor monitoramento de pessoas com DC. Dois instrumentos (CDAT e pontuação BIAGI) são validados em diferentes idiomas, porém nenhum para o português. Além disso, há uma predominância de estudos no ocidente, concentrado na Europa, principalmente na Itália; poucos de estudos no sul global e ausência na Ásia para os critérios estabelecidos.

Não houve diferença estatisticamente significativa entre a avaliação da adesão à DSG por entrevista, autorreferida e pontuação BIAGI. O CDAT foi a ferramenta com menor poder de predição de adesão à DSG quando comparado aos testes laboratoriais. Este instrumento é mais extenso, com avaliação por sete itens e cinco classificações para cada item, totalizando até 35 pontos. O questionário BIAGI consiste em quatro questões com até quatro pontos no total. Nesse sentido, a pontuação BIAGI é mais simples de ser aplicada e com melhor resultado estatístico para predição da adesão à DSG. Entrevistas e a adesão autorreferida também demonstram bom poder de predição, ou seja, podem ser utilizadas quando os questionários não estiverem disponíveis. Porém, também apresentam limitações: a entrevista depende do profissional e seu conhecimento técnico da DSG.Além disso, o tempo de aplicação pode ser elevado e pode haver variação interprofissionais. A adesão autorreferida é simples, no entanto depende do conhecimento fidedigno e percepção do indivíduo sobre o tratamento da DC.

Os questionários são formas práticas de avaliação da adesão à DSG que dependem do conhecimento prévio do entrevistado sobre o tratamento da DC e de uma boa investigação e identificação do profissional. Por isso, é importante reforçar a ampla divulgação e educação sobre a DC. Nesse sentido, se faz necessária a condução demais estudos para uma possível padronização de instrumento que possa ser aplicado em diferentes culturas, com boa acurácia e reprodutibilidade.

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3. APÊNDICES

APÊNDICE 1 – tabela de anotações da estratégia de busca de cada base de dado.

TABELA DE ANOTAÇÕES

BASE DE DADOS	ESTRATÉGIA DE BUSCA (16/11/2023)	RESULTADOS
PubMed 16/11/2023 14:15:26 Filter: All Fields	("celiac disease"[MeSH Terms] OR "celiac disease"[All Fields] OR "Gluten Enteropathy"[All Fields] OR "Gluten Enteropathies"[All Fields] OR "gluten sensitive enteropathy"[All Fields] OR "Gluten-Sensitive Enteropathies"[All Fields] OR "gluten sensitive enteropathy"[All Fields] OR "Gluten-Sensitive Enteropathies"[All Fields] OR "Celiac Sprue"[All Fields] OR "Nontropical Sprue"[All Fields] OR "Sprue"[All Fields] OR "Coeliac disease"[All Fields] OR "gluten-related disorders"[All Fields]) AND ((((("diet, gluten free"[MeSH Terms] OR "Diet Therapy"[MeSH Terms:noexp] OR "Adherence"[All Fields] OR "Adherence Test"[All Fields]) AND "gluten-free diet"[All Fields]) AND "gluten-free diet"[All Fields]) OR "gluten free diets"[All Fields] OR "gluten free diets"[All Fields] OR "Compliance"[All Fields] OR "Diet Therapy"[All Fields] OR "dietary adherence"[All Fields] OR "effectiveness"[All Fields] OR "dietitian assessment"[All Fields]) AND ("Surveys and Questionnaires"[MeSH Terms] OR "Survey Methods"[All Fields] OR "Survey Method"[All Fields] OR "Survey Methodology"[All Fields] OR "Community Surveys"[All Fields] OR "Community Survey"[All Fields] OR "Community Survey"[All Fields] OR "Survey"[All Fields] OR "Questionnaire Design"[All Fields] OR "Questionnaire Designs"[All Fields] OR "Questionnaires"[All Fields] OR "Questionnaire"[All Fields] OR "validation study"[All Fields] OR "Validation Studies"[All Fields] OR "structured questionnaires"[All Fields] OR "survey studies"[All Fields])	786
LILACS Filtro: título, resumo assunto	("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND ("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND ("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Disign" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")	1003
SCOPUS Filtro: titl-abs-key	TITLE-ABS-KEY ("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR	1200

	"enteropatía por gluten") AND TITLE-ABS-KEY ("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND TITLE-ABS-KEY ("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Disign" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")	
LIVIVO Filtro: exceto medline	(("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND ("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND ("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Design" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")) OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta"))	211
EMBASE Filtro: lim medline	#4. #1 AND #2 AND #3 #3. 'surveys and questionnaires'/de OR 'surveys and questionnaires' OR 'survey methods' OR 'survey method' OR 'survey methodology'/de OR 'survey methodology' OR 'community surveys'/de OR 'community surveys' OR 'community survey' OR 'survey'/de OR 'survey' OR 'questionnaire design'/de OR 'questionnaire design' OR 'questionnaire disign' OR 'questionnaire designs' OR 'questionnaires'/de OR 'questionnaires' OR 'questionnaire'/de OR 'questionnaire' OR 'validation study'/de OR 'validation study' OR 'validation studies'/de OR 'validation studies' OR 'structured questionnaires' OR 'survey studies' OR 'inquéritos e questionários' OR 'encuestas y cuestionarios' OR 'cuestionario' OR 'encuesta' #2. 'adherence'/de OR 'adherence' OR 'adherence test' OR 'gluten-free diet'/de OR 'gluten-free diet' OR 'gluten free diet'/de OR 'gluten free diet' OR 'gluten-free diets' OR 'compliance'/de OR 'compliance' OR 'diet therapy'/de OR 'diet therapy' OR 'dietary adherence'/de OR 'dietary adherence' OR 'effectiveness' OR 'dietitian assessment' OR 'dieta sin gluten' OR 'dieta livre de glúten' #1. 'celiac disease'/de OR 'celiac disease' OR 'gluten enteropathy'/de OR 'gluten enteropathy' OR 'gluten enteropathies' OR 'gluten-sensitive enteropathy'/de OR 'gluten-sensitive enteropathy' OR 'gluten sensitive enteropathy'/de OR 'gluten sensitive enteropathy' OR 'gluten-sensitive enteropathies' OR 'celiac sprue'/de OR	790

	'celiac sprue' OR 'nontropical sprue'/de OR 'nontropical sprue' OR 'sprue'/de OR 'sprue' OR 'coeliac disease'/de OR 'coeliac disease' OR 'gluten-related disorders' OR 'doença celíaca' OR 'enfermedad celíaca' OR 'enteropatia glúten intuzida' OR 'espru celíaco' OR 'enteropatía por gluten'	
WEB OF SCIENCE Filtro: topic	TS=("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND TS=("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND TS=("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Design" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")	697
GOOGLE SCHOLAR 04/11 Filtro: file	(("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Celiac Sprue" OR "Coeliac disease") AND ("Diet therapy" OR "Adherence" OR "gluten-free diet" OR "Compliance" OR "dietary adherence") AND ("Surveys and Questionnaires" OR "Survey" OR "Questionnaire" OR "validation study" OR "structured questionnaires"))	100
PROQUEST Filtro: qualquer lugar Tipo de fonte: todos Tipo de documento: dissertação/tese Idioma: todos	("Celiac disease" OR "Gluten Enteropathy" OR "Coeliac disease") AND ("Diet therapy" OR "Adherence" OR "Compliance") AND ("Survey" OR "Questionnaire")	96
Total		4883
Duplicados automático		1217
Sem duplicados automático		3666
Duplicados manual		1227
Final sem duplicados		2439

4 ANEXOS

ANEXO 1 - Predição Risk Of Bias ASsessment Tool (PROBAST)

PROBAST includes four steps

Step	Task	When to complete
1	Specify your systematic reviewquestion(s)	Once per systematic review
2	Classify the type of prediction modelevaluation	Once for each model of interest in each publicationbeing assessed, for each relevant outcome
3	Assess risk of bias and applicability(per domain)	Once for each development and validation of eachdistinct prediction model in a publication
4	Overall judgment of risk of bias andapplicability	Once for each development and validation of eachdistinct prediction model in a publication

If this is your first time using PROBAST, we strongly recommend reading the detailed explanation and elaboration (E&E) paper (27) and checking the examples on www.probast.org.

Step 1: Specify your systematic review question

State your systematic review question to facilitate the assessment of the applicability of the evaluatedmodels to your question. *The following table should be completed once per systematic review.*

Criteria	Specify your systematic review question
Intended use of model:	
***Participants** includingselection criteria and setting:*	
***Predictors (used in modeling)** including (1) types of predictors (e.g. history, clinical examination, biochemical markers, imaging tests), (2)time of measurement, (3) specific measurement issues (e.g. any requirements/ prohibitions for specialized equipment):*	
***Outcome** to be predicted:*	

Step 2: Classify the type of prediction model evaluation

Use the following table to classify the evaluation as model development, model validation, or combination.Different signaling questions apply for different types of prediction model evaluation.
When a publication focuses on adding one or more new predictors to established predictors then use “development only”. When a publication focuses on validation of an existing model in other data though followed by updating (adjusting or extending) of the model such that in fact a new model is being developed,then use “development and validation in the same publication”.
If the evaluation does not fit one of these classifications then PROBAST should not be used.

Classify the evaluation based on its aim			
Type of prediction study	**PROBAST boxes to complete**	**Tick as appropriate**	**Definitions for type of prediction model study**
Developmentonly	Dev		Prediction model development without external validation. These studies may include internal validation methods such as bootstrapping and cross-validation techniques
Developmentand validation	Dev and Val		Prediction model development combined with externalvalidation in other participants in the same article

Validation only	Val		External validation of existing (previously developed)model in other participants

This table should be completed once for each publication being assessed and for each relevant outcome inyour review.

Publication reference	
Models of interest	
Outcome of interest	

Step 3: Assess risk of bias and applicability

PROBAST is structured as four key domains. Each domain is judged for risk of bias (low, high or unclear) andincludes signaling questions to help make judgments. Signaling questions are rated as yes (Y), probably yes (PY), probably no (PN), no (N) or no information (NI). All signaling questions are phrased so that "yes" indicates absence of bias. Any signaling question rated as "no" or "probably no" flags the potential for bias; you will need to use your judgment to determine whether the domain should be rated as "high", "low" or "unclear" risk of bias. The guidance document contains further instructions and examples on rating signaling questions and risk of bias for each domain.
The first three domains are also rated for concerns for applicability (low/ high/ unclear) to your review questiondefined above.
Complete all domains separately for each evaluation of a distinct model. Shaded boxes indicate wheresignaling questions do not apply and should not be answered.

DOMAIN 1: Participants			
A. Risk of Bias			
Describe the sources of data and criteria for participant selection:			
		Dev	Val
1.1 Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?			
1.2 Were all inclusions and exclusions of participants appropriate?			
Risk of bias introduced by selection of participants	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			
B. Applicability			
Describe included participants, setting and dates:			
Concern that the included participants and setting do notmatch the review question	**CONCERN:** *(low/ high/ unclear)*		
Rationale of applicability rating:			

DOMAIN 2: Predictors		
A. Risk of Bias		
List and describe predictors included in the final model, e.g. definition and timing of assessment:		
	Dev	Val
2.1 Were predictors defined and assessed in a similar way for all participants?		

2.2 Were predictor assessments made without knowledge of outcome data?			
2.3 Are all predictors available at the time the model is intended to be used?			
Risk of bias introduced by predictors or their assessment	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			
B. Applicability			
Concern that the definition, assessment or timing of predictors inthe model do not match the review question	**CONCERN:** *(low/ high/ unclear)*		
Rationale of applicability rating:			
DOMAIN 3: Outcome			
A. Risk of Bias			
Describe the outcome, how it was defined and determined, and the time interval between predictorassessment and outcome determination:			
		Dev	Val
3.1 Was the outcome determined appropriately?			
3.2 Was a pre-specified or standard outcome definition used?			
3.3 Were predictors excluded from the outcome definition?			
3.4 Was the outcome defined and determined in a similar way for all participants?			
3.5 Was the outcome determined without knowledge of predictor information?			
3.6 Was the time interval between predictor assessment and outcome determinationappropriate?			
Risk of bias introduced by the outcome or its determination	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			
B. Applicability			
At what time point was the outcome determined: *If a composite outcome was used, describe the relative frequency/distribution of each contributing outcome:*			
Concern that the outcome, its definition, timing ordetermination do not match the review question	**CONCERN:** *(low/ high/ unclear)*		
Rationale of applicability rating:			
DOMAIN 4: Analysis			
Risk of Bias			
Describe numbers of participants, number of candidate predictors (for DEV only), outcome events and eventsper candidate predictor (for DEV only):			
Describe how the model was developed (predictor selection, optimism, risk groups, model performance):			
Describe whether and how the model was validated, either internally (e.g. bootstrapping, cross validation, random split sample) or externally (e.g. temporal validation, geographical validation, different setting, differenttype of participants):			

Describe the performance measures of the model, e.g. (re)calibration, discrimination, (re)classification, netbenefit:
Describe any participants who were excluded from the analysis:
Describe missing data on predictors and outcomes as well as methods used for missing data:

		Dev	Val
4.1 Were there a reasonable number of participants with the outcome?			
4.2 Were continuous and categorical predictors handled appropriately?			
4.3 Were all enrolled participants included in the analysis?			
4.4 Were participants with missing data handled appropriately?			
4.5 Was selection of predictors based on univariable analysis avoided?			
4.6 Were complexities in the data (e.g. censoring, competing risks, sampling of controls)accounted for appropriately?			
4.7 Were relevant model performance measures evaluated appropriately?			
4.8 Were model overfitting and optimism in model performance accounted for?			
4.9 Do predictors and their assigned weights in the final model correspond to the results fromthe reported multivariable analysis?			
Risk of bias introduced by the analysis	**RISK:** *(low/ high/ unclear)*		
Rationale of bias rating:			

Step 4: Overall assessment

Use the following tables to reach overall judgments about risk of bias and concerns for applicability of the prediction model evaluation (development and/or validation) across all assessed domains.
Complete for each evaluation of a distinct model.

Reaching an overall judgment about risk of bias of the prediction model evaluation	
Low risk of bias	If all domains were rated low risk of bias. If a prediction model was developed without any external validation, and it was rated as low risk of bias for all domains, consider downgrading to **high risk of bias**. Such a model can only be considered as low risk of bias, if the development was based on a very large data set and included some form of internal validation.
High risk of bias	If at least one domain is judged to be at **high risk of bias**.
Unclear risk of bias	If an unclear risk of bias was noted in at least one domain and it was low risk for all other domains.

Reaching an overall judgment about applicability of the prediction model evaluation	
Low concernsfor applicability	If low concerns for applicability for all domains, the prediction model evaluation is judgedto have **low concerns for applicability**.
High concernsfor applicability	If high concerns for applicability for at least one domain, the prediction model evaluationis judged to have **high concerns for applicability**.
Unclear concerns for applicability	If unclear concerns (but no "high concern") for applicability for at least one domain, theprediction model evaluation is judged to have **unclear concerns for applicability** overall.

Overall judgment about risk of bias and applicability of the prediction model evaluation		
Overall judgment of risk of bias	**RISK:** *(low/ high/ unclear)*	

Summary of sources of potential bias:		
Overall judgment of applicability	**CONCERN:** *(low/ high/ unclear)*	
Summary of applicability concerns:		

PROBAST = Prediction model Risk Of Bias ASsessment Tool.

ANEXO 2 - CHARMS 2014 Relevant items to extract from individual studies in a systematic review of prediction models

Domain	Key items	Reported on page #
SOURCE OF DATA	Source of data (e.g., cohort, case-control, randomized trial participants, or registry data)	
PARTICIPANTS	Participant eligibility and recruitment method (e.g., consecutive participants, location, number of centers, setting, inclusion and exclusion criteria)	
	Participant description	
	Details of treatments received, if relevant	
	Study dates	
OUTCOME(S) TO BE PREDICTED	Definition and method for measurement of outcome	
	Was the same outcome definition (and method for measurement) used in all patients?	
	Type of outcome (e.g., single or combined endpoints)	
	Was the outcome assessed without knowledge of the candidate predictors (i.e., blinded)?	
	Were candidate predictors part of the outcome (e.g., in panel or consensus diagnosis)?	
	Time of outcome occurrence or summary of duration of follow-up	
CANDIDATE PREDICTORS (OR INDEX TESTS)	Number and type of predictors (e.g., demographics, patient history, physical examination, additional testing, disease characteristics)	
	Definition and method for measurement of candidate predictors	
	Timing of predictor measurement (e.g., at patient presentation, at diagnosis, at treatment initiation)	
	Were predictors assessed blinded for outcome, and for each other (if relevant)?	
	Handling of predictors in the modelling (e.g., continuous, linear, non-linear transformations or categorised)	
SAMPLE SIZE	Number of participants and number of outcomes/events	
	Number of outcomes/events in relation to the number of candidate predictors (Events Per Variable)	
MISSING DATA	Number of participants with any missing value (include predictors and outcomes)	
	Number of participants with missing data for each predictor	
	Handling of missing data (e.g., complete-case analysis, imputation, or other methods)	
MODEL DEVELOPMENT	Modelling method (e.g., logistic, survival, neural network, or machine learning techniques)	
	Modelling assumptions satisfied	
	Method for selection of predictors **for inclusion** in multivariable modelling (e.g., all candidate predictors, pre-selection based on unadjusted association with the outcome)	
	Method for selection of predictors **during multivariable modelling** (e.g., full model approach, backward or forward selection) and criteria used (e.g., p-value, Akaike Information Criterion)	
	Shrinkage of predictor weights or regression coefficients (e.g., no shrinkage, uniform shrinkage, penalized estimation)	
MODEL PERFORMANCE	Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test) and Discrimination (C-statistic, D-statistic, log-rank) measures with confidence intervals	
	Classification measures (e.g., sensitivity, specificity, predictive values, net reclassification improvement) and whether a-priori cut points were used	
MODEL EVALUATION	Method used for testing model performance: development dataset only (random split of data, resampling methods e.g. bootstrap or cross-validation, none) or separate external validation (e.g. temporal, geographical, different setting, different investigators)	
	In case of poor validation, whether model was adjusted or updated (e.g., intercept recalibrated, predictor effects adjusted, or new predictors added)	
RESULTS	Final and other multivariable models (e.g., basic, extended, simplified) presented, including predictor weights or regression coefficients, intercept, baseline survival, model performance measures (with standard errors or confidence intervals)	

	Any alternative presentation of the final prediction models, e.g., sum score, nomogram, score chart, predictions for specific risk subgroups with performance	
	Comparison of the distribution of predictors (including missing data) for development and validation datasets	
INTERPRETATION AND DISCUSSION	Interpretation of presented models (confirmatory, i.e., model useful for practice versus exploratory, i.e., more research needed)	
	Comparison with other studies, discussion of generalizability, strengths and limitations.	

ANEXO 3 – Arquivo suplementar do artigo

Table S1. Database search strategy.

PubMed 04/11/2023 08:01:15 Filter: All Fields	("celiac disease"[MeSH Terms] OR "celiac disease"[All Fields] OR "Gluten Enteropathy"[All Fields] OR "Gluten Enteropathies"[All Fields] OR "gluten sensitive enteropathy"[All Fields] OR "Gluten-Sensitive Enteropathies"[All Fields] OR "gluten sensitive enteropathy"[All Fields] OR "Gluten-Sensitive Enteropathies"[All Fields] OR "Celiac Sprue"[All Fields] OR "Nontropical Sprue"[All Fields] OR "Sprue"[All Fields] OR "Coeliac disease"[All Fields] OR "gluten-related disorders"[All Fields]) AND ((((("diet, gluten free"[MeSH Terms] OR "Diet Therapy"[MeSH Terms:noexp] OR "Adherence"[All Fields] OR "Adherence Test"[All Fields]) AND "gluten-free diet"[All Fields]) AND "gluten-free diet"[All Fields]) OR "gluten free diets"[All Fields] OR "gluten free diets"[All Fields] OR "Compliance"[All Fields] OR "Diet Therapy"[All Fields] OR "dietary adherence"[All Fields] OR "effectiveness"[All Fields] OR "dietitian assessment"[All Fields]) AND ("Surveys and Questionnaires"[MeSH Terms] OR "Survey Methods"[All Fields] OR "Survey Method"[All Fields] OR "Survey Methodology"[All Fields] OR "Community Surveys"[All Fields] OR "Community Survey"[All Fields] OR "Community Survey"[All Fields] OR "Survey"[All Fields] OR "Questionnaire Design"[All Fields] OR "Questionnaire Designs"[All Fields] OR "Questionnaires"[All Fields] OR "Questionnaire"[All Fields] OR "validation study"[All Fields] OR "Validation Studies"[All Fields] OR "structured questionnaires"[All Fields] OR "survey studies"[All Fields])	786
LILACS 04/11/2023 08:16 Filter: title and abstract	("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND ("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten"	1002

	OR "dieta livre de glúten") AND ("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Disign" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")	
SCOPUS 01/11/23	TITLE-ABS-KEY ("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND TITLE-ABS-KEY ("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND TITLE-ABS-KEY ("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Disign" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")	1197
LIVIVO 01/11/23	(("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND ("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR	210

	"dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND ("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Design" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta"))	
EMBASE 01/11/23	#4. #1 AND #2 AND #3 #3. 'surveys and questionnaires'/de OR 'surveys and questionnaires' OR 'survey methods' OR 'survey method' OR 'survey methodology'/de OR 'survey methodology' OR 'community surveys'/de OR 'community surveys' OR 'community survey' OR 'survey'/de OR 'survey' OR 'questionnaire design'/de OR 'questionnaire design' OR 'questionnaire disign' OR 'questionnaire designs' OR 'questionnaires'/de OR 'questionnaires' OR 'questionnaire'/de OR 'questionnaire' OR 'validation study'/de OR 'validation study' OR 'validation studies'/de OR 'validation studies' OR 'structured questionnaires' OR 'survey studies' OR 'inquéritos e questionários' OR 'encuestas y cuestionarios' OR 'cuestionario' OR 'encuesta' #2. 'adherence'/de OR 'adherence' OR 'adherence test' OR 'gluten-free diet'/de OR 'gluten-free diet' OR 'gluten free diet'/de OR 'gluten free diet' OR 'gluten-free diets' OR 'compliance'/de OR 'compliance' OR 'diet therapy'/de OR 'diet therapy' OR 'dietary adherence'/de OR 'dietary adherence' OR 'effectiveness' OR 'dietitian assessment' OR 'dieta sin gluten' OR 'dieta livre de glúten' #1. 'celiac disease'/de OR 'celiac disease' OR 'gluten enteropathy'/de OR 'gluten enteropathy' OR 'gluten enteropathies' OR 'gluten-sensitive enteropathy'/de OR 'gluten-sensitive enteropathy' OR 'gluten sensitive enteropathy'/de OR 'gluten sensitive enteropathy' OR 'gluten-sensitive enteropathies' OR 'celiac sprue'/de OR 'celiac sprue' OR 'nontropical sprue'/de OR 'nontropical sprue' OR 'sprue'/de OR 'sprue' OR 'coeliac disease'/de OR 'coeliac disease' OR 'gluten-related disorders' OR 'doença celíaca' OR 'enfermedad celíaca' OR 'enteropatia glúten intuzida' OR	1605

	'espru celíaco' OR 'enteropatía por gluten'	
WEB OF SCIENCE 01/11/23	TS=("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Gluten-Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Gluten Sensitive Enteropathy" OR "Gluten-Sensitive Enteropathies" OR "Celiac Sprue" OR "Nontropical Sprue" OR "Sprue" OR "Coeliac disease" OR "gluten-related disorders" OR "doença celíaca" OR "enfermedad celíaca" OR "enteropatia glúten intuzida" OR "espru celíaco" OR "enteropatía por gluten") AND TS=("Diet therapy" OR "Adherence" OR "Adherence Test" OR "gluten-free diet" OR "gluten free diet" OR "Gluten-Free diets" OR "Gluten-Free Diets" OR "Compliance" OR "diet therapy" OR "dietary adherence" OR "effectiveness" OR "dietitian assessment" OR "dieta livre de glúten" OR " dieta sin gluten" OR "dieta livre de glúten") AND TS=("Surveys and Questionnaires" OR "Survey Methods" OR "Survey Method" OR "Survey Methodology" OR "Community Surveys" OR "Community Survey" OR "Community Survey" OR "Survey" OR "Questionnaire Design" OR "Questionnaire Designs" OR "Questionnaires" OR "Questionnaire" OR "validation study" OR "Validation Studies" OR "structured questionnaires" OR "survey studies" OR "inquéritos e questionários" OR "Encuestas y Cuestionarios" OR "cuestionario" OR "encuesta")	696
GOOGLE SCHOLAR 04/11/23 Filter: none	(("Celiac disease" OR "Gluten Enteropathy" OR "Gluten Enteropathies" OR "Celiac Sprue" OR "Coeliac disease") AND ("Diet therapy" OR "Adherence" OR "gluten-free diet" OR "Compliance" OR "dietary adherence") AND ("Surveys and Questionnaires" OR "Survey" OR "Questionnaire" OR "validation study" OR "structured questionnaires"))	100
PROQUEST 06/11/23 Limit to: full text Source: todos Document type: thesis Language: all	("Celiac disease" OR "Gluten Enteropathy" OR "Coeliac disease") AND ("Diet therapy" OR "Adherence" OR "Compliance") AND ("Survey" OR "Questionnaire")	1896
BASE 06/11/23	((Celiac disease) AND (Adherence) AND (Survey))	95

Additional word forms		

Table S2. Excluded references and reason:

Author	Reason
[1]	1
[2]	6
[3]	6
[4]	1
[5]	6
[6]	1
[7]	5
[8]	5
[9]	4
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[78]	1
[79]	1
[80]	1
[81]	5
[82]	6
[83]	6

Reason for exclusion:

1) Studies carried out with people under 18 years of age;
2) In treatment for less than six months;
3) With no diagnosis of CD;
4) Review articles, book chapters and conference proceedings;
5) Studies without sufficient data for extraction;
6) Studies that did not evaluate adherence to a GFD

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