Marta Gabriela Rilho Maganinho

Nutrition Intervention in Inflammatory Bowel Disease: The low-FODMAP diet - a review of the literature

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Declaro para os devidos efeitos ter atuado com integridade na elaboração deste Trabalho de Projeto, atesto a originalidade do trabalho, confirmo que não incorri em plágio e que todas as frases que retirei de textos de outros autores foram devidamente citadas ou redigidas com outras palavras e devidamente referenciadas na bibliografia.

(Marta Gabriela Rilho Maganinho)

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Orientador:

Professora Doutora Ana Sofia Sousa

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I. Index

II. Figures Index

III. Abbreviations List

IBD – Inflammatory bowel disease

CD – Crohn's disease

UC – Ulcerative Colitis

IBS - Irritable bowel syndrome

FGS - Functional-like gastrointestinal symptoms

QOL - Quality of life

GI - Gastrointestinal

CRP - C-reactive protein

FC - Fecal calprotectin

SCD - Specific carbohydrate diet

IBD-AID - Anti-inflammatory diet

SCFAs - Short-chain fatty acids

EEN - Exclusive Enteral Nutrition

LFD – Low-FODMAP diet

FODMAP - Fermentable Oligosaccharide, Disaccharide, Monosaccharide and Polyol

FOS – Fructooligosaccharides

GOS – Galactooligosaccharides

IBS-SSS - Irritable Bowel Syndrome Severity Scoring System

Hbi - Harvey-Bradshaw Index

IBD-Q – Inflammatory bowel disease questionnaire

Nutrition Intervention in Inflammatory Bowel Disease: the low-FODMAP diet- a review of the literature

Intervenção Nutricional na Doença Inflamatória Intestinal: a dieta com baixo teor em FODMAP- uma revisão da literatura

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V. Abstract

The inflammatory bowel disease (IBD) includes Crohn's Disease and Ulcerative Colitis, which is a multifactorial disease, where diet is identified as a detrimental trigger of the disease.

In addition to pharmacological treatment, nutritional intervention is essential for reducing symptoms and for the disease remission. Several approaches to this end have been studied over the years. Among this approaches the low-FODMAP (Fermentable Oligosaccharides, Disaccharides, Monosaccharides and Polyols) diet seems to be promising.

Thus, this study aims to review the multiple literature existent and identify the applications, benefits and limitations of the low-FODMAP diet in IBD.

This review article was elaborated through an online bibliographic search, were electronic PubMed database was used.

The low-FODMAP diet is associated with a greater relief of functional intestinal symptoms and improvement of quality of life. However, this diet implies a specific food restriction, which increase the risk of nutritional deficiencies and dysbiosis of IBD patients, once it can negatively affect the intestinal microbiota.

In conclusion, the low-FODMAP diet may effectively improve the clinical practice on the management of IBD and ensure better quality of life for IBD patients. Notwithstanding this, it is important to individualize the nutrition intervention and monitor frequently in order to avoid negative consequences. Moreover, the long-term use of this diet is still an issue. Thus, more studies are needed in order to support the generalization of this approach for clinical practice in IBD therapy and management.

Keywords: Inflammatory Bowel Disease, FODMAPs, The Low-FODMAP Diet, Functional Intestinal Symptoms

VI. Resumo

A doença inflamatória intestinal (DII), que inclui a doença de Crohn e a colite ulcerosa, é uma doença multifactorial. Os hábitos alimentares incluem-se na etiologia desta doença.

Além do tratamento farmacológico, a intervenção nutricional é fundamental para a diminuição dos sintomas e remissão da doença. Diversas abordagens dietéticas para este fim têm sido estudadas ao longo dos anos. Entre estas abordagens, a dieta com baixo teor de FODMAPs (oligossacarídeos fermentáveis, dissacarídeos, monossacarídeos e polióis) apresenta-se como promissora.

Assim, o presente estudo foi realizado com o objetivo de rever a literatura existente quanto ao tema e identificar as aplicações, benefícios e limitações da dieta com baixo teor em FODMAPs na DII.

Este artigo de revisão foi elaborado através de uma pesquisa bibliográfica online, em que se utilizou o banco de dados eletrónico PubMed.

A dieta pobre em FODMAPs está associada ao controlo dos sintomas intestinais funcionais e à melhoria da qualidade de vida nos doentes com DII. No entanto, esta dieta implica uma restrição de alimentos específicos, o que poderá contribuir para um impacto negativo no estado nutricional e na microbiota intestinal.

Em conclusão, a dieta pobre em FODMAPs pode de facto melhorar o controlo da DII e garantir uma melhor qualidade de vida dos doentes. Não obstante, é importante a individualização e a monitorização frequente para evitar as consequências negativas. Além disso, a aplicação a longo-prazo encontra-se ainda pouco estudada. Assim, serão necessários mais estudos para suportar a generalização desta abordagem na prática clínica para a terapia da DII.

Palavras Chave: Doença Inflamatória Intestinal, FODMAPs, Dieta Pobre em FODMAPs e Sintomas Intestinais Funcionais.

1. Introduction

The inflammatory bowel disease (IBD) is a chronic and relapsing disorder, mainly represented by Crohn's disease (CD) and ulcerative colitis (UC). This disease occurs when the immune system is activated due to an imbalance in the bowel epithelium barrier (1).

The IBD is considered as a disease of westernized countries (1,2). Along with the rapid industrialization and lifestyles changes of modern societies, the incidence and prevalence of this pathology has been increasing through the years (1,2). North America and Western and Northern Europe present the highest rates and it is estimated that 1 in 198 persons present UC and 1 in 310 persons present CD (1,3). Moreover, between 1990 and 2017, an increase of 85,1% in global prevalent cases of IBD was observed, more specifically, an increase from 3,7 millions of individuals to more than 6,8 millions (4).

Population from westernized countries tend to follow hypercaloric eating patterns including ultra-processed foods and a sedentary lifestyle (5,6). This lifestyle is the main cause for the increased incidence of chronic diseases, specifically inflammatory and cardiometabolic diseases, where IBD is included besides diabetes, obesity and cardiovascular diseases (5,6).

IBD can involve the entire gastrointestinal tract (3,7). The presence of ulcerations and/or granulomatous lesions is a feature of CD, which affects the entire bowel wall and not just the inner lining layer such as in UC (7).

Several factors have been involved in etiology of IBD: environmental, infectious, immunologic, microbiome factor and genetic susceptibility (2,8). Diet is a major part of the environmental triggers of the disease, particularly dietary patterns that include a high quantity of refined carbohydrates, red meat, saturated fatty acids and processed foods which are involved in several mechanisms that lead to dysfunction of the mucosal barrier, microbiome dysbiosis, i.e., an imbalance of gut microflora characterized by a decrease in beneficial bacteria and an increase in potentially pathogenic bacteria, and malfunctioning of immune system (2).

Abdominal pain, bloating and modification in stool consistency and frequency are among the most frequent symptoms of IBD (3,9). These symptoms are similar with those of irritable bowel syndrome (IBS) (9), which is another chronic functional bowel disorder that is diagnosed by the presence of abdominal pain related to defecation or in association with a change in stool frequency or form and bloating (10). Circa 30% of IBD patients exhibit IBS-like symptoms, i.e., abdominal pain associated with changes in bowel habits (9). There is a consistent body of evidence suggesting that 35% to 57% patients with quiescent IBD (31% in CD and 41% in UC) present functional-like gastrointestinal symptoms (FGS) (3).

Some data highlight that IBD patients with FGS present higher anxiety, sleep disturbances, fatigue, depression and lower quality of life (QOL) scores (11). IBD patients and the associated structural changes and transformation in motility or gut defense predispose to small intestinal bacterial overgrowth, which can occur in up to 30% in CD patients (11). The identification of functional GI symptoms should be initiated with a detailed symptom history as well as physical examination (11). Serum C-reactive protein (CRP) and fecal calprotectin (FC) should be assessed as a noninvasive biomarker of inflammatory activity (11).

As IBD has a tendency to cause severe intestinal damage and requires lifelong treatment especially if the disorder initiates early in life (3). Moreover, the progressive increase in IBD prevalence particularly in western countries will possibly conduct to higher surgical rates, higher morbidity and higher healthcare costs (3). Thus, appropriate management of IBD throughout the lifecycle is of utmost importance.

However, treatment strategies of IBD are mainly based on immunosuppressive medication which present several adverse side effects and there therapy targets are frequently limiting (7). This situation made nutrition interventions as a new possible approach, in order to manage IBD symptoms and to extend the disease remission (3,7). Dietary strategies play an important role on the improvement of functional symptoms (9).

Nutrient composition of daily diets including proteins, fats, carbohydrates and fibers present different effects on IBD management (2). In the past few years, several dietary interventions have been studied for the potential therapeutic effects on IBD, namely specific carbohydrate diet (SCD) (12), semi-vegetarian diet (5), paleolithic diet (13), elimination enteral nutrition (2,8), anti-inflammatory diet (14) (IBD-AID) and the low-FODMAP (low-Fermentable Oligosaccharide, Disaccharide, Monosaccharide and Polyol) diet (14).

The specific Carbohydrate Diet initially aimed to treat celiac disease and was originally described by Dr. Sidney Haas in 1924 for the treatment of celiac disease (2,8). The SCD gained its popularity since the biochemist Elaine Gottschall published, in 1994 the book *Breaking the Vicious Cycle* on the successful treatment of her daughter with UC through following the diet (12). The Specific Carbohydrate Diet was based on the theory that undigested carbohydrates induce bacterial overgrowth after being fermented by colonic bacteria, which results in production of toxic substances that cause overproduction of mucus and intestinal inflammation (2,8). For this reason, food sources of simple carbohydrates such as grains, potatoes, corn, yam, sugar, dairy and most legumes must be avoided, since they are composed of disaccharides and polysaccharides that are poorly absorbed leading to bacterial and yeast overgrowth resulting in overproduction of mucus (2,8). Thus, this diet only allows the consumption of monosaccharides (such as lactose-free yogurt and some fresh fruits) (2,8). In theory, with this diet adjustment, fewer toxic molecules are produced in the fermentation of undigested carbohydrates which leads to a decrease in colonic inflammation (2). Beyond the patient difficulty to follow the diet strictly, the SCD may also result in weight loss (8). The SCD has been a popular approach in the dietary management of IBD (2), however it is not currently recommended due to the lack of evidence that proves the achievement of mucosal healing following the diet (15).

The semi-vegetarian diet (meat-free and plant-based) has been suggested as useful for the prevention of CD relapse (2), since Chiba et al. (2010) showed in a prospective study (n=22) that the implementation of this diet leads to good remission rates on CD patients (5). The high fiber content of this diet has a protective effect on mucosa inflammation through the process of fiber fermentation into short-chain fatty acids (SCFAs) (2). This fiber digestion products play an important role on intestinal microbiome diversification and protect from dysbiosis of microbiota due to the immunomodulation properties of SCFAs (2). However, this diet limits the intake of animal foods which contribute to a decrease in beneficial bacteria and in this sense, more studies are needed to clarify if intestinal microbiota are enriched or not by this diet (5).

Walter L. Voegtlin, a gastroenterologist, who theorized that the establishment of a modern diet with undigested and agriculturally derived foods was the main responsible for the new modern diseases and inflammation, since the human digestive tract has not evolved to digest this modern food (2,8). Based on this hypothesis, Walter L. Voegtlin (13) proposed the paleolithic diet. This diet is characterized by higher amount of fiber, low amount of refined carbohydrates, high amount of protein and, comparing with a regular diet, similar level of unsaturated fatty acids (2). This diet focuses on the source of caloric intake as well as the caloric intake balance (8). Besides the poor food diversity of the diet, there is still lack of intervention studies with paleolithic diet in IBD patients (2).

Another approach in the therapy of IBD is the Exclusive Enteral Nutrition (EEN). This form of nutritional support is based on the administration of specific products, namely polymeric and elemental formula (2). All dietary food are eliminated from this diet. Thus, this diet presents poor palatability, which may lead to low adherence (2). Despite the effectiveness of EEN short-term therapy, a number of studies concluded that EEN long-term therapy could be a useful strategy in CD remission maintenance (2,16) and is also effective in children with CD (2). However, and despite the existence of strong evidence that supports EEN in IBD management, this nutrition intervention has the inconvenience of tube administration and the unpalatability not well tolerated by patients (2).

In 2014, Olendzki BC et al. (14) described the anti-inflammatory diet for IBD (IBD-AID)(2,8) base on the presence of pathogenic bacteria in the intestinal lumen that use specific carbohydrates as substrates which lead to dysbiosis (8). Therefore, the IBD-AID includes pre- and probiotic foods to restore the intestinal microbiota balance, excludes refined sugar, gluten-based grains and specific starches, encourages the intake of omega-3 fatty acids while decreasing the intake of total and saturated fatty acids (2,8). This diet aims to improve the nutritional status, to reduce the inflammation and to reinforce the gut microbiota diversity (2). The benefits of IBD-AID in IBD patients include reduction of symptomatology as well as reduction of medication needs (14). Moreover, this diet has a mucosal healing potential since it encourages the minimization of irritants and increasing of nutrient delivery (14). However, this diet is restrictive and can have compliance difficulties (14).

Among all the dietary approaches, the low-FODMAP diet (LFD) has been the most studied. The FODMAP hypothesis was proposed in 2005 by P. R. Gibson et al. (17). According to this hypothesis, the excessive intake of FODMAP (Fermentable Oligosaccharide, Disaccharide, Monosaccharide and Polyol), which are extremely fermentable but insufficiently absorbed, is associated with higher susceptibility to the development of IBD (17). FODMAPs are substances with a small molecular size and a high osmotic effect (2,8) and lead to increased intestinal permeability (8). These characteristics potentiate an increasing fermentation by colonic bacteria (2,8). Thus, the symptoms associated are gas production, abdominal pain, bloating, cramping, distension and diarrhea (2,8). Among IBD patients, the consumption of FODMAPs is associated with the exacerbation of symptoms (2,8).

It has been reported that LFD probably contributes to a relief of gastrointestinal symptoms and a denoting decrease in the disease activity (1–3,8,9). However, this dietary intervention has some limiting factors such as the palatability of foods (18), the lack of fiber caused by consumption restriction of many fruits and vegetables, adverse effects on microbiota and high risk of malnutrition due to the restrictive character of the diet (1,3,7,9).

Notwithstanding this, the LFD has been currently described as the emerging treatment option given the frequently described significant improvement on functional-like gastrointestinal symptoms associated with this diet (1). Thus, the aim of the present study is to review the theoretical background, applicability, implementation and advantages of the LFD in IBD as well as the potential limitations.

2. Methodology

The information used for the elaboration of this review article was obtained through an online bibliographic search. The electronic PubMed database was used. The search did not include any limitations on the publication dates and the following search terms were used: "inflammatory bowel disease" AND "low-FODMAP diet".

Thirty-two articles were found and selected according to their relevance to the subject. Specifically, whether they included information about IBD, the dietary-therapeutic of IBD with the LFD and more important the impact of the LFD on the study disease.

Five articles were excluded because: the sample did not contemplate humans; article language was not in English; and non-association of low-FODMAP diet with IBD, such as their association with other functional disorders like IBS.

The bibliographic references of the selected articles, resulting from the initial research, made it possible to obtain additional relevant articles (seventeen articles resulted from snowball research). The flow diagram (figure 1) with the search terms used and the final articles selected for this review is presented in chapter 10 (figures).

3. FODMAPs

The consumption of foods rich in FODMAPs (figure 2) is associated with aggravated gastrointestinal symptoms in patients with IBD (1,19). However, FODMAPs also have a number of physiological effects that can play a beneficial role on immune function modulation, improvement of calcium absorption and stool bulk , and reduction of serum cholesterol and triglycerides levels (1,20). Moreover, these carbohydrates also stimulate the selective growth of microorganisms such as *Bifidobacteria* that protect from colon cancer due to a prebiotic effect (1,21). *Bifidobacteria* are present in lower concentrations in the faeces and mucosa of IBD patients (21).

Oligosaccharides are fructans (fructooligosaccharides or FOS) and galactooligosaccharides (GOS) (19). The humans are unable to digest these oligosaccharides, once they do not present enzymes to break them down (19). Fructans are characterized due to the long chain of fructose that ends in a glucose molecule (8). Thus, they are classified based on their fructose-fructose bonds and degree of polymerization (chain length) (8). Therefore, those with less than ten are denominated fructooligosaccharides and those with ate least ten are referred to as inulins (8). The inulin type-fructans have a β configuration which makes them nondigestible by the small intestine (8,20). Fructooligosaccharides are the most dietary fructans founded and the principal food sources are garlic, rye, barley, pistachio, peach, watermelon, artichoke, beetroot, leek, pea, wheat and onion (8,19,20). Commercial fructans are increasingly added to processed foods (19,20) due to their sensory and textural properties and potential health benefits such as prebiotic effect and low-energy content (20). The galactooligosaccharides are galactose monomers with a terminal glucose unit (20) and their dietary form are raffinose and stachyose (8). They are poorly absorbed due to the lack of α-galactosidase, an enzyme necessary for the GOS hydrolysis (8,20). Thus, they turns available for colonic fermentation and to play their prebiotic effect(20). Once in the colon, the resident microbiota metabolizes the GOS into lactate and into SCFAs, like butyrate, acetate and propionate (8). Common dietary sources include lentils, cabbage, chickpea, brussels sprout, chicory, onion, some grains, nuts, seeds, and human milk (8,20).

Disaccharides as lactose, are composed by two sugars units, glucose and galactose (8,19,20). Lactose is hydrolyzed by lactase at the intestinal brush border (8). However, up to 70% of humans have lactose malabsorption due to the lower level or incapacity to produce lactase (hypolactasia) (20). Therefore, this impaired situation leads to undigested lactose, which is converted to SCFAs and hydrogen gas (8). Lactose is only considered as a FODMAP when there is an inadequate lactase activity or an insufficient level of lactase (19). Dietary sources of lactose are milk, ice cream, custard, yogurt, soft cheese (8,19), although is also added to commercial foods such cakes and breads (20).

Monosaccharides like fructose**,** are simple sugars and don't need digestion (19). Fructose is a 6-carbon monosaccharide, transported across the intestinal epithelium by GLUT5 or GLUT2, which are facilitative transporters (8,20). Despite that, some adults have an inadequate capability to absorb fructose due to an ineffectively GLUT5 expression (8). Thus, when dietary fructose concentration exceeds that of glucose, the fructose absorptive capacity is compromised leading to malabsorption (8,19). Common contributors to fructose intake are fruit, fruit products and products sweetened with high-fructose sweeteners such as corn syrup (8,19,20).

Polyols such sorbitol, mannitol, maltitol and xylitol are sugar alcohols, and they are poorly absorbed across the intestinal barrier (8,19). Once in the colon, they suffer anaerobic fermentation which contributes to the production of gaseous end products (8). These ones lead to abdominal pain, flatulence and osmotic diarrhea (8). These polyols are artificial sweeteners which can be used as a sugar substitute on food industry to produce food products with low-calorie content as well as to fulfil technological functions, such as emulsifiers, stabilizers and texturizers (8). The natural food sources include apple, pear, apricot, cherry, nectarine, peach, plum, watermelon, mushroom, cauliflower and honey (8,19).

3.1 The FODMAP hypothesis

Despite the contribution of environmental factors to IBD etiology, the disease results from a complex interaction of environment and genes (17). Hence the importance of having a susceptibility marker in order to examine directly the influence of diet (17). The only recognized susceptibility biomarker of IBD is elevated intestinal permeability, which leads to a high mucosal exposure to luminal pro-inflammatory molecules and microorganisms, and consequently modulation of the immune responsiveness of the mucosa (17). Moreover, a number of studies linking dietary factors to changes in intestinal permeability such high fatty acid and protein intake with the risk of developing IBD (7,22,23) and the increase of dietary fiber with lower risk of developing CD (7,24). It is also known that diets high in processed carbohydrates and sugar can lead to the development of obesity, which in turn is associated with a pro-inflammatory state and increased intestinal permeability (25). Alongside with this, the use of emulsifiers is increasing in food industry. Emulsifiers act directly on the mucous barrier and decrease the viscosity of the mucus, facilitate bacterial translocation and cause inflammation (7). These food additives and several others affect the function of the epithelial barrier and therefore the intestinal homeostasis (7).

There are at least three pathogenic mechanisms from which food components can induce functional intestinal symptoms: food hypersensitivity, direct action of bioactive molecules and luminal distention (26).

In IBD patients, due to the inherent gastrointestinal inflammation associated and the subsequent pharmacological treatment, there is a greater likelihood of dysbiosis and decreased immune tolerance to food antigens, facilitating the incidence of food allergy (27) However, in patients with functional gut disorders, such as IBD, food hypersensitivity is more likely to cause atopic diseases than functional intestinal symptoms (26,27).

The potential bioactivity of chemicals disseminated in food seems to be related to the development of systemic syndromes (26). However, there is still lack of evidence demonstrating that the reduction of these chemicals intake leads to an improvement of functional intestinal symptoms without systemic manifestations (26). Notwithstanding this, therapeutic interventions involving the elimination of salicylates, glutamates and amines from the diet have been tested (26). Although, these chemicals are present in a wide variety of foods, so their restriction contributes to a poorly diversified diet and to a greater risk of nutritional impairment (26).

Symptoms such as bloating, abdominal pain and changes in motility patterns and bowel habits result from luminal distention (26,28). Since the presence of water and gas in the intestine are the main causes of luminal distention, foods that are highly osmotic and quickly fermentable will lead to luminal distention (26,28). In this sense, the identification of foods that lead to luminal distention, especially in the distal small intestine and proximal colon, will allow the development of nutritional interventions for the management of symptoms (26,28).

According to the FODMAP hypothesis the rapid fermentation of these short-chain carbohydrates increases intestinal permeability, a predisposing factor to the development of IBD (17). Excessive intake of FODMAPs is associated with physiological effects in the bowel (17). Mainly due to the osmotic effect, in virtue of their small molecular size and the association with increased bacterial fermentation(17). The dietary FODMAPs once in the distal small intestine lead to an expansion of bacterial populations (3,17). The excessive delivery of FODMAPs and consequent distal small intestinal bacterial overgrowth leads to an increased epithelial permeability (17). On the other hand, the rapid fermentation of FODMAPs in the proximal large intestine leads to a high production of short-chain fatty acids and lactic acid in the lumen, which in turn affects the mucous barrier and increases the activity of the surfactant in the fecal water (17). These changes in distension and luminal content irritate intestinal epithelium and affect the function (17).

3.2 The Low FODMAP Diet

Cohen, A. B. et al. (29) together with CCFA Partners, in a cohort study with patients with IBD (n=6768), used a food frequency questionnaire to measure patients' dietary consumption patterns as well as open-ended questions to identify the foods that patients more often associate to the improvement or worsening of IBD symptoms. Patients identified several foods which exacerbate symptoms and other foods that ameliorate symptoms (29). The authors concluded that the patients' dietary patterns are selected according to the influence that certain foods have on disease activity (29). Thus, patients with active disease are expected to have different dietary patterns than those with inactive disease (29). Therefore, it was confirmed that IBD patients restrict their dietary patterns due to the presence of active symptoms or the fear of exacerbation (29,30).

Given the patients' self-reported perception of the influence of specific foods on IBD (29) and also considering the effects of FODMAPs on disease worsening (1,19,26), the role of food as a triggering factor for intestinal functional symptoms becomes clear (26). However, FODMAPs should not be seen as the cause of intestinal functional disorders, but as the key factor in the treatment of the disease, as the diet restriction contributes to the relief of gastrointestinal symptoms (26,28).

The low-FODMAP diet (LFD) is now starting to be frequently applied in patients with IBD, mainly due to the success of its implementation in patients with IBS, with great efficiency in reducing intestinal functional symptoms (31). Despite the beneficial effects of LFD in reducing symptoms it is also associated with negative effects, such as the high risk of nutrition deficiencies and the negative impact on intestinal microbiota, raising some concerns when applied as a long term diet (9,31). Thus, studies indicate that great caution is needed when applying LFD and it always requires the guidance of a nutritionist (9,28,31).

3.2.1 The low-FODMAP diet implementation

The implementation of LFD can follow two different types of approach: the top-down or bottom-up approach (31). The top-down approach consists in restricting all or almost all foods rich in FODMAPs, for a period of four to eight weeks (31). If there is a benefit of this restriction on intestinal functional symptoms, the diet is restricted to a specific dosage of foods that contain FODMAPs and that can be consumed in a limited way (31). This type of approach is suitable for situations where the amount of FODMAPs tolerated by the patient is uncertain or in very symptomatic patients (31). The bottom-up approach, on the other hand, implicates the reduction of specific FODMAPs or foods that are very rich in FODMAPs for a certain period of time, and later, if necessary, restricting certain foods (31). This approach should be applied in cases of high risk of dysbiosis, where IBD patients are included (31). However, there is a consistent body of evidence mentioning that the restriction of FODMAPs should be based on a global restriction and not specific to only one type of FODMAP (28). Furthermore, LFD must be individualized, taking into account the patient's eating habits and in order to correspond to the pattern of fructose and lactose absorption (26). The proportion of fructose absorbed depends on how much glucose it is consumed with it (26), since fructose malabsorption occurs when free fructose is in excess of glucose (28). For lactose, the absorption pattern depends on lactase activity in the epithelial brush border (26). The identification of the total fructose and/or lactose absorption capacity indicates that less food restriction is required (26). Hence the importance of performing breath hydrogen testing, in order to determine the patient's ability to absorb fructose and/or lactose (26,28). Because despite the possibility do initiate immediately a total restriction of FODMAPs in the diet, without information about the pattern of fructose and lactose absorption, food restriction should be avoided as much as possible in order to preserve the patient's nutritional status (26,28). Thus, if the breath hydrogen test performed showed a efficiently fructose and lactose absorption, then dietary restriction of foods rich in these carbohydrates should be unnecessary (28).

Before the implementation of the LFD, it is necessary to carry out a pre-dietary workup in order to define the best method (figure 3) (26,28). Thus, and in a first contact with the patient, it is necessary to understand their eating habits and identify which FODMAPs the patient is most frequently exposed to (28). It is also important to explain the mechanism of action of FODMAPs and the effect of LFD on IBD, in order to a better understanding of the patient regarding the reason for the changes in the diet and to promote adherence (28). Moreover, the patient must be instructed about all the dietary recommendations regarding LFD by providing a list of foods, alternative meals, verbal or visual descriptions to support the identification and use of commercially available food alternatives (28). In terms of the most suitable period of time for the application of the LFD, some suggested a period of six to eight weeks (2,8,28) or six to twelve weeks (26). However, regardless of differences in timing, the central purpose of the diet is the control of functional intestinal symptoms (26,28). Once well controlled, gradual reintroduction should be performed in order to determine what dose of FODMAP is tolerated by the patient (26,28). It is necessary to emphasize the importance of performing tolerance tests in order to guarantee the maximum diversity of the diet (28) and also to avoid the risk of nutritional deficiencies that the diet may cause (1,3,7,9).

3.3 Advantages of low-FODMAP diet on IBD patients

IBD is an intermittent disease, with periods of remission and others of great disease activity, which is characterized mainly by discomfort and/or abdominal pain, rectal hemorrhages and changes in stool consistency and frequency (30,32). Despite the fact that periods of remission are associated with improved patient well-being, functional intestinal symptoms continue to occur, affecting their quality of life (29,31).

Prince et al. (2016) (30), in a case note review of electronic medical records of IBD patients (n=88) who had been on a low-FODMAP diet, found that at follow-up there was an increase in the proportion of patients with satisfactory relief of functional bowel symptoms, 69/88 (78%), when compared to 14/88 (16%) patients at baseline. Essentially, the scores of individual symptoms, when assessed by the Gastrointestinal Symptom Rating Scale, decreased following LFD, with a greater improvement in bloating, flatulence, abdominal pain and lethargy(30). Furthermore, according to the Bristol Stool Form Scale, there was an increase in the number of patients who reported having a normal stool consistency (type 3, 4 or 5) at follow-up (55/88, 63%) than in the baseline (36/88, 41%) (30). It was also found that in terms of ideal stool frequency, there was an increase in the number of patients that indicated a stool frequency every three days to three times a day (normal stool frequency) at following LFD (71/88, 81%) when compared with baseline (53/88, 60%) (29).

Through a randomized controlled clinical trial (n=89), Pedersen et al.(2017) randomized patients with remission IBD or with mild to moderate disease activity with coexistence of IBS-like symptoms, for two distinct groups: the low-FODMAP diet (intervention group) and normal diet (control group) for a six week period (32). At the end of the six weeks, there was a reduction in the score of the IBS-SSS, particularly in the LFD group (median IBS-SSS 115) than in the control group (median IBS-SSS 170) (32). Thus, the author observed that patients in the LFD group are 5,30 times more likely to improve IBS-like symptoms than patients under a regular diet (OR, 95% CI: 1,81-15.55) (31).

Another study (multicenter, randomized, parallel, blind, placebo-controlled trial) was conducted in patients with quiescent IBD (n=52) (33). Diet allocation was made in a 1:1 ratio: the low-fodmap diet and the placebo sham diet (33). It was found that there were significantly more participants who achieved a 50% reduction in IBS-SSS after LFD (9/27, 33%) than in the sham diet (1/25, 4%) (32). Which demonstrates a greater relief of intestinal symptoms during the low-FODMAP diet (52%) compared to the sham diet (16%) (32).

Gearry et al.(2008) (18) in a pilot study (n=72) with implementation of LFD, showed that most of the symptoms presented by the study participants, mostly bloating, abdominal pain, flatulence and diarrhea, improved significantly after following LFD.

Furthermore, Bodini et al.(2019) (34) in a six-week randomized study with implementation of LFD in patients with IBD (n=55) in remission or with mild disease activity, concluded that LFD was associated with a statistically significant decrease in Harvey-Bradshaw Index (Hbi) (35), i.e., which is a simplification version of Crohn's Disease Activity Index (CDAI), essential to assess the degree of disease activity of Crohn's disease patients, (4 versus 3) in patients with CD and a numerical decrease (2 versus 1) in the Mayo score in UC patients. It was also observed that the median value of fecal calprotectin decreased statistically significantly in the follow-up of LFD (76.6 mg/kg versus 50 mg/kg) when compared with the values obtained by patients following a standard diet (91 mg/kg versus 87 mg/kg) (34). Moreover, there was an increase in the proportion of patients with a score greater than 170 on the IBD-Q, from 42.3% to 50% at LFD (34).

Maagaard et al.(2016) (36) conducted a retrospective cross-sectional study (n=180) with patients with IBS (n=131) and IBD (n=49) treated with LFD, in order to assess long-term adherence and the effect on the course of the disease. These authors concluded that 86% of patients reported total or partial efficacy of LFD (36). The percentage of patients who reported total diet effectiveness was higher for patients with IBD than for those with IBS (42% vs. 29%) (36). Regarding associated symptoms, bloating and abdominal pain were those who achieved an improvement during LFD (36). In addition, 37% of patients with IBS and 24% of patients with IBD became asymptomatic after following LFD (patients were to stay for six to eight weeks) (36). In terms of disease progression, after intervention with LFD, it was found that the number of patients with chronic continuous disease progression, i.e., without periods of remission, decreased and, in contrast, the number of patients with mild and indolent disease progression, in which disease activity disappears over time, increased (IBS: +37%; IBD: +23%) (36). The mild and indolent course of the disease when associated to LFD leads to a better quality of life and a normal stool pattern (36). It is worth noticing that the mild and indolent course of the disease at the beginning of the study was considered as a factor associated with the permanence in this course after treatment (36).

However, patients who started with one of the less favorable disease courses were more likely to present transition to a mild and indolent course (36). These results suggests that patients with numerous severe chronic courses may improve the disease course through LFD (36).

All the studies mentioned above show the beneficial effect of LFD in improving symptoms associated with IBD as well as the potential positive impact on disease activity and its progression. Nonetheless, there are also several studies that highlight the importance of adherence and commitment to the diet as fulcral factors for a better outcome (18,36,37).

Croagh et al.(2007) (37) reported that one of the reasons for the success of the diet is the perception of patients about the continuous effectiveness that LFD can have in the management of symptoms. Therefore, the effectiveness of the diet can also be demonstrated by the continuous adherence of patients (35).

Maagaard et al.(2016) (36) in their retrospective study, showed that high patient compliance was associated with a longer duration of dietary treatment. They also found that 54% of the patients in the study followed the recommendations of the LFD according to the severity of the symptoms, while the rest remained continuously (36). In other words, 54% of the patients only felt the need to follow the LFD in moments of greater exacerbation of symptoms (36). Which is in line with the state claimed by Cohen et al. (2013) (29) who has observed that IBD patients change their eating pattern according to the activity of the disease.

In the pilot study carried out by Gearry et al.(2008) (18) in which most patients adhered to the diet for a period of more than three months, the author identified some of the factors that can contribute to the adherence process and which are positively associated with the improvement of symptoms: the use of specific guides and cookbooks for LFD that allow a greater variety of diet (18); higher education level and work with a workload of no more than 35 hours per week (18). These factors were associated with a greater understanding of the principles of the diet and more time available to search for the necessary foods (18). Moreover, high income is also important, since having enough money allows to greater purchasing power of specific foods (18). All of these factors are considered as markers of greater motivation and consequently of diet success (18).

3.4 Limitations of low-FODMAP diet on IBD patients

Despite the benefits of a low FODMAP diet in relieving the symptoms of patients with IBD, it is important to consider the possible adverse effects. There is evidence highlighting some issues of concern (3,9,15).

The major problem is the restrictive nature of LFD and the potential to worsen nutritional deficiencies in a population already at high risk of malnutrition (1,3,7,9). Therefore, it is necessary to pay attention mainly to the possibility of deficiencies in micronutrients, especially zinc (25) and vitamin D (7,25). There is a high probability of vitamin D deficiency in IBD patients, since vitamin D receptor polymorphisms have already been identified as a genetic factor in this patients (25). Furthermore, due to the essential role of vitamin D in the normal functioning of the immune system, particularly in the GI tract (7), low levels of vitamin D may be associated with dysbiosis and increased IBD-related hospitalization (25). Moreover, zinc deficiency has been linked with excessive loss of GI secretions during chronic diarrhea and drainage of fistulas (25). Given that zinc is an essential enzyme cofactor for wound healing, cell immunity and growth, low levels of this micronutrient are also associated with increased hospitalization, surgery and other complications (25). In addition, Maagaard et al.(2016) (36) reported that 29% of patients had a weight loss during LFD, although the real impact of this reduction on the impairment of the patients' nutritional status remains unknown. The food diaries performed by the randomized controlled trial carried out by Cox et al. (33) revealed that patients with IBD during LFD have a significantly lower intake of energy, protein, fat, sugars, calcium, phosphorus, iodine when compared to those on the placebo sham diet.

Furthermore, LFD appears to frequently affect the fiber content that is ingested (38). That is why constipation is reported to be the symptom that least improves with LFD (38). Which is confirmed by the data displayed by Gearry et al.(2008) (18) that after restricting FODMAPs in the diet of 72 IBD patients, constipation was the only one that didn't improve. This seems to be explained by the restriction of the substrates responsible by supplying fluids to the intestine (18).

Through interactions with the intestinal microbiota, fiber helps in maintenance of intestinal barrier function, preserving the inner mucosal layer and acting as the first line of defense against mucosal pathogens (39). Thus, a reduction in fiber intake leads to a decrease in the production of SCFA, which are known to have the capacity to improve intestinal inflammation, as well as affect the composition of the intestinal microbiota (39,40). Such changes are associated with the thinning of the inner mucus layer and, consequently, with the increased proximity of bacteria to the intestinal epithelium (39).

Another concern is to fully understand the real effect of LFD on intestinal inflammation, since there are few studies that reveal any type of influence on inflammatory markers or disease activity (32,34,41). Cox et al.(2019) (33) in their randomized, placebo-controlled trial showed that LFD had no impact on disease activity or inflammatory markers. In another randomized, controlled crossover trial with nine patients with quiescent CD exposed to two different types of diets with different amounts of FODMAPs, there was no effect on fecal calprotectin (42). Croagh et al.(2007) (37) demonstrated that pouchitis can be naturally associated with low intake of FODMAPs. Since in their pilot study with patients (n=15) with ileal pouch, surgical treatment of UC, four out of five patients with a low habitual intake of FODMAP had pouchitis, whereas among the nine patients who used moderate to high amounts of FODMAP in their diet, only two presented pouchitis, although not statistically significant (37).

The effect of LFD on the microbiota is of particular concern, since there is already evidence reporting that the restriction of these molecules with a potential prebiotic and highly fermentative effect negatively affect the intestinal microbiota (3,11). It is known that patients with IBD have a high risk of dysbiosis, which is characterized by reduced microbial diversity, reduced levels of Bifidobacteria, a lower ratio of bacteroides and firmicutes and a decrease in *Faecalibacterium prausnitzii* (43). The decrease in the levels of *Faecalibacterium prausnitzii* is a predictor of active disease (43). Since LFD implies the restriction of natural food prebiotics, such as fructans and GOS, despite the potential improvement in functional intestinal symptoms, LFD affects the intestinal microbiota, by reducing saccharolytic bacteria, specifically, Bifidobacteria (43). In the microbiota assessment, Cox et al. (33) found a decrease in the abundance of *Bifidobacterium longum* and in *B. adolescentis* following LFD. This decrease is the result of changes in the colon's fermentable substrate, since Bifidobacteria preferentially ferment fructans and GOS (33). The decrease in the concentration of these bacteria is of particular concern given their immunoregulatory effects (33). These effects, which bring benefits to the health of the host, comprise immunological modulation through the increase of intestinal specific immunoglobulins and immuno-regulatory interleukins, as well as a reduction in pro-inflammatory interleukins (43).

LFD does not seem to affect the total number of fecal bacterial (42). However it does appear to specifically affect specific intestinal bacteria (42). Particularly, a decrease in butyrate-producing *Clostridium cluster* XIVa and *Akkermansia muciniphila* that are important for the health of the mucosa-associated microbiota and an increase in the relative abundance of *Ruminococcus torques*, which degrades mucus and is normally present in high concentrations in patients with IBD (42).

4. Discussion

First-line treatment for IBD involves pharmacological intervention (1,7). However, and due to the associated adverse effects (1,7), nutritional intervention has gained some prominence in the treatment of IBD (2,7,15) since food is among of the main triggers of functional intestinal symptoms in this patients (26).

After the publication of the FODMAPs theory (17), several studies have been conducted in order to demonstrate the effectiveness of the LFD in the management of functional intestinal symptoms (1,3). However, despite the positive impact of LFD on symptoms relief, it is also necessary to consider the adverse effects associated with the implementation of this diet (9,25,31).

The LFD has been suggested as a potential therapeutic approach for IBD patients mainly due to the good results on disease management, especially on controlling functional intestinal symptoms (18,30). Abdominal pain, bloating, flatulence and diarrhea are the principal symptoms presented by IBD patients that LFD contribute to their relief (18,30). Therefore, there is a consistent body of evidence showing that improvement on functional intestinal symptoms leads to a reduction in the score of the IBS-SSS and change the disease activity indexes (32–34). Furthermore, the use of LFD to the management of IBD can modulate the disease course and increase the remission periods (36). Thus, higher adherence to the diet is associated with better outcomes (36,37) and and better quality of life (32,34).

Notwithstanding this, the application of LFD does not have only benefits associated but also some issues concerning issues. This diet implies a specific food restriction during a certain period, which naturally can lead to nutritional deficiencies and increased malnutrition risk (25,33). The fiber content is one of the components of food ingestion that is affected by LFD, which consequently can aggravate constipation present in IBD patients (18,38). Moreover, this fiber restriction affects the normal functioning of intestinal barrier, the production of SCFA and the intestinal microbiota composition (39,40). Since IBD patients present high risk of dysbiosis, the impact of LFD on the intestinal microbiota bring special attention, mainly because LFD leads to a reduction of specific bacteria such as *Bifidobacteria* that has immunoregulatory effects with positive impact in the health of the host (33,43) and a decrease in *Clostridium cluster* XIVa and *Akkermansia muciniphila* which are specially important to the preservation function of intestinal mucosa (42).

In addition to the health implications that changes in the intestinal microbiota can cause, there is also a risk of development of eating disorders (44). In patients with restricted controlled food habits, GI symptoms can cause food aversions that can lead to food anxiety and, consequently, affect psychological well-being (44).

Besides the benefits and adverse effects of LFD described in this paper, most studies included in the present review present some limitations such as the small sample size which in turn can impair the relevance of the results, the design of the study and the the time of diet application. Moreover, there are only few studies showing data on the LFD impact on inflammatory markers or disease activity (32,34,41). There is also lack of information about the adequacy of LFD and it safety to IBD patients on long-term use.

Over the last few years, a number of studies have been demonstrating the beneficial contribution of LFD in the management of functional intestinal symptoms in patients with IBD. Therefore, LFD could be a key factor in the management of IBD, since its implementation has been demonstrating a relief of functional intestinal symptoms, a positive change on disease course as well as a better quality of life. However, despite the benefits associated it is also important to consider the inherent risks such as the restrictive nature of LFD and the consequent nutrition deficiencies, the impact on intestinal microbiota and the risk of developing eating disorders.

The incidence of IBD is increasing as well as the number of patients that are on the LFD. Thus, further studies are needed in order to assess the long-term impact of the diet on nutritional status, on intestinal inflammation, as well as on the effects on the intestinal microbiota.

In conclusion, the low-FODMAP diet may effectively improve the clinical practice on the management of IBD and ensure better quality of life for IBD patients. Notwithstanding this, it is important to individualize the nutrition intervention and monitor frequently in order to avoid negative consequences. Moreover, the long-term use of this diet is still an issue. Thus, more studies are needed in order to support the generalization of this approach for clinical practice in IBD therapy and management.

5. Critical Reflection

The information obtained with the present literature positively supports the role that LFD can have when implemented in IBD patients.

The LFD can be useful for application in clinical practice and for improving the quality of life of IBD patients. However, it is always important to remember that it should be applied individually. Therefore, not only the dietary pattern of each patient should be taken into account, but also factors such as disease activity, clinical symptoms, tolerance as well as the patient's age and clinical history. Moreover, it is important to educate the patients about every step of the diet and the associated recommendations. It is also of utmost importance that patients feel as part of the process, because the greater the compliance to the diet, the greater will be the success of the nutritional intervention.

Despite all the documented benefits of LFD, information on the consequences of long-term application is still scarce. Thus, continuous clinical and nutritional monitoring is necessary in order to ensure that LFD is adequately implemented and to prevent adverse effects.

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7. Figures

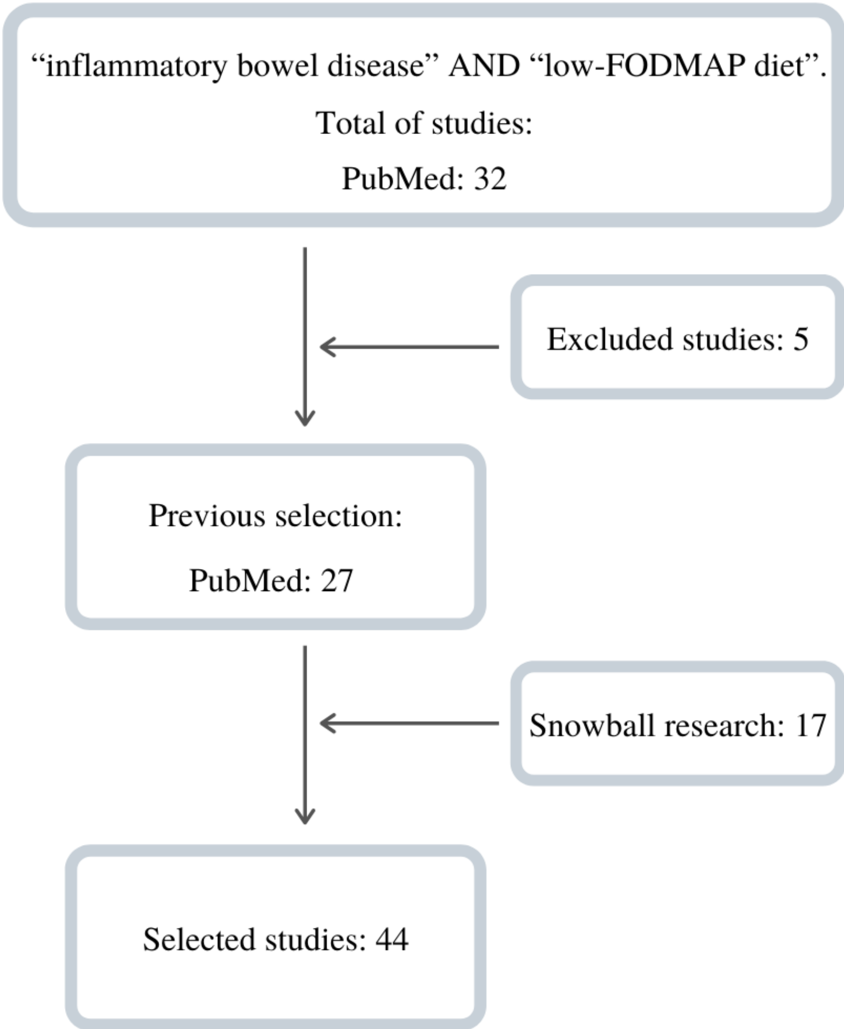

Figure 1. Flow diagram with the search terms used and the final articles selected for this review.

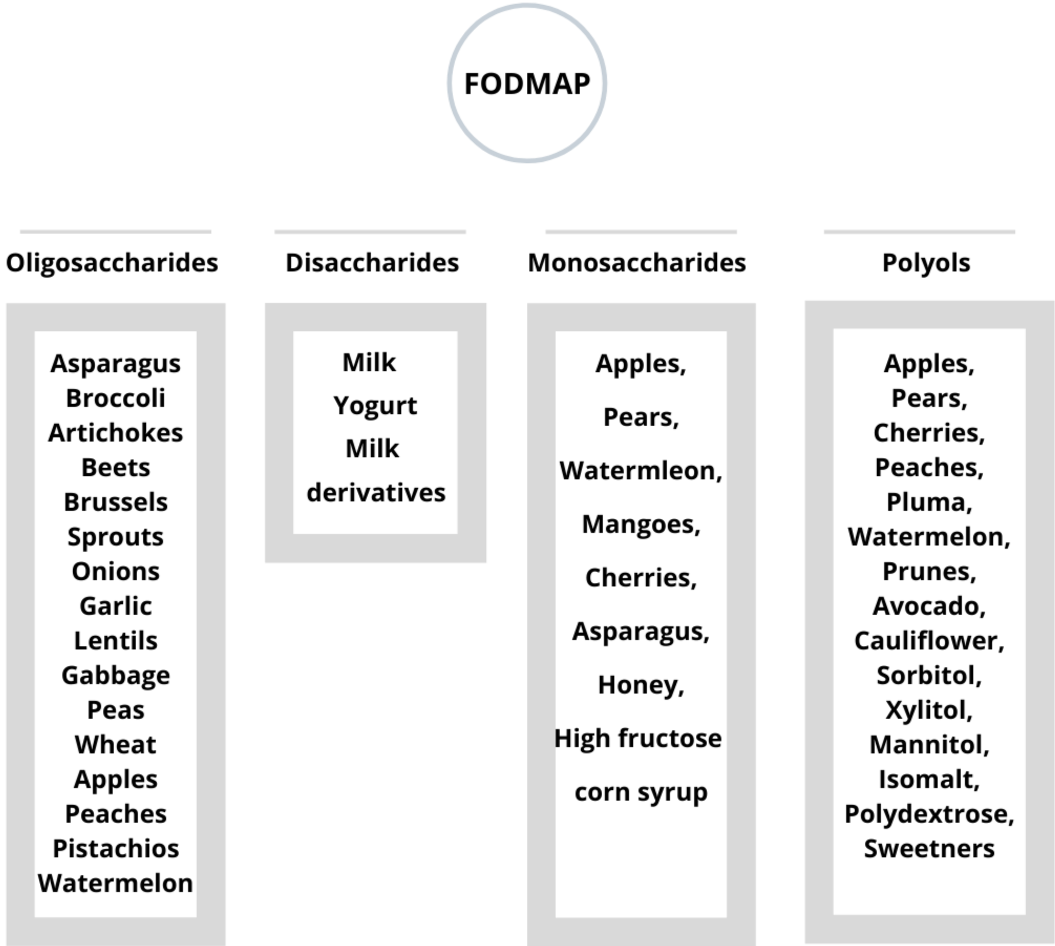

Figure 2. Common foods with fermentable short-chain carbohydrates (FODMAP). Adapted of Barbalho, S.M. et. al (2018). Inflammatory Bowel Diseases and Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols: An Overview. J Med Food (1).

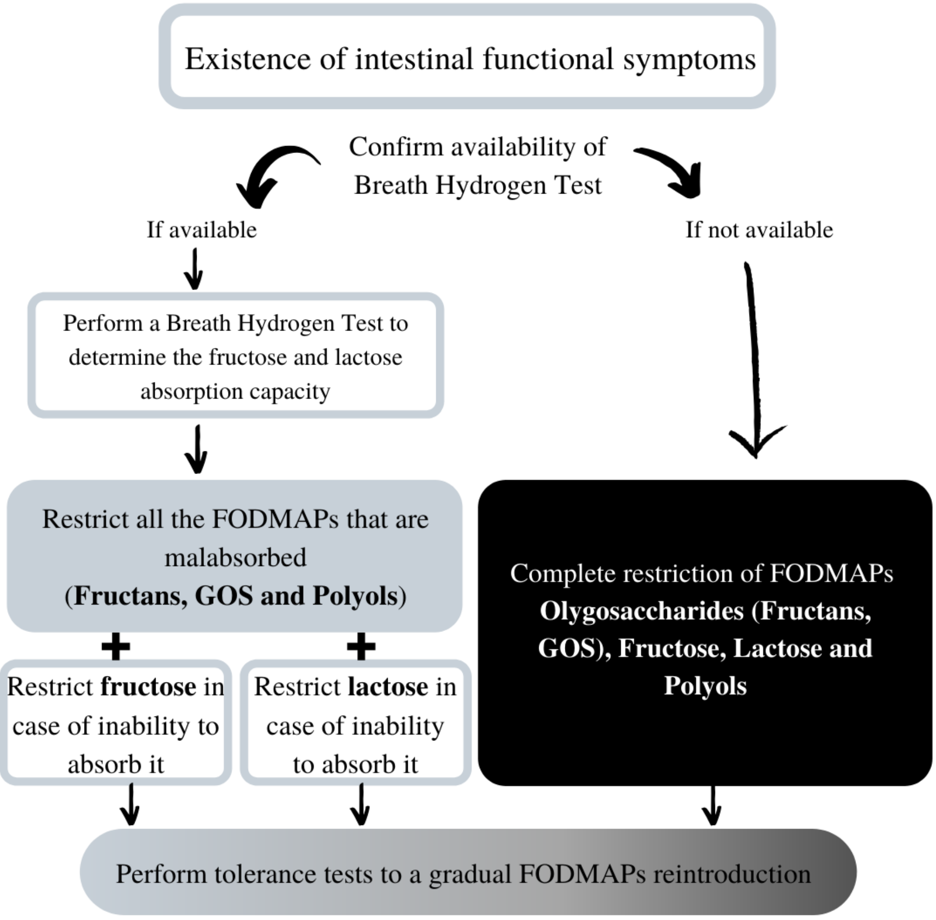

Figure 3. Differences in the implementation of LFD according to the availability of breath hydrogen tests. Adapted of Gibson, P. R. (2011) Food intolerance in functional bowel disorders. Journal of Gastroenterology and Hepatology (26).