REVIEW

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Obesity and Weight Loss Diets in Inflammatory Bowel Disease Patients: What Physicians Should Know

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ABSTRACT

Nutritional approach has been intensely investigated in inflammatory bowel disease (IBD) patients, but, despite many sparse reports, at present, there is not a universally accepted specific diet. In fact, nutritional requirements and, therefore, the ideal diet, may vary according to disease type, extension and activity. Among nutritional related issue in IBD, obesity has become a relevant one. In fact, obesity and IBD are both increasing in prevalence in last decades, and more and more IBD patients are overweight or obese. These two conditions present common metabolic pathways, leading to dysbiosis and mucosal barrier dysfunction, but the real clinical relationship and the potential reciprocal relative influences are not clear. In order to control weight, many IBD patients follow different weight loss diets, often without any specialized medical advice. Among those, low carb, intermittent fasting, paleolithic, and low-fat diets are some of the most popular, and plant based and Mediterranean diet, even though they are not just strictly weight loss diets, are followed by many IBD patients even for weight control. All the diets mentioned above have been effectively associated with weight loss, reduction in waist circumference and body mass index. However, there are still conflicting data regarding safety in IBD patients and potential experimental and clinical anti-inflammatory effect. In the present review, we described potential relations between obesity and IBD, and we analysed available evidence on efficacy and safety of weight loss diets in IBD patients, in order to provide a practical guide to physicians.

Key words: inflammatory bowel disease – IBD – obesity – diet – nutrition – weight loss.

Abbreviations: ACA: acetoacetate; BMI: body mass index; βOHB: β-hydroxybutyrate; CD: Crohn's disease; DSS: dextran sodium sulfate; IBD: inflammatory bowel disease; IF: intermittent fasting; MD: Mediterranean diet; SCFA: short-chain fatty acid; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), are chronic immune-mediated conditions that present a significant challenge to healthcare providers [1]. Therapeutic strategies for IBD patients aim to induce and maintain the disease remission, and the available options include conventional therapy (mesalamine and corticosteroids) and immunomodulatory drugs (immunosuppressant, biologics and small molecules) [2]. Despite the fact that recently many novel drugs have been approved and others are on the way, a consistent proportion of patients still do not respond ab initio or they lose response to the therapy over time, so that the concept of "breaking the therapeutic ceiling" represents nowadays a crescent emerging issue for IBD researchers. In this regard, one complementary strategy that has attracted attentionfor a long time, among both patients and physicians, is the potential utility of the nutritional approach. In fact, the idea of influencing disease activity by specific dietary intervention appears attractive, but to date, no strong evidence nor specific guidelines are available, and the patients often tend to follow self-made diets that may even cause metabolic imbalance and quality of life reduction [3, 4]. In recent years, the increasing knowledge on microbiota and its role in maintaining health status, as well as the more detailed characterization of the influence of different food on the intestinal microbial ecosystem, has determined a renewed interest on the issue.

One aspect classically related to the nutritional approach in IBD patients is the management of malnutrition [5]. In contrast

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to conventional expectations, many IBD patients present an increased body weight. In fact, some studies have reported that 15-40% of IBD patients are obese and 20-40% are overweight [6-8]. Severe obesity, [body mass index (BMI≥40 kg/m^2) was also reported in 2-3.2% of IBD patients [9]. The prevalence of obesity among IBD patients has been observed to increase over time, which correspond to the global trend of rising obesity rates. A single centre study in France showed that the proportion of obesity among CD patients from 1974 to 2000 increased from 1.7% before 1981 to 4% after 1990 [10]. Moran et al. [11], in a randomized controlled clinical trial involving 10,282 CD patients, observed a significant increase in mean BMI at enrolment, which rose from 20.8 kg/m^2 in 1991 to 27.0 kg/m^2 in 2008.

Considering that, many IBD patients are willing to lose weight and may follow different weight loss diets, often without any medical advice and/or follow-up. Instead, some patients do seek for medical advice for effective strategies to lose weight and ask about the feasibility of a specific weight loss diet. The aim of the present practical review is to summarize general principles of nutrition in IBD patients, evaluate potential links between IBD and obesity, and to analyse evidence for efficacy and safety of some of the most popular weight loss diets in IBD patients, in order to offer to the physician, the instruments to answer patients' requests.

NUTRITIONAL REQUIREMENTS IN IBD

Many variables may influence the nutritional requirements in IBD patients, and, therefore, an ideal nutritional approach and diet composition may vary according to the disease type (UC vs. CD), location (ileal vs. colonic, limited vs. extensive), and activity state (flare vs. remission) [12]. A balanced diet provides essential nutrients for the proper functioning of the body. However, in IBD patients, the chronic inflammatory process alters the utilization and absorption of nutrients by the organism. This leads to an increased demand for certain nutrients with potential limitation of the absorption of others.

One of the prominent determinants in nutritional needs for individuals with IBD is the increased energy expenditure due to the inflammatory response, and indeed one of the main factors affecting the diet is the presence of active disease. In fact, while in the remission phase the energy requirements do not differ from that of a healthy person, the persistent active inflammation results in a higher metabolic rate, requiring more energy to maintain body functions. Moreover, the presence of gastrointestinal symptoms frequently leads to avoidance of fibers and dairy products, as these elements may exacerbate bloating and diarrhea and, in moderate-severe hospitalized patients, parenteral support of fluids and nutrients is often necessary. Another important determinant for the diet is the type and location of disease. In fact, besides the potential different inflammatory burden, specific features of CD vs. UC may imply different nutritional approaches for the presence of complications (i.e. stenosis and/or fistulas) and/or previous surgery. Moreover, ileal location may represent a further risk factor for malabsorption, and upper bowel involvement may render adequate oral food intake particularly difficult. In colonic involvement, malabsorption is a more infrequent event, while fluids loss may occur. In addition, CD patients tend to have clinical problems (i.e. symptoms, lab alterations) even in quiescent disease phase, while UC patients generally develop complaints only in the active phase [13].

Considering the aforementioned factors, malnutrition is common in IBD patients, and prevalence rate varies between 20–85%, with a reported weight loss in 70–80% of hospitalized IBD patients and 20–40% of outpatients. Malnourished patients are at a higher risk of disease flare, hospitalizations and longer hospital stay, severe infections, unscheduled surgery, postoperative complications and increased mortality [4]. Besides global calories intake, malnutrition may specifically involve micronutrient and/or vitamin deficiencies (i.e. vitamin D, calcium, iron, and zinc) [14] and, most importantly, proteins, so that particular attention to the protein assumption in the diet and micro-nutrients supplements may be indicated in some patients. In fact, protein deficiency may determine an alteration of the ratio between fat mass (visceral and subcutaneous adipose tissues), and lean mass, with a consistent loss of muscle mass associated with a decreased muscle strength (sarcopenia), with an important impairment of physical performance and quality of life, potentially leading to disability [15]. Notably, those alterations persist over the acute phase of the disease and may be present even in patients with normal or even incremented BMI [16], indicating that a specific second-level nutritional assessment is indicated. In fact, the European Society for Clinical Nutrition and Metabolism (ESPEN) recommends a specific nutritional consultation for all IBD patients [17].

In the last decades, one factor that has gained a terrific relevance for health maintenance is the microbiota balance, for quanti-qualitative perturbation of this complex ecosystem may lead to different pathologic conditions. In IBD, although a specific etiological *primum movens* has not been identified so far, microbiota alteration (dysbiosis) has been recognized as a fundamental pathogenetic factor for inflammatory cascade initiation and perpetuation, because of the pivotal role of microbiota in shaping, priming and regulating immune response [18]. In fact, increased *Enterobacteriaceae* and reduction of *Firmicutes* has been described in IBD patients compared with normal subjects, with an increment of pro-inflammatory bacteria ("enteropathogens") and a reduction in possible protective species (i.e., Clostridial cluster IV and XIV, *Bacteroides fragilis* and *Faecalibacterium prausnitzii*) [19-22]. Microbiota can be modified and shaped by different environmental factors, and, among these, the diet represents the most relevant [23]. Western diet, typical of countries with high incidence of IBD, is rich in saturated fats, sugar, processed and ultra-processed foods, and poor in fiber, fresh vegetables, antioxidants and vitamins, thus contributing to dysbiosis [24]. Ultra-processed foods are defined as "formulations mostly of cheap industrial sources of dietary energy and nutrients plus additives, using a series of processes" [25]. These foods contribute to intestinal permeability increment and endotoxemia due to a reduced integrity of the intestinal barrier [26-28]. Considering the multiple factors that may contribute to increase microbiota alteration in IBD patients (inflammation, permeability increase, micronutrients reduction), the ideal IBD diet should take into account nutrients with prebiotic

activity able to promote bacterial diversity and induce and maintain eubiosis.

OBESITY AND IBD

In IBD patients, obesity may be favored by several factors, such as the imbalance of gut microbiota and the altered metabolic intestinal signaling, with alteration of satiety-related peptides function, as well as by the changing in the lifestyle and the utilization of steroids [29-31]. Obesity and IBD share common pathogenetic features that lead to chronic inflammation maintenance, synthetized in Fig. 1. A central role in both conditions is played by mucosal intestinal alterations, with physiological bacterial balance disruption leading to dysbiosis (with increment of enteropathogens and reduction of bacteria with regulatory effect), increased bacterial translocation and decreased mucosal barrier efficiency. These factors favor in turn increased bacterial and antigen load to the submucosal compartment, rich in immune cells, a subsequent hyperactivation of immune response, and the onset and perpetuation of mucosal inflammation. The mentioned alterations are strictly interrelated and reciprocally influenced, so that a self-amplifying vicious circle is generated. In fact, in obese patients, visceral adipose tissue promotes the activation of macrophages and CD4+ lymphocytes, that in turn produces pro-inflammatory cytokines, such as IL-1, TNF, IL-6, and adipokines, increasing the systemic inflammatory burden and directly inducing intestinal mucosa permeability impairment, dysbiosis and bacterial translocation [32]. Moreover, in IBD patients, particularly in those with CD, a particular form of mesenteric fat hyperplasia (namely "creeping fat"), with marked immunological activity, is present in areas of the inflamed bowel, further contributing to the local and systemic pro-inflammatory activation [33]. Despite the aforementioned pathogenetic interconnection, only sparse pre-clinical and clinical observations demonstrated a reciprocal influence, and recent meta-analysis did not find a clear increment in the incidence of IBD in obese subjects nor a more severe or aggressive disease course in obese IBD patients [34, 35]. On the other hand, visceral adiposity has been associated with a higher complication risk of IBD, further confirming the immune activity of this particular form of adipose tissue and its role in the intestinal and systemic inflammation [33]. Moreover, obesity may affect response to therapy, both influencing the pharmacokinetics of drugs and increasing the inflammatory burden, and some studies explored the beneficial effect of medical treatments, dietary intervention, and bariatric surgery in obese IBD patients [36].

One of the possible explanations for the lack of consistent data for IBD-obesity interaction may be related to the recent finding that, in IBD patients, a global alteration in the body composition occurs, more than a simple increasing of visceral adiposity. In fact, considering only the traditional markers (i.e. BMI and waist circumference) suggested by obesity guidelines [37, 38] may not be representative of the complex alteration occurring in IBD patients, that may be better evaluated by a more in deep evaluation (i.e. by bioimpedence). In fact, recent studies are consistently reporting a decrease in lean body mass and changes in fat distribution in IBD patients, particularly

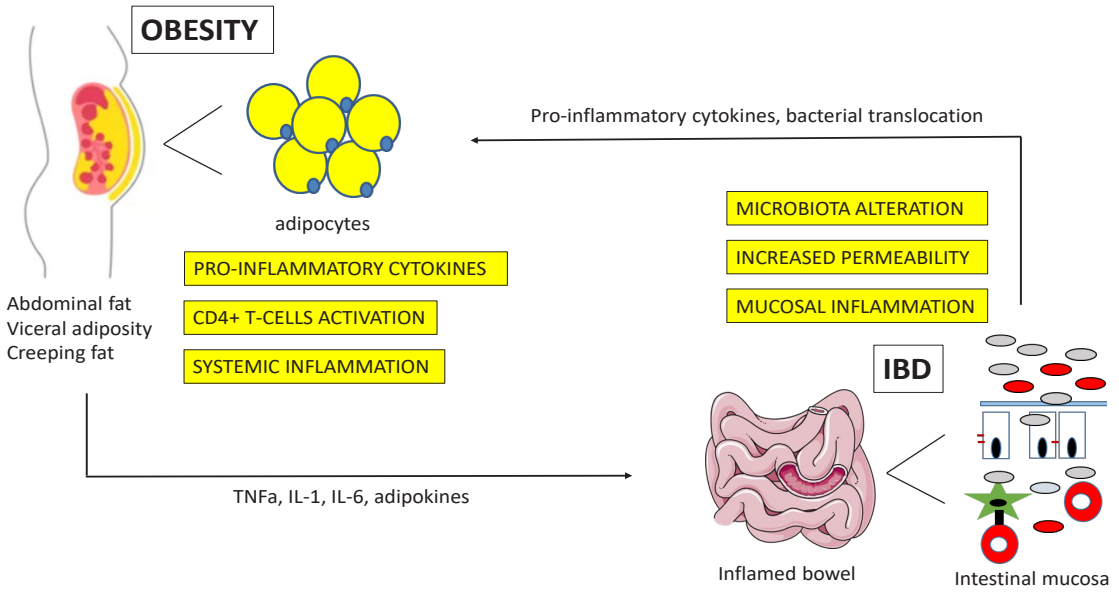

Fig. 1. Common pathogenetic pathways involved in obesity and IBD leading to chronic inflammation maintenance. These two conditions create a vicious circle primarily involving intestinal barrier dysfunction and microbiota alteration, that, in turn, lead to onset and maintenance of mucosal and systemic inflammation. In fact, adipocytes stimulated activation of pro-inflammatory cells and produce mediators that increase systemic inflammation and influence mucosal homeostasis. In IBD patients, increased enteropathogens (oval red dots) comparing with regulative bacteria (oval gray dots), and the increased permeability (epithelial cells: rectangular white cells; mucus: blue line on the top of epithelial cells) lead to the exposure of the submucosal compartment to bacteria and luminal content, activation of immune response (lymphocytes: rounded red cells; dendritic cell: star-shaped green cell), and onset and perpetuation of mucosal inflammation. The passage in the blood circulation of activated immune cells, pro-inflammatory mediators and translocated bacteria further contribute to the increment of systemic inflammation in a self-maintaining circle.

visceral adiposity, possibly attributed to chronic inflammation and malnutrition [39-40].

Indeed, obesity and IBD are both increasing in prevalence in last decades, and, as already mentioned before, up to 40% of IBD patients present excessive body weight, that often implies relevant concern both for health and esthetical reasons. Consequently, many patients search for and start to follow weight loss diets suggested by friends, social networks, and media, often without any medical supervision. In the next section, some of the most popular weight loss diets will be analyzed, and potential efficacy and safety in IBD patients, according to available evidence or personal speculations, presented and discussed (Table I). We added a brief analysis of plant based and Mediterranean diet (MD) that are part of a global lifestyle, more than simple weight loss diets, since those diets are more and more popular even in IBD patients and therefore the knowledge of their basic principles and of the available evidence in IBD patients can be useful for physicians.

NAVIGATING WEIGHT LOSS DIETS IN IBD

Low-carb Diets

Low-carb diets are a group of alimentary regimens that emphasize a reduced carbohydrate intake and an increase in fats and proteins. Despite some of them have been proposed already in the 70's, in the last decades those diets have gained a great popularity for their potential benefits in weight loss and metabolic health. In fact, low-carb diets are often effective for a rapid and sustainable weight loss, and they can help in stabilizing blood sugar levels. Among those, Atkins and ketogenic diet are probably the most popular.

Atkins diet has been proposed by Dr. Robert C. Atkins with a best-selling book in 1972 [41], and it gained a terrific popularity throughout the years for many famous people's endorsement. It consists of four different phases, two of induction and two of maintenance, aiming initially to a rapid weight loss and a subsequent consolidation of the results, with a gradual reintroduction of carbohydrates. In a recent study comparing different diets for heart disease risk reduction, Atkins diet achieved, after one year, reduction of weight (-2.1 Kg), BMI (-0.7 Kg/m^2) and waist circumference (-2.5 cm) and decrease of serum CRP and insulin [42]. The ketogenic diet was initially developed in the 20's as a treatment for children with epilepsy, and later from the 70's was proposed as a weight loss diet. The ketogenic diet is a high-fat, low-carbohydrate diet designed to induce a state of ketosis in the body, with primary utilization of fat, instead of carbohydrates, for energy production. This type of diet induces ketosis, an anti-inflammatory state characterized by an increase in blood

Table I. Weight loss diets efficacy in clinical and experimental studies

Diet	Weight loss evidence	Experimental anti-inflammatory evidence	Clinical anti-inflammatory evidence	Advice	References
Low-carb	ATKINS: Weight loss (-2.1 Kg) and decrease of BMI (-0.7 Kg/m2) and waist circumference (-2.5 cm). KETOGENIC: Weight loss (-5.6 Kg) and decrease of waist circumference (-2.3 cm)	Conflicting results in animal models	No data in IBD patients. Need for specific trials.	Caution for fiber reduction, limited nutrients, microbiota alterations and assumption of trigger foods	42, 44-46
Intermittent fasting	Weight loss (-3.4 Kg) and decrease of BMI (-4.3 Kg/m^2)	Conflicting results in animal models	Preliminary inconclusive data in IBD patients in Ramadan. Specific trials ongoing.	Personalize fasting/ feeding intervals, check for nutrients assumption.	48, 51-54
Paleo	Weight loss (-6.5 Kg) and decrease of waist circumference (-11.1 cm).	No specific studies. High fiber increases the production of SCFAs.	No data in IBD patients. Need for specific trials.	Caution for fiber in active and stenosing disease, check for nutrients assumption.	59,60
Low-fat	Weight loss (-3.3 Kg) Decrease of BMI (-1.4 Kg/m^2) and waist circumference (-2.2 cm)	High fat diet exacerbated DSS colitis comparing with low-fat.	In a pilot cross-over study amelioration of QoL and inflammatory markers. Need for further trials.	Check assumption of fat-soluble vitamins and essential fatty acids.	42, 65, 68
Plant-based	Weight loss (average -7.5% ± 4.5%).	Increases the production of SCFAs and pre-biotic effect in promoting eubiosis	In uncontrolled studies potential adjunctive effect for induction and maintenance of remission in UC and CD. Need for further controlled trials.	Caution for fiber in active and stenosing disease, check for nutrients assumption.	69, 60, 71-74
Mediterranean	Decrease of BMI (UC: -0.42 Kg/ m^2, CD: -0.48 Kg/m^2), waist circumference (UC: -1.25 cm; CD: -1.37 cm) and fatty mass (UC: -1.27%; CD: -2.75)	Modulation of inflammation-related genes, anti-oxidant and eubiotic effect.	Reduction of IBD flares (UC: -16.9%, CD: -13.2%). More studies needed.	Probably the best diet available at the moment. Caution for fiber in active and stenosing disease.	78-86

BMI: body mass index; CD: Crohn's disease; IBD: inflammatory bowel disease; UC: ulcerative colitis.

levels of acetoacetate (ACA) and β-hydroxybutyrate (βOHB), the two main ketone bodies in the liver. The main difference with Atkins diet is the limitation of proteins (20-25% of total calories) and the even stronger reduction of carbohydrates to less than 50 g per day, with a rapid and consistent weight loss. The ketogenic diet has been shown to positively affect the gut homeostasis in children by influencing the growth of commensal microbes, in particular *Bifidobacterium, Lactobacillus, Bacteroides, Faecalibacterium, Clostridium,* and *Ruminococcus*, producers of short-chain fatty acids (SCFAs). Such SCFA-producing bacteria showed an anti-inflammatory effect in IBD due to an increase in anti-inflammatory βOHB [43]. Short-chain fatty acids, butyrate and βOHB, play a key role in reducing intestinal inflammation and pro-inflammatory cytokines, and in increasing histone acetylation in macrophages. Moreover, SCFA-producing bacteria promote gut barrier integrity and reduce the dysbiosis. Kong et al. found that, while standard low carb diet exacerbates dextran sodium sulfate (DSS) induced colitis in mice and stimulated *Escherichia/Shighella*, the ketogenic diet significantly reduced inflammatory responses, stimulated *Akkermansia*, protected intestinal barrier function, reduced innate lymphoid cell (ILC3) production, and reduced expression of related inflammatory cytokines [44]. On the contrary, Li et al. [45] found that this diet in mouse models worsened colitis by increasing intestinal permeability, decreasing expressions of intestinal epithelial barrier genes, increasing body weight loss, increasing disease activity index (DAI) and histological scores, and decreasing colon length (a proxy measure of intestinal inflammation). Other recent studies confirmed that ketogenic diets increase pathogenic bacteria such as *Proteobacteria, Enterobacteriaceae, Helicobacter* and *Escherichia/Shigella* leading to a worsening of colitis [46]. In consideration of the effects on the gut microbiome, the true role of the ketogenic diet on IBD patients remains unknown and the long-term effects of this type of approach require further studies.

To date, there are no studies investigating a potential application of low carb diets in IBD patients, and direct evidence is lacking. One provocative hypothesis suggests that, more than the total amount of carbohydrates, it is their variation in the diet that may contribute to the onset and maintenance of IBD, through selective pressure on specific intestinal bacteria with a consequent reduced diversity, dysbiosis onset and pro-inflammatory pathway activation. In line with this theory, the carbohydrate monotony, that is the monotonous delivery of the same carbohydrate source in the diet, may be beneficial for prevention and treatment in IBD [47]. Further studies are needed to support this theory and to test its applicability in clinical practice.

Considering the characteristics of IBD patients, some potential issues should be taken into account for low carb diets application. First, many low-carb diets restrict high-fiber foods, which may be challenging for individuals with IBD. In fact, fiber is essential for digestive health, and its restriction may affect gut motility and overall bowel function. Secondly, individuals with IBD often face challenges in nutrient absorption, and low-carb diets may limit certain food groups potentially impacting the intake of essential nutrients, so that close monitoring and, if necessary, supplementation may be required. Moreover, the effect of low-carb diets to the microbial balance in the gut is not straightforward, and their impact on the microbiome, in particular in the long term, should be considered. Lastly, the introduction of a high-protein/high fat diet induces the consumption of some foods (fatty or fried foods and milk products) that may trigger or worsen gastrointestinal symptoms, and, on the other hand, limit some easily digestible complex carbohydrates, such as low-fiber fruits and refined grains, that have a positive metabolic role.

Intermittent Fasting Diet

Intermittent fasting (IF) diet involves cycles of eating and fasting. It is characterized by food consumption patterns in which individuals, for extended periods of time (i.e., 8-16 h; 16–48 h), assume little or no energy intake, combined with intervening periods of normal food intake. This diet became popular in the last decades for the efficacy in weight loss and the improving of metabolic profile.

In a systematic literature review including 27 studies, IF diet was able to induce weight loss (average -3.4 Kg) and decrease of BMI (average -4.3 Kg/m^2), even though studies displayed inhomogeneity for setting, protocol and duration of the diet [48]. Some evidence in the literature suggests that intermittent fasting can counteract age-related degenerative disease processes and can improve functional outcomes, from diabetes and cardiovascular disease to neurological disorders, both in animal models and in humans [49, 50].

Experimental data for intermittent fasting are not consistent. In fact, temporary fasting dramatically reduced lymphocyte numbers by 50% in Peyer's patches and can abolish the induction of antigen-specific IgA and oral tolerance, potentially exacerbating food induced diarrhea [51]. On the other side, in DSS animal model of colitis, intermittent fasting regimen improved colonic inflammation, probably through amelioration of gut microbial dysbiosis, decreased oxidative stress and enhanced colonic short-chain fatty acids [52, 53]. To date, the only study investigating intermittent fasting regimen in IBD patients is a prospective observational study investigating IBD patients (CD n=20, UC n=60) during Ramadan. Considering consistent limitation about study protocol and observation length (1 month), authors did not find significant changes in symptoms and inflammatory biomarkers, except for an increased partial Mayo score in the subgroup of elderly patients and a higher basal calprotectin level [54]. Given the profound effects of intermittent fasting on the gastrointestinal immune response, clinical trials exploring the effects of intermittent fasting or fasting mimicking diets in IBD are currently on-going. In fact, two separate randomized open-label clinical trials are currently investigating how an intermittent calorie-reduced diet, that mimics the IF diet, can affect clinical symptoms and inflammatory biomarkers, in patients with mild to moderate UC [55] and CD [56].

While this approach has gained popularity for weight loss, individuals with IBD need to carefully consider the timing of meals to avoid triggering symptoms during fasting periods. Customizing fasting windows and meal timings under the guidance of a healthcare professional can help to find a balance between weight loss and digestive health. The timing of meals during fasting periods may be differently tolerated by

individuals with IBD, and in some patients extended fasting periods may trigger symptoms. Schemes' personalization is the key, and IBD patients may start with shorter fasting windows, such as a 12-hour fasting period overnight, and gradually extending it according to tolerability.

Individuals with IBD may already face challenges in nutrient absorption. Extended fasting periods could potentially exacerbate these challenges, and individuals should work closely with healthcare professionals to ensure adequate nutrient intake.

Paleolithic Diet

The Paleolithic (or Paleo) diet, inspired by our ancestors' eating habits, emphasizes whole foods and excludes processed items. The leading idea is that the human digestive tract has not evolved to handle the dietary changes of the Westernized diet, thus determining the onset of different pathologies such as obesity, diabetes, hypertension and other chronic diseases. The diet promotes food of the Paleolithic or 'Old Stone Age' era, before the agricultural revolution, which mainly includes lean, non-domesticated meats and non-cereal, plant-based foodstuff. The Paleo diet promotes the consumption of whole foods such as lean meats, fish, fruits, vegetables, nuts, and seeds, while it excludes processed foods, grains, legumes, and dairy products. It consists of a high-fiber, low-carb diet that has proven beneficial for weight loss in the short and medium-long time [57, 58]. In particular, it induced a significant weight loss (average: -6.5 Kg in 6 months; 95% CI) and a decrease of waist circumference (average: -11.1 cm; 95% CI) in post-menopausal obese women at 24 months [59]. Besides the effect on weight reduction, a potential direct anti-inflammatory action may be mediated by the low carb regimen and the high fiber content, that can increase the production of SCFAs, which modulate local immune response (decreasing IL-6, IL-8 and TNFα) and modify the intestinal microbiota [60].

Trials evaluating the feasibility and efficacy of paleo diet in IBD patients are still lacking, and only anecdotal data exist [61].

Despite the fact that the Paleo diet may be generally feasible in IBD, patients need to be cautious about specific components, such as high fiber content and certain nuts and seeds, that might exacerbate symptoms during flare-up. In particular, in CD patients, the suitability of the Paleo diet should be carefully evaluated, considering both potential benefits and challenges. In fact, the Paleo diet focuses on whole, unprocessed foods, which can be beneficial for individuals with CD. These foods are generally easy to digest and may be well tolerated during periods of disease activity. Some components of the Paleo diet, such as omega-3 fatty acids found in fatty fish and certain nuts and seeds, are known for their potential anti-inflammatory effects. On the other side, Paleo diet tends to be rich in fiber, promoting large consumption of fruits and vegetables. While fiber is essential for digestive health, individuals with CD may need to monitor and adjust their fiber intake according to the disease phenotype and individual tolerance, especially during flare-up. CD can affect nutrient absorption, and the exclusion of certain food groups in the Paleo diet may imply challenges in achieving a well-balanced nutrient profile. In fact, the exclusion from the diet of dairy, legumes, and whole grains may potentially reduce the assumption of certain fiber, vitamins, minerals, proteins, and calcium, which represent important elements of a balanced diet. Therefore, close attention to nutrient intake and potential supplementation may be necessary.

Low-fat Diets

Low-fat diets are characterized by reduction of daily calories by restriction of dietary fat intake. They have been used as a weight-loss diet for a long time, with a consistent reduction of utilization in the last decades in favor of low-carb diets, for the more rapid weight loss and the higher feasibility of the latter. In fact, in severe obese patients, low-carb diet was more effective than low-fat diet for weight loss and triglyceride levels reduction at 6 months [62], and a meta-analysis of 53 studies confirmed higher weight loss with low carb than with low fat diet [63]. Conversely, a low-fat diet, namely Ornish diet, was comparable to Atkins diet at one year, inducing a weight loss of 3.3 Kg and a BMI and waist circumference decrease of 1.4 Kg/m^2 and 2.2 cm, respectively, with a concomitant reduction of CRP and insulin level [42].

Several studies indicate an association with high fat consumption and increased risk of IBD [64], and the high-fat Western diet is associated with dysbiosis and activation of pro-inflammatory pattern [24]. In the experimental DSS model of colitis, high-fat, comparing with low-fat diet, exacerbated intestinal inflammation through alterations of dendritic cells homeostasis [65]. A large prospective study, including more than 400 UC patients, found that a high dietary intake of specific fatty acids, including myristic acid (commonly found in palm oil, coconut oil, and dairy fats) was associated with an increased risk of flare [66]. Considering that, limiting dietary fat may contribute to reduce microbiota alteration and mucosal inflammation. Preda et al. [67] demonstrated that IBD patients following a diet avoiding some food elements, such as red meat, processed meat, deep-fried items, foods rich in added sugars, sugar-sweetened beverages, and trans fats, had a higher rate of maintenance of clinical remission, compared with patients on a free diet [67]. In a recent pilot cross-over study, 17 UC patients in remission or with mild disease were randomized to a standard or low-fat high-fiber diet for 4 weeks and, after a 2 weeks wash out, switched to the other diet regimen for 4 more weeks. The low-fat high-fiber diet was well tolerated, improved the quality of life, and reduced inflammatory markers (serum A amyloid and CRP) and dysbiosis (decrease of *Actinobacteria* and increment of *Bacteroidetes* and *Faecalibacterium prausnitzii*) [68]. On account of the small number of subjects, the short duration of the dietary intervention, and the inclusion of patients both in remission and with mild disease, further larger scale studies are needed to confirm the attractive preliminary findings of this study.

A particular concern for a low-fat diet in IBD patients could be the possible decreased absorption of important nutrients, such as fat-soluble vitamins (A, D, E, K) and essential fatty acids (omega-3 and omega-6), as these elements play an essential role in homeostasis maintenance and inflammation control. In this regard, restricting global fat consumption but assuming smaller amounts of healthy fats, such as avocados, nuts, seeds, and olive oil, may be a useful adaptation of low-fat diet in IBD patients.

Plant-based Diets

The plant-based diets promote the consumption of nutrient plant foods, such as vegetables, fruits, beans, peas, lentils, soybeans, seeds, and nuts, limiting processed foods, oils,

and animal foods (including dairy products and eggs). They include diets with various moderating consumption of animal foods, ranging from a strict vegan diet (no animal food nor products from animals, such as eggs and milk) to a lacto-ovo vegetarian or semi-vegetarian diet, where animal derived food and small amounts of lean meat are allowed. Although often the primary purpose the adoption of a whole healthy attitude of life and a nature respectful lifestyle, many individuals try plant based diets for weight loss, since these diets often promote lower calories intake and higher fiber content, inducing satiety and reducing the likelihood of overeating. In a randomized prospective study with five different nutritional regimens, vegan diet was significantly more efficient in inducing weight loss (-7.5% ± 4.5%) after 6 months, compared with other vegetarian regiments or control omnivorous group [69].

A well-balanced plant-based diet can provide essential nutrients, vitamins, and antioxidants via fruits, vegetables, whole grains, and legumes, with a positive contribution to overall health. Alimentary fibers may contribute to intestinal homeostasis and exert anti-inflammatory effect at mucosal level in IBD patients mainly through a double mechanism [60]. First, fiber represents the substrate for production of SCFAs by intestinal bacteria species, through a fermentative process. In turn, SCFAs, and in particular butyrate, exert multiple fundamental intestinal and extraintestinal effects, including immunomodulation, regulation of mucosal inflammation, stimulation of barrier function, nutrient absorption, cell proliferation and differentiation, microbiota balance, insulin sensitivity [70]. Moreover, fiber can act as prebiotic selectively stimulating intestinal bacterial species with positive effects, such as *Bifidobacteria* and *Lactobacillus*.

Although well-designed randomized clinical trials are lacking, preliminary uncontrolled studies explored the feasibility and efficacy of plant-based diets in IBD patients, suggesting a potential adjunctive effect to pharmacological therapy for induction and maintenance of remission in UC and CD patients [71-74].

Plant-based diets represent a healthy and feasible option for IBD patients, but high fiber load may not be appropriate in some cases. In fact, in patients with uncontrolled disease, fiber can exacerbate symptoms of IBD, such as diarrhea and abdominal pain, and caution should be paid in CD patients with intestinal stenosis. However, with a careful planning, consideration of individual tolerances, and careful balancing of liquids and nutrient assumption (i.e. protein, iron, calcium, and vitamin B12), plant based diets can be effectively adopted.

Mediterranean Diet

The Mediterranean diet is a typical dietary pattern adopted in the Mediterranean area, characterized by a relative high intake of fresh vegetables, fruits, unprocessed cereals, olive oil, nuts and legumes, a consistent consumption of fish and of dairy products (mostly cheese and yogurt), as well as a lower consumption of sweets, meat and meat products. It has been proposed not only for weight control but for general health promotion.

In fact, consistent evidence, mainly coming from population-based observational studies, supports a protective effect of MD against cardiovascular disease, stroke, metabolic disorders, several types of cancer, allergic diseases and Parkinson's and Alzheimer's disease [75-77]. Nonetheless, the impact of this diet on IBD course remain unclear. In an uncontrolled study, 142 IBD patients (84 UC and 58 CD), after 6 months of MD, improved BMI (UC -0.42, p=0.002; CD -0.48, p=0.032) and waist circumference (UC -1.25 cm, p=0.037; CD -1.37 cm, p=0.041), with amelioration of inflammatory biomarkers and symptoms [78]. Several experimental studies confirmed that adherence to MD has a role in modulating the expression of inflammation-related genes and suggested a potential favorable anti-inflammatory effect [79, 80]. Many studies from the Mediterranean area have linked the adherence to MD to an improvement of clinical and laboratory disease activity index in both CD and UC patients and suggest a role of MD in reducing intestinal inflammation as well [78, 81, 82]. Moreover, MD can favorably influence microbiota composition, with increment of *Bifidobacteria/Escherichia coli* ratio, *Faecalibacterium prausnitzii* and *Akkermansia*, and reduction of *Escherichia coli* and *Fusobacterium*, with an increase of SCFA production [83, 84]. Specifically, the consumption of olive oil positively stimulates the microbiota and exerts an antioxidant effect, for the presence of biophenols [85, 86]. Additionally, the MD meets the recommendation of the International Organization for the Study of IBD: reduction of saturated fatty acids, red meat and myristic acid intake and increasing consumption of fruits, vegetables and omega-3 fatty acids, reduction of the intake of emulsifiers, thickeners, maltodextrin, artificial sweeteners, and processed food containing titanium dioxide and sulphites, since all these may increase intestinal permeability and inflammatory markers in gastrointestinal tissues [87].

Besides these positive indications, there is no evidence that MD, similarly to other alimentary regimens, can modify by itself the disease course in IBD patients and reduce consistent outcomes such as disease flares, hospitalizations, and need for additional treatments and surgery [17]. However, this diet regimen may be a beneficial factor for weight and inflammation control in IBD patients, and it has been recently suggested as beneficial in such patients by the American Gastroenterological Association (AGA) [12]. Nevertheless, it must be kept in mind that some products in MD may not be tolerated by patients with CD or UC patients, and therefore MD should be personalized with the aim to reduce potential symptoms-triggering elements (i.e. raw vegetables). Moreover, MD is rich in dietary fiber, which can be challenging for individuals with IBD during flare-ups and in stenosing CD.

CONCLUSIONS

Both obesity and IBD prevalence are rapidly increasing in modern society, and the proportion of obesity among IBD patients is reported to be higher now than in the past. In this narrative review, we considered the relationship between selected diets and clinical course of IBD, focusing only on effects of most common and "trendy" weight loss diets. Hopefully, in the near future, nutritional assessment/intervention would become an integral part of the management of IBD patients, thus requiring on one hand an increased expertise in nutrition by IBD specialists, and on the other hand the closer and closer

collaboration with nutritional specialists, who would be an essential part of the multidisciplinary IBD team.

Conflicts of interest: None to declare.

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