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Take-Home Messages from 20 Years of Progress in Dietary Therapy of Inflammatory Bowel Disease

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Abstract

Background: A significant body of literature has interrogated the critical role of diet in the development and management of inflammatory bowel disease (IBD). ***Summary:*** This review provides a summary and critical appraisal of the literature in this area, focussing on four distinct themes: nutritional epidemiology, animal and in vitro experiments, enteral nutrition, and food-based dietary therapies. ***Key Messages:*** Nutritional epidemiology and data from experiments in animals indicate that a western-type diet pattern is associated with increased risk of IBD onset. However, these findings have not been consistently replicated in the dietary management of IBD. Exclusive enteral nutrition (EEN) is the only dietary therapy with reproducible evidence of efficacy in the management of active Crohn's disease (CD). Use of EEN may also be useful for improving perioperative outcomes in CD, and as an adjuvant therapy to biologic therapy. Several dietary therapies for CD and ulcerative colitis have been proposed in the literature, but replication in well-controlled studies is needed before their routine use enters the clinical setting. Precision nutritional therapy might be an attractive therapeutic paradigm in a heterogenous disease like IBD. However, no recommendations for personalised dietary therapy can currently be made, and it is imperative we unravel the complex interplay between diet and gut inflammation before we are able to do so. Undoubtedly, diet is of critical importance in the development and management of IBD. However, the exact mechanism by which diet causes gut inflammation is still elusive, and dietary guidance is difficult to formulate.

Introduction

There are few conditions for which diet and nutritional therapy are as important in the aetiology and management as that of inflammatory bowel disease (IBD). Patients have clear perceptions of the role of diet in IBD [1], but this area has also been interrogated by nutritional epidemiology, experiments in vitro, animal models of disease, and the development of mainstream and novel dietary therapies [2]. There remains, however, a fundamental question: "Are we currently in a position to use the available scientific evidence to make recommendations for the dietary management of

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patients with IBD?" In this narrative review, we summarise findings from important studies exploring the role of diet in the IBD course and allude to recommendations for dietary therapy, when such recommendations can be made.

Nutritional Epidemiological Studies of the Role of Diet in IBD

Nutritional epidemiology and genetic studies suggest that environmental exposures and their interactions with the gut microbiome, particularly in individuals with genetic susceptibility, are implicated in the underlying pathogenesis of IBD [3]. Findings from prospective cohort studies suggest that a dietary pattern based on the principles of the Mediterranean diet, characterised by high consumption of fruits, vegetables, fibre, and fish, is associated with reduced risk of IBD onset, particularly of Crohn's disease (CD) [4]. Conversely, adherence to a Western dietary pattern has been linked to an increased risk of IBD development [5, 6]. Among the various components studied, increased consumption of ultra-processed food has been linked with CD development [7]. With regard to ulcerative colitis (UC), a positive association between intake of animal protein and red meat and risk of disease onset has been observed [8, 9].

Association studies have also explored the relationships between diet and risk of disease relapse in individuals with previously diagnosed IBD receiving medical treatment, yet cumulative evidence remains largely inconclusive [10–12]. As a prime example, while the intake of processed meat was not predictive of risk of future disease relapse in patients with UC in a multicentre, prospective study [13], high intake of red and processed meat was positively associated with higher risk of clinical relapse in a research study conducted by another group [14]. One missing aspect of nutritional epidemiology is consideration of host factors, particularly the gut microbiome. It is possible that protective or causative dietary triggers might act differently in different populations, where microbiome is likely to be an important modifier of the influence of diet causing IBD development.

Most importantly, findings from nutritional epidemiology have not yet been replicated in human dietary intervention trials, neither in the prevention nor in the management of IBD. Interventions using prebiotics or high-fibre supplementation failed to induce or maintain remission in patients with CD [2] (Fig. 1). Likewise, in the DINE-CD trial, raised inflammatory biomarkers (C-reactive protein and faecal calprotectin) did not improve in patients with CD who followed a Mediterranean diet for 12 weeks [15]. There is also no supportive evidence to show that supplementation with n-3 polyunsaturated fatty acids is beneficial in the management of CD and in patients with active disease or in remission [16]. This is despite dietary enrichment with n-3 fatty acids being part of a dietary recommendation for prevention from the European Society for Clinical Nutrition and Metabolism [17]. It is also noteworthy that a diet low in red and processed meat was ineffective in maintaining disease remission in CD compared to a diet which included consumption of more than 2 portions of red and processed meat per week [18].

Like CD, nutritional epidemiology signals have not been translated into effective dietary treatments in the management of UC. Supplementation with n-3 fatty acids has failed to improve disease outcomes [19], whereas data remain inconclusive regarding the use of prebiotics or high-fibre supplementation in improving disease outcomes [20]. Emerging research has underpinned the potential benefit of curcumin in the management of UC, though data need to be further replicated in well-controlled trials [21].

There are various reasons why findings from nutritional epidemiology have not been useful in informing the dietary management of IBD. Observational data can be influenced by reverse causation, confounding variables, and the use of inappropriate dietary assessment methods to capture dietary intake. A typical example is the estimation of intake of ultra-processed food using food frequency questionnaires from cohort studies designed to explore the relationships between diet and future risk of cancer development in middle-aged adults [9, 22]. It is also likely that participants' diet has changed in the intervening period between study enrolment and close to the point of disease onset. Regarding the role of food additives in IBD onset, current legislation does not mandate manufacturers to disclose the concentration of additives in foods, making human exposure to these additives, through diet, impossible to estimate. It is also possible that the role of diet is not the same in IBD initiation compared to disease management, albeit evidence to support such speculation is currently missing.

Take-home message: *We cannot at present make firm recommendations for the dietary management of IBD based on current evidence from nutritional epidemiology.*

Animal Experiments on the Role of Food Additives and Other Food Ingredients in IBD

Mechanistic in vitro studies and experiments in animal models of colitis suggest that food additives, such as carrageenan, carboxymethylcellulose, maltodextrin, and

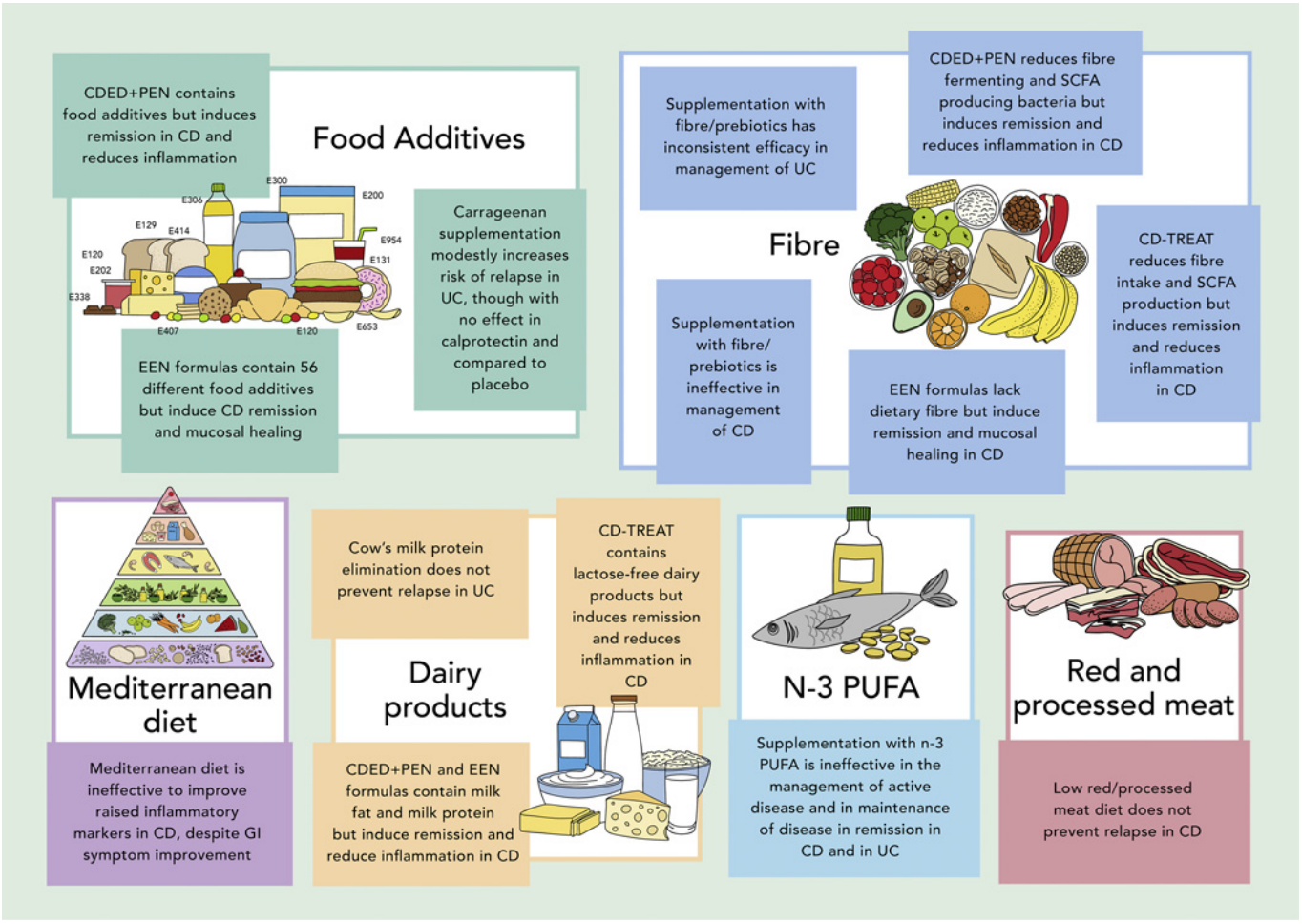

Fig. 1. Paradoxes of the role of diet and nutritional therapy in the management of inflammatory bowel disease.

polysorbate 80, initiate or aggravate gut inflammation and increase intestinal permeability through innate and adaptive immunity mediated via microbial dysbiosis [23]. Upon such preclinical evidence and supported by epidemiological findings associating ultra-processed food with the risk of IBD development, the International Organization for the Study of IBD, among other professional associations [24], introduced guidance proposing the exclusion of ultra-processed food and food additives as an important component of a management plan for people with IBD. However, it is imperative that findings from animal studies are confirmed within well-designed human randomised controlled trials (RCTs), preferably prior to any recommendations being made. In a recent pilot RCT in healthy volunteers, consumption of 15 g of carboxymethylcellulose led to alterations in the faecal metabolome and microbiome, however, importantly, without eliciting significant inflammatory effects or altering gut permeability [25]. In another small RCT in people with quiescent UC, adherence to a carrageenan-free diet was associated with lower disease relapse rates compared to participants on a carrageenan-containing diet; nonetheless, no differences were observed in levels of faecal calprotectin (FCAL), an objective biomarker of gut inflammation, between the two groups [26]. In contrast, provocative data from the comprehensive compositional analysis of exclusive enteral nutrition (EEN) formulae, with published efficacy in inducing remission and improving disease biomarkers in patients with active CD, reported 56 different food additives in 61 distinct formulae, many of which had been previously implicated in disease pathogenesis [27]. Interestingly, despite the current belief that certain food additives may instigate gut inflammation based on findings from animal studies, the clinical efficacy of EEN was found to be unrelated to the presence of these additives in the composition of EEN formulae [27] (Fig. 1).

Similar to food additives, cow's milk fat components were shown to induce dysbiosis, promote expansion of the sulfite-reducing pathobiont, *Bilophila wadsworthia*, induce pro-inflammatory Th1 immune response, and increase incidence of colitis in IL-10 −/− mice [28]. These findings mechanistically implicated milk fat in the underlying biology of CD and UC, evidence the International Organization for the Study of IBD used to recommend avoidance of dairy products in the management of IBD [24]. Once more, these preclinical findings and dietary recommendations are challenged by the use of EEN in patients with CD, which constitutes a high-fat diet rich in cow's milk fat. Similarly, these recommendations are also challenged in UC, where a diet which eliminated cow's milk protein did not influence short- and long-term disease activity compared with an unrestricted diet in children with new-onset UC [29].

Experiments in animal models are of crucial importance in understanding mechanisms of action of therapies or fundamental aspects of disease pathogenesis. Nonetheless, translation of their findings to human disease is subject to several limitations. Animal models of colitis are used to simulate human IBD, but there are inherent physiological and biological differences between animals and humans, and since the exact cause of IBD in humans remains unknown, it is impossible to simulate this precisely in an animal model. Furthermore, the dosage of food additives in animal studies is often excessive and does not necessarily mirror human exposure conditions, making direct comparisons challenging. Ongoing studies like the ADDapt Diet trial (NCT04046913), which explores the impact of a low-food additive diet on gut inflammation in people with active CD, will improve the clinical translation of research hypotheses generated from animal experiments.

Take-home message: *Firm recommendations on restriction of food additives and other food components in IBD should not be made unless preclinical evidence is replicated in human intervention trials in people with IBD.*

Enteral Nutrition in the Management of Crohn's Disease

Exclusive enteral nutrition involves the consumption of a liquid-only diet without any other food for 6–8 weeks. Exclusive enteral nutrition is a first-line therapy for induction of remission in CD in children [30]. Adherence to EEN induces remission in approximately 80% of children with active CD, ameliorates blood and faecal inflammatory markers, restores nutritional deficits, and induces higher mucosal healing rates compared to treatment with oral corticosteroids [31, 32]. A single RCT assessed the effectiveness of conventional therapy with EEN or steroids compared to treatment with anti-TNFα biologics [33]. In this study, the effectiveness of infusion with infliximab was superior to conventional therapy with EEN or oral prednisolone in patients with moderate-severe CD. Normalisation of FCAL was also observed in a higher proportion of patients on treatment with infliximab. While not denigrating the effectiveness of treatment with biologics, there are two important reasons why the effectiveness of EEN was significantly understated in this study. First, efficacy outcomes were not assessed at the point of EEN completion (6–8 weeks), but instead, they were delayed 2–4 weeks after food re-introduction. The impact of this timing is critical as we have shown that the efficacy of EEN is lost rapidly, in most patients, after return to normal diet [34]. In a previous study, levels of FCAL increased by 91% within 17 days of food re-introduction (median [IQR]; baseline, 430 [141, 1,047] vs. at EEN completion (8 weeks), 953 [519, 1,611] mg/kg, $p = 0.025$). Second, the authors did not assess compliance to EEN, nor any implications this may have had on their findings. We have recently shown that patients deemed compliant to EEN, according to clinical dietetic assessment, were still not adherent to the exclusivity of treatment, as shown by the detection of gluten immunogenic peptides in stool, a nutrient derivative which is lacking from all EEN feeds [35]. Importantly, in this previous study, patients with detectable gluten immunogenic peptide had significantly higher levels of FCAL than those with a negative test result at EEN completion; further masking the true effectiveness of EEN on gut inflammatory markers.

Although EEN is not used commonly for induction of remission in adults with CD, mainly due to palatability and compliance issues rather than lower efficacy, there is interest in the use of enteral nutrition beyond induction of disease remission. Other areas of usage of EEN include pre-surgical use as rescue therapy in patients with CD refractory to medical therapy or to improve perioperative outcomes including lowering risk of postoperative complications [36]. The use of partial enteral nutrition (PEN) as treatment for maintenance of disease remission has attracted significant interest in the literature [37]. A recent comprehensive literature review showed that an intake greater than 35–50% of calorific intake is required in general to prolong disease remission [38]. Volumes lower than these threshold values, particularly in patients who receive PEN as supplement and not as replacement to their habitual diet, are unlikely to be of any significant benefit in prevention of disease relapse.

With lower treatment costs and better long-term disease control [39], biologic agents are now increasingly used in patients with CD while EEN is still recommended as first-line therapy for children with mild/moderate luminal disease [30]. Although biologics are effective in inducing clinical remission and ameliorating mucosal inflammation, the risk of loss of response and disease relapse within 1 year of treatment initiation is still a consideration, and there is clearly a therapeutic efficacy ceiling [33]. Data from retrospective studies, mainly from Japan, show that combining biologic agents with PEN might be a more effective strategy than biologics alone for induction and maintenance of remission in adults with CD [40, 41]. Since the mechanisms of action of biologics and enteral nutrition are distinct, with the first inhibiting immune system propagation and the second postulated to be excluding dietary disease triggers and how these interact with the gut microbiome, it is possible that combining these two regimes would enhance the primary response to biologic therapy and reduce the risk of secondary loss of response and immunogenicity. We have noted an emerging trend in the use of EEN in combination with biologics in a subcohort of children with severe disease which has emerged over the past few years [42]. The BIOPIC study, a major international multicentre RCT in adults with CD, is currently underway (NCT04859088) to study the effect of monotherapy with anti-TNF alone compared to in combination with PEN.

Take-home message: *EEN remains an effective treatment in inducing remission in CD and may also be used in improving peri-surgical outcomes in patients with CD. Combination treatment with biologic therapy and enteral nutrition is a current/future treatment option in patients with active CD.*

Food-Based Dietary Therapies for the Management of IBD

Exclusive enteral nutrition is a successful treatment in the management of CD, but, given its monotony and the importance of diet in all aspects of human life, it would be impractical to recommend it for long-term disease management. Hence, there has been a strong interest from patients and healthcare professionals in developing ordinary food-based dietary therapies for managing IBD [2]. Several novel dietary therapies have shown efficacy in improving disease symptoms, clinical activity indices, and quality of life indices. None of these diets have, however, consistently demonstrated reproducible evidence in improving blood, gut biomarkers, or endoscopic disease activity [2]. Among those dietary therapies for the management of IBD, both the Mediterranean and the specific carbohydrate diet failed to improve abnormal disease biomarkers in patients with active CD in a recent RCT, though pre-treatment FCAL was raised in less than a quarter of participants, making objective assessment of efficacy difficult [15] (Fig. 1). The Crohn's disease treatment with eating (CD-TREAT) diet, based on normal foods with similar nutritional composition and microbial effects as EEN, improved gut inflammatory markers in an animal model of disease. This efficacy signal was further confirmed in a pilot study of five children with active CD, where CD-TREAT induced 80% clinical remission and a 50% reduction in baseline FCAL levels [43]. In a recent open-label trial in 57 children and adults with active CD, treatment with CD-TREAT for 8 weeks induced remission in more than 75% of patients, improved quality of life scores, and, most importantly, significantly decreased the pretreatment levels of FCAL in patients who were treatment compliant [44].

Currently, the only dietary therapy with reproducible published evidence of efficacy in the management of active CD is the Crohn's disease exclusion diet (CDED) when coupled with PEN. This is a dietary regime which excludes dietary components implicated in the development of CD from nutritional epidemiology and animal models [45]. Food additives, gluten, dairy products, and red meat are excluded, whereas the diet promotes the intake of fruit and vegetables, aiming to increase the production of presumptively beneficial SCFA and to restore microbial dysbiosis. In addition to these dietary exclusions, CDED is coupled with 50% PEN and the daily mandatory intake of 5 foods (i.e., chicken, eggs, potato, apple, and banana). Reproducible data shows that CDED + PEN improves disease activity and faecal/systemic inflammatory biomarkers [46, 47]. However, the specific mode of action remains elusive, and the choice of dietary restrictions is arbitrary rather than strictly scientifically justified.

Implicit in the use of PEN covering 50% of patients' energy requirements is that food additives, dairy protein, and fat are consumed instead of avoided. Moreover, the daily consumption of five mandatory foods alongside PEN means that ~90–95% of a patient's daily energy intake comes from these two sources (PEN and 5 mandatory foods), thereby automatically and markedly restricting the consumption of any additional foods. Additionally, the intake of dietary fibre is unlikely to be significantly increased during the CDED intervention, as microbiome signals demonstrated a reduction in the baseline abundance of *Bifidobacteria*

and *Prevotella*, two microbial groups whose colonisation is dependent on the levels of fermentable fibre in the colon [48]. These data suggest that a plausible mechanism of action of CDED might simply be via a reduced intake of fibre-containing foods, like EEN and CD-TREAT. In support of this, a recent study showed that unfermented β-fructans exacerbated inflammation in certain patients with IBD [49]. Likewise, in a pilot study in children with CD, higher intake of fibre and higher levels of faecal butyrate, a biomarker of fermentable fibre intake, were associated with higher levels of FCAL, up to 2 months following completion of successful EEN therapy [12].

More research is anticipated in the area of novel dietary therapies for CD and UC. Since placebo-controlled RCTs in dietary therapy are almost impossible to design, objective biomarkers of disease activity will help mitigate against placebo effects and investigators' bias, particularly when these two types of biases are common in dietary interventions and in patients with mild/moderate disease activity at study enrolment [50]. Irritable bowel syndrome symptoms are common in patients with IBD, and dietary therapies are often used as a mainstream management option [51]. It is therefore plausible/likely that the apparent "success" of some dietary interventions is mediated through functional symptom improvement but no fundamental change to IBD inflammation.

In most studies exploring the efficacy of food-based therapies for the management of IBD, dietary assessment was either inadequate or entirely lacking as was compliance assessment to the dietary intervention. Dietary assessment is of utmost importance as it could help pinpoint food items which might contribute positively or negatively to the efficacy of diet. Such data would ultimately allow patients to liberalise their dietary choices with no limitations on innocuous dietary components and food. Researchers and healthcare professionals should leverage opportunities to use novel, objective biomarkers to assess dietary intake and adherence to dietary therapies [52]. For instance, the measurement of gluten immunogenic peptide in faeces could serve as a valid biomarker of dietary transgressions with the use of gluten-free dietary therapies like EEN, CD-TREAT, and CDED + PEN. Combining dietary therapy with microbial therapeutics or conventional drug therapy may unlock new opportunities for future research [53].

Take-home message: *Except for EEN, PEN coupled with CDED and the daily inclusion of five mandatory foods has the best published record of effectiveness, but the mode of action remains elusive, and several dietary restrictions may be unnecessary in a population at risk of disordered eating/nutrition.*

Precision Dietary Therapy

Dietary management that applies information about a person's genetic, microbial, and environmental footprint to disease treatment has attracted significant interest in cardiometabolic diseases, yet similar attempts in IBD are only just underway. The only exception is with the use of EEN, where evidence shows that its efficacy is higher in patients with an inflammatory disease phenotype and perhaps in active disease involving the ileum [54, 55]. Microbiome data suggest that a high microbiota richness and a certain microbiota compositional profile, prior to treatment initiation, may discriminate patients who responded to EEN from those who did not, yet independent replication and testing of this hypothesis within RCT are lacking [56, 57].

Before we can properly exploit precision dietary therapy in IBD and inter-individual responses to the latter, it is of critical importance to unravel the complex role of food in causing gut inflammation in IBD and ultimately identify which dietary components initiate or propagate gut inflammation. The emergence and wide availability of omics technologies, systems biology, and artificial intelligence in the past decade presents significant opportunities for in-depth integration of complex environmental, genetic, immune, and microbial data. Studies like PREDICCT (NCT03282903) and IPENS (NCT04225689) aim to lay the groundwork for precision nutrition therapy in IBD and may allow the development of personalised dietary interventions tailored to an individual's biology, gut microbiome, and environment.

Take-home message: *While there is emerging interest in precision nutrition therapy in IBD, there is currently no data to make individualised dietary recommendations for optimal disease management.*

Conclusion

Collectively, especially over the past 10 years, there have been major advances in our understanding on how diet can influence risk of development of IBD; yet better-quality research is warranted to translate these data to routine management of IBD and to transfer it from the bench to the patient's bedside and ultimately to home.

Caution is required in advising people with IBD to restrict their diet unless there are clear reasons based on sound clinical reasoning.

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Conflict of Interest Statement

K. Gikas reports PhD studies funding from the Nestle Health Science. R Russell reports speaker's fees, travel support, advisory boards from Nestle, AbbVie, Celltrion, and Pharmacosmos. K. Gerasimidis reports personal fees from Nutricia-Danone; research grants and personal fees from Nestle Health Science; and personal fees from Dr Falk Pharma, Abbott, Servier, Janssen, AbbVie, Mylan, and Baxter. The rest of the authors have no conflicts of interest to declare.

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Author Contributions

Konstantinos Gkikas and Konstantinos Gerasimidis searched the literature and wrote the first draft. Dr. Vaios Svolos, Dr. Richard Hansen, and Prof. Richard K. Russell critically appraised the literature presented and revised the manuscript. All authors agreed to the publication of the final article.

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