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Review Article

Ultra-Processed Foods, Gut Health, Autoimmunity and Diets

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Abstract

In this mini-review the associations between ultra-processed foods (UPFs) and the rising prevalence of autoimmune disease (AD) are discussed. The role of various diets and dietary fibres suggesting a beneficial effect on both gut microbiota and autoimmunity are reviewed. Although, a lot of autoimmune diseases are associated with dysbiosis of the gut, special emphasis is given to rheumatoid arthritis(RA) and celiac disease(CD). The overlapping syndromes, Non-Celiac Gluten Sensitivity(NCGS) and the irritable bowel syndrome (IBS) are discussed too.

Introduction

Ultra-processed foods are invented by food technologists by adding industrial agents and additives to fruit, vegetables, meat or fish to cook a fresh meal at home [1] More than half of the food purchased by U.K. households is ultra-processed, reported mainstream media, recently [1,2]. Ultra-processed foods (UPFs) are not modified foods, but formulations mostly of cheap industrial sources of dietary energy and nutrients plus additives, using a series processes (hence “ultra processed”). All together, they are energy-dense, high in unhealthy types of fat, refined starches, free sugars and salt and poor sources of protein, dietary fibres and micronutrients [2].

The average household availability of UPFs ranged from 10,2% in Portugal and 13,4% in Italy to 46,2% in Germany and 50,4 % in the U.K. Each percent increase in the household availability of UPFs results in an increase of 0,25% points in obesity prevalence [3] In a large French study, the Nutrinet-Sante study (n=74.470) UPFs contributed 18,4% of the foods consumed in weight and 35,9% of total energy intake. Higher UPFs consumption was indepently associated with male gender, younger age, lower education, smoking and overweight, and obesity (all p<0,0001). Participants in the highest UPF quartile consumed lower amounts of fruits and vegetables and higher amounts of sweet products and soft drinks.

They had higher intakes of energy and added sugar and lower intakes of fibres, beta-carotene and calcium (all p<0,001) [4]. Most UPFs packaging features nutrition and health, and health statements or claims, despite the high prevalence of added sugars [5]. Influencing purchasing UFPs by short-term social media –campaigning provided little evidence to suggest these are effective [6].

Unprocessed or minimally processed foods had the highest dietary energy contribution (54% of energy), followed by UPFs (29.8% of energy), processed culinary ingredients (10,2%) and processed foods (6.0%) of all NOVA food classes [7]. The energy contribution of UPFs was the highest in pre-school children. In 2012, about 30% of energy in the Mexican diet came from UPFs [8]. In fact, about half of American adults have one or more diet-related chronic diseases such as obesity, heart disease, hypertension and cancer [9]. More and more evidence shows that the types of food we eat have a worsening effect on our gut health and the immune system. Autoimmune disorders are on the rise for the last 3 decades and a link between UPFs, and the microbiome-leaking gut syndrome has been suggested [10-12]. In this mini-review the role of ultra-processed foods, dietary fibres and various diets, suggesting a beneficial effect on both gut microbiota and linked autoimmunity, with a special emphasis on rheumatoid arthritis (RA) and celiac disease (CD) are discussed [13].

The gut microbiome and autoimmunity

Several autoimmune diseases are associated with dysbiosis of the gut, including rheumatoid arthritis (RA), primary Sjögren; syndrome (pSS), SLE, systemic sclerosis(SSc), Behcet's syndrome (BS), ankylosing spondilitis (AS), celiac disease and Hashimoto thyroiditis, and diabetes mellitus [14]. The role of UPFs and diets in these disorders will be discussed for RA and CD.

Rheumatoid Arthritis (RA)

Patients with RA often ask whether specific foods, popularized as inflammatory or anti-inflammatory, can improve or worsen their RA. Tedeschi *et al.* mailed a dietary survey to 300 subjects in a single-centre RA registry and a large academic centre. Subjects were aked about their consumption of 20 foods and whether these foods made their RA symptoms better, worse or unchanged. Of the 217 subjects (72% response rate),83% were female, median RA duration was 17 years and 53% were taking a biologic disease-modifying anti-rheumatic drug (DMARDs). Twenty-four percent reported that foods affect their RA symptoms, with 15% improving and 19% worsening. Blueberries and spinach were the foods most often too reported to improve RA synthesis, while soda with sugar and desserts were those most often to worsen RA symptoms.

A 2009 Cochrane library analysis, (n=837,14 RCTs,1 CCT) concluded that the effects of dietary manipulation, including vegetarian, Mediterranean, elemental and elimination diets on rheumatoid arthritis are still uncertain, due to the included studies being small, single trials with moderate to high risk of bias. Higher drop-out rates and weight loss in the groups with dietary manipulations indicate that potential adverse effects should not be ignored [16].

Bloomfield *et al.* found in a meta-analysis that a Mediterranean diet with no restriction on fat intake may reduce the incidence of cardiovascular events, breast cancer and type2 diabetes mellitus but may not affect all-cause mortality. RA was not specifically represented, but number of trials were few (2 primary prevention trials and 3 secondary prevention trials), the studies had medium risk-of –bias ratings, low or insufficiënt strength of evidence for outcomes and heterogenous diet definitions and components [17].

Among modifiable dietary factors, fish consumption is of particular interest due to its role in primary prevention of several chronic diseases [18,19]. Moreover, fish is rich in long-chain n-3 polyunsaturated fatty acids, which have been shown to be beneficial in primary and secondary prevention of RA [20,21]. The association of fish consumption with risk developing RA is still unclear, because results from both case-control and cohort studies are mixed. DiGuiseppe *et al.* tried therefore to quantitatively summarize the published evidence from epidemiological studies on the association between fish consumption and RA using a dose-response meta-analysis. They found a non-statistically significant inverse association between fish consumption and RA [22].

Recently, German researchers suggested that a diet rich in fibres significantly increased bone mass and prevented postmenopausal bone loss in mice. It is not the intestinal bacteria themselves, but rather their metabolites, which affect the immune system and therefore have a knock-on effect on autoimmune diseases such as RA. A healthy rich in fibres diet is capable changing intestinal bacteria in such a way that more short-chain fatty acids (SCFAs), in particular propionate and butyrate are formed [23]. Gut microbiota play a role in modulating the immune response both locally and systemically, beyond repressing pathogenic microbes [10]. Endocrine effects of bacteria influence a variety of host responses, including immune function. SCFAs by butyrate may play a role in gastrointestinal hormone expression. Microbiota can also produce autoantibodies, increasing the expression of peptide hormones [24].

Abdalraham *et al.* evaluated the efficacy of probiotics as an adjunct therapy in 361 patient's patients with rheumatoid arthritis. The level of the pro-inflammatory cytokine IL-6 (interleukine -6) was significantly lower in patients taking probiotics compared with patients taking placebo, but there was no significant difference between the two groups in the disease activity score. In patients with RA the use of probiotics (bacteria belonging to the microbiome) as an adjunct therapy is associated with a reduction in the proinflammatory cytokine IL-6 levels but this does not translate into a clinical benefit. Randomized trials are warranted to investigate this further. However, this meta-analysis of 9 studies revealed some known basic facts [14,24,26,27].

a) Dysbiosis occurs in patients with auto-immune and inflammatory rheumatic diseases.
b) Genetic susceptibility and environmental factors interact with the host microbiotic.
c) Taxonomic and metagenomics sequencing reveal host-microbiota interactions.
d) Work is needed to understand how the microbiome changes over time in autoimmunity.

e) Altered diet, as e.g., UPFs, the explosion of antibiotic use and decreasing contact with the microbe – packed natural world of animals and plants have all combined to transform the bacteria that humans call "home", changing the microbiome over the past 50 years.

The large bowel microbiome is designed to never see sugar. Fructose is cleared by the small intestine in mice and that protects the liver and large bowel microbiome from sugar exposure. But as soon you drink the soda of juice of ultra-processed foods theoretically fructose might reach and alter the colonic microbiome [28].

Celiac Disease (CD)

Ultra-processed foods are ready-to-heat and ready to- eat products, created to replace homemade meals and dishes due to convenience and accessibility. They could impact in the prevalence of autoimmune diseases such as type 1 diabetes and celiac disease by causing dysbiosis, promoting a proinflammatory response and consequently a "leaky gut". These factors have been associated with increased risk in genetically predisposed children. In addition, food emulsifiers, commonly used in ultra-processed products could modify the gut microbiota and intestinal permeability, which could increase the risk of autoimmunity. In contrast, unprocessed and minimally processed food-based diets have shown the capacity to promote gut microbiota eubiosis, anti-inflammatory response, and epithelial integrity, through bacterial butyrate production [29].

About 3 million Americans have celiac disease, an autoimmune disorder that is triggered when they eat gluten. Gluten is a protein found in wheat, barley, rye and other grains. Gluten is the protein that makes dough elastic and gives bread its chewy texture. Celiac disease is not the same thing as a food allergy, so the symptoms will differ. If you are allergic to wheat, you may have itchy or watery eyes or a hard time breathing if you eat something that has wheat in it [50].

Celiac disease (CD) is an ideal model to study autoimmune disease, as it is the only autoimmune disease for which the trigger (gluten) is known. Thus the autoimmune process once developed, can be turned on and off with the addition and removal of gluten containing grains. The time of introduction of gluten can be precisely traced and the frequency and dose can be calculated. There is a highly specific humoral autoimmune response (auto-antibodies to tissue transglutaminase) that can be measured, which indicates the loss of tolerance to gluten [30]. Finally, there is a close genetic association with HLA (human leukocyte antigen) genes, DQ2 or DQ8. While 40% of the population may carry one of these genes, only 3% go on to develop CD [31]. However, essentially all individuals who go on to develop CD carry one or both of these genotypes. This allows for uniquely informative control groups. Patients who go on to develop CD can be compared to those who carry the genetic risk but do not go on to develop the disease (or who not yet developed the disease). These patients also can be compared to individuals with a family history of CD, but which do not carry the compatible genes and thus cannot develop CD [32].

CD is characterized by duodenal villous atrophy and can cause a wide variety of intestinal and extra intestinal symptoms.CD may be associated with abdominal distension, chronic diarrhoea and weight loss although the majority of patients present with a variety of non-classical manifestations, such as anemia, bloating, fatigue and lethargy. CD diagnosis is often delayed [33]. CD is also associated with excess mortality, lymphoproliferative disorders and osteoporotic fractures [34-36]. The path to the diagnosis of CD typically

starts with clinical suspicion for the disease and is followed by serologic testing, which in positive cases prompts esophagogastroduodenoscopy with duodenal biopsy. It is estimated that 20% of CD patients in the USA are not diagnosed [37-39].

Non Celiac Gluten Sensitivity (NCGS)

There has been a growing interest over time in the gluten free diet (GFD) among patients without CD or wheat allergy (WA), but who experience intestinal and extraintestinal symptoms related to the ingestion of gluten containing Foods. These patients are said to have NCGS [40]. An analysis of the NHANES (National Health and Nutrition Examination Survey) in 2009-2010 found that the majority of patients who maintain a gluten free diet (GFD) were not diagnosed with CD [41]. A market research study found that 30% of Americans reported that they have decreased their intake or are avoiding gluten completely [42]. A questionnaire in the UK found that more than 25% of patients with inflammatory bowel disease have tried a GFD [43].

But if you aren't celiac then should you really be on a gluten free diet? The gluten free food market is reported to have made $3,5 billion worth of global sales in 2016, as people look to reduce their intake of high GI (glycemic index) carbohydrates present in foods like white bread, which have long been linked to weight gain. However, researchers at Hertfordshire's University found that GF products contained more fat, salt and sugar than regular versions, while being up to two and half times more expensive [44,45]. A study, that followed more than 100,000 people from 1986 to 2012 found that while overall gluten consumption in celiac disease may not be related to heart disease risk, avoiding whole grain like wheat, barley and rye in order to avoid gluten may be associated with an increasing risk of heart disease [46]. Getting enough vitamin B and fibres in your diet is important, when going gluten free. Yet, despite the increasing awareness that a gluten free diet is no better for health, that hasn't stopped its soaring popularity. A 2016 poll of 2035 consumers showed 27% regularly bought lactose, dairy, gluten or grain free products. These are all on the supermarket shelves and are frequently ultra-processed [44].

Like CD the clinical picture of NCGS is variable and diverse and include symptoms such as diarrhea, constipation, bloating and abdominal pain as well as extra intestinal symptoms including anxiety, fatique, fibromyalgia, foggy mind, and headache [48].

There is a great overlap between NCGS and wheat-sensitive irritable bowel syndrome (IBS)- [49]. Ensuring exclusion of CD, prevalence figures of NCGS range between 0,6% and 10,6% [49]. The huge variability in prevalence figures is mainly explained by lack of diagnostic biomarkers. Therefore, a DBPC (double blind placebo controlled) approach using 8 gram of gluten is recommended as a challenging test [40]. However, this is difficult to undertake in clinical practice. Patients frequently refuse to re-introduce gluten into the diet. So, there are still very limited data on the overlap between NCGS and IBS-type symptoms. This is also reflected in the high levels of unsuccessful patient recruitment in studies to resolve these specific issues.

The hypothesis that NCGS could be a non-IgE mediated wheat allergy is based on clinical aspects, histological data and by new endoscopic findings. Recent findings have shown immunological activation in the intestinal mucosa of NCGS patients and gastrointestinal food allergies is often mediated by

IgE-independent mechanisms, involving mast cells, eosinophils and other immune cells. An increase in mucosal lymphocytes has been reported in a consistent percentage of patients with NCGS diagnosed by DBPC gluten challenges. An increased infiltration of innate lymphocytes in the rectal mucosa of NCGS patients has been reported with a decreased infiltration after resumption of a wheat-free diet (WFD). Further work is required to clarify if NCGS could have an association with either IgE or non IgE mediated allergy. Until now, trials are small, biased by patient intake and of insufficiënt power [49].

The presence of innate T-regulator cells (Tregs) in mucosa points to activation of the innate system indeed, but is no proof for an association with either an IgE or non-IgE mediated allergy, by for example activating the alternative complement system [14,50].

Symptoms of functional bowel disorders including irritable bowel syndrome (IBS) can be treated with a diet low in fermentable carbohydrates, named FODMAPs (fermentable, oligosaccarides, disaccharides, monosaccharides, and polyols)- [51]. The low FODMAPs diet is now included as first-line therapy and has been shown to provide symptom improvement in approximately 68%-76% of individuals [52]. Symptom improvement generally occurs following 3-4 weeks on the restrictive phase of the diet [53]. After the restrictive phase, patients are encouraged to reintroduce high FODMAPs foods to assess their tolerance to the individual subgroups. The aim of this re-challenge phase is to find a balance between good symptom control and expansion of the diet. Patients requiring the diet long-term the follow a "modified FODMAP diet" based on their tolerance without challenging [53].

High FODMAP foods, especially those containing fructans and galacto-oligosaccharides (GOS) are known to be prebiotic (the food microbiota eat) and 3-4 weeks of a low FODMAP diet has been shown to lead to marked alterations in the colonic microbiota [54,55]. However, the clinical significance of these changes is not known [53]. If reintroduction of some prebiotic high FODMAP foods, even in small quantities, have long term impact of dietary alteration on the microbiota has not been investigated.

Although the low FODMAP diet does not restrict entire food groups, reintroduction of high FODMAP foods will assist in improving food variety. There is a risk of nutritional inadequacy with implementation of any exclusive diet or dietary restriction [56]. Indeed, recent data demonstrate that more than half of patients, following a low FODMAP diet did not meet their recommended intakes of calcium and iron, although values were not dissimilar to the healthy population on a habitual diet. Those who met fibres recommendations from baseline to follow-up had sufficient calcium and iron intake [57] Some packaged, pre-made or ready to order foods (UPFs) can contain high FODMAP ingredients and it isn't always easy to spot them. Therefore, Low-FODMAP and High-FODMAP grocery lists and app's as the Monash FODMAP app have been developed [58].

Probiotics in CD

CD is an autoimmune enteropathy triggered by gluten proteins. Consequently, damage in the mucosa often occurs, accompanied by altered intestinal microbiota and increased epithelial impermeability. The causality association is not yet defined. It has been demonstrated that levels of Bifidobacteria and Lactobacilli are reduced in CD patients and thus these bacteria have seen as promisinsg targets for probiotic

(bacteria belonging to the microbiome) therapy. However, there is still lack of consensus regarding the shifts in bacterial composition, primarily at the species levels. Thus future studies should emphasize microbiota characterization with potential benefits to gut health. Strains capable of producing enzymes that degrade gliadin peptides and induce anti-inflammatory effects are believed to be better suited for the the treatment of this disorder [59]. The human microbiom with more than 100 trillion microorganisms is complex, however. In a recent study, Rochester' researchers showed that impairing Paneth cells, which serve as guard cells in the small intestine, by stressing them with Toxoplasma gondii, allowed microbiome bacteria of mice to invade the organs and cause major inflammation [60].

Conclusion

Ultra-processed Foods(UPFs) are now available in more than half of households in the U.S, and U.K. These ready to make and ready to order formulations consist mostly of cheap industrial sources of dietary energy and nutrients, plus additives and emulsifiers. They are energy-dense, high in unhealthy types of fat, refined starches, free sugars and salt and are poor sources of protein. Dietary fibres and micronutrients, while being up to two and half times more expensive than regular versions. UPFs are associated with diet-related chronic diseases such as obesity, heart disease, hypertension, cancer, but also with rising prevalence rates of autoimmune disease (AD).

More and more evidence shows that the types of food we eat have a worsening effect on our gut health, causing dysbiosis, which affects the immune system. RA patients clearly indicate their symptoms improve on blueberries and spinach and worsen on soda, sugar and desserts. A 2009 Cochrane analysis concluded that the effect of dietary manipulation of all sort of diets on RA is still uncertain due to small, single trials (n=847) with moderate to high risk bias.

Celiac disease(CD) is an ideal model to study autoimmune disease, as it is the only for which the trigger (gluten) is known. A gluten-free diet restores the histological hallmark of duodenal villous atrophy. Gluten proteins cause dysbiosis demonstrated by decreased levels of Bifida bacteria and Lactobacilli bacteria but the causality association is not yet defined. There is still lack of consensus regarding the shift in bacterial composition, primarily at the species levels. Strains capable of producing enzymes that degrade gliadin peptides and induce anti-inflammatory effects are believed to be better suited for the treatment of CD, but are not known yet.

There has been growing interest over time in the gluten-free (GF) diet by patients with Non-Celiac Gluten Sensitivity (NCGS) who were not diagnosed with CD. This resulted in a $3,5 billion worth of global sales of gluten-free products. Yet, despite the increasing awareness that a GF diet is no better for health in this population, that has't stopped its soaring popularity.

There is a great overlap between NCGS and wheat-sensitive irritable bowel syndrome (IBS) If NCGS is a non IgE mediated wheat allergy is not clear [50].

Symptoms of functional bowel disorders including IBS can be treated as first line therapy with a diet low in fermented carbohydrates, the FODMAP diets. These have a success percentage at 3-4 weeks of 70%. A shopping FODMAP app is available.

Our perception of the microbiome has changed rapidly the last decade, due to the metagnomic sequencing of the DNA and RNA repertoire present in the intestinal ecosystem and the reemergence of gnotobiotic approaches [24]. Fecal Microbiota Transplantation (FMT) showed a cure rate up to 90% in recurrent antibiotic resistant Clostridium difficile infection, but results for inflammatory bowel disease (IBD) are less convincing. If FMT is not suitable for most microbiome-based therapeutic developments refinement of microbiotic engineering by selecting a single bacterium could be a solution. Bacteriophage treatment is another possibility, but this needs an improved understanding of ecological interactions between bacterial and bacteriophage communities in the intestine [24].

There is a lack of standardization in the landscape of microbiome techniques, because the study of microbiota is still in its infancy. There is a surge of urgency to improve reproducibility between laboratories. Nevertheless, the future of microbiota seems bright. The role of the microbiome has to be elucidated further, preferable starting in paediatric CD patients [14].

As most modern drugs find their origin in endocrinology, a pharmacological approach could be based on future research in microbial endocrinology [24,61].

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