DIET AND THE GUT

WGO Handbook on
DIET AND THE GUT

World Digestive Health Day
WDHD – May 29, 2016

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YOUR DIET AND GUT HEALTH

Dear Colleagues,

For some time the public have been asking us about the relationship between what we eat and the subsequent development of gastrointestinal symptoms. One good example of this is celiac disease, which affects 1% of the population with the damage occurring in the gut as a result of eating gluten, a protein present in the wheat. More recently a new entity is emerging termed non-celiac gluten sensitivity which may affect more than 10% of the population.

Food intolerances are reported to be very common affecting up to 40% of individuals who have irritable bowel syndrome (IBS) type symptoms. A further exciting development is the dietary interventions studies showing benefit to patients with IBS when trying a FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, gluten free diet, or probiotics. However one area of confusion for both clinicians and the public alike are the entities of Food Allergy and Food Intolerance. Food allergy is predominantly a childhood diagnosis and is reported to affect 4-7% of children. Making the diagnosis is based on the presence of either an IgE immunoglobulin blood or skin prick test, however crucially patients must also report allergic symptoms. It is possible to have a positive IgE test as a marker of having been sensitized to the allergen but not actually develop an allergic response. Nevertheless we now consider that 1-2% of adults may also have food allergy (for example peanut allergy or seafood allergy). There are at present no tests for food intolerances, so distinguishing between food allergy and food intolerance is vital.

The World Gastroenterology Organisation (WGO) wishes to raise awareness of the relationship between what we eat and gastrointestinal symptoms through its annual public advocacy and awareness campaign, World Digestive Health Day (WDHD). WDHD is celebrated each year on May 29th, with associated activities and initiatives continuing throughout and beyond the campaign year. WDHD aims to provide a broad overview on this common association by providing gastroenterologists, and hence their patients and the lay public, with an understanding of the latest basic and clinical research in the role of food in our gut. "Diet and the Gut – '***Your Diet and Gut Health***'" is the WDHD campaign theme for 2016 and seeks to translate research into clinical practice and facilitate communication between healthcare providers, healthcare payers, and the public. We want to ensure that patients receive appropriate dietary and lifestyle advice as well as appropriate investigations and treatment, relevant to their condition, whether this is celiac disease, non-celiac gluten sensitivity, IBS, food intolerance, or food allergy. The WGO's task will be supported by the development of educational and training materials, around the world, in collaboration with WGO Member Societies and by the concurrent development and publication of the WGO Guidelines and Cascades on the management of different conditions where our diet may play a role.

Our colleagues and we from the WDHD 2016 Steering Committee look forward to a productive and successful campaign in providing a global perspective on diet and gut health.

Yours sincerely,

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WORLD DIGESTIVE HEALTH DAY 2016 STEERING COMMITTEE

The World Digestive Health Day Campaign is led by the following individuals representing a global view and expertise. They have guided the course of the WDHD campaign, leading in the development of tools and activities throughout 2016 and beyond.

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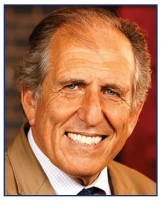

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MESSAGE FROM THE WGO PRESIDENT-ELECT AND CHAIR OF THE WGO FOUNDATION AND THE VICE CHAIR OF THE WGO FOUNDATION

World Digestive Health Day (WDHD) represents a very successful initiative of the World Gastroenterology Organisation (WGO) with the aim of raising awareness of important gastrointestinal problems. This initiative started 11 years ago when WDHD 2005 was devoted to "Health and Nutrition." Since then WDHD is celebrated every year on May 29. What started as a one day event has now developed into a full year long campaign. As might be expected, the target of WDHD are not only health care professionals but also the general public. We aim to put into perspective several aspects related to the WDHD topic, from prevalence to diagnosis, prevention, and management. The WGO embodies the optimal platform for the WDHD with its outreach to over 100 countries through its Member Societies. We are happy to say that WDHD campaigns in the past have captured the interest of not only our member societies, but also governmental or non-governmental organizations and the biomedical industry. This broad range of interest has helped enormously for us to reach our goals of promoting WDHD and raising awareness of the topic selected.

This year's topic is of very special interest to the general public and to our patients and is entitled "Diet and the Gut." Probably one of the main questions patients are seeking to ask their doctor, and especially their gastroenterologist or hepatologist, everywhere around the world is what they should and should not eat. It is fair to say that while the patient may see a gastroenterologist as THE expert to whom this question should be asked, many gastroenterologists do not like this question and may not consider themselves an expert on diet. Thus, for many gastroenterologists, the handbook prepared by David Sanders and Govind Makharia and their team will give a happy sigh of relief! While some of the topics covered in this handbook will be more or less familiar, some topics will be new or cover issues which they have long overlooked but now have the opportunity to read in compact reviews by world experts in the field. The topics such as "food-induced symptoms," "food supplements," "Global perspective on food allergies," and Food allergy and eosinophilic esophagitis" are good examples. This handbook covers, beyond what has been already mentioned, other very interesting topics.

On behalf of the WGO Foundation, we congratulate Professors Govind Makharia and David Sanders, the 2016 Steering Committee, fellow authors, partners, and supporters on this wonderful work which we hope you will not only enjoy but find helpful in your daily practice.

Sincerely,

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UNDERSTANDING OF NORMAL GUT HEALTH

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INTRODUCTION

Approximately one third of people in the general population complain of some gut-related symptoms, such as flatulence, bloating, heartburn, nausea, vomiting, constipation, diarrhea, food intolerance, incontinence, and abdominal pain. While most physicians look at these gut-related symptoms in the context of the gastrointestinal (GI) diseases, gut-health related symptoms occur more often in the absence of demonstrable functional and structural diseases in the GI tract. These digestive symptoms may not be life threatening, but they can significantly affect the general wellbeing and quality of life of the affected individuals.[1,2]

Furthermore, the health of the gut is deeply rooted in the psyche of society and the presence of any of these gut symptoms may prompt an individual to consult a doctor. Ancient medicine, such as Ayurveda, the 'science of life' originating in India more than 3,000 years ago, and Asian medicine, suggest that many of the human diseases arise from the gut and that strengthening of the digestive system, with the foods we eat, holds the key to good health.[3]

HOW TO DEFINE GOOD GUT-HEALTH?

'What constitutes a healthy gut" is as yet not well defined. As the World Health Organization defines "health" as a positive state of health, rather than "the absence of diseases," the healthy gut can be defined as a state of physical and mental well-being without gastrointestinal symptoms that require the consultation of a doctor, absence of any disease affecting the gut, and also the absence of risk factors for diseases affecting gut.[1,4] Therefore, to maintain good gut-health, one needs to undertake measures not only at the tertiary level of prevention to retard the disease process, but also consider both primary and secondary levels of prevention to maintain

Table 1: *Indicators of gut health*

Criteria for a healthy GI system	Specific featues of gut-health
Effective digestion and absorption of food	Effective absorption of food, water, and minerals Regular bowel movement, passage of normal stool No diarrhea, constipation, and bloating Normal nutritional status
Absence of GI illness	No acid peptic disease, gastroesophageal reflux disease (GERD), or other gastric inflammatory disease No enzyme deficiencies or carbohydrate intolerances No inflammatory bowel disease (IBD), celiac disease, or other inflammatory state No colorectal or other gastrointestinal cancer
Normal and stable intestinal microbiota	No bacterial overgrowth Normal composition and vitality of the gut microbiota
Effective immune status and gut barrier	Effective GI barrier function Normal levels of immunoglobulin A Normal number and activity of immune cells
Quality of life	Normal quality of life

Adapted from, Bischoff SC. 'Gut health': a new objective in medicine? BMC Med. 2011;9:24.

a disease free gut as far as possible. Good gut-health should be all encompassing so that it covers all perspectives, ranging from the Asian understanding of the gut as the middle of spiritual and physical strength to the Western understanding of the GI barrier as a central body site interacting with the environment and involved in the pathophysiology of many intestinal and extra-intestinal symptoms and diseases.[3]

INDICATORS OF GUT-HEALTH

The GI system is complex and comprised of absorptive mucosa, epithelial transport, gastrointestinal motility, immune system, and gut microbiome; normality in all or most of its constituents provides a healthy gut. Any defect or abnormality in any or many of the above constituents may predispose one to diseases or may cause disease. (see Table 1)

HOW TO MAINTAIN GUT-HEALTH?

Our knowledge about how to maintain or restore gut-health is limited in evidence-based medicine terms, but general observations suggest that there is a wide range of possible ways to support gut-health and GI well-being. Current medical research is much more focused on the treatment of defined GI disease rather than on the primary and secondary prevention of the diseases. For example, we know of several effective drugs to treat autoimmune liver disease or inflammatory bowel disease (IBD), but very little on how to prevent such diseases.[5,6]

Evidence-based approaches to maintain gut-health and to prevent GI diseases are limited. This is still an open and relevant field for clinicians, epidemiologists, and scientists to ponder on the enormous value of preventive strategies to maintain a healthy gut and prevent GI diseases. While measures such as regular physical activity, avoidance of smoking, mainatining a balanced diet schedule, and avoidance of saturated fat in the diet have proven to be effective cardioprotective strategies, we need to define similar strategy for good gut-health.[7]

Certain lifestyle characteristics, such as balanced diet, moderate but regular exercise, avoidance of chronic stress, ingestion of adequate amount of fibers, and use of well-defined and specific pre- and probiotics, have been shown to have a positive effect on gut health.

Since the GI system is complex, it follows that any preventive strategy should include measures to address each aspect of the GI system. The following could be proposed as individual preventive steps to maintain different aspects of the GI system. Here we present some guidance for which there is an evidence base but in some aspects this information remains empirical. (see Table 2)

GENERAL HYGIENE AND GUT-HEALTH

The GI tract, unlike other systems of the body, is exposed to the environment at both its ends and it is exposed to enormous amount of junk, some of which is toxic, on a daily basis. Therefore the hygiene of an individual will impact the hygiene of their GI tract. Any disturbance of the balance between the microbiome and the mucosal immune system will lead to impairment of the GI barrier and subsequently to an increased risk to gut health and the development of GI disease.[8-9] In fact many diseases, such as GI infection, antibiotic-associated diarrhea, IBD, irritable bowel syndrome (IBS), food allergy, and so on, are related to the hygiene hypothesis.[8-10] Therefore, any

Table 2: *Preventive strategy to maintain good digestive health*

- General hygiene
  - Maintenance of hygiene in food and water
  - Proper washing of hands
- Dietary advices
  - Healthy and well-balanced diet
  - Adequate amount of fibre in the diet
  - Avoidance of processed food
  - Low FODMAP diet
  - Eating of food slowly
  - Avoidance of food that leads to food allergic symptoms
  - Drinking of lot of fluids (non-sugar based)
- Maintenance of healthy gut microbiota
  - Probiotics and prebiotics
  - Avoidance of proton pump inhibitors and nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Maintenance of hygiene
- Avoidance of injurious agents to gut
  - Smoking: predisposes to gastroesophageal reflux
  - Drugs which damages intestinal mucosa, such as NSAIDs
  - Excess and unindicated use of proton pump inhibitors
  - Avoidance of excess of alcohol
- Maintenance of epithelial integrity
  - Maintenance of healthy microbiome
  - Prevention of GI infections
- Maintenance of enterocytes

UNDERSTANDING OF NORMAL GUT HEALTH, *continued*

conditions that might disturb the intestinal microbiome and the mucosal immune system should be avoided.

DIET AND GUT-HEALTH

A balanced diet is one of the important ways to keep the digestive system healthy. One of the important reasons for constipation in healthy individuals is inadequate intake of fibers in their diet. Adequate fiber in the diet encourages passage of contents through the digestive system and gives the correct consistency and bulk to stools. The dietary fibers could be soluble or insoluble. While the recommended daily intake of dietary fibers varies between 25-35g/day from country to country, only a proportion of the world's population is able to meet the recommended daily amount of dietary fibers.[11,12] While fiber intake is generally adequate in many Asian countries, the intake however is much lower in both Europe and the USA. Other than its benefit in proper laxation, dietary fibers protect from diverticular disease and colorectal cancer.[13] Furthermore, a high-fiber diet has many other benefits, including lowering of cholesterol, control of blood sugar in diabetics, and weight reduction.[14] Furthermore, dietary changes have been shown to help prevent major societal diseases such as allergy, obesity, and cancer.[15] A low FODMAP diet or gluten free diet has been reported to be beneficial in patients with IBS.[16,17]

There are evidences to suggest that high-fat, as well as high-fructose, diets disturb the GI barrier and induce fatty liver disease and subclinical inflammatory conditions associated with metabolic disturbances.[18,19]

Therefore, measures to maintain a good gut-health include eating of a healthy and balanced diet, ingestion of adequate amount of fibers, reduction in the ingestion of saturated and processed food, slow and regular eating, and, finally, avoidance of foods that may lead to digestive symptoms. An individualized elimination diet in selected individuals with food intolerances, food allergy, or celiac disease may also contribute to good gut health. [20,21]

AVOIDANCE OF FACTORS WHICH CAN INDUCE DAMAGE TO GI TRACT

Tobacco abstinence, moderate alcohol consumption, maintenance of normal body weight, avoidance of nonsteroidal anti-inflammatory drug (NSAID) ingestion, and control of stress can support gut-health.[22]

AVOIDANCE OF STRESS

The psychological and cognitive factors, including stress, affect the GI motility, GI secretion, and overall function of the GI tract.[23] While there is a lack of high quality evidence to support that improvement in lifestyle affect GI functions, there has been increase in the popularity of meditative strategy to calm down the mind. Despite the limitations of the literature, the evidence suggests that meditation programs could help reduce anxiety, depression, and pain in some clinical populations.[24] Thus, clinicians should be prepared to talk with their patients about the role that a meditation program could have in addressing psychological stress.[24] Furthermore, such methods are now practised by many health professionals for attaining not only the general well-being but for maintenance of a good gut health too.

USE OF DRUGS TO PREVENTION OF GI DISEASES

Chemoprevention by taking aspirin, cyclooxygenase-2 inhibitors, and calcium may reduce the recurrence of adenomas and/or the incidence of advanced adenomas in individuals with an increased risk of colorectal cancer (CRC), and taking aspirin may reduce the incidence of CRC in the general population.[25,26] However, both aspirin and NSAIDs are associated with adverse effects, so it will be important to consider the risk-benefit ratio before recommending these agents for chemoprevention.

An interesting idea is whether gut health can be further supported by using modulators of the intestinal microbiome or the GI barrier, such as probiotics or prebiotics. Indeed, it has been shown that chronic bowel diseases, such as IBD, are associated with adherence of commensal bacteria to the otherwise sterile intestinal epithelium and that selected probiotics can prevent the adhesion of pathogenic bacteria to the intestinal mucosa or restore leaky gut by improving the molecular composition of tight junctions.[27-30] Moreover, probiotic bacteria can support the normal development of the mucosal immune system.

In summary, nearly one third of world's population suffer from some form of gut related symptoms, most of which may be unrelated to specific structural or functional disease in the GI tract. There is a need to popularize the primary preventive strategies for maintenance of good gut health.

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DIETARY FIBER; DEFINITION, RECOMMENDATION FOR INTAKE, AND ROLE IN DISEASE PREVENTION AND MANAGEMENT

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Dietary fiber is the edible parts of plants or analogous carbohydrates that are resistant to digestion and absorption by the human intestine. Dietary fiber includes polysaccharides, oligosaccharides, lignin, and associated plant substances. The sources of fiber vary in chemical and physiological properties.[1,2]

"Dietary fiber" was first used in the literature in 1953 by Hipsley, who used the term to refer to celluloses, hemicelluloses, and lignin.[3] Since then, the definition has undergone many revisions. According to Codex Alimentarius, dietary fiber is defined as carbohydrate polymers with 10 or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans. The decision to include carbohydrates from three to nine monomeric units was left to national authorities.[4] Several authorities from Canada, Australia, New Zealand, and the European Union considered carbohydrates with three to nine monomeric units as a part of dietary fiber definition. The definition has been expanded to include oligosaccharides, such as inulin and resistant starches. A universal definition, or consistency among definitions, is necessary for food labels and for research purposes.

There are several different classification systems for dietary fiber. Classifications of components of dietary fiber are based on their gastrointestinal solubility, site of digestion, products of digestion, or physiological properties.[1] Most common fiber classification categories include water-insoluble/less fermented fibers (cellulose, hemicellulose, lignin) and the water-soluble/well fermented fibers (pectin, gums, and mucilages).[5] Physiological effects of fiber differ from one non-digestible carbohydrate to another. The same amount from different sources of fiber does not really infer the same levels of impact on health. There are many different forms of fiber in food and there is also a wide range of foods delivering fiber. Dietary fibers can be extracted from edible material (intrinsic) or modified and added back into a food (extrinsic).[6] Dietary fiber supplements have the potential to play an adjunctive role in offering the health benefits provided by high-fiber foods.

Current recommendations for dietary fiber intake are related to age, gender, and energy intake; and the general recommendation for adequate intake is 14 g/1000 kcal.[2] This average intake includes non-starch polysaccharides, analogous carbohydrates, lignin, and associated substances.[2] Using the energy guideline of 2000 kcal/day for women and 2600 kcal/day for men, the recommended daily dietary fiber intake is 28 g/day for adult women and 36 g/day for adult men. The Institute of Medicine in the USA recommended intakes of 30 g dietary fiber daily for adults based on protective effects against cardiovascular disease.[7] Other organizations followed suit, recommending an intake of at least 25 g dietary fiber daily for the general population. Most people, however, under consume dietary fiber, and usual intake averages only 15 g per day.[8]

Dietary fiber intake provides many health benefits. A generous intake of dietary fiber reduces risk for developing various diseases, including coronary heart disease, stroke, hypertension, diabetes, obesity, and certain gastrointestinal (GI) disorders. Increased consumption of dietary fiber improves serum lipid concentrations, lowers blood pressure, improves blood glucose control in diabetes, aids in weight loss, and appears to improve immune function.[9] High dietary fiber intake may reduce the risk of total mortality (See Table 1).

INCREASED FECAL BULK/LAXATION

Solubility, viscosity, and water holding properties of fiber affect digestion and the absorption function of the GI tract. High insoluble fiber intake increases fecal bulk and decreases

Table 1: *Beneficial effects of dietary fiber in disease prevention and management*

• Increased laxation
• Decreased colonic transit time
• Increased colonic fermentation/short chain fatty acid production
• Positive modulation of colonic microflora
• Beneficial effect on mineral absorption
• A protective role in the prevention of colon cancer and other malignancies
• Improvement in immune function.
• Reduced total and/or LDL serum cholesterol levels
• Attenuation of postprandial glycaemia/insulinaemia
• Reduced blood pressure
• Weight loss, Increased satiety
• Decreased mortality

DIETARY FIBER; DEFINITION, RECOMMENDATION FOR INTAKE, AND ROLE IN DISEASE PREVENTION AND MANAGEMENT, *continued*

transit time, thereby helping in the prevention and treatment of constipation.[10] Fibers in diet are effective promoters of normal laxation, as are psyllium seed husk and methylcellulose in the form of supplements. Beside insoluble dietary fibers, soluble fructans have been shown to have a beneficial effect in the large intestine.[11] Diverticular disease is one of the most common GI diseases. A generous intake of dietary fiber is considered to be protective, ameliorative, and preventive of recurrences of diverticular disease.[10,11] Similarly, several trials have shown that supplementation of some types of dietary fiber can prolong remission during the course of the inflammatory bowel disease (IBD). These effects are primarily related with increased luminal production of immunomodulator short chain fatty acids (SCFA). There is general agreement that if there is no intestinal strictures and the patient is in remission, dietary fiber consumption should not be limited in IBD.

GUT MICROBIOTA AND PREBIOTIC EFFECTS

Dysbiosis in gut microbiota is associated with the pathogenesis of many diseases, including infectious diseases, allergy, IBD, obesity, diabetes, liver disease, and colon cancer.[12] Gut microbiota can be affected by many factors, including medications, stress, and diet. Dietary fibers acting as a prebiotic selectively enrich beneficial gut bacteria, mainly *bifidobacteria* and/or *lactobacillus*.[2] Prebiotics that include fructo-oligosaccharides, oligofructose, and inulin were shown to increase the concentrations of bifidobacteria and or lactobacillus species in the gut. Bacterial fermentation of the ingested fiber in the colon produces SCFAs, primarily acetic, propionic, and butyric acid. These SCFAs provide various health benefits to the host, such as: supplying fuel to colonocytes; regulating proliferation and differentiation of epithelial cells; increasing colonic blood flow, reducing colonic pH; stimulating pancreatic secretions, other gut hormones, and the autonomic nervous system; promoting sodium and water absorption; and regulating gut motility.[12]

MINERAL AND MICRONUTRIENT ABSORPTION

There are concerns that micronutrient absorption may be adversely impacted by diets high in fiber. Diet high in insoluble fiber is not associated with poorer micronutrient status in healthy population consuming their usual diet.[13] On the other hand, certain fiber types play a beneficial role in mineral and micronutrient absorption. Highly fermentable fibers have resulted in improved metabolic absorption of certain minerals, such as calcium, magnesium, and iron. Fermentation of fiber by colonic microbiota and subsequent SCFA production leads to reduction in luminal pH. The SCFA and lower pH may, in turn, dissolve insoluble mineral salts, especially calcium, magnesium, and iron, and increase their absorption.[1]

CANCER PREVENTION

Recent studies support this inverse relationship between dietary fiber and the development of several types of cancers, including colorectal, small intestine, oral, esophageal, larynx, and breast.[14] Cellulose is the major type of fiber that has been shown to reduce risk of colon cancer. This effect is related to decrease in colon transit time and excretion of mutagens, as well as decrease in fecal bile acid concentration.[15] Pectin and pectic oligosaccharides were shown to induce apoptosis in human colonic adenocarcinoma cells *in vitro*.[16] Although the mechanisms responsible are still unclear, several explanations have been proposed. First, dietary fibers are fermented to produce SCFAs, which have anti-carcinogenic properties. Second, there is less contact time between potential carcinogens and mucosal cells. Third, dietary fiber increases the binding between bile acids and carcinogens. Fourth, increased intake of dietary fiber yields increased levels of antioxidants. Fifth, fibers may decrease estrogen absorption in the intestines.[14,15] Dietary fiber is also preventive against esophageal carcinogenesis, most notably esophageal adenocarcinoma by modification of gastroesophageal reflux and weight control.

CARDIAC DISEASE

Cardiac disease is attributed to lifestyle, such as diet, physical activity, and cigarette abuse. High levels of dietary fiber intake are associated with significantly lower prevalence rates for cardiac disease, stroke, and peripheral vascular disease.[2] A pooled analysis of 10 prospective cohort studies indicated that every 10 g/d increase of dietary fiber was associated with decreased risk of coronary events and coronary death by 14 and 27 %, respectively.[17] Control and treatment of cardiac risk factors by high fiber intake decreases the prevalence of cardiac disease. Soluble fibers have been shown to increase the rate of bile excretion, therefore reducing serum total and LDL cholesterol. Dietary fiber regulates energy intake and blood glucose, thus enhancing weight loss. Dietary fiber has been shown to decrease pro-inflammatory cytokines, such as interleukin-18 which may have an effect on plaque stability. By controlling all of these risk factors, enough fiber intake

decreases the risk of cardiac events. Improved cardiovascular condition then improves blood pressure regulation. However, short term direct antihypertensive effects of dietary fiber is very controversial.

BLOOD GLUCOSE AND INSULIN REGULATION

Dietary fiber has been shown to modify postprandial blood glucose and insulin responses.[18] Mainly, the viscosity of a fiber affects glucose absorption. When viscous soluble dietary fibers mix with water, it thickens. Intake of soluble dietary fiber increases viscosity of the stomach content, prolongs gastric emptying, increases transit time through the small intestine, and reduces the rate of starch digestion and glucose absorption. Studies have shown that arabinoxylan (AX), β-glucan, fructo-oligosaccharides, and synthetic carbohydrate analogues, such as dextrins, can reduce post-prandial glucose and insulin responses.[17] Daily 20 g of fructo-olygosaccaride intake decreases hepatic glucose production.[19] Resistant dextrins also decrease postprandial blood glucose concentrations.[20]

REDUCED TOTAL AND/OR LDL SERUM CHOLESTEROL LEVELS

The cholesterol lowering effect of dietary fiber is well-known. Soluble fibers form a viscous layer in the small intestine. This reduces the reabsorption of bile acids and in turn increases the synthesis of bile acids from cholesterol and reduces circulating blood cholesterol.[21] The U.S. Food and Drug Administration has concluded that a minimum dose of 3 g/day of oat or barley β-glucan is needed for a beneficial reduction in blood cholesterol levels and subsequent decrease in the risk of coronary heart disease. Psyllium and guar gum have been shown to lower serum cholesterol and LDL in subjects with elevated serum cholesterol, in subjects with non-insulin dependent diabetes, and in subjects receiving lipid-lowering drug therapy.

OBESITY

Satiation is commonly linked with dietary fiber intake; in particular, β-glucan influences appetite and enhances postprandial satiety. Indigestible dextrins increase satiety and weight reduction. Overall, ingestion of both insoluble and soluble fibers have been linked with positive effects on weight control. The decrease in obesity and metabolic syndrome parallels with the decrease in liver steatosis and steatohepatitis.

INCREASING THE FIBER INTAKE

When fiber is being increased for a specific purpose, a more careful choice of fiber type is important. If it is desired to lower cholesterol or to improve glycemic control, soluble fiber (such as oat bran or psyllium) should be chosen. If bulking or correction of constipation is desired but the patient suffers from flatulence, insoluble fiber should be used.[22] A gradual increase in fiber intake is usually recommended to improve tolerance by minimizing problems of gas and bloating.

Large amounts of purified soluble fiber alone may be harmful. High-fiber diet may cause inadequate energy intake. Studies conducted in rats have shown injurious effects of very high fiber diets in the distal colon and enhancement, rather than suppression, of tumorigenesis. This finding may in part relate to massive fermentation of excess fiber in the proximal colon with relatively poor delivery of health-promoting fermentation products to the distal colon. Fiber-induced expansion of the bacterial populations might lead to utilization of alternative metabolic pathways by these populations and these alternative pathways may have more toxic products.[22] The production of excess gases from fermentation, with the bulking effects of fiber, can induce bloating. Such symptoms are poorly tolerated by patients with IBS. The colon does adapt to these dietary changes, but this requires several weeks to occur and a gradual introduction is recommended. So enough fiber intake in regular diet is recommended, while too much fiber alone might be hazardous in different aspects.[22]

SUMMARY

Regular fiber intake is recommended for general health. Different fiber types can be useful for the treatment of several gastrointestinal diseases like constipation, diarrhea, IBS, or IBD.[23] Patients diagnosed with diabetes, obesity, hyperlipidemia, hypertension, and other cardio-metabolic diseases can get a clinical improvement with soluble fiber intake. Dietary fiber has been demonstrated to play a role in the prevention of colorectal cancer and other neoplastic diseases.

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DIET AND THE GUT

WHAT ARE FODMAPS? EVIDENCE FOR USE OF LOW FODMAP DIETS IN GI DISORDERS

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Summary of IBS, Gluten, and Wheat studies

Lead Author	Country	Year	Patients	Outcome
Wahnscaffe	Germany	2001	102 IBS-D without CD	Stool frequency significantly improved in patients with HLA DQ2/DQ8
Wahnscaffe	Germany	2007	145 IBS-D without CD	HLA-DQ2 predicted response to GFD
Biesierski	Australia	2010	34 self reported gluten sensitive IBS	Significant reduction in overall symptoms in GFD group
Carroccio	Italy	2011	920 patients with IBS	70 patients **wheat** sensitive and 206 multiple food sensitivities including **wheat**
Vazquez-Roque	USA	2012	45 IBS-D	Increased intestinal permeability in patients receiving gluten
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Aziz	UK	2015	40 IBS-D	UEGW 2015
Di Sabatino	Italy	2015	59 Self reported NCGS	DBPC 4.375 gm

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Summary of IBS and FODMAP studies

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Ong	Australia	2010	N=30	Randomised Cross Over Single Blind
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Staudahcer	UK	2011	82 IBS randomised	76% response versus 54% standard diet advice
Staudahcer	UK	2012	41 IBS randomised	68% response versus habitual diet 23% response
Ostgaard	Norway	2012	N=79 & N= 35 Healthy Subjects (Retrospective)	Significant Improvement in Pain
Biesierski	Australia	2013	37 with IBS on GFD	**FODMAPs** then GFD and gluten containing arms
De Roest	New Zealand	2013	N=90 Prospective Uncontrolled	72% satisfied with symptom improvement
Mazzawi	Norway	2013	N=46 Prospective Uncontrolled	Improvement in total symptoms
Wilder-Smith	Switzerland	2013	N=312 patients with a functional GI disorder	Of the 76% who completed adequate relief in 93%
Pedersen	Denmark	2014	19 IBS patients	67 (37-120) points improvement
Halmos	Australia	2014	30 IBS	~ 50% reduction in symptoms
Bohn	Sweden	2014	82 IBS	65 completed with equal response to FODMAP diet (56%) versus Traditional Dietary Advice (52%)

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WHAT IS THE ROLE OF FOOD IN IBS?

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Irritable bowel syndrome (IBS) is common, with a pooled global prevalence of 11.2%.[1] The etiology of IBS is not entirely clear, but 40% to 84% of IBS patients believe that food-items are important triggers of their gastrointestinal symptoms. Carbohydrates are reported as a source of symptoms in 70% and gluten-based products cited as an offending culprit by roughly one-in-four.[2] Furthermore, IBS patients who report adverse food reactions tend to have more severe symptoms, associated subjective health complaints of musculoskeletal pains and chronic fatigue, and reduced quality of life.[2,3,4] Most recent work has focused on wheat, gluten, and FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols).

Carbohydrate malabsorption (e.g. lactose malabsorption), by virtue of its resultant distension of the intestine with increased water content and gas from bacterial fermentation, has long been documented to cause IBS-like symptoms and restriction of perceived culprits has been an adjunct to standard therapy. Restricting all slowly-absorbed and indigestible short-chain carbohydrates (a low FODMAP diet) has randomized controlled evidence from multiple centers across many countries of efficacy in patients with IBS. It benefits up to three of four patients with IBS and is proposed as a primary therapy for IBS. Most patients who benefit can de-restrict the diet and maintain the benefits.

More controversial has been the role of gluten in IBS; and the entity of non-celiac gluten sensitivity (NCGS) is now accepted by consensus. Unfortunately, the study of its epidemiology, pathophysiology, and characteristics has been hindered by the lack of objective diagnostic criteria and reliance upon self-report of improvement with a gluten-free diet and exacerbation by subsequent ingestion of wheat. Furthermore, what component(s) of wheat that is/are driving symptoms in any individual is difficult to define. The population prevalence of NCGS when self-reported ranges from 0.6% to 13%.[5] The pathophysiology of NCGS may involve an innate immune responses being driven by gluten or non-gluten wheat-associated proteins, such as alpha-amylase trypsin inhibitors, or the FODMAPs, which co-exist with gluten in cereals.[5] Some may have celiac disease that has yet to fulfill all diagnostic criteria. Definitive demonstration of gluten/wheat-protein sensitivity is by randomized, placebo-controlled, double blind cross-over studies using FODMAP-depleted gluten. Three prospective studies have been reported in patients with self-reported NCGS, with the consistent finding of less than 5% of such patients having specific responses to gluten. A major hurdle has been strong nocebo effects in these studies. Results of double-blind placebo-controlled challenges in 920 adults with self-reported wheat sensitivity but not celiac disease or wheat allergy found minimal nocebo response in general and were able to detect 30% with positive wheat reactions, although the majority of these also reacted to other foods, particularly milk protein.[6] Nearly all of the patients had evidence of immune activation in the intestine and/or colon, particularly increased density of intraepithelial lymphocytes and eosinophilic infiltration. This contrasted with patients in the randomized controlled trials (RCTs) where such patients were mostly excluded. Interestingly, when patients with apparent NCGS were re-challenged with gluten or placebo in parallel-group studies, significant differences were observed with greater symptom severity in the gluten-treated group.

Hence, gluten-containing cereal sensitivity is likely to represent one or more entity in individual patients – previously undiagnosed celiac disease, FODMAP sensitivity, gluten or other wheat protein sensitivity, multiple food protein sensitivity, or none. Defining the specificities in an individual is largely done by judicious clinical evaluation including assessment of duodenal histology, and 'n-of-one' dietary re-challenge studies with the ultimate aim of gaining the greatest symptomatic benefit with the least dietary restriction and of achieving sustained benefits.

WHAT IS THE ROLE OF FOOD IN IBS, *continued*

Figure 1.

Globally, when looking at the evolving literature, a response rate of about 70% might be anticipated when IBS patients are placed on either a low FODMAP diet or gluten-free diet (GFD). Furthermore, there may be long-term benefits with patients continuing their dietetic intervention of their own accord 12-18 months after the initial dietetic consultation.[9] However, the risks associated with restrictive diets (especially nutritional inadequacy, unfavorable effects on the gut microbiota or the encouragement of eating disorders) must be seriously considered, especially when dietary manipulations are professionally unsupervised or purely patient-initiated.

In summary there is now an emerging evidence base that nutritional therapies can be used for IBS patients with an expectation of benefit. The selection of diet could be based on clinical judgement, patient preference and local skill-base, or categorization according to the absence or presence of 'celiac lite' features (See Figure 1).

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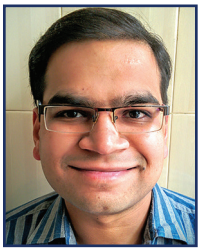
CARBOHYDRATE INTOLERANCE (LACTOSE, SUCROSE, AND FRUCTOSE): IDENTIFICATION AND TREATMENT



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INTRODUCTION

Intolerance to carbohydrates, such as lactose intolerance, is a common type of non-allergic food intolerance.[1] The number of patients diagnosed with carbohydrate intolerance has increased during the last few decades mostly as a consequence of increase in carbohydrate consumption, especially added sugar, in the diet. There has been increasing awareness among both general population and physicians about dietary intolerances and hence more and more patients with this disorder are now diagnosed. Carbohydrate intolerance can either be genetic or non-genetic in origin[2] (See Table 1).

LACTOSE INTOLERANCE

The intolerance to lactose is due to either relative or absolute deficiency of lactase enzyme and the deficiency can occur because of three disorders:

- Congenital lactase deficiency
- Secondary lactase deficiency
- Adult type lactase deficiency

Table 1: *Classification of carbohydrate intolerance*

Genetic	Non-genetic
Early onset	Functional impairment
Congenital lactase deficiency	Fructose intolerance
Congenital sucrase-isomaltase deficiency	Sorbitol intolerance
Glucose-galactose malabsorption	Trehalose intolerance
Late onset	
Adult type lactose intolerance	

CONGENITAL LACTASE DEFICIENCY

Congenital deficiency of lactase is rare and it is most often described in reports from Finland. There is a severe deficiency of lactase, the enzyme responsible for the digestion of lactose. Premature stop codons and a truncated protein as a result of frame shifts missense mutations in the coding region of lactase enzyme, or exon duplication are the most common genotypes identified. Symptoms occur shortly after birth. Symptoms subside when diet is changed to lactose free substances. The activities of all other disaccharidases remain normal.

SECONDARY LACTASE DEFICIENCY

Deficiency of lactase occurs secondary to diseases of the intestinal mucosa both during acute settings (such as after an episode of gastroenteritis, or due to chronic diffuse mucosal diseases such as celiac disease or Crohn's disease). With the healing of the intestinal mucosa, the level of lactase improves with resolution of the symptoms. The recovery of lactase may take a longer time even when mucosa has healed, which reflects the observation that lactase activity is the last to recover in comparison to other disaccharidases activities.

ADULT TYPE LACTASE DEFICIENCY

This is the most common cause of lactase enzyme deficiency and up to 70% of world's population has an activity of lactase a level below a critical threshold for the digestion of dietary lactose.[3] It is an autosomal recessive condition in which there is a gradual reduction in the activity of lactase after two years of age. The prevalence of lactase deficiency varies widely in the different geographic locations around the world. In the USA, 20% of Caucasian people have deficiency of enzyme, while 80-100% of Asians have deficiency of lactase enzyme. The prevalence of lactase deficiency is about 70-95% in Africa and 15-70% in Europe. The persistence or non-persistence of the

CARBOHYDRATE INTOLERANCE (LACTOSE, SUCROSE AND FRUCTOSE): IDENTIFICATION AND TREATMENT, *continued*

lactase is associated with the point polymorphism C/T 13910. This consists of a substitution in a sequence of DNA that regulates the lactase gene. While genotype CC correlates with hypolactasia, TT genotype correlates with lactase persistence.[4]

PATHOPHYSIOLOGY AND CLINICAL SYMPTOMS

The lactase enzyme is located in the brush border (microvilli) of the small intestinal epithelial cells. The enzyme splits and hydrolyzes dietary lactose into glucose and galactose for transport across the cell membrane. The absence or deficiency of lactase leads to failure of hydrolysis of lactose, hence unabsorbed lactose remains in the intestinal lumen and fluid drives osmotically into the intestinal lumen.[5,6] In addition to increasing the volume and fluidity of the gastrointestinal contents, unabsorbed lactose enter colon. The fermentation of lactose by colonic microflora produces lactic acid and hydrogen. In the presence of methanogenic bacteria, hydrogen and carbon dioxide combine together to form methane in the colon. The excessive production of hydrogen and methane in the intestine leads to bloating, distention of the abdomen, excessive flatulence, nausea, and abdominal pain (non-specific in nature). The excessive unabsorbed lactose with osmotically driven water, in excess of colonic absorption, can lead to diarrhea in some patients.

In patients with common adult-type hypolactasia, the amount of ingested lactose required to produce symptoms varies from 12 to 18 g, or 8 to 12 ounces of milk. Ingestion of small to moderate amounts of lactose usually produces bloating, cramps, and flatulence, but not diarrhea. Ingestion of larger amounts of lactose, a faster gastric emptying time, and faster intestinal transit time all contribute to more severe symptoms. Several factors determine the symptoms onset of symptoms of lactose intolerance, such as lactose content in the diet, gut transit time, fermentation capacity of gut, and (possibly) neuropsychological factors.

DIAGNOSIS

The diagnosis of lactose intolerance should be suspected in patients who have symptoms of bloating and chronic diarrhea. A relationship of symptoms occurring with the intake of milk and milk products and relief in symptoms with avoidance further strengthens the diagnostic possibility of lactose intolerance. The diagnosis of lactose intolerance can be confirmed by lactose hydrogen breath test, lactose tolerance test, and genetic study. Lactose hydrogen breath test is most commonly used test for the diagnosis and the test has a sensitivity of 88% and specificity of 85%. The test is performed and the results are interpreted as depicted in Figure 1.[2]

LACTOSE TOLERANCE TEST

Patient consumes 50g of lactose dissolved in water. Samples of capillary blood are obtained to test the plasma glucose concentration at –5, 0, 15, 30, 45, and 60 minutes. A maximal plasma glucose increase of 1.4 mmol/L(25.2 mg/dl) or higher indicates lactose intolerance.[7] The sensitivity and specificity of lactose tolerance test is high (both >90%).

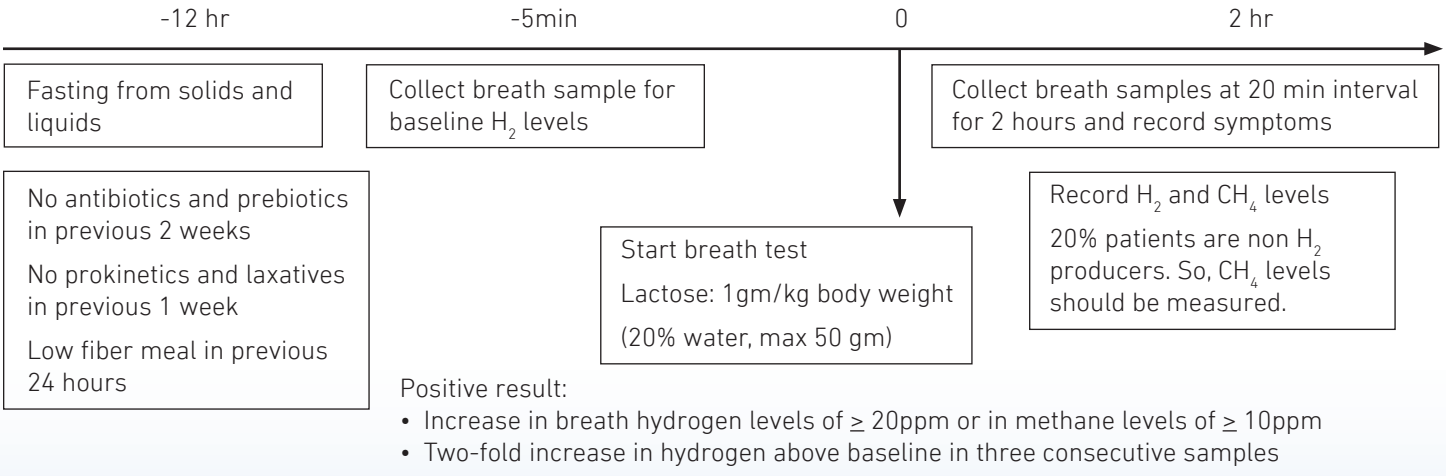

Figure 1.

GENETIC TEST

The genetic test to identifies single nucleotide polymorphism associated with lactase persistence/non-persistence. Genotype CC correlates with hypolactasia, while TT genotype with lactase persistence. One should know that all those who have CC genotype will not develop symptoms of lactose intolerance.

TREATMENT

The mainstay of treatment of lactose tolerance is avoidance of all lactose containing milk and milk containing products (Table 2). In adult type lactase deficiency, lactose-containing foods are limited for 2-4 weeks to induce remission. After 4 weeks, lactose-containing products can be reintroduced gradually as per the tolerance of the individual. In secondary lactose intolerance, lactose is restricted only for a limited duration and can be reintroduced safely after recovery from the intestinal damage.[8] Patients with lactose intolerance are prone to calcium deficiency, so supplementation of calcium should be given. Patients with mild lactose malabsorption may benefit from using lactase enzyme supplements. The incubation of milk with lactase enzymes may also be helpful. Lactase enzyme supplementation should be an adjunct to, not a substitute for, dietary restriction. Non-dairy synthetic drinks and soy milk are a useful substitute for milk. It is common for health providers to mistakenly tell the patient not to eat any dairy products, which deprives them of a healthy source of protein and the most bioavailable source of calcium. Instead patients should be instructed about low or no lactose dairy products (See Table 2).

It should be noted that lactose content may be included in the list of ingredients depending on the country in which the product was processed, manufactured, or sold.

Table 2: *Food items, which are restricted and allowed in patients having lactose intolerance*

Food items that should be avoided	Food items that are allowed
All kinds of milk: whole, low fat, nonfat, cream, powdered, condensed and evaporated,	Lactose-free milk and soy milk
Chocolate containing milk	Lactose-free dairy and hard cheeses
Butter, cottage cheese, ice cream, creamy/cheesy sauces, cream cheeses, soft cheese and mozzarella	Yogurts unless unfermented milk is added back in
Whipped cream	Kiefer
Milk, bread, crackers, and creamer	All fruits
Muffin, biscuit, waffle, pancake, and cake mixes	All vegetables
Bakery products and desserts that contain the ingredients listed above	All legumes
	All cereals
	All meat, fish, and eggs
	All vegetable fats

SUCROSE INTOLERANCE (CONGENITAL SUCRASE- ISOMALTASE DEFICIENCY)

Congenital sucrase-isomaltase deficiency is a rare autosomal recessive disorder with decreased ability to digest sucrose, maltose, short 1–4 linked glucose oligomers, branched (1–6 linked) α-limit dextrins, and starch.[9] Over 25 mutations have been identified in genes responsible for sucrose-isomaltase synthesis on the chromosome 3. These mutations affect different parts of protein synthesis to cause enzyme deficiency (e.g. transport, processing, folding, and anchoring to the enterocyte membrane). This phenotypic heterogeneity is reflected in a range of enzymatic capability ranging from complete absence of sucrase activity to a low residual activity and from completely absent isomaltase activity to a normal activity.

Prevalence of congenital sucrase-isomaltase deficiency in North American and European populations range from 1 in 500 to 1 in 2000 among non-Hispanic whites, with a lower prevalence in African Americans and whites of Hispanic descent. Prevalence of this disorder is 5% to 10% in Greenland Eskimos, 3% to 7% in Canadian native peoples, and about 3% in Alaskans of native ancestry.[10,11]

CLINICAL SYMPTOMS

Clinical manifestations are similar to that observed in patients having lactose intolerance, and the severity of the symptoms depend upon the content of the sucrose and starch in diet. The activity of enzyme sucrase can also be induced by diet containing high sucrose and carbohydrates and its expression can be reduced by diet containing high protein and low carbohydrates. Hormones such as corticosteroids and thyroxine induce expression of sucrase-isomaltase in the mucosa of small intestine. All these factors collectively affect onset and severity of symptoms.

CARBOHYDRATE INTOLERANCE (LACTOSE, SUCROSE AND FRUCTOSE): IDENTIFICATION AND TREATMENT, *continued*

DIAGNOSIS

In clinically suspected patients, diagnosis is made on small intestinal biopsy, which was gold standard for years. Criteria applied to make the diagnosis include normal small bowel morphology in the presence of absent or markedly reduced sucrase activity, isomaltase activity varying from 0 to full activity, reduced maltase activity, and normal lactase activity, or in the setting of reduced lactase, a sucrase:lactase ratio of <1.0.

Molecular genetics helps in making early diagnosis and avoids invasive, repetitive procedures. At least 80% of patients have one of four common mutations, namely p.Val577Gly, p.Gly1073Asp, and p.Phe1745Cys in the sucrase domain and p.Arg1124X in the isomaltase domain.[12] It has replaced the need for small intestinal biopsy for diagnosis.

TREATMENT

The sucrase-isomaltase intolerance is treated mainly by the dietary restriction. (See Table 3) Oral supplementation of sucrosidase (derived from Saccharomyces cerevisiae) can also be used, if available.

Table 3: *Food items, which are restricted and allowed in patients having sucrose-isomaltose intolerance*

Foods to avoid	Food items which are allowed
Apple, apricot, banana, cantaloupe, grapefruit, melon, mango, orange, peach, pineapple, and tangerine	Wheat, rice, corn, einkorn, oats, kamut, spelt, rye, bread, pasta, flour, and cereals with no added sugar
Carrot and potato	Avocado, berries, cherries, fig, grapes, kiwi, lemon, lime, olives, papaya, pear, pomegranate, prunes, and strawberries
Beans, chickpeas, green peas, lentils, peas, and soy	All vegetables
Yogurt sweetened with sucrose, sweetened condensed milk, and sweetened cream	Milk, dairy product, butter, cream, cheeses, and yogurt sweetened with dextrose or fructose
Sugar (sucrose), ice cream, all desserts made with sugar, marmalade, candies, jellies, chocolate, and licorice	All meat, fish, and eggs
	All fats
Commercial cookies and cakes with added sugar, sweetened drinks	Fructose, honey, cocoa, unsweetened juice, homemade low-sucrose cookies, and cakes

FRUCTOSE INTOLERANCE

Fructose is a monosaccharide, which is naturally present in fruits and vegetables.[13] Fructose, because of its sweet taste, is used extensively in food industry as a sweetener such as in juices, candies, and beverages. Fructose is also a constituent of disaccharides sucrose along with glucose.

HEREDITARY FRUCTOSURIA

Hereditary fructosuria is a rare clinical disease, which occurs due to a deficiency of this aldolase B enzyme. The deficiency of enzyme leads to incomplete metabolism of fructose, which leads to accumulation of fructose-1-phosphate in the liver, kidney, and intestine. Patients may have symptoms in the form of hypoglycemia, abdominal pain, vomiting, and diarrhea.[14]

FRUCTOSE INTOLERANCE

Fructose is generally absorbed passively along with glucose via GLUT-2 transporter present on the basolateral membrane of enterocytes. Fructose is also absorbed by GLUT-5 is non glucose dependent transporter located in the brush border of the small intestine. Defects in these transporters can lead to fructose malabsorption. Transportation of ingested glucose through SGLT-1 activates GLUT-2 which in turn gets inserted on the apical membrane. Therefore, ingestion of glucose enhances absorption of fructose as well. Glucose also increases paracellular absorption of fructose. These mechanisms explain the possible fructose malabsorption after eating foods whose fructose component is in excess of glucose. Fructose intolerance can also occur because of diffuse mucosal diseases of intestine such as celiac disease.

Clinical features are similar to symptoms caused by other carbohydrates intolerances such as lactose intolerance, as described above.

The diagnosis of fructose malabsorption can be made by hydrogen breath test after ingestion of fructose 0.5 gm/kg (maximum 25 gm) dissolved in water. The diagnosis is confirmed by an increase of >20 ppm in hydrogen or >10 ppm in methane levels over the baseline twice in succession and abdominal discomfort after the consumption of the test dose. Fructose-hydrogen test has both sensitivity and specificity of over 80%.

CARBOHYDRATE INTOLERANCE (LACTOSE, SUCROSE AND FRUCTOSE): IDENTIFICATION AND TREATMENT, *continued*

The treatment of fructose malabsorption involves mainly the food items, which are rich in fructose. (See Table 4) Patients should be advised to adhere to a low fructose diet (< 10 gm/day). Emphasis should be given on balanced intake of glucose and fructose. Supplementation of xylose isomerase, which converts fructose into glucose, can also be provided which decrease symptoms of fructose intolerance [15].

Table 4: *Food items, which are restricted and allowed in patients having fructose intolerance*

Food items, that which should be avoided	Food items, which should be allowed
All fruits Fructose, honey, high-fructose corn syrup, sorbitol, jams, gelatin desserts, candies, and all desserts sweetened with fructose Condiments such as barbeque sauce, ketchup, sweet and sour sauce, pancake syrup, and plum sauce Broccoli, carrots, cauliflower, green beans, green peppers, sweet potatoes, and tomatoes Beans and peas	All cereals All meat, fish, and eggs All dairy All fats Sugar (sucrose), molasses, and saccharine Pumpkin, radish, scallions, spinach, spinach, white potatoes, shallots, cucumber, and lettuce

CONCLUSIONS

Amongst the carbohydrate intolerances, lactose intolerance is the most common. Because of overlapping symptoms with other small intestinal diseases, carbohydrate intolerance should be kept in mind and suspected clinically. The mainstay of treatment is avoidance of carbohydrate causing symptoms.

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FOOD ALLERGY AND THE DIGESTIVE TRACT

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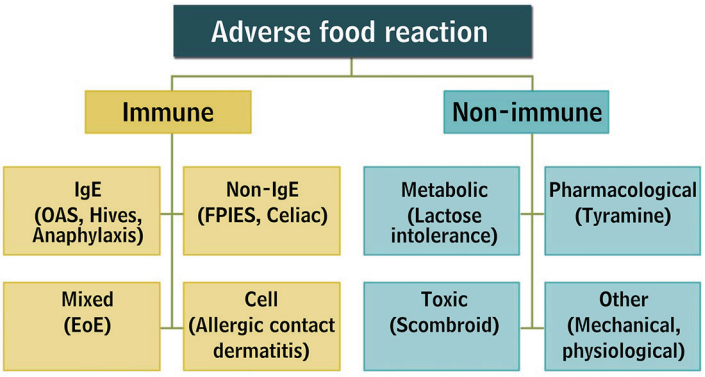
DEFINITION AND FORMS OF FOOD ALLERGY

Adverse immune responses to proteins in a food constitute a food allergy. All other forms of adverse reactions to foods (ARF) are non-immune reactions (see Figure 1), commonly referred to as food intolerances, which comprise physiological, pharmacological, psychological, and unknown mechanisms.[1] A clinician's ability to discern food allergies from food intolerances is absolutely essential, as prognosis and management of allergy and intolerance require vastly different approaches.[2, 3]



Modified from Boyce JA, et al. JACI 2010 Dec; 126(6):1105

Figure 1.

Classical food allergy or hypersensitivity results from a humoral response involving immunoglobulin E (IgE) antibody directed to specific proteins. These antibodies bind to effector cells, basophils in the circulation, mast cells in skin, and mucosal tissues of the gastrointestinal (GI) and respiratory tracts and upon exposure to the offending food, these cells degranulate, releasing histamine and other mediators which give rise to a variety of symptoms.[4] Other forms of food allergy arise from an abnormal cellular response to specific foods.

Celiac disease is an example of a T cell-mediated disease.[5] Specific peptide sequences of proteins known as gluten can activate T lymphocytes in genetically susceptible individuals. The T cells release cytokines and other cellular events lead to the enteropathy which characterizes the disease. Celiac disease (discussed elsewhere) is unique as it is both a food allergy and an autoimmune condition.

Food allergy can be mediated by eosinophils that infiltrate the entire luminal digestive tract.[6] Only the mucosal layer of the esophagus is involved in eosinophilic esophagitis (EoE), but in the remaining rare forms of the disease that involve the stomach, intestine, and/or colon, eosinophils are found in the mucosa (most common), the muscular layer, and/or the serosa.

CLINICAL PRESENTATIONS

IgE-mediated responses to food allergy present a wide range of clinical manifestations with a rapid onset, a spectrum that ranges from self-limited, localized hives to potentially fatal anaphylaxis. Hives and angioedema are the most common symptoms of food allergy. GI, cardiovascular, and/or respiratory systems may be affected. The most serious symptom of IgE-mediated food allergy is generalized anaphylaxis. The primary manifestations of a GI allergic reaction are a) GI anaphylaxis (nausea, vomiting, abdominal pain, diarrhea) which typically develops along with allergic symptoms beyond the digestive tract, such as wheezing and urticarial and b) the oral allergy syndrome.[7] GI allergy symptoms typically present within a span of a few minutes to a couple of hours after ingesting the culprit food.

A rare type of anaphylaxis—food-dependent exercise-induced anaphylaxis—triggers an anaphylactic response when an individual consumes an offending food within 2 to 4 hours of participating in exercise, though no allergic consequences occur if the individual ingests that same food and does not exercise.[2]

Table 1: *Cross-reactivity between pollens and fruits and vegetables in oral allergy syndrome.*[2]

Birch	Almond, aniseed, apple, apricot, carrot, celery, cherry, hazelnut, parsley peach, peanut, pear, and plum
Ragweed	Banana, cantaloupe, cucumber, honeydew, watermelon and zucchini
Mugwort	Aniseed, bell pepper, broccoli, cabbage, caraway, cauliflower, celery, fennel, garlic, mustard, onion, and parsley
Orchard	Cantaloupe, honeydew, peanut, tomato, watermelon, and white potato
Timothy	Swiss chard and orange

Symptoms of the oral allergy syndrome—also called pollen-food allergy syndrome, which is a form of contact hypersensitivity almost entirely confined within the oropharynx—include the rapid onset of pruritus and swelling of the lips, tongue, palate, and throat.[7]. These symptoms usually resolve within minutes of onset, however. Individuals who have seasonal allergic rhinitis to birch or ragweed pollens commonly show signs of oral allergy syndrome after eating raw fruits and vegetables (see Table 1).

Eosinophilic esophagitis (EoE) is a new disease, not reported until very late in the past century. It presents with dysphagia, food impaction, heartburn, and regurgitation. It occurs more often in males and is often associated with other atopic disorders. Endoscopic findings include edema, concentric fixed rings, exudates, linear furrows (as demonstrated in Figure 2), and in advanced disease, strictures. Currently, there are no established markers that aid in determining which foods are the culprits other than eliminating common foods (6-food diet or 4-food diet) to observe if there is clinical and endoscopic improvement, as well as reduced numbers of eosinophils in mucosal samples. After a response to food elimination, one food group at a time is reintroduced to assess clinical, endoscopic, and histological endpoints. If there is no worsening of esophageal mucosal eosinophil counts another food group is introduced and so on, until there is worsening of symptoms, endoscopy, and pathology. Eventually through repeated periods of avoidance and challenges a specific exclusion diet can be established for an individual patient. In general, wheat and milk should be the last group to test as they are the most likely to produce a recrudescence of EoE. Additional therapies include proton pump inhibitors (PPIs) to treat co-existing acid reflux and/or PPI-responsive EoE, topical corticosteroids (swallowed fluticasone or oral budesonide suspension), and rarely systemic corticosteroids. Oral prednisone and budesonide capsules are usually used for treating eosinophilic gastroenteritis (EGE). EGE is less associated with food-allergy and food elimination has little benefit compared to EoE. Interestingly, while EoE prevalence is increasing, the frequency of EGE has not changed since the mid-1950s.

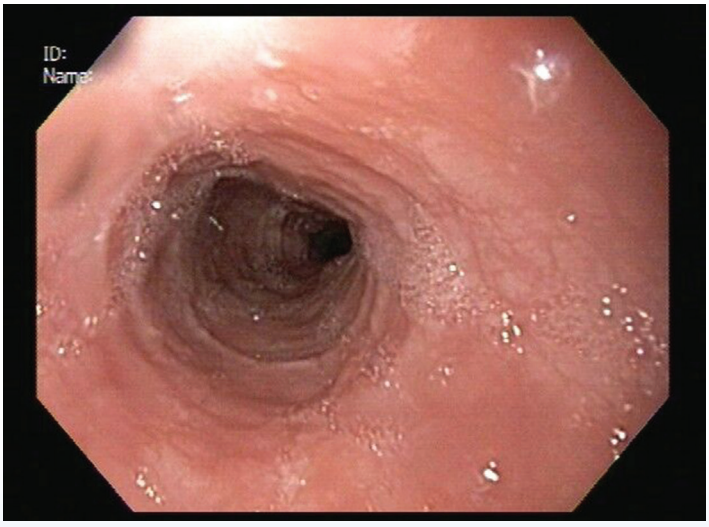


Figure 2.

FOOD ALLERGY AND THE GLOBAL PERSPECTIVE

More than 50 million Americans are estimated to have allergies and up to 15 million of them have food allergies.[8] One in every 13 children under the age of 18 years have food allergy. US healthcare dollars spent on food allergy approaches $25 billion per year. Although the vast majority of ARFs, more than 85%, are not due to true food allergies. One-fifth of the US population self-imposes diet modifications because of perceived ARFs.[2] Most ARFs are due to food intolerances that, though often unexplained, do not involve the immune system.

Food allergies affect 4% of adults and 8% of children in the USA and the prevalence seems to be on the rise.[8] The U.S. Centers for Disease Control and Prevention (CDC) reported a 50% increase in food allergy between 1997 and 2011. Approximately 200,000 emergency room visits and 300,000 ambulatory-care visits annually in the United States are related to food allergy.[2] Eight foods account for 90% of all

FOOD ALLERGY AND THE DIGESTIVE TRACT, *continued*

food allergic reactions in North America: milk, eggs, peanuts, tree nuts, soy, wheat, fish, and shellfish.[9] The most common food allergens affecting adults are shellfish, fish, peanuts, and tree nuts.[2] By the time a child reaches school age—in approximately 80% of cases—allergies to milk, eggs, soy, and wheat have usually abated.[9]

A recent systematic review provides a relatively recent estimate of the prevalence of food allergy in Europe.[10] Studies published in Europe from January 1, 2000 to September 30, 2012 were identified from searches of four electronic databases. Two independent reviewers appraised the studies and extracted the estimates of interest. Data were pooled using random-effects meta-analyses. Fifty studies were included in a narrative synthesis and 42 studies in the meta-analyses. Although there were significant heterogeneity between the studies, the overall pooled estimates for all age groups of self-reported lifetime prevalence of allergy to cow's milk, egg, wheat, soy, peanut, tree nuts, fish, and shellfish were 6.0, 2.5, 3.6, 0.4, 1.3, 2.2, and 1.3, respectively. The prevalence of food-challenge-defined allergy to these same foods were on average 10-fold less compared to the self-reported food reactions. Allergy to cow's milk and egg was more common among younger children, while allergy to peanut, tree nuts, fish, and shellfish was more common among the older ones. Allergy to most foods, except soy and peanut, appeared to be more common in Northern Europe. The heterogeneity between studies was high and participation rates varied across studies, reaching as low as <20% in some studies.

Asia is a populous and diverse region and a recent review aimed to summarize the current literature on food allergy from this region, comparing it with western populations. A PubMed search using strategies "Food allergy AND Asia", "Food anaphylaxis AND Asia", and "Food allergy AND each Asian country" was conducted.[11] Fifty-three articles, published between 2005 and 2012, were reviewed. The overall prevalence of food allergy in Asia was comparable to the West, but the types of food allergy differed in order of relevance. Shellfish was the most common food allergen in Asia, likely reflecting the abundance of seafood consumption in this region. Symptoms varied widely, from oral symptoms to anaphylaxis, within given individuals. In contrast, peanut prevalence in Asia was extremely low compared to the West for unclear reasons. Egg and cow's milk allergy were the two most common food allergies in young children and infants, with prevalence data comparable to western populations. Differences within Asia were also noted. Though uncommon in most Asian countries, wheat allergy is the most common cause of anaphylaxis in Japan and Korea, and is increasing in Thailand. This study highlights important differences between East and West, and within the Asian region.

Eosinophilic esophagitis (EoE) occurs in children and adults with a strong male preponderance. There has been a marked increase in EoE in North America, Europe, and Australia. The reasons for this increase remain unclear, but are likely to be influenced by genetic and environmental factors, as well as early-life exposures. Based on recent population-based data, the estimated EoE prevalence in the USA is 56.7 per 100,000 persons.[12] The peak prevalence was observed in patients between 35 and 39 years of age. Prevalence figures in Asia and the Middle East generally appear to be lower than in Western countries, but population-based studies are not available. Although celiac disease and EoE can occur in given individuals, typically males, a causal association between celiac disease and EoE appears unlikely. Additional population-based studies are needed to define the epidemiology of EoE.

In summary, food allergy occurs worldwide with varying prevalence according to specific food consumption and geographic regions. Food allergies, including EoE and celiac disease, are increasing in prevalence over time and are more frequent in western countries. However, data for all countries and regions of the world is incomplete.

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CELIAC DISEASE

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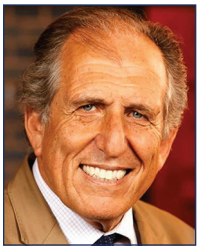

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DEFINITIONS

Celiac disease (CD) is a chronic enteropathy produced in genetically predisposed subjects by the ingestion of gluten.

Gluten represents the protein mass that remains when wheat dough is washed to remove starch. Gliadins and glutenins are the major protein components of gluten and are present in wheat, rye, and barley.

Non-celiac gluten sensitivity is a condition in which people in whom CD and wheat allergy has been excluded present symptoms which improve with a gluten free diet (GFD).

Wheat allergy is an adverse immunologic reaction to wheat proteins, mostly IgE- but rarely also non-IgE mediated. It may present as an allergy affecting the skin, gastrointestinal or respiratory tract, a contact urticarial, but also as the so called exercise-induced anaphylaxis, or as asthma/rhinitis (baker's asthma).

EPIDEMIOLOGY

CD is common, with a world prevalence of about 1%, varying from 0.14%-5.7%. The observed increased number of new cases in the last decades is due to better diagnostic tools and thorough screening of individuals considered to be at high-risk for the disorder. However, the ratio of diagnosed to undiagnosed cases of CD varies from country to country, suggesting that most cases of CD are still undetected. Globally, there is the need to increase the knowledge of disease, especially among primary care doctors.

ROLE OF GENETICS

The MHC-HLA locus is the most important genetic factor in the development of CD. The disorder is associated with human leukocyte antigen (HLA)-DQA1 and HLA-DQB1 genes, and the alleles HLA DQ2 (95%) and DQ8 (the rest) are present in the vast majority of CD patients. Recent data showed that also HLA class-I molecules are associated to the disorder.

SYMPTOMS

CD may present at any time in life with an ample spectrum of symptoms and signs.

Classical CD presents with signs and symptoms of malabsorption, including diarrhea, steatorrhea, and weight loss or growth failure in children.

In the so called non-classical form of CD, patients may present with mild gastrointestinal symptoms without clear signs of malabsorption or with extra-intestinal manifestations. In this case the patient will suffer from abdominal distension and pain and a myriad of extraintestinal manifestations such as: iron-deficiency anemia, chronic fatigue, chronic migraine, peripheral neuropathy unexplained chronic hypertransaminasemia, reduced bone mass and bone fractures, and vitamin deficiency (folic acid and B_{12}), late menarche/early menopause and unexplained infertility, dental enamel defects, depression and anxiety, dermatitis herpetiformis, etc. The family screening that follows a CD diagnosis has shown that CD may run asymptomatic, in asymptomatic CD patients, however, the GFD will also improve the quality of life and health.

DIAGNOSIS

The gold standard for CD diagnosis relies on the presence in serum of CD specific serology and the intestinal biopsy shows the presence of increased number of intra-epithelial lymphocytes (IELS) and various degrees of villous shortening.

CELIAC DISEASE, *continued*

Table 1.

The celiac disease clinical presentation may be monosymptomatic or oligosymptomatic, or with low intensity. The following signs or symptoms may be present at any age.
Gastrointestinal symptoms (diarrhea, abdominal distension and/or pain, chronic constipation in children, dyspepsia, early satiety, and loss of appetite)
Iron deficiency and anemia
Chronic fatigue and lack of energy
Chronic migraine
Dermatological manifestations (such as rash, psoriasis, and blisters)
Peripheral neuropathy - numbness and parasthesias
Unexplained chronic hypertransaminasemia
Vitamin deficiency (folic acid, vitamin D, vitamin B_{12})
Reduced bone density
Unexplained infertility
Delayed puberty, late menarche/early menopause
Unexplained miscarriage, premature birth, or small for gestational age infant
Incidentally recognized at endoscopy performed for GERD
Dental enamel defects
Depression and anxiety, moodiness, and irritability
Celiac crisis (cholera-like syndrome)

The CD serology encompasses serological markers targeting the auto-antigen, such as antiendomysial (EMA) and anti-tissue transglutaminase (anti-tTG), and those targeting the offending agent, against synthetic deamidated gliadin peptides (anti-DGPs). All of these antibodies are based on immunoglobulin A (IgA) or immunoglobulin G (IgG). Specifically, IgG-based tests are useful for detecting CD in selected IgA-deficient patients. It is recommended to test also the level of the serum total IgA, as IgA deficiency is present in 2% of population. In case of selective IgA deficiency in a second blood samples, IgG-based tests should be performed (anti-DGP, anti-tTG or EMA) because negative IgA antibodies will not be diagnostic.

Patients having a low titer of antibodies, and having histologically normal mucosa, may be a false positive test. The recommendation is to repeat the serology after six months while on a gluten-containing diet. If serology remains to be positive, these patients may be called potential CD and they should be followed. Majority of potential CD patients later develop the disorder. The long-term follow up of such patients is not well known.

The **intestinal (duodenal) biopsy** has been considered as essential for diagnosing CD. CD predominantly affects the mucosa of the proximal small intestine, with damage gradually decreasing in severity towards the distal small intestine. Under light microscopy, the most characteristic histological findings in patients with CD who are taking a gluten-containing diet are:

- Increased density of intraepithelial lymphocyte (>25/100 epithelial cells)
- Crypt hyperplasia with a decreased villi/crypt ratio
- Blunted or atrophic villi
- Mononuclear cell infiltration in the lamina propria
- Epithelial changes, including structural abnormalities in epithelial cells.

A modified Marsh classification for villous abnormalities is now widely used for assessing the severity of villous atrophy in clinical practice. It is highly recommended that the pathologists include report changes in a structured format, including the abovementioned histological changes, intraepithelial lymphocytes count, and interpretation in terms of modified Marsh´s classification. A negative histological diagnosis may justify a second biopsy in selected patients who have positive autoantibodies, such as high titre anti-tTG, anti-DGP, and/or endomysial antibodies. Patients with dermatitis herpetiformis having a positive serology may have normal histology.

Upper endoscopy, performed for other causes than biopsy procuration, may show scalloping and/or flattening of duodenal folds, fissuring over the folds, and a mosaic pattern of mucosa of folds. Four to six biopsy samples must be taken from the second part of the duodenum, and from the duodenal bulb, even if the mucosa appears normal. Biopsies must be taken when patients are on a gluten-containing diet (e.g. two slices of toast per day during four weeks).

The intestinal biopsy is always necessary if the antibodies are negative. However (and according to very new concepts for children), biopsies may be omitted in the presence of symp-

CELIAC DISEASE, *continued*

toms and signs of malabsorption, very high tTG-IgA titer (>10 time upper limit of normal), and positive EMA in a second blood sample. When the country resources are low, CD diagnosis can rely on the sole presence of positive serology or even of a histology demonstrating intestinal damage, followed both by the good clinical response to GFD. Presumptive GFD followed by dramatic clinical improvement has been considered an indirect diagnostic tool for CD. However, this strategy (sometimes useful in underprivileged countries) must be strongly discouraged as the GFD will by time decrease the specific antibody levels and restore the damaged mucosa, not allowing a proper CD diagnosis.

IMPORTANCE OF GENETICS FOR DIAGNOSIS OF CD AND POPULATION AT RISK

First-degree and (to a lesser extent) second-degree relatives have an increased risk for CD. Because of the genetic predisposition, in HLA positive people the onset of the disease or symptoms, on a gluten-containing diet, may occur at any time in life. On the converse, a negative HLA test will exclude the possibility of CD. All first-degree relatives should be screened for celiac disease. Approximately 7% to 10% of first-degree relatives may develop CD; the risk varies considerably with their relationship with the index patient (the maximum risk in presence of the HLA haplotype DR3-DQ2, especially homozygotes, the minimum in presence of DR4-DQ8).

Some other conditions (even if they may not be related pathogenically to CD) are considered at higher risk for CD. Therefore, there is the recommendation to test for CD the patients affected with type 1 diabetes mellitus, autoimmune thyroid disease, autoimmune liver disease, Down syndrome, Turner syndrome, Williams syndrome, and selective immunoglobulin A (IgA) deficiency.

TREATMENT, THE GLUTEN-FREE DIET

Patients with CD should not eat products containing wheat for the rest of their lives. Patients should consult a dietitian who is knowledgeable about gluten-free diets, especially during the first year after diagnosis. The safe limit of gluten intake varies across patients and has been considered to be 10-100 mg/day, although a subsequent study indicated that the upper limit should be closer to more like 50 mg/day.

Celiac patients cannot eat the following cereals and flours: semolina, spelt, triticale, wheat germ, wheat starch, wheat bran, bulgur, couscous, durum flour, farro, gluten flour, Kamut, Einkorn, Emmer Graham flour, rye, or barley (including malt, malt extract, malt flavoring, and malt syrup).

Gluten-free grains, flours, and starches that are allowed in a gluten-free diet include: amaranth, arrowroot, bean flours, buckwheat, corn, garbanzo beans, seeds, millet, Montina flour (Indian rice grass), nut flour, nut meals, oats (uncontaminated), potato flour, potato starch, quinoa, rice (all forms), sorghum flour, soy flour, tapioca, and teff flour.

A small subgroup of patients with CD may also be intolerant to pure oats. Oats must be pure and uncontaminated by gluten to be suitable per most CD patients.

The majority of industrially produced foods may contain gluten. Any dietary deficiencies, starting from the correct fiber content, but also iron, folic acid, calcium, and (very rarely) vitamin B_{12}, should be corrected.

DIFFERENTIAL DIAGNOSIS

In absence of a positive serology, the histological lesions suggestive of CD may suggest the presence of conditions other than CD.

The differential diagnosis includes infective diseases (tropical sprue, giardiasis, cholera, *H. pylori,* HIV), immunodeficiency states, drug-induced enteropathy (olmesartan, mycophenolate, chemotherapy), allergy (eosinophilic gastroenteritis, in children enteropathy caused by food allergy), radiation damage, graft-versus-host disease, chronic ischemia, Crohn's disease, and autoimmune enteropathy.

EXTRAINTESTINAL MANIFESTATIONS AND COMPLICATIONS

There are increased risks for unexplained infertility (12%), osteoporosis (30–40%), and bone fractures (35%) in classically symptomatic CD. Patients with (long-term untreated) CD have an elevated mortality risk due to an increased risk for malignancy. In particular, CD has been related to higher risk of malignant lymphomas, small-bowel adenocarcinoma, and oropharyngeal tumors. Likely, less than 1% of diagnosed patients may develop a severe complication called refractory CD, which is defined as persistence or recurrence of clinical symptoms and histopathological abnormalities despite excellent adherence to GFD for at least 12 months. Refractory CD must be considered, particularly in patients with CD diagnosed over the age of 50. This complication should be differentiated from the very common non-responsive CD,

which often is the consequence of persistent gluten intake (intentional or non-intentional) (see below).

MANAGEMENT OF CELIAC DISEASE

The vast majority of CD patients report an improvement in symptoms within few weeks after starting the GFD. Although most patients have a rapid clinical response to a GFD, the rate of response varies.

Patients who are extremely ill may require hospital admission, nutritional support, and, occasionally, steroids. With strict dietary adherence, the titer of CD-specific antibodies falls. The complete histological resolution, however, may take years and may not be achieved in every patient. There is evidence that the lack of histological resolution could be determined by persistent consumption of gluten.

Key issues when following up CD are:

- Serological tests cannot detect minimal gluten intakes (traces), so expert physicians and nutritionists should evaluate of the clinical situation and the GFD.
- Repeated duodenal biopsy to evaluate healing and for assessing adherence to a GFD is a controversial area among experts. However, intestinal biopsy should be considered as mandatory in patients persisting with symptoms despite evidence of strict GFD.
- Dietary lapses are the first cause of the lack of response to the treatment.
- In case of persistence of symptoms in patients with CD consider: overlapping irritable bowel syndrome (IBS) or inadvertent gluten ingestion (most common causes), but also a wrong CD diagnosis. Consider also other diseases, such as lactose intolerance, food allergies other than wheat, pancreatic insufficiency, microscopic colitis, bacterial overgrowth, IBS, ulcerative jejunitis, enteropathy-associated T-cell lymphoma, and refractory CD.
- During the first year after diagnosis of CD it is important to check symptoms and laboratory tests (best predictors: quantitative determination of anti-DGP IgA and anti-tTG IgA) and, if possible, to visit a nutritionist.
- In women, a DEXA bone mineral density scan serves as a baseline measure of bone mass.
- Facilitate the approach to support groups for CD patients.
- If necessary and/or requested, offer a psychological consultation.

Cascade with resource-sensitive options for the diagnosis of celiac disease.

Resource level	Cascade of diagnostic options
Gold standard	Medical history and physical examination Celiac disease–specific antibodies assessment and intestinal biopsy • Anti-tTG IgA and anti-DGP IgG. Total IgA to exclude IgA deficiency. Intestinal (duodenal) biopsies are always recommended • In certain situations biopsies may be omitted after discussing the pros and cons with an expert physician with special knowledge in celiac disease.
Medium resources	Medical history and physical examination Antibody assessment as a single diagnostic tool – when endoscopy is not possible or trained pathologists are not available; titer levels should be considered. Intestinal biopsies as a single tool* – in settings in which pathology is (perhaps remotely) available but clinical laboratories cannot reach the required standards.
Low resources	Medical history and physical examination Antibody assessment as a single diagnostic tool • Start with testing anti-tTG IgA. If negative and still suspected for celiac disease, add total IgA or DGP-IgG, if available.

Diagnosis only based on symptoms and/or response to the gluten-free diet is strongly discouraged.

MANAGING ADULT CELIAC DISEASE IN THE OUTPATIENT CLINIC

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INTRODUCTION

Celiac disease (CD) is a chronic enteropathy in genetically predisposed individuals in response to gluten intake.[1] CD as we know it is, rather than being a rare and incurable disease until the 1950's, both quite common in screening studies and readily treatable. The treatment is a gluten-free diet (GFD).[2] Most patients report clinical improvement within weeks. However, mucosal recovery may last years after the start of a GFD.[3] CD occurs only in patients who express HLA-DQ2 and/or DQ8 molecules.[4] The prevalence of CD in adults varies between one in 100 and one in 300 in most parts of the world.[5]

Three conditions are triggered by a systemic immune reaction to gluten consumption: celiac disease, the skin rash dermatitis herpetiformis, and gluten ataxia, which involves damage to the brain, especially the cerebellum. Celiac disease is a serious medical condition that requires a long-term follow-up plan to maintain excellent health and to prevent complications from occurring.

Maintaining a strict GFD is difficult in the East and West and has both financial and quality of life implications.[6] Evidence-based follow-up for out clinic management should be developed in the years to come.

GLUTEN FREE DIET

The one and only therapy for CD is a life-long gluten-free diet. Willem-Karel Dicke started this in the Netherlands in 1933; this is over 80 years ago.[2] No food, beverages, or medications containing any amount of gluten from wheat, rye, barley, spelt, kamut, or other gluten containing cereals can be taken; even small quantities can be harmful. Only food and beverages with a gluten content of maximum 20 ppm are accepted. Oats have been reported to be non-toxic in almost 100% of patients with CD.[7] GFD will result in symptomatic, serologic, and histological remission in most patients. With a strict GFD, antibody levels (tTgA and EMA) decrease very rapidly.[1] However, histological normalization takes 2-5 years, especially in adults.[3] In children, histological normalization occurs within 3-6 months, although antibody levels can take 1-1.5 years before normalization is reached. Compliance is often difficult, especially when a patient is "asymptomatic" or does not have the classical symptoms. It helps patients and their relatives to be properly informed about the chronic disease, the do's and don'ts, and the risk of untreated CD to increase knowledge and encourage self-empowerment of the patients. Despite the importance of adequate information, leading celiac support groups and working groups did not define guidelines so far to assess the outcome and standardize adherence to the GFD.

FOLLOW UP IN GENERAL

There is a lack of data about the best logistic outpatient clinic approach of patients during a lifelong GFD. Amongst the many guidelines for celiac follow-up, there is a lack of clarity regarding "What, who, and when." We do follow-up with 700 patients at our out-clinic. In the past, we saw the majority of patients on a regular annual face-to-face follow-up. Now we control (if necessary by telephone and laboratory controls in their local cities) and make appointments "at request". We have the impression that the adherence to a gluten-free diet improves by having a regular follow up, even by telephone, within the setting of a dedicated celiac clinic.

The question is if with the adherence to a GFD, quality of life and the avoidance of complications is indeed improved. In the past, one of the key factors relating to the adherence to a GFD was supposed to be the quality of the dietician. Of course, GE-clinics do have dietetic experience, but the majority of patients nowadays also have excellent access to the internet and thereby to websites advocating and explaining GFD; this is an advantage and a risk/ pitfall at the same time, as the internet is spoiled with erroneous information, confusing the necessarily strict follow-up of the diet. The majority of patients manage their diets without any problems as gluten free products are widely available. The diet is difficult to follow for non-native speakers, immigrants, illiterates, the elderly, and patients on a low budget.

This is even more outspoken and problematic in the Middle-East, North Africa, the Indian Subcontinent, and Latin America.[6] Only in the first years is dietetic follow-up part of the regular follow-up. However, refractory celiac and gluten ataxia patients should be controlled by a dietician every 6-12 months.

FOLLOW UP SEROLOGY

IgA tissue Transglutaminase (tTgA) is the preferred method for monitoring the quality of GFD-compliance. Minor dietary mistakes are not detected by this. Interpreting this test is straightforward, a celiac patient on a GFD for at least 6-12 months should have a negative test. EMA can remain positive in follow-up during GFD for years. The tTgA levels should be as close to zero as possible, indicating a minimal antibody response to gluten, or at least show a significant and ongoing dropping. A negative test is what most celiac patients want to see some time after beginning the GFD. A normal tTgA value can sometimes be reached only after a year or more on the diet, especially if the initial value was very elevated. What matters is that the number declines consistently over time. One should be aware that in non-compliant patients, a mucosal and serological relapse might develop even after many years of gluten challenge.[8]

Also, there is no reliable way to monitor compliance with a GFD. Recent studies indicate that measuring the amount of the protein I-FABP in the blood may provide in the future a useful tool to supplement the currently accepted assays.[9]

LABORATORY FOLLOW UP

A significant decrease (or normalization) of markers for malabsorption, such as fat in the stool, was the hallmark of control until the late eighties. We rarely check for this anymore as a standard procedure. For those presenting with severe malnutrition, as well as ongoing weight loss, we assess nutritional status and intestinal absorption capacity should be assessed.[10] Checking if the small intestine normalizes is mandatory: hemoglobin, iron, vitamin B_6, folic acid, vitamin B_{12}, calcium, alkaline phosphatase, vitamin D, and parathyroid hormone. We advise checking for the so-called common associated autoimmune conditions (Thyroid-stimulating hormone, Thyroid hormone), and finally tTgA to check the diet adherence. The sensitivity of tTgA for the quality of diet adherence control is not well studied. The key endpoints in the clinical follow-up are normalization of weight, prevention of overweight, and mucosal healing, which means normalization of histology to Marsh 0-1.

HISTOLOGICAL FOLLOW-UP

Rates of mucosal healing are highly variable. In some studies up to 40% of patients had persisting villous atrophy after two years and about 10% after five years on a GFD.[3,11] This raises the question whether symptoms alone constitute a reliable guide to mucosal healing. Ongoing villous atrophy can lead to persisting deficiencies and problems such as osteoporosis and mimic irritable bowel syndrome (IBS). Clinical symptoms, celiac serology, and laboratory markers of inflammation are unfortunately not robust enough measures to confirm mucosal healing. Until better non-invasive tests of mucosal healing can be developed, a repeat intestinal biopsy after one year of GFD is recommended. The majority of patients diagnosed after the age of 40-45 years do have a slow normalizing histological recovery. As part of our research, we repeated intestinal biopsies after one year of dietary therapy in the mid-nineties. However, this is not our approach in 2015. We repeat biopsies only in patients with severe abnormalities, especially if diagnosed above the age of 50, or based on lack of improvement and persistent or recurrent complaints.

Our principal problem is whether re-biopsies indeed change the clinical outcomes in the majority of patients.

Recently Biagi *et al.* showed that the majority of celiac patients do not present a satisfactory histological response, and they suggested a duodenal biopsy to be the only tool that could identify patients with unsatisfactory histological response.[12]

ADHERENCE TO GFD

So far reports never defined the frequency of monitoring for assessing compliance and outcome. Training families to adhere to GFD is important; consultation by gastroenterologists and cooperating dieticians should take place every 4-8 months in the first year. Celiac families with additional screen-detected relatives need in general fewer controls, as they are already familiar with our advice about GFD.

Dietary adherence guarantees mucosal healing and at least improvement of non-gastrointestinal symptoms. Non-invasive biomarkers for complete mucosal recovery might be useful. The majority of patients who normalize rapidly, with normal diet and a BMI 20-25, need less follow-up. In general, we advise controlling those patients in the out-clinic only once every two years. Patients with a lack of improvement we see at least twice a year. In between the two-year interval follow-up we ask the general practitioner to check serum hemoglobulin,

MANAGING ADULT CELIAC DISEASE IN THE OUTPATIENT CLINIC, *continued*

folic acid, vitamin B_{12}, vitamin D, and tTgA and that Thyroid function to be checked annually.

SYMPTOMS DURING FOLLOW-UP

If patients present themselves with low BMI, we try to normalize the BMI between 18.5 - 25, and above 20 for elderly and refractory celiac patients, however at the moment 40% of our newly diagnosed celiac patients are overweight with a BMI over 25 kg/m^2.[15] In a substantial part of those patients, the weight goes down in the first year after initiation of GFD, not just because the diet is "unpalatable", but also because some hungry feeling is disappearing. So far studies about the appropriate attitude for this subgroup are lacking. Normally BMI increases on the GFD. On GFD 15-20% of patients move from a normal or low BMI-class into an overweight BMI-class and 20 % of those already overweight at diagnosis gain weight.[16]

The disappearance of fatigue, especially in females over the age of 30, is one of the most significant problems and goals in daily clinic routine; the proportion of patients who do have a slow response to a gluten-free diet and/or histologic recovery is another topic.[1]

SCREENING IN CELIAC FAMILIES

We observed a high positive screening rate of 10% in both first and second-degree relatives.[17] However, there probably was a selection bias; only those relatives with a low threshold for screening were screened. Maybe, this selection of patients in the family already had (albeit minor) complaints. A large multi-center study from the USA showed a rate of only 5% in both first and second-degree relatives.[18,19] We suggest that 4-5% reflects the true rate in daily practice appropriately. Patients with a first-degree family member with a confirmed diagnosis of CD should be offered to be tested if they show possible signs or symptoms of CD. We advise offering newly diagnosed celiac patients screening on their first and second family degree family members. Screening should include DQ2/8 typing, tTgA antibodies, hemoglobulin, folic acid, vitamin B_{12}, iron, and Thyroid function.

FOLLOW UP AND DIETICIANS

Malabsorption, weight-loss, and vitamin/mineral deficiencies characterize classical CD. We recently reported that the majority of patients in an "early diagnosis" adult untreated CD patient group, with non-classical presentation, had serum vitamin and mineral deficiencies at diagnosis.[15] A majority of celiac patients were zinc deficient at diagnosis. Based on our experience and supported by others, we suggest monitoring body weight at diagnosis and nutritional serum parameters: at least vitamin B_6, folic acid, vitamin B_{12}, zinc, and (25-hydroxy) vitamin D of the fat soluble vitamins. Moreover, we suggest follow-up until serum values are at satisfying levels or upon indication (bone density deviations, chronic or recurrent diarrhea, or zinc related skin lesions).

Careful dietetic review once a year was part of the deal in our out clinic. However, the majority of well-educated patients are reluctant to this approach. Therefore, inadvertent gluten intake is discussed during the out-clinic visit, especially in patients with a poor educational state or low-income families. In that case, we check if there is adequate nutrient vitamin and mineral intake. There is a lack of studies about GFD check in different countries.[6] We and others have already reported 30 years ago that the dietary adherence is poor in a substantial part of patients.[20] In our out-clinic we control around 30-40 patients who do not adhere at all. The majority of those patients normalize the diet to an adequate GFD within five years of follow-up due to an increase in symptoms.

Recently an Israeli study reported about pediatric celiac patients who were lost to follow-up.[21] This cohort had not only lowered adherence to GFD, but also failed periodic serological monitoring, which left them oblivious to the consequential disease activity status. This is problematic in young patients, who may not reach their growth potential (catch-up growth, etc.) and are still too young to consider the long-term effects of their attitude with an enlarged risk for auto-immune disease in general. Continuation time of mineral and vitamin interval has yet to be determined since patients are at risk for deficiencies even after 10 years of a GFD.[22]

FOLLOW UP AND DERMATITIS HERPETIFORMIS

Dermatitis herpetiformis (DH) is the cutaneous manifestation of gluten-sensitive enteropathy. It is a herpetiform clustering of extremely itchy urticated papules, especially on the extensor side of the elbows and knees, buttocks, and scalp.

Improvement of DH with GFD takes several months according to the current literature.[23] However, remission can take some years, but is poorly documented in current literature. Diamonodiphenyl sulfone and sulfapyridine are the primary medications to treat DH. Diamonodiphenyl sulfone is almost always indicated and initiated due to rash and the itching.

The exact mechanism of action is unknown but thought to be related to inhibition of neutrophil migration and function. Patients should be monitored for the adverse effects of diamonodiphenyl sulfone, primary hemolytic anaemia, methemoglobinaemia, agranulocytosis, and neuropathy. For patients unable to tolerate dapsone, sulfapyridine may be substituted; however dapsone does not improve GI mucosal pathology. More than 70% of patients on GFD are able to slowly wean off dapsone over a period of 2-3 years.[24] More than 90% of our 80-100 DH patients on a strict GFD cannot wean off dapsone in the first years. More than 50% of patients go on for at least 5-10 years. No reports are available on long term follow up of dapsone in DH.

FOLLOW UP AND GLUTEN ATAXIA

Of the three gluten-induced conditions, gluten ataxia is the only one without a straightforward path to diagnosis.[24] In fact, although awareness is growing, it has not been accepted by all mainstream neurologists.

If any antibodies to gluten are present in lab tests, then our recommendation is to consider for all ataxia patients "with no alternative cause for their ataxia" to start GFD for 12-24 months. Stabilization or even improvement after 1 – 2 years would be a strong argument that the patients suffer from gluten ataxia.[25] We need proper observational studies about this issue.

MEDICAL MANAGEMENT IN FOLLOW-UP

Follow-up can be arranged in primary care as long as the expertise is available. Unfortunately, the critical number of celiac patients per general physician is insufficient. In the Netherlands, only 25,000 patients are known in a population of 16 million inhabitants. We have around 10,000 GPs. This means that a general GP controls as a mean only 2.5 patients. This suggests that their expertise is insufficient. The number of gastroenterologists in the country is 500, so in general, gastroenterologists should control at least 50 celiac patients per doctor. Prompt access for our celiac patients to specialized centers around the country is recommended but not well-organized. So far only 15-20 gastroenterologists in our country are devoted to CD. However, access to those doctors is limited; the majority of them is each controlling only 150-200 celiac patients per year. Access for patients to a well-trained celiac interested gastroenterologists is limited. Secondary, especially tertiary, care is recommended if complicated CD arises. It should be noted that this care is not well organized, not only in Europe, but worldwide.

FOLLOW UP AND BONES

Long-term adherence to GFD leads to significant improvement in bone density. However, we see major abnormalities in bone density in our population diagnosed above 50 years of age, females as well as males. All of these high-risk patients for bone fractures should be treated with calcium and vitamin D. All osteopenia/ osteoporotics in these age-groups are treated for 36 months with intravenous bisphosphonates, four times per year 60mg APD. During our yearly follow-up we measure calcium, alkaline phosphatase, vitamin D, and Parathyroid hormone for a compensatory increase of the bone mass. Bone density should be measured in every adult newly diagnosed celiac patient.

A 24-months treatment course with risedronate 35mg once weekly, concomitant with calcium and Vitamin D supplementation, in osteopenic inflammatory bowel disease (IBD) patients improved bone density.[27] Similar studies are urgently needed in CD.

Appropriate criteria for follow-up bone density in daily practice for CD are lacking. We repeat bone density investigation in the case of osteopenia in general after an interval of three years. In general, gastroenterologists pay more attention to post-menopausal women with CD in supplementation of calcium than to males; however, we do have the impression that the lumbar spine quality of males is more severely hampered than in females.

HYPOSPLENISM

Hyposplenism associated with CD may result from impaired immunity to encapsulate pathogenic microorganisms. Arbitrarily, we vaccinate all celiac patients with a spleen volume below 100cc with Pneumovac®.

MICROSCOPIC COLITIS

Microscopic colitis (MC), including lymphocytic and collagenous colitis, are associated with autoimmune disorders, especially with CD. In case celiac patients during follow-up develop watery diarrhea, we always screen for MC.[28] MC is very common in our celiac center, maybe even too common based on selection bias in our referral celiac patients. We treat them with slow release budesonide (Entocort®) for three months and in the case of a relapse with thiopurines especially tioguanide (thiosix®).[29]

MANAGING ADULT CELIAC DISEASE IN THE OUTPATIENT CLINIC, *continued*

(PRE)-MALIGNANT CELIAC CONDITIONS

There is an increased risk for malignancies, already recognized over 50 years ago.[30] Small-bowel cancer, cancer of the esophagus, female celiac patients in their twenties and thirties with B-cell Non-Hodgkin lymphoma, and seniors in their sixties for Enteropathy Associated T-cell Lymphomas (EATL) are well recognized in current literature.[1]

Celiac disease is a common diagnosis, but malignant outcomes are rare. EATL is such an infrequent complication that the majority of gastroenterologists may never see it amongst the population of celiac patients they diagnose and see for follow-up.[31,32]

Evidence suggests the risk for increased mortality and malignancies is reduced in those who adhere to the diet. However, EATLs present themselves especially in those patients diagnosed above 50 years of age.[30] Only 10% of patients referred to us with suspicion for (Pr)-EATL are diagnosed with those complications.[32] The risks of malignancy related to CD reported in literature are likely to remain overestimated owing to either bias or confounding.[32,33]

REFRACTORY CELIAC DISEASE

In the situation of non-responsiveness to a GFD, dietary adherence should be meticulously evaluated. Monitoring levels of tTgA and/or EMA are suitable for this purpose. Additionally, all patients should be referred to a skilled dietician. When inadvertent gluten ingestion is reasonably excluded, the CD diagnosis should be re-evaluated. Absence of the CD-related genotypes (HLA-DQ2.5 or HLA DQ8) at diagnosis is highly suggestive of misdiagnosis. When other causes or VA have been excluded, these patients are referred to as refractory CD (RCD).

Since 2001, we have divided RCD into two types based on the absence (Type I) or presence (type II) of an, usually clonal, intraepithelial lymphocyte population with aberrant phenotype.[34] Our diagnostic approach and the latest insights in treatment options are readily available in literature.[4]

ESOPHAGEAL CANCER

Around 90% of all esophageal cancers are related to lifestyle, such as tobacco, alcohol, diet, and overweight. Esophageal cancer is more than 10 times higher in patients with Barret's esophagus. However, esophageal cancer is also higher in people with CD.[35] In case of Barret's esophagus, we screen our celiac patients in follow-up. Otherwise, we do not screen them for this minor risk factor.

COLON CANCER

Unfortunately, CD has strongly been suggested in the past to be related with some site specific intestinal malignancies. In contrast to this, according to the available reports the risk of colorectal cancer (CRC) has been described a similar or lower to that of the general population.[36] Untreated CD may be protective, probably owing to impaired absorption of fat, hydrocarbons, and putative co-carcinogens implicated in the pathogenesis of CRC, which may be poorly absorbed and rapidly excreted.[37] The reflex of gastroenterologists when patients present with diarrhea at their out-clinics is to recommend a colonoscopy with a very low threshold, so the majority of the elder celiac patient population already had a colonoscopy at diagnosis or follow-up.

RISK OF CARDIOVASCULAR DISEASE

Cardiovascular diseases that have been suggested to be associated with CD include ischemic heart disease (IHD), cerebrovascular events, and cardiomyopathy. The risk of IHD may be related to the pro-inflammatory activated immune cells like in Rheumatoid arthritis[38] and with low folic acid state, could affect the development of arteriosclerotic lesions.

In 2004, West *et al.* studied almost 4,000 patients with CD with respect to hypertension, hypercholesterolemia, heart disease, and stroke.[39] However, they showed a lower prevalence of hypertension and hypercholesterolaemia in CD in comparison with controls. GFD gives a significant increase in BMI and cholesterol in celiac patients adherent to the diet.[40] There is a body of reports published on cardiovascular risks in celiac patients, however, conclusions of some studies are at odds with each other. The co-occurrence of T1DM in some celiac patients should be taken into consideration.[41]

When we find arteriosclerosis during abdominal CT in the work-up of complicated CD referred for second opinion we start aspirin 100mg daily and keep the cholesterol below 4 mmol/L. Recent studies, however, did not recognize an increased risk of IHD in celiac patients.[39]

CONCLUSION

A life-long GFD improves health and the quality of life in a vast majority of patients with CD, even in those with minimal symptoms.[1]

GFD is in daily practice (especially in the second and third world) difficult to sustain, owing to several barriers including social, cultural, economical, and practical aspects. Adher-

ence to the diet varies and has been reported to range between 40-90%. The majority of the middle-class patients manage their diet without any problems. The diet is difficult for underprivileged patients. Pediatric data have shown that regular follow-up is associated with a significant increase in long-term compliance with GFD. Medical follow-up by gastroenterologists interested in CD is, in our opinion, essential for monitoring patients with CD to identify and prevent nutritional deficiencies, medical complications, and support adherence to GFD. However, the best way to follow up celiac patients has not yet been established.

We do see the majority of our patients face-to-face every two years and in between by telephone within our setting of a dedicated celiac clinic (see Table 1). We hope to standardize this with celiac support groups and workings groups to assess the outcome and standardize the adherence to a GFD.[42]

Table 1: *Follow-up plan for patients with Celiac Disease in the VUmc*

AT DIAGNOSIS (PHYSICIAN AND DIETITIAN)
• Complete physical examination • Education on celiac disease • Gluten-Free dietary counselling by a skilled dietician • Recommend family screening (DQ2/D8 and celiac serology) • Recommend membership in celiac support group • Bone Densitometry (not routinely recommended for children) • Celiac serology (if not previously obtained) • Routine Tests (complete blood count, iron studies, folate, thyroid function tests, liver enzymes, calcium, phosphate, vitamin D, and DQ2/8)
AT 2-4 MONTHS (PHYSICIAN AND DIETITIAN)
• Assess symptoms and coping skills • Dietary review
AT 6 MONTHS (PHYSICIAN) (BY TELEPHONE)
• Assess symptoms • Complete physical examination (on indication) • Dietary review • Celiac serology (tTgA) • Repeat Other Routine Tests (if previously abnormal)
AT 12 MONTHS (PHYSICIAN AND DIETITIAN)
• Assess symptoms • Abdominal physical examination (on indication) • Dietary review • Celiac serology (tTgA) • Repeat Other Routine Tests • Small intestinal biopsy (not routinely recommended for children)
AT 24 MONTHS (PHYSICIAN) (BY TELEPHONE AS CLINICALLY INDICATED)
• Assess symptoms • Dietary review • Celiac Serology • Thyroid function tests • Other Tests as clinically indicated • Dietitian as clinically indicated
AT 36 MONTHS (PHYSICIAN)
• Bone densitometry (if previously abnormal) • Assess symptoms • Dietary review • Celiac Serology • Thyroid function tests • Test as clinically indicated

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EATING DISORDERS AND THE GI TRACT: DEFINITION, RECOGNITION, THE ROLE OF THE PSYCHOLOGIST IN CARE

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INTRODUCTION

Eating disorders (EDs) represent a group of psychiatric disorders which commonly have significant concurrent gastrointestinal (GI) symptoms, creating significant management challenges for gastroenterologists, psychologists, and other health professionals involved in their care. Further, diagnosis is made more challenging due to the cyclical patterns associated brain-gut interactions associated with EDs (e.g., psychopathology and behaviors associated with EDs can influence GI function and in turn GI function can influence psychopathology and behaviors). At the core of all EDs are abnormalities of eating or eating-related behaviors resulting in altered consumption and/or absorption leading to significant impairment in health and/or psychosocial functioning.[1] The most common EDs which may present to an adult gastrointestinal (GI) practice are Anorexia Nervosa (AN; Restricting type or Binge-eating/purging type), Bulimia Nervosa (BN), Binge-Eating Disorder (BED), and Avoidant/Restrictive Food Intake Disorder (ARFID). It should be noted that several other EDs, such as Other Specified Feeding or Eating Disorder, Unspecified Feeding or Eating Disorder, and atypical conditions associated with mental health problems (e.g., muscle dysmorphia), may also present at an adult GI practice, but are beyond the scope of this chapter.

DEFINITION AND PREVALENCE OF EDS

AN and BN share a common focus on an individual's self-evaluation being strongly influenced by their body shape or weight. In AN, an individual is of a significantly lower weight than would be expected. Despite this low weight, there is a strong fear of gaining weight that is accompanied by restrictions of energy intake to prevent weight gain. Individuals with AN may belong to a subtype that is restrictive and achieves weight loss through low food intake or high exercise or to a binge-eating/purging subtype that eat large quantities of food and use compensatory methods to control weight (e.g., vomiting, laxatives, or exercise). AN has a 12-month prevalence of 0.4% and is more common in young females. In contrast, individuals with BN, although also engaging in binge-eating and purging to control weight, are not significantly underweight

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and instead experience a sense of lacking control during binge-eating episodes. BN has a 12-month prevalence of 1.0-1.5% and is also more common in females.[1]

In contrast, BED and ARFIDs are more focused on the food or the process of eating itself. In BED, episodes of binge-eating occur with a sense of lacking control, however, there are no compensatory methods to control weight. Instead, after eating large amounts without feeling hungry, an individual may conceal symptoms, feel guilty, depressed, or disgusted with themselves. The BED group may also be under recognized in part because they do not fit the young female stereotype. BED has a 12-month prevalence of 1.6% in females and 0.8% in males. ARFIDs involve falling below energy and nutritional needs due to a lack of interest in eating, dislike for the sensation of food, or concern for possible consequences of eating (e.g., choking or vomiting).[1]

COMMON GI COMPLAINTS REPORTED BY INDIVIDUALS WITH EDS

It is very common for individuals with EDs to experience GI symptoms. For example, in BN compensatory methods to control weight after a binge-eating episode can include self-induced vomiting or laxative abuse. The use of these methods can be problematic for GI health and lead to a variety of complications, such as dental, esophageal, motility, or impaired gastric emptying.[2] Conditions such as AN are often associated with abnormal GI sensations and motility, however some of these may be reversible with weight gain and others may relate to underlying psychiatric manifestations, possibly a common cause (such as previous abuse). Individuals with EDs who attend a GI clinic prior to ED treatment request more tests and have more hospital admissions than other GI patients or ED patients who first attend ED treatment.[3] Additionally, individuals with functional gastrointestinal disorders (FGIDs) are significantly more likely to have a history of eating disorders than a gallstone disease comparison group, indicating that coexisting GI symptoms may persist after the ED has resolved.[4] Both upper and lower GI symptoms are common among individuals with EDs,[2] and the eating disorder itself may be 'hidden' by the GI symptoms. Consequently, awareness of EDs in gastroenterologists is important as patients with EDs may approach them before approaching other professionals, such as a psychologist.

RECOGNITION OF EDS IN GI PRACTICE:

Individuals with EDs have been found to frequently approach practitioners regarding physical GI symptoms prior to talking about EDs.[2] A recent systematic review (based on four studies with total of 691 GI patients) suggests that disordered eating patterns occur in around 23% of GI patients.[5] Gastroenterologists can help patients with EDs by being aware of EDs and routinely screening patients for these, as some symptoms may become salient during psychological distress.[4] Establishing a multi-disciplinary team of healthcare professionals (such as physicians, registered dieticians, psychologists, and psychiatrists) may also be helpful.[6] This can help patients with EDs to receive support for their EDs and avoid unnecessary and potentially dangerous tests and/or hospitalization, whilst having their FGID symptoms and also the physical complications of their EDs managed appropriately.

SIGNS TO HELP IDENTIFY GI PATIENTS WITH EDS

- Younger female demographic
- Psychological distress or comorbid mental disorder
- Concerned with size or shape of body
- Underweight or over-eating
- Excessive focus on foods and engagement with restrictive eating patterns based upon beliefs relating to foods (e.g., most healthy/pure)
- Erosion of tooth enamel
- Reflux symptoms
- Extensive investigations required to identify GI issue
- Functional motility disorders
- Score on an ED screening survey

TREATMENT OF EDS

The latest guidelines from the American Psychiatric Association[6] and the UK based National Institute for Clinical Excellence[7] provide detailed and evidence-based recommendations in the treatment of EDs. The first steps in the treatment for AN and BN are to restore a healthy weight, reduce or eliminate binge-eating or purging, and to treat any physical complications of the disorders.[6] Focus should also include goal setting to restore a healthy eating pattern and the provision of nutritional information on how to achieve this. Additionally, therapy is recommended to reassess unhelpful thinking, treat comorbidity, build family support, and to prevent relapse. Patients are often treated in the outpatient setting, and may benefit

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Table 1: *Definition and summary of the primary forms of ED-focused psychological therapies*

Psychological treatment form and definition:
Cognitive-Behavior Therapy (CBT): Symptoms targeted directly to re-evaluate thinking (i.e., identifying and correcting negative core beliefs/unhelpful thoughts), promote helpful behavioral responses, and reduce individual distress. Focus on unhelpful behaviors and dysfunctional attitudes relating to eating, weight, body shape, exercise, and other psychosocial issues (e.g., bullying, and family discordance).
Psychodynamic Interpersonal Therapy (IPT): Interventions that have a primary focus on understanding and working with transference (the unconscious transferring of feelings from one person to another). Focus is to foster psychological insight and address underlying personality disorders.
Dialectical Behavioral Therapy (DBT): Disordered eating is viewed as an attempt to regulate uncomfortable emotions, and are treated with mindfulness, tolerance of distress, regulation of emotion, and interpersonal skills. Regulating emotions can address the sense of losing control and binge-eating, reducing its frequency.
Family Therapy (FT; e.g., The Maudsley Approach): Interventions that incorporate the whole family system and focus on fostering new skills in relationships, communication, and problem-solving. When individuals are younger and of shorter illness duration, parental support of re-nutrition is effective.

from psychotropic medications such as selective serotonin reuptake inhibitors (SSRIs).[7]

Cognitive-Behavior Therapy (CBT; including self-help oriented CBT) and Psychodynamic Interpersonal Therapy (IPT) have been identified as an effective treatment for AN, BN, and BED.[7,8] For BN, both CBT and IPT, but not Dialectical Behavioral Therapy (DBT), are effective in reducing binge-eating and compensatory methods, and also decreased body dissatisfaction.[9] CBT has also been demonstrated to reduce the frequency of binge-eating episodes in adults diagnosed with BED.[10] Specifically regarding AN, Family Therapy (FT) shows the most potential when patients are younger and in the earlier stages of their ED.[11] The research is less advanced in the treatment of ARFID. No treatments have been recommended for ARFID, due to a lack of research trials.[12] Although it has been found hospitalization tends to be longer than in AN.[13] It should be noted that psychological therapies for EDs range in terms of their format (individual, group, or combined), frequency, and duration, for a detailed summary and recommendations for the treatment of EDs.[6,7] See Table 1 for definition and summary of several common forms of ED-focused psychological therapies.

ROLE OF THE PSYCHOLOGIST FOR PATIENTS WITH EDS

- Provide psychological assessment and associated ED-specific psychological interventions
- Develop treatment formulations that identify and take into account patient predisposing factors (e.g., developmental traumas, attachment style, and cognitive development), precipitating factors (e.g., stressors), perpetuating factors (e.g., defense styles, level of insight, and ED maintaining cognitions/behaviors), protective factors (e.g., personal strengths), and ED severity
- Provide psychological interventions associated with, but not directly related to, the eating disorder, such as school/socialization problems, and family difficulties
- Provide input to team treatment plan for patient with an ED
- Providing psychoeducation to both patients and families affected by an ED
- Providing ongoing advice and support to medical and allied health team
- Facilitate insight, self-esteem, and psychological and physical recovery
- Facilitate positive coping strategies and resilience to manage future stress and challenges
- Work with medical and allied health professionals to monitor and reduce patient self-harm
- As relapse is extremely common for AN, BN, and BED, long term monitoring and relapse prevention work is often needed

ORTHOREXIA NERVOSA

Orthorexia Nervosa (ON) is a dysfunctional eating condition not yet recognized by the Diagnostic and Statistical Manual (DSM-5),[1] but may be observed in GI cohorts.

ON involves an obsession with an increasingly limited diet focused upon consuming the most healthy or 'pure' foods and

the focus is not related to losing weight or reducing energy intake. The exclusion of foods that are categorized as less healthy or pure can lead to malnutrition and have a significant impact on psychosocial wellbeing. In a recent review, Varga and colleagues[14] identify that the average prevalence of ON in a general population is 6.9% and up to 57.8% in high-risk groups such as healthcare professionals and artists. No research has tested the efficacy of a treatment for ON.[15] Koven and Abry[15] suggest that a combination of CBT and psychotropic medication may be efficacious due to the success in treating AN and Obsessive-Compulsive Disorder. However, recent research suggests that 30% of outpatients with AN or BN can go on to develop ON after treatment.[16] As such, it is also important to notice whether a previous restriction or compensation becomes a preoccupation with food that is categorized as healthy or impure.

CONCLUSION

Individuals with EDs often have GI symptoms for which they may seek treatment with a gastroenterologist before seeking treatment for the symptoms of their ED. This can result in unnecessary tests, hospitalizations, and missed opportunity to address their underlying distress. It is an ongoing challenge for gastroenterologists to identify and support patients with EDs. However, screening for EDs and establishing a team approach can help effectively treat EDs and any physical complications effectively, and work toward the best outcome for ED patients.

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PROBIOTICS AND PREBIOTICS FOR GUT HEALTH: THE ESSENTIALS

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Probiotics, defined by the World Health Organization (WHO), are *"live microorganisms that when administered in adequate amounts, confer a health benefit on the host."*[1] It is specified by genus, species, and strain (using an alphanumeric designation) for example *Bifidobacterium infantis* 35624. Common probiotic species include *Lactobacillus, Bifidobacterium, Saccharomyces* (a yeast), and some *E. coli* and *Bacillus* species. Probiotic strains must be assessed for biosafety based on the seven criteria listed by the European Union (EU).[2] Clinical indications of probiotics for gut health are given in **Table 1**.

Prebiotics are *"selectively fermented ingredients that allow specific changes, both in the composition and/or activity in the gastrointestinal microflora that confers benefits upon host well-being and health."*[2] The common prebiotics include the fructooligosaccharides (FOS), galactooligosaccharides (GOS), lactulose, and inulin. Given together (synbiotics), prebiotics can enhance the gut effects of probiotics.

Table 1*: Clinical indications of probiotics for gut health*

PEDIATRIC
Acute infectious diarrhea
Prevention of antibiotic-associated diarrhea
Prevention of nosocomial diarrhea
Adjuvant therapy for *Helicobacter pylori* eradication
Alleviate some symptoms of functional bowel disorders
Infantile colic
Prevention of necrotizing enterocolitis in preterm infants
Mildly active ulcerative colitis

ADULTS
Acute onset infectious diarrhea
Prevention of antibiotic-associated diarrhea
Prevention of *Clostridium difficile*-associated diarrhea
Adjuvant therapy for *Helicobacter pylori* eradication
Irritable bowel syndrome
Ulcerative colitis (maintenance of remission, treatment of mildly active colitis and pouchitis, and prevention and maintenance of remission in pouchitis)
Constipation
Hepatic encephalopathy

VIABILITY OF PROBIOTICS

Probiotic bacteria exert their effects by transiently adhering to the intestinal mucosa and eventually the strains would pass out in the feces. Fecal recovery is useful as an indirect measure of gut colonization. The half-life of a probiotic can vary from strain-to-strain, but it has been established that certain microbial strains survive and remain detectable in stools for up to four weeks after discontinuation of intake. Survival in the host for a longer period may require continuous intake, but whether prolonged colonization is beneficial remains unclear. A third of probiotics are estimated to survive in adequate numbers in order to affect gut microbial metabolism and exert its intended clinical responses.

The probiotic preparations available in the market include capsules, sachets, yogurts, and fermented milk or fruit drinks. There are also external factors that affect viability of probiotics, including storage (refrigeration or shelf) and transportation. Microbial strains are sensitive to external environment (in particular to oxygen, moisture, and heat). Furthermore, in order to be viable in the gut, probiotics should be able to tolerate gastric acid, bile, and pancreatin; adhere to mucus and/or

PROBIOTICS AND PREBIOTICS FOR GUT HEALTH: THE ESSENTIALS, *continued*

human epithelial cells; possess antimicrobial activity against potentially pathogenic bacteria; reduce pathogen surface adhesion; possess bile salt hydrolase activity; and be resistant to spermicides. Depending on the final applications and entry routes of hosts, most industries will first pre-screen putative probiotic strains for these properties prior to health and nutraceutical assessments.

DOSING AND TIMING OF PROBIOTICS

The optimal effective dose at which probiotics produce clinical benefit remains unclear. Present clinical studies have utilized a minimum daily therapeutic dose of 10^6 to 10^9 colony forming units (CFU).[3] The duration of probiotic therapy also varies among hosts and targeted therapeutic effects, and thus it is advisable for probiotics to be taken continuously. Although host and physiology dependent, *Saccharomyces boulardii* has been reported to be cleared from the body within three to five days after stopping as compared to *Enterococcus faecium*, which reportedly persisted for five weeks after probiotic intake in humans. A meta-analysis by Ritchie *et al.* reported that some probiotic strains showed significant clinical efficacy when taken for as little as one week up to 240 weeks.[4] Hunger *et al.* suggested that probiotics should be taken for at least one month in those with lower gastrointestinal (GI) symptoms[5] and a longer period is needed for metabolic diseases. Various factors affect such dosing variations; a) the original gut microbiota profile of hosts, as probiotics need to colonize to exert certain health benefits and should the original gut microorganisms prevent such colonization, thus the effects of probiotics are hindered; b) the diet and physiology of hosts such as fibers and polysaccharide intake which alter the unstirred layer of the intestinal epithelium will change the attachment of probiotics to gut lining; c) gut-related diseases which increase the concentration of toxic metabolites to probiotics will hinder their survival; d) metabolism of hosts often vary, leading to different dosage and time needed for a beneficial effect to be materialized; e) unlike drugs, most mechanisms and specific targeted sites of health benefits by probiotics remain unknown, thus variation will remain.

No definite recommendation on proper timing of probiotic consumption has been made so far. Certain strains, such as *Lactobacillus rhamnosus* and *Saccharomyces boulardii*, may be administered before a meal or just after a fat-containing meal to avoid resistance to gastric acid but many commercial strains nowadays have been tested for acid resistance before production. Tripathi *et al* reviewed the literatures on acid and bile tolerance of several Bifidobacteria species and noted that *Bifidobacterium longum* survived best.[6] Some *Lactobacillus* species are able to survive in environments between pH 3.7 up to 6.0. Presently, commercial products have addressed this issue by providing more effective delivery systems via microencapsulation, enhanced coatings, and drying methods to enhance strain viability. Consumption would clearly depend on individual probiotic strain properties, as well as, product formulation.

SAFETY OF PROBIOTICS

The US Food and Drug Administration (FDA) defined probiotics as Generally Recognized as Safe (GRAS).[7] However, there are many commercial probiotic preparations available with different species, strains, and efficacy. Therefore, safety assessments are strain-specific and the GRAS status does not cover all probiotic products *per se.* The European Union (EU) project on biosafety evaluation of probiotics (PROSAFE) recommends the following safety measures: proper identification of microbial strain via biochemical and molecular methods; determination of antibiotic resistance and transfer; standard antimicrobial susceptibility testing; *in vitro* assessment of virulence; and *in vivo* assessment of strain pathogenicity.[8]

The Agency of Healthcare Research and Quality (AHRQ) together with the National Institutes of Health (NIH) have reviewed in detail the existing literatures on safety of probiotics.[7] Amid rare systematic reporting of adverse events, the authors concluded that present randomized controlled trials (RCTs) did not show an increased risk of adverse events for children, adults, or elderly.[7] In this regard, probiotics can be theoretically consumed in people of all ages. Common side effects include abdominal cramps, nausea, flatulence, and taste disturbances, which are usually observed only in the first three days of consumption and may not be attributed to the probiotics. Excipient materials used for production and the addition of prebiotics to probiotics can impart GI side effects due to their indigestible nature. Although rare, certain probiotic strains could produce more acids than others, leading to increased gut motility and subsequently exerting gut discomfort. This is normally not detrimental to health and may actually be useful in combating pathogenic bacteria in the gut.

The most important concern regarding probiotic use is the risk of sepsis. Probiotic bacteria, such as *Lactobacillus casei* and *Lactobacillus rhamnosus*, have been observed to cause

infective endocarditis and liver abscess in immuno-compromised hosts. Several cases of fungal sepsis have been documented in relation to *Saccharomyces boulardii* in patients with central venous catheters.[7] Although the exact mechanisms for bacterial translocation remain unknown, host factors such as intestinal mucosal injury, immunodeficiency, and abnormal intestinal flora are likely important reasons.

The following risk factors for sepsis are associated with probiotic, namely: (1) major risk factors - immunocompromised host and premature infants; (2) minor risk factors - presence of a central venous catheter, history of cardiac valvular disease, impaired intestinal epithelial barrier, concomitant administration of broad spectrum antibiotics to which probiotic is resistant, administration by jejunostomy tube, and probiotics with properties of high mucosal adhesion. Premature infants, patients with chronic diseases, and/or debilitation are also considered as high-risk populations. Probiotics, though generally safe, should be used in caution in these specific patient groups.

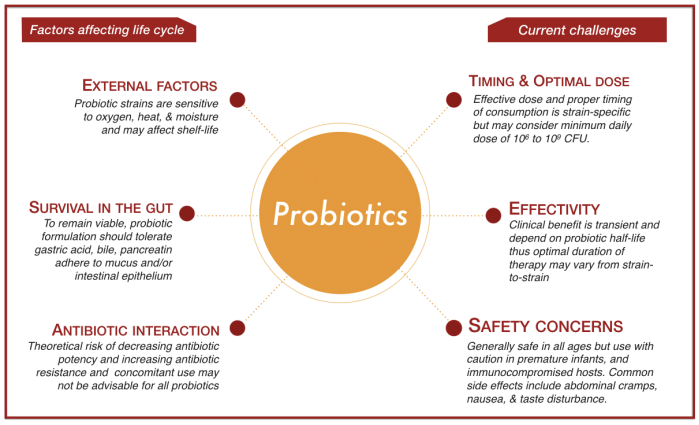

Figure 1*: Factors affecting the probiotic life cycle and current challenges in the use of probiotics*

PROBIOTICS-ANTIBIOTICS INTERACTIONS

A theoretical interaction is the potential for antibiotic-resistance transfer between probiotics and pathogenic bacteria, as a result of chromosomal mutations or horizontal gene transfer. Antibiotic resistance to vancomycin, chloramphenicol, and erythromycin have been identified in *Lactobacillus* species. Again, this emphasizes the importance of appropriate regulation with proper strain identification, *in vitro* evaluation, and antimicrobial susceptibility testing of probiotic strains.[8]

Some resistance traits are in-borne chromosomal and non-plasmid associated and thus are allowed as a natural trait in certain genera of probiotics. These are allowed within certain resistance allowance limits.

Another debatable issue is the inhibitory effect that antibiotics have on probiotics. Probiotics have been used as an adjunct to prevent antibiotic-induced super-infections. For example, *Saccharomyces boulardii* has protective effect for antibiotic-associated diarrhea. Likewise, concomitant probiotics and antibiotics can reduce the incidence of *Clostridium difficile*-associated diseases in high-risk patients. Studies, however, differed in the timing of probiotic administration after antibiotics. Some patients are given probiotics within 48 hours of antibiotic initiation up to the entirety of antibiotic course and some up to seven to 10 days after. It is recommended that *Lactobacilli* probiotic strains be given at least two to four hours after antibiotic, unlike *S. boulardii*.

Figure 1 summarizes the factors affecting the probiotic life cycle and current challenges in the use of probiotics.

ROLE OF PREBIOTICS

All prebiotics are fibers but not vice versa. Some prebiotics (e.g. galacto-oligosaccharides or inulin-type fructans) exert similar functions as the human milk oligosaccharides (HMO) and are important for the development of metabolic, immune, and nervous systems of infants.[9] A specific mixture of short-chain galactooligosaccharides (scGOS) and long-chain fructooligosaccharides (lcFOS) in a 9:1 ratio has been suggested for infant use. Generally, prebiotics improves gut metabolism, stool consistency, and stool transit by increasing bacterial mass and osmotic water-binding capacity in the gut lumen, thereby reducing the risk of constipation.[10] Other gut modulatory benefits of prebiotic supplementation include alleviation of GI discomfort (e.g. bloating, flatulence and abdominal pain) and reduction of the risk of immune-related diseases, infection, and inflammation. Fermentation of prebiotics in the colon generates short-chain fatty acids in particular butyrate. Colonic inflammation is associated with low production of butyrate. Prebiotics can also enhance calcium absorption, mainly the fructans.

SUMMARY

Probiotics, like any live microorganisms, are affected by *ex vivo* and *in vivo* conditions. Much clinical evidence has shown that probiotics and/or prebiotics can be used as a natural

PROBIOTICS AND PREBIOTICS FOR GUT HEALTH: THE ESSENTIALS, *continued*

intervention to alleviate many gut disorders and they are largely safe. Further research is needed to determine the right strains (often in combination), the optimal dosage, and duration of therapy to cater for various indications and population groups.

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THE HUMAN GUT MICROBIOME

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STATE OF THE ART

Microbial cells in the human body outnumber human cells by about ten to one. The vast majority of these reside in the gastrointestinal tract. Non-culture based technologies have evolved over the past several years, revolutionizing the feasibility and accuracy of the human microbiome analysis. There had been longstanding belief that the fetus resides in a sterile environment, but this has been challenged in recent years with microbial discoveries in both the placenta and meconium[1] thanks to these advanced technologies. It is also now well established that mode of delivery, maternal diet, infant diet, antibiotic exposure, and the home environment can all have significant impact on the early development of the infant intestinal microbiome[2] (See Figure 1). The intestinal microbiome of the infant and young child is susceptible to dramatic shifts secondary to environmental exposures until 1-3 years of age. This implies that disruptions in normal, healthy microbiota development in infancy can have lasting effects even in adulthood.[3]

Increased hygiene and a lack of exposure to various microorganisms have been held responsible for the "epidemic" of chronic inflammatory diseases that over the past 30-40 years has been recorded in industrialized countries. That is the essence of the hygiene hypothesis that argues that rising incidence of asthma, inflammatory bowel disease (IBD), multiple sclerosis, type 1 diabetes, irritable bowel syndrome (IBS), celiac disease (CD), and other chronic inflammatory diseases may be, at least in part, the result of lifestyle and environmental changes that have made us too "clean" for our own good. The hygiene hypothesis, first proposed by Greenwood in 1968 and subsequently by Strachan in 1989, suggested lack of early childhood infections in the developed world might be responsible for this rise in allergic and autoimmune diseases.[4]

Over the past several years, knowledge of the human microbiome has been rapidly accelerating thanks to the Human Microbiome Project Initiative. As our understanding of the human microbiome expands, the hygiene hypothesis continues to be revised and frequently challenged and was recast more recently as the "microflora hypothesis."[5] This suggested that Western lifestyle alters exposure to microbes (rather than infection *per se*), causing perturbations in the colonization of the intestinal mucosa and affecting mucosal immune system development and predisposition to cause inflammation through mechanisms that are still being elucidated, and thus increasing the risk for chronic diseases. Specifically, there is mounting evidence suggesting that microbiome-mediated maturation of gut epithelial barrier and of the immune system impact capacity for the host to develop responses that maintain immune tolerance and prevent aberrant pro-inflammatory or allergic responses. Indeed, it appears that there is a two-way connection between the microbiota and immune dysfunction, with both influencing and shaping each other, and a complex relationship maintained to ensure homeostasis. Additionally, by causing increased gut permeability, gut dysbiosis may lead to passage of endotoxins and/or food-

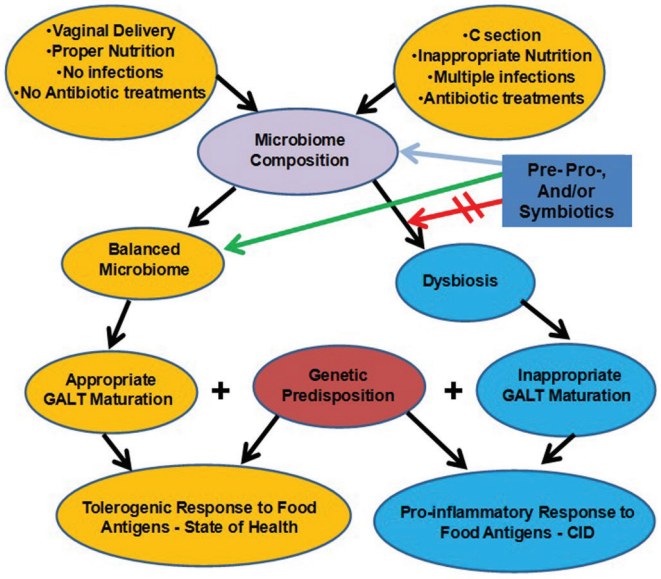

Figure 1: Factors influencing the epidemics of chronic inflammatory diseases by affecting microbiome composition. *Prenatal, perinatal, and postnatal factors play a key role in shaping gut microbiome composition and, in turn, the proper maturation of the gut associated lymphoid tissue (GALT) to exert either a tolerogenic or pro-inflammatory function that, together with genetic predisposition, may lead to a state of health or diseases, respectively.*

THE HUMAN GUT MICROBIOME, *continued*

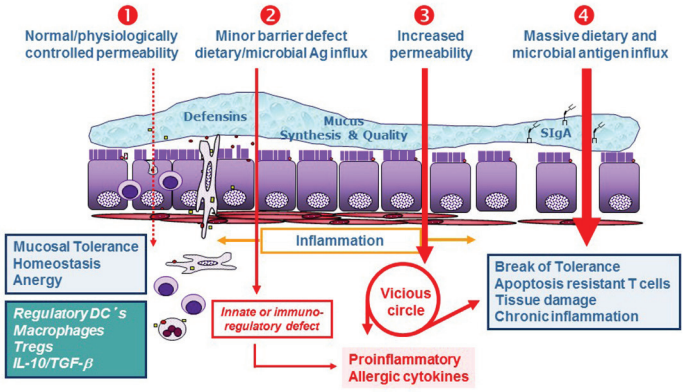

Figure 2: Mechanisms leading to loss of intestinal mucosal homeostasis: *Under physiological circumstances a very tightly controlled antigen trafficking assure gut mucosal homeostasis, anergy and, therefore, state of health[1]. Functional loss of gut barrier function leads to inappropriate passage of undigested nutrients an/or endotoxins causing innate immune response or immune regulatory defects leading to the productions of po-inflammatory cytokines, including IFNγ and TNFα[2]. They in turn causes further increase in intestinal permeability causing a vicious circle[3] that leads to massive dietary and microbial influx from gut lumen to submucosa, break of tolerance and, ultimately, to chronic inflammation.[4] Adapted from P. Brandtzaeg. Beneficial Microbes 2010.*

derived peptides into the intestinal mucosal and eventually blood stream with subsequent increased interactions with immune cells leading to break of tolerance and, ultimately, onset of chronic inflammation (See Figure 2).

Early in life, exposure to healthy and diverse commensal species promotes protection against chronic inflammation by those mechanisms, and therefore that pre-, peri-, and post-natal environmental factors (including physical, chemical, biological, behavioral, and social environmental factors) which strongly influence our gut ecosystems, thereby setting us up to be susceptible to or protected from the development of diseases throughout the entire lifespan (See Figure 1). Of all these factors, nutrition is by far the most influential one, suggesting that Western diet is indeed one of the key driving forces of the epidemics of these chronic diseases through changes in microbiota composition.

ONGOING DISCOVERY IN COMMON GI CHRONIC DISEASES

Research is blossoming in the area of the microbiome in nearly all human diseases. Here, we will discuss the current state of the field in three of the most common chronic GI diseases in which the microbiome is suspected to play a significant role in disease pathogenesis: IBD, CD, and IBS. Mechanistic discovery, ongoing prospective studies, interventions tried, and areas of promising future development will be highlighted.

INFLAMMATORY BOWEL DISEASE

The involvement of microorganisms in the pathogenesis of IBD has been postulated for many years. However, despite the great effort spent in search of the pathogen(s) triggering the chronic inflammatory process that characterizes IBD, the identification of microorganism(s) causing IBD has remained elusive. Now there is good evidence that the pathogenesis of IBD is the consequence of an inappropriate immune response to commensals rather than the consequence of infection with specific pathogens. This exaggerated response seems secondary to the combination of genetic mutations and imbalance of the gut microbiome.[6] However, disparities in methodological approaches, including different techniques used to analyze gut microbiome, disease activity, site of inflammation, and different site of microbiota sampling (stools vs. mucosa), make comparison among the studies reported in literature very difficult. Nevertheless, a common theme emerges, suggesting that this dysbiosis is characterized by reduction in biodiversity (α-diversity) and altered representation of several taxa. Gut dysbiosis is often associated with specific dysfunctions of microbial metabolism and bacterial protein signaling, including involvement of oxidative stress pathways and decreased carbohydrate metabolism and amino acid biosynthesis counterbalanced by increase in nutrient transport and uptake.[6] While these changes suggest a possible mechanistic link between modifications in microbiota composition and IBD pathogenesis, these studies remain mainly associative.

CELIAC DISEASE

CD is unique among autoimmune diseases in that there is a strong association with HLA DQ2 and/or DQ8(39), the environmental trigger (gluten) is known, and disease-specific autoantibodies have been identified and can be measured. Therefore, exposure to the environmental trigger can be carefully studied and frequent prospective screening against the autoantibody tissue transglutaminase (tTG) can determine precisely when the loss of tolerance to gluten occurs.[7] Dysbiosis has been implicated in the development of CD. *In vitro* studies suggest that microbes can influence the digestion of gliadin, the production of cytokines in response to gliadin, and

the increased intestinal epithelial permeability induced by gliadin.[8] The vast majority of research describes differences in the composition, structure, and diversity of the fecal and small intestinal microbiota in patients with CD based on age, disease status, and associated signs and symptoms. Associated metabolic activity, as measured by patterns of short chain fatty acids (SCFA) in the stool, is altered in patients with active CD and linked to the described dysbiosis. However, differences in specimen collection, analysis techniques, age of the study population, and disease status make it difficult to compare studies.

IRRITABLE BOWEL SYNDROME

Several studies suggest that gut microbiota is altered in IBS, with different composition and decreased complexity in microbiota of IBS patients compared to healthy controls as well as within the subgroups of IBS patients.[9] Although these microbiota signatures are a meaningful step towards a better understanding of a link between gut dysbiosis and IBS, it must be taken into consideration that these results are obtained from relatively small sample populations. Considering that IBS is a multifactorial syndrome with many possible causes and different clinical presentations, it is possible to predict that results derived from these studies will explain the role of specific microbiota composition in subgroups of patients rather than explaining the pathogenesis of the IBS population as a whole.[9]

CONCLUSIONS AND FUTURE DIRECTIONS

The major limitation of current studies linking gut microbiome with clinical outcomes is their descriptive nature. To link gut microbiome composition with disease pathogenesis, it is necessary to generate solid mechanistic evidence of disease onset and progression in relation to dynamic changes of abnormal microbiome causing host epigenetic modifications controlling gut barrier, immune functions, and, ultimately, loss of tolerance. Currently there are limited effective strategies for the treatment or prevention of these chronic diseases. The advent of genomics, proteomics, and now advanced microbiome analysis raised the expectation of therapeutic solutions that have yet to materialize. It is now becoming clear that these diseases are final destinations, but that the paths to disease development vary from patient to patient. To date, a myriad of cross sectional studies have described alterations in the gut microbiota composition in a variety of disease states, after the disease has already presented.

It now appears clear that to understand and study these microbiome shifts, prospective cohort design is required to capture changes that precede or coincide with disease and symptom onset. Additionally, prospective studies integrating microbiome, metagenomic, metatranscriptomic, and metabolomic data with comprehensive clinical and environmental data are necessary to build a systems-level model of interactions between the host and the development of disease.[10] The creation of novel network models is essential to providing a mechanistic approach to exploring the development of disease. As the field expands exponentially in the wake of non-culture-based technologies to study the microbiome, a multi-omic research approach has the potential to revolutionize our understanding of most common diseases affecting humankind. This knowledge will provide personalized therapeutic (precision medicine) and preventive (primary prevention) targets for microbiome manipulation using prebiotics, probiotics, and/or symbyotics (See Figure 1).

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GREAT SIGNIFICANCE OF LATEST PAN AMERICAN HEALTH ORGANIZATION NUTRIENT PROFILE MODEL TO PREVENT GROWING OBESITY INCIDENCE

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Obesity prevalence is an alarming health problem worldwide, but even more so for the Americas, where it reaches the highest rates. Over the last few decades, global strategies aimed to stop or slow down this pandemic phenomenon have clearly failed. Obesity and overweight related diseases have turned out to be the first causes of morbidity and mortality throughout American countries, surpassing disabilities and deaths due to malignancies, infection, and malnutrition. Fifty-five percent of all deaths are currently caused by associated obesity and overweight diseases.

Obesity and being overweight affect 62% of adults in the Americas, with Mexico, Chile, and the USA being at the top of the list. Seven out of ten adults in these countries are obese or overweight. Concern grows further when checking prevalence rates in childhood and adolescence; obesity and being overweight have also been constantly increasing in this group, reaching prevalence rates of 25%.

Several robust investigations have already found a cause/effect relationship between diet and obesity. Unanimously, studies show that energy excessive input is a hallmark of the modern diet. This energy excess poses a threat to physiological mechanisms of weight homeostasis.

After many years of hard scientific search, investigations managed to disclose the main issue behind the excess of energy in diet. It is not only the energy excess itself, but also its quality, that really makes the difference for human health. Belief in the caloric hypothesis has finally weakened since components in alimentary products are now considered potent hormone and neurotransmitter triggers for nutrition science. Most of the ingredients used in the process of food production add a powered effect in terms of metabolic responses, when compared to "in natura" food effects, which have less impact on energy body regulation. Subsequently, repetition in the consumption of processed food leads to well-known underlying hyperinsulinemia, the very early stage in the development of overweight and obesity disorders.

In order to facilitate the recognition of healthy or unhealthy food, four categories have been proposed:

1. "In natura" food is directly obtained from plants or animals (such as leaves, fruits, eggs, and milk) and is ready to consume without any kind of modification after leaving nature. This type of food couples physiologically with human metabolic pathways and helps to preserve weight homeostasis.
2. "Minimally processed" food is the result of "in natura" food after a minimum modification process, such as drying, polishing or grounding of grains, meat freezing, or milk pasteurization. In this group, components like oils, fats, sugar, and salt (critical nutrients) are moderately used in culinary preparation to add flavor and diversity to dishes without affecting nutritional balance. This kind of food is still harmonious with human metabolism.
3. "Processed" food is mainly produced by the addition of critical nutrients to "in natura" food or "minimally processed" food. Some examples include: canned vegetables, syrup fruits, canned meats, cheese, and packaged bread. This kind of food is created to last longer than "in natura" or "minimally processed" foods, but it loses original nutritional qualities detrimental to health balance.
4. "Ultra-processed" food is characterized by several manufactured steps. Most of it is represented by industrial exclusive components, such as refined vegetable oils, high fructose syrup, synthetic proteins, modified starch, petroleum and coal derived synthetics, colorants, flavoring, and additives. Some examples include: soft drinks, stuffed biscuits, ice cream, sweets, sweetened cereals, cakes mixtures, cereal bars, soups, pasta and sauces ready to heat, sweetened milks and yogurts, energy drinks, and frozen meal products ready to heat. These are all high energy dense and their components impact directly on metabolic pathways, impairing hormonal and sensorial balance, and accelerating weight gain.

When compared to "in natura" or "minimally processed" foods, "processed" and "ultra-processed" foods have much more sugar, unhealthy fat, and sodium. Furthermore, "processed" and "ultra-processed" foods lack diet fiber, minerals, and vitamins, while carrying higher energy density. Even with all of these harmful characteristics, "processed" and "ultra-processed" foods are still conveniently practical, ubiquitous, strongly publicized, extremely palatable, and habit stimulat-

GREAT SIGNIFICANCE OF LATEST PAN AMERICAN HEALTH ORGANIZATION NUTRIENT PROFILE MODEL TO PREVENT GROWING OBESITY INCIDENCE, *continued*

ing. In fact, all these features may explain why handmade meal preparations are being replaced by "processed" and "ultra-processed" food. Consequently, many traditional culinary customs are gradually extinguishing.

The Pan American Health Organization (PAHO) met recently to find new resources to tackle the concerning health consequences of this nutritional transition on the American population. The PAHO Nutrient Profile Model was formulated to cover all countries in the American region. It aims to involve all governments in making crucial decisions to create environments conducive to healthy eating.

Some of its most remarkable strategies include:

- Preventing unhealthy food consumption.
- Quantifying and controlling "critical nutrients" present in processed food, including: salt, sugar, trans fats, and saturated fats.
- Warning about "critical nutrients" contained in food products by adding an information label on the front side of packaging.
- Establishing specific guidelines for food and beverage consumption in schools.
- Restricting marketing of unhealthy food and beverages among children.
- Applying tax policies to limit unhealthy food consumption.
- Avoiding sweeteners in children's food and beverages, since repetitive sweet flavor (regardless of calories) stimulates and defines consumer habits.

These guides claim that implementing new nutritional programs, saving food health benefits, and combating "ultra-processed" food's harmful effects is urgent for public health. The PAHO requires countries to inform consumers about certain "critical nutrients" hidden in packaging and to restrict confusing messages behind food publicity. They focus as well on encouraging people to cook and prepare their own fresh dishes, in an attempt to reinforce traditional flavors and help regional customs reappear and survive among nutritional globalization.

In the Americas, sweetened beverage consumption increased 33% between 2000 and 2013. During this period, snacks consumption also increased 56%. These are only two examples in a huge field of investigations that show certain predominance of "ultra-processed" food over "minimally processed" or "in natura" foods. Dietary energy input provided by "ultra-processed" food has flagrantly accelerated during recent

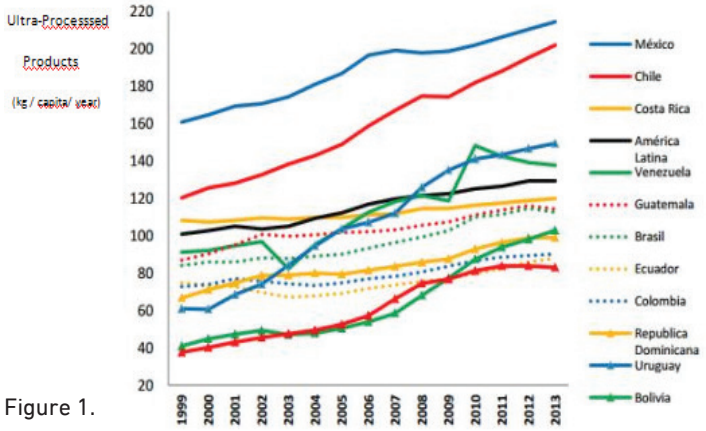

Figure 1.

decades. In 1987, energy input provided by "ultra-processed" food in Brazil was 19%; this had reached 32% by 2008. Moreover, in 1938, energy input provided by "ultra-processed" food in Canada was 24%; by 2001 this had increased to 55%.

Figure (1) shows the evolution of "ultra-processed" food sales from 1999 to 2013 in 12 countries from Latin America. This study was conducted by the PAHO in order to estimate "ultra-processed" food consumption trends through over the last few years. Results showed that "ultra-processed" food sales continuously grew in all countries, with marked elevations in Uruguay (+145%), Peru (+121%), and Bolivia (+151%).

Thereafter, these consumption trends were analyzed against obesity growing rates in those countries and significant statistical association was found.

When epidemiological data is put together, the human metabolic dialogue between diet and obesity is clearly understood. Then, taking decisions to fight this problem becomes essential. Health and education workers, media outlets, and governments can join efforts to improve the public's nutritional status. The PAHO Nutrient Profile Model attempts to serve as a roadmap in this complex context.

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THE GUT RESPONSE TO FOOD; A PHYSIOLOGICAL PERSPECTIVE ON FOOD-INDUCED GASTROINTESTINAL SYMPTOMS

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Before launching into a discussion of the potential roles of food allergy or intolerance in gastrointestinal symptomatology, or even in the pathophysiology of a common functional gastrointestinal disorder, such as irritable bowel syndrome (IBS), one must first consider the potential role of a more fundamental factor in the precipitation of GI symptoms and gut distress on, or soon after, food ingestion; namely, the **physiological response to food**. All physiological processes in the gut, including motility, secretion and blood flow respond to food intake, or the anticipation thereof, in order to maximize digestion and absorption. Both neural (and the vagus, in particular) and hormonal elements contribute to these responses. Signals along the gut-brain axis, a bidirectional pathway between the GI tract and the brain, may initiate, perpetuate or modulate the food response. Other factors, including mucosal immune responses and even the gut microbiota may participate in this bidirectional interaction, the latter leading to the concept of the microbiota-gut-brain axis.[1-3] The interplay between these factors in the genesis of gastrointestinal post-prandial symptoms is nicely illustrated by IBS where these phenomena have been studied in some detail; food responses in IBS and their regulation will, therefore, be used as an illustrative example throughout this chapter.

NEURAL REGULATION OF GUT RESPONSES

The central nervous system (CNS) communicates with the enteric nervous system via the sympathetic and parasympathetic branches of the autonomic nervous system. The anticipation and/or ingestion of food stimulate the autonomic nervous system leading to such well-described physiological responses as the cephalic phase of gastric acid secretion, receptive relaxation of musculature in the upper gastrointestinal tract and the gastro-colonic response. Given the frequent localization by sufferers of their pain to the left lower quadrant and of the prominence of post-prandial urges to defecate in IBS, the gastro-colonic response, a neurally-mediated homeostatic reflex, was an early target of investigation in this disorder.

Not only were IBS subjects shown to exhibit an exaggerated gastro-colonic response[4-6] but exaggerated responses to food ingestion were also demonstrated in the small intestine and, even, in the gall bladder.[7-11] That autonomic nervous dysfunction in response to a meal might contribute to symptom generation is nicely illustrated again by IBS; alterations in the autonomic nervous system have been reported in patients with IBS; the most consistent finding being increased sympathetic nervous system activity.[12-16] In other words, IBS sufferers are more susceptible to, and experience more exaggerated manifestations of the "gut distress" that we all experience on occasion when extremely stressed. Such reactions are seen in perhaps their most florid form in the individual with a severe anxiety disorder. Changes in parasympathetic nervous system activity have been less consistent in IBS and, while responses have varied, decreased parasympathetic responses have been observed most frequently.[12-16]

ENDOCRINE REGULATION OF THE RESPONSE TO FOOD

A number of gut hormones play an integral part in the responses to food[17.] Enteric endocrine cells populating the gut secrete an array of hormones, such as motilin, gastrin, cholecystokinin (CCK) and peptide YY and respond to the anticipation and/or arrival of food or the products of digestion, and, thereafter, modulate the fate of gut contents in either a paracrine or endocrine manner. Motilin is secreted in the inter-digestive period when it released on distension of the duodenum by intense contractile activity of phase III of the migrating motor complex and stimulates gastric motility. Ghrelin, thought to play a major role in satiety and also released on food ingestion, also stimulates motility. Interestingly, higher circulating ghrelin levels have been described in IBS patients and could contribute to associations between food ingestion, dysmotility and IBS symptoms in some affected individuals.[18,19] Cholecystokinin release is stimulated by the arrival of fat and protein into the proximal gut and delays gastric emptying, increases gut motility and enhances rectal hypersensitivity.[20] Both fasting and post-prandial levels of CCK are elevated in IBS and an exaggerated response or hypersensitivity to CCK can cause symptoms of constipation, bloating or abdominal pain.[21] In disorders of maldigestion and/or malabsorption the arrival of unabsorbed nutrients in the distal ileum (and fat in particular) stimulates the release of peptide YY from ileal neuro-endocrine cells and leads to

delayed gastric emptying and small bowel transit in an attempt to halt caloric losses: the so-called ileal brake.[22]

ROLE OF NEUROMODULATORS AND NEUROTRANSMITTERS

Serotonin is a neurotransmitter and paracrine signaling molecule and is secreted primarily from enterochromaffin (EC) cells, which accounts for approximately 80% of total body serotonin secretion. Increased enterochromaffin (EC) cells, elevated post-prandial serotonin levels and decreased serotonin reuptake due to decreased affinity for the reuptake transporter protein have been reported in different IBS subtypes; the former being observed in post-infectious IBS and the latter two in IBS-D[23-25]Serotonin stimulates receptors responsible for peristalsis and secretion in the GI tract, and acts to promote communication along the got and on the gut-brain axis. The post-prandial diarrhea and urgency commonly reported by sufferers with IBS-D may be due to an exaggerated serotonin response leading to increased peristalsis and secretions.[23]

FOOD-MICROBIOTA INTERACTIONS

The gut microbiota plays a pivotal role in gut homeostasis in health and in the pathogenesis of a number of intestinal and extra-intestinal diseases. It includes a diverse population of approximately 10^{14} bacterial cells; 10 times more than that total number of human cells. The functions of the gut microbiota include the protection of the host from enteric pathogens, the development of the host immune system, participation in host metabolism and contributing to nutrition. Our diet has a major impact on the composition of the microbiota and differences in dietary patterns are a major determinant of inter-individual variations in microbiota diversity. For an excellent overview of many aspects of the gut microbiota, please refer to the 2014 World Digestive Health Day publication "WGO Handbook on Gut Microbes", which can be downloaded for free at: http://www.worldgastroenterology.org/UserFiles/file/WDHD-2014-handbook-FINAL.pdf.

Interactions between components of the diet and/or the products of digestion could play a role in the genesis of food related symptoms and changes in diet or microbiota could exacerbate or alleviate such symptoms. As a by-product of bacterial fermentation is liberation of gases (e.g. nitrogen, hydrogen, carbon dioxide and methane) an increase in the numbers of gas-producing organisms (e.g. *E. coli, Veillonella* species) may cause flatulence and bloating.[26] Flatulence could occur as a consequence of a reduction in methanogenic bacteria, (*Methanobrevibacter smithii* and certain *Clostridium* and *Bacteroides* species) which convert hydrogen produced by other intestinal bacteria to methane and greatly reduce gas production.[27,28] In contrast, excess methane production has been linked to constipation.[27] The arrival of undigested carbohydrates into the colon will provide more substrate for fermentation, as well as acting as a prebiotic. Local changes in gas production, in conjunction with enhanced sensitivity to gas distension may contribute to bloating, a remarkably prevalent post-prandial symptom in a number of functional gastrointestinal disorders. Bacterial metabolism of carbohydrates also produce short chain fatty acids which stimulate colonic and ileo-colonic motility and secretion[29,30] and could cause diarrhea; stool volume and consistency will also be influenced by the extent of bacterial deconjugation of bile acids.

CONCLUSION

Many are the physiological interactions between the act eating and gut function; interactions that can be accentuated in a variety of diseases and disorders and that could account for postprandial symptomatology without having to invoke food intolerance or allergy.

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DIET AND THE GUT

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