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## Sugars and Gastrointestinal Health

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**ABSTRACT**

Sugar overconsumption is linked to a rise in the incidence of noncommunicable diseases such as diabetes, cardiovascular diseases and cancer. This increased incidence is becoming a real public health problem that is more severe than infectious diseases, contributing to 35 million deaths annually. Excessive intake of free sugars can cause many of the same health problems as excessive alcohol consumption. Many recent international recommendations have expressed concerns about sugar consumption in Westernized societies, as current consumption levels represent quantities with no precedent during hominin evolution. In both adults and children, the World Health Organization strongly recommends reducing free sugar intake to less than 10% of total energy intake and suggests a further reduction to below 5%. Most studies have focused on the deleterious effects of Western dietary patterns on global health and the intestine. Whereas excessive dietary fat consumption is well studied, the specific impact of sugar is poorly described, while refined sugars represent up to 40% of caloric intake within industrialized countries. However, high sugar intake is associated with multiple tissue and organ dysfunctions. Both hyperglycemia and excessive sugar intake disrupt the intestinal barrier, thus increasing gut permeability and causing profound gut microbiota dysbiosis, which results in a disturbance in mucosal immunity that enhances infection susceptibility. This review aims to highlight the roles of different types of dietary carbohydrates and the consequences of their excessive intake for intestinal homeostasis.

**Keywords:** sugars; carbohydrates; gut microbiota; nutrition; intestine; glucose; fructose.

## INTRODUCTION

Food and nutrition are important factors in maintaining health, and their key role in chronic diseases is well established<sup>1</sup>. The concerned countries are mainly the richest, where diet has been profoundly transformed over the last 50 years. The same trends are now being observed in Asia and Africa. The Western diet (WD) is characterized by increased intake of red and processed meat, saturated fat, high-fat dairy products, eggs, refined grains, white potatoes, and high-sugar drinks<sup>2-4</sup>. Fast food, processed food and ultraprocessed food (UPF) are now extensively consumed, while the consumption of fresh fruits and vegetables has decreased<sup>3</sup>. The first consequence of excess caloric intake (without sufficient energy expenditure) is overweight, which is also associated with numerous diseases, such as metabolic and cardiovascular diseases, diabetes<sup>5</sup>, musculo-articular disorders, and some cancers, such as colorectal cancer (CRC)<sup>6</sup>. It is becoming increasingly clear that the dietary habits of modern societies on the one hand and a high body mass index on the other hand constitute risk factors for autoimmune diseases as well as obesity and inflammatory states<sup>7</sup>. Regardless of obesity, this "junk food" phenomenon underlies other chronic pathologies, such as nonalcoholic steatohepatitis and other inflammatory diseases<sup>8</sup>. Many recent recommendations concern sugars because population-wide sugar intake in Westernized societies represents quantities with no precedent during hominin evolution<sup>2,9,10</sup>. Excessive consumption of sugars has been linked with poor oral health, obesity, cardiovascular disorders, metabolic syndrome, and chronic diseases (type II diabetes mellitus, chronic inflammation, cancer, kidney dysfunction, and nonalcoholic fatty liver disease)<sup>11-14</sup>. At the intestinal level, sugars and hyperglycemia strongly affect the gut microbiota and the intestinal barrier by increasing permeability and sensitivity to infections, and they seem to be aggravating factors for CRC<sup>15-18</sup>. Given the ongoing controversies related to sugar in the diet, a symposium entitled "Sugars and Health Controversies: What Does the Science Say?" was held in 2014 during the American Society for Nutrition Scientific Sessions annual meeting and concluded that more research trials are needed in many areas regarding sugar consumption and health<sup>19</sup>. For a long time, the WD has been implicated in triggering intestinal inflammation, focusing on the specific role of a high-fat diet on intestinal homeostasis, while a high-sugar diet has been poorly studied. Here, we reviewed the different dietary sugar types, their metabolism and the effects of excessive intake on intestinal homeostasis, the gut microbiota, and gastrointestinal diseases.

## LITERATURE SEARCH STRATEGY

*See supplementary text.*

## SUGAR IN THE WESTERN DIET: A PUBLIC HEALTH PROBLEM

Considering structural and property differences, dietary carbohydrates can be classified into nondigestible carbohydrates (such as fibers) and digestible carbohydrates<sup>20</sup> (sucrose, lactose, and some starch), which are converted into monosaccharides<sup>21</sup>. According to the World Health Organization (WHO), the term “free sugars” refers to all monosaccharides and disaccharides added to foods by the manufacturer, cook or consumer, plus the sugars naturally present in honey, syrups and fruit juices<sup>22</sup>. When analyzing unhealthy elements of the WD and UPF, refined carbohydrates, particularly added sugar and processed grains (such as white flour or white bread), are elements to be considered in the negative effect on the intestine and immune system<sup>23</sup>.

In humans, total carbohydrate intake represents approximately 50-55% of total nutrient intake in a balanced diet<sup>22</sup>. Eating habits have increased the respective share of sugars and fats<sup>24</sup>. In Europe, 10 years ago, the respective share of carbohydrates in the total caloric availability was approximately 45-55%. In both adults and children, the WHO strongly recommends reducing the intake of free sugars to less than 10% of the total energy intake and suggests a further reduction in the intake of free sugars to below 5% of the total energy intake<sup>22,25</sup>. In addition, all reports recommend limiting the intake of added sugars<sup>26</sup>. The relative proportions of the different types of carbohydrates consumed in Westernized countries are difficult to determine precisely. Even if recent studies use standardized questionnaires, careful documentation of outcomes with common definitions, and contemporary statistical approaches to minimize confounding effects, most nutritional studies have generated a substantial body of evidence that challenges the conventional thinking that fats are harmful. The focus of nutrition research has recently shifted to the potential harms of carbohydrates<sup>27</sup>.

National representative dietary surveys worldwide have shown excessive sugar intake in many Westernized countries (**Figure 1**)<sup>26</sup>. The prevalence of overconsumption of free sugar has been shown to be high in the UK (61%) and in France (41%)<sup>28</sup>. Overall, in 2007, the USA global sugar supply was over 600 calories per person per day, between 300-500 calories in Europe and less than 100 calories in central Africa<sup>10</sup>, and added sugar intake was higher in children and adolescents than in adults<sup>26,28,29</sup>. A meta-analysis of longitudinal studies has shown that free sugar intake does not decrease from adolescence to early adulthood<sup>30</sup>. Very early nutritional interventions are therefore necessary (between 13 and 30 years old)<sup>30</sup>.

Free sugar intake increases overall energy intake by increasing the energy density and reduces nutrient density (micronutrients), leading to an unhealthy diet, weight gain, and an increased risk of noncommunicable diseases<sup>22</sup>. Thus, excessive free sugar-containing diets are considered

to have low nutritional quality<sup>28</sup>. Excessive free sugar intake results from the consumption of high-sugar-content drinks, snacks, “ready to consume” food, and UPF<sup>12</sup>, for which numerous studies have shown exponential growth in consumption in industrialized countries (**Figure 1**)<sup>31</sup>. Indeed, UPF displaces unprocessed or minimally processed foods and freshly prepared meals and represents an important proportion of the total energy intake in many Westernized countries (**Figure 1**). These products are described as higher in energy, saturated fat, sugar and sodium and lower in nutrients<sup>32</sup>. Particularly in baby/child food, in most food categories, UPFs have higher energy, fat, saturated fat and sugar contents than minimally processed and processed foods<sup>33,34</sup>.

A systematic review<sup>35</sup> and many studies have reported a negative correlation between added sugar or UPF intake and diet quality<sup>36,37</sup>. Overconsumption of these UPF diets can be explained by low cost, eating location convenience and confusion in reading the product composition<sup>38</sup>. In addition, the sugar addiction phenomenon is not negligible<sup>30</sup>, as the reduction in total fat consumption with low-fat diets leads to excess intake of refined carbohydrates and added sugar<sup>39</sup>. Public health interventions - mainly via nutritional education/counseling - are moderately successful at reducing sugar-sweetened beverage intake and increasing water intake in children<sup>40</sup>. Importantly, it would be beneficial to policy guidance if future dietary surveys employed a uniform way of expressing sugars that is feasible to measure and has public health significance<sup>26,41</sup>.

## **CARBOHYDRATE METABOLISM**

Carbohydrates are the most important food energy provider among the macronutrients (between 40-80% of total energy intake). In nutrition research, the role of dietary carbohydrates has been less extensively studied than those of proteins and fats, even though their properties have implications for our overall health<sup>42</sup>. First, carbohydrate terminology and classification depend on their polymerization degree or digestibility (**Figure 2**)<sup>43</sup>. Some carbohydrates present the same degree of polymerization but different effects, and physicochemical, technological, or functional characteristics influence sugar metabolism (**Table 1**)<sup>44</sup>. Carbohydrates have a wide range of physiological effects that may be important to health, such as provision of energy, effects on satiety, control of blood glucose levels (insulin metabolism), protein glycosylation, lipid metabolism, bile acid dihydroxylation, fermentation (short-chain fatty acid (SCFA) production, control of colonic epithelial cell function), bowel habits and the gut microbiota<sup>45</sup>.

### **Digestion of carbohydrates**



Digestible carbohydrates (*e.g.*, sucrose, lactose and some starch) need to be degraded into monosaccharides (glucose, fructose and galactose) to be absorbed in the small intestine<sup>21</sup>. This digestion involves specific enzymes secreted by the pancreas and the intestinal mucosa. Starch and sucrose are degraded by pancreatic amylase, sucrase-isomaltase (small intestine), and maltase-glucoamylase, while lactose is degraded into glucose and galactose by lactase (**Figure 3**). In most mammals, in contrast with sucrase and maltase activities, lactase activity declines after weaning, a condition known as lactase nonpersistence<sup>46</sup>. Mammalian genomes do not encode most enzymes needed to degrade the structural polysaccharides present in plant material<sup>47</sup>. In particular, fibers are nondigestible carbohydrates: some are part of cell wall components (*e.g.*, cellulose and hemicellulose) or other structural and nonstructural compounds (*e.g.*, resistant starch (RS), inulin, chitin, pectin,  $\beta$ -glucan, and oligosaccharides) (**Table 1**)<sup>48</sup>. The contribution of the gut microbiota to carbohydrate degradation is necessary since humans produce only 17 carbohydrate-active enzymes, whereas some bacterial species in the gut have more than 200 carbohydrate-active enzymes<sup>49</sup>.

### **Carbohydrate absorption**

The human body can metabolize fructose, galactose and glucose and generate energy as a consequence<sup>20</sup>. Monosaccharide absorption from the small intestine occurs via both energy-coupled and non-energy-coupled mechanisms<sup>20</sup>. Glucose is a universal energy transport molecule within the body, and it is absorbed by cotransport of sodium ions with glucose via SGLT1, facilitating diffusion via GLUT2<sup>50</sup>. Fructose is transported into enterocytes by facilitated diffusion with a specific fructose transporter, GLUT5, and passes by facilitated diffusion to the blood capillaries through GLUT2, which has a lower affinity for fructose than GLUT5<sup>51</sup>. Compared to that of glucose, the intestinal absorption of fructose appears to be relatively limited and is influenced by many factors, especially aging<sup>52</sup>. In rats, absorption can be increased by fructose itself or by a diet rich in saturated fatty acids<sup>53</sup>. People with malabsorption of fructose, *i.e.*, people who absorb fructose poorly, are prone to diarrhea and flatulence. This intestinal clearance of dietary fructose by the small intestine limits the harmful impact of this sugar and may be a general feature of mammalian metabolism<sup>54</sup>. Recent studies indicate that fructose can stimulate *de novo* palmitate synthesis both *in vivo* and *in vitro*<sup>55</sup>. Moreover, the small intestine converts fructose into glucose and organic acids<sup>54</sup>; research has shown that monosaccharides can not only modulate *de novo* lipogenic pathways but also be used as a substrate for the synthesis of triglycerides and exported in lipoproteins<sup>55</sup>. Therefore,

chronic fructose overfeeding is linked to alterations in the postprandial lipid profile and decreased hepatic insulin sensitivity, leading to metabolic diseases<sup>56</sup>.

### **Fate of absorbed sugars**

Glycemia is among the most strictly controlled physiological variables of organismal homeostasis, and the liver plays a critical role in maintaining this homeostasis<sup>8</sup>. Glucose is delivered by the liver in a controlled manner and is absorbed by peripheral tissues according to their needs. In cells, the glycolysis pathway uses glucose to generate adenosine triphosphate (ATP). This synthesis is highly negatively regulated by ATP itself at the first steps of the glycolysis pathway (production of glyceraldehyde-3-phosphate, G3P).

In contrast, fructose and galactose are almost completely cleared from the blood by the liver. Galactose is entirely transformed into glucose-6-phosphate (G6P), a substrate for glycolysis and the glycogenesis pathways. Hepatic fructose metabolism generates G3P, a major glycolysis intermediate, but bypasses the ATP-dependent regulation steps of glycolysis<sup>57</sup>, producing an "unlimited", unregulated source of glycerol-3-phosphate and acetyl-CoA for hepatic lipogenesis. Other tissues, such as white adipose tissue, may metabolize the remaining fructose<sup>58</sup>.

### **Fate of nonabsorbed carbohydrates**

Approximately 40 g of dietary carbohydrates reach the colon daily, escaping digestion by host enzymes<sup>47</sup>. The main categories are RS, nonstarch polysaccharides and oligosaccharides, although some di- and monosaccharides (*e.g.*, sugar alcohols) may also reach the colon<sup>59</sup>. The human gut microbiota is particularly well adapted to perform the degradation of polysaccharides<sup>60</sup>: 10 000 bacterial enzymes implicated in sugar digestion have been identified<sup>61</sup>. While insoluble fibers are weakly or not metabolized and pass through the intestine, resident microbes in the distal small intestine and colon rapidly ferment soluble fibers<sup>48,59</sup> and produce SCFAs, *e.g.*, acetate, propionate and butyrate. Butyrate is one of the most important metabolites produced through gastrointestinal microbial fermentation and functions as a major energy source for colonocytes by directly affecting their growth and differentiation<sup>62</sup>. Moreover, butyrate has various physiological effects, including enhancement of intestinal barrier function and mucosal immunity<sup>63,64</sup>.

## **EXCESSIVE SUGAR INTAKE AND INTESTINAL HOMEOSTASIS**

### ***In vitro* evidence**

*See supplementary text.*

### **Animal studies**

*See supplementary text.*

### **Gut microbiota**

*See supplementary text.*

## **SUGAR AND HUMAN GASTROINTESTINAL DISEASES**

Since the 1970s, based on observational studies rather than prospective causality, dietary recommendations have focused on reducing saturated fat intake<sup>42</sup>. However, an increasing number of studies in large cohorts of humans and especially a landmark prospective cohort study, named PURE, found that in >135,000 participants from 18 countries, nutritive carbohydrates increase human mortality, whereas dietary fat reduces it, indicating the need for a fundamental change in current nutritional guidelines<sup>65</sup>.

Evidence suggests that processed, simple sugars also reduce white blood cell phagocytosis and possibly increase inflammatory cytokine marker levels in the blood<sup>66</sup>. In contrast, fiber consumption seems to protect against inflammation<sup>67</sup>. Subsequently, the accumulation of sugar in the colon increases the osmotic load, as well as the fermentation rate by the colonic microbiota, and promotes abdominal pain and intestinal dysfunctions<sup>20,21,68</sup>.

High sugar intake is associated with multiple tissue and organ dysfunctions<sup>69,70</sup> and promotes overweight, cardiovascular diseases, type II diabetes (TIID), insulin resistance, and systemic inflammation (**Figure 4**). Interestingly, excessive intake of fructose can disrupt metabolic processes and impair organ function<sup>58,71</sup>. As we focused here on the intestine, metabolic syndrome and hepatic consequences of high sugar intake are beyond of the scope of this review. Likewise, even though sugar malabsorption (lactose or fructose intolerance) contributes to some gastrointestinal disorders, we will not discuss these diseases, as they are not caused by sugar overconsumption.

Enterocytes in the intestine can produce fatty acids, with both glucose and fructose used as substrates. Compared with glucose, fructose may be a poor substrate for *de novo* lipogenesis in enterocytes<sup>55</sup>, and fatty acid accumulation might impair intestinal function. Thus, excessive sucrose intake has been recognized as a primary cause of metabolic syndrome, the toxicity resulting from excess fructose rather than sucrose, as fructose undergoes glycation to proteins and, physiologically, its metabolic substrate rapidly flows into *de novo* lipogenesis, which promotes liver inflammation<sup>72</sup>. Additionally, the pro-oxidative and proinflammatory effects of

fructose lead to an increase in gut permeability and endotoxemia that exacerbate chronic inflammation<sup>18,73</sup>.

### **Irritable bowel syndrome**

Irritable bowel syndrome (IBS) is a functional bowel disorder associated with a wide variety of clinical symptoms, and soluble fiber appears to improve IBS symptoms. There is no evidence for recommending insoluble fiber for IBS<sup>74</sup>. A low-fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) diet is a possible therapy for IBS<sup>75</sup>. A recent meta-analysis showed that lactose intolerance is more frequent in IBS patients but failed to prove the association of IBS with lactose maldigestion due to the lack of statistical power<sup>76</sup>. Few recent studies have attempted to elucidate the mechanisms by which fermentable carbohydrates may trigger IBS symptoms<sup>77</sup>.

### **Inflammatory bowel diseases**

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic inflammatory diseases of the gastrointestinal tract with increasing incidence worldwide<sup>78,79</sup>, especially in the pediatric population<sup>80</sup>. Many studies have been conducted to identify environmental factors triggering or exacerbating IBD<sup>81</sup>. Notably, different epidemiological data have suggested that the consumption of a WD is associated with increased IBD risk<sup>4</sup>. Moreover, overweight and obesity are clearly defined as risk factors for IBD aggravation<sup>82,83</sup>. In the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, consumers of high levels of sugar and soft drinks were at higher UC risk if they had low vegetable intake<sup>84</sup>. Moreover, in retrospective studies, patients with CD showed an increased consumption of monosaccharides prior to feeling ill<sup>85,86</sup>. Accordingly, a recent prospective cohort study reported that a higher intake of UPF was positively associated with an increased risk of IBD<sup>87</sup>. Considering the critical role of UPF in IBD and colitis, fructose might have the same effect in the intestine as in the liver<sup>88</sup>.

IBD patients have reported that their perception of the disease manifestation is related to their dietary intake, and they often employ an elimination diet to prevent disease exacerbation<sup>89,90</sup>. In addition to the deleterious effect of sugar described above, the presence of enteral glucose protects the gut epithelium in ischemic conditions<sup>91</sup>. In particular, soda was considered to worsen symptoms. Exclusion of some specific carbohydrates in IBD<sup>92</sup> (such as the specific carbohydrate diet or IBD anti-inflammatory diet) was associated with an improvement in clinical manifestation, remission and mucosal healing<sup>93</sup>.

However, while evidence of varying quality has identified potential harmful or beneficial dietary components, physicians and patients do not currently have guidance as to which foods are safe or may be protective or harmful for IBD<sup>94</sup>. According to the International Organization for the Study of IBD, evidence is insufficient to recommend any specific changes in refined sugar or complex carbohydrate intake<sup>94</sup>.

### **Colorectal cancer**

Evidence suggests a positive association between sugar intake and CRC outcomes<sup>95</sup>. In particular, high fructose intake and obesity have been found to be associated with the prevalence of CRC and its progression<sup>96</sup>. Higher sugar-sweetened beverage intake has been shown to be associated with a significantly increased risk of cancer recurrence and mortality in stage III colon cancer patients<sup>96</sup>. Indeed, higher postdiagnosis total fructose and glucose intake has been found to be associated with higher all-cause mortality in stage I-to-III CRC patients<sup>97</sup>. Experimental studies suggest that advanced glycation end products (AGEs) may promote CRC, but prospective epidemiologic studies are inconclusive<sup>98</sup>. Further insight into the metabolism of AGEs and their dicarbonyl precursors and their roles in CRC development is needed<sup>98</sup>.

### **CONCLUSION**

Despite an ongoing focus on the role of diet in promoting health and longevity, we have only a limited understanding of the nature and impact of concepts at the cellular and molecular levels. In recent decades, there has been a dramatic change in the way people eat and drink, contributing to the increase in the incidence of several noncommunicable diseases<sup>9,10,22,24</sup>. Many recent international recommendations have expressed concerns about sugar consumption in Westernized societies, as they the quantities have no precedent during hominin evolution<sup>10,24</sup>. UPF consumption leads to excessive sugar intake. Sugar metabolism can be divided into two main parts: digestible carbohydrates used as fuel or stored and poorly absorbed carbohydrates, of which some are used by the gut microbiota<sup>44</sup>. Like all nutrients, excessive intake results in accumulation. Because humans have an innate preference for sugar, limiting consumption will not be easy, despite the documented health problems associated<sup>99</sup>. The perception of lipids as “fats!” has been very negative in recent decades, with demonization and drastic avoidance recommendations. This focus seems to turn now to carbohydrates, in particular sugars. In both adults and children, the WHO strongly recommends reducing the intake of free sugars to less than 10% of total energy intake and suggests a further reduction in the consumption of free sugars to below 5% of total energy intake<sup>10,22,24</sup>. Despite the growing interest of the scientific and medical community, the direct effects of sugars on healthy individuals' intestines remain

poorly described<sup>19</sup>. For this reason, an increased focus on the overall effects and quality of carbohydrate sources and meals for food-based guidelines rather than individual component-based recommendations is needed<sup>44</sup>. However, a recent article suggests that carbohydrate quality seems to have a more important role in population health than carbohydrate amount<sup>45</sup>. Specific effects of sugar (separately from other nutrients (high fat, high sodium, emulsifiers, etc.)) remain difficult to interpret based on available evidence, highlighting the need for experimental studies looking at the individual contributions of each food<sup>100</sup>. Hopefully, continued work in this area will lead to a science-based approach based on high levels of evidence from randomized controlled trials and meta-analyses. This approach can only improve public health and guide wise public policy as well as inform individual nutritional decisions<sup>19</sup>.

## FIGURE LEGENDS

**Figure 1: Ultraprocessed food intake seems to lead to sugar overconsumption.** Data on total volume sales of ultraprocessed food (UPF) per capita were sourced from the Euromonitor International Passport Global Market Information Database for 80 countries for 2016<sup>34</sup>. Data on sugar (raw equivalent) supply were sourced from the Food and Agriculture Organization (FAO) of the United Nations (FAO 2017).

**Figure 2: Classification of carbohydrates based on the degree of polymerization and digestibility.** Nondigestible carbohydrates are poorly digested by the host<sup>43</sup>. Fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAPs) are responsible for gut symptoms (luminal distension). Prebiotics have putative health benefits (selective growth of bacteria).

**Figure 3: Carbohydrate absorption and digestion.** Carbohydrate digestion begins in the mouth, where mechanical digestion breaks food into smaller pieces, and salivary amylase (from the parotid and submandibular glands) begins chemical digestion by converting starch into maltose and maltotriose alpha-dextrins (starch fragments). Then, stomach acid halts amylase action. In the small intestine, the breakdown of starch into smaller di- and trisaccharides continues in the lumen of the duodenum and jejunum through the action of pancreatic amylase. The intestinal brush border contains enzymes, including maltase, isomaltase, sucrase, and  $\beta$ -galactosidase, which degrade carbohydrates into simple sugars. Most simple sugars are then absorbed in the proximal parts of the jejunum via both energy-coupled and non-energy-coupled mechanisms. These transporters are specific small intestine-located protein families (isoforms) of sodium-driven sugar cotransporters (SGLTs) and concentration gradient-dependent glucose

transporters (GLUTs). Glucose, galactose and fructose are then metabolized in the liver. Other undigested complex polysaccharides then arrive in the colon, where fibrolytic and glycolytic bacteria from the gut microbiota are able to digest cellulose compounds (called xyloglucans) into nutrients – mainly for the bacteria themselves. Other bacteria degrade dietary fiber into short-chain fatty acids (SCFAs) that provide nutrition to cells of the colonic mucosa. SCFAs are the main metabolites produced by the microbiota through the anaerobic fermentation of indigestible polysaccharides such as dietary fibers and resistant starch. They are absorbed by colonocytes, mainly via H<sup>+</sup>-dependent monocarboxylate transporters (MCTs) or sodium-dependent monocarboxylate transporters (SMCTs). Through binding to G protein-coupled receptors (GPCRs), SCFAs influence intestinal mucosal immunity and barrier integrity and function.

**Figure 4: Overview of the consequences of excessive sugar intake.** Sugar utilization and metabolism are carefully regulated by the body via a range of mechanisms. Thus, in the case of excessive sucrose intake, compensation mechanisms fail, leading to hyperglycemia, hyperfructosemia and lipogenesis. The latter causes are risk factors for many pathologies, including nonalcoholic fatty liver disease (NAFLD), inflammatory bowel diseases (IBDs), colorectal cancer (CRC), type II diabetes (TIID) and coronary heart disease (CHD).

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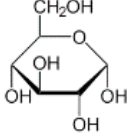
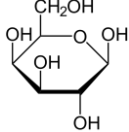
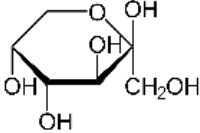
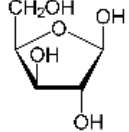
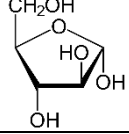
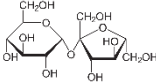
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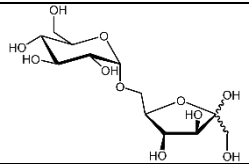
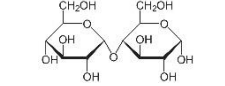
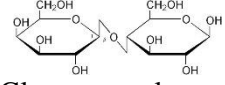
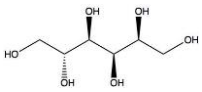
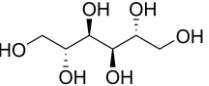
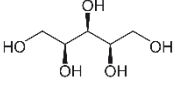
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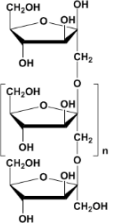
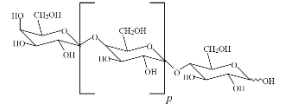
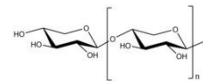
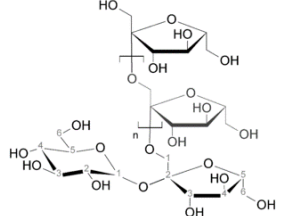
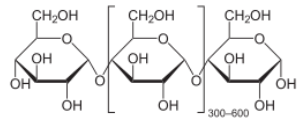
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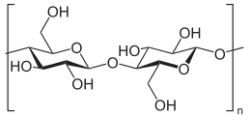
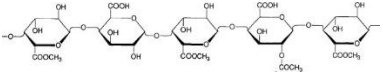
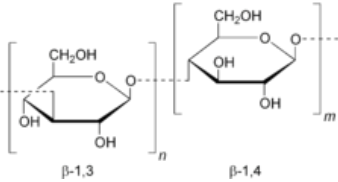
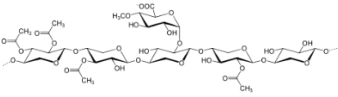
**Table 1: Fate and sources of major carbohydrates**

	<b>Molecules</b>	<b>Characteristics</b>	<b>Source</b>	<b>Metabolic Fate</b>
<b>Glucose</b>		Most abundant monosaccharide, most important source of energy in all organisms.	Fruits, vegetables and honey	Fuel, stored as glycogen, convert to other metabolites
<b>Galactose</b>		Sweetness equal to 33% of sucrose	Dairy products, avocados, sugar beets, gums	Converted to glucose in liver
<b>Fructose</b>		In nature, among sugars, it is the most sweet, though its sweetness depends on the physical state and the temperature in which it is.	Fruits (juices), Vegetables and honey	Partially converted to lactic acid and glucose → used as fuel or stored as glycogen and fatty acids used as fuel or stored as lipid
<b>Xylose</b>		Sweetening power properties close to glucose for a lower caloric intake	Fruits, cereals, bread and vegetables like potato, peas and carrots	Poorly metabolized, excreted by kidneys in the urine
<b>Arabinose</b>		Sweetening power properties close to glucose	Plant-based carbohydrate, commercialized as a sweetener	Uncompetitive inhibitor of sucrase, the enzyme that breaks down sucrose into glucose and fructose in the small intestine
<b>Sucrose</b>	 Glucose $\beta(2\leftrightarrow 1)\alpha$ fructose	Ordinary sugar “table sugar”.	Produced from cane or beet.	Digestive enzyme sucrase or isomaltase glycoside hydrolases in the duodenum → glucose and fructose which are absorbed and enter the bloodstream
<b>Isomaltulose</b>	Glucose $\alpha(1\rightarrow 6)$ fructose	Provides a natural sucrose-like sweetness profile with a sweetening power	Naturally present in honey and sugarcane. Industrially produced from sucrose.	Digestive enzyme isomaltase-sucrase in the small intestine → glucose and fructose which are absorbed and enter the bloodstream

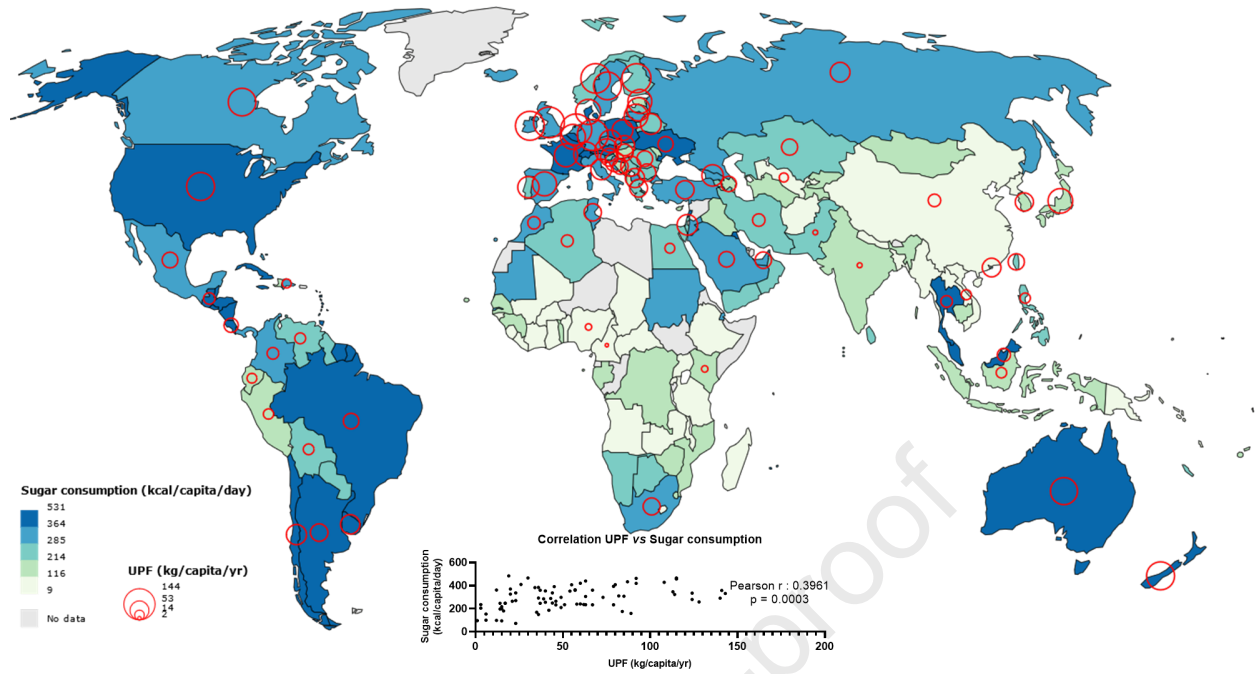
		about half that of sucrose		
<b>Maltose</b>	 Glucose + glucose	Only about 30–60% as sweet as sugar, depending on the concentration	Obtained from malt, corn syrup or partially hydrolyzed starch products like maltodextrin	Digestive enzyme maltase → 2 glucose which is absorbed and enter the bloodstream
<b>Lactose</b>	 Glucose + galactose	mild flavor and easy handling properties led to its use as a carrier and stabilizer of aromas and pharmaceutical products	Dairy products	Digestive enzyme lactase in the small intestine → glucose and galactose which are absorbed and enter the bloodstream. Depending on lactase activity and ingested dose, undigested lactose act as dietary fiber.
<b>Sorbitol</b>		Used as sugar substitute. About 60% as sweet as sucrose.	Sweetener (E420) Made from potato starch, naturally found in apples, pears, peaches and prunes	Poorly absorbed but converted to glucose and fructose in liver
<b>Mannitol</b>		Used as sugar substitute and medication.	Sweetener (E421). Naturally found in algae and plants.	Poorly absorbed. Increases blood glucose to a lesser extent than sucrose (lower glycemic index)
<b>Xylitol</b>		Used as sugar substitute.	Sweetener (E967). Naturally found in strawberries, mushrooms and prunes. Made from birch sap.	About 50% is absorbed, metabolized in liver in D-xilylose and then goes to pentose phosphate pathway. 50% non-absorbed is fermented by gut bacteria into short-chain acids and gases. at high doses, may cause gastrointestinal discomfort.

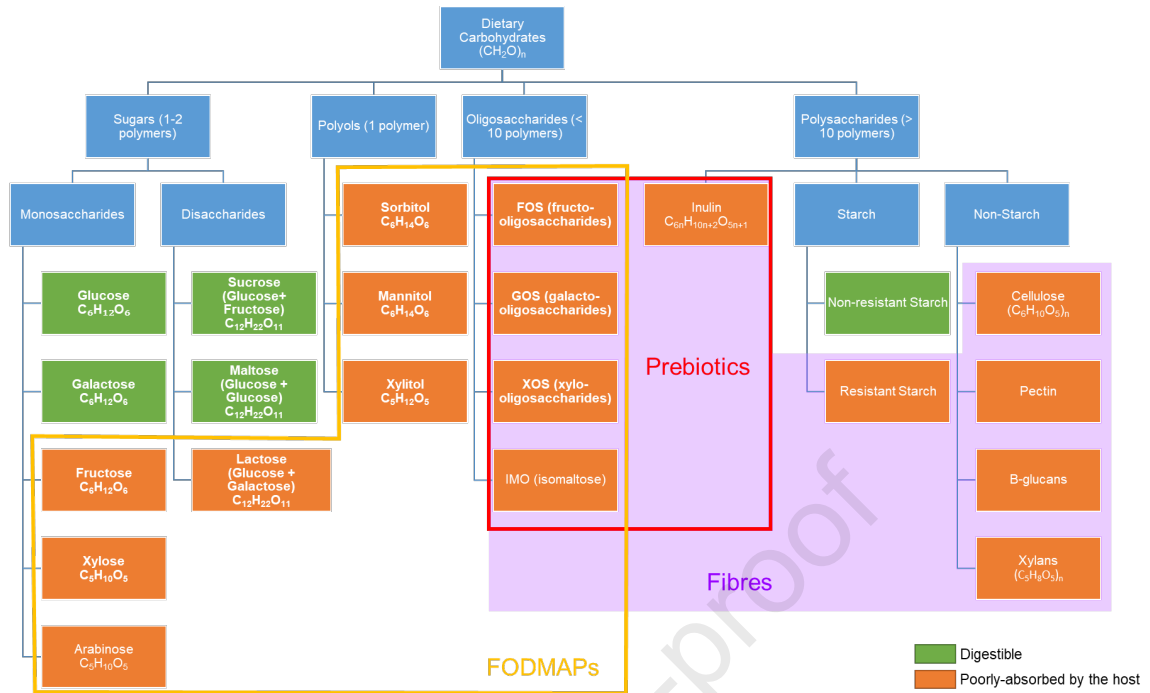


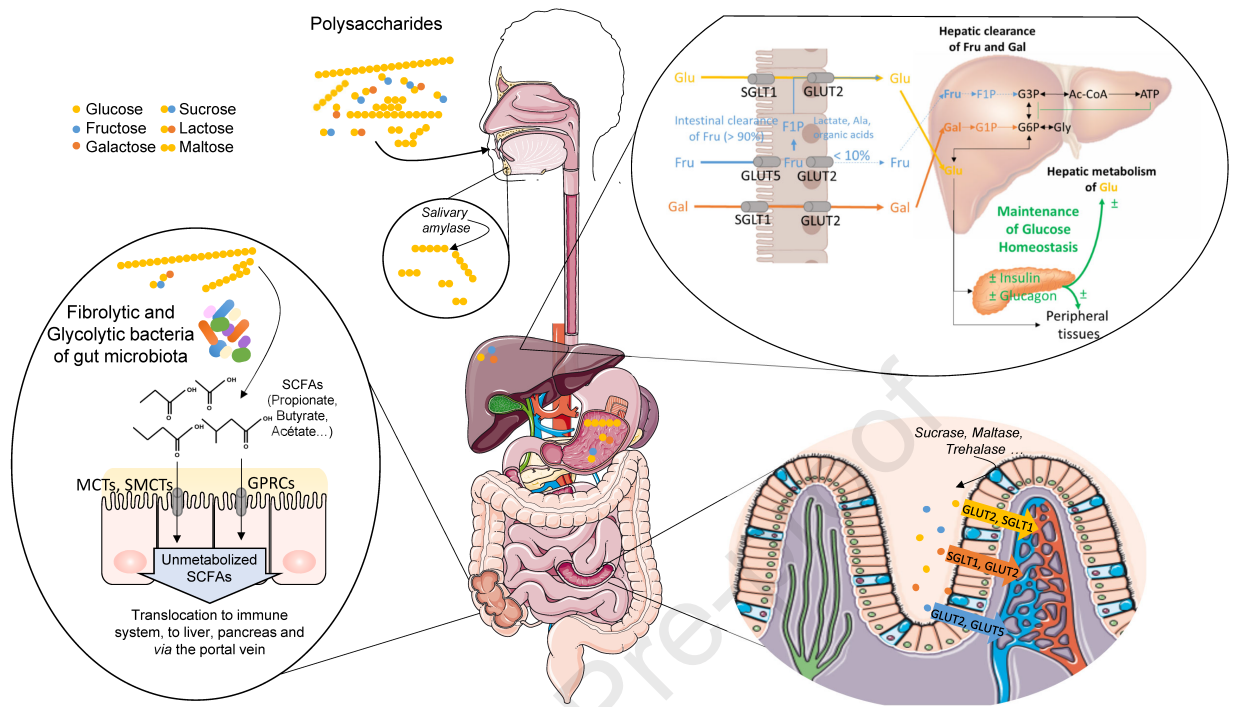
<p><b>Fructo-oligosaccharides (FOS)</b></p>	 <p>Short chains of fructose and glucose.</p>	<p>Used as an alternative sweetener and prebiotics</p>	<p>Naturally found in fruits and vegetables (sunchoke, bananas, onions, chicory root, garlic, asparagus, and leeks). Some grains and cereals (wheat, barley). Extracted from blue agave.</p>	<p>Prebiotic dietary fibres: not hydrolyzed by salivary and digestive enzymes, fermented by anaerobic bacteria of the gut microbiota stimulating the growth of Bifidobacterica species (produce short-chain fatty acids and gases)</p>
<p><b>Galacto-oligosaccharides (GOS)</b></p>	 <p>Short chains (2-8 monomeric units) of glucose and galactose.</p>	<p>Available commercially in food products for both infants and adults</p>	<p>Occurring naturally in human milk can be produced from lactose by <math>\beta</math>-galactosidase.</p>	<p>Prebiotic dietary fibres: not hydrolyzed by salivary and digestive enzymes, fermented by the gut microbiota stimulating the growth and/or activity of beneficial bacteria (bifidobacterial and lactobacilli species) in the colon (produce short-chain fatty acids).</p>
<p><b>Xylo-Oligosaccharides</b></p>	 <p>Oligomers of xylan, made up of xylose units.</p>	<p>Available commercially as prebiotic.</p>	<p>Relatively abundant in cell walls of grains and plants (bamboo, shoots, fruits, vegetables, milk and honey)</p>	<p>Prebiotic dietary fibres: not hydrolyzed by digestive enzymes, fermented by the gut microbiota stimulating the growth and/or activity of beneficial bacteria (bifidobacterial and lactobacilli species) in the colon (produce short-chain fatty acids).</p>
<p><b>Inulin</b></p>		<p>Dietary fiber ingredient used to improve the nutritional value of manufactured food products.</p>	<p>Storage carbohydrates of many plants' types, traditionally extracted from chicory but present in agave, wheat, onion, bananas, garlic, asparagus, and Jerusalem artichoke.</p>	<p>Non-digestible oligosaccharide. Prebiotic dietary fibres: not hydrolyzed by digestive enzymes, fermented by the gut microbiota stimulating the growth of beneficial bacteria.</p>
<p><b>Starch</b></p>		<p>Most common carbohydrate in human diet. Largely used as an insoluble dietary fiber for food processing and in pharmaceutical industry.</p>	<p>Major source are cereals (rice, maize and wheat) or root vegetables (potatoes)</p>	<p>Poorly digested in the small intestine (digestibly increased with cooking), bacterial degradation in the colon. Resistant starch escapes from digestion in the small intestine of healthy individuals <math>\rightarrow</math> fermented by the gut microbiota in the colon (produce short-chain fatty acids).</p>

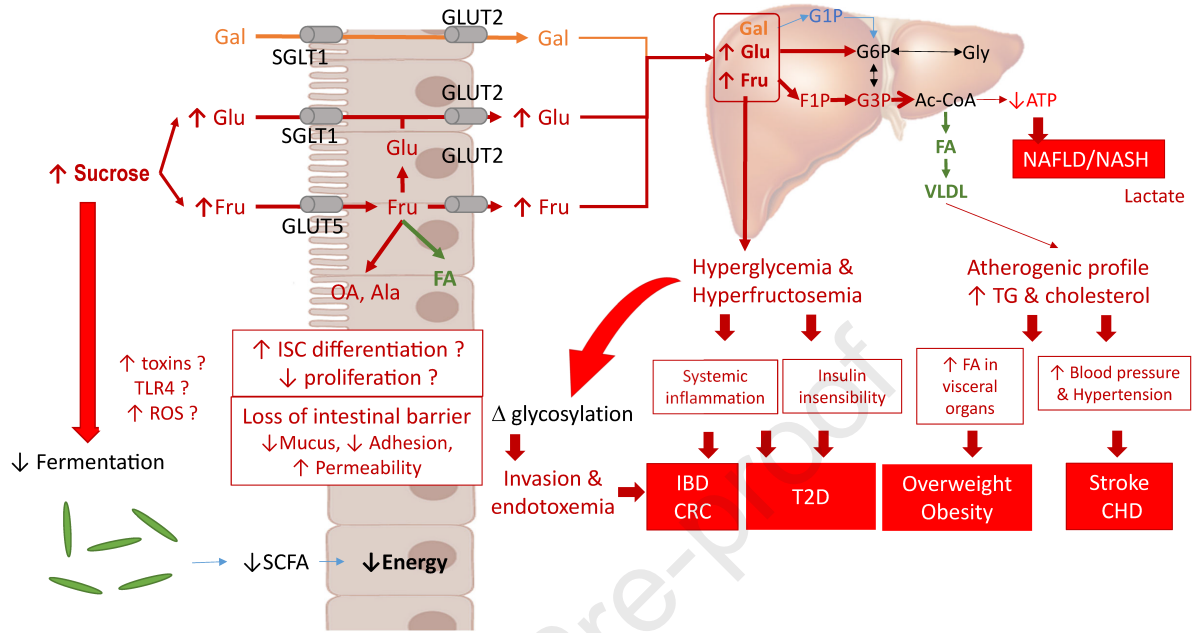
				Non-resistant starch are hydrolyzed by salivary and pancreatic amylases → maltose and glucose which are absorbed and enter the bloodstream
<b>Cellulose</b>			Most abundant organic polymer, naturally occurring in the cell walls of all plants and algae.	Insoluble dietary fiber, inert to digestive enzymes.
<b>Pectins</b>		Used as gelling, thickening agent and stabilizer in food.	Naturally occurring in the cell walls of fruits and vegetables (apples, oranges, carrots, citrus peels, .	Soluble dietary fiber binds to cholesterol in the gastrointestinal tract and slows glucose absorption by trapping carbohydrates. Then, digested by gut microbiota ( <i>Bacteroides thetaiotaomicron</i> )
<b><math>\beta</math>-glucans</b>		Used as soluble fiber supplements.	Naturally occurring in the cell walls of cereals (oat, barley, wheat).	Soluble, fermentable fiber acting as a prebiotic for gut microbiota bacteria. Enterocytes facilitate the transportation of $\beta(1,3)$ -glucans and similar compounds across the intestinal cell wall into the lymph, where they interact with macrophages to activate immune function.
<b>Xylans</b>		Used as dietary fiber in bread industry.	Most abundant type of hemicellulose, naturally occurring in the vegetal cell walls.	Dietary fibres, poorly absorbed.

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## Supplementary Informations Sugars and Gastrointestinal Health

### LITERATURE SEARCH STRATEGY

Relevant studies published up to July 2021 were searched through PubMed, Medline, Scopus and Google Scholar to identify all studies assessing the influence of dietary sugar consumption on the intestine. The following MeSH terms alone or combined with the Boolean operators ‘and’ or ‘or’ were used: ‘sugar’, ‘sucrose’, ‘carbohydrates’, ‘ultraprocessed food’, ‘Western diet’, ‘dietary patterns’, ‘metabolism’, ‘colitis’, ‘gastrointestinal diseases’, ‘inflammatory bowel disease’, and ‘colorectal cancer’.

### In vitro evidence

*In vitro* evidence suggests that processed simple sugars reduce white blood cell phagocytosis and possibly increase inflammatory cytokine markers in the blood<sup>1</sup>. Using Caco-2 cells (intestinal epithelial cells from human colon), Thaiss *et al.* showed that high glucose exposition drives a global reprogramming of the epithelial cell transcriptome, and modifies the morphology of the cell-cell junctions leading to an abnormal influx of immune-stimulatory microbial products<sup>2</sup>. Interestingly, high fructose concentration affects the composition of N-Glycans bound to membrane-associated glycoproteins present on the surface of Caco-2 cells<sup>3</sup>. These changes were associated with an increased invasion of bacteria, suggesting a preference for the types of cells they infect depending on the host glycome (intestinal epithelial cell surface glycans comprising the outermost layer of all eukaryotic cells)<sup>4</sup>.

### Animal studies

Sweetness is the preferred taste of humans and many animals, likely because sugars are a primary source of energy and rather rare in nature<sup>5</sup>. Many nutrients can influence gut homeostasis; while it is well known that chronic intake of high-fat diets differentially affect glucose tolerance in mice<sup>6,7</sup>. Most studies use diets enriched with fats and sugars or only with fats (**Table S1**). *In vivo* studies reported that fatty and sugary western diets promote intestinal inflammation because they alter the intestinal barrier (*e.g.* decreased mucus secretion), by increasing intestinal permeability and infection susceptibility, decreasing SCFA production by the microbiota and inducing dysbiosis<sup>8,9</sup>.

This inflammation results from an increase of natural killer NK T cells, a decrease of regulatory T cells (Treg) and a disequilibrium of dendritic cells. It correlates with the modulation of the expression of inflammatory proteins, exacerbating disease severity in colitis context<sup>8,10–16</sup>.



Also, chronic low-grade inflammation has been linked to the overconsumption of Advanced Glycation End-Products (AGEs e.g. proteins or lipids glycated as a result of exposure to sugars) which lead to an increase in local and systemic pro-inflammatory biomarkers in humans and animal models<sup>17</sup>.

Nevertheless, if numerous studies describe the impact of a high fat diet on intestinal homeostasis, only a few were dedicated to sugar's specific implications<sup>18,19</sup>.

High sugar intake might disturb intestine homeostasis with several other manners. Firstly, the consumption of sugar-enriched diet might alter the architecture of the intestinal mucosa. High sugar diet promotes Intestinal Stem Cells differentiation into absorptive enterocytes and secretive enteroendocrine cells in *Drosophila*, caused the gut to become thinner, and produce high levels of ROS in the gut<sup>20</sup>. For example, fructose reduces mucus thickness in the colon and defensin secretion<sup>21</sup>. Recent studies demonstrated that dietary fructose worsens colitis in mice by altering the composition, localization, and metabolism of gut microbiota through mechanisms involving GLUT5 expression (fructose transporter)<sup>22,23</sup>.

In contrast, fibres consumption seems to protect from inflammation<sup>24</sup>. In both microbiota-dependant and independent manner, pectin attenuates experimental colitis in mice<sup>25</sup>. Indeed, fibres deficiency reduces the epithelial cell proliferation<sup>26,27</sup>.

Secondly, high sugar intake might dysregulate essential pathways (appetite regulation, circadian rhythms...) in the intestinal mucosa<sup>28</sup>. Conversely L-arabinose (a monosaccharide extracted from plants or fibres) has been reported to inhibit colitis by modulating gut microbiota in mice<sup>29</sup>. Finally, it should be noticed that sugar impact on the intestine might differ according to the physiological conditions. In mice, bovine milk oligosaccharides supplementation reversed the western-diet induced increase in para- and transcellular flux, counter-balancing the dysbiosis and attenuated inflammation in the large intestine<sup>30</sup>. In mouse models of intestinal tumorigenesis, High Fructose Corn Syrup facilitates tumor growth<sup>31</sup>. In fact, luminal fructose absorption and utilization is more efficient in tumor cells than adjacent cells, and the excessive synthesis of Fructose-1-Phosphate leads to an acute drop of cytosolic ATP and subsequently enhances glucose metabolism in order to restore the ATP stores<sup>32</sup>. It also activates fatty acids and eicosanoids syntheses that could contribute to tumorigenesis.

### **Gut Microbiota**

Diet is a main modulator of the gut microbiota and is implicated in many diseases. Importantly, diet rapidly and reproducibly alters the human gut microbiome<sup>33</sup>. The evaluation of specific high-sugar diets is difficult because it often correlates with low fiber and high fat intake. Each

type of nutrient seemingly can have cumulative effects (sucrose + high fat or fructose + high fat)<sup>34</sup>. Dietary additives endemic to Western human populations can impact gut colonization by the microbiota independently of their ability to serve as nutrients<sup>35</sup>. Considering total carbohydrates, the lack of fermentable fibers leads to a shift toward an enrichment in mucin-degrading bacteria that use the mucus layer as a source of nutrients<sup>26</sup>.

In both animals and humans, by changing the suite and amounts of sugars and sweeteners consumed, we create a novel gut environment that alters our microbial community, changes microbial metabolism and excreted metabolites, and selects for novel microbial strains (**Table S1**)<sup>36</sup>. Moreover, early-life sugar consumption significantly has been found to alter the gut microbiome independently of obesity and total caloric intake in a rodent model<sup>37</sup>.

High glucose and high fructose-fed mice lose gut microbial diversity (characterized by a reduced proportion of Bacteroidetes and a markedly increased proportion of Proteobacteria)<sup>38</sup>. Dietary sugars that escape absorption by the host intestine and reach the microbiota also regulate gut colonization by beneficial microbes<sup>35</sup>. High-sucrose diets (containing 70% of the kilocalories from carbohydrates, mainly in the form of sucrose) have previously been shown to elevate *Clostridiales* (a class of Firmicutes) and reduce *Bacteroidales* (an order of the phylum Bacteroidetes) abundance in adult rodents<sup>39</sup>. Dietary fructose intake was negatively associated with the abundance of the bacterial species *Eubacterium eligens*. It is known that *E. eligens*, along with other members of the phylum Firmicutes, have fewer polysaccharide-degrading enzymes than members of the phylum Bacteroidetes. Dietary fructose consumption is negatively associated with microbes belonging to the genus *Streptococcus*, including the species *Streptococcus thermophilus*. This bacterium has been shown to ferment lactose and sucrose and can also metabolize the monosaccharide fructose<sup>40</sup>. Recently, a study highlighted the importance of intestinal symbiosis to prevent chronic inflammation and the fact that the intestinal microbiota should always be studied from an ecosystem perspective instead of focusing on select bacterial species whose relative abundance correlates with the inflammatory level<sup>41</sup>.

Altogether, these data suggest that sugar promotes considerable differences in the gut microbiota at all taxonomic levels, with no apparent effect of the glucose-to-fructose *ratio*<sup>37</sup>, and modulates microbes and metabolites influencing lipid accumulation<sup>42</sup>.

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**Table S1: Summary of recent dietary studies where carbohydrates are linked to gut microbiota modifications in mice. – depletion + presence ↓ decrease ↑ increase**

Ref	Diet / Model	Described				
		Phyla	Order	Family	Genus (specie)	
Arnone et al. 2021 <sup>112</sup>	High-fat high-sucrose (HFHS) diet (30% sucrose, 25% fat)  8-week-old male C57BL/6J mice	Firmicutes	Clostridiales			↓
		Firmicutes	Clostridiales	Lachnospiraceae		↑
		Bacteroidetes	Bacteroidales	Porphyromonadaceae	Barnesiella	↓-
Li et al. 2021 <sup>113</sup>	High-fat high-sucrose (HFHS) diet (20% sucrose, 20% fat)  8-week-old male C57BL/6J mice	Firmicutes				↑
		Bacteroidetes				↓
		Verrucomicrobia				↓
		Proteobacteria				↓
		Actinobacteria				↑
		Patescibacteria				↑
Khan et al. 2020 <sup>114</sup>	10% glucose or fructose or sucrose in drinking water during 7 days  Wild-type C57B16/J	Bacteroidetes	Bacteroidales	Tannerellaceae		↑
			Bacteroidales	Odoribacteraceae		↓
			Bacteroidales	Muribaculaceae		↑
			Bacteroidales	Bacteroidaceae		↑
			Marinilabiliales	Marinilabiliaceae		↑
			Bacteroidales	Rikenellaceae		↓
		Verrucomicrobia	Verrucomicrobiales	Akkermansiaceae		↑
		Proteobacteria	Desulfovibrionales	Desulfovibrionaceae		↓
			Sutterellaceae	Sutterellaceae		↑
		Firmicutes	Lactobacillales	Lactobacillaceae		↓
Eubacteriales	Hungateiclostridiaceae			↓		
Erysipelotrichales	Erysipelotrichaceae			↓		
Eubacteriales	Ruminococcaceae			↓		

				Lachnospiraceae		↓
<b>Laffin et al. 2019</b> <sup>115</sup>	High sucrose diet (55% sucrose) during 2 days	Proteobacteria				↓
		Bacteroidetes	Bacteroidales	Prevotellaceae Porphyromonadaceae		↓ ↑
	Wild-type mice on a 129S1/SvimJ background were female mice 6-8wks	Tenericutes	Anaeroplasmatales	Anaeroplasmataceae		↓
		Firmicutes	Eubacteriales	Lachnospiraceae		↓
		Verrucomicrobia	Verrucomicrobiales	Verrucomicrobiaceae		↑
<b>Magnusson et al. 2015</b> <sup>72</sup>	High sucrose diet in mice for 2 weeks	Bacteroidetes	Bacteroidales (than both normal and high fat diet mice)	Porphyromonadaceae Porphyromonadaceae Rikenellaceae	Barnesiella Other Alistipes	↓
		Firmicutes	Lactobacillales (than both normal and high fat diet mice)	Enterococcaceae Lactobacillaceae Streptococcaceae	Enterococcus + Lactobacillus↑ Lactococcus ↑	↑
			Clostridiales	Lachnospiraceae Ruminococcaceae	Other ↑ Other ↑	↑
		Tenericutes – Mollicutes – Anaeroplasmatales -				-
<b>Martinez-Medina et al. 2014</b> <sup>15</sup>	High fat High sucrose diet in mice for 12 weeks	Firmicutes				↓
			Clostridiales	Ruminococcaceae	Ruminococcus (gnavus and torques)	↑
				Clostriaceae	Faecalibacterium (prausnitzii) Clostridium (coccoides)	- -
		Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium	-
		Bacteroidetes				↑
			Bacteroidales	Prevotellaceae	Prevotella	↑
		Proteobacteria				↑
		Deferribacteres				↓
		Spirochaetes				↓
		Tenericutes				↓
		Bacteroidetes	Bacteroidales	Prevotellaceae	Prevotella copri	↓

<b>Kovatcheva-Datchary et al. 2019</b> <sup>116</sup>	High sucrose zero fat diet (62% sucrose) in Simplified Intestinal Microbiota (ten sequenced strains isolated from human gut) mice for 2 weeks	Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium adolescentis	↓
			Coriobacteriales	Coriobacteriaceae	Collinsella aerofaciens	↓
		Firmicutes	Clostridiales	Ruminococcaceae	Ruminococcus inulinivorans	↓
				Eubacteriaceae	Eubacterium hallii	↑
Verrucomicrobia	Verrucomicrobiales	Akkermansiaceae	Akkermansia muciniphila	↑		
<b>Rosas-Villegas et al. 2017</b> <sup>67</sup>	High fat high sucrose in rats for 4 months	Bacteroidetes				↓
		Firmicutes	Erysipelotrichales	Erysipelotrichaceae	Turicibacter P75- a5	↓↓ ↓↓
			Lactobacillales	Lactobacillaceae	Lactobacillus	↑
			Clostridiales	Eubacteriaceae	Eubacterium	↓
			Clostridiales	Lachnospiraceae	Coprococcus ( <i>C. eutactus</i> )	↓
	Selenomonadales	Acidaminococcaceae	Acidaminococcus	↓		
	Proteobacteria	Enterobacteriales	Enterobacteriaceae	Klebsiella	↓↓	
	Sphingomonadales	Sphingomonadaceae	Sphingomonas	↓↓		
	Desulfovibrionales	Desulfovibrionaceae	Bilophila	↓↓		
	Pasteurellales	Pasteurellaceae	Aggregatibacter	↓↓		
High fat high fructose in rats for 4 months	Bacteroidetes				↓	
	Firmicutes	Erysipelotrichales	Erysipelotrichaceae	Turicibacter P75- a5	↓ ↓	
		Lactobacillales	Lactobacillaceae	Lactobacillus ( <i>L. reuteri</i> )	↑	
		Clostridiales	Eubacteriaceae	Eubacterium	↓	
		Clostridiales	Lachnospiraceae	Coprococcus ( <i>C. eutactus</i> )	↓	
Selenomonadales	Acidaminococcaceae	Acidaminococcus	↓			
Proteobacteria	Enterobacteriales	Enterobacteriaceae	Klebsiella	↓		
Sphingomonadales	Sphingomonadaceae	Sphingomonas	↓			
Desulfovibrionales	Desulfovibrionaceae	Bilophila	↓			
Pasteurellales	Pasteurellaceae	Aggregatibacter	↓			
	Bacteroidetes	Bacteroidales	Bacteroidaceae	Bacteroides	↓	



<b>Shan et al. 2019</b> <sup>75</sup>	High fat high sucrose diet in mice for 120 days	Firmicutes	Clostridiales	Lachnospiraceae	Coprococcus	↑
			Erysipelotrichales	Erysipelotrichidae	Allobaculum	↑
			Lactobacillales	Lactobacillaceae	Lactobacillus	↓↓
		Verrucomicrobia	Verrucomicrobiales	Akkermansiaceae	Akkermansia	↑↑
		Actinobacteria	Coriobacteriales	Coriobacteriaceae	Adlercreutzia	↓↓
			Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium	↑
<b>Volynets et al. 2017</b>	High fat high fructose diet or control + fructose in mice for 12 weeks	Bacteroidetes				↓
			Bacteroidales	Bacteroidaceae	Parabacteroides	↓
		Firmicutes				↑
			Clostriales	Peptostreptococcaceae		↓
		Proteobacteria	Burkholderiales			↑
		Actinobacteria	Bifidobacteriales	Bifidobacteriaceae	Bifidobacterium	↑↑
<b>Meng et al. 2019</b> <sup>117</sup>	High sugar diet in rats for 12 weeks	Proteobacteria				↑
		Actinobacteria				↑
		Firmicutes	Lactobacillales	Lactobacillaceae	Lactobacillus	↑
				Streptococcaceae	Streptococcus	↑
			Erysipelotrichales	Erysipelotrichidae	Allobaculum	↑
		Bacteroidetes				↓
<b>Agus et al. 2016</b> <sup>118</sup>	High fat high sugars diet in mice for 18 weeks	Bacteroidetes	Bacteroidales	Bacteroidaceae	Bacteroides	↑
		Firmicutes				↓
			Clostridiales	Lachnospiraceae	Ruminococcus torques	↑
		Proteobacteria	Deferribacterales	Deferribacteraceae		↑
		Deferribacteres				↑↑
		Actinobacteria				↑
<b>Rahman et al. 2016</b> <sup>119</sup>	High fat high fructose and cholesterol diet in mice for 8 weeks	Bacteroidetes				↓
			Bacteroidales	Bacteroidaceae	Bacteroides	↑
			Bacteroidales	Prevotellaceae	Prevotella	↓
		Cyanobacteria				↓
		Proteobacteria				↑
			Desulfovibrionales	Desulfovibrionaceae		↑
		Firmicutes				↑
			Clostridiales	Ruminococcaceae	Ruminococcus	↓
Tenericutes	Mollicutes	Mycoplasmataceae		↓↓		

		Verrucomicrobia	Verrucomicrobiales	Verrucomicrobiaceae	Akkermansia	↑
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