Nutrition 30 (2014) 497–502

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Review

Designing future prebiotic fiber to target metabolic syndrome

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ARTICLE INFO

Article history:
Received 26 June 2013
Accepted 17 August 2013

Keywords:
Dietary fiber
Short-chain fatty acids
Metabolism
Inflammation
Microbiota

ABSTRACT

The metabolic syndrome (MetS), characterized by obesity, hyperlipidemia, hypertension, and insulin resistance, is a growing epidemic worldwide, requiring new prevention strategies and therapeutics. The concept of prebiotics refers to selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host. Sequencing the gut microbiome and performing metagenomics has provided new knowledge of the significance of the composition and activity of the gut microbiota in metabolic disease. As knowledge of how a healthy gut microbiota is composed and which bacterial metabolites are beneficial increases, tailor-made dietary interventions using prebiotic fibers could be developed for individuals with MetS. In this review, we describe how dietary fibers alter short-chain fatty acid (SCFA) profiles and the intrinsic and extrinsic effects of prebiotics on host metabolism. We focus on several key aspects in prebiotic research in relation to MetS and provide mechanistic data that support the use of prebiotic fibers in order to alter the gut microbiota composition and SCFA profiles. Further studies in the field should provide reliable mechanistic and clinical evidence for how prebiotics can be used to alleviate MetS and its complications. Additionally, it will be important to clarify the effect of individual differences in the gut microbiome on responsiveness to prebiotic interventions.

Introduction

The metabolic syndrome (MetS), characterized by obesity, hyperlipidemia, hypertension, insulin resistance (IR) and type 2 diabetes (T2D), is a growing epidemic worldwide, requiring new prevention strategies and therapeutics. Dietary regimens for weight loss have so far been unsuccessful in the general population and focus has turned to improving the quality of food. One strategy could be to develop prebiotics, dietary components that are fermented by the colonic microbiota and stimulate the growth of specific bacteria, where some of the bacterial metabolites formed may have beneficial effects on health. In this review, we focus on several points in prebiotic research in relation to MetS and provide mechanistic data that support the use of prebiotic fibers in order to alter the gut microbiota composition and short-chain fatty acid (SCFA) profiles. Some types of SCFAs may stimulate the mucosal proliferation and improve the gut barrier function and the risk for influx of toxic and proinflammatory substances such as lipopolysaccharides (LPS) will decrease, which likely will be key steps toward prevention of MetS.

Dietary fibers and the metabolic syndrome

The definition of dietary fibers is under constant review, the current Codex Alimentarius definition is: “Carbohydrate polymers with ten or more monomeric units, which are not hydrolyzed by the endogenous enzymes in the small intestine of humans” [1]. Oligosaccharides with a degree of polymerization of 3–9 also may be included if decided by national authorities, which is the case for the European Commission and the American Association of Cereal Chemists [2–4]. A related concept is the term *prebiotics*, which is defined as: “The selective stimulation of growth and/or activity(ies) of one or a limited number of microbial genus(era)/species in the gut microbiota that confer(s) health benefits to the host” [5]. The most well-known sources of prebiotics are the fructo-oligosaccharides (FOS). However, in principal, all dietary fibers that are fermented are potential prebiotic components. Dietary fibers of higher molecular weight also are more slowly fermented than those of low molecular weight, causing less bloating, which may be an advantage.

All authors have contributed substantially in writing the review and have approved the final version of the manuscript.

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http://dx.doi.org/10.1016/j.nut.2013.08.013

Consumption of dietary fibers have repeatedly shown a relationship to positive health effects and improvements of individual components of MetS. Many studies have investigated one or more components of MetS, whereas fewer studies have focused on MetS as a whole. In a recent study of adolescents (ages 12–19 y) an inverse correlation between the fiber index (grams fiber/1000 kcal [i.e., a measure of nutrient density of a diet]) and MetS was observed [6]. It is worth noting that dietary fibers were the only component in the diet that had an effect. The mechanisms behind these results usually are linked to the fact that dietary fibers, especially soluble and viscous ones, are more satiating and therefore reduce appetite and energy intake [7,8] and in turn improve blood glucose levels and dyslipidemia. The effects are due to physical means in the upper part of the gastrointestinal tract. However, today there is mounting evidence that an unbalanced colonic microbiota is working as a driving force for MetS and that the beneficial effects associated with MetS can be mediated in the colon. If this is the case, non-viscous dietary fibers, such as low-molecular-weight carbohydrates, also may have an effect on MetS. Furthermore, other types of components found in fiber-rich materials, more or less associated with the fiber complex, may be important for MetS. One study [6] raised an interesting hypothesis that minerals (e.g., chromium and vanadium), which are found in whole-grain cereals and antioxidants found in berries, for example, might decrease the risk for the development of MetS. Components with antioxidative capacity, such as phytochemicals, often found in fruits, berries, and fiber-rich foods, also can lower levels of inflammation and oxidative stress. This is interesting because individuals with MetS often have elevated levels of LPS in the blood, a component occurring early in the development of MetS and associated to oxidative stress [6]. The prevalence of MetS is increasing and it also is more common in children. Strong associations between childhood MetS and T2D, as well as between MetS and cardiovascular diseases later in life have been demonstrated [9], thus it is important to reduce the burden of MetS in children and adolescents.

Dietary fibers and weight loss

Obesity and high body weight can be altered by the consumption of dietary fibers, as observed previously [10]. There was an increased weight reduction, after 12 wk, in overweight and obese individuals when the diet was supplemented with a natural fiber complex from cactus (Litramine IQP G-002AS) compared with a placebo group. This weight reduction was thought to be due to the viscosity of the soluble fiber complex and its ability to bind fat and form fat-fiber complexes in the intestinal tract, which are excreted in feces [10]. As the viscosity of the soluble fibers increases the stronger the effect gets. Increased dietary fiber intake also has been shown to lower the risk for childhood obesity by 17% to 21% [11]. Weight gain in middle-aged women, in a prospective cohort study, was inversely related to consumption of whole-grain food over 12 y [12]. The women consuming the greatest amounts of dietary fibers had 49% lower risk for weight gain than those with the lowest consumption (20 versus 13 g/d). Consumption of fruits also may have positive effects. Eating three apples or pears daily for 12 wk contributed to weight loss in hypercholesterolemic and overweight women ages 30 to 50 y [13]. According to previous studies [8,14], the positive effects seen with dietary fiber-rich foods on weight and weight loss can be explained by hormonal, intrinsic, and colonic effects. The hormonal and intrinsic effects are probably due to physical properties of the fibers and are mediated in the upper part of the intestinal tract. This results in a decline of the gastric-emptying rate and absorption of nutrients, and as a consequence a greater satiety, lowered postprandial glycemia and decreased energy intake [8,14]. The secretion of hormones/peptides in the gut like cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) are affected [15]. Another increasingly discussed mechanism is facilitated by an unbalanced microbiota and the SCFAs formed in colon. The role of the gut microbiota is discussed below. The SCFAs *per se* are thought to influence satiety, insulin sensitivity, and energy intake, the formation of free-fatty acids and the secretion of hormones and cell-signaling molecules present in colon [8,15]. If this is a mechanism of importance, other indigestible carbohydrates than highly soluble and viscous fibers, such as the oligosaccharides also may have beneficial health effects. Prebiotic carbohydrates often have been shown to be low-molecular-weight carbohydrates (FOS, galacto-oligosaccharides, and arabinoxylan-oligosaccharides).

SCFA profiles after intake of dietary fibers

The colonic fermentation of dietary fibers gives rise to SCFAs and gases (CO_2, CH_4, and H_2). The main SCFAs formed are acetic, propionic, and butyric acids, and minor amounts of isobutyric, valeric, and isovaleric acids [16]. The amounts and patterns vary with different dietary fibers reaching the colon, which is of great importance when designing foods for specific health effects. However, there is a need for human trials and because SCFAs cannot be analyzed in the cecum of humans it may be questioned whether SCFAs in blood would be a good measure. A study in rats showed a correlation between the concentrations of propionic and butyric acids in cecal content and portal and aortic blood, meaning that profiles of these SCFAs in blood are representative of the profiles formed in cecum. Furthermore, it indicates that the evaluation of SCFAs in venous blood from different dietary fibers in humans is representative of profiles formed in cecum and colon [17]. Few studies presenting SCFAs in human blood are available, probably due to low concentrations in venous blood and the lack of suitable methods. However, a method has been developed for SCFAs analysis in blood using gas chromatography [18]. It is important to keep in mind that evaluating the rate of utilization of SCFAs in humans is very difficult, nevertheless a few studies on victims of sudden death are available, showing increased proportion of acetic acid, while the proportion of propionic and butyric acids were decreased, from the large intestine through the body (to portal vein, hepatic vein, and peripheral vein) [19]. Additionally, the timing of sample collection is a factor influencing the SCFA concentrations and possible profiles [20]. High amounts of acetic and propionic acids are formed from pectin and guar gum, respectively, whereas β-glucan, inulin, some types of resistant starch, and FOS yield high amounts of butyric acid [21,22]. This has been seen both in *in vitro* studies of human fecal inoculum and in *in vivo* studies in rats. One may speculated whether the different patterns are due to the chemical composition of the fibers because pectin largely consists of polymers containing uronic acids, guar gum of galactose, and resistant starch of glucose. Other factors can affect the formation of SCFAs, like the composition of the colonic microbiota; the type of glycosidic linkages, which is crucial for the degree of fermentation (e.g., cellulose or β-glucans); the chain length of the dietary fibers, which is central for the place of fermentation; and the gut transit time. These food factors are of vital importance because different types of SCFAs have been linked to different physiological effects, and it is also possible to control the formation of SCFAs by the choice of raw material and

process/process conditions. Thus, the place of fermentation was changed to the lower part of the hindgut of rats with a crystalline and insoluble form of FOS [22]. Similar results were seen when mixing an easily fermentable and resistant type of fiber [21]. Also the availability of fibers may be important.

Of the different SCFAs, butyric acid has been most emphasized. It is the most important energy source for the colonic epithelial cells [23], but also thought to be involved in the lipid metabolism and to slow down the transport of fat from the intestine [24,25]. Furthermore, butyric acid increases the nutritional status of the colon mucosa, and the risk that toxic and inflammatory substances pass through the mucosa into the circulation decreases [26]. Propionic acid is another SCFA that has been shown to lower cholesterol levels [27], and to affect glucose and lipid metabolism beneficially in animal models [28,29]. A decreased ratio of acetic to propionic acids is favored because acetic acid is one of the primary substrates for cholesterol synthesis in the liver. As the amount and pattern of SCFAs formed in the colon is affected by different food factors, it may be possible to influence the cholesterol and fat metabolism via the diet, for example [30].

SCFAs and satiety

Several hormones regulating appetite and that are involved in the control of gastric emptying may be affected by SCFAs, as shown in rats with FOS [31]. A study in rats showed increased levels of both GLP-1 (inhibits appetite) and peptide YY (PYY) in groups fed high dietary fiber diets (mixture of inulin and FOS) for 15 wk compared with a cornstarch diet. The mechanism behind this was suggested to be the SCFAs, which may regulate the expression of the intestinal pro-glucagon gene [32]. Similar results have been seen in several human studies regarding GLP-1 and PYY. In one study [33], participants fed a prebiotic fiber (Orafti Synergy1) resulted in higher concentrations of GLP-1 and PYY (changes from baseline) compared with a group fed dextrin maltose. Another study [34] showed slower and prolonged release of PYY after a meal enriched with soluble psyllium fiber than after a eucaloric fiber-free meal. Additionally a positive correlation was seen between plasma GLP-1 and breath-hydrogen excretion [33]. These results support that fermentation of dietary fiber plays a part in appetite control. Furthermore, butyric acid also has been shown to increase the satiety hormones PYY and GLP-1 in gut cells from rats [35] and mice. Supplementation of a probiotic mixture (VSL#3) to mice ($Lep^{ob/ob}$) for 13 wk resulted in higher fecal concentrations of butyric acid and GLP-1 secretion from intestinal L-cells. The secretion of GLP-1 possibly is increased by the presence of butyric acid [36]. In another study [37], lean C57BL/6N mice were fed for 4 wk with a high-fat diet supplemented with sodium salts of butyrate, propionate, acetate, or a mixture of these SCFAs. The group supplemented with butyrate gave the highest concentrations of GLP-1 and PYY in blood, in addition to insulin. Butyric acid, therefore, is thought to stimulate secretion of endocrine cells in the proximal small intestine [37]. FOS, a well-known prebiotic component, has been shown to increase the production of GLP-1 in streptozotocin-treated rats and might therefore affect satiety and glucose metabolism [38]. Again a possible mechanism behind this phenomenon is the formation of SCFAs because rectal infusion of SCFAs delays gastric emptying and is part of the "ileal break mechanism". CCK also might be affected by SCFAs, as intake of meals containing hydrolyzed guar gum [39], β-glucan–enriched barley pasta [40], or beans [41] increased the release of this hormone. Furthermore, the postprandial levels of CCK were greater and with prolonged elevations as compared with a low-fiber or a placebo meal [42]. The mechanisms behind the secretion of gut hormones are poorly understood; free-fatty acid receptor 2 (FFAR2) might play a role [37].

SCFAs and low-grade inflammation

There is increasing evidence that a low-grade systemic inflammation is a denominator of MetS, but the causal reason underlying the increased inflammatory level is unknown. One hypothesis is that an unbalanced microbiota of the gastrointestinal tract is working as a driving force for the inflammation. An interesting approach deals with the effects of the metabolically active products formed by the bacteria, from food components reaching the colon (mainly SCFAs from dietary fibers but could also be metabolites from e.g., polyphenols). The composition of the bacterial flora and the type of plant product consumed (e.g. cereals versus berries) may thus be of importance.

Population studies show a strong negative correlation between the intake of dietary fibers and inflammatory markers, like interleukin (IL)-6, IL-18, and C-reactive protein (CRP) and disturbances of risk factors associated to MetS [15]. Some mechanistic studies have been performed in experimental models both *in vitro* and *in vivo* but further studies are needed, especially in humans. Butyrate has been shown to have anti-inflammatory effects locally in the colon of patients with ulcerative colitis and therefore anti-atherogenic effects are also a possibility. Butyric acid has been shown to limit the lipid release from the small intestine into the circulation [24] and to decrease the expression of vascular molecules in endothelial cells through the inhibition of peroxisome proliferator-activated receptor-α and nuclear factor-κ B [43]. Furthermore, anti-inflammatory effects of three SCFAs (butyric acid, butyric acid derivate, and acetic acid derivate) in macrophage cells and its underlying molecular mechanisms were demonstrated, where butyric acid seemed to be the most efficient of the three tested [44].

Apart from inflammation, there are correlations between MetS and cognitive diseases such as Alzheimer's disease and other forms of dementia. Interestingly, people with higher glucose tolerance performed better at cognitive tests than those with lower glucose tolerance [45], despite the fact that glucose tolerance values were within the normal range for all study participants. A breakfast meal with low glycemic index (GI) improved results compared with a high GI breakfast, indicating that a certain food composition might be beneficial for cognition in people with reduced glucose tolerance and T2D [45]. IR has been linked to neurologic decline and proposed mechanisms include vascular inflammation and neuronal damage due to hyperglycemia [46]. To circumvent this pathologic brain aging due to IR, early prevention is warranted. Hence, a diet that maintains an even blood glucose, is anti-inflammatory and reduces oxidative stress would be beneficial. A multifunctional diet might provide a tool to accomplish this. This type of diet was tested in a recent study where middle-aged women and men with body mass index 25 to 33 kg/m^2 were given a diet consisting of known anti-inflammatory food items, cholesterol-lowering products, and probiotics and prebiotic fibers [47]. The randomized crossover intervention diet was given for 4 wk with a 4-wk washout period and resulted in significantly lower CRP, cholesterol, blood pressure, and HbA_{1c} during the active diet period [47]. This approach illustrates the potential for using a multifunctional dietary intervention to reduce the health hazards of the MetS in humans.

Human trials related to SCFA formation

Human trials aimed at understanding the effect of dietary fibers on SCFA formation have been conducted [48,49]. Rye breads, given as breakfast in the morning, resulted in a lower glycemic indices compared with white wheat flour bread [50]. There also are some human trials where the effects can be related to fermentation in colon. The positive effect on blood glucose levels also has been seen in semi-acute studies in healthy participants, where evening meals rich in dietary fibers, consisting of brown beans, barley kernels, barley kernel-based bread or white wheat flour bread enriched with a mixture of barley fiber and resistant starch improved glucose tolerance, compared with white wheat flour bread, the following morning after consumption of a standardized breakfast of white wheat flour bread [49,51–53]. Furthermore, in similar studies, blood glucose levels correlated positively with markers of colonic fermentation, such as hydrogen excretion in breath, possibly through the increased secretion of GLP-1 and PYY [51,53]. Additionally, plasma concentration of butyric acid has been shown to increase after fiber intake, which might also improve blood glucose levels [49]. Additionally, a positive correlation has been observed between breath hydrogen excretion and satiety, indicating that the colonic effect and formation of SCFA may reduce gastric-emptying rate [53]. The mechanisms behind these effects are not clearly understood but lowered levels of free-fatty acids and colonic fermentation, especially the formation of butyric, acid are linked to insulin sensitivity and therefore improved blood glucose levels [53]. Similar results have been seen when healthy individuals were fed barley kernels as a late evening meal, the barley kernels promoted a higher excretion of breath hydrogen, indicating a greater colonic fermentation, which tended to reduce the fasting levels of ghrelin (increases appetite). Colonic fermentation and SCFAs has been proposed to reduce ghrelin levels in healthy individuals after administration of inulin [54].

What characterizes the gut microbiota composition in people with metabolic syndrome?

Groundbreaking experiments [55–58] have shown that the gut microbiota is involved in host energy metabolism and that an “obese microbiota” can be transferred between mice. Accordingly, an obese microbiota has an increased capacity to extract energy from the diet. Germ-free mice display decreased adiposity despite higher food intake compared with conventional mice [56]. Additionally, germ-free mice have higher insulin sensitivity and higher glycogen synthesis in the liver, suggestive of a role for the gut microbiota in glucose homeostasis [56,59]. Furthermore, it has been shown that the composition of bacteria in the gut differed between lean and obese individuals [57]. Proposed mechanisms for how the gut microbiota affects host adiposity are microbial regulation of the lipoprotein lipase inhibitor angiopoietin-related protein 4 (ANGPTL4) and differing capabilities of bacteria for food degradation and energy availability. Additionally, two studies [60,61] pinpointed inflammation as a key initiating step toward increased adiposity and IR. As bacteria are capable of initiating immune responses in the gut, the composition and activity of the gut microbes play an important role for host inflammatory processes. The gut barrier acts as a gate keeper to control which substances, nutrients, and microbes can be allowed to enter the body and bacterial-derived LPS has been shown to impair the barrier function through a TLR4-dependent effect on tight junction permeability in the gut [62]. Furthermore, the gut microbiota is involved in bile–acid metabolism and recent work has shown that deoxycholic acid (DCA) increases gut permeability in mice in a high-fat setting [63,64]. When combining DCA administration with an LPS challenge, the gut barrier is further impaired [64]. Hence, the gut microbiota composition has a large effect on exposure to LPS, both directly through available LPS and indirectly through LPS-mediated increased gut permeability, bile–acid metabolism, and subsequent systemic inflammation.

The diet is an important factor shaping the composition of the gut microbiota, which has been illustrated in animal models. For example, dietary changes such as switching from a low-fat, plant polysaccharide-rich diet to a high-fat Western diet was shown to result in decreased abundance of *Bacteroidetes* along with increased abundance of *Firmicutes*, specifically the classes *Erysipelotrichi* and *Bacilli* [65]. These changes occurred rapidly: only 1 d after the switch the gut microbiota had adapted to the new substrates. Also in humans, the influence of different dietary components on the gut microbiota is starting to be delineated with DNA-based next-generation sequencing techniques. Using pyrosequencing of the 16S rRNA gene to compare the gut microbiomes of children in Burkina Faso and Europe revealed that the higher fiber intake of the former led to increased *Bacteroidetes*, decreased *Firmicutes*, and increased SCFA levels in the stool [66].

Large comprehensive analyses of the gut microbiota composition in humans using next-generation sequencing techniques are currently being used to screen for diseases where bacteria might be of significance. In relation to different aspects of MetS, several studies show separation of the gut microbiome when comparing lean and obese individuals [57,67]. There appear to be differences between individuals with T2D and healthy individuals [67,68], as well as between patients with symptomatic atherosclerosis and healthy individuals [69]. Hence, MetS is characterized by specific shifts in the gut microbiota, including increased abundance of the phylum *Firmicutes* and decreased abundance of *Bacteroides* in obese individuals, whereas in patients with T2D, decreased butyrate-producing bacteria (e.g., *Clostridiales* sp. SS3/4, *Faecalibacterium prausnitzii*, *Eubacterium rectale*, *Roseburia intestinales*) and increased abundance of the mucin-degrader *Akkermansia muciniphila* as well as opportunists such as *Escherichia coli* and *Bacteroides caccae* have been observed [57,67]. It has been proposed that the lower levels of butyrate-producing bacteria in patients with T2D signify a “functional” dysbiosis [67] and recent work further illustrated that patients with T2D display a microbiota with different functional profiles compared with individuals with normal glucose tolerance [68]. In atherosclerosis, *Collinsella* has proven to be enriched in patients with symptomatic atherosclerosis, whereas healthy people were enriched in the butyrate-producers *Roseburia* and *Eubacterium* [69]. Thus, a general pattern of lower levels of butyrate-producers in the different aspects of MetS is suggested. That opens up the possibility of designing new prebiotics that increase butyrate-producing bacteria in the gut. However, it remains to be determined whether these shifts are a cause or consequence of disease. Animal models indicate that changes in the gut microbiota might trigger metabolic changes leading to disease. Mechanistic studies, such as mono-colonization experiments in germ-free mice combined with trials on effects of bacterial supplements (i.e., probiotics) could shed light on the true effect of the changes observed when sequencing the gut microbiome in patients with MetS.

Future direction

The future of the prebiotic field will most likely be in the development of preventive diets. Because of the large individual variations in the human gut microbiota and the pathology and

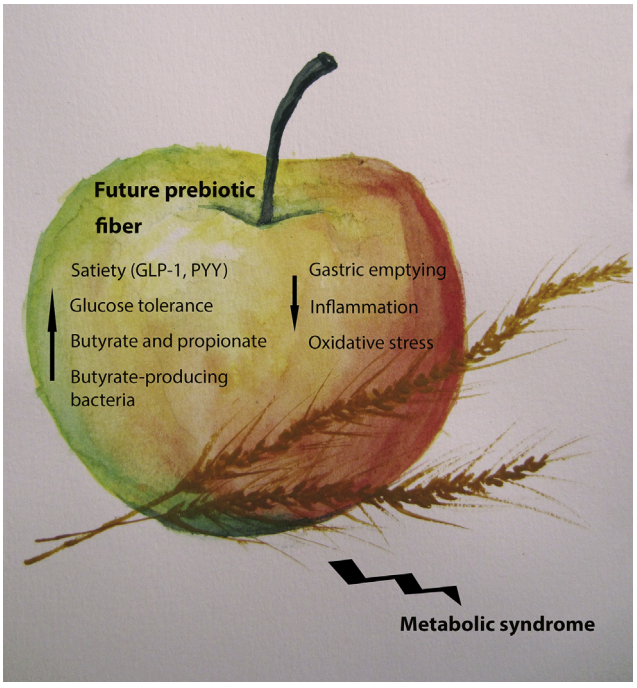

Fig. 1. Characteristics of new prebiotic fibers designed for prevention or treatment of metabolic syndrome should include stimulation of beneficial microbes in the gut, increased production of short-chain fatty acids, and improvement of glucose tolerance. Furthermore, increased gut satiety peptides and reduction in inflammation and oxidative stress will be key aspects in combating the health hazards of metabolic syndrome.

sequelas of MetS are multifaceted, targeting subgroups of patients with specific complications of MetS also will be greatly important. Thus far, it has been difficult to achieve large effects of clinical value in individuals with MetS using single bacterial manipulations such as probiotic interventions, whereas a prebiotic approach allows for relatively larger changes in the gut microbiota and SCFA composition. However, as our knowledge of how a healthy gut microbiota and SCFA profile is composed increases, targeted probiotic interventions might prove efficient in patients with MetS. The multifunctional diet concept is another way of imposing a larger effect on the metabolic system. Additionally, it will be important to clarify the effect on individual differences in the gut microbiome on responsiveness to prebiotic interventions. Taken together, future prebiotics should have the capacity to alter the gut microbiota, insulin levels, and SCFA profiles; decrease systemic inflammation; increase satiety; and reduce oxidative stress and gastric emptying (Fig. 1). Further studies in the field should provide reliable mechanistic and clinical evidence for how we can use prebiotics to alleviate MetS and its complications.

Acknowledgments

This work was supported by the Antidiabetic Food Centre, a VINNOVA VINN Excellence Center at Lund University.

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