REVIEW

Modulation of the gut microbiota-adipose tissue-muscle interactions by prebiotics

Julie Rodriguez and Nathalie M Delzenne
Metabolism and Nutrition Research Group, Louvain Drug Research Institute, UCLouvain, Université catholique de Louvain, Brussels, Belgium
Correspondence should be addressed to N M Delzenne: nathalie.delzenne@uclouvain.be

Abstract
The gut microbiota is now widely recognized as an important factor contributing to the regulation of host metabolic functions. Numerous studies describe an imbalance in the gut microbial ecosystem in response to an energy-dense diet that drives the development of metabolic disorders. In this context, the manipulation of the gut microbiota by food components acting as prebiotics appears as a promising strategy. Several studies have already investigated the beneficial potency of prebiotics, mostly inulin-type fructans, on host metabolism and key intestinal functions including gut hormone release. For the last 20 years, several non-digestible compounds present in food have been shown to modulate the gut microbiota and influence host metabolism in essential organs involved in the control of energy homeostasis. To date, numerous reviews summarize the impact of prebiotics on the liver or the brain. Here we propose to describe the mechanisms by which prebiotics, through modulation of the gut microbiota and endocrine functions, modulates the metabolic cross-talk communication between the gut, the adipose tissue and skeletal muscles.

Key Words
- gut microbiota
- fat mass
- prebiotic
- skeletal muscles

Glucose homeostasis disruptions are associated with changes in the gut microbiota in diabetes and obesity

Obesity is often associated with a range of metabolic alterations including insulin resistance, type 2 diabetes, dyslipidemia, cardiovascular or non-alcoholic fatty liver diseases. Even if these alterations certainly result from a dysregulation of the balance between energy intake and energy expenditure, it has been now clearly established that some other factors can participate to the development and progression of cardio-metabolic diseases. Over the last decade, gut microbial changes (composition and/or function) have been associated with obesity, metabolic disorders, and ‘pre’ diabetes leading to a ‘dysbiotic state’ (Qin et al. 2012, Allin et al. 2018). This suggests that the gut microbiota can be involved (as a cause or consequence) in the insulin resistance process, and therefore in the disruption of endocrine system. Indeed, compared to non-diabetic individuals, the gut microbiota from type 2 diabetic patients (T2D) were characterized by a lower abundance of several bacteria (Clostridiales spp. SS3/4, Eubacterium rectale, Faecalibacterium prausnitzii, Roseburia intestinalis and Roseburia inulinivorans) able to generate butyrate, one important short chain fatty acid (SCFA) produced upon fermentation of carbohydrates and fibers (Qin et al. 2012). The decreased abundance of butyrate-producing bacteria was confirmed in a Chinese cohort and seemed to appear early, in the period of prediabetes (Zhang et al. 2013). Indeed, the abundance of some bacteria (such as Akkermansia muciniphila and Faecalibacterium prausnitzii) were higher in individuals with normal glucose tolerance, compared to prediabetic subjects (Zhang et al. 2013).
Butyrate has been previously described as a beneficial metabolite for the intestinal physiology (including gut barrier function, intestinal inflammation, adherence of beneficial microbes in colonic epithelial cells, gut permeability) but it can also be linked with metabolic health by regulating body weight gain and glucose homeostasis (Blaak et al. 2020). A higher abundance of opportunistic pathogens (Bacteroides caccae, Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum, Eggerthella lenta and Escherichia coli) characterizes diabetics from non-diabetic controls (Qin et al. 2012). Moreover, the fecal metagenome from European women with normal, impaired or diabetic glucose control revealed positive associations for Clostridium clostridiiforme with triglycerides and C-peptide levels, and Lactobacillus gasseri with fasting glucose and hemoglobin A1c (HbA1c), in T2D patients (Karlsson et al. 2013). In addition, 21 metagenomic clusters were depleted in T2D women, particularly clusters belonging to Roseburia genus, Clostridium species, Eubacterium eligens, several Clostridiales and one Bacteroides intestinalis, the latter being negatively correlated with waist circumference and insulin level. In addition, among a population of Danish obese individuals, those with a low bacterial richness seem to be susceptible to have a more marked adiposity, insulin resistance and inflammatory phenotype compared to the ones with a higher bacterial richness (Le Chatelier et al. 2013). Individuals with reduced microbial gene richness were also more susceptible to present dysmetabolism and low-grade inflammation in a cohort of French obese or overweight subjects (Cotillard et al. 2013). Interestingly, a diet-induced weight loss improved the gut bacterial richness and partially reversed the metabolic alterations. More recently, in the same French cohort, the authors established a link between a low gut microbiota richness and a high level of ceramides, lipids mediators involved in the development of type 2 diabetes (Kayser et al. 2019). They highlighted a decreased abundance of Methanobrevibacter smithii and anti-inflammatory bifidobacteria species associated with higher ceramides levels. Another recent study highlighted that Danish adults with prediabetes exhibit an aberrant gut microbiota in which the main differences (compared to individuals with normal glucose regulation) are a lower abundance of both Clostridium genus and the mucin-degrading bacterium A. muciniphila (Allin et al. 2018). However, the analysis of gut microbiota changes in the context of impaired glucose homeostasis is quite difficult since largely prescribed antidiabetic treatments, such as metformin, generate confounding effects by modulating per se the gut microbiota composition (Forslund et al. 2015, Rodriguez et al. 2018). In this context, a study performed in Swedish subjects naïve for diabetic treatments, showed that gut microbiota composition was altered in people with impaired glucose tolerance, glucose intolerance (impaired glucose tolerance associated to impaired fasting glucose) and T2D individuals, but not in those with impaired fasting glucose (Wu et al. 2020). This study confirmed a decreased abundance of several butyrate producers, but also highlighted an alteration of butyrate production with glycemic status in both prediabetes and T2D groups. Interestingly, these gut microbiota alterations were present in prediabetic individuals, but increased with glucose intolerance and linked with insulin resistance. In addition to the SCFA production alterations, an elegant review recently summarized the modification of gut microbiota dysfunctions that are occurring in type 2 diabetes patients, namely an increased sugar-related membrane transport that promotes cellular glucose uptake, a higher transport of the branched-chain amino acids (BCAA) and a lowered metabolism of cofactors and vitamins (Fan & Pedersen 2020). This strongly supports the association between the gut microbiota and the endocrine system, especially in the glucose homeostasis control.

The gut microbiota as modulator of host metabolism disturbances

The causal role of the gut microbiota in the development of obesity and insulin resistance

In 2004, a pioneering study highlighted that the gut microbiota can control the host metabolism by regulating fat storage in murine model (Backhed et al. 2004). Indeed, the colonization of germ-free (GF) mice with cecal microbiota from the conventionally raised mice was sufficient to promote the triglycerides storage in adipocytes and insulin resistance, despite a reduction of energy intake. This supported for the first time that the gut microbiota has a causal role in the occurrence of adiposity and glucose homeostasis. In addition, the same group reported that, contrary to conventionalized mice, GF mice are protected against the obesity induced by a high-fat/high-sugar (HF/HS) diet (Backhed et al. 2007). This protection was associated with a higher phosphorylation of AMP-activated protein kinase, and its downstream targets involved in fatty acid (FA) oxidation, in both skeletal muscles and liver from GF mice, compared to conventionalized ones. The suppression of intestinal
expression angiopoietin-like protein 4 (Angpt14) in GF mice abolished the protection of mice against the diet-induced obesity and was associated with increased serum insulin levels. Interestingly, the deficiency of Angpt14 in GF fed a high-fat/high-sugar diet is associated with a decreased expression of markers involved in FA oxidation in skeletal muscles, independently of AMPK regulation. In 2010, another team confirmed the resistance of GF mice to the high-fat/high-sugar diet-induced obesity (Rabot et al. 2010). They showed that this protection was due to an improvement of insulin sensitivity and a reduced plasma level of proinflammatory cytokine tumor necrosis factor alpha (TNF-alpha) in GF mice fed with a HF/HS diet, compared to conventional mice. Indeed, the inflammatory process creates a linkage between the gut microbiota and insulin resistance. In 2007, it was demonstrated in mice that a HF diet generated endotoxemia, defined as an increase of plasma lipopolysaccharide (LPS), a bacterial component from the Gram-negative bacteria (Cani et al. 2007a). This endotoxemia was associated with changes in the gut microbiota. Among these changes, a lower abundance of Bifidobacterium spp. and E. rectale-Clostridium coccoides group were found. Interestingly, mimicking endotoxemia by infusing LPS induced body weight gain, adiposity, liver insulin resistance and triggered the expression of inflammatory markers in adipose tissue, liver and skeletal muscle. In addition, antibiotic treatment in both high-fat–fed and ob/ob mice reduced endotoxemia, glucose intolerance, fat mass expansion and inflammation in adipose tissue. Finally, colonization of GF Swiss Webster mice with a microbiota obtained from conventionally raised mice has been shown to promote inflammation in the white adipose tissue (WAT) by favoring the recruitment of macrophages, LPS being involved in this process (Caesar et al. 2012). In addition to the involvement of gut microbiota, the type of dietary lipids in the diet also plays a crucial role in the development of WAT inflammation. Indeed, mice fed lard for 11 weeks exhibit WAT inflammation, increased Toll-like receptor (TLR) activation and reduced insulin sensitivity compared with mice fed fish oil (Caesar et al. 2015). Actually, this result was associated with a different regulation of gut microbiota composition in response to different dietary fat sources. For instance, lard induced an increase of Bilophila, Bacteroides, Turicibacter genera whereas fish-oil favored the growth of bacteria associated with beneficial effects on health such as Akkermansia, Bifidobacterium or Lactobacillus genera (Caesar et al. 2015).

The causal role of the gut microbiota in insulin sensitivity has also been reported supported by fecal material transfer (FMT) interventions in humans (Vrieze et al. 2012). By infusing the intestinal microbiota from lean donors to individuals with metabolic syndrome, an improvement of insulin sensitivity and an increased abundance of butyrate-producing bacteria was observed in recipient patients after 6 weeks. Five years later, the same group repeated the intervention on other patients and demonstrated that insulin sensitivity improvement was accompanied by changes in plasma metabolites profiling (including modifications of γ-aminobutyric or lysophosphatidic acid) but no change in fasting plasma SCFA was reported (Kootte et al. 2017). Interestingly, the authors demonstrated that the baseline fecal microbiota composition has a determinant role in the improvement of peripheral insulin sensitivity since its composition can predict the success of the allogenic FMT. Indeed, metabolic responders were characterized by a lower microbial diversity, a higher abundance of Subdoligranulum variabile and Dorea longicatena and lower abundance of Eubacterium ventriosum and Ruminococcus torques, compared to non-responders. Finally, recent works highlighted the importance for identifying and studying the impact of gut bacterial metabolites on health. Indeed, current research in the field of metabolic diseases focus on the relation of some bacterial products derived from carbohydrates or protein fermentation and the obesity-associated insulin resistance (Canfora et al. 2019).

Focus on bacteria prone to improve glycemic control and metabolic disturbances

In addition to the beneficial effects observed by transferring the fecal gut microbiota from lean donors into recipients with metabolic syndrome, it has been demonstrated that some specific bacteria can also improve the obesity and associated disorders, these bacteria being thus proposed as probiotics. Probiotics have been defined as ‘live microorganisms that, when administered in adequate amounts, confer a health benefit on the host’ (Hill et al. 2014). For instance, the administration of Bifidobacterium and Lactobacillus strains in HF-fed mice lowered the body weight gain, and improved glycemic control (Wang et al. 2015, Alard et al. 2016). Lactobacillus acidophilus N51 (LNS1) inhibited the development of insulin resistance in HF mice by restoring the phosphorylation of Akt protein (involved in the insulin pathway) in the liver, adipose tissues and skeletal muscles (Park et al. 2018). Similarly, a treatment with a mix of probiotics containing Lactobacillus and Bifidobacterium strains also improved blood glucose in mice by regulating the phosphorylation of Akt protein.
both in the liver and skeletal muscles (Bagarolli et al. 2017). The treatment with *A. muciniphila* in HF-fed mice also reduced fasting glycemia and improved glucose tolerance (Everard et al. 2013, Plovier et al. 2017). This bacterium reduced the macrophage infiltration and improved the FA oxidation in visceral fat depots. Interestingly, the administration of pasteurized form of *A. muciniphila* enhances energy expenditure, oxygen consumption and physical activity in HF mice (Depommier et al. 2020). *A. muciniphila* reduces fat mass accumulation and decreases the expression of perilipin 2 – a factor associated with lipid droplets – in both brown and white adipose tissues. Finally, in small cohort of obese human volunteers, three months of supplementation with pasteurized *A. muciniphila* improved insulin sensitivity, reduced insulinemia and plasma total cholesterol (Depommier et al. 2019). Other bacteria seem interesting in the context of insulin resistance such as *Eubacterium hallii* (now called *Anaerobutyricum hallii*). Daily oral gavage with *A. hallii* during 4 weeks significantly improved adiposity, insulin sensitivity and increased energy expenditure in *db/db* mice (Udayapann et al. 2016). Additionally, oral treatment with *F. prausnitzii* in HF-fed mice improved hepatic fat content, both insulin sensitivity and inflammation in adipose tissues and increased skeletal muscle mass (Munukka et al. 2017). All these studies support the idea that specific bacteria isolated from the human gut microbiota participate to the regulation of host metabolism in peripheral tissues, targeting the liver, the adipose tissue and the muscle.

Finally, it is now obvious that the gut microbiota contributes to metabolic function in healthy individuals and disruption of this ecosystem promoted a diseased state associated with some detrimental metabolic outcomes: systemic inflammation, altered gut barrier function, insulin resistance, increased adiposity and plasma cholesterol or triglycerides… (Green et al. 2020). To date, there are different ways by which the gut microbiota can modulate the mechanisms of obesity including the processes of energy extraction and absorption, the induction or prevention of metabolic endotoxemia, and the production of bacterial metabolites such as SCFA which are able to stimulate the release of the satiety-inducing hormones peptide YY (PYY) and glucagon-like peptide-1 (GLP-1) (da Silva et al. 2020). In this context, the modulation of gut microbiota by promoting the growth of some specific bacteria by a prebiotic approach can be an effective strategy to reverse some features of the microbial dysbiosis and improve some metabolic alterations. A recent review summarized the experimental work and the available human intervention studies that evaluated the anti-obesity effect of prebiotics (Cerdo et al. 2019). In our review, we describe the influence of prebiotic interventions on the gut microbiota composition and function, with a focus on the endocrine system regulation and consequences in the metabolism of the adipose tissues and skeletal muscles.

### Prebiotic approach in the modulation of the gut microbiota in obesity: gut endocrine system, adipose tissue and muscles as host targets

Over the past decade, numerous studies have investigated the beneficial impact of gut microbiota modulation by prebiotics in the context of obesity and metabolic disorders. Prebiotics are defined as a ‘substrates that are selectively utilized by host microorganisms conferring a health benefit’ (Gibson et al. 2017). Indeed, several nondigestible carbohydrates can be fermented by the gut microbiota, including oligosaccharides, arabinoxylans, glucans, resistant dextrin or resistant starch. Table 1 summarizes the main studies performed *in vivo* in rodents supplemented with prebiotics. The outcomes reported relate to the gut microbiota composition (Fig. 1), and of biological markers of metabolic alterations.

From those data, we can elaborate the molecular mechanisms evoked to explain how prebiotics control energy homeostasis in obesity, which are summarized in Fig. 2. Due to the high number of reviews focusing on the impact of prebiotics on the liver steatosis and related metabolic disorders, we chose to present the existing literature related to the effects on the adipose tissue and the skeletal muscles, two organs playing a key role in storage vs oxidation of fatty acids. The modulation of the endocrine function by prebiotics is often cited as an important mechanism behind the systemic effects on lipid and glucose homeostasis, as well as on food related behavior.

In 2007, our team demonstrated that dietary supplementation with oligofructose (OFS) – a short chain inulin-type fructan – in HF-fed mice restored the amount of Bifidobacteria in the cecal content, normalized the endotoxemia and reduced fat mass accumulation (Cani et al. 2007b). This was linked to an improvement of glucose homeostasis through a better glucose-induced insulin secretion. Interestingly, OFS supplementation in *ob/ob* or high fat fed mice reduced adipose tissue weights, increased muscle mass and regulated both pancreatic...
Table 1  Experimental data supporting the impact of prebiotic supplementation on endocrine system, adipose tissues and skeletal muscles in rodent models of obesity.

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<td>Cani et al. 2007b</td>
<td>HF-fed mice</td>
<td>ITF (oligofructose) for 14 weeks</td>
<td>14 weeks</td>
<td>HF-ITF vs HF (qPCR): ↑ Bifidobacterium spp. ↑ Eubacterium rectale/Clostridium coccoides group ↓ Enterobacteriaceae</td>
<td>HF-ITF vs HF: ↓ BW gain ↑ Glucose tolerance ↑ Colon proglucagon mRNA</td>
<td>HF-ITF vs HF: ↓ glucose-induced insulin secretion ↓ fasting plasma insulin</td>
<td>ob-ITF vs ob-cellulose: ↓ VAT mass ↓ EAT mass ↓ SAT mass</td>
<td>ob-ITF vs ob-cellulose: ↑ muscle mass</td>
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<td>Cani et al. 2009</td>
<td>ob/ob mice</td>
<td>ITF (oligofructose) for 5 weeks</td>
<td>5 weeks</td>
<td>ob-ITF vs ob-cellulose (qPCR): ↑ Bifidobacterium spp. ↑ E. rectale/C. coccoides group ↑ Lactobacillus spp.</td>
<td>ob-ITF vs ob-cellulose: ↓ Intestinal permeability Improved systemic and hepatic inflammation</td>
<td>ob-ITF vs ob-cellulose: ↑ GLP1, GLP2 ↓ GIP ↓ Pancreatic polypeptide ↑ Amylin</td>
<td>ob-ITF vs ob-cellulose: ↓ VAT mass ↓ EAT mass ↓ SAT mass</td>
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<td>Everard et al. 2011</td>
<td>ob/ob mice</td>
<td>ITF (oligofructose) for 5 weeks</td>
<td>5 weeks</td>
<td>ob-ITF vs ob-cellulose (16S rRNA): ↑ Bifidobacterium spp., Tannerella, Barnesiella, Subdoligranulum, Parasutterella</td>
<td>ob-ITF vs ob-CT: ↑ Glucose tolerance ↓ Plasma triglycerides ↑ colon proglucagon mRNA</td>
<td>ob-ITF vs ob-CT: ↑ plasma GLP1</td>
<td>ob-ITF vs ob-CT: ↓ VAT mass ↓ EAT mass ↓ SAT mass ↓ oxidative stress</td>
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<td>Respondek et al. 2013</td>
<td>Humanized gnotobiotic diet-induced obesity mice</td>
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<td>HF-fed mice</td>
<td>ITF (oligofructose) for 4 weeks</td>
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<td>HF-ITF vs HF (qPCR): ↑ Bifidobacterium spp. ↓ Roseburia spp. ↓ E. rectale/C. coccoides group</td>
<td>HF-ITF vs HF: ↓ HOMA-IR</td>
<td>HF-ITF vs HF: ↓ SAT mass ↓ SAT adipocytes size ↑ Basal SAT lipolysis ↓ SAT Grp43 mRNA ↓ Cd36, Lpl mRNA ↓ SAT inflammation (Tlr4, F4/80 mRNA) ↓ SAT adipocytes differentiation (aP2, CEBPα mRNA)</td>
<td>HF-ITF vs HF: ↓ lean mass</td>
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<td>30 weeks</td>
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<td>HF/HS with 5% gluten-fed mice</td>
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<td>HF/HS-ITF vs HF/HS-G: ↑ <em>Bifidobacterium</em>, <em>Butyricoccus</em>, Prevotella, Parasutterella, Butyricimonas ↓ Clostridium XI, <em>Oscillibacter</em>, <em>Peptococcus</em>, <em>Alistipes</em>, <em>Pseudoflavonifractor</em></td>
<td>↓ Gluten immunogenic peptide in the cecal content ↑ Cell renewal in the jejunum (Intectin)</td>
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<td>HF/HS-ITF vs HF/HS-G: ↓ Gluten immunogenic peptide in the cecal content</td>
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<td>Rodriguez et al. 2020</td>
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<td>18 bacterial genera regulated by inulin (donor-dependent effects)</td>
<td>Inulin: ↓ BW gain for one donor ↓ Hepatic lipids accumulation for two donors</td>
<td>Inulin: ↓ SAT and EAT mass for two donors ↓ SAT adipocytes size for one donor In SAT, inulin: ↓ <em>Cd36</em> mRNA for one donor ↓ <em>Ppar</em> for two donors In VAT, inulin: ↑ Browning process (Ppargc-1a, Ucp1, Prdm16 mRNA) for one donor With GOS: ↓ SAT and VAT compared to HF-diabetic mice ↓ Phospho-Akt in VAT compared to HF-diabetic mice</td>
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<td>Inulin: ↓ Intramuscular lipids accumulation and triglycerides for one donor ↓ <em>Cd36</em> and <em>Cpt-1α</em> mRNA for one donor ↓ <em>Ppar</em> for two donors</td>
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<td>3 months</td>
<td>With GOS (pyrosequencing): ↑ <em>Bacteroidetes</em>, ↑ <em>Actinobacteria</em>, ↑ <em>Parabacteroides</em>, ↓ <em>Oscillibacter</em>, <em>Alistipes</em>, <em>Olsenella</em>, <em>Mucispirillum</em></td>
<td>With GOS: Glucose tolerance similar to the HF-diabetes resistant mice, but lower compared to HF-diabetic mice. ↓ Plasma LPS compared to HF-diabetic mice. ↓ Triglycerides compared to HF-diabetic mice.</td>
<td>With GOS: ↓ Fasting insulin compared to HF-diabetes resistant mice ↓ Leptin and resistin compared to HF-diabetic mice.</td>
<td>With GOS: ↓ SAT and VAT compared to HF-diabetic mice ↓ Phospho-Akt in VAT compared to HF-diabetic mice</td>
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<td>Mistry et al. 2020</td>
<td>HF/H5-fed mice</td>
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<td>16 weeks</td>
<td>HF-GAL vs HF (16S rRNA); ↑ Bifidobacterium, Parvibacter, Akkermansia, Parasutterella ↓ Olsenella, Allostipes, Faecalibaculum, Bilophila</td>
<td>↓ BW gain; Improves insulin tolerance; ↓ Plasma cholesterol and triglycerides ↑ GLP-1 mRNA in proximal intestine</td>
<td>HF-GAL vs HF: ↓ BW gain</td>
<td>↓ Perirenal mass; ↓ EAT mass; In BAT: ↑ Ucp1</td>
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<td>HF-fed mice</td>
<td>Mannan-oligosaccharides (MOS) for 11 weeks</td>
<td>11 weeks</td>
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<td>↓ BW gain; ↓ HOMA-IR</td>
<td>HF-MOS vs HF: ↓ BW gain; ↓ HOMA-IR; ↓ Serum cholesterol, HDL and triglycerides</td>
<td>↓ WAT Adipocytes size; ↓ WAT Leptin and adiponectin mRNA; ↓ Inflammatory markers (Tnf-α, Tlr4, Itgax)</td>
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<td>↓ Total Fat mass; ↓ Mesenteric adipocytes size</td>
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<td>Neyrinck et al. 2012a</td>
<td>HF-fed mice</td>
<td>Chitin-glucan for 4 weeks</td>
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<td>HF-CG vs HF (qPCR); ↑ Bifidobacterium spp., Roseburia spp., E. rectale/C. coccoides group ↓ Bacteroides/Prevotella spp., Lactobacillus spp.</td>
<td>↓ BW gain; ↓ Fasting glycemia; ↓ Insulinemia; ↓ Glucose tolerance</td>
<td>HF-CG vs HF: ↓ BW gain; ↓ Fasting glycemia; ↓ Insulinemia; ↓ Glucose tolerance</td>
<td>↓ VAT mass; ↓ EAT mass; ↓ SAT mass</td>
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<td>HF-AX vs HF (metagenomic); ↓ Blautia</td>
<td>HF-AX vs HF: ↓ BW gain, improves glucose tolerance; ↓ Serum triglycerides, NEFA, cholesterol, LDL, VLDL</td>
<td>HF-AX vs HF: ↓ Serum ghrelin, leptin, insulin</td>
<td>In VAT: ↓ Inflammatory markers (F4/80, Il6, Mcp1, Il6, NfkB)</td>
<td>↓ VAT mass</td>
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<td>Neyrinck et al. 2011</td>
<td>HF-fed mice</td>
<td>Arabinoxylans AX for 4 weeks</td>
<td>4 weeks</td>
<td>HF-AX vs HF (qPCR); ↑ Bifidobacterium spp., Roseburia spp., Bacteroides/Prevotella spp.</td>
<td>HF-AX vs HF: ↓ BW gain; ↓ Insulin resistance index; ↓ Total, LDL and HDL cholesterol</td>
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<td>↓ VAT mass</td>
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<td>HF-fed mice</td>
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<td>8 weeks</td>
<td>HF-AXOS vs HF (qPCR); ↑ Bifidobacterium spp., ↓ Lactobacillus spp.</td>
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<td>HF-AXOS vs HF: ↓ PYY, GLP1</td>
<td>↓ VAT mass; ↓ EAT mass; ↓ SAT mass; In VAT: ↓ Inflammatory markers (F4/80)</td>
<td>↓ VAT mass</td>
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<td>Arabinoxylan oligosaccharides AXOS for 8 weeks</td>
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### References

- Olivares et al. 2019
- Miyamoto et al. 2018
- Drew et al. 2018

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polypeptide and gut peptides (glucose-dependent insulinotropic polypeptides GIP, active amylin and active glucagon-like peptide GLP-1 and GLP-2) (Cani et al. 2009). Interesting, counteracting GLP-1 effect (by antagonists or in GLP-1 receptor knock-out mice) blunted the improvement of appetite and glucose homeostasis by OFS, supporting the importance of the modulation of the gut endocrine function to explain systemic effect of inulin-type fructans (ITF) prebiotics. In addition to their impact on Bifidobacterium spp. and adiposity, OFS also improved the intramuscular lipids accumulation in ob/ob mice, attributed to a reduction of muscle triglycerides content (Everard et al. 2011). These beneficial impacts also occurred in obese rats in which an OFS-enriched inulin mixture improved adiposity, steatosis and lean mass, and increased GIP and GLP-1 levels (Kumar et al. 2016). In addition, short-chain fructo-oligosaccharides administration in humanized gnotobiotic mice fed a HF confirmed the expansion of Bifidobacterium spp. and the control of adiposity, this being associated with a reduction of plasma leptin and adiponectin (Respondek et al. 2013). However, the regulation of plasma triglycerides level by ITF is more controversial (Everard et al. 2011, Respondek et al. 2013, Kumar et al. 2016).

The mechanisms of action of ITF is often related to their fermentation into SCFA that lead researchers to analyze their influence on molecular targets of SCFA. For instance, one possible mechanism of ITF action could be the regulation of G protein-coupled receptor-3 (GPR43 FFAR2) (Dewulf et al. 2011). The activation of GPR43 receptor, upon a HF diet, drives the inhibition of lipolysis and the stimulation of adipocytes differentiation. Interestingly, OFS reduced the expression of Gpr43 in subcutaneous adipose tissue (SAT) and reduced both the expression of cluster of differentiation 36 (Cd36) and lipoprotein lipase (Lpl; involved in lipid accumulation in adipocytes), and the mRNA levels of aP2 and CEBP-α (two markers of adipocytes differentiation) contributing to the anti-obesogenic effect of OFS (Dewulf et al. 2011). In addition to the effect reported in SAT, inulin also decreased Cd36 expression, in the jejunum of western diet fed mice (Hiel et al. 2018) and in the skeletal muscles of mice fed a western diet supplemented with gluten (Olivares et al. 2019), suggesting a role of ITF prebiotic in the regulation of FA uptake in several tissues. Another possible mechanism is an improvement of brown adipose tissue (BAT) activity and/or activation of ‘browning’ process in the WAT by ITF. Indeed, inulin increased the mRNA levels of Ppargc-1a, Ucp1 and Cidea, three markers of adipocyte ‘browning’ in SAT, and stimulated the activity of the cytochrome c oxidase in the BAT, suggesting a higher mitochondrial oxidative capacity in this tissue (Weitkunat et al. 2017). Interestingly, the basal gut microbiota influences the response to ITF in terms of microbial changes and metabolic effects in the peripheral tissues (Rodriguez et al. 2020). Indeed, the inulin effects on fat mass expansion, BAT thermogenesis and intramuscular lipids accumulation differently occur in groups of mice inoculated with the feces from different obese donors. In humans, fat oxidation was increased in the early postprandial phase in overweight to obese men consuming high-fat milkshake enriched in inulin, compared to a maltodextrin-based placebo (van der Beek et al. 2018). Finally, the impact of ITF on the adiposity and the growth of Bifidobacterium spp. has been confirmed in obese women and in a multicenter-clinical study performed in obese individuals after 3 months of supplementation (Dewulf et al. 2013), as well as upon a supplementation of FOS-enriched inulin during 16 weeks in overweight or obese children (Nicolucci et al. 2017).

In addition to the effects of ITF, several other food components, responding to the definition of dietary fibers and considered as prebiotic or prebiotic candidates, are of interest in the management of diet-induced obesity. It is the case of gluco-oligosacharides (GOS), β-galacto-oligosaccharides (β-GAL) or mannan-oligosaccharides (MOS) (Serino et al. 2012, Wang et al. 2018b, Mistry et al. 2020). For instance, GOS, β-GAL and MOS improved the expansion of white adipose tissue, insulin sensitivity or glucose tolerance, and plasma triglycerides in HF or western diet fed mice (Serino et al. 2012, Wang et al. 2018b, Mistry et al. 2020). β-GAL and MOS modulate the gut microbiota by favoring the growth of Bifidobacterium spp. and A. muciniphila (Wang et al. 2018b, Mistry et al. 2020). Finally, GOS and MOS could regulate the levels of some adipokines in plasma and WAT (Serino et al. 2012, Wang et al. 2018b). Furthermore, supplementation with milk oligosaccharides in HF-fed mice also affected the WAT since it decreased the number of crown-like structures in mesenteric adipose tissue, a marker of dead adipocytes and macrophages infiltration, which increases in obesity (Cinti et al. 2005, Hamilton et al. 2017).

Supplementation with chitin-glucan, another dietary fiber, increased the number of Bifidobacterium spp., Roseburia spp. and E. rectale/C. cocoideus group in HF-fed mice, these effects on the gut microbiota were associated with a decreased adiposity and an improvement of glucose tolerance (Neyrinck et al. 2012a). The dietary fibers present in cereals are also of interest. Similar changes were found with arabinoxylan (AX) in HF-fed mice since 4 or...
10 weeks of supplementation was sufficient to improve body weight and adiposity and stimulates the growth of *Bifidobacterium* (after 4 weeks) and *Roseburia* genera (independently of duration) ([Neyrinck et al. 2011](https://joe.bioscientifica.com/), [Sarma et al. 2018](https://joe.bioscientifica.com/)). Interestingly, this cereal dietary fiber (DF) was able to down-regulate inflammation, lipogenesis, FA oxidation and adipocytes differentiation in adipose tissues after a short- or long-term administration. The hydrolysis of AX generates arabinosyl oligosaccharides (AXOS) which also exhibit interesting prebiotic properties. Indeed,
8 weeks of AXOS supplementation in HF- and western (HF/HS) diet-fed mice led to a common signature that was an increase of *Bifidobacterium* spp. (Neyrinck et al. 2012b, Suriano et al. 2017, Olivares et al. 2019). In addition to their impact on the gut microbiota, AXOS can also regulated both body weight gain and fat accumulation (Neyrinck et al. 2012b, Olivares et al. 2019). In a HF model, AXOS increased the plasma levels of satiating hormones GLP-1 and (PYY) (Neyrinck et al. 2012b). Interestingly, in a western diet supplemented with gluten, which worsens the metabolic alterations, AXOS decreased inflammation in white adipose tissue and limited the intramuscular lipids accumulation (Olivares et al. 2019). Furthermore, the supplementation with AXOS allowed a significant reduction of CD36 involved in FA transport in both adipose tissue and skeletal muscle (Olivares et al. 2019).

Barley β-glucan addition in a HF diet also improved the WAT expansion in mice, associated with an increased plasma levels of satiating hormones PYY and GLP-1 (Drew et al. 2018, Miyamoto et al. 2018). Moreover, addition of barley β-glucan in a HF diet reduced the level of plasma insulin (Drew et al. 2018, Miyamoto et al. 2018).

Supplementation with some other DF (bamboo shoot, soluble corn and flaxseed fibers) can also decrease the body weight gain, associated with an improvement of adipose tissues mass (Li et al. 2016, Wang et al. 2018a, Arora et al. 2019).

Finally, similarly to ITF supplementation, barley kernel-based bread (containing a ratio of 13% non-starch polysaccharides/11% resistant starch (Nilsson et al. 2015)) differentially modulate the gut microbiota and metabolic parameters in a cohort of volunteers (Kovatcheva-Datchary et al. 2015). Indeed, after three days of barley kernel-based bread consumption, the authors observed inter-individual variability for the improvement of glucose metabolism. Subjects exhibiting an improvement of glucose and insulin profiles are characterized by an enrichment of fecal *Prevotella copri* after barley kernel-bread supplementation.

Regarding the impact of resistant starch (RS), one study previously reported that increased level of GLP-1...
and PYY by RS is important to mediate the effect of RS on body fat accumulation in mice (Zhou et al. 2015). Indeed, the anti-obesity effects of RS were not found in mice daily injected with a PYY receptor antagonist and in GLP-1-receptor deficient mice. However, this study did not address the impact of RS on the gut microbiota. In another study, Bindels et al. showed that RS feeding improved insulin sensitivity (especially the chemically modified RS type 4) in conventionalized mice, but this improvement also occurred in absence of gut microbiota - in germ-free mice-, supporting a microbiota-independent mechanism to explain the improvement of metabolic disorders by RS (Bindels et al. 2017). Although the macrophages markers were reduced by RS type 2 (granular starches) and type 4 in SAT and VAT (independently of the presence of gut microbiota), the authors did not report any effects of RS on adiposity and plasma GLP-1 or PYY.

Finally, in humans, 84 days of supplementation with different formula enriched in diverse structures of fibers (β-glucan, arabinoxylan, cellulose, resistant starch, gums, oligosaccharides, inulin and resistant dextrin) improved glucose homeostasis by reducing both the fasting blood glucose and glycated hemoglobin HbA1c in type 2 diabetes (T2D) patients, and promoted the growth of SCFA-producing strains (Zhao et al. 2018). In this study, the trend of increased fecal acetate and butyrate concentrations in the treated group coincided with a significantly greater postprandial GLP-1 area under the curve, and a higher level of fasting PYY.

Some polyphenols also respond to the definition of prebiotics (Gibson et al. 2017). Some studies demonstrated the impact of these phenolic compounds on the gut microbiota and their metabolic consequences. Using the same strategy, we summarize recent discovery about the impact of polyphenols on both gut microbiota composition and adipose tissue or skeletal muscle (Table 1). The majority of studies, related to the impact of polyphenols on gut microbiota and metabolic alterations induced by a HF diet, demonstrated beneficial effects of polyphenol on adipose tissues (Qiao et al. 2014, Anhe et al. 2015, Collins et al. 2016, Gao et al. 2018, Liao et al. 2018, Anhe et al. 2019, Jiao et al. 2019, Sheng et al. 2019, Diez-Echave et al. 2020, Wang et al. 2020). However, little is known about the regulations observed in skeletal muscles in these conditions. Regarding the adipose tissues, it seems evident that polyphenols supplementation during a HF diet impact the homeostasis of this organ. Most of the in vivo studies reported an increase of markers (such as Ucp1, Ppargc1a, Ppary, Sirt1, Prdm16 or Cidea) involved in the browning of WAT after polyphenols supplementation during a HF diet (Gao et al. 2018, Liao et al. 2018, Anhe et al. 2019, Zhou et al. 2019, Wang et al. 2020). Some studies also demonstrated the induction by polyphenols of specific markers of BAT activation, including energy expenditure or thermogenesis (Ucp1, Ppary, Cptα, Ppargc1a and β, CEBP/α and β) (Anhe et al. 2019, Sheng et al. 2019). Finally, polyphenols also modulate the lipogenesis or FA oxidation, leading to a decreased mRNA expression of Cpt1, Ppary and Fasn in WAT (Qiao et al. 2014, Collins et al. 2016, Jiao et al. 2019, Wang et al. 2020). In addition, they exert anti-inflammatory properties in WAT and in skeletal muscles of HF-fed mice (Dao et al. 2011, Neyrinck et al. 2013, Collins et al. 2016, Gao et al. 2018). Interestingly, since a great improvement in both glucose and lipid metabolism by polyphenols are observed in these different studies, those effects are not necessarily linked to a change in adiposity (Neyrinck et al. 2013, Van Hul et al. 2018, Jiao et al. 2019). The signature of polyphenols on the gut microbiota appears complex due to the large diversity of this class of compounds. However, a regulation of some bacteria associated with beneficial outcomes (and known to be increased with other kind of prebiotics) was also observed in some polyphenols studies, such as Bifidobacterium spp., Roseburia spp. or Akkermansia (Neyrinck et al. 2013, Qiao et al. 2014, Anhe et al. 2015, Gao et al. 2018, Van Hul et al. 2018, Anhe et al. 2019, Jiao et al. 2019, Sheng et al. 2019).

**Bacterial metabolites linking prebiotic intake and metabolic feature in gut hormones, fat and muscle tissues**

Prebiotics alter the composition of the gut microbiota, and thereby, or through their fermentation, can modulate the profile of the microbial metabolites prone to exert metabolic effects in the gut, or at distance in peripheral organs. Microbial SCFA production is essential for gut integrity but also for the modulation of host metabolic health through a range of tissue-specific mechanisms related to appetite regulation, energy expenditure, glucose homeostasis and immunomodulation (Blaak et al. 2020). Some studies support a beneficial role for some SCFA in the adipose tissue, the skeletal muscle, as well as in the liver, that can contribute to improved insulin sensitivity (for review Canfora et al. 2015, Blaak et al. 2020).

However, all SCFA exhibit different effects and while butyrate, acetate seem to be associated with beneficial impact on metabolism, the microbial-derived succinate could contribute to the progression of
insulin resistance. Propionate and butyrate can activate intestinal gluconeogenesis and released glucose initiates a neural signal leading to satiety and metabolic benefits including insulin sensitivity (Blaak et al. 2020). SCFA can be also important regulators of pancreatic insulin secretion and β-cell functioning, such as demonstrated with propionate (Blaak et al. 2020).

As already mentioned, SCFA are mainly produced from the carbohydrate and DF fermentation and are ligands of G-protein coupled receptors (GPR41 and GPR43). By binding these receptors, SCFA can regulate glucose homeostasis through the control of satiety hormones production (PYY, GLP-1) and adiposity through peroxisome proliferator-activated receptor γ (PPARγ)-dependent mechanisms (Dewulf et al. 2011, Canfora et al. 2015).

Six months of acetate injections in obese rats improved the expression of myoglobin, glucose transporter 4 (Glut4) and activated AMPK protein by increasing the AMP/ATP ratio in abdominal muscles (Yamashita et al. 2009). In addition, acetate induced smaller lipids droplets in both SAT and BAT from obese rats. Surprisingly, SCFA-mediated activation of GPR43 seemed to suppress insulin signaling only in adipocytes, leading to an inhibition of fat accumulation, but not in the liver and skeletal muscles, (Kimura et al. 2013). Butyrate also had a beneficial impact on insulin sensitivity and adiposity in HF-fed mice, which coincided with an increased FA oxidation in skeletal muscles and increased thermogenesis in BAT (Gao et al. 2009). Acetate and propionate also prevented diet-induced metabolic alterations (body weight gain, adiposity, hepatic steatosis, insulin resistance) in mice, acetate being the sole to enhance markers of ‘beiging’ in WAT and increased body temperature reflecting oxidation processes (Weitkunat et al. 2017). A recent study also highlighted that SCFA mixture can control both muscle mass and strength (Lahiri et al. 2019). Indeed, compared to untreated GF mice, the addition of SCFA mixture in the drinking water of treated GF mice increased gastrocnemius weight, hindlimb grip strength and the mRNA expression of MyoD in tibialis, a marker involved in myogenesis (Lahiri et al. 2019).

In addition to the SCFA, the chronic administration of 4-cresol, a metabolite produced from amino-acid fermentation, in HF-fed mice reduced body weight gain, adiposity, glucose intolerance and liver fat content (Brial et al. 2020). This was associated with an improvement of insulin secretion and a stimulation of pancreatic β-cell function. Other secondary metabolites can be produced by the gut microbiota from polyphenols and regulates metabolic processes in adipose tissues or skeletal muscles. Indeed, urolithin A produced by the gut microbiota from ellagic acid, can prevent HF-induced and genetic obesity in mice, as well as dysfunctional glucose homeostasis and this was associated with enhanced BAT thermogenesis and white fat browning (Xia et al. 2020). Moreover, independently of metabolic alterations, urolithin A can promote the skeletal muscle mitochondrial function in preclinical models of aging and elderly individuals (Ryu et al. 2016, Andreux et al. 2019). In addition, the isoform urolithin B can also impact skeletal muscle health by regulating insulin signaling and promote protein synthesis (Rodriguez et al. 2017).

Bile acids (BA) are endogenous steroid molecules derived from cholesterol, produced in hepatocytes and then converted through deconjugation and reduction, into secondary BA by gut microbiota. BA can regulate host metabolism through Takeda G-protein receptor 5 (TGR5) and Farnesoid X receptor (FXR), both expressed in various tissues (for review Chavez-Talavera et al. 2017, Molinaro et al. 2018). Indeed, activation of FXR by BA decreases hepatic lipogenesis and hepatic inflammation, increases adipocytes differentiation and function in WAT, and enhances insulin secretion by pancreas. On the other hand, TGR5 stimulation enhances the intestinal production and secretion of GLP1, the insulin secretion by pancreas, and increases the energy expenditure and activation of BAT. Both receptor are able to modulate the intestinal GLP-1 secretion, but in an opposite way.

Of note, not all bacterial metabolites derived from foods are associated with beneficial effects on metabolism. For instance, imidazole propionate produced from histidine can directly impair glucose tolerance and insulin signaling (Koh et al. 2018). This metabolite is increased during type 2 diabetes and inhibits insulin receptor substrate 1 and/or 2 in tissues with a high metabolic activity such as liver, WAT or soleus muscle. Furthermore, the bacterial metabolite trimethylamine (produced by gut microbiota mainly from red meat) can be metabolized by the host hepatic enzyme flavin-containing monooxygenase 3 (FMO3) to produce trimethylamine-N-oxide (TMAO), a product exhibiting deleterious effects on host metabolism such as atherosclerosis (Koeth et al. 2013). Interestingly, genetic deletion of FMO3 enzyme conferred protection against obesity in mice, through the stimulation of WAT beiging, meaning that decreased TMAO induced a metabolically active beige adipose tissue (Schugart et al. 2017).

Taken together, these data strongly support the hypothesis that some gut-related metabolites from the diet could link the gut microbiota with molecular events.
occurring in circulation and peripheral tissues for the maintenance of energy homeostasis.

**Conclusion and future prospects**

In the present review, we have discussed about the importance to modulate the gut microbiota composition in order to control the energy homeostasis in adipose tissues vs skeletal muscle. It is surprising to note that few studies have investigated the response of skeletal muscles after dietary intervention using prebiotics. However, an important factor to take into consideration beside the nutrition is, obviously, the physical activity status. An elegant recent study highlighted that the gut microbiota fermentation determines the efficacy of exercise in the control of glucose metabolism in prediabetic individuals (Liu et al. 2020). By demonstrating the variability of glycemic response to exercise, the authors showed that the high-responders for amelioration of insulin resistance were characterized by a higher carbohydrate fermentation (increased SCFA production) and amino acid catabolism (decreased BCAA availability). Interestingly, fecal microbial transplantation from responders in obese mice reproduced the beneficial effects of exercise on insulin resistance.

Whether the fermentation ability of the gut microbiota can influence the metabolic response to exercise, thus we hypothesize that the diet can also modulate the efficacy of exercise. Indeed, promoting fermentable foods can be a good strategy to increase the substrate for fermentation and improve the beneficial effects of exercise on energy metabolism.

Finally, the therapeutic perspectives issued from the better knowledge of gut -muscle-adipose tissue dialogue are not restricted to the problem of overweight and related diseases. Due to their beneficial impact on several host molecular process, the use of prebiotic cannot be limited to the metabolic alterations, but also envisioned in different (physio-)pathological situations such as cancer cachexia (for review Potgens et al. 2018). Indeed, pectin derived oligosaccharides (POS) and inulin have been evaluated in leukemic mouse model of cachexia (Bindels et al. 2015). Very nicely, whereas inulin was more efficient to decrease hepatic cancer cell invasion, POS supplementation improves metabolic phenotype (to a higher extent than inulin), and reduced fat mass loss. On a mechanistic point, POS reversed the induction by cachexia of both Cpt1a and Ppargc1a mRNA in SAT, two markers controlling FA oxidation. Interestingly, during cachexia, POS enhanced (better than inulin) the growth of _Bifidobacterium_ spp., _Roseburia_ spp. and _Bacteroides/Prevotella_ spp. In addition, combining both prebiotic with probiotic could also be a promising therapy in this context. Indeed, a symbiotic containing inulin-type fructans and live _Lactobacillus reuteri_ administered to leukemic mice reduced cachexia, and more specifically the loss of skeletal muscle mass (Bindels et al. 2016). This was linked to a reduction of both _cathepsin L_ and _LC3_ mRNA in muscles, two markers involved in the protein degradation in skeletal muscles. These studies based on prebiotics and performed in another context reinforces the hypothesis that metabolic regulations occur between different organs rely from the gut microbiota modifications.

To conclude, future studies should be addressed in order to investigate, among other approaches, the interest of the different tools able to modulate the gut microbiota (FMT, prebiotics, probiotics, symbiotics) to face problems of malnutrition (covering both overeating and undernutrition) worldwide. The fact that prebiotics and dietary fibers may improve concomitantly the endocrine function, and energy metabolism in most organs (liver, muscle adipose tissues….), support their interest as drivers of systems biology in the context of a healthy diet.

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this review.

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