

Review

Current Research on the Effects of Non-Digestible Carbohydrates on Metabolic Disease

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Abstract: Metabolic diseases (MDs), including cardiovascular diseases (CVDs) and diabetes, occur when the body's normal metabolic processes are disrupted. Behavioral risk factors such as obesity, physical inactivity, and dietary habits are strongly associated with a higher risk of MD. However, scientific evidence strongly suggests that balanced, healthy diets containing non-digestible carbohydrates (NDCs), such as dietary fiber and resistant starch, can reduce the risk of developing MD. In particular, major properties of NDCs, such as water retention, fecal bulking, viscosity, and fermentation in the gut, have been found to be important for reducing the risk of MD by decreasing blood glucose and lipid levels, increasing satiety and insulin sensitivity, and modifying the gut microbiome. Short chain fatty acids produced during the fermentation of NDCs in the gut are mainly responsible for improvement in MD. However, the effects of NDCs are dependent on the type, source, dose, and duration of NDC intake, and some of the mechanisms underlying the efficacy of NDCs on MD remain unclear. In this review, we briefly summarize current studies on the effects of NDCs on MD and discuss potential mechanisms that might contribute to further understanding these effects.

Keywords: cardiovascular diseases; diabetes; dietary fiber; non-digestible carbohydrates; metabolic disease; short chain fatty acid



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1. Introduction

Metabolic disorders occur when the normal processes of macronutrients, such as proteins, carbohydrates, and lipids, in the human body are disrupted by various factors resulting in dysfunctions, including atherogenic dyslipidemia, insulin resistance, hypertension, and obesity [1]. Individuals with these dysfunctions are at high risk for developing metabolic diseases (MD), such as cardiovascular diseases (CVD) and diabetes [2], both of which are the most common cause of death globally [3]. The most important behavioral risk factors of MD are obesity, physical inactivity, and dietary habits [1]. In particular, several clinical trials and epidemiological studies suggest that dietary patterns characterized by high consumption of sugars, fat, and salt and low consumption of polyunsaturated fatty acids, vegetables, fruit, and fiber are strongly associated with a higher risk of MD [4]. Studies over the past decade using multiple genetic and diet-induced animal models have shown that insulin and leptin signaling cascades and the brain and its central nervous system are strongly involved in key metabolic signaling pathways of MD [5–9]. However, some of the mechanisms underlying the pathogenesis of MD are still unclear [10] and the use of drug therapies developed for the treatment of MD are also limited due to various side effects [11]. Therefore, physical activity, weight control, and diet control are very important to suppress the development of MD [12–14]. In particular, scientific evidence accumulated over the last few decades strongly suggests that balanced healthy diets rich in fruits, vegetables, legumes, whole grains, fish, nuts, and low-fat dairy products can decrease the risk of MD [15,16]. Consumption of certain plants, seaweeds, and fermented food-derived

compounds is known to have excellent health effects in preventing and suppressing the development of MD [17,18]. Among these compounds, non-digestible carbohydrates (NDCs), mainly represented by resistant starch and dietary fiber, have received considerable attention as one of the most important components of MD development because of their numerous physiological advantages [19]. Many clinical and animal studies revealed that high intake of NDCs increased intestinal viscosity, fecal bulking, and production of short chain fatty acids (SCFAs) via gut fermentation, resulting in improving blood glucose, lipid, and insulin levels, reducing energy intake, and promoting satiety [19]. It was released that these physiological changes due to the high intake of NDCs were strongly correlated with suppression of the incidence of MD. Moreover, many meta-analysis results have confirmed the correlation between intake of NDCs and MD incidence [20]. However, their correlation was different according to the type, source, dose, and duration of NDC intake [21] and some of the mechanisms underlying the efficacy of NDCs on MD remain unclear.

Therefore, the aim of this review is to discuss how NDCs regulate the incidence of MD, including obesity, diabetes, and CVD, by focusing on mechanisms by which the physical and fermentation properties of NDCs in the gastrointestinal (GI) system interfere with the absorption of MD risk-associated metabolites, increase satiety, and improve gut health.

2. NDCs

NDCs are complex carbohydrates that resist hydrolysis by salivary and intestinal digestive enzymes in the small intestine of humans owing to the configuration of their osmotic bonds. NDCs, which are a heterogeneous group of carbohydrates with varying chemical structures, consist primarily of carbohydrate polymers, such as resistant starch [22] and non-starch polysaccharides that are components of plant cell walls, including cellulose, psyllium fiber, β -glucan, hemicellulose, and pectin, as well as other polysaccharides and oligosaccharides, such as gums, alginate, and inulin [23,24]. As shown in Table 1, these NDCs are generally separated into water-soluble and insoluble NDCs [23,25,26]. Soluble NDCs, including pectin, psyllium fiber, β -glucan, fructans, fructooligosaccharide (FOS), galactooligosaccharide (GOS), gums, and hydrocolloids, are generally separated from oats, fruits, vegetables, barley, seaweeds, or pulses [23,27,28], while insoluble NDCs, including cellulose and some hemicellulose, are separated from whole grains, cereal brans, fruits, and vegetables [29]. The solubility of NDCs is determined according to the length, type, location, and binding type of monosaccharide units, which are generally joined by β -glycosidic bonds [25], and is an important factor for determining their physical properties, such as water retention, viscosity, and fecal bulking ability, as well as their fermentation properties in the large intestine [25,26]. Many clinical and animal studies have suggested that these properties are strongly associated with the health benefits of NDCs [21,23,24].

Table 1. Types of NDCs and their properties.

Type	Structure	Source	Properties	References
<i>Soluble dietary fiber</i>				
Guar Gum	A linear chain of β 1,4-linked mannose residues to which galactose residues are 1,6-linked at every second mannose	Seeds of the drought tolerant plant	Gel-forming, thickening, and stabilization.	[27]
Locust Bean Gum	Galactomannan composed of galactose and mannose units combined through glycosidic linkages	Seeds of the carob tree	Film-forming.	[21]
Pectin	Chain of α -(1 \rightarrow 4)-linked D-galacturonic acid units interrupted by the insertion of (1 \rightarrow 2)-linked L-rhamnopyranosyl residues in adjacent or alternate positions	Cell walls and intracellular tissues of fruits and vegetables	Emulsifier, gelling agent, thickener, stabilizer, and fat or sugar replacer in low-calorie foods	[23]
Hydroxypropylmethylcellulose (HPMC)	Propylene glycol ether of methylcellulose		Film forming, stabilizing, and thickening.	[21]
β-Glucan	Mixed-linkage polysaccharide (1 \rightarrow 3), (1 \rightarrow 4) β -D-glucan	Cell walls of oats, barley, rye and wheat	Altering foods structure, texture, and viscosity	[23]
Psyllium husk	Arabinoxylan with (1 \rightarrow 4) and (1 \rightarrow 3) xylopyranose backbones	Seeds of <i>Plantago ovata</i>	Gel-forming, produce low-calorie, and high fiber foods	[28]
Arabinoxylan	Diversely composed (1 \rightarrow 4)- β -D-xylan polymer	Wheat	Film-forming, balance of carbohydrate-rich foods, improve the viscosity, texture, sensory characteristics, and shelf-life of food products	[24]
Alginate	Linear unbranched polysaccharides which contain different amounts of (1 \rightarrow 4')-linked β -D-mannuronic acid and α -L-guluronic acid residues	Brown seaweeds	Gelling, viscosifying, and stabilizing	[21]
Inulin and inulin-type fructans	A mixture of linear fructose polymers with different chain length and a glucose molecule at each C2 end	Chicory roots	Bulking agent in foods, improve the texture, mouthfeel, taste, and replace sugar or fat.	[21]
High amylose starch (resistant starch II)	D-Glucose units linked by R-1,4/R-1,6 glucosidic bonds	Raw starch (green banana and raw potatoes)	Increase of food's functional properties does not change its sensory characteristics.	[22]
Galactooligosaccharide (GOS)	β -Linked galactose moieties with galactose or glucose at the reducing end.	Soybeans and lactose from cow's milk	Improve the texture of foods and as a bulking agent.	[30]
Polydextrose	A polysaccharide composed of randomly cross-linked glucose units with all types of glycosidic bonding	Produced from the naturally occurring components: glucose, sorbitol, and citric acid	Bulking agent, stabilizer, thickener, and humectant	[21]

Table 1. Cont.

Type	Structure	Source	Properties	References
Resistant maltodextrin/dextrin (resistant starch V)	Oligosaccharides of glucose molecules that are joined by digestible linkages and non-digestible α -1,2 and α -1,3 linkages	Corn, wheat, potato, and tapioca	Increase the nutritional value of food	[31]
<i>Insoluble dietary fiber</i>				
Cellulose	Linear homopolymer of β -(1 \rightarrow 4) linked β -D-glucose residues	Cell wall of plant (vegetables, fruits, and cereals)	Increase the content of fiber in food, thickening, gelling, and stabilizing	[29]
<i>Soluble/Insoluble dietary fiber</i>				
Mixed plant cell wall fibers	Cellulose, hemicelluloses, and pectin	Fruits, vegetables, grains, legumes, pulses, nuts, and other plants	Increase the viscosity or gel strength	[21]
<i>Non-dietary fiber NDCs</i>				
Resistant starch I	Physically embedded starch	Seeds or legumes and unprocessed whole grains	Ingredients for creating fibre-rich food, increase swelling, viscosity, and gel-forming capacity	[22]
Resistant starch III	Regenerated starch	Starch-containing foods are cooked and cooled (corn starches, pasta, stale bread)	Improves texture, strength, and crispness in baked goods and extruded products such as cereals and snack foods	[22]
Resistant starch IV	Chemically modified starch	Chemically modified starches food (breads and cakes)	Improve taste and texture, increase swelling, viscosity, and gel-forming capacity	[22]

3. NDC Characteristics Related to Health Benefits

The main characteristics of NDCs related to health benefits in the human body are water retention, fecal bulking, viscosity, and fermentation, and these characteristics mainly differ according to their water solubility, as mentioned above. Soluble NDCs are generally viscous and can ferment quickly in the intestine, whereas insoluble NDCs are non-viscous and slowly fermentable. A high intake of soluble NDCs with high viscosity-forming properties reduces postprandial blood glucose and blood cholesterol levels because high viscosity can interfere with the absorption of cholesterol and monosaccharides in the intestine [32]. Moreover, some in vitro studies have suggested that soluble NDCs could decrease gastric and pancreatic lipase activities because of the reduction of lipid emulsion caused by the high viscosity of these soluble NDCs, resulting in a decrease in lipid absorption, small bowel motility, and intestinal miscibility and an increase in the thickness of the unsettled water layer, which might delay the final stage of lipid assimilation [32]. In addition to soluble NDCs, a high intake of insoluble NDCs provides a fecal bulking effect linked to various intestinal functions, including promoting regular bowel movement and increasing fecal volume [33]. Although differences in the effects of soluble and insoluble NDCs on gut microbiota are not clear, these properties are strongly related to changes in the gut microbiota population [34]. The many functions of gut microbiota include contributing to changing the bile acid pool in the gut, especially secondary bile acids, such as deoxycholic acid and lithocholic acid, which are associated with a number of physiological functions, including inflammation, CVDs, the immune system, and colon cancer [35]. Moreover, during fermentation, the population of healthy gut microbiota increases, and by-products such as SCFAs, including acetate, butyrate, and propionate, are produced [36]. SCFAs play important physiological roles associated with various health benefits [37] throughout the body as well as in the large intestine, including reducing the risk of coronary heart disease, diabetes, CVD, and some cancers, and improving the immune system [35,38]. Accumulating evidence suggests that the population and diversity of gut microbiota associated with the production of secondary bile acids and/or SCFAs significantly change according to the type, source, dose, and duration of NDC intake [37,39]. A piglet model study showed that insoluble fibers such as cellulose and soluble fibers such as inulin increased the relative abundance of *Bacteroidetes*, *Phascolarctobacterium*, and *Coprococcus*, and *Actinobacteria*, *Proteobacteria*, and *Blautia*, respectively, which are the main bacteria that produce SCFAs [40].

4. NDCs and SCFAs

During the last few decades, scientific evidence of the health benefits of NDC consumption has accumulated. In particular, the relationship between gut health and NDCs is well-demonstrated. The mechanisms by which NDCs modulate host health through the gut microbiota are summarized in Figure 1. NDCs are fermented by the gut microbiota and SCFAs; primarily, acetic acid, butyric acid, and propionic acid associated with various physiological functions in the human body [41] are produced during fermentation. SCFAs produced from NDCs stimulate the secretion of satiety hormones, glucagon-like peptide (GLP-1) and peptide tyrosine tyrosine (PYY) [42], through the activation of G protein-coupled receptors (GPRs), GPR41 and GPR43, of the enteroendocrine L-cells in the intestine, especially in the ileum and colon [41]. Both hormones influence the hypothalamus to promote satiety. PYY acts on the arcuate nucleus in the hypothalamus, leading to the suppression of neuropeptide Y neurons to promote satiety, activate proopiomelanocortin neurons, reduce intestinal transit time from the mouth to the cecum, and decrease the gastric emptying rate [5,43]. Moreover, GLP-1 stimulates the hypothalamus by binding to the GLP-1 receptor, improving insulin sensitivity, and promoting glucose tolerance by acting on pancreatic β -cells [6,7]. Furthermore, SCFAs can be converted into glucose via intestinal gluconeogenesis (IGN), which activates adipocytes to produce leptin, thereby improving satiety and preventing obesity [8]. Additionally, an increase in IGN by SCFAs

inhibits hepatic gluconeogenesis, resulting in increased glucose tolerance. For example, butyrate activates IGN gene expression through a cAMP-dependent mechanism, whereas propionate, an IGN substrate, stimulates IGN via a gut-brain neural circuit [44]. Along with the direct effects of SCFAs, SCFAs shift the intestinal environment by decreasing pH, preventing overgrowth of pH-sensitive pathogenic bacteria [45,46] and protease activity associated with the production of harmful metabolites, such as ammonia, a potentially carcinogenic product of protein fermentation [47,48]. Moreover, SCFAs are involved in the intestinal defense system against pathogens and toxic compounds [49]. The primary physical intestinal barriers that protect the gut from pathogen infection or toxic compounds are mucin secreted from goblet cells and tight junctions (TJs) between mucosal epithelial cells [9]. SCFAs improve gut barrier function by modulating the expression of mucin and TJ proteins [50]. SCFA signaling through GPRs stimulates L-cells to secrete GLP-2, leading to an increase in expression of TJ proteins, including zonula occludens-1 (ZO-1) and Claudin-3, consequently reducing LPS translocation, inhibiting endotoxemia-induced inflammation, and improving gut permeability [51]. Similarly, SCFAs increase goblet cell mucin secretion, resulting in a reduction in LPS translocation through the epithelium. SCFAs also exert immunomodulatory effects by regulating antimicrobial peptide (AMP) synthesis, Treg expansion, and myeloid cell function, leading to reduced inflammation. Consequently, the overall effect of NDC-induced SCFA production was associated with improvement in MD, including obesity, T2D, and CVD [39].

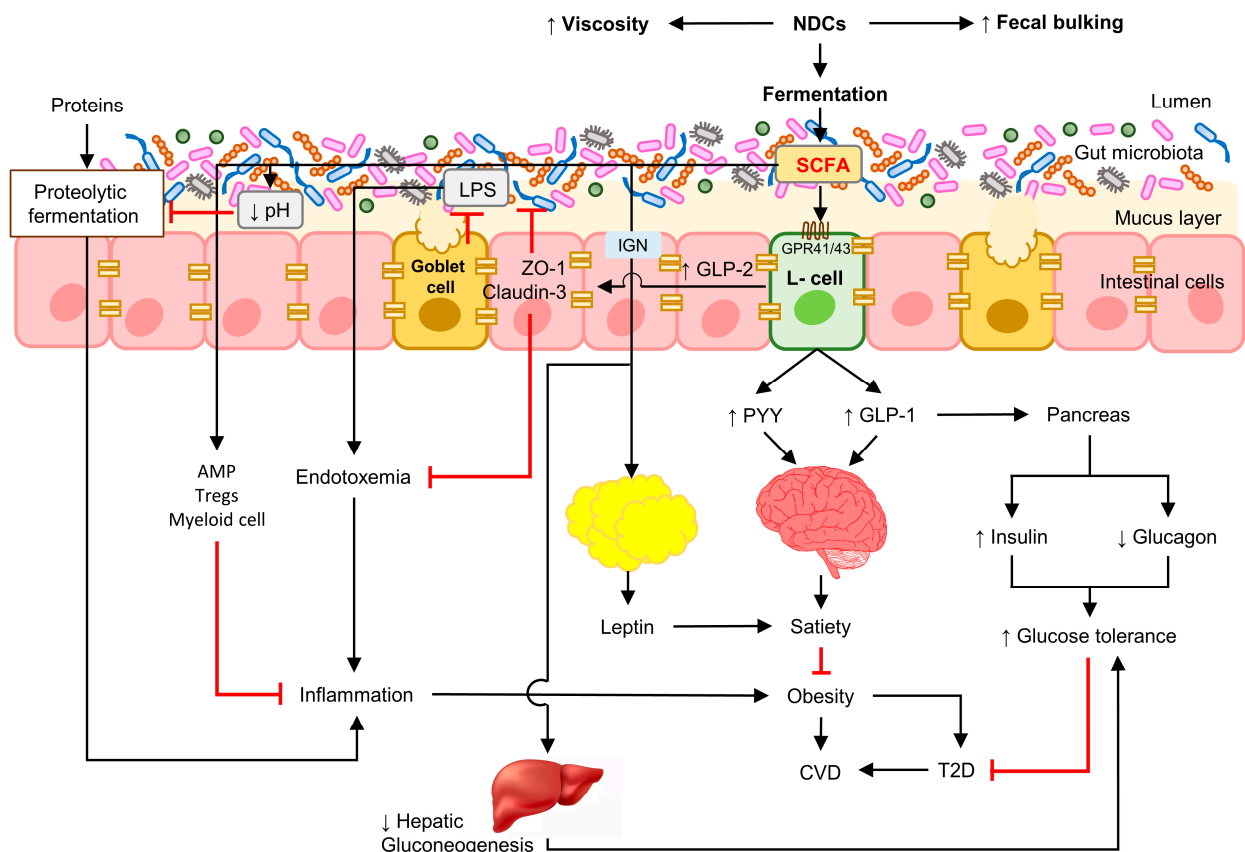


Figure 1. Effect of non-digestible carbohydrates (NDCs) on metabolic diseases (MD) through short-chain fatty acids (SCFA) produced by gut fermentation. AMP, antimicrobial peptides; CVD, cardiovascular disease; GLP, glucagon-like peptide; IGN, intestinal gluconeogenesis; LPS, lipopolysaccharides; PYY, peptide tyrosine tyrosine; SCFAs, short-chain fatty acids; T2D, type 2 diabetes; Tregs, regulatory T-cells; Zo-1, Zonula occludens.

5. NDCs and MDs

5.1. Obesity

Obesity, defined as a state of excess adiposity, is one of the most important risk factors for MD [52]. Obesity is related to the balance between energy intake and expenditure; thus, reducing energy intake and increasing energy expenditure are ways to control obesity. Energy intake is particularly associated with eating habits. Among various foods, a high intake of NDCs has a strong correlation with a reduction in obesity [53].

Intake of NDCs interferes with the absorption of energy sources, including glucose and lipids, and with the accessibility of digestion enzymes to substrates in the intestine because of the viscous and fecal bulking properties of NDCs, although SCFAs produced from NDCs by gut microbiota are used as an energy source. Additionally, both properties can increase the gastric emptying time, resulting in an increase in satiety [54]. SCFAs can also stimulate satiety through the activation of satiety hormones, such as PYY and GLP-1, and energy-balancing hormones, such as leptin [55]. Consequently, energy intake can be reduced by the intake of NDCs, whereas the breakdown of stored energy sources, such as fat in the body, can be increased through energy production metabolism, including β -oxidation and the citric acid cycle, resulting in a reduction in obesity [56]. Therefore, intake of NDCs can reduce obesity and related disorders.

The anti-obesity effects of pectin, β -glucan, psyllium, FOS, GOS, and non-fiber NDCs have been investigated (Table 2). Animal studies showed that fruit pectin intake showed anti-obesity effects by regulating the circulation of energy balancing hormones such as adiponectin, leptin, and ghrelin [57–59]. In particular, high-esterified pectin, a major component of soluble dietary fiber present in vegetables and fruits, was more effective in suppressing obesity than low-esterified pectin [60]. Intake of 2% barley β -glucan for 12 weeks or 10% FOS for 6 weeks also reduced body weight gain and fat mass in HFD-induced obese mice and increased secretion of gut hormones, PYY and GLP-1 in the plasma [61]. Moreover, mice fed with non-fiber soluble NDCs, such as malto-oligosaccharides (MOS 6 g/kg for 11 weeks), chitin oligosaccharides (COS 200 mg/kg for 21 weeks), and bovine-milk oligosaccharides (BMO, 6% BMO diet for 6 weeks) showed a reduction in BW, improved lipid profile, and increased glucose tolerance [62–64]. However, some studies have shown that the anti-obesity effect of NDCs differs according to their type and source. Mice fed with 10% (*w/w*) insoluble cereal fiber for 45 weeks had lower weight gain and improved insulin sensitivity compared with those fed with soluble guar fiber [65]. In a human study, the anti-obesity effects of pectin were also reported [66] as similar to the results of animal studies [57–59]. Psyllium husk has also been shown to have anti-obesity effects in obese humans [67], but there was no significant difference in almost all anthropometric measures in NAFLD patients consuming psyllium husk at 10 g/day for 12 weeks, except for the reduction in body weight and BMI [68]. FOS and GOS showed decreased hunger, desire to eat, energy intake, body weight, waist circumference, waist-to-height index, sagittal abdominal diameter, body fat, and serum TG levels in obese adults and children [69–72]. To further explain the differences in the impact of NDCs on obesity according to the type and source of NDCs, other mechanisms, such as population and diversity of gut microbiota and their metabolites, including secondary bile acids, except for SCFAs, may be needed because many studies suggest that gut microbiota and secondary bile acids affected by high intake of NDCs are strongly related to obesity [39].

5.2. CVD

Many clinical trials have found that a high intake of NDCs reduces the risk of CVD [20,73,74], which is the most common cause of mortality worldwide [4]. According to a systematic review and meta-analysis of 22 cohort studies, the association between CVD risk and NDC intake was dose-dependent (risk ratio 0.91 per 7 g/day). Moreover, Marc et al. (2017) reviewed 31 meta-analyses and confirmed that NDC intake significantly reduced the relative risk (RR) of CVD mortality (RR = 0.77–0.83), the incidence of CVD (RR = 0.72–0.91), coronary heart disease (RR = 0.76–0.93), and stroke (RR = 0.83–0.93), which is

particularly noticeable with water-soluble, gel-forming NDCs, such as β -glucan and psyllium [20]. In particular, NDCs such as β -glucan and FOS have been shown to lower blood cholesterol because their viscous properties interfere with the absorption of cholesterol and bile acids in the intestine and reduce lipase activity [75]. Decreased reabsorption of bile acid leads to increased hepatic conversion of cholesterol into bile acid; as a result, more cholesterol stored in the body is used to produce bile acid [76]. NDCs also enhance digestive regularity by promoting rapid gastric emptying, decreasing intestinal transit time, and increasing fecal bulk [75]. Moreover, SCFAs suppress endotoxemia-induced inflammation by increasing tight junction gene expression, which reduces LPS translocation [77,78].

Rats fed a 32% FOS diet for 12 weeks showed significantly increased hypertrophy of cardiomyocytes through subcellular changes in cardiac metabolism and contractility, which could affect myocardial function and alter the risk of CVD [79]. In humans, intake of barley or oat β -glucan at 3–5 g/day for 3–5 weeks improves blood lipid profile and reduces CVD risk factors such as body mass index, waist circumference, blood pressure, LDL, and triglyceride levels [80–82]. Moreover, patients with non-diabetic CVD who consumed 12 g/day of FOS for 3 months had lower circulating levels of IL-6, a pro-inflammatory cytokine, and preserved endothelial function [83]. Non-dietary fiber NDCs, such as some types of resistant starch (RS), such as RS IV, have also been reported to have a preventive effect on CVD. Participants with several MD comorbidities who consumed a diet containing 30% RS4 for 4 weeks [84] and elderly patients with type 2 diabetes with a diet containing 53.7% fructose-free RS IV for 6 weeks [85] had improved dyslipidemia and cardiovascular risk biomarkers, including monocyte chemotactic protein-1 and soluble E-selectin.

However, not all trials provide similar results. A cohort study of 31,036 women from the UK for 14.3 years reported that increased total NDC intake may not provide cardiovascular benefit in terms of mortality, but it may help to reduce the risk of fatal stroke in those without CVD risk factors such as hypertension and angina. A systematic review of 23 randomized controlled trials with 1513 participants also showed that there is no evidence of the effects of NDCs on CVD clinical events because the majority of studies were short-term, had a risk of bias, and insufficient information [86]. In addition, young healthy adults with an intake of extracted oat and barley β -glucans of 3.3 g/day for 3 weeks had no effect on cholesterol metabolism [87]. These results showed that the effects of NDC intake on the reduction of CVD risk are dependent on the type and source of fiber, doses, health condition, and sex of the participant, as well as the size and duration of the trial. To further understand the relationship between intake of NDCs and the reduction of CVD risk, studies focusing on the effect of NDCs on gut health and the biological networking of NDCS-related gut metabolites and other tissues are needed, although some studies have shown that gut microbiota profiles are affected by NDCs, and the metabolites they produce differ according to NDC type [39].

5.3. Diabetes

The relationship between NDC intake and type 2 diabetes mellitus (T2DM) has been clinically investigated for decades. Many recent meta-analyses and clinical studies have shown that a high intake of NDCs, especially dietary fiber, for >1 month lowered the risk of developing T2DM and might have therapeutic effects in patients with T2DM [88,89], although some studies have shown no significant effects of dietary fiber on T2DM [90]. Randomized studies of 15 studies from 1980 to 2010 suggested that an increasing dietary fiber diet reduced fasting blood glucose and glycosylated hemoglobin (HbA1C) levels in patients with T2DM [91,92]. Similar results were reported in a meta-analysis of 28 randomized controlled trials ($n = 1394$) on T2DM patients with a viscous fiber diet at a median dose of approximately 13.1 g/day [93]. However, the effect of NDCs on the risk reduction of T2DM depends on the type and intake of NDCs.

In particular, soluble fibers with viscous and/or gel-forming properties, such as psyllium, β -glucan, and pectin, have been associated with lower postprandial glucose and blood cholesterol levels because the increased viscosity of intestinal contents by soluble

fiber can delay gastric emptying, reduce the accessibility of digested enzymes, including amylase and lipase, and slow the intestinal absorption of nutrients, such as monosaccharides and cholesterol [94]. Delayed gastric emptying in the stomach can enhance satiety and consequently lower energy intake, resulting in an increase in fat oxidation, eventually leading to a decrease in body weight [95]. In this mechanism, various hormonal responses associated with satiety and insulin sensitivity, which are relevant factors contributing to diabetes, can be affected by viscous soluble fibers. Moreover, soluble fibers can be easily fermented in the gut, resulting in the production of various metabolites, especially SCFAs, and changes in the gut microbiome [39,96]. SCFAs can be absorbed via GPR41/43 metabolism in the gut and used as an energy source [41]. Absorbed SCFAs can increase satiety, decrease fat accumulation, and increase glucose tolerance via modification of lipid metabolism and insulin sensitivity, and consequently, can decrease the risk of T2DM [6,95]. In addition to the high production of SCFAs, the population of the healthy gut microbiome can be increased by the intake of soluble fibers, which can improve inflammation and the immune system associated with many diseases, including T2DM [39].

Unlike soluble fibers, insoluble fibers with non-viscous properties are mostly poorly fermented in the gut and thus produce fewer SCFAs than soluble fibers [92]. However, accumulated insoluble fibers in the gut decrease gut transit time and increase fecal bulk because of their water-holding and swelling capacities [96]. Decreased gut transit time and increased fecal bulk due to insoluble fibers interfere with the absorption of glucose and cholesterol, resulting in the reduction of blood glucose and cholesterol levels [94,97]. Moreover, similar to soluble fibers, insoluble fibers can modify the population of the gut microbiome, reduce inflammation, increase insulin sensitivity, and consequently, reduce the risk of T2DM [94,97]. However, the difference between the effects of soluble and insoluble fibers on T2DM is not clear, and the mechanism is currently unclear, although there is an accumulation of scientific evidence on soluble fibers.

Many studies have suggested that soluble NDCs are more effective in reducing the risk of T2DM than insoluble NDCs, but recent studies have shown contrasting results. Prospective cohort studies have shown that a high dietary fiber diet (>25 g/day in women and >38 g/day in men) reduces the risk of developing T2DM by 20–30%. In particular, a high intake of whole grains and insoluble cereal fibers improved diabetes risk, but soluble fiber did not [98]. Other cohort studies have shown that cereal fiber intake has a strong inverse association with the risk of T2DM (relative risk (RR) = 0.75; 95% confidence interval (CI) 0.65–0.86), whereas only a very weak association was observed for fruit soluble/viscous fiber (RR = 0.95; 95% CI 0.87–1.03) unlike other soluble fibers, such as psyllium and β -glucans, although many studies clearly indicated that soluble fibers, including fruit fiber, reduce glycemic response [94,99].

In addition to the type of NDC, the amount and feed period of NDC intake are also associated with a reduction in the risk of developing T2DM. A randomized, crossover study of 13 patients with T2DM showed that the intake of a high-fiber diet (50 g/day; 25 g of soluble fiber and 25 g of insoluble fiber) for 6 weeks lowered plasma glucose, insulin, and cholesterol levels by 6–12%, compared with the diet recommended by the American Diabetes Association (24 g/day; 8 g of soluble fiber and 16 g of insoluble fiber) [100]. Cereal fibers, especially β -glucans in oats, barley, psyllium and rye, have been shown to lower glycemia in healthy people, but only when the daily dose of β -glucans is at least 4 g [94]. A soluble fiber diet of 10 g and 20 g/day for one month reduced the risk of developing T2DM and may have therapeutic effects, as per a study conducted on 117 patients with T2DM aged between 40 and 70 years. In particular, soluble fibers such as pectin, GOS, HPMC, and hemicellulose were also shown to improve T2D [101–106] Fasting blood glucose, insulin resistance, TG, and connected (C)-peptide levels in patients with T2DM were lowered by the soluble dietary fiber diet for the short-term intervention period. However, there were no significant differences in these effects between the 10 g/day and 20 g/day groups [107].

Table 2. The effect of NDCs on metabolic diseases.

Types	Model	Dosage (g/day or %)	Duration (weeks)	Related Disease	Physiological Effects	References
<i>Soluble dietary fiber</i>						
Guar Gum	Human	≥15	96	L/M	↓ Serum LDL-C and TC with cardiometabolic problems	[108]
Pectin						
- Pectin	Human	650 or 1300	12	Ob	↓ Fasting BG, TG, cholesterols, AIP, HOMR-IR, insulin level, BW, body mass, leptin, and ghrelin. ↑ Adiponectin	[66]
- Pectin (soybean)	Human (Man)	10 g	3 h	IR	↓ Plasma glucose, insulin, and iAUC	[101]
- Pectin (citrus peel)	Mice	2%	8	Ob	↓ Body and fat weight gain, dyslipidemia, hyperglycemia, and insulin resistance	[58]
	Rat (DB)	0.25–2 (g/kg/day)	4	T2D	Improve glucose tolerance, hepatic glycogen content, BG, and blood lipid level. ↑ pAkt and ↓ GSK3β expression	[87]
- High-esterified pectin (HEP, apple)	Rat/Mice	2–10%	6–8	Ob/NAFLD	Improve/restored adipostatic/adipokine sensitivity. Prevented the development of NAFLD, ↑ browning of adipose tissue	[57,59]
Hydroxypropylmethylcellulose (HPMC)	Rat (ZDF)	4–8%	6	DB/Ob	↓ BG, urinary excretion of glucose, ketone bodies, epididymal fat pad, liver lipid, liver weight, adipose, and plasma cholesterol	[102,103]
β-glucan						
- Oat β-glucan	Human	3–3.5	4	CVD	↓ LDL-c, TC, TC: HDL, non-HDL-c, and Framingham CVD risk	[81,82]
- Barley β-glucan	Human	3 or 5	5	CVD	Change in microbiota profile: Bacteroides, Prevotella, and Dorea composition correlated with shifts of CVD risk factors: BMI, waist circumference, blood pressure, and TG levels	[80]
	Mice (HFD)	2–5%	12	Ob	↓ Weight gain and fat mass (2%), ↑ secretion of PYY and GLP-1 (5%)	[55]
- Yeast β-glucan	Mice (HFD)	0.4 (g/kg/day)	10	MD	↓ IL-6 and IL-1β in plasma, ↑ HDL-c and ↓ BG, TC, LDL-c + VLDL-c, TG	[109]

Table 2. Cont.

Types	Model	Dosage (g/day or %)	Duration (weeks)	Related Disease	Physiological Effects	References
Psyllium husk	Human	5	52	Ob	↓ BW	[67]
	Human (T2D)	20	12	T2D	↓ BW, blood glucose, blood lipid, HbA1c, cholesterol, and TG	[88]
	Human Human (NAFLD)	9–10 10	8–10 12	T2D/NAFLD NAFLD	↓ Waist circumference, oxidized lipoproteins, calorie and carbohydrate intake, ALT, weight, and body fat ↓ BW, BMI	[68,110,111]
Inulin and inulin-type fructans						
- Fructans (75% FOS)	Human (Ob)	8	12	Ob	↓ Hunger, desire to eat, and energy intake	[69]
- FOS /FOS + probiotics	Human (T2D)	0.1–10	6–8	Ob/CVD	↓ BW, waist circumference, serum TG, fat mass, fasting BG, HbA1c, LCL-c, TC/HDL-c and LDL-c/HDL-c	[70,71,112]
- Fructooligosaccharide (FOS)	Human (CVD)	12	12	CVD	↓ IL-6 level, total p-cresyl sulfate (PCS)	[83]
	Rat	32%	12	CVD	↑ Hypertrophic of cardiomyocytes	[79]
	Rat	10%	6	Ob	↓ Energy intake, BW, fat mass, plasma glucose, and GIP. ↑ PYY	[61]
	Mice	0.38	5	Ob	↓ Cecal content pH ad BW. ↑ Cecal SCFAs	[113]
High amylose starch (resistant starch II)						
- High-amylose corn starch	Human (T2D)	6.8 or 25	8	T2D	No significant different in fasting BG, ↓ fasting insulin level	[90]
	Human (women)	0–30	4–6 h	IR	No significant different in fasting BG and insulin, ↓ the post-prandial glucose and insulin AUCs	[114,115]
Galactooligosaccharide (GOS)	Human	5–18	2–3	Ob	↓ Colonic permeability, food intake, lipopolysaccharides, CRP, and BMI. ↑ antioxidative enzymes	[72,116]
	Mice	0.083–0.83	6	Ob/DB	↓ BG, TC, TG, LDL-C, and liver lipid deposition. ↑ HDL-c, SCFAs	[104,105]

Table 2. Cont.

Types	Model	Dosage (g/day or %)	Duration (weeks)	Related Disease	Physiological Effects	References
Polydextrose	Human (men)	12	15–75 min	Ob	↓ Energy intake in low protein group but not high protein group	[117]
<i>Insoluble dietary fiber</i> Cellulose	Rat	10%	24	G/M	↓ TG	[118]
<i>Soluble/Insoluble dietary fiber</i> Mixed plant cell wall fibers (corn starchhemicellulose)	Human	10 g/day	48	T2D	Improve insulin release, peripheral insulin sensitivity, and blood glucose control	[106]
<i>Non-dietary fiber NDCs</i> Resistance starch III	Mice	23%	4	T2D	Improve glucose and lipids profile (TC, TG, LDL, HDL)	[119]
Resistance starch IV	Human	30%/53.7%	12/6	CVD/T2D	Improve dyslipidemia and body composition. ↓ HbA1c, improve glycaemic control and cardiovascular risk without altering lipid metabolism	[84,85]
Maltooligosaccharides (MOS)	Mice	6 g/kg	11	Ob/DB	↓ BW gain, adipose size, serum TC, TG, and insulin resistance	[62]
Chitosan oligosaccharides (COS)	Mice	200 mg/kg	21	MD	↓ BG, TG, lipopolysaccharides, and adipose inflammation	[63]
Bovine-milk oligosaccharides (BMO)	Mice	6%	6	Ob	↑ glucose tolerance, insulin secretion and HDL-C. ↓ BW, LBP, hepatic steatosis, gut permeability, total fat, mass, and adipocyte cell size	[64]

AIP, atherogenic index of plasma; AXOS, arabinoxyylan oligosaccharides; BG, blood glucose; BW, body weight; BMI, body mass index, CVD, cardiovascular disease; DB, diabetes; DM, methyl-esterification; G/M, glucose metabolism; GIP, gastric inhibitory polypeptide; GOS, galactooligosaccharide; HDL-c, high-density lipoprotein cholesterol; HEP, high-esterified pectin; HFD, high fat diet; HMAP, highly methoxylated apple pectin; HOMA-IR, homeostasis model assessment insulin resistant; iAUC, incremental area under the curve; IR: insulin resistant; LBP, binding protein; L/M, lipid metabolism; LDL-c, low-density lipoprotein cholesterol; MD: metabolic disease; NAFLD, non-alcoholic fatty-liver disease; Ob, obesity; PYY, peptide YY; T2D, type 2 diabetes; TC, total cholesterol; TG, triglycerides; XOS, xylooligosaccharide; ZDF, Zucker Diabetic Fatty.

6. Conclusions

A high intake of NDCs, such as dietary fibers and resistant starch, is strongly associated with a reduced risk of MD, including CVD and T2DM, because of their physical and fermentation properties. In particular, the properties of NDCs, such as water retention, fecal bulking, viscosity, and fermentation in the gut, are important for reducing the risk of MD by decreasing blood glucose and lipid levels, increasing satiety and insulin sensitivity, and modifying the gut microbiome. Moreover, SCFAs produced by certain gut bacteria mainly contribute to reducing the risk of MD by controlling satiety hormones and energy metabolism, decreasing inflammation, and enhancing the immune system. However, these mechanisms are not sufficient to explain the differences in the impact of NDCs on MD according to the type and source of the NDCs and the answers to many questions about how NDCs suppress the development of MD still remain unclear. In particular, the study on the structural property of NDCs, the effects of NDCs on the gut microbial ecosystem, and the biological networking of gut metabolites produced by fermentation of NDCs have been limited. In structural property, the structures of NDCs and their sizes after partial digestion by the GI system are associated with various health benefits [120], but the study on structural property on MD has been rarely conducted except for the degree of esterification in pectin [60]. In the gut microbial ecosystem, although the microbial profiles are significantly different according to individual NDC and the metabolites profiles they produce are also different [121], the factors related to the fermentation property of NDCs except for their physical property mentioned in this review and other metabolites produced by fermentation except for SCFAs have been rarely investigated [122]. In the biological networking of gut metabolites, various metabolites can be produced during gut fermentation, but studies over the past decade have focused only on SCFAs [120]. Gut metabolites can transfer to the whole body, including the brain, liver, kidney, lung, and skin, via blood and the central nervous system, and can affect many physiological functions associated with the risk of MD through biological networking [123]. However, the biological networking of other gut metabolites has been rarely investigated. Although there remain gaps in understanding how NDCs reduce the risk of MD, this review showed how NDCs regulate the incidence of MD by focusing on mechanisms by which the physical and fermentation properties of NDCs in the GI system, and we believe that a better understanding of the relationship between NDC intake and MD is imperative to improve NDC intake guidelines for MD.

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