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Impact of Dietary Fiber Consumption on Insulin Resistance and the Prevention of Type 2 Diabetes

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Abstract

Large prospective cohort studies consistently show associations of a high dietary fiber intake (>25 g/d in women and >38 g/d in men) with a 20–30% reduced risk of developing type 2 diabetes (T2D), after correction for confounders. It is less well recognized that these effects appear to be mainly driven by high intakes of whole grains and insoluble cereal fibers, which typically are nonviscous and do not relevantly influence postprandial glucose responses [i.e., glycemic index (GI)] or are strongly fermented by the gut microbiota in the colon. In contrast, a dietary focus on soluble, viscous, gel-forming, more readily fermentable fiber intakes derived from fruit and certain vegetables yields mixed results and generally does not appear to reduce T2D risk. Although disentangling types of fiber-rich foods and separating these from possible effects related to the GI is an obvious challenge, the common conclusion that key metabolic effects of high-fiber intake are explained by mechanisms that should mainly apply to the soluble, viscous type can be challenged. More recently, studies in humans and animal models focused on gaining mechanistic insights into why especially high-cereal-fiber (HCF) diets appear to improve insulin resistance (IR) and diabetes risk. Although effects of HCF diets on weight loss are only moderate and comparable to other types of dietary fibers, possible novel mechanisms have emerged, which include the prevention of the absorption of dietary protein and modulation of the amino acid metabolic signature. Here we provide an update of our previous review from 2008, with a focus on mechanistic insights of how HCF diets may improve IR and the risk of developing T2D. *J Nutr* 2018;148:7–12.

Keywords: dietary fiber, insulin resistance, type 2 diabetes, amino acid metabolic signature, short-chain fatty acids

Introduction

Definition, types, and properties of dietary fiber. Dietary fiber (DF) comprises highly complex substances that can be defined as any nondigestible carbohydrate and lignin not degraded in the upper gut. Major sources of DF are whole-grain cereals, fruit, vegetables, and legumes, which typically contain diverse types of DF. Whole-grain foods, by weight, generally contain some 12% of total (mainly insoluble cereal) DF, and there is a strong correlation between cereal DF and whole-grain consumption. Some bran-derived food products contain ≤25% DF (1).

The classification of DFs according to their solubility in water is most common, although grading related to gel-forming capabilities, viscosity, or fermentation rate by the gut microbiota might be as relevant (2) (**Figure 1**). Most natural-fiber products share some of these properties, but generally it can be stated that main sources of soluble, viscous, more readily fermentable types of DF are fruit, certain vegetables, and some products derived from barley and oats that are rich in both insoluble DF and soluble β-glucans, whereas in US cohorts, main sources of whole grains and insoluble cereal fibers are bran products from corn and wheat, which contain cellulose, hemicelluloses, and lignin and which are typically not gel-forming, nonviscous, and with only moderate fermentability in the colon (1) (**Table 1**). Consequently, insoluble cereal fibers do not directly influence postprandial glucose excursions and therefore have no relevant direct influence on the glycemic index (GI) or glycemic load of carbohydrate-containing foods.

Recommended DF intake. The American Diabetes Association recommends that fiber intake in patients with diabetes should match the recommendations for the general population, to increase intake to 14 g fiber/1000 kcal daily, or about 25 g/d

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Abbreviations used: DF, dietary fiber; GI, glycemic index; HCF, high-cereal-fiber; IR, insulin resistance; S6K1, ribosomal protein S6 kinase 1; T2D, type 2 diabetes.

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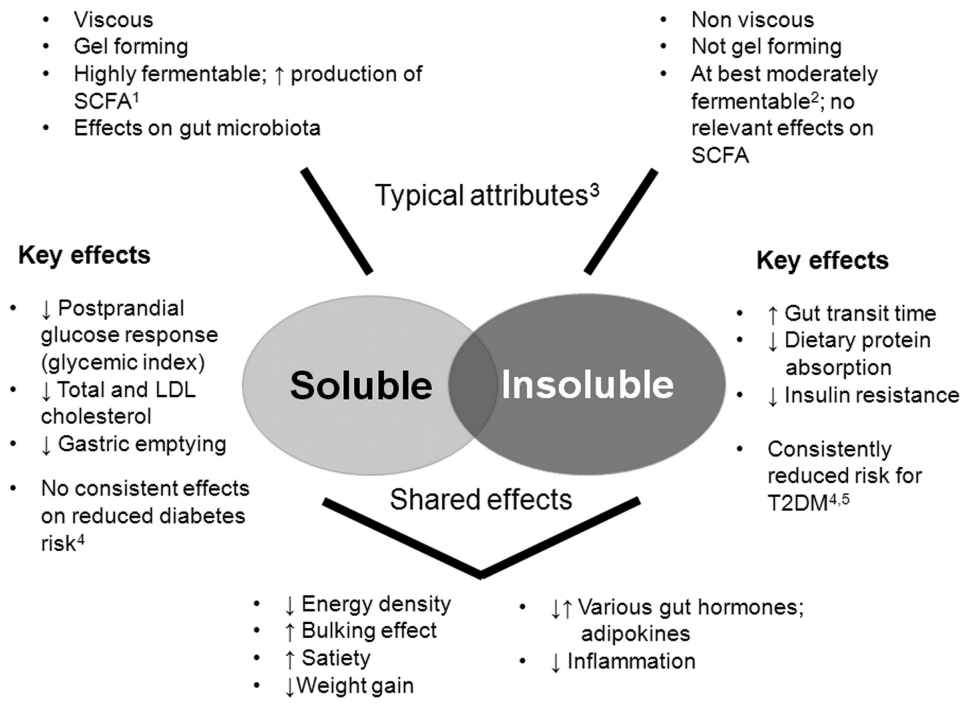

FIGURE 1 Effects of dietary fiber intake on various metabolic factors, insulin resistance, and the risk of developing type 2 diabetes. [1]SCFAs including acetate, propionate, and butyrate that are produced by bacterial fermentation of indigestible dietary fiber polysaccharides and resistant starch in the colon. [2]Main exception: insoluble resistant starch, which is highly fermentable by the gut microbiota in the colon. [3]Some of the attributes are shared between soluble and insoluble fiber types but tend to be more prominent with the respective type of fiber, as listed. In addition, many natural fiber–rich foods contain a mixture of soluble and insoluble types of dietary fibers. [4]Meta-analyses of prospective cohort studies (1). [5]Applies to both cereal fibers and whole-grain products that are typically rich in cereal fiber contents. T2DM, type 2 diabetes; ↓, decreased; ↑, increased.

for women and 38 g/d for men (5). No specific recommendations have been made related to the preferred types of DF consumption, although it is recommended that ≥50% of all grains consumed should be whole grains (5). It has been acknowledged that fiber intake of >50 g/d is difficult to achieve without the use of DF supplements. Most commonly used DF supplements are primarily soluble-fiber types, such as guar gum, glucomannan, xanthan gum, psyllium, pectin, alginate, β-glucan concentrates, and various fiber combinations (3).

DF intake and risk of developing type 2 diabetes in prospective cohort studies. Results from large prospective cohort studies unequivocally indicate that especially high intake of insoluble cereal fibers (in most studies, >30 g/d) (1, 4, 6–8) or whole-grain products (in most studies, >30–40 g/d) rich in cereal fibers (1, 9–11) may reduce insulin resistance (IR) and the risk of developing type 2 diabetes (T2D) by some 20–30%. In contrast, and perhaps surprisingly, any associations of soluble, more readily fermentable fiber-rich foods, such as fruit, vegetables, and certain germ-derived products from grains, with reduced diabetes risk are either weak or absent (1). For instance, in a meta-analysis of 9 large, prospective cohort studies including 328,212 participants, the risk of developing T2D was significantly reduced by 33% in people consuming high-cereal-fiber (HCF) diets, but this risk was unchanged (+4% and –4%, respectively; NS) in participants who had reported an increased intake of vegetables or fruit, which are rich in soluble fibers (1). Causal relations cannot be stated from prospective cohort studies, and estimations of food intake on the basis of semiquantitative FFQs and residual confounding when adjusting for confounding factors are known limitations. Thus, the observed associations of reduced diabetes risk with cereal fiber could be explained by other nutrients found in whole grains, or by the absence of nutrients found in foods that cereal fibers and whole grains are replacing. However, these known limitations of epidemiologic studies should apply to all types of diets and singling out certain dietary ingredients as being consistently more protective than others would not be expected.

With the above in mind, the common assumptions that insoluble cereal fibers are metabolically inactive and that the observed beneficial metabolic effects of high-DF intake could be mainly related to viscous properties of soluble, highly fermentable types of DF are unconvincing (2). Novel mechanisms

TABLE 1 Types and main dietary sources of dietary fiber

	Soluble dietary fiber	Insoluble dietary fiber
Types	Pectins, inulin, mucilages, glucomannan, β-glycans (1, 2)	Cellulose and hemicelluloses; some types of resistant starch (1, 2)[1]
Typical sources[1]	Fruit, berries, certain vegetables (i.e., pectins from guava, carrots; beans, lentils; nuts); germ fraction from oat and barley products; guar; psyllium (1, 2, 3, 4)	Whole-grain and bran products[2] (1); also skins of fruit; cucumbers, tomatoes; hull of grains; brown rice; legumes; nuts, almonds (1, 2, 4)

[1]Many natural foods contain a mixture of both soluble and insoluble types of dietary fibers (1, 2).
[2]In US cohorts, insoluble cereal fiber is mainly derived from wheat bran and corn products (1).

of how DF and especially insoluble cereal fiber intake may influence IR and diabetes risk have been proposed and are discussed below, along with an update on previously proposed concepts.

Potential Mechanisms

Type of diet, satiety, and body weight. IR is mainly caused by excessive energy intake leading to adiposity and has been proposed as the strongest single predictor for T2D (12, 13). Therefore, any nutritional measure that results in even modest weight loss should improve IR (14). However, generally in obese individuals energy expenditure begins to decrease as soon as body weight starts to decline, and potent hypothalamic hormonal responses are induced to prevent further weight loss (13, 15). Moreover, most individuals following weight-loss diets are overweight or obese and typically sedentary, with relevant increases in lean mass under these conditions being unlikely. Physical activity can result in acute improvement of IR lasting from 2 to 72 h, but must be regular to have continued beneficial effects (16). Finally, after intentional weight loss, fat mass is regained to a greater degree than is lean mass in those who do experience weight regain (17), further contributing to worsening of IR.

DF intake may indeed increase postmeal satiety or decrease subsequent hunger, both under conditions of ad libitum or fixed-energy intake, but results are inconclusive and when there were effects these were moderate, with no differences between intakes of soluble, insoluble, fermentable, or nonfermentable types of DF and no differences between natural sources or intake of DF supplements (1). Therefore, some beneficial effects on moderate weight loss in individuals consuming high-DF diets are likely to contribute to reduced IR and the risk of developing T2D but cannot explain the observed stronger associations on these outcomes for insoluble cereal DF.

Role of DF intake on influencing postprandial glucose excursions and the GI of carbohydrate-rich foods. The GI is a measure of the blood glucose–increasing ability of the available carbohydrate in foods (2). Soluble-fiber intake is closely related to the concept of the GI, by hindering or delaying the absorption of dietary carbohydrates related to viscous, gel-forming properties of these fibers and, as such, reducing postprandial glucose excursions.

In studies in rodents, high- compared with low-GI diets significantly increased body fat mass and IR (18). These changes appear to be preceded by early-onset (after 3 wk) and significantly impaired FA oxidation, indicating a potentially causal involvement (18). In observational studies in humans, however, beneficial effects of low-GI diets have not been consistently shown (19, 20), which is partly explained by the known problem of controlling confounding factors such as fiber intake and the lack of suitable control diets (1). Moreover, in most observational studies that reported associations of GI with risk of T2D, participants were relatively young and, even in interventional studies in rodents, the metabolic benefits of a low-GI diet appear to be more pronounced in younger animals (21).

Furthermore, disentangling the metabolic effects of DF content from effects of the GI per se, especially in human interventions, is challenging. Low-GI diets are typically high-fiber diets. In a randomized, parallel, controlled-intervention study in 210 participants with T2D, Jenkins et al. (22) reported moderately reduced concentrations of glycated hemoglobin in patients treated with a low-GI diet compared with an HCF diet over 6 mo. However, the low-GI diet in their study contained more fiber than the so-called HCF diet (18.7 compared with 15.7 g fiber/1000 kcal; $P < 0.001$), and many of the fibers that were emphasized in the "high-cereal-fiber group" were, in fact, high in soluble types of fiber (i.e., pectins) or starchy high-GI foods such as baked potatoes (23). This example shows the challenges when designing dietary intervention studies in humans with the use of real food as opposed to the use of dietary supplements.

Finally, lowering of postprandial glucose responses upon DF intake is mainly related to viscous, gel-forming properties of soluble DF (**Figure 1**). No relevant effects on the GI can be achieved when consuming diets high in insoluble cereal fibers (1), and therefore, fiber-related modulation of the GI cannot convincingly explain the consistently observed effects of insoluble-cereal-fiber intake (and absent effects of soluble-fiber intake) on reduced T2D risk in prospective cohort studies. Although reducing postprandial glucose excursions can be a valuable additional tool to improve glucose control in patients with all types of diabetes (3), there is no conclusive evidence that low-GI diets per se indeed play a role in the prevention of IR and T2D (3, 20).

Influence of fermentable DF intake on the production of SCFAs and composition of the gut microbiota. A considerable number of interventional studies have investigated the effects of fermentable nondigestible carbohydrates on metabolic control, related to increased production of SCFAs in the colon (2). High concentrations of SCFAs are assumed to be beneficial (i.e., by reducing hepatic glucose output and improving lipid homeostasis) (2) and may also influence the composition of the gut microbiota (2, 24). However, in a series of intervention studies in our laboratories, the beneficial effects on IR were identical when using highly fermentable (resistant starch) or nonfermentable (wheat fiber extracts) sources of insoluble DF (1), and to our knowledge, there are no published long-term studies to prove benefit from the use of resistant starch in the prevention or treatment of T2D (3). This could be related to the fact that SCFAs relevantly contribute to total energy intake (25), with ≤10% of daily energy intake being derived from SCFAs also in humans (1). Therefore, in the long term, the observed acute beneficial effects of increasing SCFA output on metabolic factors might be abolished by weight-gain–induced worsening of IR (25).

Almost all studies in animal models that have shown improved IR after soluble-fiber–induced increases in SCFAs were relatively short term (2); and in part, controversial results were observed in the few longer-term interventions (24). For instance, in a study in male Wistar rats, short-term feeding (for 20 wk) with guar gum compared with cellulose or bran reduced body weight and improved carbohydrate tolerance, but the effects were reversed in the long term, with significantly lower pancreatic insulin and glucagon concentrations in the cellulose-fed rats after 67 wk (26). In our studies in C57BL/6 mice, long-term (45 wk) supplementation with soluble guar gum led to an obese phenotype in obesity-prone mice fed a Western-style diet (25). In contrast, supplementing the same diet with insoluble cereal fiber led to significantly lower weight gain and improved IR and was further associated with a pattern in liver gene expression consistent with increased FA oxidation (25). Hence, increased energy digestion related to soluble, highly fermentable fiber intake and increased expression of SCFA target genes might unfavorably affect energy homeostasis and IR after prolonged exposure (25, 26). Long-term controlled studies in humans are needed to further investigate this potentially important aspect.

It has been proposed that the observed relation between the amino acid metabolic signature and IR (27) may be linked to certain members of the gut microbiota. A recent study that

combined measures of IR with metabolomics and microbiome shotgun sequencing in humans observed significant correlations of serum BCAAs with IR, which were related to increased microbial production and reduced microbial transport mechanisms for BCAAs, thereby explaining the increased BCAAs (28). The study further identified *Prevotella copri* as a major contributor to the elevated BCAAs and IR by using fecal transplantation to gnotobiotic mice. However, findings are not consistent: *P. copri* was also recently shown to be required for the improvement in IR in response to barley-kernel intake, which was caused by altered hepatic glucose handling in fecal transplantation studies (29). Furthermore, in our intervention studies in overweight and obese humans, the consumption of supplemented, isoenergetic, high-plant-based-protein diets compared with HCF resulted in large and significant differences in IR (30), but the composition of dominant groups of the gut microbiota was not influenced by the respective diets and the cereal fiber extract used was neither fermented in vivo nor in vitro (31), indicating that other mechanisms were involved that conveyed improved IR on increasing cereal fiber intake.

Interference of cereal fiber with the absorption of dietary protein, a novel mechanism that may explain improved IR in participants consuming high-fiber diets. More recent controlled-intervention studies indicate that high insoluble-cereal-fiber intake may improve IR independently of weight loss, by interfering with the absorption of dietary protein (30). Indeed, high-protein diets, despite their beneficial effects on satiety, weight loss, and blood lipids (32), may under certain conditions increase IR and diabetes risk (33–38). High-protein intake during weight-loss therapy eliminates the weight loss–induced improvement in IR in obese postmenopausal women (39) and consuming 5% of energy from protein at the expense of carbohydrates or fat increased diabetes risk by 30% in prospective cohort studies (36). This appears to mainly apply to individuals who are more obese and, as such, assumed to be more sedentary (34, 37) as well as to those who consume diets high in animal protein (33, 38, 40, 41), although associations with total protein intake and the risk of developing T2D have been reported as well (36, 37).

Diets high in plant protein are typically also rich in DF content, which might be protective in this context. For instance, replacing 1% of energy from carbohydrates with energy from protein is associated with a 5% increased risk of T2D, but adjustment for DF intake attenuates the association; and replacing 1% of energy from animal protein with energy from plant protein is associated with a 18% decreased risk of developing T2D (38). In our randomized, controlled, 18-wk ProFiMet trial (30) in 111 group-matched, overweight adults with ≥1 further metabolic risk factor, we compared the effects of isoenergetic, supplemented diets varying in cereal fiber and mainly plant-derived protein contents on whole-body and hepatic IR (30). After 6 wk, IR expressed as an M-value was 25% lower in participants who consumed an HCF diet compared with those who consumed a high-protein diet. Worsening of IR in the high-protein group was associated with a significantly higher expression of ribosomal protein S6 kinase 1 (S6K1) (30). Furthermore, diet-induced alterations of complex amino acid profiles in ProFiMet were related to 70% and 62% of changes in whole-body and hepatic IR (27), whereas body weight, fat mass distribution, and energy expenditure were not influenced by the respective diets (30). Notably, IR did not worsen with the high-protein challenge when cereal fibers were added. Furthermore, the significant high-protein intake–induced increases in the urinary ratio of nitrogen to creatinine (a biomarker for dietary protein intake and systemic absorption of ingested protein) were entirely prevented when adding cereal fibers to a high-protein diet, whereas fecal isovaleric acid concentrations (which reflect the appearance and subsequent metabolization by the gut microbiota of ingested dietary protein in the colon) significantly increased both with and without adding cereal fibers to a high-protein diet. Therefore, the combination of biomarkers of protein intake in feces and urine indicates that cereal fibers interfere with the digestion, absorption, or both of dietary protein in the small intestine (30) (**Figure 1**). Impaired absorption of dietary protein by other dietary components (i.e., cereal fibers), and thus reduced systemic amino acid availability from ingested protein, is further supported by recent studies from van Loon and colleagues (42), who showed significantly improved dietary protein digestion and absorption throughout the night when dietary protein was ingested before sleep, with overnight sleep typically being the longest postabsorptive period during a 24-h cycle.

Importantly, humans exposed to amino acid infusions rapidly develop IR, with impaired glucose uptake being related to phosphorylation of downstream factors of the insulin-signaling cascade by S6K1. In contrast, S6K1-knockout mice are protected from diet-induced IR (2, 13, 15). In agreement with this, high protein–induced worsening of IR is associated with upregulation of factors involved in the mammalian target of rapamycin/S6K1 signaling pathway (30), increased stimulation of glucagon and insulin within the endocrine pancreas, high glycogen turnover, and stimulation of gluconeogenesis (2, 13, 30). In the short term, these negative effects of high-protein intake on IR may be compensated for by the also-observed satiating effects of dietary protein, reduced choice of foods, and an aversion against high-dietary-fat contents in the absence of carbohydrates, potentially leading to weight loss (15), and, at least in physically active people, possible increases in lean mass that are also mediated via the mammalian target of rapamycin/S6K1 pathway (13, 15).

However, sustained weight loss with any diet is difficult to achieve (13, 15). In the European multicenter Diet, Obesity, and Genes (DioGenes) trial in overweight nondiabetic participants, a modest increase in protein content and a modest reduction in the GI resulted in more successful maintenance of weight loss after an initial energy-reduced diet (43). However, even under strictly controlled trial conditions, maintenance of weight loss was only marginally better with a high-protein intake (−0.71 or −1.1. kg after 6 mo compared with a low-protein intake, depending on the combination with low- or high-GI diets) and failed to reach significance in the full model, despite the considerable number of completers ($n = 548$) in the study (13, 43). In addition, both the high-protein and the high-GI diets appeared to increase low-grade inflammation (44), which could further contribute to worsening of IR (1), especially upon weight regain.

The long-term safety of high-protein diets in at-risk individuals remains to be investigated. However, our findings in the ProFiMet study (30) may explain the observations of others that, when simultaneously increasing protein and DF intakes (which can be indirectly achieved, e.g., by focusing on plant-derived protein sources), no deleterious effects of high-protein diets on IR are apparent (33, 36).

Further potential mechanisms that may contribute to explaining beneficial metabolic effects of high-fiber diets. Various other concepts have been proposed that may contribute to explaining the beneficial metabolic effects of high-fiber

TABLE 2 Effects of soluble and usually fermentable, compared with insoluble and often only moderately fermentable, types of dietary fiber consumption on the risk of developing type 2 diabetes, body weight regulation, insulin resistance, and other factors[1]

	Soluble dietary fiber	Insoluble dietary fiber
Association with reduced risk of type 2 diabetes in prospective cohort studies	No consistent associations (1, 2, 4, 6–11)	Strong associations for cereal fiber (1, 2, 4, 6–8) and whole-grain intake (1, 2, 9–11); consistent risk reduction of 20–30%
Effects on satiety	Moderate (1)	Moderate (1)
Effects on weight loss	Moderate (1)	Moderate (1)
Effects on gastric emptying	Delayed (1)	No relevant effects (1)
Improved insulin resistance	Inconsistent results in human studies (1, 2, 15)	Improved whole-body insulin resistance after short-term and prolonged cereal fiber intake (1, 2, 15)
Reduced postprandial glucose excursions and lower glycemic index	Consistently shown, relevant effects (1, 2, 15, 19, 20)	No relevant effects (1, 2, 15)
Impairment of the absorption or digestion of dietary protein	Unknown	Effect shown (30, 38)
Effect on the amino acid metabolic signature	Unknown	Effect shown (27)
Improved blood lipids	Modest reductions in total and LDL cholesterol (1, 2)	No direct effects (1, 2)
Fermentability by the gut microbiota	Usually high (1, 2, 24, 29)	Usually low or nonfermentable (apart from insoluble resistant starch); may be cofermented to some degree together with other, fermentable types of dietary fibers (1, 2, 24, 31)
Influence on composition of the gut microbiota	Shown in increasing number of studies (2, 24, 29)	Not consistently shown; possibly minor effects (1, 15, 24)

[1]The definition of high-fiber intake varies between studies. Generally, daily fiber intake of >25 g in women and >38 g in men, or 14 g/1000 kcal, is accepted as increased intake. Most studies define cereal fiber consumption or whole-grain consumption of >30 g/d as increased intake.

intake. Some of the effects of fiber intake on IR, gut hormones, adipokines, markers of inflammation, or its influence on the composition of the gut microbiota were discussed in our previous review (1). Searching PubMed for "dietary fiber AND insulin resistance (or insulin sensitivity)" yields >500 additional publications in the past 10 y, but generally, most studies have focused on aspects of fiber intake that can be related to soluble, viscous, fermentable fibers or metabolically active compounds that can be extracted from fiber-rich foods (45). Insoluble cereal fibers, which represent the type of DF with the most conclusive protective effects on risk of developing T2D in large prospective cohort studies, remain underinvestigated.

Conclusions

Prospective cohort studies clearly indicate that diets high in insoluble cereal DF and whole grains might significantly reduce diabetes risk. In contrast, there is no compelling evidence that soluble DFs from fruit and vegetables play a key role in this context. Many of the proposed protective mechanisms of DF consumption are either shared by soluble and insoluble DFs or they are more likely to be relevant with soluble, viscous DF consumption (Table 2).

Interference of insoluble cereal fibers with the absorption or digestion of dietary protein is a concept that deserves further investigation and may contribute to explaining both the opposite directions of observed diabetes risk in individuals who consume HCF compared with high-protein diets and the increasing number of observations that mainly a high intake of animal protein, but not plant-derived protein (which also provides additional fiber), appears to increase IR and the incidence of T2D in high-risk individuals.

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