

Fiber and Insulin Sensitivity

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1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) continues to increase at an alarming rate. Approximately 18.8 million people in the United States have diagnosed diabetes, whereas 7.0 million people are estimated to be living with the disease undiagnosed (Centers for Disease Control and Prevention [CDC], 2011). Another 79 million adults 20 years and older have pre-diabetes: impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG) (CDC, 2011). Approximately 20-30% of individuals with pre-diabetes progress to T2DM within 3-4 years (DeFronzo et al., 2011; Knowler et al., 2002).

The progression from normal glucose tolerance to the onset of T2DM is protracted and preceded by metabolic abnormalities that ultimately lead to hyperglycemia. Early in the disease process, individuals typically exhibit resistance to insulin-stimulated glucose uptake at the cellular level (Reaven et al., 2005). Insulin resistance is also associated with a cluster of metabolic disorders including central obesity, dyslipidemia and hypertension that are risk factors for T2DM and atherosclerotic cardiovascular disease (Alexander et al., 2000). The aggregation of these disorders is often referred to as metabolic syndrome or cardiometabolic syndrome (Reaven et al., 2005).

Insulin resistance manifests as decreased insulin-stimulated glucose uptake at adipose and skeletal muscle tissues, as well as impaired suppression of hepatic glucose output by a given circulating level of insulin (DeFronzo, 2009; Goldstein 2003). Normal glucose tolerance is maintained via compensatory hyperinsulinemia, thus preventing hyperglycemia in the earliest stages (Reaven et al., 2005). Over time, the pancreatic beta-cell response becomes inadequate to maintain normoglycemia, and hyperglycemia ensues. It is unclear whether there is an exhaustion of the beta-cells, or if the beta-cells become progressively less responsive to the changes in circulating glucose, or a combination of these defects (Ferannini et al., 2005; Butler et al., 2003; Khan, 2001). Regardless, progressive beta-cell dysfunction ultimately leads to an inability to secrete sufficient insulin to maintain normoglycemia after a carbohydrate load. In frank T2DM, insulin secretion becomes sufficiently impaired to result in hyperglycemia in the fasting state (Stolar, 2010). By the time T2DM is diagnosed, the insulin secretory response is generally 70-80% below that which would be appropriate for the prevailing level of insulin resistance (Ferannini et al., 2005; Maki et al., 2009). The interplay between insulin resistance and beta-cell dysfunction in the development of T2DM (DeFronzo, 2009; Khan 2001) and methods of assessing insulin sensitivity in clinical research (Muniyappa et al., 2008; Singh 2010) have been reviewed in detail elsewhere.

2. Dietary patterns and diabetes risk

Diabetes prevention trials have shown that interventions which increase insulin sensitivity significantly reduce the rate of conversion to diabetes in high risk individuals (Knowler et al., 2002; Tuomilehto et al., 2001; Lindstrom et al., 2003; Pan et al., 1997; Zinman et al., 2010; DeFronzo et al., 2011). In the Diabetes Prevention Program, a lifestyle intervention with targets of 150 minutes per week of moderate intensity physical activity and weight loss of 7% reduced the rate of progression to diabetes by 58% relative to a group that received placebo without lifestyle intervention (Knowler et al., 2002), which was greater than the 31% reduction in new-onset diabetes with metformin treatment. Other lifestyle intervention studies of weight loss and enhanced physical activity have shown reductions in the incidence of new-onset type 2 diabetes of 25-60% over 3-6 year timeframes in individuals with pre-diabetes (Lindstrom et al., 2003; Pan et al., 1997). Both weight loss and increased physical activity enhance insulin sensitivity, which results in a reduced requirement for insulin secretion, thus “unloading” the beta-cells. In turn, this may extend the time during which the available insulin secretory response can maintain normoglycemia. In addition, there is evidence that some interventions that improve insulin sensitivity may arrest, or even partially reverse, the progression of beta-cell dysfunction (Utzschneider et al., 2008; Gastaldelli et al., 2007).

Although weight loss and increased physical activity have received the most attention, particularly in clinical intervention trials, a number of other lifestyle factors may have important influences on the risk for T2DM. Dietary patterns characterized by high intakes of fruits and vegetables, whole grains, low-fat dairy products, and a low glycemic load have been inversely associated with T2DM risk (Figure). In contrast, dietary patterns characterized by high intakes of processed meats, refined grains, and foods containing high

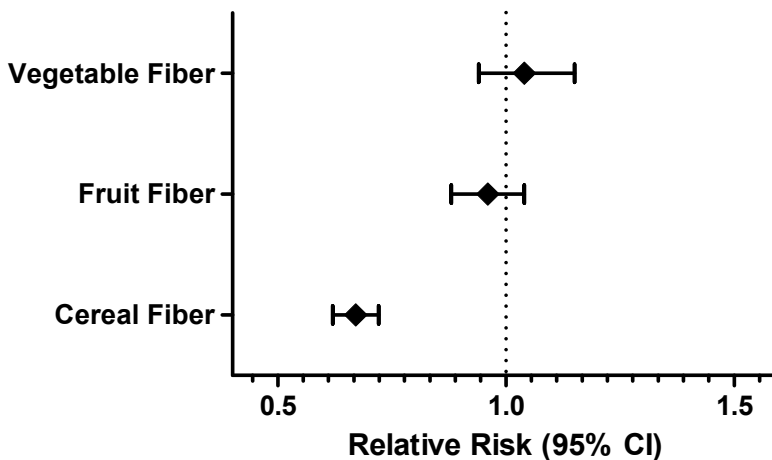


Fig. Relative risks for the associations between cereal fiber, fruit fiber, and vegetable fiber with risk of type 2 diabetes mellitus. Adapted from Schulze et al. 2007. CI = confidence interval.

amounts of added sugars have been associated with increased T2DM risk (Heidemann et al., 2005; Montonen et al., 2005; Fung et al., 2007; Gittelsohn et al., 1998; van Dam et al., 2002; Hodge et al., 2007; Montonen et al., 2005; Brunner et al., 2008; Williams et al., 2000). In particular, an inverse association with T2DM risk has been identified for higher consumption of whole-grain foods (Liu et al., 2000; Murtaugh et al., 2003). Prospective studies have shown that consumption of approximately 3 servings per day of whole grain foods is associated with a reduced risk for T2DM by 20-30% versus consumption of <3 servings of whole grain foods per week (de Munter et al., 2007; Kastorini & Panagiotakos, 2009).

Whole grains contain a number of constituents that may influence T2DM risk, including fibers, vitamins, minerals, lignans, and phytochemicals. The focus of this review is on the potential influences of dietary fibers on risk for T2DM, and the mechanisms that may account for these associations. Nevertheless, the reader should keep in mind that dietary fiber intake correlates with a number of other dietary and lifestyle factors that may influence risk for T2DM, thus fiber intake is likely only one component of the apparent protective effect of a low-risk eating pattern.

3. Intakes of dietary fibers and risk for T2DM

Greater consumption of dietary fiber is associated with lower risk for the development of T2DM, and this may explain, at least in part, the relationship between consumption of whole grains and diabetes risk (Björck & Elmståhl, 2003). Previously, it was thought the reduction in risk might be attributable to the consumption of viscous soluble fibers such as beta-glucan, psyllium, and pectin. Such fibers form viscous solutions when mixed with fluid in the gastrointestinal (GI) tract, creating a physical barrier to digestive enzymes and through which simple sugars must travel to reach the intestinal brush border for absorption (Dikeman & Fahey, 2006; Wolever, 1991; Jenkins et al., 1978). As such, postprandial glucose responses are attenuated when viscous fibers are consumed as part of carbohydrate-rich meals, effectively lowering the glycemic index of such foods (Jenkins et al., 2000; Maki et al., 2007). Prospective epidemiological and observational studies have shown associations between intakes of high-glycemic index foods and high-glycemic load diets and a greater risk of T2DM, consistent with this potential mechanism (Biesalski 2004, Salmeron et al., 1997a, 1997b).

However, results from prospective cohort studies have shown that consumption of insoluble cereal fibers is more strongly inversely associated with risk of T2DM than consumption of soluble fibers (McKeown et al., 2004; Schulze et al., 2007; Weickert & Pfeiffer, 2008). For example, in a cohort of ~25,000 men and women ages 35 to 65 years, greater intake of cereal fibers, but not fruit or vegetable fibers, was inversely associated with developing diabetes over an 11 year period after adjusting for lifestyle and dietary confounders (Schulze et al., 2007). Similarly, a meta-analysis of nine cohort studies on fiber also showed an inverse association for cereal fiber and T2DM risk, but not other fibers (Schulze et al., 2007). Most sources of dietary fiber contain both soluble and insoluble fiber in varying amounts, but whole grain products generally contain a high proportion of insoluble cereal fiber (Weickert & Pfeiffer, 2008; McKee & Latner, 2000). In the U.S. diet, the main sources of soluble fiber are fruits and vegetables, and to a smaller extent, oats and barley (McKee & Latner, 2000).

4. Dietary fiber, colonic fermentation and T2DM risk

Results from several recent studies suggest that fermentability may be a more important factor in the association between dietary fiber intake and T2DM risk than solubility or viscosity. In particular, there is accumulating evidence for a metabolic link between consumption of fibers which are fermented in the lower intestine and insulin sensitivity. This relationship appears likely to be mediated, at least in part, by the inverse association between short chain fatty acid (SCFA) and free fatty acid (FFA) levels in circulation (Robertson et al, 2003, 2005).

Elevated levels of circulating FFA are associated with insulin resistance and it is thought that they contribute to reduced insulin action in the skeletal muscle and liver (Kim et al, 2007). FFA disrupt glucose metabolism by enhancing beta-oxidation in peripheral tissues and by competing with glucose for oxidation, resulting in a reduction of peripheral glucose uptake (Tarini & Wolever, 2010). Sustained elevation of FFA, induced through intravenous infusion of a lipid emulsion, down regulates glycogen storage and leads to a reduction of non-oxidative glucose disposal, thus reducing insulin sensitivity (Ferrannini et al., 1983; Kashyap et al., 2003; Homko et al., 2003). Potential mechanisms by which FFA might affect glycogen regulation include increased expression and activation of glucose-6-phosphatase (Clore et al., 2000; Van de Werve et al., 2000). Conversely, suppression of FFA levels with an infusion of acipimox, a niacin derivative that inhibits hormone sensitive lipase, improves glucose tolerance and peripheral insulin sensitivity (Ferrannini et al., 1983).

The release of FFA shows diurnal variation and is correlated with hepatic glucose output during sleep (Morgan et al., 1999, Kim et al., 2007). In normal weight individuals the fall of hepatic glucose output during sleep is highly synchronized with a decrease in FFA levels (Clore et al., 1989). Conversely, T2DM subjects have an increased rate of FFA appearance at night and elevated plasma FFA levels that are correlated with increased overnight hepatic glucose output (Miles et al., 2003; Taskinen et al., 1989). This increase in FFA levels and release of insulin can be acutely reduced with a pharmacological block of lipolysis, suggesting that a reduction in FFA release may lead to improved glucose homeostasis (Andreotti et al., 1994). In the canine model of moderate obesity, an increase in nocturnal FFA levels and reduced insulin sensitivity occurred after 6 weeks of high-fat feeding, despite no changes in fasting FFA, fasting glucose or postprandial glucose levels, providing further support that the overnight period may be particularly important (Kim et al., 2007). Given the known diurnal fluctuations of FFA observed in overweight and obese subjects, and in the moderately obese canine model, it is likely that the nocturnal increase in FFA is a key factor in the development of insulin resistance and may play a significant role in the risk for T2DM.

Consumption of indigestible fibers provides available substrate for resident microbiota in the large intestine, which form fermentation products, particularly SCFA (acetate, butyrate, and propionate). Upon absorption into the circulation, SCFA suppress the release of FFA from adipose tissue, thus lowering the concentrations of FFA in circulation, which, in turn, could lead to improved insulin sensitivity and concomitant reduced risk for T2DM (Tarini & Wolever, 1991).

Feeding studies in humans support this proposed relationship between colonic fermentation and peripheral metabolic effects (Table). Nilsson et al. (2008) provided healthy subjects

evening meals containing a variety of cereal-based foods with varying levels of resistant starch and fermentable fiber. They demonstrated a relationship between colonic fermentation, as measured by breath hydrogen, and glucose tolerance at the subsequent breakfast meal more than nine hours later (Nilsson et al., 2008). Compared to white bread in the evening, consumption of bread made with barley kernels, high beta-glucan barley, or white bread supplemented with resistant starch and barley fiber all reduced the postprandial curves for glucose and insulin after a subsequent standard breakfast, consistent with improved insulin sensitivity. Additionally, the glucose response was inversely associated with SCFA concentrations (butyrate and acetate) and was positively correlated with FFA during the postprandial period.

Several studies have demonstrated enhanced insulin sensitivity, measured with the euglycemic clamp (the reference standard method) or other methods, after consumption of fermentable fibers or resistant starches over periods ranging from several hours to several weeks (Landin et al., 1988; Robertson et al., 2003, 2005; Maki et al., 2011). Landin et al. (1988) showed improved insulin sensitivity in healthy, nonobese men measured by euglycemic-clamp following intake of 30 g/d guar gum. More recently, Robertson et al (2003) examined the role of resistant starch (RS) on insulin sensitivity in healthy subjects following a 60 g load of RS consumed over the course of one day. Increased insulin sensitivity was positively associated with fasting breath hydrogen levels and lower FFA levels in the late postprandial period (Robertson et al., 2003). In a subsequent study comparing 30 g RS/day for four weeks versus a control starch, insulin sensitivity during a meal tolerance test was 33% higher and glucose clearance adjusted for insulin concentration was 44% higher following RS intake compared with the control condition. Insulin sensitivity, as measured by the euglycemic-hyperinsulinemic clamp, was also higher following RS (Robertson et al., 2005). In a chronic (12-week) study in insulin resistant subjects, 40 g RS/day (supplied in sachets to mix into their daily foods) was associated with improved insulin sensitivity compared to placebo (Johnston et al., 2010). Insulin sensitivity was also correlated with changes in waist circumference, however there was no difference in body mass index, total adipose tissue content or regional distribution between the groups suggesting the observed improvement in insulin sensitivity is not directly attributable to changes in body composition (Johnston et al., 2010). In a study of overweight and obese subjects with normal glucose metabolism, Weikert et al. (2006) reported a 13% improvement in insulin sensitivity in subjects who consumed white bread supplemented with 31.2 g/d insoluble fiber fraction from oat fiber over 72 hours, compared to a white bread control.

Not all studies have shown favorable effects of fermentable fibers on insulin sensitivity. Ebeling et al. (1988) studied the effects of 5 g/d guar gum for 4 weeks in individuals with type 1 diabetes mellitus and showed that guar gum lowered the postprandial glucose response and reduced insulin requirements, suggesting an improvement in hepatic insulin sensitivity. However, there was no measurable effect on peripheral insulin sensitivity, as measured by euglycemic insulin clamp. Given that this study was small ($n = 9$), a type II error (lack of power) cannot be ruled out. A study in 21 men with metabolic syndrome also failed to show differences in insulin sensitivity measured by euglycemic insulin clamp following a 5-week dietary intervention with 28 g/day of acacia gum and pectin (Pouteau et al., 2010).

Authors	Study Population	Design	Study Products	Results
Andersson et al., 2007	Healthy volunteers (n=30) Age (y): 59±5 BMI (kg/m ²): 28.3±2.0	Randomized crossover 6-week study of diet rich in whole grains vs. diet containing equal amount of refined grain	<ul style="list-style-type: none"> • Whole grain diet contained 112 g/d of whole grain, 18 g fiber • Refined grain diet contained 6 g/d fiber 	No effect of whole grains on insulin sensitivity
Ebeling et al., 1988	Type 1 diabetics (n=9) Age (y): 27±2 Body Weight (kg): 71±3	Double-blind crossover with two 4-week study periods	<ul style="list-style-type: none"> • 5 g/d granulated guar • Control- 0 g/d 	No effect on insulin sensitivity
Johnston et al., 2010	Insulin resistant subjects (n=20) Age (y): <ul style="list-style-type: none"> • Resistant starch- 45.2±3.55 • BMI (kg/m²): • Resistant starch- 31.3±1.70 • Placebo- 30.4±1.15 	Single-blind, randomized, parallel 12-week intervention	<ul style="list-style-type: none"> • Resistant starch supplement -40 g/d • Control- 0 g/d 	Improved insulin sensitivity with resistant starch
Landin et al., 1992	Healthy, nonobese middle -aged men (n=25) Age (y): 52.0±5.2 BMI (kg/m ²): 24.6±1.6	Double-blind placebo-controlled, cross-over with two 6-week interventions	<ul style="list-style-type: none"> • 30 g/d granulated guar, given in 3-10 g doses • 30 g/d granulated gelling starch (control), given in 3-10 g doses 	Improved insulin sensitivity with guar diet
Maki et al., 2011	Healthy subjects with increased waist circumference (n = 33) Age (y): 49.5 ± 1.6 BMI (kg/m ²): 30.6 ± 0.5	Double-blind crossover with two 4-week interventions.	<ul style="list-style-type: none"> • High-resistant starch diet- 30 g/d • Low-resistant starch diet- 15 g/d • Control- 0 g/d 	Improved insulin sensitivity with both resistant starch diets, but effect only reached statistical significance for men.

Authors	Study Population	Design	Study Products	Results
Nilsson et al., 2008	Healthy volunteers (n=15) Age (y): 25.9±3.2 BMI (kg/m ²): 22.5±2.1	Crossover of cereal-based evening test meals with varying GI and amount of resistant starch	Cereal-based meals: <ul style="list-style-type: none"> • White bread (control) • White bread enriched with barley fiber and 8 g resistant starch • Barley kernel based bread 	Improved glucose tolerance with resistant starch
Pouteau et al., 2010	Men with metabolic syndrome (n=21) Age (y): 47±12 BMI (kg/m ²): 33.4±3.0	Double-blind crossover with two 5-week interventions.	Beverages: <ul style="list-style-type: none"> • 28 g/d acetogenic fibers (acacia gum and pectin) • Control 	No effect on insulin sensitivity
Robertson et al., 2003	Healthy subjects (n=10) Age (y): 23-65 BMI: (kg/m ²): 20.3-35.9	Single-blind crossover with two 24-hour interventions	<ul style="list-style-type: none"> • High-resistant starch diet- 60 g/d • Low-resistant starch diet- 0 g/d 	Improved insulin sensitivity with resistant starch.
Robertson et al., 2005	Healthy subjects (n=10) Age (y): 48.5±3.4 BMI (kg/m ²): 23.4±1.4	Single-blind, crossover with two 4-week interventions	<ul style="list-style-type: none"> • Resistant starch diet-30 g/d • Control-0 g/d 	Improved insulin sensitivity with resistant starch.
Weickert et al., 2006	Overweight and obese subjects with normal glucose metabolism (n=17) Age (y): 52.9±8.7 BMI (kg/m ²): 30.4±2.0	Single-blind crossover with two 72-hour interventions	Macronutrient-matched breads <ul style="list-style-type: none"> • Fiber-enriched with 31.2 g insoluble fiber • Control (white bread) 	Improved insulin sensitivity with increased insoluble fiber

Table: Clinical trials on the effects of fermentable fibers on insulin sensitivity

5. Conclusion

A dietary pattern characterized by high intakes of whole grains, fruits and vegetables, low-fat dairy products, and a low glycemic load has been associated with lower T2DM risk. Whole grains possess a number of constituents that may influence T2DM risk, including vitamins, minerals, lignans and phytochemicals. Greater dietary fiber intake is also associated with lower risk for the development of T2DM, and this may explain, at least in

part, the relationship between consumption of whole grains and reduced diabetes risk. Results from recent intervention studies suggest that fermentability may be the key characteristic of fibers associated with improved insulin sensitivity, providing a metabolic link between dietary fiber intake and reduction in T2DM risk. Future studies on the relationships between dietary fiber, production of SCFAs, circulating FFA release, and physiological mediators such as incretins (glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide), and inflammatory markers (e.g., interleukin-6, adiponectin), are warranted. There is also a need for longer-term intervention trials to determine the mechanisms by which dietary fibers, particularly fermentable fibers, influence health and T2DM risk.

6. References

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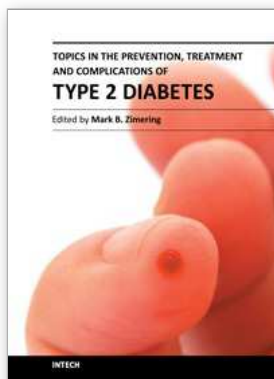
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Type 2 diabetes is estimated to affect 120 million people worldwide- and according to projections from the World Health Organization this number is expected to double over the next two decades. Novel, cost-effective strategies are needed to reverse the global epidemic of obesity which is driving the increased occurrence of type 2 diabetes and to less the burden of diabetic vascular complications. In the current volume, Topics in the Prevention, Treatment and Complications of Type 2 Diabetes, experts in biology and medicine from four different continents contribute important information and cutting-edge scientific knowledge on a variety of topics relevant to the management and prevention of diabetes and related illnesses.

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