Whole grain foods and the prevention of type 2 diabetes mellitus
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Results and discussion

1 Evidence from epidemiological studies for a preventive effect of whole grain foods on the development of type 2 diabetes mellitus

In our systematic review (Appendix 1) we found one randomised controlled trial and 11 prospective cohort studies that investigated the effect of consumption of whole grain foods on the development of T2DM. The prospective studies consistently showed a reduced risk of a high intake of whole grain foods (27–30 %) or cereal fiber (28–37 %) on the development of T2DM. We concluded that the evidence from only prospective cohort trials is too weak to be able to draw a final conclusion about the preventive effect of whole grain foods on the development of T2DM. These studies strongly suggest the preventive effect of whole grain foods but can not prove that the high consumption of whole grain foods is the cause of the reduced risk. Properly designed long-term randomised controlled trials are needed to establish a causal relationship between intake of whole grain foods and the development of T2DM. To facilitate this, relevant intermediate endpoints or biomarkers for T2DM are needed and subgroups of the population at risk have to be identified that are most susceptible to dietary intervention. In addition, plausible biological mechanisms that explain the putative protective effect would strengthen the evidence obtained from the prospective studies. Information about underlying mechanisms can be derived from experimental studies investigating the effect of specific characteristics of whole grain foods and factors involved in the pathogenesis of T2DM.

2 The role of specific characteristics of whole grain foods and underlying physiological mechanisms in the possible T2DM-preventive effect

Beneficial effects of whole grain foods are related to lower postprandial glycemia and increased content of non-digestible carbohydrates. To further investigate the possible preventive effect of whole grain foods, we examined how reduced postprandial glycemia and increased consumption of non-digestible carbohydrates influence factors implicated with an increased risk of developing T2DM. In the following paragraphs the effects of both characteristics on glucose tolerance, insulin sensitivity and markers of inflammation will be addressed.
2.1 Effects related to reduced postprandial glycemia

Effect on glucose tolerance and insulin sensitivity
In our systematic review concerning the underlying mechanisms (Appendix 2) we found 9 trials that investigated the effect of interventions (20 days – 4 months) with low versus high glycemic index (GI) foods. We included only trials in which the low and high GI diets had the same amount of fat, total carbohydrates as well as mono- and disaccharides. Therefore, the reduced glycemia after ingestion of the low GI foods could not be caused by a lower glycemic load but was due to the higher content of slowly digestible starch. Only 2 trials observed a beneficial effect of a low GI diet on whole body insulin sensitivity independent of a change in body weight. None of the trials reported improved hepatic insulin sensitivity.

Effect on inflammation
Recently, studies have shown that ingestion of high GI food can result in an increase in oxidative stress and inflammation markers in the postprandial phase (30–33). The relevance of this – if exerted chronically – is not clear and needs to be investigated in long term trials. So far, only one intervention trial aimed to examine the effect of a dietary intervention with low GI foods on TNF-α and did not find any effect (Appendix 2).

Effect on plasma concentrations of incretin hormones
We found that rapidly and slowly digestible carbohydrates differ considerably in their potency to stimulate secretion of incretin hormones. Slowly available carbohydrates induced a late postprandial GLP-1 response. In view of the capacity of GLP-1 to slow down gastric emptying rate (34), it could be speculated that elevated GLP-1 concentrations at the time point of the intake of a subsequent meal could retard nutrient delivery to the small intestine. This could result in lower glucose concentrations after the subsequent meal. Furthermore, the rate of exogenous glucose appearance was strongly correlated with the plasma concentrations of GIP. (Appendix 3) The physiological consequence of this phenomenon might be important because, in addition to its insulinotropic effect, GIP plays an important role in nutrient uptake into adipocytes. The presence of functional GIP receptors on adipose but not on liver tissue has been documented, which suggests that GIP might play an important role in glucose uptake and fat accumulation in adipocytes. Accordingly, several studies in animal models have
shown that preventing GIP signaling resulted in reduced fat mass (35;36). This mechanism could play a role in the beneficial effect of low GI diets on weight reduction, which, however, remains to be elucidated.

**Issues related to studying the effect of reduced glycemia**

- **Choice of endpoint parameter and study population**
  In the trials investigating the effect of low versus high GI diets on insulin sensitivity (IS) no effect was found with analyses of hepatic IS (homeostatic model assessment). Positive results were only observed after an insulin- and glucose challenge, which are methods to obtain information about whole-body IS. (Appendix 2) As postprandial hepatic glucose uptake accounts only for 30% of the total glucose disposal, this could imply that a low GI diet selectively improves IS in peripheral tissue (mainly muscle). Accordingly, results of other studies suggest that diets in general mainly affect peripheral insulin sensitivity (13). Therefore, to be able to draw a conclusion about the effects of low GI diets, more studies are needed that investigate whole-body or peripheral IS. In addition, all but one trial were conducted in volunteers with normoglycemia. Thus, information about the effect of low GI diets on glucose tolerance or IS in persons with impaired glucose tolerance are lacking.

- **Differentiation between the effect of dietary fiber and reduced glycemia**
  In trials investigating the effect of low versus high GI diets the amount of dietary fiber was often increased in the low GI dietary intervention. (Appendix 2) This means that the observed effect can also be caused by the increased fiber consumption. If this is not recognized, the effects of different foods or diets can be misinterpreted, which also hinders exploration of the underlying mechanism of the observed beneficial effects. In future trials, the dietary fiber intake should be controlled, to be able to differentiate between the effects of reduced glycemia and that of non-digestible carbohydrates.

- **Determination of slowly digestible starch content**
  For prediction of the in vivo digestibility of starch in food products in vitro measurements are used. We showed (Appendix 4) that whole meal bread contains starch that is partly rapidly and partly slowly digestible in vivo. In vitro analysis, however, predicted a high content of rapidly and a low content of slowly digestible...
starch. This implies that *in vitro* techniques not necessarily predict *in vivo* digestive characteristics of starch correctly. In addition we showed that the glucose and insulin response after whole meal bread consumption is not only determined by the digestive characteristics of the starch – as generally expected – but also by other components of bread.

– **Consequences of slowing the rate of starch digestion**

In persons with impaired glucose tolerance, slowing the rate of starch digestion with the α-glucosidase inhibitor acarbose, has been shown to delay the onset of T2DM. This beneficial effect is thought to be caused by the reduction of the postprandial glucose responses. However, slowing the rate of starch digestion can also lead to incomplete starch digestion and increased colonic fermentation of starch. We showed ([Appendix 5](#)) that even a low dose of acarbose (12.5 g per meal) resulted in incomplete digestion of starch. This implies that beneficial affects observed in intervention trials with acarbose can partly be ascribed to increased fermentation of starch.

### 2.2 Effects related to non-digestible carbohydrates

**Effect on glucose tolerance and insulin sensitivity**

Four interventions with a moderately increased consumption of non-digestible carbohydrates consistently improved GT and IS in persons with impaired glucose tolerance and hyperinsulinemia. In 2 of 6 trials in healthy volunteers a beneficial effect of increased ingestion of non-digestible carbohydrates was found. In 3 of these studies addition of non-digestible carbohydrates to the meals did not affect postprandial glycemia. This suggests that not the reduced glucose response, but factors related to increased fermentation of indigestible carbohydrates are related to the beneficial effect. ([Appendix 2](#)) In addition, 10 studies examined the effect of evening meals rich in non-digestible carbohydrates on glucose tolerance following a high GI breakfast. Certain (combinations of) non-digestible carbohydrates – when ingested as evening meal – increased the glucose tolerance after the high GI breakfast. This effect was independent of the GI of the evening meal. ([Appendix 2](#))

We found that a barley kernel evening meal (rich in non-digestible carbohydrates) increases tissue glucose uptake the next morning. ([Appendix 6](#)) The hepatic glucose production and the postprandial insulin response were the same, which indicates improved peripheral insulin sensitivity. Hydrogen in breath,
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an indicator of colonic fermentation of indigestible carbohydrate was significantly increased in the morning after the barley kernel evening meal and so was the plasma concentration of butyrate. The results of our study thus indicate that food associated factors acutely can influence peripheral insulin sensitivity, even in healthy volunteers. They also suggest that butyrate, or butyrate associated factors, could be involved in this effect.

Effect on inflammation

Whole grain foods contain a high number of micronutrients and phytochemicals as compared to refined grain foods. They are released during the small intestinal digestion as well as during colonic fermentation and have the potency to reduce oxidative stress and inflammation (25). Results of a limited number of animal studies using polyphenol rich cereal fractions or a whole grain diet offer some support for this hypothesis (25;37;38). To date only two intervention trials investigated the effect of the intake of whole grains or cereal fiber, rich in micronutrients and phytochemicals, on markers of inflammation. They did not observe decreased inflammation. However, lower IL 6 concentrations were found in one study that examined the effect of an evening meal rich in non-digestible carbohydrates on inflammation markers the next morning. (Appendix 2)

Our own studies (Appendix 6) showed that the late rise of the pro-inflammatory cytokines IL 6 and TNF-α after a glucose load in the morning was moderated by the consumption of a barley kernel evening meal, rich in non-digestible carbohydrates. Previously, it had been shown that a high glucose or meal-induced inflammatory response could be prevented by concomitant intake of antioxidants (glutathione, vitamin C) (39;40) or antioxidant rich food (olive oil, red wine) (41;42). Thus, our finding suggests that not only concomitant intake of antioxidants but also so far unknown antioxidant or anti-inflammatory factors derived from a previous evening meal can moderate meal-associated inflammation. Potential mediators of this effect could be SCFA or phytochemicals released during colonic fermentation of cereal fiber.

Issues related to studying the effect of non-digestible carbohydrates

– Differentiation between the effect of products of colonic fermentation of indigestible carbohydrates and phytochemicals released during colonic fermentation

The beneficial effect of indigestible carbohydrates on glucose tolerance, insulin
sensitivity and inflammation markers could be mediated by two different mechanisms. Firstly, colonic fermentation of increased amounts of resistant starch and cereal fiber leads to increased amounts of the fermentation products SCFA. These SCFA could be responsible for mediating the observed beneficial effect. Secondly, cereal fiber deliver an increased amount of phytochemicals to the colon, which can be released during the fermentation process. Also, these phytochemicals could be responsible for the beneficial effect. To be able to distinguish between both these mechanisms, results of trials using resistant starch, which is devoid of phytochemicals, are necessary. So far, two studies (22;43) investigated the effect of RS supplementation and reported improved IS. This indicates an important role for colonic SCFA, which needs further confirmation. Studies in our laboratory are ongoing to investigate the possible mechanisms involved. (Appendix 2)

– Effects of different types of non-digestible carbohydrates on production of short-chain fatty acids

From our review (Appendix 2) it became clear that certain (combinations of) non-digestible carbohydrates – when ingested as an evening meal – increased the glucose tolerance after the high GI breakfast, while other combinations did not. Furthermore, the production of SCFA is implicated with increased glucose tolerance or insulin sensitivity and also with reduced inflammation markers (Appendix 2 and 6). In vitro analyses have shown that fermentation of different (combinations of) non-digestible carbohydrates results in different proportions of acetate, propionate and butyrate (44;45). Thus, we tested the hypothesis that different combinations of non-digestible carbohydrates result in different SCFA profiles also in vivo. We applied a newly developed analytical technique that allowed us to evaluate SCFA profiles after administration of different indigestible carbohydrates in humans. The results of this study showed that meals containing dietary fiber combined with resistant starch result in altered SCFA profiles as compared to meals containing dietary fiber alone (Appendix 7). The underlying mechanism of this phenomenon is, however, not clear yet.

Future perspectives

The finding that ingestion of rapidly digestible starch is correlated with increased plasma GIP concentrations is interesting with regard to the beneficial effect of low GI diets on weight reduction. Assessing plasma GIP concentrations in low
versus high GI intervention trials could provide valuable information about this relationship.

The predictive value of *in vivo* digestibility of starch with *in vitro* methods needs further evaluation. Reliable prediction of the digestive starch characteristics is especially important for mechanistic studies examining the metabolic effects of slowly digestible starch as well as for the evaluation of food products developed to contain more slowly digestible starch.

Our study with an evening meal rich in non-digestible carbohydrates demonstrated the potency of factors related to colonic fermentation to increase peripheral insulin sensitivity the next morning. There are strong indications that 
SCFA are involved in this insulin sensitizing effect and we propose that the relative amount of the individual short-chain fatty acids plays a more important role than their total concentrations. The underlying molecular mechanisms of this effect need to be explored.

The capacity of an evening meal rich in non-digestible carbohydrates to moderate meal-associated inflammation the next morning is a novel finding. Further studies should focus on identifying factors involved in this anti-inflammatory effect.

No conclusion could be drawn about the effect of reduced glycemia on insulin sensitivity. It seems necessary that a distinction is being made between outcome measures of hepatic and peripheral insulin sensitivity. The homeostatic model assessment (HOMA) is easily to apply because for that model only one fasting blood sample is needed. However, insulin sensitivity assessed with HOMA reflects hepatic insulin sensitivity and trials comparing low with high GI food interventions using this method have not found an effect. This may be not surprising as there are indications that diet mainly affects peripheral insulin sensitivity. Therefore, to be able to draw a conclusion about the efficacy of dietary interventions, methods should be used that reflect peripheral or at least whole body insulin sensitivity.

In view of the relevance of chronic low-grade inflammation for the development of T2DM and the potency of cereal fiber-associated phytochemicals to reduce oxidative stress and inflammation *in vitro*, more dietary intervention trials should explore this relationship.
Concluding remarks

Taken together the results presented in this thesis suggest that consumption of whole grain foods can contribute to the prevention of type 2 diabetes. Currently, it seems that physiological effects associated with the presence of non-digestible carbohydrates play a more important role in this preventive effect than reduction of postprandial glycemia.

Intake of whole grain foods is already recommended as part of a healthy food pattern, but especially persons with a risk of developing T2DM could benefit from this advice. Early interventions are needed to prevent irreversible damage by unnoticed hyperglycemia, which underlines the need of development of early biomarkers of this disease. In addition, detection of subpopulations most susceptible to dietary interventions due to their genetic make-up would enable more efficient personalized dietary advice. Currently, the assortment of whole grain products is small and the consumer acceptance of whole grain foods is low. Our finding that non-digestible carbohydrates could mediate the protective effect are valuable for the development of cereal grain products with T2DM preventive potential (functional foods), which are more acceptable than traditional whole grain foods.