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Malin SK, Kullman EL, Scelsi AR, Godin JP, Ross AB, Kirwan JP. A Whole-Grain Diet Increases Glucose-Stimulated Insulin Secretion Independent of Gut Hormones in Adults at Risk for Type 2 Diabetes. Mol Nutr Food Res. 2019;63(7):e1800967.

What We Know, Think We Know, or Are Starting to Know

With the modern hyperbole around carbohydrates, the dialogue is often lured into a simplistic mechanism of 'carbs=blood sugar=bad'. Certainly, hyperglycaemia is an issue [amongst others] for the pathogenesis of type 2 diabetes, and post-prandial glucose levels are predictive of cardiovascular disease in people with T2DM [(1)]. However, the reality is that peripheral insulin resistance, followed by progressive pancreatic beta-cell dysfunction, is the core aetiology of T2DM - not dietary carbohydrate intake.

The assumption that the only means of improving blood glucose regulation through diet is through dietary carbohydrate restriction is over simplistic. Dating back to the 1970's, research has indicated that very high-fibre, high-carbohydrate diets could be effective in reducing insulin requirements - and in nearly of half of patients resulting in discontinued insulin - in participants with T2DM [(2,3)].

In the interim, cohort study after cohort has consistently found reduced risk for T2DM, with Aune et al. [(4)] finding a 36% relative risk reductions for T2DM comparing high [60-90g/d] vs. low levels of wholegrain intake, while Ye et al. [(5)] found a 26% relative risk reduction for T2DM, comparing 3-5 servings [50-80g/d] to the lowest level. Intervention studies have indicated a number of potentially plausible biological mechanisms, specifically improved insulin sensitivity, and reduced post-prandial glucose levels [(6)].

The present study investigated the effects of a diet high in wholegrains vs. refined grains on glucose tolerance and insulin parameters.

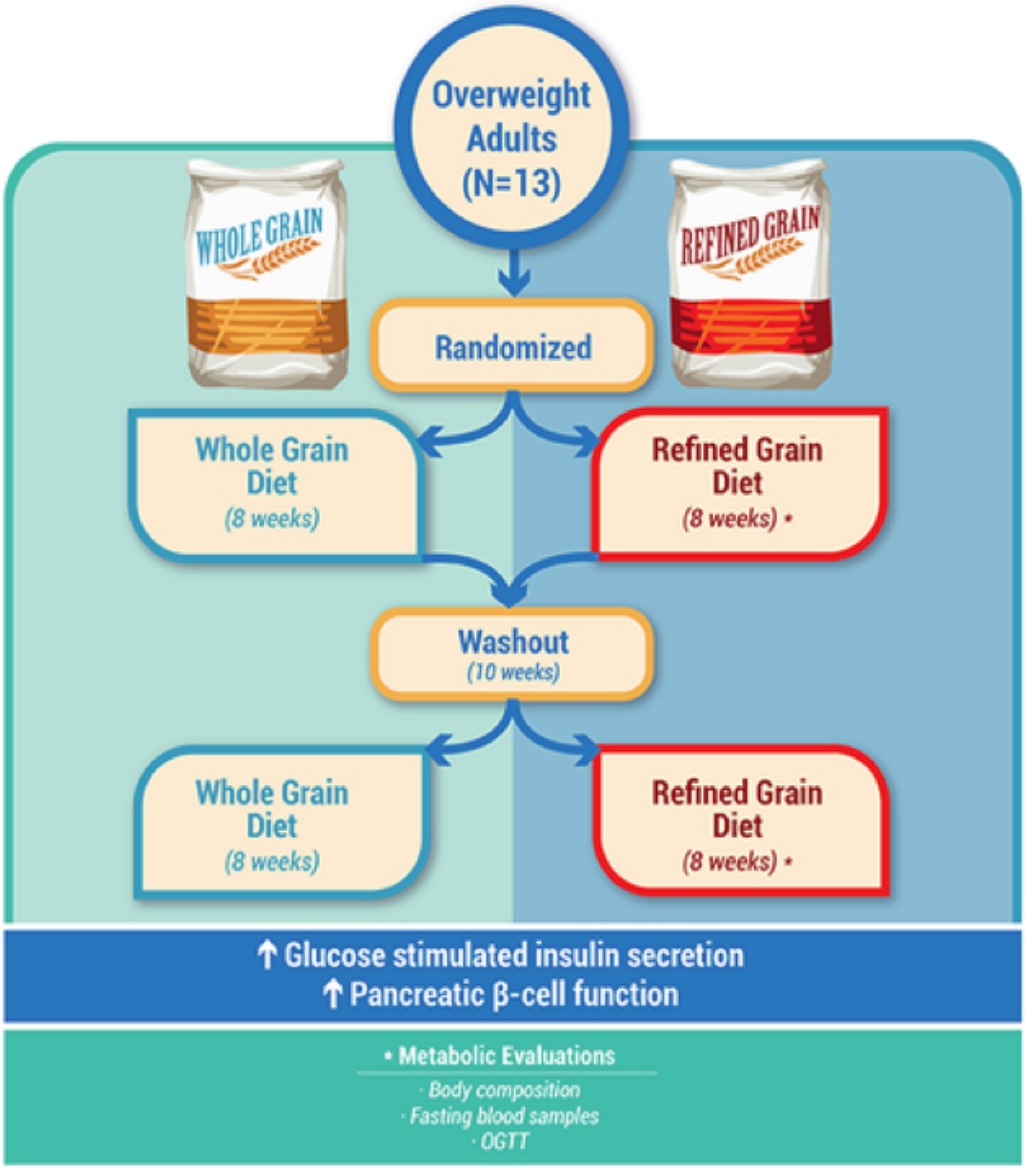
The Study

13 middle-aged adults at risk for T2DM, with a BMI of 28-40, physically inactive (<60min/wk), and weight stable in the previous 6-months, were enrolled in a randomised, double-blind, diet-controlled, crossover* trial. Only the study dietitian and statistician aware of the randomisation assignment.

Diet was calculated according to individual energy requirements and matched for macronutrients, with either 50g/d wholegrains in the wholegrain diet [WG] or 50g/d refined grains in the refined grain diet [RG]. The WG diet consisted of 57% wheat, 21% rice and 16% oats, and provided 90g/d wholegrains; the RG diet consistent of 73% wheat and 27% rice, and provided 0g/d wholegrains.

All meals were prepared by the investigators and provided to participants for the 8-week intervention periods for both diets. Sauces were used to mask any visual or taste differences in the WG and RG meals. The diet phases were separated by an 8-10 week washout period, during which subjects returned to habitual diet. Dietary compliance was assessed by weekly weigh-backs from the food containers provided, and in addition, alkylrecorcinols - which are compounds in a cereal grain - were assessed as biomarkers confirming dietary adherence.

Testing for glucose and insulin parameters was conducted during 3-day inpatients stays at a research facility. Glucose and insulin were assessed using stable isotope tracers. The primary outcomes were body composition, insulin secretion and glucose tolerance.



*Geek Box: Crossover Design

In a traditional comparative trial, a parallel design is often employed, where the intervention group receives a treatment, and the control group is either a placebo or other standard treatment [like habitual diet]; both arms run through the trial at the same time. In a crossover design, all participants receive both treatments sequentially, separated by a washout period, i.e., Treatment A - Washout - Treatment B. Randomisation means that the order of treatments is random, i.e., some participants start with Treatment B then switch to Treatment A, and vice versa. Generally, crossover studies are appropriate where the effects of the treatments will be short-term, such that a washout period may have the effect of returning to pre-treatment baseline. However, this is not always the case, and there may be a legacy, carryover effect of treatments, meaning it is important to statistically analyse any potential interaction of treatment order. Crossover designs are, however, quite useful for nutrition science given the inherent issue of a lack of true placebo for food, which means we're left comparing differences in the same dietary variables. Crossover designs can be helpful in this respect, to compare Diet A vs. Diet B, and manipulate specific variables between the two treatments.

Results: This study presented results in relation to 13 participants for whom glucose - stimulated insulin secretion [GSIS] data was available

- ***Anthropometrics:*** Bodyweight decreased by 2.4kg in the WG diet and 2.3kg in the RG group; fat mass decreased by 1.9kg in the WG diet and 2.4kg in the RG group. Fat-free mass decreased by 1.1kg in the WG diet and 0.2kg in the RG group.
- ***Blood glucose/insulin:*** 2-hour insulin levels were significantly lower on the WG diet compared to the RG diet. C-peptide, a marker of insulin production, was significantly higher on both diets compared to baseline, however, the RG diet tended to higher levels [not statistically significant] compared to the WG diet.
- ***Pancreatic Beta-cell Function:*** Glucose - stimulated insulin secretion [GSIS] significantly increased on the WG diet compared to baseline, but there was no significant difference between WG and RG diets. The total beta-cell* response significantly increased after WG diet, compared to the RG diet.

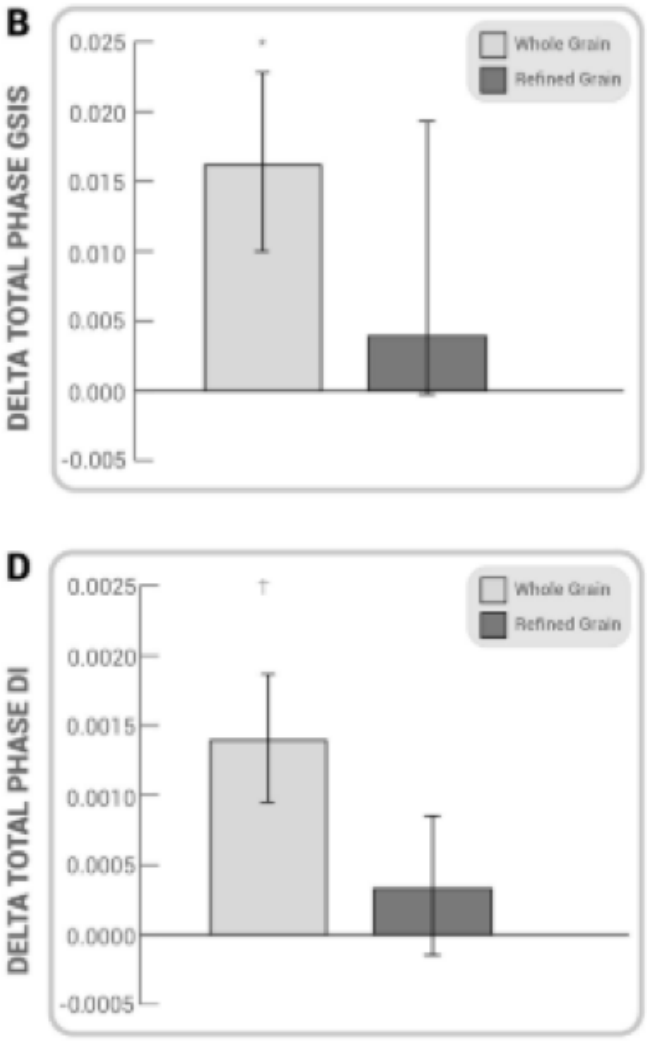


Figure *from study illustrating:* ***B*** *(top) glucose-stimulated insulin secretion [GSIS] for the total phase, i.e., the total 2-hour post-prandial period, and;* ***D*** *(bottom) the disposition index [DI], which measures beta-cell function adjusted for insulin sensitivity.*

*Geek Box: Pancreatic Beta-Cells

Understanding the role of beta-cells of the pancreas is critical to grasping the pathogenesis of T2DM. While impaired sensitivity to insulin in peripheral tissues, particularly the liver, skeletal muscle and adipose tissues, is an important factor, progression of T2DM is characterised by insufficient secretion of insulin from pancreatic beta-cells, and ultimately, failure of beta-cells to produce and secrete insulin in response to rising blood glucose levels. Insulin secretion from beta-cells is highly sensitive to changes in blood glucose levels, and is characterised by a bi-phasic response: first-phase insulin secretion is an immediate response to an increase in blood glucose following a meal, and is the release of insulin stored in beta-cells, and the second-phase response, which occurs from new insulin synthesised and released during the post-prandial period. In T2DM, glucose-stimulated insulin secretion becomes defective over time, resulting in a loss of the first-phase insulin response. Understanding of the critical role beta-cells has moved T2DM away from a purely glucose-centric view, to greater appreciation for the role of visceral fat in imparting hepatic glucose and fatty acid uptake, and the spillover of fat into the pancreas. While drugs, like sulfonylureas, target insulin secretion, to date the most effective intervention targeting restoration of beta-cell functionality appears to be from Roy Taylor's research group investigating very-low-calorie-diets [VLCD]. However, it should be stated that there appears to be a time-sensitive component to restoring beta-cell function, as beta-cells decline inexorably over time, i.e., intervention within 5-years of diagnosis may be more efficacious.

The Critical Breakdown

Pros: Only the study dietitian and statistician aware of assignment, thus both researchers and participants were 'blinded' to which diet participants were receiving. Diets were prepared for participants, and all foods and fluids provided. Efforts were made to make both diets indistinguishable, and only frozen ready meals and breakfast differed in carbohydrate source. Stable isotopes were used to assess glucose - stimulated insulin secretion [GSIS].

Cons: There is no information presented in the paper about order of diet in the paper. If it wasn't for the graphical abstract in PubMed, we wouldn't know! The authors state that an order effect was analysed, and while the washout period could be assumed to revert participants to baseline, we can't state this because but no data is presented. Further, participants were characterised as 'at risk', and had mildly elevated glucose tolerance, thus the findings may not extrapolate to over pre-diabetes or T2DM. Finally, the overall sample size was small [n=13], and thus is exploratory rather than confirmatory.

Key Characteristic

The assessment of pancreatic insulin secretion provides greater potential insight than basic calculations of peripheral tissue insulin sensitivity. It is often assumed that 'insulin sensitivity' means the ability to clear glucose into cells, particularly muscle and fat cells, however, the mechanism by which wholegrains may improve glycaemic control is in fact through effects on insulin secretion and production. In this regard, the use of the glucose - stimulated insulin secretion [GSIS] and oral disposition index [DI], which measures beta-cell function adjusted for insulin sensitivity, provided a method to elucidate whether wholegrains influence beta-cell secretion of insulin from secretory islets during the first-phase response after the initial post-prandial glucose intake, and/or influence the synthesis of insulin during the second-phase secretion. The results are for our ***Interesting Finding***, below.

Interesting Finding

The data indicate that the effect of wholegrains on overall glycaemic control may result from enhanced beta-cell function and insulin secretion. This has important implications for research, as it indicates that peripheral insulin sensitivity may not be best assessment of the glycaemic effects of a diet.

Interestingly, there was no effect on first-phase, early GSIS, suggesting that wholegrains do not influence the immediate secretion of insulin from beta-cells, but influence further synthesis of new insulin for the second-phase of secretion. This is supported by the significant finding in relation to total phase GSIS, which indicates that the effect of wholegrains encompasses the entire post-prandial period.

Adding to this interesting finding in relation to wholegrains is that adjusting for fibre did indicate that fibre was the factor influencing improved GSIS response. The effect of wholegrains on pancreatic beta-cell function has been hypothesised to result from the biological activity of the whole grain kernel, which includes the bran, germ, and endosperm, and may relate to phenolic compounds and other nutrient factors lost in the process of refinement [7]. Nonetheless, the exploratory data here suggests that the potential mechanism of action of wholegrain foods on glycaemic control relates to enhanced insulin synthesis during the post-prandial response to meals.

Relevance

Is the 'whole' in wholegrain' physiologically relevant? Some commentators have argued that refined grains are 'guilty by association' , insofar as they are consumed in food matrices rich in energy, fat, salt, and added sugars [8]. Indeed, it may be that the degree of processing may influence energy excess to a greater degree than an isolated dietary constituent, as we examined with a recent Deepdive. In addition, it is becoming clear that T2DM, and pancreatic beta-cell dysfunction in particular, is driven by accumulation of visceral fat in the liver and pancreas [9]. Thus, at the level of first principles, T2DM is a condition driven by energy excess, rather than carbohydrate alone.

Nonetheless, there is sufficient evidence to have confidence in concluding that carbohydrate type does matter, and there is growing mechanistic understanding of the biological activity of wholegrain foods [6,7]. It has to be stated that, overall, the present study is not a resounding victory for wholegrains over refined grains. Anthropometric changes were similar, although that would be expected when diets are controlled at the same level of energy intake, and many post-prandial glucose and insulin parameters were not statistically significance.

However, closer scrutiny of the data indicates that within the non-significant findings, or findings which ' trended' to significance [i..e, p-values of 0.08 or 0.09], the WG diet resulted in a net reduction in post-prandial values, while the RG diet resulted in increases. For managing blood glucose levels, therefore, to state "there is no difference" because there is no statistically significant difference is not quite correct; there is a difference, it just falls short of a statistical significance, i.e., this study falls into the category of statistically insignificant but potentially relevant. Don' t fall for p-value idolatry. A larger study could detect more significant effects.

Application to Practice

The study is exploratory, and while suggestive of an underlying mechanism through which wholegrains may improve pancreatic beta-cell function, requires replication in a larger, more powered study. Nonetheless, advice to opt for more wholegrain sources of carbohydrate foods vs. refined is a general mainstay of public health nutrition. In this respect, nothing changes: proceed as normal.

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