Whole Grain Consumption in Glycaemic Control

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Whole grain consumption is beneficial for glucose metabolism in people with diabetes.

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1. Introduction

Diabetes mellitus (DM), which is usually characterized by an absolute or relative deficiency of serum insulin concentrations, is one of most serious metabolic diseases with a sharply increasing incidence globally. It is estimated that there were about 537 million diabetics among the population aged from 20–79 worldwide in 2021, and this number is expected to reach 784 million in 2045 [1]. According to a report from the World Health Organization, since 1980, the global prevalence of DM has almost doubled from 4.7% to 8.5% in the adult population [2]. In China, there is one diabetic patient in each 12 adults; worse, the estimated prevalence of prediabetes had risen to 35.7% in 2017 [3], indicating a serious economic burden in the future.

DM is caused by both genetic and environmental factors. Findings from mechanistic studies suggest that DM can lead to abnormal changes including metabolic profiles, energy production, redox status, and extracellular matrix remodelling [4], eventually resulting in atherosclerotic cardiovascular diseases. It is reported that adults with diabetes have a 2–4 times higher cardiovascular risk than adults without diabetes [5]. A meta-analysis performed by Einarson et al. indicated that about half of the deaths in patients with type 2 diabetes mellitus (T2DM) comprise cardiovascular diseases (CVDs) [6]. Therefore, researchers believe that poor management of DM patients can increase the possibility of suffering from reduced life quality and expectancy.

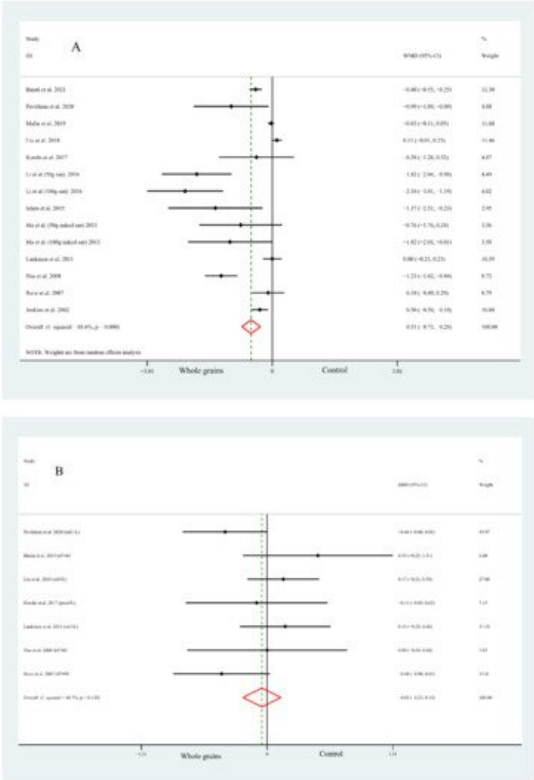
Previous studies have provided credible evidence for the key role of diet in the prevention of DM [7][8]. Whole grains are a group of cereal foods in which the endosperm, germ, and bran are intact. They are also a good source of dietary fibres, vitamins, antioxidants, and phytochemicals [9], such as phenolic compounds (including ferulic acids and cinnamic), beta-glucan, and lignans, which have been reported to play a protective role in many metabolic diseases, such as T2DM, obesity and CVDs [10][11]. The gut microbiota is referred to as a community of more than 10^{14} bacteria residing in the human intestine, and emerging discoveries have suggested that dysbiosis of the gut microbiota can result in many age-related and lifestyle diseases such as diabetes, obesity, inflammation, and CVDs [12][13][14]. A study by Zhao et al. suggested that T2DM could be alleviated by dietary fibres, which can be fermented by the gut microbiota and produce the beneficial metabolites of short-chain fatty acids (SCFAs) [15]. Indeed, a 6-week randomized controlled parallel-design trial conducted in postmenopausal women indicted that whole grain consumption led to an increased abundance of *Lachnospira* and the level of stool acetate; furthermore, *Lachnospira* was positively associated with acetate [16]. Similarly, a cross-sectional study has proposed significant associations between circulating SCFA, particularly acetate and propionate, and peripheral insulin sensitivity, whole body lipolysis and glucagon-like peptide-1 (GLP-1) concentrations [17]. In an in vivo study, Lappi et al. and Nilsson et al. also found that the consumption of barley kernel-based bread or wholegrain rye bread resulted in improved markers of glucose metabolism with increased serum SCFAs concentrations in healthy individuals [18][19]. A meta-analysis of cohort studies has established an inverse association between whole grain intake and the risk of T2DM [20]. However, the results are inconsistent in clinical trials. Li et al. found that replacing a healthy diet (low-fat and high-fibre diet) with 100 g of oats for 30 days leaded to a significant improvement in fast plasma glucose (FPG), glycosylated hemoglobin (HbA1c), and homeostasis model assessment of insulin resistance (HOMA-IR) in overweight diabetics [21]. On the other hand, a study by McGeoch et al. showed no significant differences in terms of glycaemic control following intervention with the oat-enriched diet [22]. This discrepancy may be a consequence of differences in population selection and the type and amount of whole grain production consumed. Given the inconsistent results from clinical randomized controlled trials and the absence of any systematic reviews and meta-analyses, it is necessary to perform the present study.

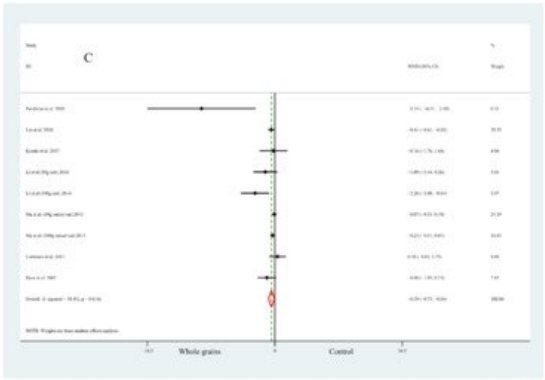
2. Effects of Whole Grain Consumption on Parameters Involve Glycaemic Control

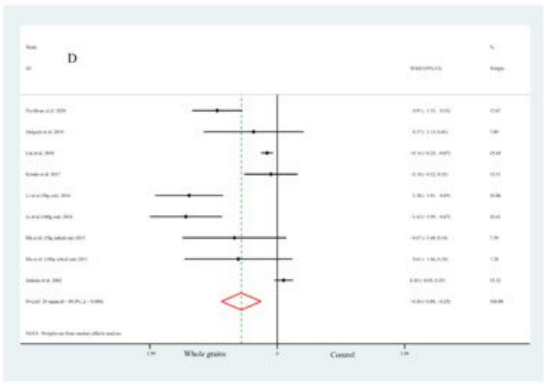
Since about 1980, because of shifts in dietary patterns and a more sedentary lifestyle, the global prevalence of DM has nearly doubled. Raised blood glucose, a common effect of uncontrolled diabetes, may, over time, lead to serious damage to the heart, blood vessels, eyes, kidneys, and nerves. However, results from a meta-analysis of prospective studies indicated that whole grain may have beneficial effects on glucose modulation [8]. These findings provide us with a new strategy for managing DM and avoiding undesirable effects caused by drug treatments.

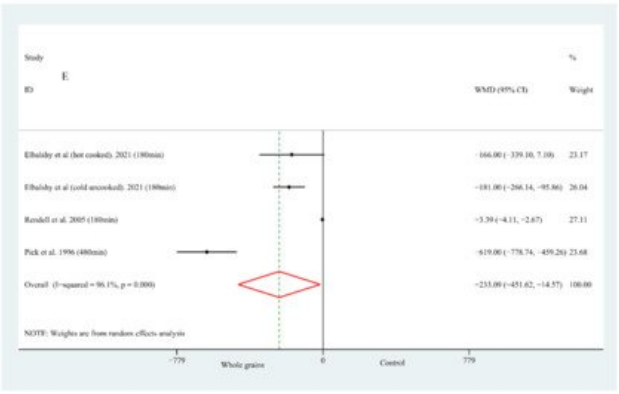
2.1. Fast Plasma GLUCOSE Concentrations

The pooled effects of whole grain consumption on FPG concentrations were reported by fourteen studies in twelve articles, which showed a significant decrease in FPG concentrations (WMD = −0.51 mmol/L, 95% CI: −0.73, −0.28, **Figure 1**A) in subjects who consumed whole grain than those in a control group, while substantial evidence of heterogeneity was found between the studies (**Figure 1**A). Of note, the results of subgroup analysis by national economic level indicated no heterogeneity within studies performed in developed countries; moreover, no significant difference was observed between groups (WMD = −0.03 mmol/L, 95% CI: −0.11, 0.04).









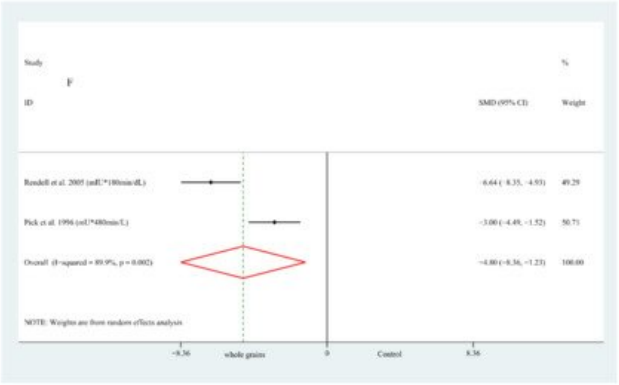


Figure 1. Forest plot of the effects of whole grain consumption on FPG (**A**), FPI (**B**), HOMA-IR (**C**), HbA1c (**D**), G-iAUC (**E**) and I-iAUC (**F**) in diabetic patients.

2.2. Fast Plasma Insulin Concentrations

The present meta-analysis consisting of seven studies demonstrated that, compared with the control group, the concentrations of FPI were not significantly changed by whole grain consumption (SMD = −0.05, 95% CI: −0.25, 0.14, **Figure 1**B), with a moderate heterogeneity (**Figure 1**B). In addition, researchers found a lower heterogeneity when it comes to the subgroup analysis by matching foods (0% for standard diet and 34.7% for others), which suggested that the controlled foods may play an important role in the evaluated outcomes.

2.3. Homeostasis Model Assessment of Insulin Resistance

Data on the effects of whole grain consumption on HOMA-IR were calculated by nine studies based on seven articles. As is shown in **Figure 1**, whole grain consumption led to a significant reduction in HOMA-IR (WMD = −0.39 μU × mol/L^2, 95% CI: −0.73, −0.04, **Figure 2**C), though with obvious heterogeneity (**Figure 1**C). Further subgroup analysis suggested that the pooled effect concluded from three studies conducted in developed countries was not significant and with low heterogeneity, which showed some similarities to FPG.

2.4. Glycosylated Haemoglobin

Overall, nine effect sizes from seven clinical trials were eligible to assess the pooled effects of whole grain consumption on HbA1c in diabetic patients. A notable decrease in pooled effect on HbA1c was observed after whole grain consumption (WMD = −0.56%, 95% CI: −0.88, −0.25, **Figure 1**D); however, there was still a serious heterogeneity before subgroup analysis (**Figure 1**D). Consequently, subgroup analysis was conducted to explore the potential sources of heterogeneity. Interestingly, when researchers focused on short-term studies (<8 weeks) or those conducted in developed countries, the results became non-significant.

2.5. Glucose/Insulin Incremental Area under the Curve

Fewer studies had reported the effects of whole grain consumption on the G-iAUC and I-iAUC. As shown in **Figure 1**, the pooled WMD for whole grain on the G-iAUC was −233.09 min × mmol/L (95% CI: −451.62, −14.57; **Figure 1**E) and with high heterogeneity (**Figure 2**E); on the other hand, there were only two studies that reported data on I-iAUC, and the pooled SMD value was −4.80 (95% CI: −8.36, −1.23; **Figure 1**F). A serious heterogeneity (**Figure 1**F) was observed as well. Since the relevant studies were scarce, it is unnecessary to conduct any further subgroup analysis

3. Discussion

To the best of The knowledge, the present study is the first systematic review and meta-analysis of randomized controlled trials to provide evidence for the effects of whole grain consumption on glucose metabolism in diabetic patients. The results, concluded from 16 studies involving 1068 subjects, indicated that compared with the control group, whole grain consumption could significantly decrease the concentration of FPG, HOMA-IR, and HbA1c, while no significant difference was observed in FPI. Additionally, significant decreases in G-iAUC and I-iAUC after whole grain intake were also observed, although the relevant studies were scarce. Different matching foods and national economic levels may explain some unknown heterogeneity.

Recently, the results from a meta-analysis of prospective cohort studies suggested that compared with a low daily intake of dietary fibre, a 35 g daily intake could make an absolute reduction of 14 fewer deaths for each 1000 participants [23]. Indeed, a pilot study conducted by Khalil et al. suggested that a 12-week whole grain plant-based diet significantly decreased the level of FPG and HbA1c in newly diagnosed diabetics [24]. Consistently, The results also showed notable improvements in FPG and HbA1c after whole grain intake, in which HbA1c is more commonly used to diagnose and identify those at higher risk of developing diabetes in the future [25]. One proposed mechanism for those effects is that fibres contained in whole grain could increase the viscosity of intestinal content, which results in slowing down the absorption of glucose and eventually delaying the gastric emptying rate [26]. In an in vitro study, Abbasi et al. found that oat-derived β-glucan could significantly reduce the uptake of glucose in non-transformed rat small intestine epithelial cells by downregulating the expressions of glucose transporters sodium–glucose-linked transport protein 1 and glucose transporter 2 [27]. Moreover, the evidence for the relationship between the gut microbiota and health has been well-established, which drives us to consider the extensive role of the gut microbiota in the glucose metabolism. A study by Qin et al. indicated that the gut microbiota of patients with T2DM is mainly characterized by a decreased abundance of butyrate-producing bacteria, namely *Roseburia* and *Faecalibacterium prauznitzii,* compared with healthy subjects [28]. Furthermore, the gut microbiota was reported to be able to deconjugate bile acid, splitting off taurine or glycine molecules. Subsequently, the unconjugated bile acids can be dehydroxylated by specific strains from the *Clostridium* genus in the large intestine, which can act as better ligands for the farnesoid X receptor (FXR) and G protein-coupled (such as TGR5) receptors [29]. TGR5 activation in pancreatic α-cells induces pro-convertase-1 expression, shifting glucagon production to GLP-1, hence increasing β-cell mass and function in a paracrine manner [30], while FXR can reduce postprandial glucose utilization by inhibiting hepatic glycolysis and lipogenesis [31]. Interestingly, when researchers focused on the trials performed in developed countries, the beneficial effects of whole grain consumption on glucose metabolism became non-significant. Similarly, a randomized controlled trial conducted in Japan indicated that there is no effect of brown rice intake on glycolipid index, but not for parameters involving endothelial function [32]. On the other hand, researchers also found evidence supporting the beneficial effects of whole grains in subjects with metabolic diseases from a published meta-

analysis [33]. Given that the study conducted in Japan did not assess the real increases in fibre intake in an experimental group; the number of local economic level-based studies in the present subgroup analysis is also relatively small. These biases may confound the results and need to be verified with well-designed trials in the future.

Insulin, which acts as a unique hormone that lowers the blood glucose in the body, plays a key role in maintaining the nutrient homeostasis during the postprandial state. It has been reported that insulin can exert many effects in a variety of tissues, including stimulating the influx of glucose into skeletal muscles and promoting the glycogen synthesis; on the other hand, in the liver and adipose tissues, insulin can suppress the production of hepatic glucose, and promote the synthesis and storage of lipids [34]. Indeed, a significant decrease in HOMA-IR value was observed upon whole grain consumption in the study. Similarly, according to Wirstrom et al., whole grain intake showed a negative correlation with HOMA-IR [35]. Moreover, evidence from a high-fat fed-diet animal study suggested that barley β-glucan could improve insulin sensitivity by decreasing serine phosphorylation of insulin receptor substrate 1 and activating Akt and downregulating the mRNA levels of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase [36]. The possible mechanism behind this may be partly attributed to SCFAs, which are produced by bacterial fermentation for dietary fibres. It has been reported that the metabolic actions of SCFAs in improvements of insulin sensitivity including increasing glucose oxidation and insulin clearance and decreasing fatty acid release [37]. Moreover, other metabolites (including lipopolysaccharide, branched-chain amino acid and bile acids) from the gut microbiota may also play an important role in insulin resistance [38]. For example, Faits et al. found that consuming an unrefined carbohydrate diet resulted in a significant increase in abundance of *Roseburia*, as well as a decreased concentration of secondary bile acid [39]. Results from another randomized controlled crossover feeding study suggested that whole grain consumption led to significant increases in circulating concentrations of taurolithocholic acid, taurocholic acid, and glycocholic acid; moreover, significant associations between bile acids and HOMA-IR were also found in this study [40]. However, the present meta-analysis indicated that whole grain consumption could not improve FPI concentration significantly, even though various subgroup analyses were further conducted. This result is consistent with the meta-analysis performed by Marventano et al., in which they also found that compared with refined foods, the consumption of whole grain is not able to significantly decrease FPI levels in healthy subjects [41]. Of note, when researchers focus on the specific whole grain (e.g., oats), relevant evidence is still needed to be confirmed. Bao et al. suggested that oat intake resulted in a significant reduction in fasting insulin by −6.29 pmol/L [42], while in a meta-analysis performed by Shen et al., there is no significant effect of oat β-glucan intake on FPI, although only two studies were included [43]. Since the diet selections of the control group may vary when studies were performed with different objectives, in current opinion, the types of control diet are very important and should be taken into consideration when exploring the potential biases.

References

1. International Diabetes Federation. IDF Diabetes Atlas, 10th ed.; International Diabetes Federation: Brussels, Belgium, 2021.
2. World Health Organization. Global Report on Diabetes; WHO: Geneva, Switzerland, 2016.
3. Li, Y.Z.; Teng, D.; Shi, X.G.; Qin, G.J.; Qin, Y.F.; Quan, H.B.; Shi, B.Y.; Sun, H.; Ba, J.M.; Chen, B.; et al. Prevalence of diabetes recorded in mainland China using 2018 diagnostic criteria from the American Diabetes Association: National cross sectional study. BMJ Br. Med. J. 2020, 369, m997.
4. De Rosa, S.; Arcidiacono, B.; Chiefari, E.; Brunetti, A.; Indolfi, C.; Foti, D.P. Type 2 Diabetes Mellitus and Cardiovascular Disease: Genetic and epigenetic Links. Front. Endocrinol. 2018, 9, 2.
5. Dal Canto, E.; Ceriello, A.; Ryden, L.; Ferrini, M.; Hansen, T.B.; Schnell, O.; Standl, E.; Beulens, J.W.J. Diabetes as a cardiovascular risk factor: An overview of global trends of macro and micro vascular complications. Eur. J. Prev. Cardiol. 2019, 26, 25–32.
6. Einarson, T.R.; Acs, A.; Ludwig, C.; Panton, U.H. Prevalence of cardiovascular disease in type 2 diabetes: A systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovasc. Diabetol. 2018, 17, 83.
7. Zheng, Y.; Ley, S.H.; Hu, F.B. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat. Rev. Endocrinol. 2018, 14, 88–98.
8. Aune, D.; Keum, N.; Giovannucci, E.; Fadnes, L.T.; Boffetta, P.; Greenwood, D.C.; Tonstad, S.; Vatten, L.J.; Riboli, E.; Norat, T. Whole grain consumption and risk of cardiovascular disease, cancer, and all cause and cause specific mortality: Systematic review and dose-response meta-analysis of prospective studies. BMJ Br. Med. J. 2016, 353, i2716.

9. Zhu, Y.D.; Sang, S.M. Phytochemicals in whole grain wheat and their health-promoting effects. Mol. Nutr. Food Res. 2017, 61, 1600852.
10. Calinoiu, L.F.; Vodnar, D.C. Whole Grains and Phenolic Acids: A Review on Bioactivity, Functionality, Health Benefits and Bioavailability. Nutrients 2018, 10, 1615.
11. Durazzo, A.; Lucarini, M.; Camilli, E.; Marconi, S.; Gabrielli, P.; Lisciani, S.; Gambelli, L.; Aguzzi, A.; Novellino, E.; Santini, A.; et al. Dietary Lignans: Definition, Description and Research Trends in Databases Development. Molecules 2018, 23, 3251.
12. Gilbert, J.A.; Blaser, M.J.; Caporaso, J.G.; Jansson, J.K.; Lynch, S.V.; Knight, R. Current understanding of the human microbiome. Nat. Med. 2018, 24, 392–400.
13. Valdes, A.M.; Walter, L.; Segal, E.; Spector, T.D. Role of the gut microbiota in nutrition and health. BMJ Br. Med. J. 2018, 361, k2179.
14. Sender, R.; Fuchs, S.; Milo, R. Revised Estimates for the Number of Human and Bacteria Cells in the Body. PLoS Biol. 2016, 14, e1002533.
15. Zhao, L.P.; Zhang, F.; Ding, X.Y.; Wu, G.J.; Lam, Y.Y.; Wang, X.J.; Fu, H.Q.; Xue, X.H.; Lu, C.H.; Ma, J.L.; et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 2018, 359, 1151.
16. Vanegas, S.M.; Meydani, M.; Barnett, J.B.; Goldin, B.; Kane, A.; Rasmussen, H.; Brown, C.; Vangay, P.; Knights, D.; Jonnalagadda, S.; et al. Substituting whole grains for refined grains in a 6-wk randomized trial has a modest effect on gut microbiota and immune and inflammatory markers of healthy adults. Am. J. Clin. Nutr. 2017, 105, 635–650.
17. Müller, M.; Hernández, M.A.G.; Goossens, G.H.; Reijnders, D.; Holst, J.J.; Jocken, J.W.E.; van Eijk, H. Circulating but not faecal short-chain fatty acids are related to insulin sensitivity, lipolysis and GLP-1 concentrations in humans. Sci. Rep. 2019, 9, 12515.
18. Lappi, J.; Mykkanen, H.; Knudsen, K.E.B.; Kirjavainen, P.; Katina, K.; Pihlajamaki, J.; Poutanen, K.; Kolehmainen, M. Postprandial glucose metabolism and SCFA after consuming wholegrain rye bread and wheat bread enriched with bioprocessed rye bran in individuals with mild gastrointestinal symptoms. Nutr. J. 2014, 13, 104.
19. Nilsson, A.C.; Johansson-Boll, E.V.; Borck, I.M.E. Increased gut hormones and insulin sensitivity index following a 3-d intervention with a barley kernel-based product: A randomised cross-over study in healthy middle-aged subjects. Br. J. Nutr. 2015, 114, 899–907.
20. Aune, D.; Norat, T.; Romundstad, P.; Vatten, L.J. Whole grain and refined grain consumption and the risk of type 2 diabetes: A systematic review and dose-response meta-analysis of cohort studies. Eur. J. Epidemiol. 2013, 28, 845–858.
21. Li, X.; Cai, X.; Ma, X.; Jing, L.; Gu, J.; Bao, L.; Li, J.; Xu, M.; Zhang, Z.; Li, Y. Short- and Long-Term Effects of Wholegrain Oat Intake on Weight Management and Glucolipid Metabolism in Overweight Type-2 Diabetics: A Randomized Control Trial. Nutrients 2016, 8, 549.
22. McGeoch, S.C.; Johnstone, A.M.; Lobley, G.E.; Adamson, J.; Hickson, K.; Holtrop, G.; Fyfe, C.; Clark, L.F.; Pearson, D.W.M.; Abraham, P.; et al. A randomized crossover study to assess the effect of an oat-rich diet on glycaemic control, plasma lipids and postprandial glycaemia, inflammation and oxidative stress in Type 2 diabetes. Diabet. Med. 2013, 30, 1314–1323.
23. Reynolds, A.N.; Akerman, A.P.; Mann, J. Dietary fibre and whole grains in diabetes management: Systematic review and meta-analyses. PLoS Med. 2020, 17, e1003053.
24. Sa'ad-Aldin, K.; Altamimi, M. Effect of whole-grain plant-based diet on the diabetes mellitus type 2 features in newly diagnosed patients: A pilot study. Int. J. Diabetes Dev. Ctries. 2019, 39, 535–546.
25. Assoc, A.D. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 2013, 36, S67–S74.
26. Muller, M.; Canfora, E.E.; Blaak, E.E. Gastrointestinal Transit Time, Glucose Homeostasis and Metabolic Health: Modulation by Dietary Fibers. Nutrients 2018, 10, 275.
27. Abbasi, N.N.; Purslow, P.P.; Tosh, S.M.; Bakovic, M. Oat beta-glucan depresses SGLT1-and GLUT2-mediated glucose transport in intestinal epithelial cells (IEC-6). Nutr. Res. 2016, 36, 541–552.
28. Qin, J.J.; Li, Y.R.; Cai, Z.M.; Li, S.H.; Zhu, J.F.; Zhang, F.; Liang, S.S.; Zhang, W.W.; Guan, Y.L.; Shen, D.Q.; et al. A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012, 490, 55–60.
29. Kuipers, F.; Bloks, V.W.; Groen, A.K. Beyond intestinal soap-bile acids in metabolic control. Nat. Rev. Endocrinol. 2014, 10, 488–498.
30. Kumar, D.P.; Asgharpour, A.; Mirshahi, F.; Park, S.H.; Liu, S.C.; Imai, Y.M.; Nadler, J.L.; Grider, J.R.; Murthy, K.S.; Sanyal, A.J. Activation of Transmembrane Bile Acid Receptor TGR5 Modulates Pancreatic Islet Cells to Promote

Glucose Homeostasis. J. Biol. Chem. 2016, 291, 6626–6640.

31. Caron, S.; Samanez, C.H.; Dehondt, H.; Ploton, M.; Briand, O.; Lien, F.; Dorchies, E.; Dumont, J.; Postic, C.; Cariou, B.; et al. Farnesoid X Receptor Inhibits the Transcriptional Activity of Carbohydrate Response Element Binding Protein in Human Hepatocytes. Mol. Cell. Biol. 2013, 33, 2202–2211.
32. Kondo, K.; Morino, K.; Nishio, Y.; Ishikado, A.; Arima, H.; Nakao, K.; Nakagawa, F.; Nikami, F.; Sekine, O.; Nemoto, K.I.; et al. Fiber-rich diet with brown rice improves endothelial function in type 2 diabetes mellitus: A randomized controlled trial. PLoS ONE 2017, 12, e0179869.
33. Marshall, S.; Petocz, P.; Duve, E.; Abbott, K.; Cassettari, T.; Blumfield, M.; Fayet-Moore, F. The Effect of Replacing Refined Grains with Whole Grains on Cardiovascular Risk Factors: A Systematic Review and Meta-Analysis of Randomized Controlled Trials with GRADE Clinical Recommendation. J. Acad. Nutr. Diet. 2020, 120, 1859.
34. Janus, A.; Szahidewicz-Krupska, E.; Mazur, G.; Doroszko, A. Insulin Resistance and Endothelial Dysfunction Constitute a Common Therapeutic Target in Cardiometabolic Disorders. Mediat. Inflamm. 2016, 2016, 3634948.
35. Wirstrom, T.; Hilding, A.; Gu, H.F.; Ostenson, C.G.; Bjorklund, A. Consumption of whole grain reduces risk of deteriorating glucose tolerance, including progression to prediabetes. Am. J. Clin. Nutr. 2013, 97, 179–187.
36. Choi, J.S.; Kim, H.; Jung, M.H.; Hong, S.; Song, J. Consumption of barley beta-glucan ameliorates fatty liver and insulin resistance in mice fed a high-fat diet. Mol. Nutr. Food Res. 2010, 54, 1004–1013.
37. Canfora, E.E.; Jocken, J.W.; Blaak, E.E. Short-chain fatty acids in control of body weight and insulin sensitivity. Nat. Rev. Endocrinol. 2015, 11, 577–591.
38. Saad, M.J.A.; Santos, A.; Prada, P.O. Linking Gut Microbiota and Inflammation to Obesity and Insulin Resistance. Physiology 2016, 31, 283–293.
39. Faits, T.; Walker, M.E.; Rodriguez-Morato, J.; Meng, H.C.; Gervis, J.E.; Galluccio, J.M.; Lichtenstein, A.H.; Johnson, W.E.; Matthan, N.R. Exploring changes in the human gut microbiota and microbial-derived metabolites in response to diets enriched in simple, refined, or unrefined carbohydrate-containing foods: A post hoc analysis of a randomized clinical trial. Am. J. Clin. Nutr. 2020, 112, 1631–1641.
40. Ginos, B.N.R.; Navarro, S.L.; Schwarz, Y.; Gu, H.W.; Wang, D.F.; Randolph, T.W.; Shojaie, A.; Hullar, M.A.J.; Lampe, P.D.; Kratz, M.; et al. Circulating bile acids in healthy adults respond differently to a dietary pattern characterized by whole grains, legumes and fruits and vegetables compared to a diet high in refined grains and added sugars: A randomized, controlled, crossover feeding study. Metab. Clin. Exp. 2018, 83, 197–204.
41. Marventano, S.; Vetrani, C.; Vitale, M.; Godos, J.; Riccardi, G.; Grosso, G. Whole Grain Intake and Glycaemic Control in Healthy Subjects: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients 2017, 9, 769.
42. Bao, L.; Cai, X.X.; Xu, M.H.; Li, Y. Effect of oat intake on glycaemic control and insulin sensitivity: A meta-analysis of randomised controlled trials. Br. J. Nutr. 2014, 112, 457–466.
43. Shen, X.L.; Zhao, T.; Zhou, Y.Z.; Shi, X.Q.; Zou, Y.; Zhao, G.H. Effect of Oat beta-Glucan Intake on Glycaemic Control and Insulin Sensitivity of Diabetic Patients: A Meta-Analysis of Randomized Controlled Trials. Nutrients 2016, 8, 39.
