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Does Whole-Grain Intake Matter for the Risk of Developing Nonalcoholic Fatty Liver Disease?

Rikard Landberg

Department of Biology and Biological Engineering, Division of Food and Nutrition Science, Chalmers University of Technology, Gothenburg, Sweden

Nonalcoholic fatty liver disease (NAFLD) is a major liver disease worldwide, with a prevalence of 20% to 46% of the adult population in Westernized countries (1). NAFLD may progress from simple steatosis—that is, accumulation of fat in the liver—to nonalcoholic steatohepatitis. The latter is characterized by additional inflammation and, in some individuals, both fibrosis, which may progress to cirrhosis, and hepatocellular carcinoma (2). The rise of NAFLD has occurred in parallel with the global rise of metabolic diseases fueled by the obesity epidemic. The main risk factors of NAFLD include a positive energy balance, obesity, insulin resistance, and hypertriglyceridemia, all of which are key targets for prevention. There is currently no effective medication for treatment of NAFLD, but clinical treatment often focuses on addressing the obesity or insulin resistance rather than NAFLD itself. Lifestyle modifications resulting in weight loss have been shown to decrease inflammation, fibrosis, and steatosis (3). Improvement of diet could play an important role in prevention and treatment, and patients with NAFLD are often given recommendations to decrease intakes of saturated fats, calories, and carbohydrates (3). It has been shown that a low-carbohydrate (<30 g/d) diet decreased hepatic de novo lipogenesis, increased hepatic β-oxidation, and had a favorable alteration in the gut microbiome among subjects with NAFLD (4).

Cereal grains represent the largest global source of energy, carbohydrates, dietary fiber, and plant protein in the diet (5). Whether grains are consumed as whole grains or refined grains has a major impact on the disease risk (6). A high whole-grain intake has consistently been associated with lower risks of developing type 2 diabetes and coronary heart disease across different populations, and an increasing number of studies are supportive of its beneficial effects on obesity and inflammation (7, 8). On the contrary, accumulating evidence suggests a high intake of refined grain is associated with higher risks of developing similar conditions in observational studies (9–11).

Given the importance of whole grain as a cornerstone of a healthy, sustainable diet; its positive effects on body-weight control, inflammation, and blood lipid profiles; and its favorable metabolic function of the gut microbiota (such as production of SCFAs), it is surprising that its role in liver-fattening conditions such as NFALD has not been more widely studied (1). Only 1 small, case-control study (58 cases and 58 controls) has been reported, and no association between self-reported consumption of whole grains and the likelihood of NAFLD was observed (11). In a cross-sectional study including 2127 nonvegetarians and 1273 vegetarians in Taiwan, an inverse association between self-reported whole-grain intake and fatty liver was observed, but disappeared after adjustment for BMI (12). In the 1 and only (GRAANDIOOS-) intervention study (13), 50 overweight men and women received a high whole-grain-wheat intervention (98g/d) compared with a high refined-wheat intervention (98g/d) for 12 weeks. A substantial increase in intrahepatic triglycerides was observed after 12 weeks on the refined-grain diet, whereas no effects were found after daily intake of whole-grain wheat, despite the high volume (13).

In this issue of *The Journal of Nutrition*, Sun et al. (14) investigated whether an alkylresorcinol metabolite in plasma 3,5-dihydroxyphenylpropionoic acid (DHPPA), a putative biomarker of whole-grain wheat and rye intake, was associated with NAFLD in a case-control study of Chinese adults. The study included 940 NAFLD cases and 940 age- and sex-matched non-NAFLD controls. Study participants were diagnosed with NAFLD if their hepatic ultrasound disclosed hepatic steatosis at any stage, after the exclusion of alcohol abuse or other liver diseases. Plasma DHPPA was inversely associated with NAFLD across tertiles [OR, 1 (lowest value; referent); OR, 0.75 (95% CI: 0.54–1.05); and OR, 0.65 (95% CI: 0.45–0.93), respectively; P-trend = 0.026). The authors concluded that a high DHPPA concentration was associated with a lower risk of NAFLD in Chinese adults, independently of common confounders, and that the results support health benefits of whole-grain wheat.

The study was relatively large and provides important data that link whole-grain intake to NAFLD, but several questions remain to be answered before causality can be established. First, the whole-grain intake in the population at study was not measured per se, but is expected to be low since the daily intake of whole grain in China (mainly from rice and wheat) is low and estimated as 24 g in 2002 (15). This is supported by the very low concentrations of DHPPA measured in the blood of study participants (the median plasma DHPPA was 10 nmol/L among healthy controls). The lack of dietary data in the study makes it difficult to judge the performance of the biomarker under the conditions at study. Second, only very few studies so far have measured the concentration of DHPPA in plasma, and even if the apparent half-life is longer for DHPPA (16 hours) than for intact alkylresorcinols in plasma (5 hours), the long-term reproducibility was found to be similar (ICC, ~0.4) (16). This suggests that DHPPA in plasma performs similarly as intact

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Address correspondence to RL (e-mail: rikard.landberg@chalmers.se).

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alkylresorcinols, despite the longer half-life, potentially because of other, as-yet-unknown sources of nonintake-related variation affecting the metabolite. Third, only 1 study has investigated the whole-grain plasma DHPPA dose-response under controlled intake conditions (17). In that study, the plasma concentrations reached 76, 89, and 110 nmol/L ($n = 20$ per group) after controlled intakes of 23, 44, and 68 g, respectively, of rye bread per day in Finnish adults. DHPPA in plasma correlated modestly with the estimated intake ($r = 0.42$; $P < 0.05$). Sun et al. (14) found that the multivariable-adjusted OR was 0.65 for the highest plasma DHPPA tertile, where DHPPA concentrations were >15 nmol/L, while in the referent tertile the DHPPA concentrations were <8 nmol/L. Based on the estimations from the Finnish study, where a difference in rye bread intake of 45 g corresponded to a 36 nmol/L difference in the plasma DHPPA concentration, a difference of 8 nmol/L between the highest and lowest tertiles in the study by Sun et al. (14) would correspond to about 16 g/d of whole-grain-wheat intake [assuming a linear dose-response without intercept, that the Finnish rye breads contained 80% whole-grain rye, and the fact that whole-grain wheat contains about 50% of alkylresorcinols (precursors of DHPPA) compared to whole-grain rye]. It is difficult to compare biomarker measurements from different laboratories and across different populations, but the example gives at least an indication about the intake in the study by Sun et al. (14) that can be compared to the estimated risk reduction. Although it has been shown that an increase in whole-grain intake may be most efficient at a low intake (0–2 servings per day) for lowering the risk of developing type 2 diabetes (9), the observed OR of 0.65 of developing NAFLD for an estimated 16 g/d difference in whole-grain wheat intake in the study by Sun et al. (14) must be considered an unexpectedly large observed relative risk reduction. This finding is totally opposite to the results from the GRAANDIOOS- intervention, where a regular intake of as much as 98 g/d of whole-grain wheat for 12 weeks did not change lipid accumulation in the liver. Instead, the findings from the GRAANDIOOS- study clearly showed that refined grains caused substantial lipid deposition in the liver during a 12-week intervention. It is difficult to compare results from an observational study with those of a dietary intervention, but it is puzzling why the results are so fundamentally different. This calls for well-designed prospective studies, preferably using dietary biomarkers in addition to self-reported data in populations where the overall whole-grain intake is higher and from several grain sources, and where careful precautions are taken to minimize the risk of residual confounding. Moreover, the specific role of refined grain in NAFLD warrants further attention in both observational and intervention studies. It also remains to be clarified to what extent whole grains other than wheat may contribute to the reduced risk of developing NAFLD. DHPPA only reflects wheat and rye intakes. Controlled interventions to investigate the effects of whole grains with potentially stronger metabolic effects than wheat (such as oats, barley and rye) are warranted to assess the full potential of whole grains on NAFLD. RL is the project leader for the Nordic Rye Forum, a pre-competitive collaboration platform between researchers from Nordic universities, institutes and food industry with interest in the health effects of rye. RL is the principal investigator in research projects funded by Lantmännen and Barilla. RL holds no remuneration, salary, or any other financial recompense from the food industry.

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References

1. Ross AB, Godin J-P, Minehira K, Kirwan JP. Increasing whole grain intake as part of prevention and treatment of nonalcoholic fatty liver disease. Int J Endocrinol 2013;2013:585876.
2. Marengo A, Rosso C, Bugianesi E. Liver cancer: connections with obesity, fatty liver, and cirrhosis. Annu Rev Med 2016;67(1):103–17.
3. Chalasani N, Younossi Z, Lavine JE, Charlton M, Cusi K, Rinella M, Harrison SA, Brunt EM, Sanyal AJ. The diagnosis and management of nonalcoholic fatty liver disease: practice guidance from the American Association for the Study of Liver Diseases. Hepatology 2018;67(1):328–57.
4. Mardinoglu A, Wu H, Bjornson E, Zhang C, Hakkarainen A, Räsänen SM, Lee S, Mancina RM, Bergentall M, Pietiläinen KH, et al. An integrated understanding of the rapid metabolic benefits of a carbohydrate-restricted diet on hepatic steatosis in humans. Cell Metab 2018;27(3):559–71.e5.
5. Poutanen KS, Kårlund AO, Gómez-Gallego C, Johansson DP, Scheers NM, Marklinder IM, Eriksen AK, Silventoinen PC, Nordlund E, Sozer N, et al. Grains - a major source of sustainable protein for health. Nutr Rev [accessed 2022 Jan 19]. doi:10.1093/nutrit/nuab084.
6. Reynolds A, Mann J, Cummings J, Winter N, Mete E, Te Morenga L. Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. Lancet North Am Ed 2019;393(10170):434–45.
7. Tieri M, Ghelfi F, Vitale M, Vetrani C, Marventano S, Lafranconi A, Godos J, Titta L, Gambera A, Alonzo E, et al. Whole grain consumption and human health: an umbrella review of observational studies. Int J Food Sci Nutr 2020;71(6):668–77.
8. Hajihashemi P, Haghighatdoost F. Effects of whole-grain consumption on selected biomarkers of systematic inflammation: a systematic review and meta-analysis of randomized controlled trials. J Am Coll Nutr 2019;38(3):275–85.
9. Aune D, Norat T, Romundstad P, Vatten LJ. 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(11):845–58.
10. Sanders LM, Zhu Y, Wilcox ML, Koecher K, Maki KC. Effects of whole grain intake, compared with refined grain, on appetite and energy intake: a systematic review and meta-analysis. Adv Nutr 2021;12(4):1177–95.
11. Georgoulis M, Kontogianni MD, Tileli N, Margariti A, Fragopoulou E, Tiniakos D, Zafiropoulou R, Papatheodoridis G. The impact of cereal grain consumption on the development and severity of non-alcoholic fatty liver disease. Eur J Nutr 2014;53(8):1727–35.
12. Chiu TH, Lin MN, Pan WH, Chen YC, Lin CL. Vegetarian diet, food substitution, and nonalcoholic fatty liver. Ci Ji Yi Xue Za Zhi 2018;30(2):102–9.
13. Schutte S, Esser D, Hoevenaars FPM, Hooiveld G, Priebe MG, Vonk RJ, Wopereis S, Afman LA. A 12-wk whole-grain wheat intervention protects against hepatic fat: the GRAANDIOOS study, a randomized trial in overweight subjects. Am J Clin Nutr 2018;108(6):1264–74.
14. Sun T, Deng Y, Geng X, Fang Q, Li X, Chen L, Zhang M, Li D, Zhu K, Li H, Liu L. Plasma alkylresorcinol metabolite, a biomarker of whole-grain intake, is inversely associated with risk of nonalcoholic fatty liver disease in a case-control study of Chinese adults. J Nutr 2022;152(4):1052–8.
15. Ge K. The transition of Chinese dietary guidelines and food guide pagoda. Asia Pac J Clin Nutr 2011;20:439–46.
16. Montonen J, Landberg R, Kamal-Eldin A, Åman P, Boeing H, Steffen A, Pischon T. Reliability of fasting plasma alkylresorcinol metabolites concentrations measured 4 months apart. Eur J Clin Nutr 2012;66(8):968–70.
17. Aubertin-Leheudre M, Koskela A, Samaletdin A, Adlercreutz H. Responsiveness of urinary and plasma alkylresorcinol metabolites to rye intake in Finnish women. Cancers 2010;2(2):513–22.