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File: ■ Rye (*Secale cereale*) Bread
■ Metabolomics

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RE: Mechanism for Beneficial Effects of Rye in Disease Prevention Illuminated

Moazzami AA, Bondia-Pons I, Hanhineva K, et al. Metabolomics reveals the metabolic shifts following an intervention with rye bread in postmenopausal women- a randomized control trial. *Nutr J.* 2012;11:88. doi: 10.1186/1475-2891-11-88.

Whole grains contain fiber, as well as various active phytochemicals, and are known to protect against chronic diseases such as type 2 diabetes, cardiovascular disease (CVD), and some cancers. Of the whole grains, rye (*Secale cereale*) has been most closely associated with a lower mortality in prospective studies. It has been shown to significantly lower postprandial insulin response, without any change in glycemia, which has been termed the "rye effect." One way to assess the physiological effects of rye is through the use of metabolomics, the study of the unique biochemical footprint that is left when a substance is metabolized that helps shed light on the underlying reasons for its health benefits. Metabolomics was used recently by the authors to compare the differential effects of high-fiber rye bread (RB) and refined wheat bread (WB). In this randomized, controlled, crossover study, they further explore the metabolomics of these 2 breads in a population at high risk for type 2 diabetes and CVD, namely, postmenopausal women.

Subjects were recruited in Finland through newspaper advertisements. They were admitted to the study if they had a body mass index (BMI) of 20-33 kg/m^2, serum total cholesterol concentration of 5.0-8.5 mmol/L, non-high-density lipoprotein (n-HDL) cholesterol concentration of 3.5-6.5 mmol/L, and serum triglyceride concentration of <2.5mmol/L; were not taking lipid-lowering drugs, laxatives, or corticosteroid medication; and had not been diagnosed with diabetes. Postmenopausal status was confirmed by measuring the concentration of follicle-stimulating hormone concentration in serum (>30 U/L). Of the 43 women recruited (aged 58.8 ± 5.8 years), 39 completed the study; however, serum samples were only obtained for 33 subjects, so analyses were done only on these 33 subjects.

The first intervention was preceded by a 2- to 3-week run-in period during which the subjects were advised on how to maintain lifestyle habits, regular medication, and body weight. The two 8-week intervention periods were separated by an 8-week washout period. During the intervention, 20% of the diet was supplied by the breads (minimum 4-5 portions per day), and additional carbohydrate sources were limited to 1 portion per day. The subjects were asked to avoid foods containing plant stanols/sterols, probiotics, and products that affect bowel function. Four-day food records were kept during the run-in period and each intervention period. Blood samples were drawn at the end of the run-in and intervention

periods. A quantitative nuclear magnetic resonance (NMR)-based metabolomics analysis was used.

The high-fiber RB (~17% dietary fiber; 24-28 g of bread per portion) was prepared by increasing the amount of rye bran in the bread. WB was 21-25 g of bread per portion. The authors do not report the source of the breads, though they do note that the study was supported by Fazer Bakeries Limited; Helsinki, Finland.

Compliance was reported to be good, with the number of portions of both breads exceeding the minimum 4 (8 portions/day). The total energy and fat intake did not differ between the intervention periods, while protein, carbohydrate, and dietary fiber intake was higher after the RB period than after the WB period ($P<0.05$). Total fat, saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid (PUFA) intake was lower at the end of each intervention period than at the end of the run-in period ($P<0.05$).

Metabolomic analysis found that there were 4 substances that were different between the 2 interventions. Plasma leucine and isoleucine were lower after the RB period than the WB period; elevation of these branched-chain amino acids has been associated with incidence of diabetes in 2 large, longitudinal studies. These amino acids can explain 60-100% of the increased risk, compared to 5-37% that can be explained by known genetic risk factors. The authors note that it is interesting that there were no effects on fasting insulin and glucose levels for either intervention.

Plasma levels of betaine were higher after the RB period than the WB period, which can be explained by the fact that bran is a rich source of betaine. Betaine acts as a methyl donor in the betaine-homocysteine methyltransferase reaction (BHMT-R), which converts homocysteine and betaine to methionine and N,N-dimethylglycine. Plasma levels of N,N-dimethylglycine were also higher after the RB intervention than after the WB intervention ($P<0.05$), which may be a result of this process. Facilitating the BHMT-R pathway has been shown to lead to a reduction in homocysteine, an independent risk factor for CVD.

Juxtaposed with this benefit is a possible drawback of higher betaine levels; total serum and low-density lipoprotein (LDL) cholesterol levels were higher after the RB period than after the WB period ($P<0.05$). No significant differences were found between HDL cholesterol and triglycerides after the RB period compared with after the WB period. A slight but significant reduction in body weight was observed within the RB group ($P<0.05$), but there was no significant difference in body weight after the RB intervention compared with after the WB intervention.

This study reveals the metabolic shifts that occur with consumption of a high-fiber RB, namely, changes in 2 pathways involving single-carbon metabolism: branched-chain amino acids and betaine-related metabolites. These 2 pathways are known to be associated with the development of chronic diseases. These insights provide a mechanism for the beneficial effects of rye in the prevention of diseases such as type 2 diabetes and CVD..

—Risa Schulman, PhD

Referenced article can be found at http://www.nutritionj.com/content/pdf/1475-2891-11-88.pdf.