Whole grain food intake elevates serum enterolactone

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Both intake of whole grain and higher levels of serum enterolactone have been related to reduced risk for CHD and some cancers. Because lignans are prevalent in the outer layers of grains, these findings may be related. We carried out a crossover feeding study in which overweight, hyperinsulinaemic, non-diabetic men (n 5) and women (n 6) ate, in random order, wholegrain foods or refined-grain foods in a diet with 30 % energy from fat. The dominant whole grain was wheat, followed by oats and rice. All food was supplied by the investigators and each diet lasted for 6 weeks, with an intervening washout period of 6–9 weeks. Serum enterolactone concentrations were higher when eating the wholegrain than the refined-grain diet by 6·2 (within person SE 1·7) nmol/l (P = 0·0008). Most of the increase in serum enterolactone when eating the wholegrain diet occurred within 2 weeks, though the serum enterolactone difference between wholegrain and refined-grain diets continued to increase through 6 weeks. Serum enterolactone concentrations can be raised by eating a diet rich in whole grains.

Phyto-oestrogens: Feeding study: Wholegrain food

There is considerable interest in the possibility that intake of wholegrain foods rich in phytochemicals such as phyto-oestrogens may play a role in reducing risk of several chronic diseases, including CHD, diabetes and cancer (Jacobs et al. 1999; Wiseman, 1999; Tikkanen & Adlercreutz, 2000; Wiseman et al. 2000). The phyto-oestrogens pinoresinol, lariciresinol, syringaresinol, secoisolariciresinol and matairesinol, which are plant lignans, are converted into the mammalian lignans enterolactone and enterodiol by intestinal bacteria (Borriello et al. 1985; Glitsø et al. 2000; Heinonen et al. 2001) and subsequently absorbed. Studies by Adlercreutz et al. (1998) and Stumpf et al. (2000b), using a time-resolved immunofluorometric assay, have demonstrated that the risk of incident heart disease was reduced in Finnish men whose serum enterolactone concentrations were in the upper quartile (Vanharanta et al. 1999). Lignan intake may also be related to cancer risk (Thompson, 1998; Ford et al. 1999). In a case-control study of 194 Finnish women with breast cancer (who entered the study before diagnosis) and 208 controls, the odds ratio in the highest quintile of enterolactone values adjusted for all known risk factors for breast cancer was 0·38 (Pietinen et al. 2001).

In the Finnish population, much of the lignan intake is believed to come from whole rye foods, as well as vegetables and berries (Adlercreutz et al. 1987; Stumpf et al. 2000a; Kilkkinen et al. 2001). Whole rye is rarely available in the USA; however, wholewheat and other wholegrain foods may also be important sources of phyto-oestrogens. If so, those who eat more wholegrain foods generally would be expected to have higher serum enterolactone than those who eat more refined-grain foods.

Based on our observation of reduced CHD (Jacobs et al. 1998) and diabetes (Meyer et al. 2000) in women from IA, USA, who habitually ate wholegrain foods, and of reduced fasting insulin in young adults who habitually ate wholegrain foods (Pereira et al. 1998), we carried out a crossover feeding study to compare metabolic differences in hyperinsulinaemic, overweight men and women when eating a diet high in wholegrain foods compared with one high in refined-grain foods, all other foods being identical between the two diets. In the present paper, we report serum

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enterolactone levels while consuming these two diets, with
the prior hypothesis that intake of wholegrain foods, com-
pared with intake of refined-grain foods, increases serum
enterolactone.

Subjects and methods

Study design

During 1998 and 1999, we conducted a randomized, non-
blinded, crossover, controlled feeding trial, fully described
elsewhere (Pereira et al. 2002). There were two 6-week
feeding periods and a washout period of 6–9 weeks.
During feeding periods, the participants were asked to con-
sume all of the food provided to them by the metabolic
kitchen of the General Clinical Research Center, University
of Minnesota, and no other food, except for energy-free
beverages. One day from the 6 d menu cycle is presented
in Table 1. Each participant received the wholegrain or
refined-grain diet during the first feeding period and then
was fed the other diet during the second period. Energy
intake for each person was based on the Harris–Benedict
equation (Harris & Benedict, 1919). It was calibrated to
maintain weight after the first 10 d of feeding during
period 1; specifically, energy intake had to be reduced in
only one participant eating whole grain and one eating
refined grain at that time. There was no statistically signifi-
cant weight change during the remainder of the study. Each
diet contained about twelve 30 g servings per d of foods
(about eight eating occasions) made with grain flour.
Wholegrain foods, including bran and germ as well as
endosperm, were substituted isovolumically for refined-
grain foods, which excluded bran and germ. Therefore,
the wholegrain foods contributed to a slightly lower
energy intake. White bread and refined wheat, rice and
corn products were substituted with commercially avail-
able wholegrain items, of which about 80 % were wheat
and the remainder oats, rice, corn, barley and rye. The
refined-grain diet had 54·6 % energy as carbohydrate,
15·7 % as protein and 30·7 % as fat. The corresponding
wholegrain diet had 54·2 % energy as carbohydrate,
17·1 % as protein and 31·7 % as fat. The saturated:
monounsaturated:polysaturated fatty acid goal was
1:1:1. The cholesterol content was controlled at a level
of 100 mg/4·18 MJ (1000 kcal). Dietary fibre intake was
17 and 28 g/8·36 MJ (2000 kcal) energy intake in the
refined- and wholegrain diets respectively. Because the
substitution of wholegrain for refined grain was isovolumic
and the bran and germ contained little energy, the whole-
grain diet contained 8·13 MJ (1943 kcal) for every
8·36 MJ (2000 kcal) in the refined-grain diet. Nutrient cal-
culations were performed using the Nutrition Data
System for Research software, version 4.02 (University
of Minnesota, Minneapolis, MN, USA).

Subject recruitment

Twelve subjects (six women and six men), recruited from
the University of Minnesota and surrounding community,
were aged between 26–54 years, had BMI between 27
and 36 kg/m², and fasting insulin between 96 and
288 pmol/l, were non-diabetic, non-smokers and otherwise

Table 1. Sample menu from the refined and wholegrain diets

<table>
<thead>
<tr>
<th>Breakfast</th>
<th>Amount (g)</th>
<th>Lunch</th>
<th>Amount (g)</th>
<th>Dinner</th>
<th>Amount (g)</th>
<th>Late night snack</th>
<th>Amount (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orange juice</td>
<td>140</td>
<td>Pasta salad: Lemon dill fish</td>
<td>150</td>
<td>Rice–brown rice, cooked†</td>
<td>170</td>
<td>Ritz crackers – wheat thins†</td>
<td>25</td>
</tr>
<tr>
<td>Rice chex–wheat chex†</td>
<td>30</td>
<td>TriColor rotini–wholewheat TriColor elbow noodle, cooked†</td>
<td>150</td>
<td>Rice–brown rice, cooked†</td>
<td>170</td>
<td>String cheese</td>
<td>30</td>
</tr>
<tr>
<td>Banana muffin–wholewheat muffin†</td>
<td>75</td>
<td>Chicken breast, cooked</td>
<td>75</td>
<td>Safflower oil</td>
<td>6</td>
<td>Grape juice</td>
<td>100</td>
</tr>
<tr>
<td>Promise margarine</td>
<td>5</td>
<td>Black olives</td>
<td>30</td>
<td>Orange roughey (raw weight)</td>
<td>85</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 % Milk Coffee–tea–herbal tea</td>
<td>180</td>
<td>Green pepper</td>
<td>20</td>
<td>Lemon juice–dill</td>
<td>80</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sugar</td>
<td>6</td>
<td>Wishbone Italian dressing</td>
<td>6</td>
<td>Salad:</td>
<td>50</td>
<td></td>
<td>50</td>
</tr>
<tr>
<td>Orange juice</td>
<td>140</td>
<td>Fat-free Italian dressing</td>
<td>20</td>
<td>Lettuce mix</td>
<td>30</td>
<td></td>
<td>30/15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Egg yolk</td>
<td>5</td>
<td>With tomato &amp; onion</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Bread stick–mixed grain</td>
<td>35</td>
<td>French bread–100 %</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>bread†</td>
<td>35</td>
<td>wholewheat bread†</td>
<td>35</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Promise margarine</td>
<td>6</td>
<td>Butter</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gingersnap–wholewheat</td>
<td>25</td>
<td>Fruit cocktail</td>
<td>100</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>gingersnap†</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Salt–pepper–herbs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Coffee–tea–herbal tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* This menu is one of six menus that were rotated over the two 6-week treatment periods.
† Grain foods (refined-grain – whole grain).
healthy according to self-report (including specific questions about major chronic diseases). Apart from one participant on hormone-replacement therapy, none was taking any prescription medication at the beginning of the study. Antibiotic use is known to reduce intestinal enterolactone production (Adlercreutz et al. 1986; Kilkkinen et al. 2002). No participant was taking an antibiotic at the beginning of the study; however, we did not inquire about antibiotic use in the months before the study began. The habitual diets of the subjects as reported prior to baseline in a food-frequency questionnaire indicated 40% energy as carbohydrate, 40% as fat and 15% as protein. Dietary fibre was 13.4 g/8.36 MJ (2000 kcal) (lower than in the refined-grain diet because of increased fruits and vegetables in the experimental base diet). Subjects consumed little alcohol and were either sedentary or moderately active in leisure time. Moderately active individuals were encouraged to maintain steady habits throughout the study. One man did not complete the study due to illness during the washout period. His results are entirely omitted from these analyses.

Clinic measurements

Participants attended the clinic at baseline and after 2, 4 and 6 weeks in each of the two diet periods. Participants were asked to avoid strenuous exercise for 24 h prior to each clinic visit. On each occasion, the Center’s nurses measured height, weight, and blood pressure and drew blood in the morning following a fast of at least 12 h. With the subject seated quietly, blood was then drawn from an antecubital vein into vacutainer tubes. Within 30 min of phlebotomy, whole blood samples were centrifuged for 10 min at 2800 g and 0.5 to 1.0 ml samples of serum were pipetted into polyethylene cryovials. Samples for serum enterolactone were stored at −70°C until shipped in dry ice for analysis in Helsinki, Finland, in 2000. Serum enterolactone was measured by the time-resolved fluororimmunoassay of Adlercreutz et al. (1998), as slightly modified by Stumpf et al. (2000b).

Statistical analysis

We present mean values with their standard errors of serum enterolactone at baseline by treatment to establish approximate equality of the starting point under each treatment. However, we did not adjust for the baseline values, because they reflect self-selected and uncontrolled dietary conditions and are assumed to washout during the first 2 weeks of each treatment period. Three of the sixty-six follow-up observations were missing. We analysed the effect of wholegrain v. refined-grain diet on serum enterolactone both non-parametrically and parametrically. In the non-parametric analysis, we carried out a sign test, with the null hypothesis that the serum enterolactone difference (wholegrain diet – refined-grain diet) is equally likely to be positive or negative. In the parametric analysis, we used the PROC MIXED program (SAS® software, version 6.12; Statistical Analysis Systems Inc., Cary, NC, USA) to perform repeated measures regression of the week 2, 4, and 6 serum enterolactone on treatment (whole v. refined), time (continuous weeks), feeding period (one v. two) and gender. These findings were presented as the mean treatment differences (with their standard errors, computed from variation within person) observed over the three follow-up time points (weeks 2, 4 and 6). A graphical presentation shows baseline and week-by-week changes by treatment (Fig. 1). This figure was based on the primary model, using discrete time and treatment × time interaction terms. Standard errors were computed within person, except when between person standard deviations are specified. An additional model included period × treatment interaction to assess whether the crossover design assumption (no memory in the second diet period of the changes in the first diet period) was violated.

Results

Compliance to the diets was assessed using reports filled out by each participant every day of the study. The energy level of protocol food not eaten during the two 6-week diets did not differ between wholegrain (160 (SD 75) kJ/d (38 (SD 18) kcal/d)) and refined grain (222 (SD 125) kJ/d (53 (SD 30) kcal/d)); treatments. The same was true of extra (non-protocol) food from sources other than the treatment diets (wholegrain 46 (SD 25) kJ/d (11 (SD 6) kcal/d)) refined 63 (SD 33) kJ/d (15 (SD 8) kcal/d)). No side effects were noted. The validity of the crossover design was supported by the observation that period × time interaction was not significant in any model (results not shown).

Baseline serum enterolactone showed substantial variation between subjects (SD 14.3 nmol/l) and within subjects (SD 9.3 nmol/l); the intraclass correlation was 0.70. At baseline, women appeared to have higher serum enterolactone than men by 14.1 (between person SE 9.6) nmol/l (baseline mean value 20.1 nmol/l in women, 6.0 nmol/l in men)
men, \(P=0.17\)). The baseline serum enterolactone did not differ significantly between treatments (mean value 16.8 nmol/l before the refined-grain diet and 10.6 nmol/l before the wholegrain diet (within person SE 4.0 nmol/l, \(P=0.15\)).

Table 2 gives the serum enterolactone concentrations for each participant at each measurement point. In non-parametric analysis, serum enterolactone concentration was higher when eating the wholegrain diet than when eating the refined-grain diet in twenty-one of the thirty available post baseline measurement pairs (sign test \(z=2.2\), \(P=0.028\). In parametric analysis, serum enterolactone concentrations were higher when eating the wholegrain than the refined grain diet by 6.2 (within person SE 1.7) nmol/l (\(P=0.0008\)). The week-by-week changes in serum enterolactone are shown in Fig. 1. The difference in serum enterolactone between the wholegrain and refined-grain diets was evident after 2 weeks. Nevertheless, the serum enterolactone difference between wholegrain and refined-grain diets continued to increase over the 6-week period.

Despite higher serum enterolactone concentrations in women than in men, the wholegrain – refined-grain diet difference was similar in the six women (6.7 (within person SE 2.5) nmol/l, \(P=0.009\)) and the five men (5.6 (within person SE 2.6) nmol/l, \(P=0.04\)). We note that power to study gender-specific differences is limited in this small study.

Two participants took antibiotics during this feeding study (Table 2). In the first, during the refined-grain diet, serum enterolactone decreased from 19 nmol/l at study week 2 to 8 nmol/l at study week 4 shortly after beginning the antibiotic; it remained at 8 nmol/l at study week 6. In the second case, during the wholegrain diet, serum enterolactone decreased from 13 nmol/l at baseline to 3 nmol/l at study week 2. 2 d after beginning the antibiotic; it increased to 31 nmol/l at study week 4 and 42 nmol/l at study week 6. Omission of these observations from the analysis did not qualitatively alter the findings of this study.

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### Table 2. Serum enterolactone (nmol/l) for each subject at weeks 0, 2, 4 and 6 of each feeding period*

<table>
<thead>
<tr>
<th>Subject†</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
<th>Week 0</th>
<th>Week 2</th>
<th>Week 4</th>
<th>Week 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25.5</td>
<td>15.2</td>
<td>25.2</td>
<td>35.9</td>
<td>5.8</td>
<td>29.2</td>
<td>24.2</td>
<td>23.3</td>
<td>−19.7</td>
<td>14.0</td>
<td>−1.1</td>
<td>−12.6</td>
</tr>
<tr>
<td>B‡</td>
<td>13.5</td>
<td>19.5</td>
<td>8.1</td>
<td>8.4</td>
<td>6.8</td>
<td>19.8</td>
<td>23.0</td>
<td>23.9</td>
<td>−6.7</td>
<td>0.3</td>
<td>14.9</td>
<td>15.5</td>
</tr>
<tr>
<td>C</td>
<td>7.0</td>
<td>9.9</td>
<td>6.8</td>
<td>9.7</td>
<td>2.8</td>
<td>12.4</td>
<td>19.0</td>
<td>9.4</td>
<td>−4.2</td>
<td>2.4</td>
<td>12.2</td>
<td>−0.3</td>
</tr>
<tr>
<td>D</td>
<td>80.0</td>
<td>28.9</td>
<td>28.6</td>
<td>31.6</td>
<td>41.9</td>
<td>56.4</td>
<td>39.3</td>
<td>30.8</td>
<td>−38.1</td>
<td>27.5</td>
<td>10.7</td>
<td>−0.9</td>
</tr>
<tr>
<td>E</td>
<td>5.4</td>
<td>0.2</td>
<td>0.0</td>
<td>0.0</td>
<td>5.8</td>
<td>0.1</td>
<td>2.1</td>
<td>2.9</td>
<td>0.4</td>
<td>0.0</td>
<td>2.1</td>
<td>2.9</td>
</tr>
<tr>
<td>F§</td>
<td>18.0</td>
<td>11.6</td>
<td>14.4</td>
<td>10.7</td>
<td>13.1</td>
<td>3.3</td>
<td>30.9</td>
<td>42.4</td>
<td>−4.9</td>
<td>−8.3</td>
<td>16.5</td>
<td>31.7</td>
</tr>
<tr>
<td>G</td>
<td>7.7</td>
<td>12.9</td>
<td>20.7</td>
<td>11.1</td>
<td>17.0</td>
<td>25.6</td>
<td>−</td>
<td>46.1</td>
<td>9.2</td>
<td>12.6</td>
<td>−</td>
<td>35.1</td>
</tr>
<tr>
<td>H</td>
<td>17.8</td>
<td>4.7</td>
<td>9.9</td>
<td>7.2</td>
<td>16.9</td>
<td>−</td>
<td>9.6</td>
<td>17.8</td>
<td>−0.9</td>
<td>−</td>
<td>−0.1</td>
<td>10.6</td>
</tr>
<tr>
<td>I</td>
<td>1.8</td>
<td>0.5</td>
<td>1.2</td>
<td>1.5</td>
<td>0.2</td>
<td>0.7</td>
<td>1.7</td>
<td>0.7</td>
<td>−1.5</td>
<td>0.2</td>
<td>0.5</td>
<td>−0.8</td>
</tr>
<tr>
<td>J</td>
<td>7.4</td>
<td>6.8</td>
<td>6.8</td>
<td>3.2</td>
<td>5.4</td>
<td>10.0</td>
<td>1.9</td>
<td>8.0</td>
<td>−1.9</td>
<td>3.1</td>
<td>−1.0</td>
<td>4.0</td>
</tr>
<tr>
<td>K</td>
<td>1.2</td>
<td>0.6</td>
<td>−</td>
<td>2.8</td>
<td>0.3</td>
<td>2.9</td>
<td>11.8</td>
<td>5.9</td>
<td>−1.5</td>
<td>2.3</td>
<td>−</td>
<td>3.1</td>
</tr>
</tbody>
</table>

*, Not done or non-computable.
† For details of diets, subjects and procedures, see Table 1 and p. 112.
‡ Subject B took antibiotic for illness after week 2 of the refined-grain diet.
§ Subject F took antibiotic for illness 2 d before week 2 of the wholegrain diet.

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**Discussion**

We found that serum enterolactone can be raised by eating a diet containing about twelve 30 g servings of wholegrain foods/8.36 MJ (2000 kcal) per d, compared with an identical American Heart Association step I diet containing refined instead of wholegrain foods (Krauss et al. 1996). The present controlled feeding study had 85% statistical power for detecting a wholegrain effect on serum enterolactone as small as 5.1 nmol/l. It demonstrated the possibility of changing serum enterolactone using commercially available wholegrain products (mostly wheat, oats and rice). Lignans may play a causal role in chronic disease risk (Thompson, 1998; Ford et al. 1999; Vanharanta et al. 1999; Pietinen et al. 2001), although it is not known whether the mammalian lignan enterolactone itself is involved in pathogenic processes. Other components of wholegrain and other minimally processed plant foods may also play a role in pathogenesis (Slavin et al. 1999; Pins et al. 2001). At minimum, serum enterolactone may be reflective of whole grain intake, including rye (Juntunen et al. 2000) in the Finnish diet and whole wheat in the US diet (Gerrior & Bente, 2001).

Many vegetables and berries and some fruits increase the serum enterolactone level. In the present study, the 30% energy as fat diet included various lignan-containing foods apart from grains, such as oranges, pineapple, blueberry, black olives, carrots, broccoli, onions, green beans, celery, lettuce, peanuts, green pepper, mushrooms and tea (Mazur & Adlercreutz, 1998). As these foods were present in identical quantities in both wholegrain and refined-grain feeding periods, the observed effect of whole grain intake on serum enterolactone is above and beyond that of other enterolactone-inducing foods. To reach levels of serum enterolactone of more than 30 nmol/l that were associated with significantly reduced breast cancer risk in women (Pietinen et al. 2001) and acute coronary events in men (Vanharanta et al. 1999), whole grain, vegetable, fruit and berry consumption has to be adequate. In a dietary
intervention study in a Finnish population regularly consuming wholegrain rye bread, the consumption of vegetables, fruit and berries was increased and this resulted in an increase of the mean plasma enterolactone level from 12.2 to 19.5 nmol/l but still only 30% of the subjects reached a level above 30 nmol/l and 35% still had levels below 15 nmol/l (Stumpf et al. 2000a).

Although wholegrain breads and cereals, vegetables and berries are related to serum enterolactone, they do not explain much of the variability of serum enterolactone. It is believed that the composition and activity of the bacterial flora on fermentation in the upper part of the colon plays a dominant role in the maintenance of serum enterolactone concentrations (Glitsø et al. 2000; Kilkkinen et al. 2001). Administration of antibiotics drastically reduces the levels (Adlercreutz et al. 1986; Kilkkinen et al. 2002) and after intake of antibiotics the pretreatment plasma concentration of enterolactone was not reached again for about 1 year. In the present study, serum enterolactone rebounded after 2 weeks in the single subject who took antibiotics while consuming the wholegrain diet. That the effect of antibiotics on gut flora may be an important factor in the aetiology of disease is shown by the recent study that observed that women taking several antibiotic courses for urinary tract infections had increased risk of breast cancer (Knekt et al. 2000). Whether lowering of plasma enterolactone concentration itself played a role in the increased risk for development of breast cancer is not known.

In summary, a diet high in foods containing wholegrain or wholemeal wheat, oats, rice and other grains caused an elevation in serum enterolactone.

Acknowledgements

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References


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