Interaction between cholesterol and glucose metabolism during dietary carbohydrate modification in subjects with the metabolic syndrome¹⁻³

Maarit Hallikainen, Leena Toppinen, Hannu Mykkänen, Jyrki J Ågren, David E Laaksonen, Tatu A Miettinen, Leo Niskanen, Kaisa S Poutanen, and Helena Gylling

ABSTRACT

Background: Carbohydrate modification based on rye bread and pasta enhances early insulin secretion in subjects with the metabolic syndrome.

Objective: Because the actions of insulin and cholesterol metabolism are interrelated, the question is raised of whether it is possible to alter cholesterol metabolism by means of dietary carbohydrate modification.

Design: We investigated the 12-wk effects of dietary carbohydrate modification on cholesterol synthesis and absorption by measuring the ratios of surrogate markers of precursor (cholestenol, desmosterol, and lathosterol) and absorption (cholestanol and plant sterols) sterols to cholesterol and their association to glucose metabolism in 74 subjects with the metabolic syndrome. The subjects were randomly assigned to diets with rye bread and pasta (RPa) or oat, wheat bread, and potato (OWPo) as the main carbohydrate source (34% and 37% of energy intake, respectively).

Results: During the study, serum cholesterol concentrations remained unchanged. Cholesterol synthesis was lower (6–10% for cholestenol and lathosterol; P < 0.05) and absorption higher (9%; P < 0.05 for sitosterol) with the OWPo diet than at baseline. With the RPa diet, cholesterol absorption was lower and synthesis higher than with the OWPo diet. The increment in the glucose area under the curve with the RPa diet was positively related to baseline cholesterol synthesis (eg, lathosterol; r = 0.480, P < 0.05) and negatively to absorption (for cholestenol; r = −0.520, P < 0.05). In the combined group, the changes in the cholestenol ratio and the insulinogenic index were interrelated (r = −0.464, P < 0.001).

Conclusions: Carbohydrate modifications had dissimilar effects on cholesterol metabolism. Consumption of RPa, as compared with OWPo, may be clinically more favorable because it seems to inhibit the absorption of cholesterol, a factor crucial in the development of arterial atherosclerosis. Am J Clin Nutr 2006;84:1385–92.

KEY WORDS Rye, oat, wheat, metabolic syndrome, glucose metabolism, cholesterol metabolism, sitosterol, campesterol, lathosterol, randomized controlled trial

INTRODUCTION

In epidemiologic studies, high intakes of total and cereal fiber, whole-grain cereals, and low–glycemic index foods have been found to be associated with decreased risks of type 2 diabetes (1–3) and cardiovascular diseases (4–6). In healthy adults, the consumption of rye bread has been noted to decrease the postprandial insulin response, and daily consumption of rye bread improves first-phase insulin secretion compared with that after consumption of refined wheat bread (7). Furthermore, carbohydrate modification of rye bread and pasta has been found to enhance early insulin secretion in subjects with the metabolic syndrome (8). That effect was not solely due to the fiber content of rye and pasta, however, because consumption of low–fiber rye bread can decrease insulin and incretin responses just as effectively as does high-fiber rye bread (9).

The reduced postprandial insulin response to rye bread may be due to the firm bread matrix of rye bread (9). Consumption of rye bread and pasta has been claimed to improve acute insulin secretion by chronically lowering postprandial insulin responses and improving β cell function (8). In addition to insoluble fiber, rye fiber contains soluble fiber in the form of arabinoxylans (9%) and β-glucan (2–3%) (10, 11). It is well known that ingestion of soluble fiber can affect serum cholesterol concentrations. Serum total and LDL-cholesterol concentrations are reduced by 10–15% if an individual consumes 8 g soluble fiber/d (12, 13). This effect is largely based on the ability of soluble fiber to increase fecal bile acid excretion and to inhibit cholesterol absorption from the intestine (14).

Recent findings indicate that there is an interrelation between overall insulin sensitivity and cholesterol metabolism, such that insulin-resistant persons have reduced cholesterol absorption but elevated cholesterol synthesis (15). This poses the question of whether cholesterol synthesis and absorption can be altered by dietary carbohydrate modification. Therefore, the aim of the present study was to investigate whether 2 diets, one based on rye

¹ From the Departments of Clinical Nutrition (MH, LT, HM, and HG), Physiology (JJA and DEL), and Medicine (DEL and LN) and the Food and Health Research Centre (KSP), University of Kuopio, Kuopio, Finland; Kuopio University Hospital, Kuopio, Finland (HG, DEL, and LN); the Department of Medicine, Division of Internal Medicine, University of Helsinki, Helsinki, Finland (TAM); and VTT Biotechnology, Espoo, Finland (KSP).
² Supported by the Diabetes Research Association, the Finnish Cultural Foundation of Northern Savo, Kuopio University Hospital (EVO), and the Yrjö Jahnsson Foundation.
³ Address reprint requests to M Hallikainen, Department of Clinical Nutrition, University of Kuopio, PO Box 1627, FIN-70211 Kuopio, Finland. E-mail: maarit.hallikainen@uku.fi.
Received April 6, 2006.
Accepted for publication July 31, 2006.
bread and pasta and the other on oat-wheat bread and potato, would have different effects on cholesterol metabolism as assessed via serum noncholesterol sterols, ie, surrogate markers of cholesterol synthesis and absorption (16). The ratios of the serum cholesterol precursor sterols cholestenol, lathosterol, and desmosterol to cholesterol reflect sterol balance data (16, 17). Furthermore, the serum concentration of lathosterol is a measure of the activity of hydroxymethylglutaryl CoA reductase (18). Serum campesterol, sitosterol, and cholestanol ratios are related to the absolute and percentage absorptions of dietary cholesterol (16, 17).

SUBJECTS AND METHODS

Subjects

The subjects, study design, and diets have been described more precisely elsewhere (8). In brief, 81 subjects with the metabolic syndrome were recruited into the study. To be included in the study, the subjects had to be 40–70 y old with a body mass index (BMI; in kg/m²) of 26–40. In addition, they had to meet the National Cholesterol Education Program criteria (19) for the metabolic syndrome, ie, ≥3 of the following 5 conditions had to be present: 1) a waist circumference > 102 cm (for men) or 88 cm (for women), 2) a fasting serum triacylglycerol concentration > 1.7 mmol/L, 3) a fasting HDL-cholesterol concentration < 1.0 mmol/L (for men) or 1.2 mmol/L (for women), 4) impaired fasting glucose (plasma glucose between 6.1 and 6.9 mmol/L), and 5) blood pressure > 130/85 mm Hg or use of blood pressure medication. Subjects were excluded if they had been diagnosed with diabetes, were taking any cholesterol-lowering medication or functional food products for cholesterol lowering or were using corticosteroids. Seven subjects dropped out of the study: 2 disliked the test breads and 5 suffered health problems unrelated to the study. Thus, 74 subjects completed the study (Table 1), but the insulinogenic index was available for 72 subjects only.

Seven subjects had been taking thyroxin therapy for hypothyroidism for years, and they were euthyroid. Fourteen women were taking hormone replacement therapy. Forty-four subjects were receiving medication for hypertension (Table 1). Eight subjects had previously undiagnosed type 2 diabetes with fasting glucose concentrations between 7.1 and 7.3 mmol/L, but because in other respects they met the inclusion criteria, they were included in the study. Thirty subjects had impaired glucose tolerance as diagnosed by a 2-h oral-glucose-tolerance test (Table 1).

The subjects provided their informed consent for the study. The study protocol was approved by the ethics committee of the University of Kuopio.

Study design

The study was carried out with a parallel study design with 2 groups, and it consisted of a 4-wk baseline period and a 12-wk test period (8). At the end of the baseline period, the subjects were randomly assigned to 1 of 2 groups on the basis of sex, median age, and plasma 2-h glucose concentration: one group (16 men and 22 women) received oat-wheat bread and potato (OWPo), and the other group (20 men and 16 women) received rye bread and pasta (RPa). Fifty-five subjects began the study in autumn 2003 and 19 in spring 2004. The baseline characteristics of the subjects are presented in Table 1. The subjects were requested to maintain their medication and weight and to not change their alcohol consumption, smoking habits, or physical activity during the study.

Test diets

In the OWPo group, the test bread consisted of 3 commercial breads (wheat bran bread, gram flour toast, and gram crisp bread) and an oat bread (60% whole-meal oat flour and 40% wheat flour), which was produced by VTT Biotechnology (Espoo, Finland). In the RPa group, the test breads were 3 commercial whole-meal rye breads and a low-fiber endosperm rye bread, which was prepared by VTT Biotechnology. The commercial breads were widely used breads from Finnish bakeries (Fazer Bakeries Ltd, Vantaa, Finland, and Vaasan & Vaasan Bakeries Ltd, Espoo, Finland). All test breads were provided to the subjects from the study center.

The subjects replaced their customarily used breads and baked products with the test breads during the test period, aiming to meet ≥25% of their daily energy intake from the breads. About one-half of the daily bread consumption was to be oat bread in the OWPo group and endosperm rye bread in the RPa group. The subjects in the RPa group received a package (400 g) of dark pasta or spaghetti once weekly, and they were advised to use one portion of pasta (70 g dry pasta) ≥3 times per week as part of warm dishes. The OWPo group was advised to use mainly potatoes as part of their warm food and were therefore given a package (210 g) of powdered mashed potatoes once weekly. Otherwise, the diet was to be maintained unchanged. The nutrient composition of the test products is presented in Table 2.

Adherence to the diets was monitored by daily records of bread use and by three 4-d food records, 1 conducted before the study.
and 2 conducted during the experimental period. One of the recording days was a weekend day. The subjects kept daily records of the number of portions of the test breads, potato, and pasta as well as of the quantity, quality, and frequency of the other cereals eaten. The nutrients in the food records were calculated by using Micro-Nutrica dietary analysis software (The Social Insurance Institution, Turku, Finland) on the basis of Finnish food analyses and international food-composition tables (21).

Two-hour glucose tolerance test

An oral-glucose-tolerance test was conducted at the beginning and the end of the study (8). Blood samples to measure plasma glucose and serum insulin concentrations were drawn at 15, 30, 45, 60, 90, and 120 min after the start of drinking the glucose solution. The glucose and insulin areas under the curve (AUCs) were calculated.

Calculations

The insulinogenic index was calculated as the increment in insulin during the first 30 min after oral glucose ingestion divided by the corresponding increment in glucose. The homeostasis model assessment index of insulin resistance was calculated as the fasting serum insulin concentration/L1154 the fasting plasma glucose concentration/22.5 (22).

Laboratory measurements

Body weight was measured with the same calibrated digital scale throughout the study. Plasma glucose was analyzed by an enzymatic photometric method using Konelab Glucose HK reagent (Thermo Clinical Labsystems Oy, Vantaa, Finland) and a Kone Pro Clinical Chemistry Analyzer (Thermo Clinical Lab systems Oy). LDL cholesterol was calculated (23). Serum high-sensitivity C-reactive protein was measured by the chemiluminescence-immunoassay method with reagent Immulite 2000 High Sensitivity CRP and Immulite 2000 (DPC, Los Angeles, CA).

Synthesis and absorption markers of cholesterol in serum were quantified from nonsaponifiable serum material by capillary gas-liquid chromatography (HP 5890 Series II plus; Hewlett-Packard, Wilmington, DE) with a 50-m Ultra 1 capillary column (5% phenyl-methyl siloxane) (Agilent Technologies, Wilmington, DE) (24). Squalene and noncholesterol sterol values were quantified from nonsaponifiable serum material by capillary gas-liquid chromatography (Agilent Technologies, Wilmington, DE) (24). Squalene and noncholesterol sterol values were expressed in terms of 10² mmol/mol cholesterol (referred to as ratio in the text), ie, by dividing the squalene and sterol values by the cholesterol value from the same gas-liquid chromatography run to eliminate the effects of different serum cholesterol concentrations. In addition, we determined the ratios of cholesterol synthesis sterols (cholestenol, desmosterol, and lathosterol) to absorption markers (cholesterol, campesterol, and sitosterol) to evaluate cholesterol metabolism even more accurately (16); in some cases, specific sterol ratios will be used.

Statistical analyses

All statistical analyses were performed with SPSS for WINDOWS 11.5 (SPSS, Chicago, IL). The results are given as means ± SEMs.

Normal distribution and homogeneity of variance were checked before further analyses. Univariate analysis of variance was used to compare baseline values between groups. The analysis of variance for repeated measurements (general linear model) was used to compare the overall changes and the effect of the time of entrance into the study (autumn or spring) and sex in between-group comparisons. When significant time-by-group interactions were found, paired t tests were used in further analyses. In addition, the changes between groups were assessed by using univariate analysis of variance. The changes in nutrient intakes (saturated fatty acids, proteins, carbohydrates, and total, soluble, and insoluble fiber) that differed between the study groups were included as covariates in analyses of covariance. For

---

**TABLE 2**

Nutrient composition of the test products

<table>
<thead>
<tr>
<th>Available carbohydrates</th>
<th>Total fiber</th>
<th>Soluble fiber</th>
<th>Insoluble fiber</th>
<th>Proteins</th>
<th>Fat</th>
<th>Energy</th>
</tr>
</thead>
<tbody>
<tr>
<td>% by wt</td>
<td>% by wt</td>
<td>% by wt</td>
<td>% by wt</td>
<td>% by wt</td>
<td>% by wt</td>
<td>kJ/MJ</td>
</tr>
<tr>
<td>Oat-wheat-potato group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oat bread</td>
<td>31.2</td>
<td>5.4</td>
<td>1.8</td>
<td>3.6</td>
<td>13.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Graham toast</td>
<td>42.1</td>
<td>5.3</td>
<td>1.4</td>
<td>3.9</td>
<td>8.9</td>
<td>5.7</td>
</tr>
<tr>
<td>Wheat-bran bread</td>
<td>43.5</td>
<td>4.6</td>
<td>1.2</td>
<td>3.4</td>
<td>16.4</td>
<td>4.5</td>
</tr>
<tr>
<td>Graham crisp bread</td>
<td>67.7</td>
<td>8.3</td>
<td>2.3</td>
<td>6.0</td>
<td>11.0</td>
<td>6.3</td>
</tr>
<tr>
<td>Powdered mashed potatoes</td>
<td>73.5</td>
<td>6.7</td>
<td>1.9</td>
<td>4.8</td>
<td>5.7</td>
<td>4.3</td>
</tr>
<tr>
<td>Rye-pasta group</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endosperm rye bread</td>
<td>44.6</td>
<td>5.7</td>
<td>2.1</td>
<td>3.6</td>
<td>4.1</td>
<td>0.7</td>
</tr>
<tr>
<td>Whole-meal rye 1 bread</td>
<td>45.2</td>
<td>10.1</td>
<td>2.5</td>
<td>7.6</td>
<td>9.8</td>
<td>1.6</td>
</tr>
<tr>
<td>Whole-meal rye 2 bread</td>
<td>45.3</td>
<td>15.3</td>
<td>3.9</td>
<td>11.4</td>
<td>12.5</td>
<td>2.5</td>
</tr>
<tr>
<td>Whole-meal rye crisp bread</td>
<td>56.1</td>
<td>17.0</td>
<td>5.0</td>
<td>12.0</td>
<td>9.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Dry dark pasta</td>
<td>59.4</td>
<td>5.9</td>
<td>1.0</td>
<td>4.5</td>
<td>10.4</td>
<td>3.0</td>
</tr>
</tbody>
</table>

1 Nutrient composition data of powdered mashed potatoes and dry pasta are based on FINELI (Finnish food-composition database; 20). The nutrient composition of the test breads was analyzed by VTT Biotechnology (Espoo, Finland).
glucose, insulin, and sterol variables, Pearson or Spearman correlation coefficients were calculated. To control the overall \( \alpha \) level, Bonferroni adjustment was used. The variables that explained changes in the insulinogenic index (see the footnote to Table 6) were assessed by multiple regression analyses by including those variables with a significance of \( P < 0.25 \) in the univariate analysis. Highly related variables were not included into the same model. Variables that were not normally distributed even after different transformations, were not homogeneous in variance, or were noncontinuous were tested with Mann-Whitney or chi-square tests. \( P \) values < 0.05 were considered statistically significant.

**RESULTS**

**Baseline characteristics**

There were no significant differences in baseline values or in any of the background variables between the groups (Table 1), ie, the subjects were successfully randomly assigned to the OWPo and RPa groups. In addition, neither time of entrance into the study nor sex affected the results of the between-group comparisons.

**Feasibility of diet**

According to the daily records, adherence to the diet was good (8), and in both groups the consumption of the bread portions exceeded the minimum recommendation during the test period. The consumption of the higher fiber diet did not evoke any negative side effects. The mean consumption of test breads was 247.3 ± 11.2 and 244.3 ± 10.2 g/d with the oat bread and endosperm rye breads, respectively, which accounted for 146.6 ± 5.1 and 155.0 ± 5.9 g/d in the OWPo and RPa groups, respectively. The oat-wheat breads made up 33.2 ± 1.4% and the rye breads 28.8 ± 1.2% of daily energy intake. In the OWPo group, potato intake averaged 3.6 ± 0.2% of energy and pasta intake averaged 1.4 ± 0.2% of energy. In the RPa group, pasta intake averaged 5.4 ± 0.4% of energy and potato intake 2.3 ± 0.2% of energy. Plant sterol intakes from the study products were 36.4 ± 1.4 mg/d (\( P = 0.019 \)) in the OWPo group and 10.8 ± 0.6 mg/d (\( P = 0.001 \)) in the RPa group, respectively.

**BMI and waist circumference**

BMI increased (by 0.13–0.21) and waist circumference decreased (by 0.9–1.5 cm) significantly from baseline in both groups, but the changes did not differ significantly between the groups nor were any effects detected on serum lipid or sterol values.

**Glucose, insulin, and serum lipids**

The effects of carbohydrate modification on glucose and insulin metabolism have been presented in detail elsewhere (8). Briefly, the insulinogenic index increased more in the RPa group than in the OWPo group (33.2% compared with 5.5%; \( P = 0.026 \)), but there were no significant differences in the percentage

---

### Table 3

| Nutrient intake during the study in the 2 study groups
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oat-wheat-potato group</td>
<td>Rye-pasta group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n = 38)</td>
<td>(n = 36)</td>
<td></td>
</tr>
<tr>
<td>Energy (MJ/d)</td>
<td>7.5 ± 0.3</td>
<td>8.0 ± 0.3</td>
<td>8.4 ± 0.4</td>
</tr>
<tr>
<td>Fat (% of energy)</td>
<td>31.2 ± 0.9</td>
<td>28.2 ± 0.8</td>
<td>31.5 ± 1.2</td>
</tr>
<tr>
<td>SFA (% of energy)</td>
<td>11.8 ± 0.4</td>
<td>9.2 ± 0.4</td>
<td>11.4 ± 0.5</td>
</tr>
<tr>
<td>MUFA (% of energy)</td>
<td>10.2 ± 0.4</td>
<td>7.7 ± 0.3</td>
<td>10.8 ± 0.5</td>
</tr>
<tr>
<td>PUFA (% of energy)</td>
<td>5.6 ± 0.3</td>
<td>3.7 ± 0.3</td>
<td>5.8 ± 0.3</td>
</tr>
<tr>
<td>Protein (% of energy)</td>
<td>17.8 ± 0.6</td>
<td>19.8 ± 0.5</td>
<td>17.4 ± 0.4</td>
</tr>
<tr>
<td>Carbohydrates (% of energy)</td>
<td>47.0 ± 0.9</td>
<td>47.7 ± 1.0</td>
<td>45.5 ± 1.6</td>
</tr>
<tr>
<td>Alcohol (% of energy)</td>
<td>0.03 ± 0.01</td>
<td>0.03 ± 0.01</td>
<td>0.04 ± 0.01</td>
</tr>
</tbody>
</table>

| Cholesterol (mg/d) | 237.6 ± 14.1 | 209.5 ± 12.8 | 271.6 ± 21.0 | 237.2 ± 17.3 |
| Cholesterol (mg/MJ) | 31.9 ± 1.7 | 26.6 ± 1.2 | 33.4 ± 2.7 | 28.3 ± 1.5 |
| Total fiber (g/d) | 23.7 ± 1.1 | 22.0 ± 1.0 | 24.2 ± 1.7 | 28.2 ± 1.4 |
| Total fiber (g/MJ) | 3.3 ± 0.2 | 2.8 ± 0.1 | 3.0 ± 0.2 | 3.5 ± 0.1 |
| Soluble fiber (g/d) | 5.4 ± 0.3 | 6.6 ± 0.3 | 5.3 ± 0.4 | 8.6 ± 0.4 |
| Soluble fiber (g/MJ) | 0.7 ± 0.0 | 0.8 ± 0.0 | 0.7 ± 0.1 | 1.1 ± 0.0 |
| Insoluble fiber (g/d) | 10.6 ± 0.6 | 11.9 ± 0.6 | 11.3 ± 0.8 | 16.4 ± 0.8 |
| Insoluble fiber (g/MJ) | 1.4 ± 0.1 | 1.5 ± 0.0 | 1.4 ± 0.1 | 2.0 ± 0.1 |

Note: All values are \( \bar{x} \) ± SEM. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids. Group × time interaction [repeated-measures analysis of variance (general linear model)]. Baseline values did not differ significantly between the groups for any of the variables. Change over time (general linear model). Significantly different from baseline, \( P < 0.05 \) (paired \( t \) test).
changes in fasting plasma glucose or serum insulin concentrations or in glucose and insulin AUCs between the groups.

There were no significant differences in the changes in serum total, LDL-, and HDL-cholesterol and triacylglycerol concentrations between the groups (Table 4). However, serum triacylglycerol concentrations decreased significantly (5.8–10.3%) from baseline in both groups, but the decrease was not significant after adjustment for the changes in nutrient intakes.

Cholesterol precursors, plant sterols, and cholestanol

Even though the serum cholesterol concentration was unchanged, changes were detected in cholesterol synthesis and absorption (Table 4 and Figure 1). Thus, the synthesis of cholesterol decreased by 6–10% (P = 0.004–0.030) and its absorption increased by 9% (P = 0.002 for sitosterol) in the OWPo group. Cholesterol synthesis and absorption were unchanged in the RPa group. The differences in the changes in both synthesis and absorption between the groups remained significant even after separate adjustment for intake of proteins, saturated fatty acids, carbohydrates, and total, soluble, and insoluble fiber. However, the differences in the changes in synthesis between the groups were not significant after adjustment for all variables simultaneously (P = 0.141–0.329).

Associations between variables of sterol and glucose metabolism

There was a significant interaction of group × glucose AUC for all synthesis markers (Table 5) and for the absorption markers for cholestanol (P = 0.022). In addition, there was an interaction of group × insulin AUC for lathosterol. In the RPa group, the percentage change in the plasma glucose AUC was positively correlated with the baseline cholesterol synthesis markers (P < 0.05 for all except for desmosterol, for which P = 0.326; Table 5) but negatively correlated with the cholestanol ratio (r = −0.520, P < 0.05). In the OWPo group, the percentage change in the plasma glucose AUC was negatively correlated only with the desmosterol ratio (Table 5). When the groups were combined, the percentage change in the plasma glucose AUC was negatively correlated with campesterol (r = −0.219, P = 0.073) and sitosterol (r = −0.213, P = 0.081). Furthermore, the percentage change in the serum insulin AUC was negatively correlated with cholestanol (r = −0.259, P = 0.033), campesterol (r = −0.271, P = 0.026), and sitosterol (r = −0.221, P = 0.070).
sterol values at the end of the study were compared with the changes in glucose and insulin AUCs, the associations were in parallel with the above comparisons. The ratios of serum synthesis markers (cholesterol and lathosterol) to absorption markers (cholestanol and plant sterols) at baseline and at the end of the study did not reveal any additive information to that shown in Table 5.

In the combined OWPo+RPa group, the percentage change in the serum cholestanol ratio was negatively associated with the percentage change in the insulinogenic index (Figure 2). The percentage change in the serum cholestanol ratio was negatively associated with the percentage change in the fasting serum insulin concentration \((r = -0.262, P = 0.024)\). In addition, the percentage change in the lathosterol ratio was positively associated with the percentage change in the insulinogenic index \((r = 0.347, P = 0.001)\). There were no other significant associations between the changes in sterol, glucose, and insulin variables.

In multiple regression analysis, the only variables significantly predicting the change in the insulinogenic index \((R^2 = 65.8\%)\) were the percentage changes in the serum cholestanol ratio as well as the glucose AUC, randomization group, and age (Table 6).

### DISCUSSION

The present study is the first to evaluate the associations between glucose and insulin as well as cholesterol metabolism and dietary carbohydrate modification in subjects with clinically defined metabolic syndrome. Even though there were no significant effects on overall cholesterol concentrations, the dietary carbohydrate modifications clearly altered serum markers of cholesterol synthesis and absorption. Cholesterol synthesis was decreased and cholesterol absorption increased in the OWPo group, but in the RPa group compared with the OWPo group, cholesterol synthesis was higher and absorption was lower.

In both diet groups, intakes of cholesterol and fat were decreased and those of soluble and insoluble fiber increased. The most marked differences noted between the diet modifications were the more enhanced intake of total, soluble, and insoluble fiber; the higher percentage of energy from saturated fatty acids and carbohydrates; and the reduction in protein in the RPa compared with the OWPo group. The randomization was successful, and the study groups did not differ significantly with respect to the background variables. In addition, the dietary modification was well tolerated and compliance was good.

In general, soluble fiber is considered to have a hypocholesterolemic effect (25) by increasing fecal bile acid output, which results in up-regulation of cholesterol synthesis as indicated by an increased serum ratio of lathosterol to cholesterol (26). However, confusing results exist. In a recent study, 8 g/d of soluble fiber...
fiber from oat bran had no effect on serum total and LDL-cholesterol concentrations in subjects with serum cholesterol concentrations < 6 mmol/L (27). In the present study, the increase in the intake of soluble fiber was rather minor, only on average 1.2 and 3.3 g/d from baseline in the OWPo and RPa groups, respectively.

Despite the lack of change in serum total and LDL-cholesterol concentrations, cholesterol metabolism was changed and in different ways according to whether the subjects consumed OWPo or RPa. It is evident that soluble fiber alone does not account for these changes. However, after multiple dietary adjustments, only the difference between absorption markers remained significant, which suggests that the combined effect of differences in saturated fat, carbohydrate, protein, and fiber intake may explain the lower cholesterol synthesis, but this cannot be the reason for the differences in cholesterol absorption between groups. The amount of dietary plant sterols in the test products was the same in both diets; therefore, this cannot explain the difference in serum plant sterol ratios between the groups. In addition, on the basis of the food records, there is no reason to believe that there was any difference in the total intake of plant sterols between the groups. The reasons for the increased sterol absorption during the oat-wheat-based carbohydrate modification might be related to the altered insulin-glucose response or to changes in the regulation of the intestinal absorption proteins. Both processes might enhance the intestinal cholesterol flow to the liver and decrease cholesterol synthesis.

Our interpretation of Figure 1 is that the lower cholesterol absorption during RPa carbohydrate modification compared with OWPo is clinically favorable, because lower cholesterol absorption and higher cholesterol synthesis would seem to be more preferable regarding the prevalence of coronary heart disease and the risk of coronary events. The evidence for these implications is based on several studies showing that coronary artery disease is associated with elevated cholesterol (or sterol) absorption assayed with serum absorption markers (plant sterols or cholestanol) or with cholesterol absorption efficiency (28–33). In addition, high levels of absorption markers at baseline, denoting “high absorbers,” predicted poor outcome in coronary patients during 4-y simvastatin treatment, even though these patients achieved a serum cholesterol reduction similar to that in the subjects with high baseline synthesis and low absorption of cholesterol, ie, “low absorbers” (34). These results were confirmed in a recent study including the whole Scandinavian Simvastatin Survival Study population (35).

The baseline profile of cholesterol metabolism predicted the glucose and insulin responses, which was especially seen in the RPa. Accordingly, the higher the baseline cholesterol absorption marker ratios, the smaller the plasma glucose and serum insulin AUCs after a glucose load. Interestingly, the associations remained virtually unchanged when thesterol values at the end of the study were compared with the changes in glucose and insulin responses.

Dietary carbohydrate modification with RPa increased the insulinogenic index (8), which is interpreted as representing an improvement in early insulin secretion. The change in the insulinogenic index was inversely associated with the change in the serum cholesterol ratio in both the univariate and the multivariate models. This suggests that the more dietary sterol absorption was diminished, the more the insulinogenic index became increased. It is interesting that the serum cholesterol ratio was the absorption marker that changed least during the study (Table 4, Figure 2). Cholesterol (5α-cholestan-3β-ol) is mostly derived from endogenous cholesterol by enzymatic action and it is distributed in small amounts in most mammalian tissues (36), but its amount in the diet is very low (37). The major pathway in the biosynthesis of cholestanol involves a rate-limiting oxidation of cholesterol into 4-cholestene-3-one and conversion into cholestanol. Cholestanol is eliminated into bile as such or it is degraded to 5α-bile acids by the same or similar enzymes as those involved in the biosynthesis of normal 5β-bile acids (36). The cholestanol content in serum is regulated by its endogenous synthesis, its conversion to 5β-bile acids, and its biliary secretion (36). The reason it is such a sensitive marker of cholesterol and, in general, of sterol absorption (37) is not completely clear. Accordingly, because cholestanol seemed to have an important role in the present study, one question now arises of whether the cholestanol ratio is a sensitive signpost at the crossroads between cholesterol, glucose, and insulin.

In conclusion, carbohydrate modification altered cholesterol synthesis and absorption, even though serum cholesterol concentrations remained practically unchanged. Higher dietary cholesterol absorption was associated with lower glucose responses to an oral glucose load during dietary modification with RPa, whereas lower cholesterol synthesis was associated with increases in the glucose responses during high OWPo intake. The changes in cholesterol absorption were inversely associated with changes in early insulin secretion. These findings emphasize the complex interrelations of the metabolic effects of glucose, insulin, and cholesterol. A comparison of long-term consumption of RPa with that OWPo from a clinical standpoint favors RPa because it improved short-term postprandial insulin secretion and reduced cholesterol absorption. These changes would be anticipated to also have antiatherogenic effects in patients with the metabolic syndrome.

We thank the laboratory nurses Anne Honkonen, Leena Kaijainen, Eeva Lajunen, and Päivi Turunen for their technical assistance.

The sterol analyses from serum were performed in the laboratory of HG and MH in collaboration with TAM and those from the study products in the laboratory of TAM. LT, HM, DEL, LN, and KSP contributed to the original planning of the dietary carbohydrate modification study. MH, HM, JJÅ, TAM, and HG contributed to the design of the present study. LT was responsible for recruiting, dietary counseling, and dietary analysis of the subjects. MH performed the statistical analyses and wrote the manuscript. All authors contributed to the data interpretation and revision of the manuscript. There were no conflicts of interest.

REFERENCES


