Dietary carbohydrate modification enhances insulin secretion in persons with the metabolic syndrome $^{1\rm -3}$

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ABSTRACT

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Background: The metabolic syndrome markedly increases the risk of type 2 diabetes and cardiovascular disease, but the influence of dietary modification on insulin and glucose metabolism independent of weight loss is still poorly understood.

Objective: Our aim was to test whether carbohydrate dietary modifications improve insulin sensitivity and secretion and glucose tolerance in overweight or obese persons with the metabolic syndrome, even in the absence of weight loss.

Design: We assessed the effect of carbohydrate modification on insulin and glucose metabolism in 72 overweight or obese men and women with the metabolic syndrome, as determined according to the National Cholesterol Education Program criteria. The subjects were randomly assigned to 12-wk diets in which either rye bread and pasta or oat and wheat bread and potato were the main carbohydrate sources (34% and 37% of energy intake, respectively).

Results: Body weight did not significantly change in either group during the trial. No significant difference was observed in the changes in fasting glucose and insulin concentrations or in glucose and insulin areas under the curve between the groups during a 2-h oral-glucose-tolerance test. The insulinogenic index (an index of early insulin secretion) increased more in the rye bread and pasta group than in the oat and wheat bread and potato group (33.2% compared with 5.5%; P = 0.026). In the combined groups, an enhanced insulinogenic index was associated with improved glucose tolerance, whereas weight gain worsened glucose tolerance. Moreover, even modest weight gains abolished the relative improvement in the insulinogenic index in the rye bread and pasta group compared with the oat and wheat bread and potato group (P for the interaction between weight change and group = 0.019).

Conclusions: Rye bread and pasta-based carbohydrate modification enhances early insulin secretion in persons with the metabolic syndrome, which may lower the risk of deteriorating glucose tolerance and development of type 2 diabetes. *Am J Clin Nutr* 2005;82: 1218–27.

KEY WORDS Rye, oat, wheat, insulin secretion, glucose tolerance, metabolic syndrome, randomized controlled trial

INTRODUCTION

In several epidemiologic studies, whole-grain cereals and diets with a low glycemic index have been shown to protect against the development of type 2 diabetes (1-3) and heart disease (4, 5). The major mechanism by which whole-grain cereals and low– glycemic index diets mediate their effects is thought to be through decreased insulin resistance and improved β cell function (6).

We previously showed that, compared with white-wheat bread ingestion, ingestion of whole-kernel rye bread reduces postprandial insulin, glucose-dependent insulinotropic polypeptide, and glucagon-like peptide 1 responses in healthy persons (7). This was not due to fiber content, because low-fiber rye bread reduced the insulin and incretin responses similar to high-fiber rye bread. In a randomized crossover trial conducted in 20 postmenopausal women, we also found that the acute insulin response measured during a frequently sampled intravenous-glucose-tolerance test increased after 8 wk of a diet high in high-fiber rye bread compared with a diet high in white or wheat bread, but insulin sensitivity remained unchanged (8).

Men and women with the metabolic syndrome are particularly at a high risk of developing type 2 diabetes and cardiovascular disease (9-11). Insulin resistance is a core component of the metabolic syndrome (12, 13). Compensatory hypersecretion of insulin is the normal response, but β cell dysfunction is also frequently present, especially in persons who are susceptible to impaired glucose tolerance and diabetes. β cell dysfunction, commonly characterized by the loss of first-phase insulin secretion, is a prerequisite for the development of impaired glucose tolerance (IGT) and type 2 diabetes and seems to be a primary determinant of persons with insulin resistance who will eventually develop IGT or diabetes (14-16). Therefore, interventions that alleviate insulin resistance or enhance insulin secretion without long-term deleterious effects on β cell function are especially important for the prevention of worsening glucose tolerance in these high-risk persons.

Dietary carbohydrate modification would be expected to have especially pronounced effects on insulin and glucose homeostasis in persons with the metabolic syndrome, but such data,

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FIGURE 1. Flow diagram of the subjects' progress through the phases of the study. IGI, insulinogenic index.

especially in the absence of weight loss, are largely lacking. Therefore, we assessed the effect of carbohydrate modification on insulin and glucose metabolism in 72 overweight or obese men and women with the metabolic syndrome, which was defined according to the National Cholesterol Education Program criteria (17). Carbohydrate modification consisted of a diet based on rye bread and pasta compared with a diet high in wheat and oat bread and potatoes. We hypothesized that repeatedly lower postprandial insulin and glucose excursions with the rye bread and pasta diet would improve insulin sensitivity and secretion and glucose tolerance, even in the absence of weight loss.

SUBJECTS AND METHODS

Subjects

Subjects with the metabolic syndrome were recruited with announcements placed in the newspaper and on the University and hospital employee announcement boards. In all, we screened 133 men and women aged 40–70 y with a body mass index (in kg/m²) between 26 and 40 and who reported ≥ 1 of the following: high blood pressure, abnormal lipid profile, or elevated blood glucose in the absence of diabetes. Of these, 81 subjects met the inclusion criteria and were taken into the study, but 7 subjects dropped out (2 because they did not like the test breads and 5 because of health problems). Technical problems occurred during the blood sampling for one subject in each group, and thus these subjects was 72 (37 women and 35 men; **Figure 1**). With respect to age, sex, body mass index, waist circumference, blood pressure, use of blood pressure medication, HDL-cholesterol

concentrations, LDL-cholesterol concentrations, triacylglycerol concentrations, and plasma glucose concentrations, only diastolic blood pressure differed significantly between the subjects who dropped out or who had incomplete data and the subjects for whom complete data were available (diastolic blood pressure was lower in the subjects who dropped out, P = 0.037). The subjects provided written informed consent, and the study plan was approved by the university and hospital ethics committee.

To be included in the study, the subjects had to be aged 40–70 y and have a body mass index between 26 and 40. The subjects also had to meet the National Cholesterol Education Program criteria for the metabolic syndrome (17); ie, ≥ 3 of the following 5 conditions had to be met: *I*) a waist circumference >102 cm for men or >88 cm for women, *2*) a fasting total 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), or 5) blood pressure >130/85 mm Hg or use of blood pressure medication. Subjects were excluded if they were diagnosed with diabetes, receiving any cholesterol-lowering medicine, or using cortisone (which impairs glucose tolerance).

Height, weight, systolic and diastolic blood pressure, routine hematological measurements, thyroid function, serum creatinine, alanine aminotransferase activity, and urine albumin were measured before entry into the study. The 7 subjects with treated hypothyroidism had normal thyroid-stimulating hormone concentrations. All other subjects had normal thyroid function. Alanine aminotransferase concentrations exceeded the reference value slightly (<2-fold) in 15 subjects, which is often observed in persons with the metabolic syndrome. Altogether, 45 subjects

TABLE 1

Characteristics of the 72 subjects at baseline¹

	Oat-wheat-potato group	Rye-pasta group	
	(n = 37)	(n = 35)	P^2
Age (y)	55.4 ± 6.2^{3}	55.5 ± 7.2	0.95
Sex			0.24
Male	16	20	
Female	21	15	
Weight (kg)	91.2 ± 11.5	93.0 ± 14.9	0.57
BMI (kg/m^2)	31.9 ± 3.7	31.4 ± 3.2	0.56
Waist circumference (cm)	108.0 ± 8.7	108.7 ± 9.8	0.76
Systolic blood pressure (mm Hg)	145 ± 16	139 ± 15	0.086
Diastolic blood pressure (mm Hg)	89 ± 9	88 ± 9	0.78
Blood pressure medication $[n(\%)]$	22 (58)	23 (66)	0.58
Fasting serum total cholesterol (mmol/L)	5.8 ± 0.9	5.8 ± 0.9	0.79
LDL cholesterol (mmol/L)	3.7 ± 0.7	3.7 ± 0.7	0.79
HDL cholesterol (mmol/L)	1.2 ± 0.3	1.2 ± 0.3	0.84
Triacylglycerol (mmol/L)	$1.74(1.29-2.19)^4$	1.83 (1.29–2.48)	0.85
Fasting plasma glucose (mmol/L)	6.20 (6.00-6.60)	6.15 (6.00-6.78)	0.57
Fasting serum insulin (pmol/L)	66.9 (47.9–91.8)	61.2 (48.2-86.4)	0.86
QUICKI insulin sensitivity index	0.56 ± 0.07	0.55 ± 0.08	0.76
Impaired fasting glycemia $[n (\%)]$	24 (65)	23 (66)	0.50
Impaired glucose tolerance $[n (\%)]$	14 (38)	16 (46)	0.94
Glucose AUC $(mmol/L)^5$	306 (234–413)	369 (234-501)	0.47
Insulin AUC (mmol/L) ⁵	6,728 (4499–10 521)	7169 (5229–10 038)	0.94
Insulinogenic index	14.5 (11.6–22.6)	12.4 (8.7–21.2)	0.26
Insulinogenic index (QUICKI-adjusted)	15.1 (11.5–23.1)	13.9 (9.2–21.0)	0.21
Disposition index	49.9 (37.9–76.4)	45.9 (30.3–69.8)	0.21

¹ QUICKI, quantitative insulin sensitivity check index; AUC, area under the curve.

² Difference between the groups (independent samples t test or chi square).

 ${}^{3}\bar{x} \pm$ SD (all such values).

⁴ Median; interquartile range in parentheses (all such values).

⁵ Measured after a 2-h oral-glucose-tolerance test.

(26 men and 19 women) were receiving medication for high blood pressure. Eight subjects had previously undiagnosed early diabetes, with fasting plasma glucose concentrations between 7.1 and 7.3 mmol/L at the time of entry into the study. In other respects, the subjects filled the inclusion criteria (**Table 1**). The glucose tolerance of the subjects was screened with a 2-h oralglucose-tolerance test (OGTT) at the beginning of the study (18). Thirty subjects had impaired glucose tolerance according to the 2-h glucose concentration.

Study design

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The study design had 2 parallel groups and consisted of a 4-wk baseline period and a 12-wk test period. At the end of the baseline period, the subjects were randomly assigned to one of 2 groups: one group consumed oat and wheat bread and potatoes and the other group consumed rye bread and pasta. The randomization was carried out in subgroups on the basis of sex, median age, and 2-h glucose concentrations. Altogether, 55 subjects began the intervention in the fall of 2003 and 19 subjects began in the spring of 2004.

At the beginning of the baseline period, the subjects were advised not to change their body weight and lifestyle habits, such as exercise and alcohol consumption, during the study. The subjects were also asked not to use cholesterol-lowering foodstuffs such as Benecol (Benecol International, Raisio, Finland) and Becel pro active (Becel, Nassaukade, Netherlands). In addition, the subjects were advised not to change their medication unless necessary. The subjects kept a 4-d food record during the baseline period to determine their habitual diets.

Blood samples were taken from fasting subjects, and body weight, waist circumference, and systolic and diastolic blood pressures were measured at baseline and at the end of the 12-wk test period. Body composition was measured by bioelectrical impedance.

Two-hour oral-glucose-tolerance test

An OGTT was done at baseline and after 12 wk. An intravenous catheter was inserted into the antecubital vein of the arm. After the fasting blood sample was drawn, the subjects drank a glucose solution (75 g glucose) within 3 min. Blood samples were drawn through the catheter 15, 30, 45, 60, 90, and 120 min after the start the glucose solution ingestion for the measurement of plasma glucose and serum insulin concentrations. The glucose and insulin areas under the curve (AUCs) were calculated.

Measures of insulin resistance and β cell function

We used the quantitative insulin sensitivity check index [QUICKI; 1/(ln insulin concentration + ln glucose concentration)] (19), which was measured from the fasting blood samples that were taken at the beginning of the OGTT. As a measure of early insulin secretion, the insulinogenic index (IGI; the increment in insulin during the first 30 min after oral glucose ingestion divided by the corresponding increment in glucose) was used. Because insulin secretion has a hyperbolic relation with insulin

TABLE 2

Nutrient composition of the test breads¹

	Available starch + sugars	Total fiber	Soluble fiber	Insoluble fiber	Protein	Fat	Energy
	g/100 g	g/100 g	g/100 g	g/100 g	g/100 g	g/100 g	kJ/100 g
Oat-wheat-potato group	0 0	0 0	0 0	0 0	0 0	0 0	0
Oat bread	31.2	5.4	1.8	3.6	13.7	3.9	908
Graham toast	42.1	5.3	1.4	3.9	8.9	5.7	1078
Wheat-bran bread	43.5	4.6	1.2	3.4	16.4	4.5	1185
Graham crispbread	67.7	8.3	2.3	6.0	11.0	6.3	1571
Rye-pasta group							
Endosperm rye bread	44.6	5.7	2.1	3.6	4.1	0.7	854
Wholemeal rye bread 1 (Ruispalat)	45.2	10.1	2.5	7.6	9.8	1.6	994
Wholemeal rye bread 2 (Jälkiuunileipä)	45.3	15.3	3.9	11.4	12.5	2.5	1075
Wholemeal rye crispbread	56.1	17.0	5.0	12.0	9.8	2.2	1202

¹ All values are \bar{x} .

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sensitivity, insulin sensitivity should be taken into account when analyzing β cell function (20, 21). When taking the log of insulin secretion measurements and of insulin sensitivity measurements, the hyperbolic relation becomes an inverse linear relation. We therefore used a QUICKI-adjusted IGI, which was derived with a regression analysis to adjust the log of IGI by the log of QUICKI, and then transformed back into untransformed values by taking the antilog. We also calculated the disposition index (DI, the product of the IGI and QUICKI), which is an index of early insulin secretion that takes insulin sensitivity into account (22, 23).

Test breads

The study breads were chosen on the basis of our previous postprandial studies with whole-meal breads. In those studies, rye bread and pasta consumption produced relatively low postprandial insulin responses in contrast with oat and wheat bread consumption (7, 24). In the oat-wheat-potato group, 3 commercial breads (wheat bran bread, graham toast, and graham crisp bread) and oat bread (made of 60% whole meal oat flour and 40%wheat flour), which was made by VTT Biotechnology (Espoo, Finland), were used. In the rye-pasta group, the 3 commercial whole-meal rye breads and a low-fiber endosperm rye bread, which was made by VTT Biotechnology, were used. The oat bread and endosperm rye bread were baked in 72-kg lots and were stored at -18 °C until given to the subjects at their visits to the study center. The commercial breads were widely used breads from 2 Finnish bakeries (Fazer Bakeries Ltd, Vantaa, Finland, and Vaasan & Vaasan Bakeries Ltd, Espoo, Finland). Freshly baked commercial breads were available 1 time/wk from the study center. The nutrient compositions of the test breads are shown in Table 2.

The subjects replaced their customarily used breads and baked products with test breads during the test period; the aim was to cover $\geq 25\%$ of the daily intake of energy from the breads. About 50% of the daily bread consumption in the oat-wheat-potato group was to be oat bread, and, similarly, 50% of bread consumption in the rye-pasta group was to be endosperm rye bread. The aim was to achieve a similar fiber intake from the breads because the fiber content of these breads was almost equal (5.4 g fiber/100 g for the oat bread and 5.7 g fiber/100 g for the endosperm rye bread). In addition to the test breads, the subjects could eat a sweet pastry or a portion of porridge 1 time/d, but this was not obligatory. The latter products were recommended to be rye-based products in the rye-pasta group and wheat-based products in the oat-wheat-potato group. The subjects in the rye-pasta group were given a package (400 g) of dark pasta or spaghetti 1 time/wk and advised to use \geq 1 portion of pasta (70 g dry pasta) \geq 3 times/wk as part of warm dishes. The subjects in the oat-wheat-potato group were advised to use mainly potatoes as part of warm dishes and were given a package (210 g) of powdered mashed potatoes 1 time/wk. Otherwise, the diet was to remain unchanged. The subjects were especially advised not to change the amount and type of fat and cold cuts eaten with the bread. Another goal of the dietary counseling was that the subject's weight should not change >5% from their baseline weight.

Dietary assessment

Compliance with the diets was assessed with the daily records of bread use and with 4-d food records. The subjects kept daily records of the number of portions of test breads, potato, and pasta eaten and the quantity, quality, and frequency of other cereals that were eaten. Four-day food records, which included one weekend day, were kept by the subjects twice during weeks 4–8. All 4-d food records were analyzed with the MICRO-NUTRICA program version 2.0 (Finnish Social Insurance Institute, Turku, Finland), which included a database of Finnish foods (25).

Anthropometric, body composition, and laboratory measurements

Body weight was measured on a calibrated electronic scale. Waist girth was measured halfway between the lowest rib and the iliac crest. Body composition was measured by bioelectrical impedance (BIA 101S with BODYGRAM software; Akern Srl Bioresearch, Florence, Italy). Plasma glucose was analyzed with the glucose dehydrogenase photometric method (Merck Diagnostica, Darmstadt, Germany) and KonePro Clinical Chemistry Analyzer (Thermo Clinical Labsystems, Konelab, Finland). Serum insulin was analyzed with a chemiluminescent immunoassay (ACS 180 Plus Automated Chemiluminescence System; Bayer Diagnostics, Tarrytown, NY). Downloaded from www.ajcn.org at Prince of Songkla Univ Lib/Fac of Med on January 23, 2006

TABLE 3

Daily intakes of test bread and other cereals and weekly intakes of potatoes, pasta, and rice during the test period¹

	Oat-wheat-potato group	Rye-pasta group
Minimum amount of test bread to be consumed (portions/d)	7.6 ± 2.2	7.9 ± 1.6
Consumption of test breads		
(portions/d)	7.8 ± 2.3	8.3 ± 2.1
(g/d)	247 ± 68.9	244 ± 60.9
Consumption of oat bread or endosperm rye bread		
(portions/d)	4.0 ± 0.9	4.4 ± 1.0
(g/d)	147 ± 31.7	155 ± 35.6
Consumption of other cereals (slices, pieces, or platefuls/d)	0.9 ± 0.5	0.8 ± 0.4
Consumption of cooked, French fried, or mashed potatoes and foods that include potatoes (times/wk)	4.4 ± 1.2	2.9 ± 1.2^2
Consumption of pasta (times/wk)	0.7 ± 0.5	2.9 ± 0.8^{2}
Consumption of rice (times/wk)	0.6 ± 0.5	0.6 ± 0.6

¹ All values are $\bar{x} \pm$ SD. Each subject recorded daily consumption of test breads, other cereals, pasta, potatoes, and rice during the test period. Consumption of the test breads was recorded as portions, which were 25–37 g for the oat-wheat bread group and 6–36 g for the rye bread group.

² Significantly different from the oat-wheat-potato group, P < 0.001 (unpaired Student's t test).

Statistical analyses

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Data were analyzed with SPSS for WINDOWS 11.5 (SPSS Inc, Chicago, IL). Variables with skewed distributions were normalized by taking the log or square root before analysis, but are displayed in the tables as untransformed values. Dietary intake of protein, fat, carbohydrate, fiber, and cholesterol were measured in g/d with 4-d food records and adjusted by regression analysis for energy intake (26, 27). Analysis of dietary variables after adjustment for energy reduces the potential confounding by energy that may occur when using percentage of energy (26). Between-group differences at baseline were assessed with the Student's independent-samples t test. A repeated-measures analysis of variance was used to assess the interaction of group and time on the changes in the dietary variables. When the interaction was significant, the paired Student's t test with Bonferroni's correction for comparisons within 2 groups was used to assess within-group changes with time. An analysis of covariance was used to assess the effect of group on the change in IGI and other outcome variables after adjustment for potential confounding variables. The corresponding baseline variable was also included in the analysis of covariance model. Similarly, when the change of other variables was included as a covariate in the analysis of covariance model, the corresponding baseline variable was also included. Simple Pearson's correlation, partial correlation, and multiple linear regression analyses were also carried out. P <0.05 was considered significant.

RESULTS

Diet

Reported compliance with the diet was good, and the consumption of bread portions exceeded the minimum number of portions recommended during the test period in both groups (**Table 3**). Oat-wheat breads and rye breads made up a mean (\pm SD) 33.2 \pm 8.7% and 28.8 \pm 7.0% of energy intake, respectively. Oat bread in the oat-wheat bread group and endosperm rye bread in the rye bread group made up \geq 50% of the test bread portions. Intake of other cereals was <1 portion/d. The subjects in the oat-wheat-potato group received a mean (\pm SD) 13.7 \pm 3.6 g total fiber, 4.2 ± 1.1 g soluble fiber, and 9.5 ± 2.6 g insoluble fiber from the test breads. In the rye-pasta group, the respective mean (\pm SD) fiber contents for the test breads were 21.0 ± 6.2 , 6.3 ± 1.7 , and 14.6 ± 4.5 g. The subjects also consumed pasta and potatoes as planned. In the rye-pasta group, the mean (\pm SD) percentage of energy from pasta consumption was $5.4 \pm 2.2\%$ and from potato intake $2.3 \pm 1.4\%$. In the oat-wheat-potato group, the mean (\pm SD) percentage of energy from pasta intake $1.4 \pm 1.2\%$.

At baseline, the groups did not differ significantly in the daily intake of the dietary variables shown in **Table 4**. During the intervention, saturated fatty acid intake decreased less and intake of carbohydrate, total fiber, and insoluble and soluble fiber increased more in the rye-pasta group than in the wheat-oat-potato group (Table 4 and **Table 5**). Protein intake increased more in the wheat-oat-potato group than in the rye-pasta group.

Body weight and composition

After adjustment for the corresponding baseline values and time of entrance into the study (fall or winter), the changes in body weight and waist girth did not differ significantly between the 2 groups during the trial (Table 5). The changes in lean and fat body mass also did not differ significantly between the groups (not shown).

Glucose, insulin, and serum lipids

After adjustment for corresponding baseline values and the time of entry into the study, the relative changes in the glucose AUC and in glucose responses at individual time points during the 2 h OGTT did not differ significantly between the rye-pasta and oat-wheat-potato groups (Table 5). The relative increases in the insulin AUC (Table 5) and in the insulin responses during the 2-h OGTT also did not differ significantly between the groups. The relative change in the QUICKI insulin sensitivity index during the trial did not differ significantly between the groups (Table 5). No significant differences in the changes in the serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, or triacylglycerols were observed between the groups.

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TABLE 4

Daily energy and nutrient intakes in the oat-wheat-potato and the rye-pasta groups during the baseline and the test periods¹

	Oat-wheat-pota	Oat-wheat-potato group $(n = 37)$		roup (n = 35)	
	Baseline	Test period	Baseline	Test period	P^2
Energy (MJ)	7.4 ± 1.8	7.9 ± 2.0	8.4 ± 2.5	8.3 ± 2.1	0.13
Protein					< 0.001
(g/d, energy-adjusted)	79.4 ± 14.1	90.8 ± 11.0^{3}	79.8 ± 14.1	78.2 ± 10.8	
(% of energy intake)	17.9 ± 3.4	19.8 ± 3.0	17.4 ± 2.7	16.8 ± 2.0	
Total fat					0.55
(g/d, energy-adjusted)	68.5 ± 11.5	58.2 ± 11.0	68.2 ± 14.6	55.6 ± 9.5	
(% of energy intake)	31.1 ± 5.9	28.3 ± 5.1	31.1 ± 7.0	27.2 ± 4.7	
SFA					0.039
(g/d, energy-adjusted)	26.0 ± 4.9	19.7 ± 5.2^{3}	24.8 ± 6.0	21.5 ± 4.3^4	
(% of energy intake)	11.8 ± 2.4	9.2 ± 2.5	11.3 ± 3.1	10.2 ± 2.2	
MUFA					0.31
(g/d, energy-adjusted)	22.5 ± 4.5	16.2 ± 4.9	23.5 ± 6.0	18.7 ± 4.3	
(% of energy intake)	10.1 ± 2.4	7.7 ± 2.1	10.7 ± 2.9	8.9 ± 2.1	
PUFA					0.67
(g/d, energy-adjusted)	11.1 ± 4.0	7.0 ± 4.4	11.4 ± 3.6	7.7 ± 2.1	
(% of energy intake)	5.6 ± 1.9	3.7 ± 2.1	5.8 ± 1.5	4.0 ± 1.0	
Carbohydrates					0.022
(g/d, energy-adjusted)	215 ± 24	215 ± 35	209 ± 42	227 ± 32^4	
(% of energy intake)	47.1 ± 5.6	47.6 ± 6.4	45.7 ± 9.4	50.5 ± 7.3	
Total fiber (g/d, energy-adjusted)	24.2 ± 6.1	21.0 ± 4.3^5	23.1 ± 9.4	26.4 ± 6.6^4	< 0.001
Soluble fiber (g/d, energy-adjusted)	5.5 ± 1.7	6.3 ± 1.2^{5}	5.1 ± 2.3	8.0 ± 1.9^{3}	< 0.001
Insoluble fiber (g/d, energy-adjusted)	11.4 ± 2.8	11.1 ± 2.5	11.2 ± 4.4	15.2 ± 4.2^{3}	< 0.001
Cholesterol (mg/d, energy-adjusted)	246 ± 78.0	213 ± 66.2	261 ± 114.1	233 ± 70.9	0.75
Alcohol (g/d)	7.8 ± 12.3	9.1 ± 13.9	13.5 ± 22.1	12.8 ± 16.3	0.51

¹ All values are $\bar{x} \pm$ SD. SFA, saturated fatty acids; MUFA, monounsaturated fatty acids; PUFA, polyunsaturated fatty acids.

² Interaction of time and group (repeated-measures ANOVA). Baseline values did not differ significantly between groups for any of the variables.

 $^{3-5}$ For variables in which the group × time interaction was significant, the within-group change was tested with a paired *t* test with Bonferroni's correction for 2 comparisons: $^{3}P < 0.001$, $^{4}P < 0.05$, $^{5}P < 0.01$. For variables other than energy and alcohol, statistical analysis was performed only for the energy-adjusted variable.

Change in the insulinogenic index

After adjustment for the baseline QUICKI-adjusted IGI and the time of entrance into the study, the relative increase in the QUICKI-adjusted IGI was greater in the rye-pasta group than in the oat-wheat-potato group (P = 0.026, **Figure 2**). The relative increases in the DI (P = 0.030) and in the unadjusted IGI (P =0.030) were also greater in the rye-pasta group than in the oatwheat-potato group.

The relative changes in protein, saturated fat, carbohydrate, and soluble and insoluble fiber intakes during the trial differed between the groups (Table 5). After adjustment for the baseline values and changes for these variables, the increase in the QUICKI-adjusted IGI was still greater in the rye-pasta group than in the oat-wheat-potato group (P = 0.023). Additional adjustment for sex, baseline energy intake, and body weight and their changes during the trial (P = 0.014) did not significantly change the results. More parsimonious models and an analysis with total fiber in place of water soluble and insoluble fiber did not significantly change the results. Findings after multivariate adjustments were similar to findings for the changes in the DI and unadjusted IGI. Neither IGT nor impaired fasting glucose significantly modified the effect of randomization group on the change in the IGI. In within-group analyses, the QUICKIadjusted IGI, DI, and unadjusted IGI were higher after the test period than before the test period in the rye-pasta group (P =

0.002–0.003), but not in the oat-wheat-potato group (P = 0.58 - 0.60).

Correlations and determinants of the insulinogenic index and glucose area under the curve

The group-adjusted partial correlation of the QUICKIadjusted IGI at baseline and at the end of the trial was 0.75 (P < 0.001), which indicated good repeatability. The unadjusted IGI and the DI had identical partial correlation coefficients. The repeatability of the QUICKI insulin sensitivity index and the glucose AUC was also good (partial r = 0.74 and 0.77, respectively; P < 0.001).

The QUICKI-adjusted IGI, DI, and unadjusted IGI were inversely associated with the glucose AUC at baseline (r = -0.51, -0.48, and -0.37, respectively, P < 0.001-0.002) and after follow up (r = -0.41, -0.45, and -0.34, respectively, P = 0.001-0.017). An increase in the QUICKI-adjusted IGI, DI, and IGI during the trial was also associated with a decrease in the glucose AUC (correlation of the respective relative changes: r = -0.43 to -0.44; P < 0. 001). Changes in body weight were associated with changes in the glucose AUC (r = 0.25, P = 0.042).

We also carried out multiple regression analyses with extensive adjustment for group, age, sex, time of entry into the study and for the baseline values and relative changes of the following

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TABLE 5

Relative changes during the test period in the 72 subjects¹

	Oat-wheat-potato group	Rye-pasta group	P^2
	%	%	
Anthropometry			
Weight	0.5 ± 1.7^{3}	0.6 ± 2.1	0.69
Waist circumference	-1.4 ± 1.8	-0.1 ± 3.0	0.77
Glucose tolerance and insulin sensitivity			
Fasting plasma glucose	0.3 ± 6.8	0.5 ± 6.8	0.92
Fasting serum insulin	-7.0 ± 29	-5.6 ± 29	0.84
QUICKI insulin sensitivity index	0.4 ± 8.9	0.3 ± 10.8	0.97
Glucose area under the curve	6.4 ± 46	-8.2 ± 36	0.20
Insulin area under the curve	$1.3(-24.2-25.1)^4$	12.6 (-13.4-34.6)	0.43
Dietary energy and macronutrients			
Energy	3.9 (-11.1-18.9)	3.1 (-10.9-13.2)	0.24
Protein (energy-adjusted)	13.2 (2.6–29.8)	-0.1 (-10.9-6.8)	< 0.001
Saturated fat (energy-adjusted)	-21 (-40-10)	-18 (-29-5)	0.023
Carbohydrates (energy-adjusted)	-0.4 (-8.0-8.6)	10.2 (-0.1-21.8)	0.023
Fiber (energy-adjusted)	-9.3 (-26.9-1.3)	15.2 (-0.8-56.3)	< 0.001
Soluble fiber (energy-adjusted)	27 (-4-40)	70 (36–123)	< 0.001
Insoluble fiber (energy-adjusted)	-0.1 (-17.8-10.8)	46 (8.6–83.7)	< 0.001

¹ QUICKI, quantitative insulin sensitivity check index.

² Analysis of covariance model with adjustment for the baseline value of the respective variable.

 $^{3}\bar{x} \pm$ SD (all such values).

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⁴ Median; interquartile range in parentheses (all such values).

variables: body weight, QUICKI, dietary energy, and the energyadjusted dietary intake of saturated fat, protein, carbohydrate, and soluble and insoluble fiber. Randomization group (rye-pasta group compared with oat-wheat-potato group, P = 0.009), age (standardized $\beta = -0.42$; P = 0.004), sex (P = 0.015; females were associated with a greater increase in the IGI than were males), and the relative change in energy-adjusted saturated fat



FIGURE 2. Mean (\pm SEM) changes in acute insulin secretion [adjusted (with the quantitative insulin sensitiveity check index) insulinogenic index (IGI), disposition index (DI), and unadjusted IGI (IGI without adjustment for insulin sensitivity)] in the oat-wheat-potato (\Box ; n = 37) and the rye-pasta (\blacksquare ; n = 35) groups. *Significantly different from the oat-wheat-potato group, P = 0.026 - 0.030 (analysis of covariance model with adjustment for time of entry into the study and the respective baseline measurement of early insulin secretion).

intake (standardized $\beta = -0.39$; P = 0.051) predicted the relative change in the QUICKI-adjusted IGI. In corresponding analyses with the change in the glucose AUC as the dependent variable, the changes in the measures of β cell function ($\beta = -0.52$ for QUICKI-adjusted IGI; $\beta = -0.53$ for DI; and $\beta = -0.53$ for unadjusted IGI; P < 0.001) and changes in body weight ($\beta = 0.40-0.43$; P = 0.001) were associated with changes in the glucose AUC.

Influence of the change in body weight

In men and women whose weight did not increase during the study, the IGI increased, on average, 43% in the rye-pasta group (n = 15) but decreased by 13% in the oat-wheat-potato group after adjustment for age, sex, body weight, and the IGI at baseline (n = 15; P = 0.005 for the difference between groups). In the subjects whose body weight increased, the IGI rose by 23% in the rye-pasta group (n = 20) and by 23% in the oat-wheat-potato group (n = 22; P = 0.84 for the difference between groups). The interaction was significant between group and weight change as a continuous (P = 0.019) or dichotomized variable (P = 0.039). Similar results were found for the DI and QUICKI-adjusted IGI, but the interaction was not significant. Insulin resistance is taken into account in these latter indexes of β cell function, which may reduce the influence of weight.

DISCUSSION

In the present randomized parallel study, we modified the intake of carbohydrates by replacing nearly all cereals that were consumed by men and women with the metabolic syndrome with either oat-wheat breads or rye breads. We also modified carbohydrate intake by emphasizing potato intake in the oat-wheatpotato group and pasta intake in the rye-pasta group. The main finding was that rye bread and pasta intake increased first-phase insulin secretion, as measured by the IGI during the intervention, more than did oat-wheat breads and potato intake in these highrisk persons with the metabolic syndrome. No significant changes were seen in glucose responses during the study.

 β cell dysfunction is a prerequisite for the development of IGT and type 2 diabetes and seems to be a primary determinant of those persons with insulin resistance who will eventually develop IGT or diabetes (16, 28-34). Indeed, persons who progress from normal glucose tolerance to IGT and type 2 diabetes are characterized by a lower first-phase insulin response and an additional decline with time in the acute insulin response, even though the second-phase response is initially exaggerated. In contrast, nonprogressors generally show little decline in β cell function (31–34). Improvement in the acute insulin response in the absence of deleterious changes on insulin sensitivity may therefore lower the risk of worsening glucose tolerance and development of frank diabetes. The importance of acute insulin secretion on glucose tolerance was also evident in the present study. A higher IGI and an increase in the IGI during the study were associated with improved glucose tolerance in both groups as measured by the glucose AUC.

Rye bread and pasta intake may improve acute insulin secretion by chronically lowering postprandial insulin responses and allowing β cell function to recover. We have shown that both rye bread and pasta consumption reduce the postprandial insulin and incretin responses compared with wheat and oat bread consumption (7). For rye bread, this occurred in the absence of changes in the postprandial glycemic response (7, 35), although others have found that rye bread also has a lower glycemic index than does wheat bread (36). The lower postprandial insulin excursions that were observed after rye bread consumption may be due to bread structure (7). Fiber content does not account for the lower postprandial insulin response to rye bread, because the postprandial insulin response to low-fiber rye bread was as low as that of high-fiber rye bread (7). Rye bread contains phenylalanine derivatives (37) that are similar to nateglinide, a phenylalanine derivative that is an oral hypoglycemic agent and acts by improving early insulin secretion (38). Pasta consumption results in considerably lower postprandial glucose and insulin responses than does mashed or boiled potato consumption (24, 36). Pasta and potato intake are unlikely to explain the differences between the 2 groups, however, because energy intake from bread was several-fold greater than that from pasta and potatoes. Intake of soluble dietary fiber, the composition of dietary fat intake, and the relative proportions of dietary saturated fat, carbohydrate, and protein intakes could possibly influence insulin secretion (39, 40), but adjustment for changes in the dietary intake of soluble and insoluble fiber, carbohydrate, protein, and saturated fat did not significantly affect the results.

Our finding that rye and pasta intake improved early insulin secretion in men and women with the metabolic syndrome is consistent with our previous observation that 8 wk of high-fiber rye bread consumption enhanced the acute insulin response mainly in normoglycemic postmenopausal women (8). Lifestyle measures that are aimed at preventing type 2 diabetes usually mediate their effects by decreasing insulin resistance, with only indirect effects on insulin secretion (41). Weight loss (42) and, at least in type 2 diabetic patients, physical activity may nonetheless improve insulin secretion (43). A high-carbohydrate, low– glycemic index diet has also improved insulin secretion (as measured by the DI) compared with a high-carbohydrate, high– glycemic index diet in persons with IGT (44). Our study focused on high intake of bread with modification of the grain sources and a relatively minor differential intake of pasta and potatoes rather than focusing on the glycemic index. The low–glycemic index diet in the study by Wolever and Mehling (44) also emphasized pasta and rye bread, however, and the high–glycemic index diet emphasized potato and wheat bread. Altogether, the present and previous studies (8, 44) provide evidence that carbohydrate modification can improve early insulin secretion, even in the absence of weight loss.

We sought to maintain weight at prestudy levels to remove the confounding effects of weight change on the results. No significant changes in the mean body weight occurred in either group. Even so, modest weight gain obviated the relative benefit of rye and pasta intake. Overweight and obesity, insulin resistance, insulin secretion, and glucose tolerance are all physiologically intertwined (12, 14, 20, 21, 45). Obesity is a powerful determinant of insulin resistance. Insulin secretion and insulin resistance have a hyperbolic relation, and weight gain and increased insulin resistance result in a compensatory increase in both first- and second-phase insulin secretion, at least if B cell secretory capacity is sufficient. Moreover, changes in insulin secretion and even modest changes in weight have an effect on glucose tolerance over a relatively short follow-up period, as shown in the present study. Our findings also underscore the importance of successful weight maintenance to maximize the benefits of carbohydrate modification on insulin and glucose homeostasis.

Even though rye and pasta intake improved early insulin secretion, the improvement in glucose tolerance as measured by the glucose AUC was not significant. The modifying effect of even modest weight gain may partly explain why no significant effect was seen on glucose tolerance. Other reasons for the lack of a significant effect may be the relatively short duration of the present study and a lack of statistical power.

The IGI is a commonly used measure of early insulin secretory capacity. This index has moderately high correlations with acute insulin responses that are measured during a frequently sampled intravenous glucose tolerance test (r = 0.47-0.61) (46, 47) and an intravenous arginine stimulation (r = 0.41 - 0.50) (48). The IGI and the DI have also consistently predicted progression from normal glucose tolerance to IGT and to type 2 diabetes (29, 30, 34). Although the IGI is often considered to be less precise than intravenous methods, the IGI calculated from an OGTT may be more physiologic because the gastrointestinal contribution to insulin secretion is not bypassed. Incretins play a key role in mediating insulin secretion and account for approximately twothirds of the insulin secreted in response to a glucose load during the OGTT (49). Moreover, incretins may also be important in the pathogenesis of deteriorating glucose tolerance and of type 2 diabetes.

Because early insulin secretion and insulin sensitivity have a hyperbolic relation, insulin sensitivity should be accounted for when assessing the acute insulin response in interventions that may alter insulin secretion or sensitivity. We did this by adjusting for insulin sensitivity, which was estimated by QUICKI, and by calculating the DI (the product of the IGI and QUICKI). In principle, adjusting for insulin sensitivity rather than multiplying by insulin sensitivity should reduce the variability of the index. However, the DI was as repeatable as the QUICKI-adjusted IGI, and the effect of rye and pasta intake in improving the early insulin response was similar regardless of which measure was used.

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Modification of carbohydrate intake by replacement of cereal products with rye-based products and increased pasta intake over a 12-wk period improved early insulin secretion measured during an OGTT compared with an oat-wheat-potato-based diet in men and women with the metabolic syndrome. Glucose tolerance did not improve, possibly in part because even modest weight gains abolished the relative benefit of the rye-pasta diet on insulin secretion. Emphasis of rye and pasta intake coupled with effective weight maintenance may have long-term benefits on β cell function and glucose tolerance in persons who are at high risk for developing type 2 diabetes and cardiovascular disease.

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DEL, KSJ, KA, KHL, KP, LN, and HM contributed to the conception and design of the study. LKT carried out the practical aspects of the study, including dietary advice and dietary analyses. KA, KHL, and KP were responsible for the preparation and analysis of the breads used in the study. DEL and LKT carried out the statistical analyses. DEL, LKT, KP, LN, and HM initially interpreted the data before writing the manuscript. DEL wrote the first draft of the manuscript with help from LKT. All authors participated in the writing of the final draft of the manuscript and in the final interpretation of the data. None of the authors had any conflicts of interest.

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