Cereal Fiber Improves Whole-Body Insulin Sensitivity in Overweight and Obese Women

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OBJECTIVE — Cereal fiber intake is linked to reduced risk of type 2 diabetes in epidemiological observations. The pathogenic background of this phenomenon is unknown. Based on recent findings, we hypothesized that intake of purified insoluble oat fiber may improve whole-body insulin sensitivity.

RESEARCH DESIGN AND METHODS — A randomized, controlled, single-blind, cross-over study was performed, and 17 overweight or obese subjects with normal glucose metabolism were analyzed. After consumption of nine macronutrient-matched portions of fiber-enriched bread (white bread enriched with 31.2 g insoluble fiber/day) or control (white bread) over a time period of 72 h, whole-body insulin sensitivity was assessed by euglycemic-hyperinsulinemic clamp. Energy intake was individually adjusted by providing standardized liquid meals. Hydrogen breath tests were performed to control for dietary adherence.

RESULTS — When analyzing the entire cohort, whole-body glucose disposal was improved after fiber consumption (M value 6.56 ± 0.32 vs. 6.07 ± 0.27 mg · min^{-1} · kg^{-1}; $P = 0.043$). Thirteen subjects had increased hydrogen breath test concentrations after fiber consumption, indicating probable dietary adherence. Restricting analysis to these subjects, improvements in M value (6.85 ± 0.34 vs. 6.06 ± 0.32 mg · min^{-1} · kg^{-1}; $P = 0.003$) and insulin sensitivity, expressed as M/I ratio (M value divided by mean serum insulin at steady state: 3.73 ± 0.23 vs. 3.21 ± 0.27; $P = 0.02$), after fiber consumption were more pronounced. Plasma lipids, serum magnesium, ghrelin, and adiponectin concentrations, as well as substrate utilization and body weight, were not significantly changed by fiber intake ($P > 0.15$).

CONCLUSIONS — Increased insoluble dietary fiber intake for 3 days significantly improved whole-body insulin sensitivity. These data suggest a potential mechanism linking cereal fiber intake and reduced risk of type 2 diabetes.

Diabetes Care 29:775–780, 2006

The epidemic of obesity-associated insulin resistance and type 2 diabetes is a major burden in modern societies. In population studies, cereal fiber intake is linked, by unknown mechanisms, to reduced risk of developing type 2 diabetes and cardiovascular disease (rev. in 1). Insoluble fibers are nonviscous with negligible effects on gastric emptying, macronutrient absorption from the gut, postprandial glucose responses, and blood lipids (1). In contrast, consumption of soluble viscous fibers reduces postprandial glucose responses and positively influences certain serum lipids (2). Surprisingly, epidemiological studies clearly show that principally insoluble cereal fibers appear to offer protection from cardiovascular disease and diabetes (1). Beneficial effects of cereal fibers are frequently discussed in the context of whole-grain consumption. Fruit, vegetables, unrefined whole grains, and bran products are highly complex substances, containing both soluble and insoluble dietary fibers as well as other biologically active substances, e.g., polyphenols, antioxidants, vitamins, trace minerals, phytoestrogens, lipids, proteins, and starch. To reduce complexity, we investigated the effects of highly purified insoluble fibers in our experiments, assuming that the predominant insoluble fraction of whole grains and cereal fibers is involved in their beneficial actions.

Little is known about the effects of high-fiber diets on insulin sensitivity. Only a few studies assessed postabsorptive insulin sensitivity after fiber intake by euglycemic-hyperinsulinemic clamp (or by hyperglycemic clamp). These studies mainly focused on a combined intake of bran, cereals, fruit, or vegetables (3,4) or on the effects of soluble viscous fibers (5,6). Fukagawa et al. (7) showed increased peripheral insulin sensitivity after a low– versus high–insoluble fiber diet. However, the study was not randomized, and substantial differences (mainly in the fat contents of the diets) are likely to have confounded the results.

To date, no randomized controlled study has been performed measuring the effects of purified insoluble cereal fibers on insulin sensitivity. We have recently shown that intake of insoluble oat or wheat fibers for a 24-h period improves postprandial glucose and insulin responses upon the ingestion of a control meal (8). Due to the different study design, however, improved insulin sensitivity could only be hypothesized. Accordingly, the aim of the current study was to investigate effects of insoluble cereal fiber intake on whole-body insulin sensitivity, as assessed by the euglycemic-hyperinsulinemic clamp.

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Received for publication 5 December 2005 and accepted in revised form 2 January 2006.

Abbreviations: REE, resting energy expenditure.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Macronutrient composition of the test breads*

Test bread	High fiber	Control
Matrix	White bread	White bread
Insoluble fiber enrichment (g) per portion	10.4	None
Total fiber (g) per portion	13.3	2.9
Portion (g) per 50 g available carbohydrates	131	103
Available carbohydrates (g) per portion	50.0	50.0
Protein (g) per portion	9.8	9.6
Fat (g) per portion	0.90	0.87
Energy (kJ) per portion	1016	1011
Magnesium (g) per portion	0.02	0.02

RESEARCH DESIGN AND METHODS

The experimental protocol was approved by the local ethical committee, and all subjects gave written informed consent. As a compensation for participation, subjects were offered dietary advice by a trained clinical nutritionist after completion of the study. Eighteen overweight ($n = 7$) or obese ($n = 11$) women with normal fasting glucose and normal glucose tolerance according to World Health Organization criteria (9) were recruited by advertisement in local newspapers. Mean (±SD) age was 52.9 ± 8.7 years and BMI 30.4 ± 2.0 kg/m^2. All participants were screened for serious health problems and excluded if vascular, renal, or hepatic diseases were found. Further exclusion criteria were menstrual irregularities, a history of smoking, or a medication with antidiabetic drugs. Five of the subjects had L-thyroxin replacement therapy, two were on low-dose aspirin, and three were on β-blocker therapy throughout the study. Seventeen of the subjects were included in the final analysis. One participant had to be excluded because steady state was not achieved during one of the euglycemic-hyperinsulinemic clamps. No side effects or adverse events were reported by any of the participants.

The study was performed with a randomized, controlled, single-blind, within-subject, cross-over design. Subjects were randomized utilizing computer-generated lists of random numbers. Allocation to the treatment was performed by a person not involved in the randomization process. Preparing and blinding of the test meals was performed by the Institute for Cereal Processing (IGV, Potsdam-Rehbruecke, Germany), which was not involved in the randomization, the allocation process, or the analysis of the data. Subjects were invited to the metabolic unit after 10-h overnight fasts (at 8:00 A.M.) on two occasions for 180 min. Subjects remained in an upright sitting position throughout the experiments. All infusions were administered into an antecubital vein, while blood samples for analysis were drawn from an antecubital vein at the contralateral arm.

Dietary intervention

Subjects ingested three macronutrient-matched portions of control (white bread) or oat fiber–enriched white bread (enriched with 10.4 g insoluble fiber per portion) per day for 3 days (at breakfast, lunch, and 10:00 P.M.). Fiber enrichment was within the recommended daily range of fiber intake (10). Caloric intake was adjusted by the additional intake of standardized liquid meals (Biosorp; Pfrimmer Nutricia, Erlangen, Germany) to cover metabolic rate and avoid weight loss. To individually adjust energy intake, resting energy expenditure (REE) was determined before the study and multiplied by a factor of 1.5 to adjust for light physical activity. No other meals and only noncaloric drinks (without caffeine) were allowed throughout the study periods. There was a washout period of at least 7 days between the intervention periods.

Test breads

Test breads were produced and analyzed in one batch by the Institute for Cereal Processing (IGV, Potsdam-Rehbruecke, Germany). IGV also provided the oat fiber product (Vitacel OF 101; Rettenmaier & Söhne, Rosenberg, Germany). The processing steps were performed as previously described (8). The oat fiber product has a particle size of 50 μm and contains 96% total fiber (93% insoluble fiber and 3.0% soluble fiber [70% cellulose, 25% hemicellulose, 3–5% lignin, 0.2% β-glucan, 0.1% fat, and 0.25% protein]). Notably, most of the soluble fiber and starch as well as proteins and lipids are removed. The macronutrient composition of the test breads is shown in Table 1.

Assessment of insulin sensitivity

Euglycemic-hyperinsulinemic clamps were performed for at least 2 h using 100 mU/m^2 per min human insulin (Actrapid; Novo Nordisk, Bagsværd, Denmark) and a variable infusion of 10% glucose (Serag Wiessner, Naila, Germany). In the steady-state condition of the clamp, capillary blood glucose was adjusted at 5.5 mmol/l for at least 30 min. A deviation of a single capillary glucose concentration of >10% during assumed steady-state conditions was defined as non–steady state. Blood samples were drawn at baseline, every 10 min during the clamp, and every 5 min during steady-state conditions. With the insulin dose used, hepatic glucose output can be expected to be fully suppressed (11). Therefore, whole-body glucose disposal (M value) could be calculated from the glucose infusion rate. Insulin action was also calculated as M/I ratio, which expresses the ratio of M to the mean of the steady-state serum insulin concentration, and multiplied by a factor of 100. The posthepatic clearance rate of serum insulin was expressed as the ratio of the insulin infusion rate to the mean serum insulin concentration at steady state (12).

Measurements and laboratory parameters

An additional study day was performed for characterization of the subjects before the study, including the performance of oral glucose tolerance tests and assessment of individual metabolic rates. Trained personnel performed anthropometric measurements. Body weight was measured at each study day. Lean body mass was assessed on resting participants by bioelectrical impedance analysis (Nutriguard-M; Data Input, Frankfurt am Main, Germany) using the formula of Sun et al. (13). Three measurements were conducted, and the mean value was calculated. Substrate utilization and respiratory quotient were determined using an indirect calorimeter (SensorMedics, Bilthoven, the Netherlands) after a 20-min rest. CO_2 production and O_2 consumption were measured for 30 min at rest with the subject in the lying position. REE was calculated according to the Weir equation (14).

Body surface area was calculated as $0.007184 \times \text{height (in centimeters)}^{0.725} \times \text{weight (in kilograms)}^{0.425}$ according to Dubois and Dubois (15). BMI was calcu-

Table 2—*Unchanged postabsorptive parameters after 72 h high-fiber versus control diet* (n = 17)

Prior diet	High fiber	Control	*P*
Body composition			
Body weight (kg)	77.7 ± 8.0	77.4 ± 7.9	0.340
BMI (kg/m^2)	30.0 ± 2.1	29.9 ± 2.0	0.354
Lean body mass (kg)	48.2 ± 1.0	48.1 ± 1.0	0.514
Blood parameters			
Plasma glucose (mmol/l)	4.91 ± 0.10	4.96 ± 0.10	0.676
Serum insulin (pmol/l)	29.7 ± 4.3	32.3 ± 4.9	0.139
Serum C-peptide (nmol/l)	0.65 ± 0.05	0.68 ± 0.06	0.365
Nonesterified fatty acids (mmol/l)	0.50 ± 0.03	0.49 ± 0.03	0.645
Cholesterol (mmol/l)	4.61 ± 0.24	4.59 ± 0.22	0.789
HDL cholesterol (mmol/l)	1.23 ± 0.04	1.22 ± 0.05	0.640
LDL cholesterol (mmol/l)	2.76 ± 0.20	2.75 ± 0.18	0.941
Triacylglycerols (mmol/l)	1.39 ± 0.15	1.37 ± 0.15	0.869
Serum adiponectin (μg/ml)	15.4 ± 1.7	16.3 ± 1.9	0.161
Serum ghrelin (pg/ml)	163.7 ± 17.5	175.9 ± 18.8	0.151
Serum magnesium (mmol/l)	0.92 ± 0.02	0.90 ± 0.02	0.174
Other parameters			
Respiratory quotient	0.87 ± 0.02	0.86 ± 0.01	0.921
REE (kcal/day)	1100 ± 45	1112 ± 48	0.662

Body composition data are means ± SD; all other data are means ± SE.

lated as body weight (in kilograms) divided by the square of height (in meters).

Blood parameters

Blood samples were analyzed in random order to exclude systemic bias due to interassay variation. After sampling in ETDA or serum tubes, blood was immediately chilled on ice and centrifuged and aliquots immediately frozen at −20°C until assayed. Blood samples were analyzed for insulin, free fatty acids, cholesterol, LDL and HDL cholesterol, and triglycerides with Cobas Mira (Roche, Lörrach, Germany) (intra-assay coefficient of variation [CV]: insulin, 6.0%; free fatty acids, 10.5%; cholesterol, 5.1%; HDL cholesterol, 5.4%; and triglycerides, 5.1%). Adiponectin concentrations were measured by enzyme-linked immunosorbent assay (Biovendor, Nashville, TN) (intra-assay CV 6.7%). Capillary blood glucose was measured using the glucose oxidase method on a Dr. Müller Super-GL glucose analyzer (Freital, Germany). C-peptide was measured using an enzyme-linked immunosorbent assay (Mercodia, Uppsala, Sweden) (intra-assay CV 5%). Immunoreactive total human serum ghrelin concentrations were measured by a commercially available radioimmunoassay (Phoenix Pharmaceuticals, Mountain View, CA) using ^{125}I-labeled bioactive ghrelin as tracer and a polyclonal antibody raised in rabbits against the COOH-terminal end of human ghrelin. Intra- and interassay CVs were 5.3 and 13.6%.

Breath hydrogen analysis

All subjects were capable of producing breath hydrogen. Air breath samples were collected and measured using a Breath Hydrogen Analyzer (Quintron Model-12i-Microlyzer; Quintron Instruments, Milwaukee, WI).

Statistics and data analysis

The characteristics of the subjects are presented as means ± SD and all other results as means ± SE. Basal and steady-state concentrations were compared using two-tailed Student's *t* test for paired samples. Relative responses of blood parameters were calculated by expressing the responses of each subject after intake of the test meal compared with control. Statistical significance was defined as $P < 0.05$. Calculations were performed using SPSS version 12.0 (SPSS, Chicago, IL).

RESULTS

Insulin sensitivity

When analyzing results for the entire cohort ($n = 17$), intake of fiber-enriched bread for 72 h significantly improved whole-body glucose disposal (M value: 6.56 ± 0.32 vs. 6.07 ± 0.27 mg · min^{-1} · kg^{-1}; $P = 0.043$); this was equivalent to an 8% improvement of insulin sensitivity. Mean insulin concentrations (I), measured three times during steady-state conditions of the clamp, were not significantly changed after fiber intake compared with control (183.7 ± 5.2 vs. 193.7 ± 4.9 mU/l; $P = 0.104$). Accordingly, mean insulin action expressed as M value/I ratio was significantly enhanced by 12% after fiber intake (3.61 ± 0.20 vs. 3.21 ± 0.22 mg · min^{-1} · kg^{-1} per mU/l; $P = 0.023$). Posthepatic insulin clearance rate at steady state was not reduced by fiber consumption (fiber 1.03 ± 0.04 vs. control 0.98 ± 0.04 l/min; $P = 0.156$), indicating that improved whole-body insulin sensitivity was induced by improved insulin action and not by reduced hepatic insulin clearance after fiber intake. Analysis of hydrogen breath tests indicated that dietary nonadherence is likely to have attenuated the results (see below).

Blood parameters

Postabsorptive blood parameters after 72 h fiber versus control consumption are given in Table 2. There were no significant changes of plasma glucose, blood lipids, serum insulin, C-peptide, adiponectin, ghrelin, and magnesium concentrations after fiber consumption compared with control. Fasting insulin concentrations tended to be reduced after fiber consumption, and a larger sample size may have shown sufficient power to detect a difference.

Other parameters

Body weight, lean body mass, and BMI were not significantly altered after ingestion of high-fiber versus control bread. Additionally, there were no differences in REE and the respiratory quotient (Table 2). Accordingly, calculated rates of substrate oxidation of carbohydrates, lipids, and protein were unchanged ($P > 0.15$).

Hydrogen breath test

Intake of fiber-enriched bread for 72 h lead to significantly enhanced colonic fermentation in the postabsorptive state compared with consumption of control bread (9.5 ± 2.0 vs. 5.5 ± 1.3 ppm; $P = 0.012$) (Fig. 1*A*). Colonic fermentation was enhanced in 13 of 17 subjects after high-fiber intake, whereas in 4 subjects, fermentation was unchanged or reduced compared with control.

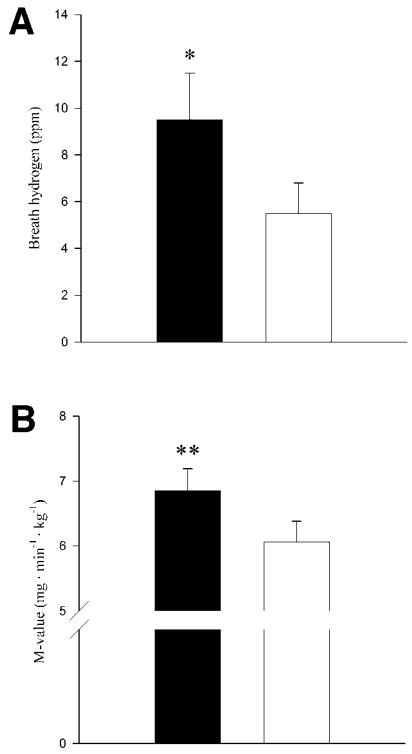

Figure 1—A: *Postabsorptive breath hydrogen concentrations, measured in the entire cohort* (n = *17) after 72 h high-fiber versus control diet.* B: *Whole-body glucose disposal expressed as M value in the subgroup* (n = *13), including only subjects who showed increased breath hydrogen concentrations after the high-fiber diet, indicating probable dietary adherence.* ■*, after 72 h fiber intake;* □*, after 72 h control intake.* *P < *0.05,* **P < *0.01 vs. control.*

Subanalysis

M values were improved in 11 of 17 subjects after high-fiber consumption for 3 days compared with control. Three of the remaining 6 subjects (but only 1 of the 11 subjects with improved M values) showed no increased hydrogen breath test concentrations after assumed fiber intake, indicating that the test meals were probably not ingested by these participants (or, alternatively, indicating low capacity for colonic fermentation of dietary fiber). Therefore, it is reasonable to restrict analysis to subjects with increased hydrogen breath test concentrations after fiber intake ($n = 13$). After doing this, intake of fiber-enriched bread for 72 h markedly improved whole-body glucose disposal (M value: fiber 6.85 ± 0.34 vs. control 6.06 ± 0.32 mg · min^{-1} · kg^{-1}; $P = 0.003$), equivalent to a 13% improvement of insulin sensitivity (Fig. 1*B*). Mean insulin concentrations (I) during steady-state conditions of the clamp were not significantly changed (186.3 ± 6.3 vs. 194.5 ± 6.2 mU/l; $P = 0.300$), and mean insulin action, expressed as M/I ratio, was significantly enhanced by 16% after fiber intake (3.73 ± 0.23 vs. 3.21 ± 0.27 mg · min^{-1} · kg^{-1} per mU/l; $P = 0.02$). Posthepatic insulin clearance rate at steady state was also not reduced in the subgroup (1.01 ± 0.04 vs. 0.97 ± 0.04 l/min; $P = 0.382$).

CONCLUSIONS — Cereal fiber consumption is linked to a reduced risk of type 2 diabetes and cardiovascular disease in prospective cohort studies. Notably, associations between cereal fiber intake and reduced diabetes risk remain significant after correction for confounding factors, e.g., changes in body weight, age, exercise, intake of fat, smoking, alcohol intake, or a family history of diabetes (16). To date, no obvious mechanisms for the beneficial effects of cereal fibers have been described. Based on recent findings by our group (8), we hypothesized that consumption of purified insoluble fiber, which is the predominant fraction of cereal fiber, might improve whole-body insulin sensitivity. Here we show that an intake of insoluble dietary fiber within the recommended daily range (10) for a time period as short as 3 days significantly improved whole-body insulin sensitivity in overweight and obese women, as assessed by the euglycemic-hyperinsulinemic clamp. Insulin sensitivity was improved by 13% in those subjects, who were likely to have ingested the test meals, and this effect was attenuated, but still significant, when results for all subjects were analyzed. Notably, the magnitude of pharmacological improvement in insulin-stimulated glucose metabolism after a 3-month treatment with the insulin-sensitizing drug rosiglitazone was between 20 and 68%, depending on the administered doses of insulin during the clamp and with the most pronounced effect using relatively low insulin doses (120 vs. 20 mU/m^2 per min) (17). Potential molecular mechanisms leading to improved insulin sensitivity remain unexplained by the current study. However, the presented data clearly indicate that insoluble fibers, containing mainly cellulose and hemicellulose, are unlikely to be physiologically inert and may be interesting candidates for future research. We have previously shown that the insoluble fiber used in our experiments is unlikely to influence macronutrient absorption or gastric emptying (8), which is in accordance with the literature (2). An increased magnesium intake has been shown to improve insulin sensitivity (18). However, magnesium contents of the test meals in the current study were virtually identical, and serum magnesium concentrations were unchanged by fiber intake. No effect of fiber intake on blood lipids, serum ghrelin, or serum adiponectin concentrations (19) could be detected as other possible drivers that might have influenced insulin sensitivity.

Dietary intervention studies in humans commonly face the problem of diet control, and dietary nonadherence is likely to increase variance and therefore to weaken the results. This may at least partly explain controversial results of former studies, with some (e.g., 20) but not all (e.g., 21) indicating metabolic improvement after longer-term interventions with insoluble dietary fibers. We have previously shown that the insoluble fiber used in the current study caused slight, but significantly enhanced, colonic fermentation compared with control, as assessed by postabsorptive hydrogen breath concentrations (8). Therefore, in the current study, we used this test as a tool for controlling dietary adherence. When performing a subanalysis, excluding four subjects with unchanged or lower hydrogen breath concentrations after the intake of the fiber-enriched meals compared with control, improvement of insulin sensitivity was highly significant, indicating that dietary nonadherence is likely to have attenuated our findings. Fermentation processes in the colon resulting in increased production of short-chain fatty acids have been proposed as being involved in improvement of hepatic insulin sensitivity (22), possibly by upregulating glucagon-like peptide 1 and thus suppressing glucagon secretion. In the current study, basal plasma glucose concentrations were not altered by fiber consumption. Moreover, we have recently shown that improved glucose handling after a 24-h intake of purified insoluble wheat or oat fiber was completely independent of the rate of colonic fermentation, and glucagon-like peptide 1 concentrations remained unchanged (8). In addition, other authors did not detect altered hepatic insulin sensitivity after intake of high-fiber diets (7,23). Therefore, it is reasonable to assume that only subjects

that indeed consumed the fiber-enriched test meals showed improved insulin sensitivity, but a lack of an insulin-sensitizing effect in subjects with low capacity of colonic fermentation upon fiber ingestion cannot be excluded.

In a randomized, controlled, crossover study, Robertson et al. (24) recently described increased insulin sensitivity after a 4-week intake of resistant starch, as assessed by euglycemic-hyperinsulinemic clamp. The authors performed muscle and fat biopsies and could not detect any differences in expression of a number of skeletal muscle genes, including insulin-receptor substrate 1, phosphatidylinositol-3-kinase, or GLUT-4. However, a complex network of downstream transcription factors and coactivators is likely to be affected by dietary interventions and might interfere with insulin signaling in diverse tissues, including the liver. Moreover, the main components of cereal fibers are cellulose and hemicellulose, which are likely to have distinct biological effects and physicochemical properties compared with resistant starch.

The use of fiber supplements in dietary recommendations has been criticized (25). However, in light of the discrepancy between recommended fiber intake of 20–35 g total fiber/day (10) and actual consumption of <15 g/day (26), it seems to be important to identify active substances of dietary fibers that might have favorable health effects (27).

The current study may be of public health relevance, providing a potential link between cereal fiber consumption and reduced risk of type 2 diabetes. By favorably influencing whole-body insulin sensitivity, intake of insoluble fiber by quantity could be underrepresented in current dietary recommendations. An emphasis on cereal, fruit, and vegetable consumption containing a particularly high proportion of insoluble dietary fiber might be a safe, effective, and low-cost approach to reduce insulin resistance. This could be of specific advantage for overweight and obese subjects at risk of developing type 2 diabetes. Further studies are needed to assess whether the current findings can be generalized to other cohorts, including males and subjects with marked insulin resistance, such as those with type 2 diabetes.

Acknowledgments— A previous study (8) that investigated the same fiber was partially supported by a grant from Rettenmaier & Söhne (Rosenberg, Germany). There were no conflicts of interest.

The authors thank Andreas Wagner, Sandra Grosch, and Andrea Ziegenhorn for excellent technical assistance.

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