

Program # 587.9

This study evaluated the effects of two levels of intake of a natural type 2 resistant starch (RS; Hi-maize 260, National Starch, LLC) on insulin sensitivity in subjects with waist circumference ≥ 89 cm (women) or ≥ 102 cm (men). Participants received 0 (control starch), 15 or 30 g/d (double-blind) of RS in random order for 4-wk periods, separated by 3-wk washouts. Insulin sensitivity index (S_I) was assessed at the end of each period using the insulin-modified intravenous glucose tolerance test (minimal model). The efficacy evaluable sample included 11 men, 11 post- and 10 pre-menopausal women with mean \pm SEM age 49.5 ± 1.6 y, body mass index 30.6 ± 0.5 kg/m² and waist 105.3 ± 1.3 cm. The analysis showed a significant treatment main effect ($p=0.008$) and a treatment by sex category interaction ($p=0.05$). Median S_I during control was $3.14 \times 10^{-4} \times \text{min}^{-1} \times (\mu\text{U/mL})^{-1}$. Median changes compared to control during the 15 g/d RS condition were 42.1%, 18.4%, and -0.4% in men, postmenopausal and premenopausal women, respectively. Corresponding changes during the 30 g/d RS condition were 59.8%, 7.3%, and -3.1%. Responses in premenopausal women may have been confounded by changes in insulin sensitivity during the menstrual cycle. These results suggest that consumption of 15-30 g/d of RS increases insulin sensitivity and that future studies in premenopausal women should control for menstrual cycle phase.

Background

- Resistant starch (RS), a type of insoluble dietary fiber, is the fraction of starch resistant to pancreatic α -amylase hydrolysis in the small intestine, and therefore passes undigested to the large bowel where it can act as a substrate for microbial fermentation (Englyst 1992).
- Results from prior studies suggest that consumption of certain RS products may improve insulin sensitivity, although the mechanisms responsible for this effect are not fully understood (Johnston 2010, Robertson 2003, 2005).
- This has important implications for human health because insulin resistance (i.e., impaired insulin sensitivity) is a central pathophysiologic feature of the metabolic syndrome, a cluster of risk factors for atherosclerotic cardiovascular disease and diabetes mellitus.
- Fermentation end products, particularly short-chain fatty acids (SCFA), are hypothesized to be involved in a cascade of events that may lead to improved insulin sensitivity.

Objective

- The aim of this clinical trial was to assess the effects of a dietary fiber/RS ingredient, at two doses, on insulin sensitivity.

Subjects

- Subjects were generally healthy, overweight and obese men and women, 18 to 69 years of age, inclusive, with waist circumference ≥ 102 cm and ≥ 89 cm, respectively. None of the subjects had diabetes.
- Individuals with a body mass index >35.0 kg/m²; abnormal lab values of clinical importance; history of clinically important endocrine, cardiovascular, renal, pulmonary, hepatic, biliary, or gastrointestinal disease; recent history of cancer, major trauma or surgery, or a current infection were excluded.
- Subjects with extreme habits that might confound the results (e.g., alcohol or substance abuse, extreme dietary or exercise habits) or using systemic medications known to influence carbohydrate metabolism were also excluded.

Methods

- This was a randomized, double-blind, controlled, crossover trial consisting of three 4-week treatment periods, separated by 3-week washouts.
- Eligible subjects received 0 g/d (control starch), 15 g/d or 30 g/d of RS (as measured by AOAC Method 991.43 for total dietary fiber; Hi-maize 260[®], National Starch LLC, Bridgewater, NJ).
- The study product was a type 2 RS packaged in ready-to-use sachets.
- Subjects were instructed to consume two servings daily of their assigned study product at separate eating occasions during the day with the last dose of their assigned study product during the evening prior to test visits. Subjects consumed the study product in the evening prior to each test visit. Subjects were instructed to mix the study product into any cold or room temperature beverage or food.
- Insulin sensitivity index (S_I) was assessed at the end of each period using the insulin-modified intravenous glucose tolerance test (IVGTT) with minimal model analysis. Blood samples were collected at the following pre- and post-glucose infusion timepoints: $t = -10, -5, 3, 5, 7, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 75, 90, 120, 150,$ and 180 min.
 - Plasma glucose and insulin values were entered into the MINMOD MILLENNIUM computer program (version 6.02; RN Bergman, USC, Los Angeles, CA) for determination of insulin sensitivity (Bergman 1979, Bloem 2008). Acute insulin response to IV glucose (AIR_G) was defined as the incremental area under the curve for the period 0 to 10 min (Maki 1996). The disposition index (DI) of pancreatic β -cell function, a measure of the appropriateness of the amount of insulin secreted for the prevailing level of insulin resistance, was calculated as $\text{DI} = S_I \times \text{AIR}_G$ (Kahn 1993).

- Differences between conditions in responses for continuous variables were assessed using SAS PROC MIXED repeated measures analysis of variance (ANOVA), including subject as a random variable and terms for treatment condition, sex, sequence, period, and treatment condition by sex interaction.
- Models for glucose homeostasis variables also included the homeostasis model assessment of insulin sensitivity (HOMA%S) value from the control condition as a covariate. Models were reduced until only treatment condition and any significant ($p < 0.05$) terms remained.

Effects of Type 2 Resistant Starch Consumption on Insulin Sensitivity in Men and Women

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Results

Table 1. Subject characteristics.

Characteristic	Total (n = 33)	Men (n = 11)	Women (n = 22)
		n (%)	
Race			
Non-Hispanic White	27 (82)	9 (82)	18 (82)
African-American	2 (6)	1 (9)	1 (5)
Other	4 (12)	1 (9)	3 (14)
Smoking Status			
Non-Smoker	17 (52)	5 (46)	12 (55)
Current Smoker	5 (15)	3 (27)	2 (9)
Past Smoker	11 (33)	3 (27)	8 (36)
Menopausal Status			
Premenopausal	N/A	N/A	9 (41)
Postmenopausal	N/A	N/A	13 (59)
Fasting Glucose Status			
Normal	22 (67)	7 (64)	15 (68)
Impaired	11 (33)	4 (36)	7 (32)
Metabolic Syndrome	15 (45)	7 (64)	11 (50)
	Mean \pm SEM		
Age (yr)	49.5 \pm 1.6	48.1 \pm 3.3	50.2 \pm 1.7
Body mass index (kg/m ²)	30.6 \pm 0.5	30.7 \pm 0.9	30.6 \pm 0.5
Waist circumference (cm)	105.3 \pm 1.3	108.8 \pm 1.5	103.6 \pm 1.8
Fasting glucose (mmol/L)	5.29 \pm 0.08	5.31 \pm 0.15	5.29 \pm 0.10
Average alcoholic drinks/week	1.8 \pm 0.5	3.2 \pm 1.3	1.1 \pm 0.3

Table 2. Glucose homeostasis variables in men.

Parameter	Control n = 11	15 g/d RS n = 11	30 g/d RS n = 11	P-Value*
	Mean \pm SEM			
S_I ($10^{-5} \times \text{pmol}^{-1} \times \text{L}^{-1} \times \text{min}^{-1}$)	5.19 \pm 1.23	7.07 \pm 1.13 [‡]	8.02 \pm 1.72 [‡]	0.012
S_G ($100 \times \text{min}^{-1}$)	2.75 \pm 0.53	2.33 \pm 0.25	2.47 \pm 0.27	0.765
K_G (min^{-1})	2.65 \pm 0.57	2.28 \pm 0.35	2.32 \pm 0.44	0.433
AIR_G ($\text{pmol} \times \text{L}^{-1} \times \text{min}$)	5070 \pm 1430	4050 \pm 1606 [†]	3880 \pm 900 [‡]	0.010
DI ($S_I \times \text{AIR}_G$)	19,462 \pm 6124	25,070 \pm 10,787	26,907 \pm 7598 ^{‡§}	0.005
Fasting Insulin (pmol/L)	60.5 \pm 12.1	48.2 \pm 11.6	56.5 \pm 10.8	0.151
Fasting Glucose (mmol/L)	5.51 \pm 0.26	5.80 \pm 0.20	5.75 \pm 0.14	0.291
HOMA%B	101.1 \pm 21.0	75.2 \pm 14.8	81.4 \pm 11.9	0.239
HOMA%S	128.5 \pm 38.2	125.4 \pm 17.0	110.5 \pm 21.2	0.136

*P values derived from analysis of variance.

[†]P < 0.05 vs. control, [‡]P < 0.02 vs. control, [§]P < 0.05 vs. low dose RS condition.

^{||}Untransformed values are shown for insulin sensitivity index, however the model was run on log(e) transformed values.

Table 3. Glucose homeostasis variables in women.

Parameter	Control n = 22	15 g/d RS n = 21	30 g/d RS n = 22	P-Value*
	Mean \pm SEM			
S_I ($10^{-5} \times \text{pmol}^{-1} \times \text{L}^{-1} \times \text{min}^{-1}$)	7.02 \pm 0.91	7.50 \pm 0.78	6.80 \pm 1.01	0.245
S_G ($100 \times \text{min}^{-1}$)	2.56 \pm 0.21	2.33 \pm 0.20	2.34 \pm 0.19	0.545
K_G (min^{-1})	2.49 \pm 0.27	2.31 \pm 0.28	2.48 \pm 0.22	0.584
AIR_G ($\text{pmol} \times \text{L}^{-1} \times \text{min}$)	2540 \pm 361	2099 \pm 280	2777 \pm 404	0.133
DI ($S_I \times \text{AIR}_G$)	17,902 \pm 3667	18,018 \pm 3997	18,393 \pm 3563	0.924
Fasting Insulin (pmol/L)	58.2 \pm 7.8	54.1 \pm 6.9	49.5 \pm 7.5	0.253
Fasting Glucose (mmol/L)	5.49 \pm 0.13	5.53 \pm 0.11	5.42 \pm 0.08	0.290
HOMA%B	89.2 \pm 7.4	84.7 \pm 7.7	80.7 \pm 7.7	0.495
HOMA%S	104.1 \pm 10.7	115.3 \pm 18.1	144.0 \pm 27.9	0.253

*P values derived from analysis of variance.

Table 4. Blood parameters in men and women.

Parameter	Control n = 22	15 g/d RS n = 21	30 g/d RS n = 22	P-Value*
	Median (IQL)			
Men (n = 11)				
hs-CRP (mg/dL)	1.30 (0.80, 2.20)	1.00 (0.60, 2.10)	1.50 (0.90, 2.60)	0.210
Adiponectin ($\mu\text{g/mL}$)	5.12 (3.38, 6.98)	5.16 (3.08, 6.18)	4.69 (3.14, 6.57)	0.697
Fructosamine ($\mu\text{mol/L}$)	199.0 (191.0, 204.0)	200.0 (196.0, 208.0)	198.5 (193.0, 209.00)	0.977
Total FFA (mmol/L)	0.48 (0.39, 0.57)	0.46 (0.36, 0.56)	0.46 (0.30, 0.61)	0.810
Total SCFA ($\mu\text{mol/L}$)	74.7 (61.4, 105.3)	116.8 (80.6, 182.0)	113.4 (97.3, 115.7)	0.162
Acetate ($\mu\text{mol/L}$)	68.4 (54.0, 88.2)	90.0 (62.9, 171.0)	101.8 (76.5, 107.0)	0.081
Butyrate ($\mu\text{mol/L}$)	2.00 (1.25, 2.65)	2.20 (1.90, 4.20)	2.55 (2.00, 6.60)	0.323
Propionate ($\mu\text{mol/L}$)	6.50 (6.10, 8.50)	7.10 (6.10, 8.60)	7.00 (5.30, 8.00)	0.101
Acetate:Propionate	10.38 (9.53, 12.09)	11.90 (9.26, 14.50)	14.43 (10.08, 15.65)	0.282
Women (n = 22)				
hs-CRP (mg/dL)	1.80 (1.10, 4.20)	1.50 (0.80, 3.70)	1.65 (0.80, 5.30)	0.238
Adiponectin ($\mu\text{g/mL}$)	10.43 (7.87, 13.29)	10.48 (8.40, 13.54)	10.75 (7.96, 15.01)	0.280
Fructosamine ($\mu\text{mol/L}$)	211.0 (193.0, 219.0)	208.0 (197.0, 211.0)	208.0 (195.0, 222.0)	0.698
Total FFA (mmol/L)	0.59 (0.44, 0.66)	0.66 (0.43, 0.85)	0.56 (0.47, 0.74)	0.069
Total SCFA ($\mu\text{mol/L}$)	71.6 (66.4, 79.4)	79.7 (62.6, 107.0)	88.9 (66.6, 106.5)	0.158
Acetate ($\mu\text{mol/L}$)	67.1 (58.3, 72.0)	76.5 (61.7, 92.7)	90.2 (62.7, 102.5) [†]	0.018
Butyrate ($\mu\text{mol/L}$)	1.50 (1.30, 2.90)	2.20 (1.10, 4.00)	1.55 (1.15, 3.50)	0.817
Propionate ($\mu\text{mol/L}$)	6.40 (5.80, 7.10)	6.40 (5.40, 7.20)	6.23 (5.00, 6.70)	0.386
Acetate:Propionate	10.38 (9.05, 12.20)	10.98 (9.49, 13.06)	14.34 (10.85, 16.19) ^{‡§}	<0.001

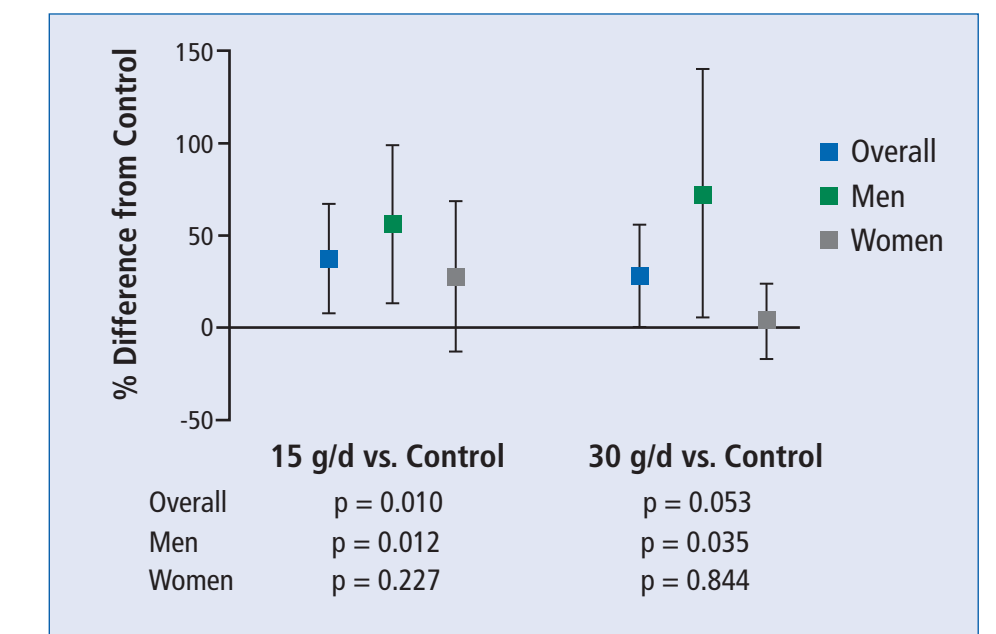
*P values derived from analysis of variance.

[†]P < 0.013 vs. control; [‡]P < 0.002 vs. control and low dose RS

Abbreviations:

AIRG = acute insulin response to intravenous glucose	LDL-C = low-density lipoprotein cholesterol
ANOVA = analysis of variance	non-HDL-C = non-high-density lipoprotein cholesterol
AUC = area under the curve	RS = resistant starch
DI = disposition index	S_G = glucose effectiveness
FFA = free fatty acids	S_I = insulin sensitivity index
HDL-C = high-density lipoprotein cholesterol	SCFA = short chain fatty acids
HOMA%B = homeostasis model of beta cell function	SEM = standard error of the mean
HOMA%S = homeostasis model assessments of insulin sensitivity	TC = total cholesterol
K_G = glucose disappearance constant	TG = triglycerides.

Figure 1. Insulin sensitivity percent differences from control by treatment condition in the overall study sample and sex-specific subgroups.



Symbols are means, error bars indicate 95% CI.

Conclusions

- As little as 15 g/d of a natural Type 2 RS markedly improved insulin sensitivity and pancreatic beta-cell function in men with central obesity — a population with elevated risk for cardiovascular disease and diabetes.
- The response was smaller and non-significant in women.
- In men, there were no differences in pre-test levels of SCFA or concentrations of the individual SCFA: acetate, propionate, or butyrate. However in women, there was a significant increase in acetate in the 30 g/d RS condition versus control ($p = 0.013$).
- There was some indication that responses in premenopausal women may have been confounded by the menstrual cycle, therefore future studies in premenopausal women should control for menstrual cycle phase.
- Given the putative role of insulin resistance in the development of diabetes mellitus and atherosclerotic cardiovascular disease, further understanding of the relationship between RS intake and insulin sensitivity has substantial potential public health significance.

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