Increased fiber intake predicts the decrease in 2nd phase glucose-induced hyperinsulinemia following a hypocaloric diet in obese subjects

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Abstract *Background and aims:* Higher fiber intake is associated with increased insulin sensitivity (IS) and reduced glucose-induced insulin secretion (GIIS) during isocaloric-diets; however, its role in hypocaloric-diets is unclear. We examined whether increased fiber intake predicts the amelioration in IS and GIIS following a hypocaloric-diet.
Methods and results: This is a post-hoc analysis of 55 adult subjects (BMI > 27 kg/m^2) who completed a 6-month hypocaloric-diet (−500 kcal/day). Dietary intake was assessed using 3-day food records at baseline and post-intervention. We evaluated glucose-induced insulin and C-peptide secretions as AUC of plasma insulin and C-peptide during intravenous-glucose-tolerance tests (IVGTT) and IS via hyperinsulinemic-euglycemic clamps. Data analysis employed regression models and 2-way RM ANOVAs. Post-intervention % change in fiber intake was associated positively with IS_{clamp} (r = 0.30) and negatively with % change in total (r = −0.37) and 2nd phase $GIIS_{IVGTT}$ (r = −0.44) but not C-peptide secretion. It remained associated with lower 2nd phase $GIIS_{IVGTT}$ after adjustment for sex and % changes in BMI and energy-intake, independently of other macronutrients. Subjects who increased fiber intake (to 28.7 ± 9.0 g/day) had a greater decrease in 2nd phase $GIIS_{IVGTT,}$ not C-peptide secretion, independently of sex or changes in adiposity or energy-intake compared to subjects who decreased intake (to 20.0 ± 6.8 g/day).
Conclusion: Higher fiber intake is an independent predictor of reduced 2nd phase glucose-induced hyperinsulinemia after a hypocaloric-diet. It was not associated with plasma C-peptide, suggesting a role in faster insulin clearance rather reduced insulin secretion. Promoting high-fiber intake may increase the effectiveness of hypocaloric-diets in preventing type 2 diabetes.
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Introduction

Type 2 diabetes (T2D) is a complex multi-factorial disease, which develops with the accumulation of risk factors such as genetics, aging, obesity, and unhealthy lifestyle. Current knowledge on the progression to T2D favors a 2-step model. In the 1st step, impaired glucose tolerance develops with progressive rise in insulin resistance (IR) driving higher insulin secretion and hyperinsulinemia [1]. In the 2nd step, T2D evolves with the progressive loss of β-cell function and eventual decline in insulin secretion [1]. Glucose-induced insulin secretion (GIIS) is mediated via 2 phases: the 1st phase involves a quick discharge of insulin in response to glucose, while the 2nd phase produces a substantial and prolonged GIIS [3,4]. Beta-cell exhaustion and hyperinsulinemia is primarily driven by 2nd phase GIIS being the bulk of total GIIS ($\sim$80%) [4].

Hypocaloric-diet-induced weight-loss of 5–10% is frequently recommended to target obesity-related T2D risk factors [5]. However, large inter-subject variability exists in the metabolic response to a hypocaloric diet-induced weight-loss that are independent of changes in adiposity [6]. We reported that higher baseline plasma number of apoB-lipoproteins, measured as apoB, predicts the decrease in 2nd phase GIIS following 6-month hypocaloric-diet in overweight and obese subjects independent of weight-changes [6]. However, in addition to baseline characteristics, inter-subject variability in the response to hypocaloric diets may be related to changes in dietary composition.

Multiple lines of evidence link higher intake of fiber to lower risk for T2D. In a recent review of prospective studies, higher intake of cereal fiber (range = 4–29 g/day) was associated with 18–40% decrease in T2D risk over 4–18 years, while higher intake of mixtures of whole grains and bran (range = 1.3 servings/day to >17.5 servings/week) was associated with 21–40% decrease in T2D risk over 6–19 years [7]. In the Insulin Resistance Atherosclerosis cross-sectional study, whole-grain intake (14 ± 6 g/day dietary fiber) was positively associated with higher insulin sensitivity (IS) assessed using an intravenous-glucose-tolerance test (IVGTT) in 978 middle-aged adults [8]. Finally, in weight-maintenance interventional-studies, higher fiber intake from food sources [9,10] or supplementation [11–14] increased peripheral IS [9–14] and reduced GIIS evaluated from plasma insulin during an IVGTT [10]. These studies suggest that fiber intake may modulate insulin metabolism in response to hypocaloric-diets in obese subjects; however, this remains unexplored.

Thus, we tested the hypothesis that a higher fiber intake predicts a greater increase in IS and decrease in insulin secretion in response to a hypocaloric-diet independent of changes in adiposity and energy-intake. This was examined in a post-hoc analysis of a 6-month hypocaloric-diet intervention in a cohort of non-diabetic overweight and obese subjects, where insulin sensitivity and secretion were examined using the gold-standard Botnia clamp technique.

Methods

Study population and design

This is a post-hoc analysis of a 6-month hypocaloric-dietary intervention, which tested the hypothesis that plasma apoB predicts baseline and post-intervention changes in T2D risk factors [6]. Subjects were included in the study if they were men and post-menopausal women between 45 and 74 years, non-smokers, sedentary (<2 h/week), with body mass index (BMI) > 27 kg/m^2, consumed <2 alcoholic drinks/day, and free of chronic disease (e.g. cardiovascular, diabetes) and medication affecting metabolism [6]. Subjects were placed on a 4-week weight-stabilization period that was verified weekly (±2 kg), after which baseline measurements were conducted. They were then placed on a 6-month hypocaloric diet followed by another 4-week weight-stabilization period, after which post-intervention measurements were conducted. Subjects signed an informed consent form prior to study initiation, which was approved by the IRCM Human Ethics Board.

Dietary intervention

Subjects were counseled to follow a balanced diet based on the Canadian Food Guide (45–65% carbohydrate, 20–35% fat, 15–35% protein) [15]. Daily energy needs were calculated as basal metabolic rate, measured by indirect calorimetry, multiplied by a sedentary activity factor of 1.4, from which 500 kcal were subtracted [6]. To encourage compliance, subjects had individual monthly meetings with the dietitian for 1 h at baseline and during the 6-month hypocaloric-diet intervention. During these 7 sessions, subjects received oral and written nutritional counseling covering food groups, energy-balance, fat, fiber, protein, energy-density and strategies to control appetite. The session covering dietary fiber explained their role in promoting satiety and recommended an intake of ≥25 g/day [15]. Subjects were instructed to maintain their sedentary habitual activity level during the hypocaloric-diet [6].

Dietary assessment

Three-day food records (two week-days, one weekend-day) were collected at baseline and in the last week of the intervention. Subjects were instructed by a dietitian on how to complete the food records, which were verified by the dietitian for missing details. Data analysis covered the intake of total fat, saturated fat, trans fat, carbohydrate, dietary fiber (soluble and insoluble), sugar, protein and was conducted using the Food Processor Software (2016 V11.3.285, ESHA Research) using a Canadian Database or food-item labels provided by the subjects [6]. Subjects were separated into 2 groups with increased (N = 27) versus decreased (N = 28) post-intervention changes in fiber intake.

Anthropometric and metabolic measurements

We measured body composition by dual-energy X-ray absorptiometry, plasma lipoprotein parameters and glucose by automated analyzers (Cobas Integra 400 and YSI Incorporated) and serum insulin and C-peptide by radioimmunoassay kits (Millipore Corporation) [4,6,16,17].

Insulin sensitivity and secretion

We conducted Botnia clamps, which consists of a 1-hour IVGTT (0.3 g glucose/kg) followed by a 3-hour hyperinsulinemic-euglycemic (HIEG) clamp (75 mU/min*m^2 primed-exogenous insulin infusion) [4,6,16,17]. Both plasma insulin and C-peptide were used to evaluate insulin secretion. First phase, 2nd phase and total glucose-induced insulin and C-peptide secretions were assessed as the AUC of plasma insulin (GIIS) and C-peptide during the first 10 min, following 50 min and total 60 min of the IVGTT. Insulin sensitivity was assessed as glucose infusion rate divided by plasma insulin (M/I$_{clamp}$) in the last 30-minutes of the clamp [4,6,16,17].

Statistical analysis

Data are presented as mean ± SD. Group differences at baseline and post-intervention were analyzed by RM 2-way ANOVA with interaction (group × time) and adjustment for multiple comparisons using Bonferroni's methods. When the interaction was significant, intra- and inter-group differences were measured by paired and independent student t-test, respectively. Pearson correlation was used to examine the associations between variables. Notably, a sample of 55 subjects can detect a correlation of r = 0.32 with a power of 80% and α-value of 0.05. The interaction of sex with % change in fiber intake or other variables was tested in regression models using sex, % change in fiber, and sex multiplied by % change in fiber as independent variables to predict the dependent variables [18]. Stepwise regression analysis was used to identify predictors of the % changes in GIIS$_{IVGTT}$, C-peptide secretion$_{IVGTT}$, and IS with adjustment for sex and % changes in BMI and energy-intake, and using % changes in carbohydrate, protein, fiber, sugar, fat and saturated fat as independent variables. Statistical analyses were performed using SPSS V19 and GraphPad Prism V7. Significance was set at p < 0.05.

Results

A total of 110 subjects were screened between 2010 and 2013, of whom 82 subjects (33 men, 49 women) met the inclusion/exclusion criteria and were enrolled [6]. Fifty-nine subjects completed the hypocaloric-diet. Complete baseline and post-intervention dietary records were available for 55 subjects (30 women, 25 men) and were thus used for this analysis.

There were sex-differences in most baseline and post-interventions parameters; however, both sexes had similar decrease in total and central adiposity in response to the hypocaloric diet (Table 1). First phase, 2nd phase and total GIIS$_{IVGTT}$, and C-peptide secretion$_{IVGTT}$ decreased in both sexes; however men had a greater decrease in 2nd phase GIIS$_{IVGTT}$ and increase in IS (M/I$_{clamp}$). There was a significant decrease in the intake of energy, total and saturated fats and carbohydrates without sex-difference, while the intake of protein, sugar or fiber was unchanged. Fiber intake was ≥25 g/day for 10 women and 14 men before the intervention and for 10 women and 12 men after the intervention.

Predictors of post-intervention changes in GIIS$_{IVGTT}$ and IS

Percent change in BMI was also not associated with changes in GIIS$_{IVGTT}$ (Fig. 1A,B) nor any measure of C-peptide secretion (p > 0.05) but was negatively correlated with % change in IS (Fig. 1C). Percent change in energy-intake was not associated with any of these parameters. Conversely, % change in fiber intake was correlated negatively with % change in 2nd phase GIIS$_{IVGTT}$ (Fig. 2B) and total GIIS$_{IVGTT}$ (r = −0.37, p = 0.005) and positively with IS (Fig. 2C) with no sex-differences. It was not correlated with 1st phase GIIS$_{IVGTT}$ (Fig. 2A) nor with C-peptide secretions (1st phase, 2nd phase or total). No other nutrient was correlated with these parameters, except for protein, which correlated negatively with % change in GIIS$_{IVGTT}$ (2nd phase r = −0.28 and total r = −0.27, p < 0.05).

In regression analysis, % change in fiber intake predicted 24% of the inter-subject variability in % change in 2nd phase GIIS$_{IVGTT}$ after adjustment for sex and % change in BMI and energy-intake (p = 0.04) (Table 2). All other macronutrients (carbohydrates, protein, fat, saturated fat, and sugar) were excluded. Conversely, similar adjustment eliminated the association of % change in fiber intake with that of IS (M/I$_{clamp}$) and total GIIS$_{IVGTT}$, and did not reveal additional association with change in 1st phase GIIS$_{IVGTT}$.

Differences between subjects with a post-intervention increased versus decreased fiber intake

There was a large inter-subject variability in the changes in fiber intake following the hypocaloric-diet (Supplemental Fig. 1A,B). To further examine the association of fiber intake with GIIS and IS while accounting for subject-characteristics, we compared subjects with post-intervention increased versus decreased fiber intake after adjustment for sex (Table 3).

Subjects with increased intake (+6.50 ± 5.38 g/day) reached a post-intervention fiber intake of 28.7 ± 9.0 g/day while those who decreased intake (−5.66 ± 3.86 g/d) reached 20.0 ± 6.8 g/day (p < 0.001). There were no baseline group-differences in any parameter, including plasma apoB. Both groups had similar decrease in total and central adiposity, while those with increased fiber intake had a greater decrease in peripheral adiposity (gynoid). Both groups had no change in plasma lipoprotein parameters, except HDLC. The only group-difference that was

Table 1 Subject characteristics at baseline and after the 6-month hypocaloric diet intervention and percent changes after the intervention.

Parameters	Women n = 30			Men n = 25			p-value		
	Baseline	Post-intervention	% change	Baseline	Post-intervention	% change	Interaction	Group effect	Time effect
Anthropometric and metabolic parameters									
Age (years)	58.3 ± 5.8	59.0 ± 5.9	1.20 ± 0.82	57.4 ± 6.5	58.0 ± 6.6	1.09 ± 0.85	–	–	<0.001
Weight (kg)	80.8 ± 12.1	76.7 ± 11.7	−5.01 ± 4.79	100 ± 19	95.2 ± 20.5	−5.03 ± 4.61	–	<0.001	<0.001
BMI (kg/m^2)	31.8 ± 3.8	30.2 ± 3.8	−5.03 ± 4.79	33.2 ± 5.4	31.5 ± 5.7	−4.98 ± 4.55	–	–	<0.001
Total fat mass (kg)	36.4 ± 8.4	33.0 ± 8.4	−9.34 ± 9.16	36.1 ± 13.3	32.3 ± 14.1	−11.3 ± 10.9	–	–	<0.001
Android fat mass (kg)	3.37 ± 0.99	2.90 ± 1.03	−14.4 ± 13.3	4.30 ± 1.61	3.68 ± 1.67	−15.5 ± 13.9	–	0.019	<0.001
Gynoid fat mass (kg)	6.19 ± 1.37	5.52 ± 1.41	−11.1 ± 10.0	4.75 ± 1.81	4.27 ± 1.76	−10.4 ± 9.4	–	0.002	<0.001
Android/gynoid fat	**0.55 ± 0.13*****	**0.53 ± 0.12***‡**	**−3.99 ± 7.30‡**	0.93 ± 0.19	**0.87 ± 0.17§**	**−6.19 ± 7.66§**	0.016	<0.001	<0.001
Waist circumference (cm)	102 ± 11	98.7 ± 11.7	−3.03 ± 6.25	114 ± 13	110 ± 14	−4.00 ± 4.67	–	0.001	<0.001
Hip circumference (cm)	112 ± 8	108 ± 10	−3.67 ± 4.96	109 ± 10	107 ± 11	−2.06 ± 2.77	–	–	<0.001
Plasma total cholesterol (mM)	5.57 ± 1.16	5.51 ± 1.22	−0.65 ± 9.68	4.90 ± 0.99	4.67 ± 1.01	−4.36 ± 13.91	–	0.012	–
Plasma HDL cholesterol (mM)	1.55 ± 0.49	1.63 ± 0.48	6.91 ± 14.07	1.05 ± 0.20	1.11 ± 0.20	6.61 ± 12.51	–	<0.001	0.003
Plasma LDL cholesterol (mM)	3.30 ± 0.99	3.26 ± 1.03	−0.60 ± 12.23	2.76 ± 0.57	2.73 ± 0.80	−0.55 ± 21.64	–	0.024	–
Plasma apoB (g/L)	0.91 ± 0.29	0.94 ± 0.31	3.52 ± 15.81	0.96 ± 0.22	0.97 ± 0.28	1.15 ± 18.53	–	–	–
Plasma triglycerides (mM)	1.59 ± 1.01	1.38 ± 0.90	−8.45 ± 30.71	2.41 ± 1.81	1.99 ± 2.08	−8.60 ± 50.10	–	0.048	–
Systolic blood pressure (mmHg)	120 ± 18	120 ± 17	0.73 ± 9.77	131 ± 13	129 ± 14	−0.17 ± 8.26	–	0.030	–
Diastolic blood pressure (mmHg)	75.8 ± 9.9	75.9 ± 9.2	0.65 ± 8.58	82.3 ± 8.2	80.7 ± 8.7	−0.75 ± 7.36	–	0.034	–
Botnia clamp parameters									
Plasma glucose (mM)	5.08 ± 0.45	4.90 ± 0.47	−3.40 ± 6.93	5.29 ± 0.50	5.21 ± 0.44	−0.96 ± 8.44	–	0.022	0.025
Plasma insulin (uU/mL)	18.3 ± 5.6	**15.5 ± 8.1†**	**−14.6 ± 30.3†**	23.0 ± 12.2	15.8 ± 6.3	**−23.0 ± 30.1§**	0.032	–	<0.001
1st phase GIIS$_{IVGTT}$ (uU/mL/10 min)	843 ± 483	680 ± 361	−12.7 ± 29.7	1176 ± 977	936 ± 759	−8.06 ± 44.13	–	–	<0.001
2nd phase GIIS$_{IVGTT}$ (uU/mL/50 min)	**2813 ± 1583***	**2387 ± 1521‡**	**−11.3 ± 27.3*†**	4355 ± 3785	**2991 ± 3172§**	**−28.1 ± 28.1§**	0.006	–	<0.001
Total GIIS$_{IVGTT}$ (uU/mL/60 min)	**3656 ± 1975***	**3068 ± 1810§**	**−12.0 ± 26.6†**	5532 ± 4600	**3927 ± 3737§**	**−24.3 ± 28.7§**	0.015	–	<0.001
1st phase C-peptide secretion$_{IVGTT}$ (ng/mL/10 min)	47.0 ± 20.5	36.9 ± 20.8	−19.3 ± 36.9	56.1 ± 30.9	45.2 ± 21.4	−7.95 ± 48.40	–	–	<0.001
2nd phase C-peptide secretion$_{IVGTT}$ (ng/mL/50 min)	267 ± 102	211 ± 91	−20.1 ± 27.6	294 ± 136	23 ± 88	−3.99 ± 73.23	–	–	<0.001
Total C-peptide secretion$_{IVGTT}$ (ng/ml/60 min)	314 ± 118	248 ± 109	−20.6 ± 27.6	350 ± 164	283 ± 102	−4.73 ± 68.07	–	–	<0.001
M/I$_{clamp}$ (mg/kg/min)/(uU/mL)	0.052 ± 0.029	0.052 ± 0.022	**5.77 ± 31.40*****	0.041 ± 0.020	**0.062 ± 0.028§**	**63.9 ± 56.4§**	<0.001	–	0.001
Dietary parameters									
Energy-intake (kcal)	1798 ± 522	1568 ± 436	−10.2 ± 21.7	2527 ± 497	2191 ± 638	−12.2 ± 24.0	–	<0.001	<0.001
Fat intake (g)	70.4 ± 25.6	52.7 ± 21.5	−22.9 ± 22.5	97.2 ± 27.9	79.1 ± 40.3	−16.3 ± 39.1	–	<0.001	<0.001
Saturated fat intake (g)	22.4 ± 9.9	16.4 ± 8.0	−23.3 ± 28.2	31.0 ± 10.1	23.9 ± 13.0	−20.0 ± 38.5	–	0.001	<0.001
Carbohydrate intake (g)	214 ± 75	192 ± 64	−4.73 ± 25.53	285 ± 63	260 ± 75	−7.38 ± 26.57	–	<0.001	0.012
Fiber intake (g)	22.4 ± 6.0	21.3 ± 7.6	−0.75 ± 35.98	25.9 ± 8.6	27.8 ± 9.5	12.1 ± 34.5	–	0.01	–
min−max (g)	9.0−34.0	5.7−37.6	−68.9−73.9	11.7−49.1	17.0−57.5	−25.8−105.5			
Sugar intake (g)	85.6 ± 44.3	67.7 ± 27.6	−7.08 ± 48.87	88.5 ± 34.3	88.6 ± 34.1	10.5 ± 50.1	–	–	–
Protein intake (g)	77.3 ± 20.8	76.4 ± 21.4	1.65 ± 24.45	108.1 ± 31.1	103 ± 30	−0.37 ± 29.61	–	<0.001	–

Data presented as averages ± SD. Data analyzed by RM 2-way ANOVA with group × time interaction with adjustment for multiple comparison. When interaction was significant, *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001 for differences from men, and †p ≤ 0.05, ‡p ≤ 0.01, §p ≤ 0.001 for differences from baseline. Data in bold represents statistically significant analysis. GIR: glucose infusion rate; HDL: high density lipoprotein; IVGTT: intravenous-glucose tolerance test; LDL: low density lipoprotein.

Table 2 Stepwise regression analysis to predict percent changes in GIIS$_{IVGTT}$ and IS after the 6-month hypocaloric diet by percent changes in macronutrients in N = 55 subjects (N = 30 women and N = 25 men).

Dependent variable	Steps	Independent variables	Constant	Coefficients	R^2	P-value
% Change in 1st phase GIIS$_{IVGTT}$			−7.70			
		Sex		−4.07		0.688
		% Change BMI		0.72		0.525
		% Change energy-intake		−0.26	0.03	0.261
% Change in 2nd phase GIIS$_{IVGTT}$			−23.53			0.001
		Sex		13.04		0.082
		% Change BMI		0.27		0.783
		% Change energy-intake		−0.03	0.17	0.896
	1	% Change in fiber intake		−0.30	0.24	0.040
% Change in M/I$_{clamp}$			43.13			<0.001
		Sex		−57.62		<0.001
		% Change BMI		−4.05		0.003
		% Change energy-intake		−0.004	0.43	0.987

Independent variables entered in stepwise forward regression analyses to predict % changes in 1st phase and 2nd phase GIIS$_{IVGTT}$ and % changes in M/I$_{clamp}$ were % changes in carbohydrate, protein, fiber, sugar, total fat and saturated fat. Regression analysis adjusted for sex and % changes in BMI and energy-intake.

observed in dietary intake was a greater decrease in energy and carbohydrate intake in subjects with decreased fiber intake.

There were no group-differences in the post-intervention decrease in fasting plasma insulin and glucose, 1st phase GIIS$_{IVGTT}$ and 1st phase, 2nd phase and total C-peptide secretion$_{IVGTT}$, nor increase in IS (M/I$_{clamp}$). However, subjects with increased fiber intake had a greater decrease in 2nd phase and total GIIS$_{IVGTT}$. Adjustment for % change in gynoid fat did not eliminate group-differences in % change in 2nd phase (p = 0.008) or total (p = 0.031) GIIS$_{IVGTT}$. Similarly, adjustment for % change in BMI did not eliminate group-difference in % change in 2nd phase (p = 0.009) or total GIIS$_{IVGTT}$ (p = 0.013), while adjustment for % change in energy-intake eliminated group-differences in total (p = 0.052) but not 2nd phase GIIS$_{IVGTT}$ (p = 0.013).

Discussion

In this post-hoc analysis of a 6-month hypocaloric-dietary intervention in 55 non-diabetic overweight and obese subjects we report that post-intervention increase in fiber intake is the only macronutrient that predicted reduced 2nd phase glucose-induced hyperinsulinemia (GIIS$_{IVGTT}$) independent of sex and changes in BMI and energy-intake. Confirming this, subjects who increased fiber intake had a greater decrease in 2nd GIIS$_{IVGTT}$, independent of sex and % changes in BMI, gynoid fat or energy-intake. There was no association of fiber intake with glucose-induced C-peptide secretion and its associated with IS was dependent on sex and changes in BMI and energy-intake.

Primarily, it is important to underscore that the objective of this hypocaloric-diet was to decrease body weight rather than to increase fiber intake, and 44% of subjects were already within the target fiber intake (≥25 g/day) at baseline. There was also no distinction between soluble or insoluble fiber nor their food sources. Nevertheless, the use of the Botnia clamp for measurement of both glucose-induced insulin and C-peptide secretions, independently of IS, and the profound characterization of the population allowed us to isolate a novel independent association of increased fiber intake with decreased 2nd phase hyperinsulinemia. Thus, this work represents a hypothesis-generating study to be tested in the future.

Our data suggest that the increase in fiber intake is strongly associated with reduced 2nd phase GIIS$_{IVGTT}$, though not C-peptide secretion, following the hypocaloric diet. Two points need to be highlighted here. C-peptide is secreted with insulin and is a better index of insulin secretion given its longer half-life (20−30 min versus 3−5 min) [19]. As the change in fiber intake was not correlated with that of C-peptide, this suggests a role for higher fiber intake in faster plasma clearance of insulin rather than in reduced insulin secretion *per se*. Defects in insulin metabolism are however interrelated, and IR is associated with both higher insulin secretion [4] and lower insulin clearance [2]. Studies in dogs suggest that decreased insulin clearance is a compensatory mechanism to preserve β-cell function while maintaining hyper-insulinemia in states of obesity-induced IR [20]. In the Insulin Resistance Atherosclerosis Study, lower insulin clearance was associated with a higher risk of T2D over 5 years after adjusting for multiple confounders including adiposity and insulin secretion [2]. Taken together, this suggest that increased insulin clearance related to high-fiber hypocaloric diets may further reduce T2D risk; however, this remains to be investigated in future studies designed for this objective. The second point to be highlighted is that the 1st phase GIIS is intact in subjects with normoglycemia [1] and GIIS and hyperinsulinemia are primarily driven by the 2nd phase (Table 1). This may explain why the association between changes in anthropometric and parametric variables were with changes in 2nd rather than 1st phase GIIS$_{IVGTT}$ in this non-diabetic population.

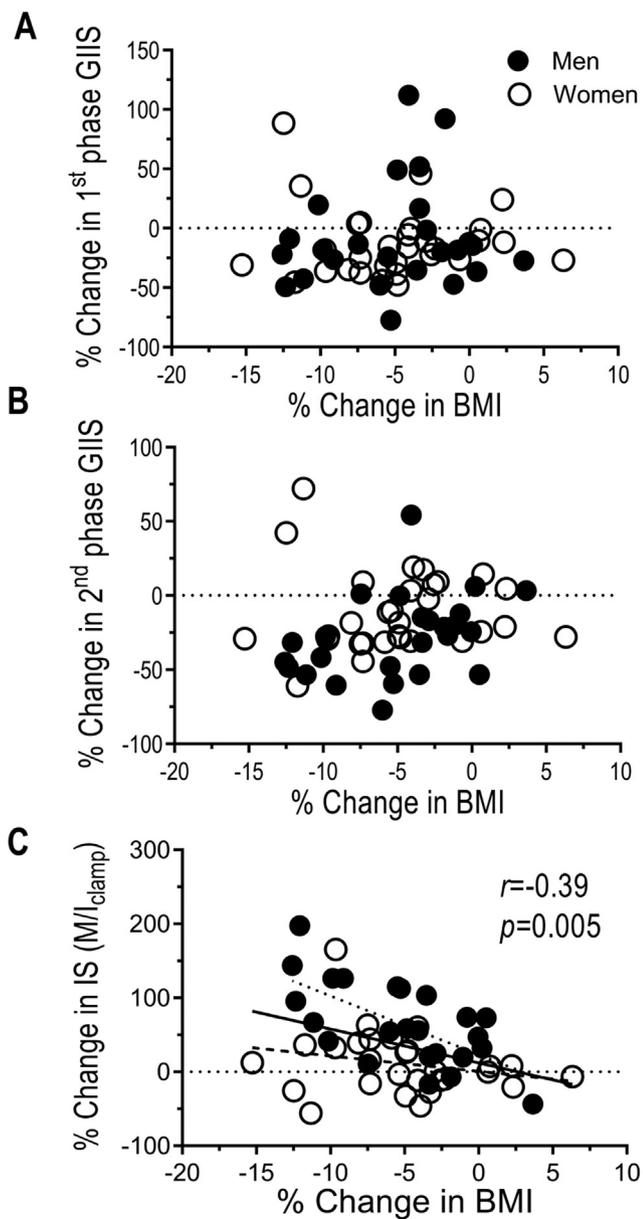While the role of fiber intake in modulating insulin metabolism during hypocaloric-diets is not reported,

Figure 1 Pearson correlation of % change in BMI following the hypocaloric-diet with that of 1st phase $GIIS_{IVGTT}$ (A), 2nd phase $GIIS_{IVGTT}$ (B), and IS (C) (n = 30 women, 25 men). BMI: body mass index; GIIS: glucose-induced insulin secretion; IS: insulin sensitivity; IVGTT: intravenous-glucose-tolerance test; M/I_{clamp}: clamp glucose-infusion rate divided by steady-state plasma insulin.

Figure 2 Pearson correlation of % change in fiber intake following the hypocaloricdiet with that of 1st phase $GIIS_{IVGTT}$ (A), 2nd phase $GIIS_{IVGTT}$ (B) and IS (C) (n = 30 women, 25 men). GIIS: glucose-induced insulin secretion; IS: insulin sensitivity; IVGTT: intravenous-glucose-tolerance test; M/I_{clamp}: clamp glucose-infusion rate divided by steady-state plasma insulin.

multiple isocaloric-dietary interventions reported an amelioration in insulin metabolism particularly related to IS. Compared to 6-weeks on a refined grain diet (~17.8 g/day), consuming a whole-grain diet (~28 g/day of soluble and insoluble fiber) reduced fasting plasma insulin and increased IS measured by HIEG clamp in hyperinsulinemic overweight and obese subjects [9]. Prebiotic supplementation or fibers that stimulate growth and/or activity of beneficial gut microbiota, were also reported to reduce postprandial glucose and insulin [21]. Additionally, supplementation with
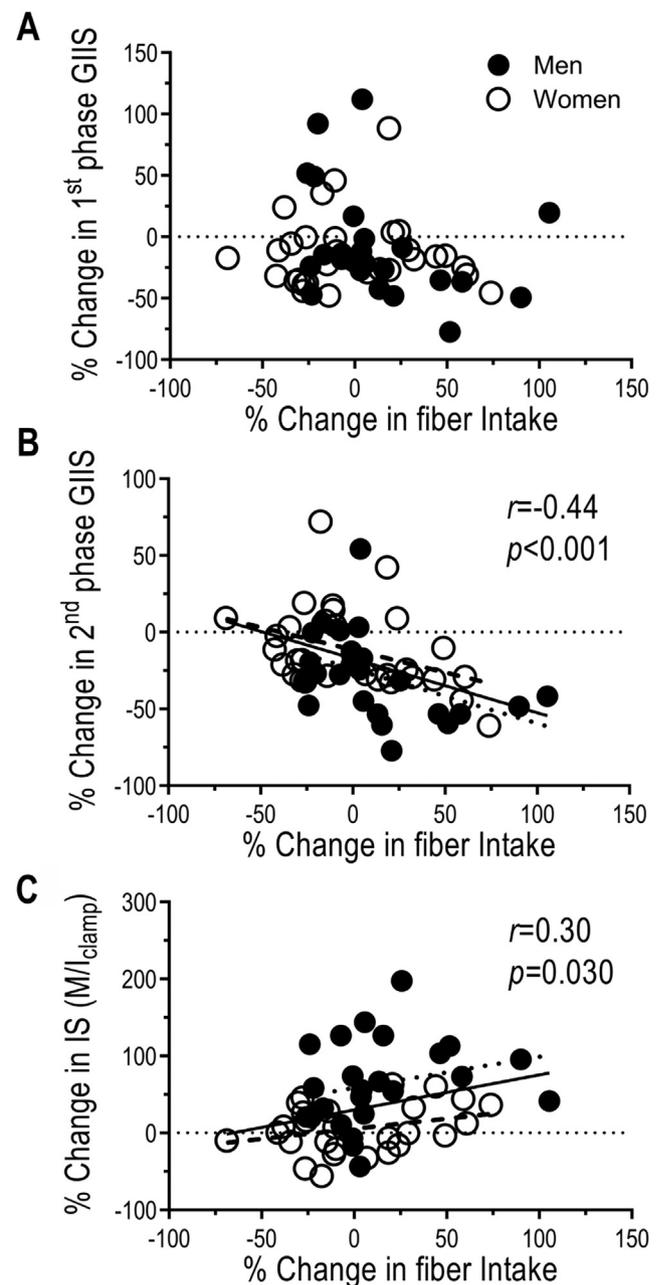
30–60 g/day of resistant starch (an insoluble fiber) increased IS and reduced postprandial insulinemia measured concomitantly during a meal tolerance test [11,12]. It also increased IS measured by HIEG clamp [12,13], similarly to insoluble oat fiber supplementation (31.2 g/day) given for 3 days in overweight or obese women [14]. Parallel association was observed between higher fiber intake with increased IS in our study; however, this relation was eliminated once adjusted for

Table 3 Group differences in sex-matched subjects with percent decreased versus increased fiber intake following the 6-month hypocaloricdiet.

	Increased fiber intake (N = 13 women, N = 14 men)[a]			Decreased fiber intake (N = 17 women, N = 11 men)[a]			p-values		
	Baseline	Post-intervention	% Change	Baseline	Post-intervention	% Change	Interaction	Group effect	Time effect
Fiber intake (g)	22.2 ± 7.3	**28.7 ± 9.0***[§]	**33.3 ± 27.6***[§]	25.6 ± 7.4	**20.0 ± 6.8**[§]	**−22.2 ± 15.0**[§]	<0.001	–	–
Min-max	9.0–40.2	15.6–57.5	3.1–105.4	16.3–49.1	5.7–39.0	−68.9−−0.6			
Anthropometric and metabolic parameters									
Weight (kg)	88.3 ± 18.4	82.9 ± 18.3	−6.13 ± 5.48	90.7 ± 18.8	87.3 ± 19.0	−3.94 ± 3.49	–	–	<0.001
BMI (kg/m^2)	31.9 ± 4.0	30.0 ± 4.2	−6.09 ± 5.46	32.9 ± 5.2	31.6 ± 5.3	−3.96 ± 3.47	–	–	<0.001
Total fat mass (kg)	34.8 ± 10.9	30.5 ± 11.9	−12.9 ± 11.1	37.6 ± 10.6	34.8 ± 10.4	−7.65 ± 8.01	–	–	<0.001
Android fat mass (kg)	3.67 ± 1.38	2.99 ± 1.41	−19.1 ± 14.0	3.91 ± 1.39	3.51 ± 1.37	−10.8 ± 11.8	–	–	<0.001
Gynoid fat mass (kg)	5.24 ± 1.78	**4.48 ± 1.58***[§]	**−14.1 ± 10.4***[§]	5.81 ± 1.67	**5.39 ± 1.69**[§]	**−7.55 ± 7.75**[§]	0.028	–	<0.001
Android/gynoid fat	0.74 ± 0.26	0.69 ± 0.24	−6.25 ± 7.83	0.70 ± 0.23	0.67 ± 0.22	−3.77 ± 7.05	–	–	<0.001
Waist circumference (cm)	106 ± 14	101 ± 15	−4.84 ± 6.07	109 ± 13	106 ± 13	−2.16 ± 4.77	–	–	<0.001
Hip circumference (cm)	109 ± 10	106 ± 10	−2.95 ± 3.56	113 ± 8	109 ± 10	−2.96 ± 4.75	–	–	<0.001
Plasma total cholesterol (mM)	5.36 ± 1.22	5.10 ± 1.14	−4.08 ± 12.33	5.18 ± 1.05	5.16 ± 1.26	−0.66 ± 11.28	–	–	–
Plasma HDL cholesterol (mM)	1.27 ± 0.38	1.36 ± 0.38	8.51 ± 14.57	1.37 ± 0.53	1.42 ± 0.53	5.09 ± 11.89	–	–	0.002
Plasma LDL cholesterol (mM)	3.05 ± 0.95	3.02 ± 1.02	0.50 ± 19.48	3.06 ± 0.79	3.01 ± 0.92	−1.61 ± 14.47	–	–	–
Plasma apoB (g/L)	0.97 ± 0.24	0.98 ± 0.28	1.81 ± 19.06	0.90 ± 0.27	0.94 ± 0.31	3.05 ± 15.04	–	–	–
Plasma triglycerides (mM)	2.28 ± 1.84	1.72 ± 2.03	−16.4 ± 44.3	1.66 ± 0.95	1.61 ± 0.96	−0.97 ± 35.15	–	–	–
Systolic blood pressure (mmHg)	128 ± 16	126 ± 15	−1.12 ± 8.99	122 ± 18	122 ± 18	−1.82 ± 9.12	–	–	–
Diastolic blood pressure (mmHg)	80.1 ± 8.3	78.7 ± 8.6	−1.36 ± 7.03	77.4 ± 10.8	77.2 ± 9.8	1.48 ± 8.85	–	–	–
Botnia clamp parameters									
Plasma glucose (mM)	5.15 ± 0.40	5.05 ± 0.43	−1.79 ± 7.65	5.19 ± 0.55	5.03 ± 0.53	−2.77 ± 7.82	–	–	0.021
Plasma insulin (uU/mL)	21.3 ± 9.4	14.9 ± 5.7	−23.0 ± 30.5	19.6 ± 9.5	16.4 ± 8.6	−14.0 ± 29.9	–	–	<0.001
1st phase GIIS$_{IVGTT}$ (uU/mL/10 min)	1083 ± 727	823 ± 543	−14.9 ± 38.7	909 ± 794	771 ± 632	−6.45 ± 34.79	–	–	<0.001
2nd phase GIIS$_{IVGTT}$ (uU/mL/50 min)	3765 ± 2134	**2342 ± 1197**[§]	**−29.8 ± 29.8****[§]	3272 ± 3481	**2970 ± 3167**[†]	−8.51 ± 23.62	0.001	–	<0.001
Total GIIS$_{IVGTT}$ (uU/mL/60 min)	4849 ± 2686	**3165 ± 1479**[§]	**−26.3 ± 31.4***[§]	4181 ± 4196	**3740 ± 3746**[‡]	**−9.24 ± 21.79**[†]	0.004	–	<0.001
1st phase C-peptide secretion$_{IVGTT}$ (ng/ml/10 min)	53.5 ± 26.1	44.7 ± 22.2	−9.32 ± 46.85	48.8 ± 25.9	36.8 ± 20.0	−18.8 ± 38.1	–	–	<0.001
2nd phase C-peptide secretion$_{IVGTT}$ (ng/ml/50 min)	290 ± 118	226 ± 87	−9.53 ± 70.20	270 ± 119	220 ± 94	−15.9 ± 30.8	–	–	<0.001
Total C-peptide secretion$_{IVGTT}$ (ng/ml/60 min)	343 ± 141	270 ± 103	−9.67 ± 65.28	318 ± 141	257 ± 111	−16.9 ± 30.5	–	–	<0.001
M/I$_{clamp}$ (mg/kg/min)/(uU/mL)	0.046 ± 0.028	0.061 ± 0.024	48.7 ± 57.7	0.048 ± 0.024	0.052 ± 0.026	16.9 ± 43.6	–	–	0.001
Dietary parameters									
Energy-intake (kcal)	2089 ± 670	1955 ± 646	**−3.12 ± 24.67****	2168 ± 588	**1750 ± 583**[§]	**−18.8 ± 17.5**[§]	0.034	–	<0.001
Fat intake (g)	81.1 ± 32.8	68.0 ± 38.5	−13.2 ± 36.9	84.0 ± 26.7	61.6 ± 29.0	−26.3 ± 22.8	–	–	<0.001
Saturated fat intake (g)	25.0 ± 11.1	20.8 ± 13.1	−12.9 ± 38.2	27.6 ± 10.6	18.8 ± 8.9	−30.4 ± 24.8	–	–	<0.001
Carbohydrate intake (g)	242 ± 73	238 ± 69	**2.35 ± 26.73***	250 ± 83	**208 ± 69**[‡]	**−13.9 ± 22.5**[‡]	0.030	–	0.011
Sugar intake (g)	83.9 ± 35.0	83.6 ± 35.3	12.4 ± 53.8	89.8 ± 44.4	71.0 ± 28.0	−10.2 ± 43.7	–	–	–
Protein intake (g)	91.1 ± 34.7	93.3 ± 30.8	9.17 ± 29.28	91.5 ± 25.4	83.4 ± 25.7	−7.40 ± 21.40	–	–	–

[a] The study population (N = 55) was divided into 2 groups of subjects who decreased versus who increased fiber intake following the 6-month hypocaloric-dietary intervention. Data is presented as average ± SD (before adjustment for sex). Data was analyzed by RM 2-way ANOVA with group × time interaction with adjustment for multiple comparison and for sex. *$p \leq 0.05$, **$p \leq 0.01$, ***$p \leq 0.001$ for differences from group with decreased fiber intake, and †$p \leq 0.05$, ‡$p \leq 0.01$, §$p \leq 0.001$ for differences from baseline. Data in bold represents statistically significant analysis. GIR: glucose infusion rate; HDL: high density lipoprotein; IVGTT: intravenous-glucose tolerance test; LDL: low density lipoprotein.

sex, adiposity and energy-intake. To our knowledge, only one study evaluated the relation of fiber intake to GIIS, and it used plasma insulin during the IVGTT. It reported that 3-week on low glycemic index/high fiber bread diet (14 g fiber/100 g) reduced GIIS$_{IVGTT}$ compared to a high glycemic index/low fiber bread (~6 g fiber/ 100 g), but did not affect clamp IS in women with impaired glucose tolerance [10]. Whether, as in our study, higher fiber intake was related to higher insulin clearance rather than secretion cannot be however determined as C-peptide was not measured [10].

Fiber intake may modulate insulin metabolism via several mechanisms. Fiber-rich diets are known to modulate gut microbiota, increase bacterial diversity, and promote growth of certain bacteria that produce short-chain fatty acids (SCFA) [22]. The increase in SCFA-producing strains is associated with improved glycated hemoglobin in diabetic patients randomized to a high-fiber diet [23]. Gut microbiota may also regulate incretin secretion and chronic inflammation ameliorating glucose homeostasis [21]. Additionally, certain types of fiber, such as psyllium and β-glucan, reduce plasma apoB-lipoproteins [24]. ApoB-lipoproteins promote the dysfunction of pancreatic β-cells [25] and white adipose tissue [17,26]. Their plasma concentrations (i.e. plasma apoB) predicts the incidence of [27,28] and risk factors for [4,17,29] T2D in humans. Moreover, we reported in the first analysis of this study that higher baseline plasma apoB predicted a greater amelioration in 2nd phase GII-S$_{IVGTT}$ and adipose tissue function following weight-loss independent of changes in adiposity [6]. However, it is unlikely that the relation of fiber intake to reduced 2nd phase hyperinsulinemia is dependent on plasma apoB as there was no group-differences in subjects who decreased versus increased fiber intake (Table 3). Fiber-rich diets also promote weight-loss, by delaying gastric emptying increasing satiety and reducing nutrients absorption [30]. Intriguingly, increased protein intake, which also increases satiety, was related to reduced 2nd phase GII-S$_{IVGTT}$ in this study. Unlike fiber-intake, this relation was eliminated with the adjustment for sex and changes in BMI and energy-intake. This suggests that the mechanisms relating fiber intake to faster insulin clearance is not mediated via effects on satiety and weight-loss alone; however, future studies are needed to explore such mechanisms.

In conclusion, increased fiber intake during a hypocaloric-diet is associated with decreased 2nd phase hyperinsulinemia, likely via faster insulin clearance, independently of sex and changes in adiposity and energy-intake. We propose that promoting fiber intake during hypocaloric-diets may reduce the inter-subject variability in the metabolic response to these interventions and increase their effectiveness in preventing T2D.

Declaration of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.01.014.

References

[1] Weir GC, Bonner-Weir S. Five stages of evolving beta-cell dysfunction during progression to diabetes. Diabetes 2004;53(Suppl 3): S16—21. https://doi.org/10.2337/diabetes.53.suppl_3.S16.

[2] Lee CC, Haffner SM, Wagenknecht LE, Lorenzo C, Norris JM, Bergman RN, et al. Insulin clearance and the incidence of type 2 diabetes in Hispanics and African Americans: the IRAS family study. Diabetes Care 2013;36:901—7. https://doi.org/10.2337/dc12-1316.

[3] Barg S, Eliasson L, Renstrom E, Rorsman P. A subset of 50 secretory granules in close contact with L-type Ca2+ channels accounts for first-phase insulin secretion in mouse beta-cells. Diabetes 2002; 51(Suppl 1):S74—82.

[4] Bissonnette S, Saint-Pierre N, Lamantia V, Cyr Y, Wassef H, Faraj M. Plasma IL-1Ra: linking hyperapoB to risk factors for type 2 diabetes independent of obesity in humans. Nutr Diabetes 2015;5:e180. https://doi.org/10.1038/nutd.2015.30.

[5] Magkos F, Fraterrigo G, Yoshino J, Luecking C, Kirbach K, Kelly SC, et al. Effects of moderate and subsequent progressive weight loss on metabolic function and adipose tissue biology in humans with obesity. Cell Metab 2016;23:591—601. https://doi.org/10.1016/ j.cmet.2016.02.005.

[6] Bissonnette S, Saint-Pierre N, Lamantia V, Leroux C, Provost V, Cyr Y, et al. High plasma apolipoprotein B identifies obese subjects who best ameliorate white adipose tissue dysfunction and glucose-induced hyperinsulinemia after a hypocaloric diet. Am J Clin Nutr 2018;108:62—76. https://doi.org/10.1093/ajcn/nqy070.

[7] Cho SS, Qi L, Fahey Jr GC, Klurfeld DM. Consumption of cereal fiber, mixtures of whole grains and bran, and whole grains and risk reduction in type 2 diabetes, obesity, and cardiovascular disease. Am J Clin Nutr 2013;98:594—619. https://doi.org/10.3945/ajcn.113.067629.

[8] Liese AD, Roach AK, Sparks KC, Marquart L, D'Agostino Jr RB, Mayer-Davis EJ. Whole-grain intake and insulin sensitivity: the insulin resistance atherosclerosis study. Am J Clin Nutr 2003;78:965—71. https://doi.org/10.1093/ajcn/78.5.965.

[9] Pereira MA, Jacobs Jr DR, Pins JJ, Raatz SK, Gross MD, Slavin JL, et al. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. Am J Clin Nutr 2002;75:848—55. https://doi.org/10.1093/ajcn/75.5.848.

[10] Ostman EM, Frid AH, Groop LC, Bjorck IM. A dietary exchange of common bread for tailored bread of low glycaemic index and rich in dietary fibre improved insulin economy in young women with impaired glucose tolerance. Eur J Clin Nutr 2006;60:334—41. https://doi.org/10.1038/sj.ejcn.1602319.

[11] Robertson MD, Currie JM, Morgan LM, Jewell DP, Frayn KN. Prior short-term consumption of resistant starch enhances postprandial insulin sensitivity in healthy subjects. Diabetologia 2003;46: 659–65. https://doi.org/10.1007/s00125-003-1081-0.

[12] Robertson MD, Bickerton AS, Dennis AL, Vidal H, Frayn KN. Insulin-sensitizing effects of dietary resistant starch and effects on skeletal muscle and adipose tissue metabolism. Am J Clin Nutr 2005;82: 559–67. https://doi.org/10.1093/ajcn.82.3.559.

[13] Robertson MD, Wright JW, Loizon E, Debard C, Vidal H, Shojaee-Moradie F, et al. Insulin-sensitizing effects on muscle and adipose tissue after dietary fiber intake in men and women with metabolic syndrome. J Clin Endocrinol Metab 2012;97:3326–32. https://doi.org/10.1210/jc.2012-1513.

[14] Weickert MO, Mohlig M, Schofl C, Arafat AM, Otto B, Viehoff H, et al. Cereal fiber improves whole-body insulin sensitivity in overweight and obese women. Diabetes Care 2006;29:775–80.

[15] Santé Canada. Apports nutritionnels de référence. 2010. http://www.hc-sc.gc.ca/fn-an/alt_formats/hpfb-dgpsa/pdf/nutrition/dri_tables-fra.pdf. [Accessed 5 December 2018].

[16] Wassef H, Bissonnette S, Saint-Pierre N, Lamantia V, Cyr Y, Chretien M, et al. The apoB-to-PCSK9 ratio: a new index for metabolic risk in humans. J Clin Lipidol 2015;9:664–75. https://doi.org/10.1016/j.jacl.2015.06.012.

[17] Lamantia V, Bissonnette S, Wassef H, Cyr Y, Baass A, Dufour R, et al. ApoB-lipoproteins and dysfunctional white adipose tissue: relation to risk factors for type 2 diabetes in humans. J Clin Lipidol 2017;11. https://doi.org/10.1016/j.jacl.2016.09.013. 34–45.e2.

[18] Pocock SJ, Assmann SE, Enos LE, Kasten LE. Subgroup analysis, covariate adjustment and baseline comparisons in clinical trial reporting: current practice and problems. Stat Med 2002;21: 2917–30. https://doi.org/10.1002/sim.1296.

[19] Jones AG, Hattersley AT. The clinical utility of C-peptide measurement in the care of patients with diabetes. Diabet Med 2013; 30:803–17. https://doi.org/10.1111/dme.12159.

[20] Kim SP, Ellmerer M, Kirkman EL, Bergman RN. Beta-cell "rest" accompanies reduced first-pass hepatic insulin extraction in the insulin-resistant, fat-fed canine model. Am J Physiol Endocrinol Metab 2007;292:E1581–9. https://doi.org/10.1152/ajpendo.00351.2006.

[21] Kellow NJ, Coughlan MT, Reid CM. Metabolic benefits of dietary prebiotics in human subjects: a systematic review of randomised controlled trials. Br J Nutr 2014;111:1147–61. https://doi.org/10.1017/s0007114513003607.

[22] Simpson HL, Campbell BJ. Review article: dietary fibre-microbiota interactions. Aliment Pharmacol Ther 2015;42:158–79. https://doi.org/10.1111/apt.13248.

[23] Zhao L, Zhang F, Ding X, Wu G, Lam YY, Wang X, et al. Gut bacteria selectively promoted by dietary fibers alleviate type 2 diabetes. Science 2018;359:1151–6. https://doi.org/10.1126/science.aao5774.

[24] Lamantia V, Sniderman A, Faraj M. Nutritional management of hyperapoB. Nutr Res Rev 2016;29:202–33. https://doi.org/10.1017/s0954422416000147.

[25] Roehrich ME, Mooser V, Lenain V, Herz J, Nimpf J, Azhar S, et al. Insulin-secreting beta-cell dysfunction induced by human lipo-proteins. J Biol Chem 2003;278:18368–75. https://doi.org/10.1074/jbc.M300102200.

[26] Bissonnette S, Salem H, Wassef H, Saint-Pierre N, Tardif A, Baass A, et al. Low density lipoprotein delays clearance of triglyceride-rich lipoprotein by human subcutaneous adipose tissue. J Lipid Res 2013;54:1466–76. https://doi.org/10.1194/jlr.P023176.

[27] Ley SH, Harris SB, Connelly PW, Mamakeesick M, Gittelsohn J, Wolever TM, et al. Association of apolipoprotein B with incident type 2 diabetes in an aboriginal Canadian population. Clin Chem 2010;56:666–70. https://doi.org/10.1373/clinchem.2009.136994.

[28] Hwang YC, Ahn HY, Park SW, Park CY. Apolipoprotein B and non-HDL cholesterol are more powerful predictors for incident type 2 diabetes than fasting glucose or glycated hemoglobin in subjects with normal glucose tolerance: a 3.3-year retrospective longitudinal study. Acta Diabetol 2014;51:941–6. https://doi.org/10.1007/s00592-014-0587-x.

[29] Faraj M, Messier L, Bastard JP, Tardif A, Godbout A, Prud'homme D, et al. Apolipoprotein B: a predictor of inflammatory status in postmenopausal overweight and obese women. Diabetologia 2006;49:1637–46. https://doi.org/10.1007/s00125-006-0259-7.

[30] Rebello CJ, O'Neil CE, Greenway FL. Dietary fiber and satiety: the effects of oats on satiety. Nutr Rev 2016;74:131–47. https://doi.org/10.1093/nutrit/nuv063.