Reduction of Glycemic and Lipid Levels in *db/db* Diabetic Mice by Psyllium Plant Fiber

KAREN WATTERS AND PETER BLAISDELL

The soluble plant fiber psyllium significantly reduced fasting glucose and total cholesterol levels in the C57BL/KsJ *db/db* diabetic mouse relative to placebo-fed mice. Insulin levels were significantly higher in psyllium-fed than placebo-fed animals, indicating this fiber may delay the progression of diabetes in the animal model. High-density lipoprotein cholesterol levels rose moderately in both psyllium- and placebo-fed animals during the study, whereas triglyceride levels remained unchanged in both groups. Psyllium's effect on glycemic, lipid, and hormone parameters was not explained by weight loss or reduced food intake; these were similar in psyllium- and placebo-fed animals during the study. Our results show that psyllium fiber can beneficially moderate glycemic and lipid parameters in the *db/db* diabetes model. *Diabetes* 38:1528–30, 1989

Several studies indicate that plant fibers moderate human diabetic patients' postprandial glucose levels if administered with a meal (1–5) and lower fasting glucose and lipid levels if administered chronically (6–8). However, studies demonstrating the chronic benefit of fiber for diabetic patients can be criticized for lacking placebo control subjects and small numbers of subjects (9). Also, results from other researchers indicate that long-term administration of high-fiber and/or high-carbohydrate diets does not reduce glucose and lipid levels (10,11). This discrepancy in the value of fiber may arise from between-study variations in study design, experimental diets, and types of fibers. In particular, soluble fibers, including guar and psyllium, are believed to be more effective than insoluble fibers such as wheat bran in reducing glucose and lipid levels (12). In nondiabetic subjects, Bell et al. (13) presented evidence of the lipid-lowering ability of psyllium.

Trials in animal diabetes models can assess the ability of soluble fibers to reduce lipid and fasting glucose levels in long-term studies when diet and fiber intake are well controlled. For this study, we chose the genetically diabetic C57BL/KsJ *db/db* mouse, an inbred strain carrying a recessive autosomal mutation on chromosome 4 at the *db* locus (14,15). This mutation is responsible for a non-insulin-dependent (type II) diabeteslike syndrome resulting in hyperinsulinemia, insulin resistance, and hyperphagia. With disease progression, β-cell necrosis occurs, resulting in a decline in insulin secretion and hyperglycemia (14). As in many human diabetic patients, lipid levels are abnormally elevated. Research with the related mouse strain C57BL/6J has demonstrated the usefulness of such models in determining the long-term effects of diet on type II diabetes (16).

In this 18-wk study, the *db/db* mouse was used to determine the effect of a defined diet supplemented with 2.5% of the soluble plant fiber psyllium on fasting glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-chol), triglyceride, and insulin levels. These measurements were followed throughout the trial, providing a chronological profile of the effect of fiber on diabetes progression. Because differences in body weight and food consumption between fiber- and placebo-fed animals could account for differences in glucose and lipid levels, weight and food consumption were also monitored throughout the study. Heterozygous *db/+* nondiabetic siblings served as controls.

RESEARCH DESIGN AND METHODS

A total of 34 female genetically diabetic, C57BL/KsJ *db/db* mice and 33 female heterozygous nondiabetic sibling littermates were purchased from Jackson (Bar Harbor, ME). The animals were 7–8 wk old on arrival and were housed in individual cages with access to food and water ad libitum. The mice were exposed to a 12-h light-dark cycle. All animals were fed a basic diet consisting of Guilford Mouse Breeder

From the Division of Health and Personal Care, the Procter and Gamble Corporation, Cincinnati, Ohio.

Address correspondence and reprint requests to Dr. Karen Watters, Division of Health and Personal Care, the Procter and Gamble Corporation, 11511 Reed Hartman Highway, The 790 Building, Biological Efficacy Test Facility, Cincinnati, OH 45241.

Received for publication 20 February 1989 and accepted in revised form 3 August 1989.

Chow 911 (Emery-Moorse, Guilford, CT), which was supplemented with either 2.5% psyllium by weight contained in 3.2% sugar-free Metamucil or 0.7% by weight of excipients in Metamucil increased to 3.2% by weight with additional mouse chow. The excipients in Metamucil consist of colorings, flavorings, and citrate. Both psyllium and nonpsyllium diets were supplemented with 1% (by wt) cholesterol (ICN Biochemicals, Cleveland, OH) dissolved in 2% corn oil (ICN) and 0.25% bile salts (Sigma, St. Louis, MO). The salts were composed of 50% sodium cholate and 50% sodium deoxycholate. The diets were prepared by homogenizing these components into the chow with a Hobart blender to provide a uniform mixture.

On arrival, the animals were randomly divided into four groups, so that 17 diabetic and 17 nondiabetic mice received psyllium-supplemented diets and 17 diabetic and 16 nondiabetic mice received placebo-supplemented diets. Then all mice were bled to obtain baseline fasting glucose and cholesterol values. The animals were maintained on their respective diets until study termination at wk 18. Blood was drawn at biweekly intervals after an 8-h fast from the orbital sinus into heparinized capillary tubes except during the final week when animals were anesthetized with CO_2 and exsanguinated by cardiac puncture.

Because of the limited volume of blood the animals could provide at a given draw without anemia, fasting glucose, total cholesterol, HDL-chol, triglyceride, and insulin levels were obtained according to the following staggered schedule. Fasting glucose and total cholesterol were measured at baseline (wk 0) and again at wk 4, 10, and 18. Triglycerides were measured at wk 4, 10, and 18, and HDL-chol was measured at wk 6 and 12. Insulin levels were determined at wk 8 and 16. For a given time point, blood samples were taken from all surviving animals. Food and water consumption was monitored weekly, and body weight was monitored biweekly throughout the study.

Glucose levels were determined by the hexokinase method (Boehringer Mannheim glucose-HK kit 620300) with a Hitachi-705 automated analyzer (MV36041). Cholesterol levels were determined with the cholesterol-esterase method (Boehringer Mannheim cholesterol kit 704121). The HDL-chol fraction was isolated after precipitating low-density lipoprotein (LDL)-chol and very-low-density lipoprotein (VLDL)-chol by adding phosphotungstic acid and magnesium to the sample and centrifuging. HDL-chol levels were determined with a cholesterol assay (Boehringer Mannheim HDL-chol precipitant kit 543004 and cholesterol kit 704121). Triglycerides were determined with Boehringer Mannheim kit 704113. Insulin levels were determined by standard radioimmunoassay methods with Cambridge kits (Billerica, MA).

Data are expressed as means ± SE. Statistical significance was defined as a two-sided value of $P \leq .05$. Data were examined by analysis of variance and by the Newman-Keuls test when comparisons between more than two means were made. Significance from pretreatment (wk 0) was assessed by paired *t* test.

RESULTS

Fasting glucose levels. As shown in Fig. 1, 18 wk of psyllium administration reduced the diabetic animals' fasting glucose levels from an initial value of 440 to 350 mg/dl at the conclusion of the study ($P < .05$). This reduction of 90 mg/dl represents a 20% decrease in glucose levels. In contrast, fasting glucose levels in placebo-fed diabetic animals increased 20%, from 360 to 440 mg/dl, during the same period ($P < 0.05$). Significantly lower fasting glucose levels were observed for psyllium-fed animals versus their placebo-fed counterparts at wk 10 ($P < .01$) and 18 ($P < .01$).

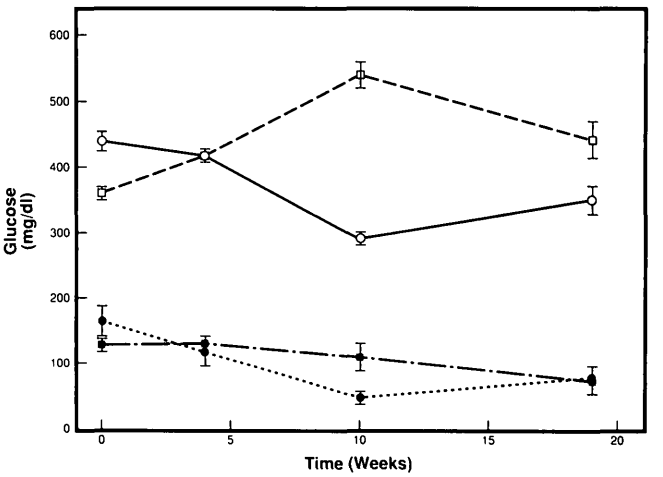

FIG. 1. Comparison of effect of psyllium- or placebo-supplemented diets on fasting glucose levels in diabetic and nondiabetic *db/db* rats. *n* = 17, 16, 16, and 14 surviving psyllium-fed diabetic (○) and *n* = 17, 16, 15, and 10 surviving placebo-fed diabetic (□) mice at wk 0, 4, 10, and 18, respectively. *n* = 17, 15, 14, and 13 surviving psyllium-fed nondiabetic (●) and *n* = 16, 15, 14, and 13 surviving placebo-fed nondiabetic (■) mice at wk 0, 4, 10, and 18, respectively. Values are means ± SE.

Figure 1 also shows that fasting glucose levels in nondiabetic mice were ~300 mg/dl lower than those in diabetic mice at wk 18 ($P < .005$). At wk 4 and 18, there was no significant difference between the psyllium- and placebo-fed nondiabetic groups. However, these levels responded transiently to the fiber at wk 10 when psyllium-fed nondiabetic animals demonstrated a modest but significant reduction ($P < .05$) in glucose levels relative to placebo-fed counterparts.

Total cholesterol levels. At the conclusion of the study, total cholesterol levels in psyllium-fed diabetic animals were 250 mg/dl lower than in placebo-fed diabetic animals (Fig. 2). This difference was significant ($P < .002$) and represents a 45% reduction. The effect of psyllium on cholesterol levels was apparent 4 wk into the study, when these levels were significantly lower ($P < .05$) in the psyllium-fed group than the placebo-fed group. Over the course of the study, in psyllium-fed animals, cholesterol levels increased only 100 mg/dl, from 200 to 300 mg/dl, whereas cholesterol levels increased by 320 mg/dl, from 220 to 540 mg/dl, in placebo-fed animals.

Psyllium significantly reduced ($P < .005$) the total cholesterol levels of nondiabetic animals compared with the placebo-fed group at wk 4 and 10. The differences, 150 and 130 mg/dl, respectively, were less than those demonstrated between psyllium- and placebo-fed diabetic animals. Moreover, these differences were transient. At the conclusion of the study, cholesterol levels were identical in psyllium- and placebo-fed nondiabetic animals.

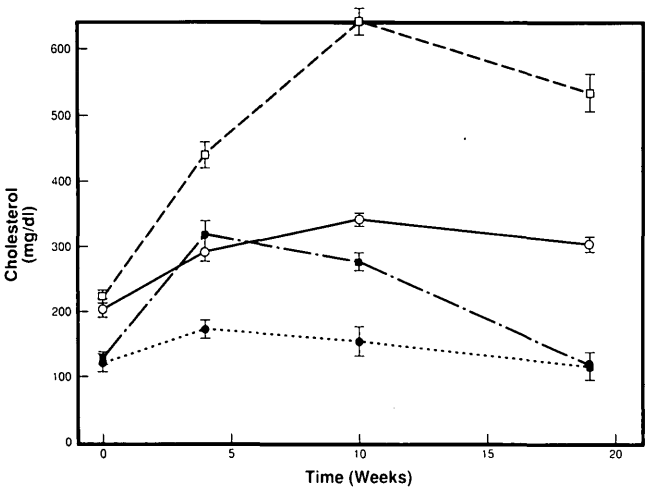

FIG. 2. Comparison of effect of psyllium- or placebo-supplemented diets on total cholesterol levels in diabetic and nondiabetic *db/db* mice. *n* = 17, 16, 16, and 14 surviving psyllium-fed diabetic (○) and *n* = 17, 16, 15, and 10 surviving placebo-fed diabetic (□) mice at wk 0, 4, 10, and 18, respectively. *n* = 17, 15, 14, and 13 surviving psyllium-fed nondiabetic (●) and *n* = 16, 15, 14, and 13 surviving placebo-fed nondiabetic (■) mice at wk 0, 4, 10, and 18, respectively. Values are means ± SE.

Triglyceride levels. Psyllium did not show a consistent effect on triglyceride levels in diabetic animals. At wk 10, these levels were modestly lower in psyllium-fed animals relative to their placebo-fed counterparts ($P < .005$), but at the conclusion of the study, no significant difference between these groups was observed (Fig. 3). In nondiabetic animals, psyllium demonstrated no significant effect on triglyceride levels during the trial.

HDL-chol levels. HDL-chol levels in placebo-fed diabetic animals were modestly but significantly higher than in psyllium-fed diabetic animals at wk 6 ($P < .05$) (Fig. 4.) HDL-chol levels in both groups increased between wk 6 and 12. At wk 12, HDL-chol levels were 90 mg/dl higher in placebo-fed animals than their psyllium-fed counterparts, representing a significant difference ($P < .005$).

In nondiabetic animals, HDL-chol levels were not significantly different in psyllium- and placebo-fed animals. However, both groups demonstrated significantly lower levels than either psyllium- or placebo-fed diabetic groups at wk 6 ($P < .01$) and 12 ($P < .005$).

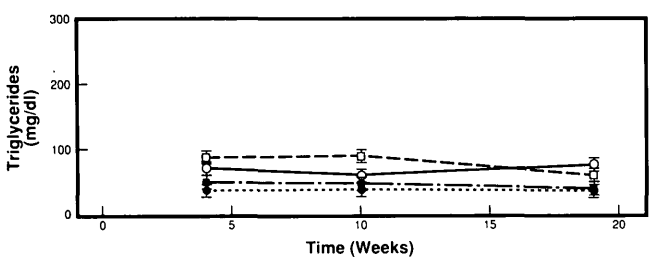

FIG. 3. Comparison of effect of psyllium- or placebo-supplemented diets on triglyceride levels in diabetic and nondiabetic *db/db* mice. *n* = 17, 16, 16, and 14 surviving psyllium-fed diabetic (○) and *n* = 17, 16, 15, and 10 surviving placebo-fed diabetic (□) mice at wk 0, 4, 10, and 18, respectively. *n* = 17, 15, 14, and 13 surviving psyllium-fed nondiabetic (●) and *n* = 16, 15, 14, and 13 surviving placebo-fed nondiabetic (■) mice at wk 0, 4, 10, and 18, respectively. Values are means ± SE.

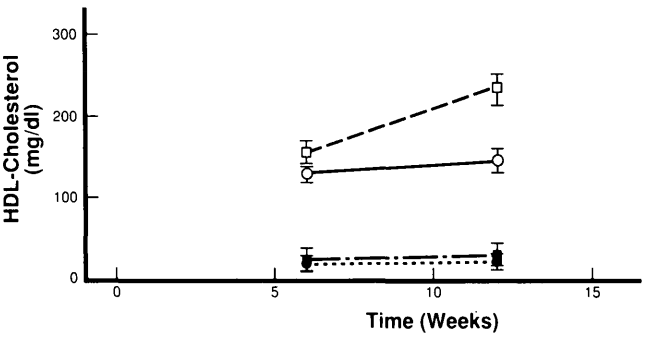

FIG. 4. Comparison of effect of psyllium- or placebo-supplemented diets on high-density lipoprotein (HDL) cholesterol levels in diabetic and nondiabetic *db/db* mice. *n* = 16 surviving psyllium-fed diabetic (○) and *n* = 15 surviving placebo-fed diabetic (□) mice at wk 6 and 12, respectively. *n* = 14 surviving psyllium-fed nondiabetic (●) and *n* = 14 surviving placebo-fed nondiabetic (■) mice at wk 6 and 12, respectively. Values are means ± SE.

Insulin levels. To determine whether differences in fasting glucose and lipid levels were reflected in hormones responsible for carbohydrate metabolism, fasting insulin levels were measured. Figure 5 shows these levels elevated in psyllium-fed diabetic animals relative to diabetic animals receiving placebo at wk 8 and 16. At both time points, this difference was marginally significant ($P < .1$). Insulin levels for both groups decreased between wk 8 and 16, the psyllium-fed group decreasing from 135 to 50 μU/ml and the placebo-fed group decreasing from 85 to 33 μU/ml.

Nondiabetic animals demonstrated significantly lower fasting insulin levels than diabetic animals at wk 8 and 16 ($P < .05$). However, there were no significant differences in insulin levels between psyllium- and placebo-fed animals in these groups.

Body weight, food consumption, and survival. Biweekly monitoring indicated a gradual weight gain in all groups during the study and showed that the average weights of psyllium- and placebo-fed diabetic animals were not significantly different (Table 1). Similarly, the average weights of psyllium- and placebo-fed nondiabetic mice were not sig-

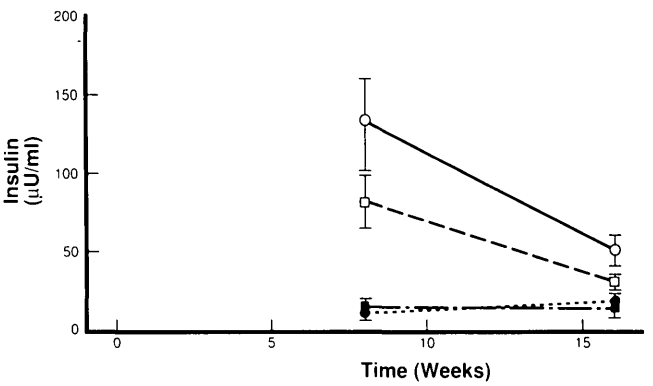

FIG. 5. Comparison of effect of psyllium- or placebo-supplemented diets on insulin levels in diabetic and nondiabetic *db/db* mice. *n* = 16 and 15 surviving psyllium-fed diabetic (○) and *n* = 15 and 12 surviving placebo-fed diabetic (□) mice at wk 8 and 16, respectively. *n* = 14 and 13 surviving psyllium-fed nondiabetic (●) and *n* = 14 and 13 surviving placebo-fed nondiabetic (■) mice at wk 8 and 16, respectively.

TABLE 1
Effect of psyllium on mean ± SE weight, food and water consumption, and survival length

	n	Weight during study (g)	Daily food consumption (g)	Daily water consumption (ml)	Survival (days)
Diabetic					
Psyllium	17	38.9 ± 3.4	5.0 ± 0.6	9.9 ± 3.8	118
Placebo	17	38.0 ± 3.9	5.2 ± 0.8	13.2 ± 3.2	110
Nondiabetic					
Psyllium	17	20.0 ± 1.5	3.4 ± 0.3	5.8 ± 1.0	118
Placebo	16	20.7 ± 1.8	3.6 ± 0.3	5.5 ± 1.0	118

Average weight during study was determined by summing average weights during study of individual animals within a given diet and disease group and determining the average. The same method was used for food and water consumption. Survival was determined by summing the number of days individual animals within a group survived before all remaining animals were killed at 126 days. This sum was then divided by the number of animals in the group.

nificantly different. Both diabetic groups had significantly greater weights than the nondiabetic control groups ($P < .05$).

Average daily food consumption did not differ significantly between psyllium- and placebo-fed diabetic animals. However, placebo-fed diabetic mice drank significantly more water than their psyllium-fed counterparts ($P < .01$). Nondiabetic mice, regardless of treatment, demonstrated no significant differences in food or water consumption.

Analysis of survival indicated no significant difference in longevity between psyllium- and placebo-fed diabetic groups. Table 1 shows the average number of days animals survived in the four groups before all remaining animals were killed at 126 days (18 wk). Although survival did not differ significantly between groups, placebo-fed diabetic animals were subject to a greater number of infections and lacked the muscle tone of the psyllium-fed group, indicating they were in generally worse health.

DISCUSSION

This study demonstrates that psyllium reduces fasting glucose levels in the *db/db* diabetic mouse compared with placebo-fed mice. Although the diabetic syndrome in this model results in a chronic increase in glucose levels (14), this progression appears to have been retarded in psyllium-fed animals, which may have contributed to prolonging their insulin-secreting ability compared with placebo-fed counterparts. Psyllium also substantially reduces total cholesterol levels relative to placebo. These reductions in glucose and cholesterol levels were achieved with the addition of a modest 2.5% fiber supplement to the study diet. Although fiber can cause satiety, the reductions observed herein are not explained by weight loss or decreased food intake in the psyllium-fed mice compared with placebo-fed mice.

In human nondiabetic hypercholesteremic patients, Bell et al. (13) showed evidence that psyllium can reduce lipid levels. Available studies in human diabetic patients also indicate psyllium can lower cholesterol levels (8,17,18). However, interpretation of the studies in diabetic patients is complicated by lack of placebo control (8), the presence of other diseases (17), or patient weight loss and small base size (18). Given the magnitude at the cholesterol elevation seen in response to exogenous cholesterol, the model is clearly not directly analogous to humans. However, the data presented herein provide a well-controlled example, in animals consuming defined diets, of the potential of psyllium to reduce cholesterol levels.

In contrast with total cholesterol levels, triglycerides were not dramatically reduced by psyllium. High-carbohydrate diets are known to raise triglyceride levels in human diabetic (19) and nondiabetic (20,21) subjects. However, psyllium has been shown not to reduce triglycerides in nondiabetic, hypercholesterolemic (22) or type II diabetic (8) subjects. The similar effect in *db/db* mice and humans indicates that the animal model may provide a reasonable representation of the effect of psyllium on triglycerides in humans.

The modest difference in HDL-chol levels between animals receiving psyllium or placebo is not reflected in data available from human type II diabetic subjects. Fagerberg (8) has shown that psyllium appears to have no significant effect on these levels. This disparity probably arises from differences between the distribution and character of mouse and human lipoproteins. HDL fractions represent the major portion in mice, and mouse LDL and VLDL fractions are more heterogeneous than in humans (23). Thus, additional work is needed to determine the correspondence between the effect of fiber on mouse and human HDLs.

The reductions in glycemic levels we observed may have contributed to the psyllium-fed diabetic animals' generally more healthy appearance than placebo-fed animals. In a 52-wk trial, Leiter et al. (15) demonstrated that diets high in glucose dramatically reduced survival in this mouse strain, whereas diets containing the complex carbohydrate dextrin starch resulted in lower blood glucose levels and improved longevity. However, analysis of survival for this trial indicates no significant difference between psyllium- and placebo-fed animals despite placebo-fed diabetic mice surviving an average of 8 days less before they were killed than the other groups. Clearly, longer trials are needed to confirm psyllium's effect on diabetic subject longevity.

This study indicates psyllium does not reduce fasting glucose and cholesterol levels by preventing absorption of carbohydrate and fat. The animals' weights and food consumption were similar in placebo- and psyllium-fed groups allowed free access to food. Instead, the fiber may have slowed the access of glucose to the small intestine's absorptive epithelium because of its gelling properties, thereby blunting postprandial glucose peaks and decreasing the insulin response (24,25). Such postprandial blunting has been observed in human diabetic subjects given psyllium

with single meals (3). Continuous postprandial blunting during this study may have reduced insulin need and preserved insulin sensitivity.

Typically, in the C57BL/KsJ *db/db* mouse, initial hyperinsulinemia is followed by insulin depletion (14). Psyllium may act indirectly to retard β-cell exhaustion by reducing glucose levels, thereby lowering the insulin demand and prolonging the *db/db* mouse's capacity to secrete insulin; high fasting insulin levels in the psyllium-fed mice relative to the placebo-fed mice could indicate this. Reflecting the difference in insulin levels, fasting glucagon levels were depressed in psyllium-administered diabetic mice relative to placebo-fed mice at wk 8 and 16 (unpublished observations). These effects could be further assessed with a more complete hormone profile.

An additional mechanism of glucose and lipid reduction might involve the colonic fermentation products of psyllium, the short-chain fatty acids acetate, propionate, and butyrate, which may act to reduce hepatic glucose production or cholesterol synthesis (26). Butyrate apparently remains in the epithelium, whereas propionate and acetate pass to the liver via the portal vein (27). Acetate may reduce cholesterol synthesis in isolated rat hepatocytes (28), and ingested acetate reduces the rise in free fatty acids in fasting humans (29). Propionate also may reduce cholesterol levels as Chen et al. (30) have shown during 2 wk of oral administration in rats.

Acetate does not appear to control glucose levels; recent work by Scheppach et al. (29,31) indicates that acute, oral acetate administration does not alter glucose turnover in nondiabetic humans. However, propionate may reduce glucose production in isolated rat hepatocytes (32). Clearly, additional research is needed before definitely associating short-chain fatty acids with lowered lipid and glucose levels. In this regard, Nyman et al. (33) have shown that intestinal fermentation of dietary fiber in rodents and humans is similar, indicating that the *db/db* mouse could provide a convenient model to better assess the role of short-chain fatty acids in diabetes.

Alternately, psyllium may reduce cholesterol levels by binding intestinal bile acids and increasing their fecal excretion in a manner similar to the bile acid–binding resin cholestyramine. Because cholesterol is the precursor for bile acids, their removal could result in decreased blood cholesterol levels. Recent work indicates that the colonic contents of mice fed lignin-supplemented diets demonstrated a fourfold increase in deoxycholate binding relative to animals fed a fiber-free diet (34). However, lignin contributes only ~10% to the fiber content of psyllium, and it is not yet clear whether psyllium binds bile acids in vivo.

The ability of psyllium to reduce glucose and total cholesterol levels was also observed in nondiabetic heterozygotes, albeit to a lesser extent than in diabetic heterozygotes. This demonstrates that its mechanism of action is not dependent on a diabetic condition. However, in contrast to diabetic mice, the differences in glucose levels between fiber and placebo-fed nondiabetic mice were transient, indicating that psyllium-fed mice compensate for lowered glucose levels to maintain euglycemia. The temporary effect of psyllium on total cholesterol levels may show that placebo-fed nondiabetic animals can also compensate for elevated cholesterol levels by suppression of endogenous cholesterol synthesis, as has been demonstrated in humans fed high-cholesterol diets (35). In conclusion, the *db/db* mouse has provided a convenient model to demonstrate the value of psyllium in reducing glycemic and lipid levels.

ACKNOWLEDGMENTS

Expert technical assistance during all assays was provided by Carol Hudson.

REFERENCES

1. Jenkins DJ, Wolever TM, Leeds AR: Dietary fibers, fiber analogues, and glucose tolerance: importance of viscosity. *Br Med J* 1:1392–94, 1978
2. Parsons SR: Effects of high fiber breakfasts on glucose metabolism in noninsulin-dependent diabetics. *Am J Clin Nutr* 40:66–71, 1984
3. Florholmen J, Arvidsson-Lenner R, Jorde R, Burhol PG: The effect of Metamucil on postprandial blood glucose and plasma gastric inhibitory peptide in insulin-dependent diabetics. *Acta Med Scand* 212:237–39, 1982
4. Jenkins DJ, Goff DV, Leeds AR, Alberti KG, Wolever TM, Gassull MA, Hockaday TD: Unabsorbable carbohydrate and diabetes: decreased postprandial hyperglycemia. *Lancet* 2:172–74, 1976
5. Karlstrom B, Vessby B, Asp NG, Ytterfors A: Effects of four meals with different kinds of dietary fiber on glucose metabolism in healthy subjects and non-insulin-dependent diabetic patients. *Eur J Clin Nutr* 42:519–26, 1988
6. Aro A, Uusitupa M, Vontilaimen E, Hersio D, Korhonen T, Siitonen O: Improved diabetic control and hypocholestremic effect induced by long-term dietary supplementation with guar gum in type 2 (insulin-dependent) diabetics. *Diabetologia* 21:29–34, 1981
7. Doi K, Matsuura M, Kawara A, Baba S: Treatment of diabetes with glucomannan (konjac mannan). *Lancet* 1:987–89, 1979
8. Fagerberg SE: The effects of a bulk laxative (Metamucil) on fasting blood glucose, serum lipids and other variables in constipated patients with non-insulin dependent adult diabetes. *Curr Ther Res Clin Exp* 31:166–72, 1982
9. Weinstock RS, Levine RA: The role of dietary fiber in the management of diabetes mellitus. *Nutrition* 4:187–93, 1988
10. Hollenbeck CB, Coulston AM, Reaven GM: To what extent does increased dietary fiber improve glucose and lipid metabolism in patients with non-insulin-dependent diabetes mellitus (NIDDM)? *Am J Clin Nutr* 43:16–24, 1986
11. Beattie VA, Edwards CA, Hosiar JP, Cullen DR, Ward JD, Read NW: Does adding fiber to a low energy, high carbohydrate, low fat diet confer any benefit to the management of newly diagnosed overweight type II diabetics? *Br Med J* 296:1147–49, 1988
12. Vinik AI, Jenkins DJ: Dietary fiber in management of diabetes. *Diabetes Care* 11:160–73, 1988
13. Bell LP, Hectorne K, Reynolds H, Balm TK, Hunninghake DB: Cholesterol-lowering effects of psyllium hydrophilic mucilloid. *JAMA* 261:3419–23, 1989
14. Coleman DL: Obese and diabetes: two mutant genes causing diabetes-obesity syndromes in mice. *Diabetologia* 14:141–48, 1978
15. Leiter EH, Coleman DL, Ingram DK, Reynolds MA: Influence of dietary carbohydrate on the induction of diabetes in C57BL/Ksj-*db/db* diabetes mice. *J Nutr* 113:184–95, 1983
16. Surwit RS, Kuhn CM, Cochrane D, McCubbin JA, Feinglos MN: Diet-induced type II diabetes in C57BL/6J mice. *Diabetes* 37:1163–67, 1988
17. Uribe M, Dibildox M, Malpica S, Guillermo E, Villalobos A, Nieto L, Vargas F, Ramos GG: Beneficial effect of vegetable protein diet supplemented with *psyllium plantago* in patients with hepatic encephalopathy and diabetes mellitus. *Gastroenterology* 88:901–907, 1985
18. Frati-Munari AC, Fernandez-Harp JA, Becerril M, Chavez-Negrete A, Banales-Ham M: Decrease in serum lipids, glycemia and body weight by plantago psyllium in obese and diabetic patients. *Arch Invest Med* 14:259–68, 1983
19. Bierman EL, Hamlin JT: The hyperlipemic effect of a low-fat, high-carbohydrate diet in diabetic subjects. *Diabetes* 10:432–37, 1961
20. Olefsky JM, Farquhar JW, Reaven GM: Reappraisal of the role of insulin in hypertriglyceridemia. *Am J Med* 57:551–60, 1974
21. Ullrich IH: Evaluation of a high-fiber diet in hyperlipidemia: a review. *J Am Coll Nutr* 6:19–25, 1987
22. Anderson JW, Zettwoch N, Feldman T, Tietyen-Clark J, Oeltgen P, Bishop CW: Cholesterol-lowering effects of psyllium hydrophilic mucilloid for hypercholesterolemic men. *Arch Intern Med* 148:292–96, 1988
23. Camus MC, Chapman MJ, Forgez P, Laplaud PM: Distribution and characterization of the serum lipoproteins and apoproteins in the mouse, *mus musculus*. *J Lipid Res* 24:1210–28, 1983
24. Edwards CA, Johnson IT, Read NW: Do viscous polysacharides slow

absorption by inhibiting diffusion or convection? *Eur J Clin Nutr* 42:307–12, 1988
25. Jenkins DJ, Jenkins AL: Dietary fiber and glycemic response. *Proc Soc Exp Biol Med* 180:422–31, 1985
26. Pomare EW, Branch WJ, Cummings JH: Carbohydrate fermentation in the human colon and its relation to acetate concentrations in venous blood. *J Clin Invest* 75:1448–54, 1985
27. Cummings JH, Pomare EW, Branch WJ, Naylor CPE, Macfarlane GT: Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut* 28:1221–27, 1987
28. Beynen AC, Buechler KF, Van Der Molen AJ, Geelen MJH: The effects of lactate and acetate on fatty acid and cholesterol biosynthesis by isolated rat hepatocytes. *Int J Biochem* 14:165–69, 1982
29. Scheppach W, Wiggins HS, Halliday D, Self R, Howard J, Branch WJ, Schrezermeir J, Cummings JH: Effect of gut-derived acetate on glucose turnover in man. *Clin Sci* 75:363–70, 1988
30. Chen WJ, Anderson JW, Jennings D: Propionate may mediate the hypocholesterolemic effects of certain soluble plant fibers in cholesterol-fed rats. *Proc Soc Exp Biol Med* 175:215–18, 1984
31. Scheppach W, Cummings JH, Branch WJ, Schrezermeir J: Effect of gut-derived acetate on oral glucose tolerance in man. *Clin Sci* 75:355–62, 1988
32. Anderson JW, Bridges SR: Short-chain fatty acid fermentation products of plant fiber affect glucose metabolism of isolated rat hepatocytes. *Proc Soc Exp Biol Med* 177:372–76, 1984
33. Nyman M, Asp NG, Cummings JH, Wiggins H: Fermentation of dietary fibre in the intestinal tract: comparison between man and rat. *Br J Nutr* 55:487–96, 1986
34. Temple NJ, Tapan BK: Dietary fibre and the mouse colon: its influence on luminal pH, reducing activity and bile acid binding. *Cancer Lett* 41:111–18, 1988
35. McNamara DJ, Lolb R, Parker TS, Batwin H, Samuel P, Brown CD, Ahrens EH: Heterogeneity of cholesterol homeostasis in man. *J Clin Invest* 79:1729–39, 1987