

Integrative Medicine

Evidence-based summaries and critical reviews on
the latest developments in integrative therapies [ALERT]

DIABETES

Do Certain Fruits Decrease the Risk of Type 2 Diabetes?

By Melissa Quick, DO, and David Kiefer, MD

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Dr. Quick reports no financial relationships relevant to this field of study.

SYNOPSIS: The daily whole fruit and fruit juice consumption of 187,382 participants who were free of major chronic diseases at baseline was analyzed over 3,464,641 person-years of follow-up to determine the association between certain fruits and the risk of type 2 diabetes. Specific whole fruits, particularly blueberries, were significantly associated with a lower risk of type 2 diabetes. Fruit juice was associated with a greater risk.

SOURCE: Muraki I, et al. Fruit consumption and risk of type 2 diabetes: Results from three prospective longitudinal cohort studies. *BMJ* 2013;347:f5001.

Do certain fruits put you at risk for diabetes? The authors of this article reviewed three prospective longitudinal cohort studies evaluating the relationship between individual fruit consumption and the risk of developing type 2 diabetes. The subjects of the study were 66,105 women from the Nurses' Health Study (established in 1976; timeframe evaluated in this study: 1984-2008; n = 121,700), 85,104 women from the Nurses' Health Study II (established in 1989; time frame evaluated in this study: 1991-2009; n = 116,671), and 36,173 men from the Health Professionals Follow-Up Study (established in 1986; timeframe evaluated in this study: 1986-2008; n = 51,529).

Participants were excluded from the study if they reported any baseline diagnosis of any form of diabetes, cardiovascular disease, or cancer. Additional exclusion criteria included if missing data existed for the consumption of individual fruit or fruit juice or if daily energy intake was unusual (< 500 or > 3500 kcal/day for the Nurses' Health Study and the Nurses' Health Study II and < 800 or > 4200 kcal/day for the Health Professional Follow-Up Study).

The original questionnaire for this study was developed in 1984 and was sent to the women in the Nurses' Health Study to assess the frequency of consumption of 118 food items over the past year. In 1986, a similar but more extensive questionnaire

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was developed and this version was sent every 4 years to participants in each study (starting in 1986 for the Nurses' Health Study II and in 1991 for the Health Professionals Follow-Up Study.) To account for covariates, a follow-up questionnaire administered every 2 years assessed for updates on anthropometric and lifestyle factors, including body height, weight, cigarette use, physical activity, and family history of diabetes. The follow-up rate of all three cohorts was approximately 90%.

The frequency of individual food consumption was gauged by asking how often, on average, participants consumed food in a standard portion size. Ten individual fruits were consistently evaluated: grapes or raisins; peaches, plums, or apricots; prunes; bananas; cantaloupe; apples or pears; oranges; grapefruit; strawberries; and blueberries.

There were nine possible responses to how often the participant ingested these fruits, ranging from "never, or less than once per month" to "six or more times a day."

The authors validated food frequency questionnaires against diet records of a handful of the participants (n = 173, Nurses' Health Study; and n = 127, Health Professionals Follow-Up Study). Corrected correlation coefficients between the questionnaire and diet records were not available for all individual fruits, but in general ranged from 0.38 (strawberries in men) to 0.95 (bananas). "Total whole fruit" consumption was calculated by the sum of the consumption levels of the 10 individual fruits and watermelon, a fruit that was sporadically inquired about during follow-up.

The main outcome of the study — incident cases of type 2 diabetes — was evaluated by sending supplementary questionnaires to participants who reported physician-diagnosed diabetes in their routine follow-up questionnaires. A type 2 diabetes diagnosis was confirmed if at least one of the following National Diabetes Data Group criteria were met (see Table 1). Sixty-two self-reported cases of type 2 diabetes were randomly selected from the Nurses' Health Study and 61 (98%) were confirmed after an endocrinologist reviewed the information. In the Health Professionals Follow-Up Study, 57 of 59 (97%) of self-reported type 2 diabetes cases were confirmed by medical record review.

The results of this study show that during 3,464,641 person-years of follow-up, 12,198 participants developed type 2 diabetes. After adjusting for personal, lifestyle, and dietary risk factors for diabetes, the pooled hazard ratio of type 2 diabetes for every three servings/week of total whole fruit consumption was 0.98 (95% confidence interval [CI], 0.96-0.99). For individual fruits, the pooled hazard ratios of type 2 diabetes for every three servings/week were 0.74 (CI, 0.66-0.83) for blueberries; 0.88 (CI, 0.83-0.93) for grapes and raisins; 0.89 (CI, 0.79-1.01) for prunes; 0.93 (CI, 0.9-0.96) for apples and pears; 0.95 (CI, 0.91-0.98) for bananas; 0.95 (CI, 0.91-0.99) for grapefruit; 0.97 (CI, 0.92-1.02) for peaches, plums, and apricots; 0.99 (CI, 0.95-1.03) for oranges; 1.03 (CI, 0.96-1.1) for strawberries; and 1.1 (CI, 1.02-1.18) for cantaloupe. To summarize, the authors found the risk of type 2 diabetes differed significantly between individual fruits: blueberries, grapes, apples, bananas, and grapefruit consumption were significantly associated with a reduced risk of type 2 diabetes.

Table 1. National Diabetes Data Group Criteria — Diagnosis of Diabetes

- One or more classic symptom (excessive thirst, polyuria, weight loss, and hunger)
- Raised blood glucose levels (fasting levels ≥ 126 mg/dL)*
- Random blood levels ≥ 200 mg/dL
- Two-hour blood glucose levels ≥ 200 mg/dL during oral glucose tolerance testing
- Raised blood glucose levels on two different occasions in the absence of symptoms
- Treatment with antidiabetic drug (insulin or oral antidiabetic agent)

* In June 1998, the diagnostic criteria changed from fasting level ≥ 140 mg/dL to ≥ 126 mg/dL

Summary Points

- Dietary modifications among other lifestyle changes prevent development of type 2 diabetes.
- Whole fruits contain more phytochemicals, fiber, and antioxidants, and thus more health benefits, than fruit juice.
- Blueberries significantly decrease the risk of developing type 2 diabetes.
- Fruit juice significantly increases the risk of developing type 2 diabetes.

Another endpoint of this study demonstrated no association between the glycemic index or glycemic load of individual fruit consumption and the risk of type 2 diabetes. Additionally, the consumption of fruit juice was analyzed (juices evaluated include apple, orange, grapefruit, and others) and the pooled hazard ratio for three servings/week of fruit juice was 1.08 (CI, 1.05-1.11). Lastly, the authors found that substitution of whole fruits for fruit juice was also associated with a lower risk of type 2 diabetes.

■ COMMENTARY

In 2010, 25.8 million people (8.3% of the U.S. population) were affected by diabetes.¹ Approximately 18.8 million of those affected had an official “diabetes” diagnosis, and 90-95% of these diagnosed cases were type 2 diabetes. (See Table 2.) We know the sequelae of diabetes can be devastating: Heart disease, stroke, kidney failure, new cases of blindness, and non-traumatic limb amputation are commonly seen in uncontrolled diabetics. Furthermore, prediabetes, or an impaired glucose tolerance or impaired fasting glucose level, can place individuals at a greater risk of developing type 2 diabetes.¹ As such, it is critical for medical providers to be well versed in not only the treatment of diabetes, but perhaps even more crucially, strategies to prevent diabetes’ development. Current management guidelines for prediabetes recommend a multifactorial approach — from weight loss to lifestyle and dietary changes to metformin use — in order to reduce individual risk.²

Increasing the amount of whole fruits and vegetables in our diets — an all too familiar edict from parents to physicians nationwide — has been associated with decreased incidence of and mortality from various health outcomes including obesity, hypertension, and cardiovascular disease.³ We know that fruits provide a plethora of phytonutrients (a group of at least

5000 bioactive compounds) that have been linked to reductions in the risk of major chronic diseases.⁴ Additionally, the soluble fiber found in fruits can decrease postprandial glucose levels.⁵ Furthermore, the antioxidants in fruits, such as carotenoids, vitamin C, vitamin E, and flavonoids, may reduce diabetes risk by relieving oxidative stress that interferes with the glucose uptake by cells.⁶

Interestingly, despite the known benefits of consuming whole fruits and vegetables, prior epidemiological research has inconsistently shown a link between increased fruit consumption and a decreased risk of diabetes.⁷ Thus, the authors of the above reviewed study sought to explain these inconsistencies by postulating that perhaps it is not enough just to increase the *generic* amount of fruit one eats, but rather, *specific* fruits may have more positive effects than others.

So, with respect to the reported results in the above study, did blueberries, grapes, apples, bananas,

Table 2. Criteria for Testing for Diabetes in Asymptomatic Adult Individuals from the ADA Standards of Medical Care in Diabetes — 2013

1. Testing should be considered in all adults who are overweight (BMI ≥ 25 kg/m²) and have additional risk factors:

- Physical inactivity
- First-degree relative with diabetes
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- Women who delivered a baby weighing > 9 lbs or were diagnosed with gestational diabetes
- Hypertension ($\geq 140/90$ mmHg or on therapy for hypertension)
- HDL cholesterol level < 35 mg/dL (0.90 mmol/L) and/or a triglyceride level > 250 mg/dL (2.82 mmol/L)
- Women with polycystic ovary syndrome
- A1C $\geq 5.7\%$, impaired glucose tolerance, or impaired fasting glucose on previous testing
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- History of cardiovascular disease

2. In the absence of the above criteria, testing for diabetes should begin at age 45 years.

3. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results (e.g., those with prediabetes should be tested yearly) and risk status.

and grapefruit reduce the risk of developing type 2 diabetes *more* than peaches, plums, apricots, oranges, and strawberries? More to the point, does eating cantaloupe three times a week actually *increase* your risk of type 2 diabetes? Upon careful examination of the results — specifically reviewing hazard ratios and confidence intervals among individual cohorts — it appears that the only individual fruit with consistent significant findings among each cohort are blueberries when consumed five or more times a week (Nurses’ Health Study: 0.82 [CI, 0.69-0.98]; Nurses’ Health Study II: 0.69 [CI, 0.55-0.87]; and Health Professionals Follow-Up Study: 0.74 [CI, 0.55-1.00]). (See Table 3).

Furthermore, cantaloupe *does* seem to increase risk of type 2 diabetes, but *only* among the men’s cohort when consumed more than once a month (Health Professional Follow-Up Study — adjusted hazard ratio: 1-3 servings/month = 1.15 [CI, 1.03-1.27]; 1 serving/week = 1.08 [CI, 1.02-1.14]; and 2-4 servings/week = 1.19 [CI, 1.01-1.40]). Of note, the authors mention that they “pooled” their hazard ratios and this explains the results that they list are significant.

Another significant and surprising finding in this study is the lack of association between the glycemic index of individual fruits and their effect on the risk of type 2 diabetes. In traditional diabetes

management, patients are often taught to count carbohydrates. Additionally, many patients are taught that elevated glycemic indices (measure of the incremental glucose response per gram of carbohydrate) and glycemic loads (the amount of carbohydrate multiplied by its glycemic index) may increase the risk and progression of type 2 diabetes.^{8,9} However, many studies have shown that the total amount of carbohydrate in food is generally a better predictor of blood glucose response than the glycemic index.^{10,11} Interestingly, and as noted in the above study, the glycemic index/glycemic load of individual fruits does *not* correlate to their abilities to reduce diabetes risk.

This study also found that fruit juice consumption does not prevent the risk of type 2 diabetes. Evidence from this and other studies shows that the consumption of whole fruit has profound positive health benefits that fruit juice lacks. Although fruit juices may have a portion of the antioxidant activity found in whole fruits, juices have minimal fiber, are less satiating, and often contain large amounts of sugar.³

There are several potential limitations of this study. The authors admit that their surveying system was imperfect and that there were “inevitable errors” in the estimates of fruit consumption and that some individual fruits were often combined in food-

Table 3. Hazard Ratios and Glycemic Load and Glycemic Index Values for Studied Fruits

	Adjusted Hazard Ratios for 2-4 servings/week			Glycemic Load	Glycemic Index
	Nurses’ Health Study	Nurses’ Health Study II	Health Professionals Follow-up Study		
Grapes and raisins	0.80 (0.72-0.88)	0.83 (0.72-0.97)	0.87 (0.76-1.01)	High	High
Peaches, plums, and apricots	1.04 (0.94-1.14)	0.99 (0.86-1.14)	0.88 (0.75-1.04)	Low	Low
Prunes	0.89 (0.75-1.06)	1.16 (0.88-1.53)	0.86 (0.66-1.12)	High	Moderate
Bananas	1.04 (0.94-1.15)	0.82 (0.72-0.94)	0.93 (0.80-1.07)	High	High
Cantaloupe	1.07 (0.96-1.19)	1.11 (0.94-1.30)	1.19 (1.01-1.40)	Moderate	High
Apples and pears	0.85 (0.77-0.95)	0.79 (0.68-0.91)	0.91 (0.77-1.07)	High	Low
Oranges	0.96 (0.87-1.05)	0.93 (0.81-1.07)	0.89 (0.78-1.03)	Moderate	Low
Grapefruit	0.88 (0.80-0.96)	0.97 (0.83-1.14)	0.93 (0.81-1.06)	Low	Moderate
Strawberries	0.87 (0.77-0.98)	1.09 (0.93-1.27)	1.16 (0.95-1.42)	Low	Low
Blueberries	0.82 (0.69-0.98)	0.69 (0.55-0.87)	0.74 (0.55-1.00)	Moderate	Moderate

frequency questionnaires, complicating accurate individual fruit to diabetes associations. Additionally, all study participants were either female nurses or male health professionals (dentists, veterinarians, pharmacists, optometrists, osteopathic physicians, and podiatrists).¹² It could be argued that this educated population may make healthier dietary and lifestyle decisions than those not in the health care profession. These study participants were also overwhelmingly white (95-98% in each study), which makes it difficult to connect these results with the much more diverse U.S. population. Also, the average body mass index (BMI) of both female and male participants overall ranged from 24.3-25.2 kg/m² — less than the average U.S. adult man (BMI of 26.6 kg/m²) and the average U.S. adult woman (BMI of 26.5 kg/m²).¹³ Lastly, recall bias cannot be excluded in this study, as is inherent in most questionnaire-based studies and has potential confounding implications.

Despite the restraints discussed above, there are also many positive aspects of this study. The sheer number of participants evaluated in this study along with the huge amount of person-years analyzed is impressive. Additionally, though the population studied were all medical professionals, it could be argued that if this potential “healthier” subset of the population still developed diabetes despite their increased knowledge of diabetes and diabetes prevention, then the results of this study would be even more pronounced in a more diverse and “lay” population.

How should we counsel our patients about the relationship between fruit and diabetes? The World Health Organization recommends a minimum intake of 400 g or five portions of combined fruits and vegetables daily for the prevention of type 2 diabetes and other common noncommunicable diseases.¹⁴ Also, a study published in 2012 suggests that a greater *variety*, not *quantity*, of fruit and vegetable consumption is associated with a lower risk of type 2 diabetes.¹⁵ These two arguments, along with the study reviewed in this article, suggest that perhaps reiterating the common “5-a-Day” anthem to our patients may be tremendously high-yield guidance. It may even be most useful to emphasize vegetable consumption *more* than fruit by reversing this tagline to “eat 5 vegetables and fruits a day.” It is important to keep in mind that not all fruits and vegetables have equivalent safety profiles in terms of risk of pesticides (See Table 4 for the “dirty dozen” and the “clean fifteen”). Of course, consuming vegetables and fruits regardless of farming techniques is certainly preferred to avoidance if more expensive organic versions are unavailable. Finally, discouraging patients from substituting fruit

Table 4. Pesticide Exposure of Common Fruits and Vegetables

Dirty Dozen: Best to eat organic if possible	Clean Fifteen: Safer non-organic choices
Apples	Asparagus
Celery	Avocado
Cherry tomatoes	Cabbage
Cucumbers	Cantaloupe
Grapes	Sweet corn
Hot peppers	Eggplant
Nectarines	Grapefruit
Peaches	Kiwi
Potatoes	Mangos
Spinach	Mushrooms
Strawberries	Onions
Sweet bell peppers	Papayas
	Pineapple
	Sweet peas
	Sweet potatoes

From the Environmental Working Group.

juice for whole fruits and limiting overall fruit juice consumption will surely reduce patient’s risk of developing type 2 diabetes. ■

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OBESITY

Obesity and Microbiota

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Dr. Decker reports no financial relationships relevant to this field of study.

Trillions of microbes are known to colonize the human body, with different strains of flora common to locations such as the gastrointestinal tract, skin, vaginal canal, and oral cavity. But variations or overgrowth in specific strains of these microbes is often associated with pathology, such as the well-known conditions that bacterial vaginosis or candidiasis represent. Imbalances in flora populations are now being associated with diseases such as irritable bowel syndrome,¹ inflammatory bowel disease,² autoimmune diabetes,³ atherosclerosis,⁴ and obesity.⁵ Much study is devoted to seeking an understanding of how the microbiota is related to these diseases and if it is a result of the disease condition or a possible contributing cause.

Obesity is a compelling problem. In 2008, 11% of the world's adult population aged ≥ 20 years of age were classified as obese (body mass index [BMI] ≥ 30 kg/m²), while 35% were classified as overweight (BMI ≥ 30 kg/m²).⁶ Childhood and adolescent obesity is also an increasing statistic. In 2009-2010, 16.9% of children and adolescents between 2-19 years old were also classified as obese.⁷ Many factors lead to these statistics, and questions of diet, exercise, and genetics are often the most obvious to assess. As knowledge about the microbiota and its effect on the health of the organism continues to become more apparent, the gastrointestinal flora is being investigated to assess for possible relationship or contribution to obesity. Obesity is a disease associated with many other problems such as insulin resistance, chronic low-grade inflammation, and non-alcoholic fatty liver disease, so understanding the role the gut microbiota may play in the confluence of these diseases may lead to larger treatment solutions.

PATHOPHYSIOLOGY AND MECHANISMS

Several studies have promoted interest in the relationship of microbiota to obesity. One study involved the analysis and transplantation of the

Summary Points

- Several mechanisms by which the gut microbiota may contribute to obesity have been shown in animal studies.
- Short-chain fatty acids, prebiotics, and certain species of probiotics have been shown to affect the gut microbiota and reduce weight gain in animals subject to high-fat diet feeding.
- There are a few clinical trials showing beneficial aspects of prebiotics and probiotics on abdominal adiposity.

distal cecal microbiota from lean and obese mice into germ-free mice recipients.⁸ It was found that after a 2-week period, the germ-free mice colonized with the microbiota from the obese mice exhibited a significantly greater increase in adiposity without an increase in food consumption. Similar results were observed with the transplantation of gut microbiota in another study.⁹

The mechanisms by which the microbiota may be related to adiposity are a current research interest. It has been shown that obese mice have an increased absorption of monosaccharides and hepatic lipogenesis associated with the signaling proteins carbohydrate response element-binding protein and liver sterol response element-binding protein.⁹ The obese microbiota was also shown to suppress fasting-induced adipocyte factor, leading to increased lipoprotein lipase activity in adipocytes and increased storage of calories as fat.⁹ The genes of the microbiota from obese leptin-deficient mice have been shown to code for enzymes that break down otherwise indigestible polysaccharides, leading to increased energy extraction from food.⁸ An inflammation- and obesity-associated pathway has also been associated with diet. A high-fat diet (HFD)

has been shown to increase endotoxemia (measured by plasma lipopolysaccharide [LPS]) and affects which microbiota are present, reducing *Bacteroides* and *Bifidobacterium* spp., as well as triggering the expression of inflammatory cytokines.¹⁰ A chronic low serum level of LPS has been shown to lead to obesity, hyperglycemia, and hyperinsulinemia via immune system-associated pathways.¹¹ Increased circulating levels of LPS in rodents subject to an HFD also have been shown to be directly related to increased intestinal permeability.¹²

Short-chain fatty acids, prebiotics, and probiotics are some of the interventions being studied for the modification of the microbiota in obese populations.¹¹ Short-chain fatty acids (SCFAs) including acetate, butyrate, and propionate are a metabolic product of the gut microbiota and have an effect on the several of the aforementioned mechanisms. Prebiotics are fibers that resist absorption in the upper gastrointestinal tract, are fermented by intestinal microflora into products including SCFAs, and stimulate the growth and/or activity of gut microbiota associated with health.¹³ Inulin, oligofructose (OF), fructo-oligosaccharides (FOS), transgalacto-oligosaccharide, and lactulose are some common prebiotics.¹³ Probiotics are strains of microbiota that directly affect the intestinal flora population and have many health benefits.

ANIMAL TRIALS

SCFAs. Butyrate at a level of 5% wt/wt has been shown in mouse studies to reduce weight gain in mice on an HFD, inducing satiety¹⁴ and increasing energy expenditure via increased mitochondrial function.¹⁵ Treatment of mice with butyrate at a level of 5% wt/wt for 16 weeks prevented the development of obesity and insulin resistance despite HFD feeding.¹⁵

Prebiotics and Probiotics. The affect of FOS on minimizing the weight gain of mice fed an HFD was assessed in a study with axenic mice. The mice, inoculated with human fecal microbiota, were subject to feeding for 7 weeks of an HFD, an HFD with 10% FOS, or a control diet.¹⁶ Both groups of mice on an HFD feeding gained more weight than the control; however, the FOS fed group gained less weight and had less fat deposition. The fecal microbiota of the FOS fed mice had a significant increase in *Bifidobacteria* and *Clostridium coccoides* and decreased *C. leptum*.

The effects of prebiotics and probiotics were assessed individually and in combination in rats with diet-induced obesity.¹⁷ The diet of the rats was supplemented with 10% OF and/or 1×10^{10} colony-forming units (CFU) per day of *Bifidobacterium*

animalis BB-12, and outcomes were compared to control after 8 weeks of feeding. It was found that the prebiotics but not the probiotics reduced energy intake, weight gain, and fat mass. All interventions improved blood sugar compared to control. There was a significant increase in *Bifidobacteria* and *Lactobacilli* spp. with OF supplementation but not with *B. animalis* alone.

Several animal trials have shown varying levels of success with different strains of probiotics. Probiotic strains of *Lactobacillus rhamnosus* or *L. sakei* were supplemented to mice at a level of 1×10^8 CFU/day for 3 weeks with a normal chow feeding.¹⁸ Both strains were separately shown to reduce epididymal fat mass and obesity-related biomarkers. Supplementation with *L. sakei* also led to a significantly lower overall weight gain than the control group. No significant difference in feed consumption was noted.

Mice supplemented with *Bacteroides uniformis* CECT 7771 at a dosage of 5.0×10^8 CFU were fed either a standard diet or HFD and compared to controls with no supplementation after 7 weeks.¹⁹ The supplementation of *B. uniformis* was found to reduce body weight gain, serum cholesterol, triglyceride, glucose, and insulin levels, as well as dietary fat absorption by enterocytes in mice subject to HFD feeding. The changes in gut microbiota induced by the HFD feeding were also decreased with probiotic supplementation.

The effects of four different *Bifidobacteria* strains (L66-5, L75-4, M13-4, and FS31-12) on weight gain, lipid metabolism, and glucose metabolism in obese mice fed an HFD were assessed after supplementation at a level of 1×10^8 CFUs with HFD feeding for 6 weeks.²⁰ After the 6-week period, the body weight of the group supplemented with the *B. M13-4* strain was significantly higher, and the *B. L66-5* group was significantly lower. No significant change in body weight from the control was observed with the *B. L75-4* or *B. FS31-12* supplementation.

CLINICAL STUDIES

SCFAs. Supplementation with SCFAs has not yet been investigated in human clinical trials for the treatment of obesity.

Prebiotics. A systematic review of randomized controlled trials (RCTs) was performed to assess the effects of prebiotic intake on appetite, energy intake, and body weight in children and adults.²¹ A total of 19 RCTs met the inclusion criteria for this review. In pediatrics, only one of four RCTs showed an effect on body weight or BMI.²² In adults, of the three

RCTs that assessed body weight, two RCTs showed a significant reduction.^{23,24} Eleven of the RCTs found no effect of prebiotic supplementation on energy intake. The studies with significant findings are further detailed here.

Adolescents aged 9-13 years old were supplemented with 8 g of a 50/50 inulin/OF blend a day and BMI measurements were compared to a control group supplemented with maltodextrin after a period of 1 year.²² The individuals supplemented with the prebiotic had a BMI increase of 0.73 kg/m² while the control group had a BMI increase of 1.24 kg/m², a difference 0.52 ± 0.16 kg/m² (*P* = 0.016); confidence interval (CI) was not reported (NR). Calcium intake was also assessed in this study and found to have a negligible effect. A year after the supplementation was stopped, it was found that the BMI of the prebiotic group remained lower, with a difference in BMI of 0.68 ± 0.36 kg/m² (*P* = 0.061; CI NR).

OF supplementation was provided to adults with a BMI > 25 kg/m² at a level of 21 g/day for a period of 12 weeks.²³ It was found that there was a decrease in body weight of 1.03 ± 0.43 kg with OF supplementation, and an increase in weight of 0.45 ± 0.31 kg in the placebo group (*P* = 0.01; CI NR). A 29% reduction in self-reported calorie intake in the OF group was seen at week 6 (*P* = 0.002; CI NR) and this was associated with different hormones associated with hunger and satiety (ghrelin and peptide YY).

FOS supplementation at a dosage of 20 g or 10 g/70 kg/day was provided to obese women for a period of 120 days.²⁴ It was found that a dosage of 10 g/70 kg/day led to a significant decrease in body weight from 91.2 ± 8.4 kg to 76.2 ± 6.1 kg (*P* < 0.05; CI NR). Supplementation at a dosage of 20 g/70 kg/day led to significant gastrointestinal side effects and these subjects were excluded from analysis.

Probiotics. The probiotic strain *L. gasseri* SBT2055 has been shown to have a beneficial effect on abdominal adiposity in human studies.²⁵ *L. gasseri* SBT2055 was supplemented to individuals with a BMI of 24.2-30.7 kg/m² via fermented milk (a traditional yogurt preparation) at a dosage of approximately 10 × 10¹⁰ CFU in 200 g/day of fermented milk for a period of 12 weeks, and compared to a control supplemented with only fermented milk. Abdominal visceral and subcutaneous fat area significantly decreased (*P* < 0.01) from baseline by an average of 4.6% (mean, -5.8; CI, -10.0 to -1.7 cm²) and 3.3% (mean, -7.4; CI, -11.6 to -3.1 cm²), respectively. Other measures that decreased significantly (*P* < 0.001) were: body weight, 1.4% (mean, -1.1; CI, -1.5 to -0.7 kg); BMI,

1.5% (mean, -0.4; CI, -0.5 to -0.2 kg/m²); waist, 1.8% (mean, -1.7; CI -2.1 to -1.4 cm); hip, 1.5% (mean, -1.5; CI, -1.8 to -1.1 cm). None of these parameters were found to decrease significantly in the control group.

A second study regarding the probiotic *L. gasseri* but with strain BNR17 was performed on an overweight and obese population having a BMI ≥ 23 kg/m².²⁶ Supplementation of *L. gasseri* BNR17 at the level of 10¹⁰ CFU/day occurred for a period of 12 weeks without any other behavioral or dietary intervention. In this study, only a slight reduction in body weight, waist, and hip circumference was noted in the *L. gasseri* BNR17 supplemented group, but the differences were not significant.

Supplementation of a probiotics combination with dietary counseling was assessed in the prevention of obesity post-pregnancy and compared with dietary intervention alone or a control with no intervention.²⁷ Supplementation of both *L. rhamnosus* GC and *Bifidobacterium lactis* at a dosage of 10¹⁰ CFU/day was provided from the first trimester until the end of exclusive breastfeeding (up to 6 months). At 6 months postpartum, it was found that the risk of central adiposity (waist circumference 80 cm or more) was lowered in women in the diet/probiotics group compared with the control/placebo group (odds ratio 0.30; CI, 0.11-0.85; *P* = 0.023), while the diet/placebo group did not significantly differ from the control. The number needed to treat for the prevention of one woman from developing central adiposity was 4.

The probiotic strain *L. salivarius* Ls-33 was assessed for its effects on inflammation and metabolic syndrome in adolescents with obesity, and after supplementation of 10¹⁰ CFU/day for a period of 12 weeks, there was no significant change in any of the biomarkers related to obesity or metabolic syndrome.²⁸

DOSING

SCFAs. In animal studies, 5% wt/wt dosing of butyrate was shown to have a beneficial effect. Dosing at this level was for a period of 4-16 weeks in mouse studies.^{14,15}

Prebiotics and probiotics. Most common amounts of prebiotic supplementation in humans range from 10-20 g/day in a single or divided dose either with or before meals.²¹ Recommendations for minimal gastrointestinal side effects are to dose at 10 g FOS/70 kg/day or to gradually increase the dosage.²⁴ CFUs are the measurement unit of probiotics and describe the amount of organisms present that are viable and able to colonize under controlled

conditions in vitro. The dosing of probiotics (various strains, including possibly *L. gasseri* SBT2055, *L. rhamnosus* GC, or *Bifidobacterium lactis*) at a level between 1×10^{10} and 10×10^{10} CFU/day are what are used in the literature and may be an appropriate dose. Dosing of prebiotics and probiotics at these levels is recommended for a period of at least 12 weeks.

SAFETY AND ADVERSE EFFECTS

SCFAs. High levels of SCFAs, specifically butyrate, have been shown in vitro to have a paradoxical effect, leading to increased intestinal permeability.²⁹ However, this may be mediated by its beneficial effects on the intestinal mucosa barrier.³⁰ Oral formulations of sodium butyrate often have an unpleasant taste and odor, possibly leading to poor patient compliance.

Prebiotics. Digestion of prebiotics such as inulin, FOS, and OF is a known problem in patients with irritable bowel syndrome, and may lead to fructose malabsorption and exacerbation of gastrointestinal symptoms.³¹ In some of the studies cited, subjects experienced symptoms of diarrhea, abdominal distention, flatulence, and nausea initially during treatment; however, symptoms improved with time. A gradual increase in dosage with time also was utilized to minimize these symptoms. Supplementation with FOS has also been shown to increase lower esophageal sphincter relaxation, worsening incidence of reflux events in patients with gastroesophageal reflux disease.³²

Probiotics. The consumption of probiotics is generally recognized as safe; however, as high doses of specific strains are now being utilized for the treatment of a variety of conditions, this question must further be considered. A systemic review assessed the safety of probiotics in 72 case reports, RCTs, and nonrandomized trials.³³ The authors found 20 case reports of adverse events in 32 patients, each involving infections associated with either *L. rhamnosus* GG or *S. boulardii*. The risk factors identified in these case reports were antibiotic treatment, intravenous access, immune suppression, and conditions involving increased bacterial translocation. Of the 52 trials assessed, most showed no effect or a positive effect on outcomes, with only three trials showing increased complications. Of these three, two trials were associated with administration of a probiotic via a nasojejunal tube, and the third involved treatment of low birth weight, preterm infants. Theoretically, there also may be long-term effects on the immune system and adverse effects during pregnancy as well; however, there presently is no evidence for this.³⁴

CONCLUSION

The knowledge is far from complete pertaining to how the gut microbiota is related to obesity. Furthermore, how to specifically alter the microbiota to reduce the risk of obesity is far less known. Animal studies have shown that the dietary addition of SCFAs, prebiotics, and specific strains of probiotics confer benefits of reduced weight gain, particularly under conditions of HFD feeding. The possible effects of SCFA supplementation on obesity has no clinical evidence, as testing has only been performed with animal and in vitro studies. Supplementation with prebiotics shows some benefit on body weight clinically; however, a systemic review of RCTs shows few trials with significant effects.²¹ Adverse gastrointestinal effects also may be experienced with prebiotic supplementation, but can be minimized by gradually increasing the dosage as tolerated up to 10 g/70 kg/day. The probiotics strains of *L. gasseri* and *L. rhamnosus* GC with *B. lactis* may be beneficial for reducing abdominal adiposity, dosing at a level of 1×10^{10} to 2×10^{10} CFU/day.

RECOMMENDATION

Prebiotics may be a beneficial adjunctive treatment for promoting reduced body weight; however, gastrointestinal side effects may be experienced. Leeks, asparagus, chicory, Jerusalem artichokes, garlic, onions, and soybeans are sources of prebiotics, so increasing the consumption of these foods will introduce both prebiotics as well as other nutrients to the diet. To achieve the goal of dosing at 5-6 g of prebiotics twice a day, one would need to consume approximately 2 servings of cooked asparagus or a single serving of Jerusalem artichoke, globe artichoke, cooked onion, or leeks to get a single prebiotics serving.³⁵

Supplementation of the probiotic strains of *L. gasseri* and *L. rhamnosus* GC with *B. lactis* may be considered for the objective of weight loss; however, minimal studies have been done to show their clinical effect. Since supplements with these specific probiotic strains are not as economical and widely available as prebiotics, it should be considered as an adjunctive treatment to promote reduced abdominal adiposity if gastrointestinal side effects of prebiotics are not tolerated. The additional health benefits of probiotics, not fully addressed in this review, may also promote interest in their use. A mixed probiotic that includes these specified strains at a dosage of at least 1×10^{10} CFU/day would be an appropriate initial dosage. The intent of supplementation should be on a long-term basis of at least 12 weeks before anticipating notable changes in weight or other parameters. ■

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BACK PAIN

ABSTRACT AND COMMENTARY

Yoga in the Management of Chronic Low Back Pain — Not just for Yuppies

By Anne Cook, MD, FACP

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Dr. Cook reports no financial relationships relevant to this field of study.

SYNOPSIS: Yoga improved back pain and back-related function in minority and low-income subjects.

SOURCE: Saper RB, et al. Comparing once- versus twice-weekly yoga classes for chronic low back pain in predominantly low income minorities: A randomized dosing trial. *Evid Based Complement Alternat Med* 2013;658030.

This randomized trial examined the use and frequency of yoga classes in a racially diverse and lower socioeconomic population for the treatment of chronic low back pain. The study enrolled 95 patients of lower socioeconomic status with chronic moderate-to-severe low back pain in a 12-week yoga trial comparing once-weekly classes with twice-weekly classes. There were, therefore, two parallel groups but no control group. Patients excluded from the study included those with known back pathologies (e.g., spinal canal stenosis, spondylolisthesis, ankylosing spondylitis, severe scoliosis, malignancy, and fracture), sciatica pain equal to or greater than low back pain, back surgery in the last 3 years, severe or progressive neurologic deficits, new back pain treatments started within the previous month or anticipated to begin during the study, pregnancy, yoga practice in the last 6 months, active or planned workers' compensation, disability or personal injury claims, or perceived religious conflict. Yoga classes included 75 minutes of standardized yoga sessions as previously studied. All patients were also encouraged to participate in home practice as well and were given an audio CD and protocol. They were encouraged to participate in home practice 30 minutes per day. Patients were instructed to keep a log of time spent in practice.

The study revealed improvement in pain and back-related function in both groups, which is similar to findings in other studies. There have also been questions about how much yoga practice is needed for effectiveness. Once- and twice-weekly classes both showed clinically meaningful and statistically significant ($P < 0.001$) decreases from baseline in pain at 12 weeks: -2.1 (95% confidence interval [CI], -2.9 to -1.3) and -2.4 (95% CI, -3.1 to -1.8), respectively. Back-related function also improved for the once- and twice-weekly groups at 12 weeks: -5.1 (95% CI, -7.0 to -3.2) and -4.9 (95% CI, -6.5 to -3.3), respectively. The twice weekly group's outcomes were not statistically different from the once weekly group.

Two questions were raised in the study. First, do patients of lower socioeconomic, more racially diverse status benefit from yoga similarly to their more affluent counterparts? Second, is there a "dosage" effect that would cause a greater benefit if patients attended two yoga classes per week instead of one class? Effectiveness previously shown had been criticized because prior study groups typically were disproportionately affluent and white and there were questions about the generalizability to other populations.

COMMENTARY

The answer to the question of effectiveness across

Summary Points

- The improvement in back pain and back-related function in this predominantly minority and low-income population was similar to prior studies looking at more affluent populations.
- There did not appear to be a dose response when comparing twice-weekly to once-weekly yoga classes, but this finding was confounded by a smaller than expected difference between the groups in the time spent in yoga practice and lack of reliable data on the amount of home practice.
- The study suggests that the greatest benefit may occur in the first 6 weeks of practice.

populations appears to be yes. The outcomes from this study are similar to studies performed on more affluent and more highly educated populations with less racial diversity.^{1,2,3,4} For instance, the Sherman study compared 12 weekly yoga or exercise classes to a self-care book in patients with low back pain lasting longer than 12 weeks. In that study, back-related function in the yoga group was superior to the book and exercise groups at 12 weeks (yoga vs book: mean difference, -3.4 [95% CI, -5.1 to -1.6], $P < 0.001$; yoga vs exercise: mean difference, -1.8 [95% CI, -3.5 to -0.1], $P = 0.034$). At 26 weeks, back-related function in the yoga group was superior to the book group (mean difference, -3.6 [95% CI, -5.4 to -1.8]; $P < 0.001$). In that study, 97% of the participants had attended some college and 80% were white. Seventy-nine percent of those participants had an annual income $> \$35,000$, and 87% were employed. In the Saper study, 65% did have some education beyond high school, 18% were white, and 22% had incomes $> \$40,000$ (47% $> \$20,000$). Forty-four percent were employed.⁵

The answer to the question of yoga "dosage" is a little less clear. On the surface, there was no significant difference between the two groups based on the assignment to once-weekly vs twice-weekly classes. However, the actual time spent in yoga practice (including class and home practice) as it was calculated showed very little difference between the two groups. Patients in the twice-weekly group were less likely to attend the classes and patients in the once-weekly group did more home practice. Overall, including home practice, the once-weekly group averaged 29 hours and the twice-weekly group averaged 37 hours — only a 28% difference in time spent. These calculations were, however,

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fraught with confounders. The adherence rate for participants in the once-weekly classes was 83% and in the twice-weekly classes was only 67%. Additionally, the calculation of home yoga time was not reliable. Only seven participants completed all 12 weeks of the diary of home practice. The researchers made some rather large assumptions to calculate the time spent in home yoga practice during weeks without recorded data. It was assumed to be the same as time spent during those weeks with recorded data. These assumptions really did compromise the validity of any data extrapolated to answer the question of dosing. Therefore, it would seem that this question is not reliably answered by this study.

It should be noted that the greatest benefit in back pain scores and back-related function occurred during the first 6 weeks of the study in both groups, prompting the authors to suggest that patients may benefit just as well from weekly classes for 6 weeks as they do for 12 weeks. A few other issues should be noted. There was no significant decrease in narcotic use in the population studied, although there was significant decrease in non-steroidal use. Despite the use of incentives for class attendance in the form of gift cards and free classes, compliance was rather low in both the once-weekly classes and

twice-weekly classes. Better adherence may well have provided for different results.

In short, this study of yoga therapy in a lower socioeconomic population, though fraught with some statistical concerns, seems to show benefit similar to that seen in other populations. Although more study is needed to confirm these preliminary findings, it would seem that practitioners who have yoga instruction easily available to their patients can feel comfortable in recommending yoga practice as one treatment for chronic low back pain. ■

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CME QUESTIONS

1. Which is the most useful advice to give to a prediabetic patient?

- a. Drink more fruit juice.
- b. Do not eat whole fruit, only vegetables.
- c. Eat a greater variety of fruit.
- d. Eat a greater quantity of the same fruit.

2. Prebiotics are:

- a. easily digestible fibers that promote growth of beneficial gastrointestinal flora.
- b. digestible and indigestible fibers taken for the purpose of promoting health.
- c. fibers that resist absorption and promote the growth of gut microbiota that promote health.
- d. strains of microorganisms that are taken orally to promote health.

3. A standardized 12-week Hatha yoga protocol has been shown to:

- a. reduce narcotic use for patients with moderate-to-severe chronic low back pain.
- b. be effective in decreasing pain and increasing back-related function in patients with moderate-to-severe chronic low back pain.
- c. be more effective if patients participate in twice-weekly classes than if they only participate in once-weekly classes.
- d. be of greater benefit in patients with lower socioeconomic status.

[IN FUTURE ISSUES]

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