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ABOUT CADRE

CADRE (the Council for the Advancement of Diabetes Research and Education) is a nonprofit organization committed to reducing the burden of diabetes by providing health care professionals with scientific information and educational initiatives designed to translate research into effective clinical practice.

With this issue of the CADRE newsletter, you will notice that embedded within the articles are links to abstracts and journal articles on the PubMed web site. We hope being able to click on these links will make discovering additional information more convenient.

Also, if you have not yet completed CADRE's "Cases in Success" program, the interactive, web-based CME opportunity will continue to be open to new participants through April 2010. These case studies provide learning

opportunities in three areas (incretin therapy, insulin therapy, and multiple metabolic targets), and completion of the cases in each therapeutic area will qualify for CME credit. Participant response has been very positive; log on to the CADRE Web site to learn more.

We hope you find the articles in this issue of *CADRE's Current Diabetes Practice* informative, and that you will participate in "Cases in Success."

▲ Melissa Miles, Executive Director

GUEST EDITORIAL

HARNESSING LOCAL DATA AND SYSTEMS TO IMPROVE DIABETES CARE AND SURVEILLANCE

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(6.0%) and Minnesota (5.9%) had the lowest rates. On a state-by-state basis, obesity rates tend to track closely to diabetes; 2008 BRFSS data indicate an overall obesity prevalence of 26.6%, with Mississippi (33.3%) and Alabama (32.2%) having the highest rates and Colorado having the lowest (19.1%).

The behaviors of Americans are clearly linked to these continuing epidemics. BRFSS 2008 data indicate that 24.6%

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CADRE's
CURRENT DIABETES PRACTICE

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of Americans did not engage in *any* leisure-time physical activity in the past month. Similarly, BRFSS 2007 data show that only 24.4% of Americans met recommendations for fruit and vegetable consumption (≥ 5 servings a day). In 2000, these prevalence rates were 27.0% and 24.4%, respectively. Hence, in 8 years, with all the attention paid to obesity and diabetes, our national data indicate only a minor improvement in physical activity and no change in dietary behaviors related to fruit and vegetable consumption. Indeed, we still have a long way to go to achieve these national health objectives.

No debate exists regarding the human burden of diabetes in this country. US Centers for Disease Control and Prevention data from 2007 indicate that the prevalence of diagnosed and undiagnosed diabetes among people aged ≥ 20 years is 10.7%, or about 24 million individuals. Among individuals

aged ≥ 60 years, prevalence rises to 23.1%, or 12.2 million. However, the complications and costs of the disease also have to be kept in mind. To name a few associated comorbidities, individuals with diabetes have a higher risk for heart disease and stroke, hypertension, blindness, kidney disease, and amputation. Therefore, it is not surprising that in 2007 the estimated total direct and indirect costs for diabetes in the United States reached \$174 billion; of this figure, direct medical costs were \$116 billion (Click on the PubMed ID number to read the article/abstract: [PMID 18308683](https://pubmed.ncbi.nlm.nih.gov/18308683/)).

These statistics, however, provide only national and state-level perspectives of our diabetes epidemic. A lack of adequate local data has impeded the progress of US diabetes prevention efforts. The majority of state and local health departments currently have no information available regarding the prevalence of undiagnosed diabetes in their communities. Such data can only be accessed at the national level through the National Health and Nutrition Examination Survey (NHANES). When public health policy is being determined, national data or averages provide an inadequate surrogate to determine a response at the local level, and the prevention and treatment of diabetes are essentially a local concern.

Examples do exist to demonstrate how local data can be used to stimulate policy and prevention efforts. For example, in 2006, BRFSS data showed that New Mexico's colorectal cancer screening rates were below national levels. Citing BRFSS data, which indicated better colorectal cancer screening rates in states with mandatory coverage, New Mexico's legislature passed a law requiring health insurance providers to cover colorectal screening for residents aged ≥ 50 years, joining 22 other states with mandatory coverage.

Local data on diabetes can be used similarly to stimulate action. An ideal system would not only track diagnosed

and undiagnosed diabetes, but also track efforts to monitor patient adherence to medication and whether patients are receiving adequate medical and follow-up care (such as eye exams and hemoglobin A1C testing). Such information could be organized by demographic and socioeconomic status and would empower providers and local health officials with tools to respond to the health needs of their communities.

Examples do exist to demonstrate that when such information is available, appropriate action can be undertaken. A good example is the Diabetes Prevention and Control Program (DPCP) implemented by the New York City Department of Health and Mental Hygiene (NYCDHMH). Acknowledging the large burden of chronic disease, the NYCDHMH conducted household surveys and determined that up to one third of New York City residents with existing diabetes were undiagnosed; furthermore, approximately one third of New York City residents were assessed as likely to have abnormal glucose metabolism. Following on this, the NYCDHMH designed diabetes prevention activities based on the data obtained ([PMID: 19114627](https://pubmed.ncbi.nlm.nih.gov/19114627/)). This registry requires clinical labs to share hemoglobin A1C reports; the information is then used for both surveillance and to design decision-support tools and resources for health care providers.

As this issue of *CADRE's Current Diabetes Practice* goes to press, health reform is getting a good deal of attention, and several plans have been proposed. As we discuss the details of providing every American with health insurance, we should make it a priority that steps are taken to ensure that patients are able to access adequate medical care and follow-up. Having insurance is important, but it needs to be coupled with incentives to encourage individuals to visit their physicians for preventive care, and not only when they are sick. In other words, health care reform needs to focus on prevention and not treatment alone. Our new plan should

Continued

also include the means to empower communities to achieve specific health goals. In addition, for clinicians to better care for patients, any health reform should ensure a mechanism to share medical records between providers.

Children are known for asking, “Are we there yet?” Most of the time, when parents are asked this question, they know exactly how long the trip will take. If our children were to ask the same question about diabetes control and prevention, what would our answer be? There are numerous barriers to overcome before we arrive. I hate to admit we have been “driving blindfolded” most

of the way. It is time to empower patients, healthcare providers, and public health professionals by providing them with the information they need to better perform their jobs. It is time to prevent and control diabetes.

Dr. Mokdad has no commercial relationships to disclose related to the content of this article.

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PRACTICE POINTERS

MANAGEMENT OF HYPERTENSION AND DYSLIPIDEMIA IN PRE-DIABETES

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More than 55 million adult Americans fulfill the diagnostic criteria for pre-diabetes. In primary care clinical settings, however, complete ascertainment of pre-diabetes is difficult because oral glucose tolerance testing is not routinely performed. It has therefore been suggested that the diagnosis of metabolic syndrome may serve as a “pre-diabetes equivalent” because it better predicts future diabetes mellitus (DM) risk than even pre-diabetes, and ~50% of individuals with impaired glucose tolerance, a largely undetected condition in clinical practice and more common than impaired fasting glucose (IFG), also have metabolic syndrome. (Click on the PubMed ID to read the article/abstract: [PMID: 18996826](https://pubmed.ncbi.nlm.nih.gov/18996826/))

Recently, a joint interim statement on the diagnosis of metabolic syndrome was

issued by the International Diabetes Federation (IDF) Task Force on Epidemiology and Prevention; American Heart Association (AHA); National Heart, Lung, and Blood Institute (NHLBI); World Heart Federation; International Association for the Study of Obesity; and International Atherosclerosis Society (Table 1) ([PMID 19805654](https://pubmed.ncbi.nlm.nih.gov/19805654/)). AHA/NHLBI and IDF waist circumference cut points for selected population groups include

- *Europeans, Mediterranean, Middle Eastern, Sub-Saharan African* (IDF):
≥37 in (≥94 cm) in men
≥31 in (≥80 cm) in women
- *Asian (including Japanese), ethnic Central and South American* (IDF):
≥35 in (≥90 cm) in men
≥31 in (≥80 cm) in women
- *United States* (AHA/NHLBI):
≥40 in (≥102 cm) in men
≥35 in (≥88 cm) in women

In over 8 years’ of follow-up of the Framingham Offspring study cohort, metabolic syndrome predicted a strikingly high excess risk of incident DM with hazard ratios of 6.9 in both men and women ([PMID 16275870](https://pubmed.ncbi.nlm.nih.gov/16275870/)). Although there is a lower comorbidity burden compared with those with DM, there is a higher burden/level of traditional cardiovascular disease (CVD) risk factors such as obesity, high blood pressure (BP), and dyslipidemia in pre-diabetes relative to individuals with normal glucose metabolism. Accordingly, pre-diabetes has been linked to increased risk of both premature mortality and CVD including left ventricular hypertrophy, albuminuria, and sudden death. Moreover, a substantial portion of the excess CVD risk with pre-diabetes is related to modifiable, nonglycemic risk factors. The augmented CVD risk

Continued

Table 1. Diagnostic criteria for metabolic syndrome

Measure (Any 3 criteria constitute diagnosis)	Categorical cut points
Increased waist circumference	Population- and country-specific definitions
Elevated triglycerides (TG)	≥150 mg/dL (≥1.7 mmol/L) OR drug treatment for elevated TG
Reduced high-density lipoprotein-cholesterol (HDL-C)	<40 mg/dL (<1.0 mmol/L) in men <50 mg/dL (<1.3 mmol/L) in women OR drug treatment for reduced HDL-C
Elevated blood pressure (BP)	≥130 mm Hg systolic BP OR ≥85 mm Hg diastolic BP OR drug treatment for hypertension
Elevated fasting glucose	≥100 mg/dL (≥5.6 mmol/L) OR drug treatment for elevated glucose

From Alberti, et al. *Circulation*. 2009;120:1640-1645.

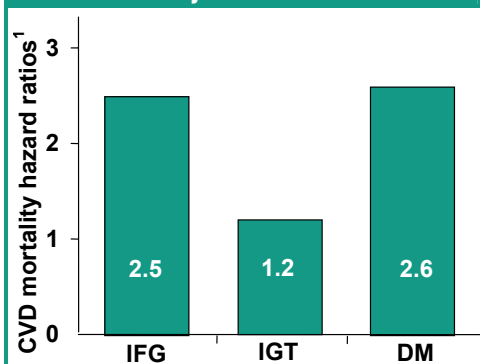
associated with IFG in the epidemiologic Australian Diabetes, Obesity, and Lifestyle Study (AusDiab) was similar to the level attributable to established DM (Figure 1) ([PMID 17576864](#)).

Clinical Trial Evidence

Most large-scale clinical trials of pharmacologic hypertension and lipid treatment do not assess glucose tolerance in eligible participants. Thus, clinical endpoint data regarding the benefits of such treatment in persons with pre-diabetes are not available and are unlikely to be forthcoming. Nevertheless, a consensus statement issued by the American College of Endocrinology/Association of Clinical Endocrinologists recommended that pre-diabetes should be considered a diabetes equivalent ([PMID 18996826](#)); accordingly, targets for BP (<130/80 mm Hg) and low-density lipoprotein cholesterol (LDL-C) (<100 mg/dL) were recommended to be identical to those for persons with DM.

There are, however, clinical endpoint data available from pharmacologic trials of hypertension and dyslipidemia treatment in persons with metabolic syndrome, a pre-diabetes equivalent. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) was a double-blind randomized clinical trial of four antihypertensive treatments in 42,418 men and women with hypertension plus one other risk factor for coronary heart disease (CHD). After 4 years of follow-up, patients with metabolic syndrome had similar CVD/CHD outcomes (including heart failure) in the chlorthalidone (a thiazide-like diuretic) and amlodipine (a dihydropyridine calcium antagonist) treatment groups; however, compared with lisinopril (an angiotensin-converting enzyme inhibitor), chlorthalidone was more effective in preventing heart failure and combined CVD ([PMID 18000186](#)). The incidence of DM (fasting glucose >126 mg/dL) over this same time frame in the chlorthalidone, amlodipine, and lisinopril groups, respectively, was 17.1%, 16.0%, and 12.1% ($P<0.05$ versus chlorthalidone). Systolic BP lowering was slightly greater with chlorthalidone

Figure 1. Hazard ratios for CVD mortality according to categories of abnormal glucose metabolism: the AusDiab study



¹Adjusted for age, sex, previously reported CVD, smoking, diastolic blood pressure, waist circumference, lipid-lowering medication, and total cholesterol:high-density lipoprotein cholesterol ratio.

AusDiab: Australian Diabetes, Obesity, and Lifestyle Study; CVD: cardiovascular disease; DM: diabetes mellitus; IFG: impaired fasting glucose; IGT: impaired glucose tolerance

Adapted from Barr ELM, et al. *Circulation*. 2007; 116:151-157.

versus amlodipine (1.4 mm Hg in blacks, 0.8 mm Hg in non-blacks) and also versus lisinopril (4 mm Hg in blacks, 0.4 mm Hg in non-blacks) ([PMID 18227370](#)).

Statins have been shown to favorably affect the atherogenic lipid profile (elevated triglycerides and apolipoprotein B; small, dense LDL-C; and reduced high-density lipoprotein cholesterol [HDL-C]) in persons with metabolic syndrome. These agents lower triglycerides, reduce LDL-C, and raise HDL-C levels. Moreover, in metabolic syndrome patients, statin therapy has been shown to slow the progression of angiographically proven CHD as well as reduce the incidence of clinical CHD events in both the setting of known coronary atherosclerosis and during the immediate postevent time frame following acute coronary syndromes ([PMID 16186288](#)).

Target BP and Lipoprotein Levels

There are insufficient clinical trial data to definitively identify the optimal levels of BP, LDL-C, or HDL-C/triglyceride control in pre-diabetes. Nevertheless, in the absence of explicit clinical trial

endpoint data, it is *prudent* to adopt the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7), the American Diabetes Association, the International Society on Hypertension in Blacks (ISHIB), and the American Heart Association target BP levels for individuals with diabetes (<130/80 mm Hg). Patients with pre-diabetes will likely require multiple antihypertensive drugs to persistently lower BP below this target—this is because these individuals will typically manifest high rates of obesity and pressure-related target-organ injury, both of which confer resistance to the BP-lowering effects of pharmacologic agents.

It is also quite logical to adopt for persons with pre-diabetes the lipid treatment goals of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (NCEP ATP III) for persons with diabetes. That is, use an LDL-C <100 mg/dL as the primary therapy target, and in persons with serum triglycerides >200 mg/dL, use a secondary target of non-HDL-C (total cholesterol minus HDL-C) of 30 mg/dL *higher* than the LDL-C goal. Very high-risk patients, with multiple CVD risk factors, have an *optional* LDL-C goal of <70 mg/dL.

Therapeutic Strategies

Multifactorial dietary and lifestyle modifications should be encouraged in all patients with pre-diabetes. These interventions include reducing overall body weight (if overweight), decreasing sodium (<2 g/day), and emphasizing sources of potassium, calcium, and fiber while reducing saturated fat, as well as limiting alcohol intake to ≤2 drinks/day for men and ≤1 drink/day for women, and encouraging aerobic exercise with the goal of normalizing body weight over the long-term. Recommendations from the widely accepted Dietary Approaches to Stop Hypertension (DASH) diet include: increasing intake of fruit and vegetables to four to five servings of each per day, choosing whole grains that are good sources of fiber, and eating two to three servings of low-fat dairy products (good sources of

Continued

calcium) daily. Recent evidence suggests that maintenance of adequate dietary calcium consumption may aid in weight loss. It is important to maintain these dietary and lifestyle modifications even after initiation of drug therapies.

Hypertension

Based on the high risk of CVD in hypertensive patients with metabolic syndrome, the ISHIB issued the only hypertension guidelines thus far to recommend a low therapeutic target BP (<130/80 mm Hg) for persons with metabolic syndrome ([PMID 12622600](#)). Once the decision to treat is made, the next major consideration is which drug(s) will be needed to gradually lower BP persistently below target levels. A good rule of thumb is, when BP is above goal by 15 mm Hg systolic and/or 10 mm Hg diastolic, to consider initiation of treatment with two drugs proven effective in combination to lower BP, rather than a single agent. Practitioners treating patients with pre-diabetes should preferentially utilize renin angiotensin system (RAS) blockers, angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers, as is done in antihypertensive therapy in persons with DM. In most situations, this will ensure that one of these agents is included in the likely multidrug regimen that will be needed to control BP. In untreated patients who are <15/10 mm Hg above their goal BP (ie, BP <145/90 mm Hg), a RAS blocker should be used as the initial antihypertensive therapeutic agent. Up-titration of anti-hypertensive drug(s) should occur approximately once every 4 weeks if BP remains above target. Logical add-on drug classes are diuretics and/or calcium antagonists. When used with RAS blockers, the hyperglycemic, as well as potassium-lowering, effects of diuretics are prevented/markedly attenuated. Thus, considerations of these potential diuretic-related metabolic side effects should not preclude their use.

Dyslipidemia

The statin drug class will be the primary means to achieve LDL-C goals. Atorvastatin, rosuvastatin, and simvastatin all significantly lower triglycerides and

modestly raise HDL-C. If add-on therapy is needed for additional triglyceride control or to lower non-HDL-C levels, then fenofibrate, omega-3 fatty acids, or, alternatively, niacin may be added to statin therapy. Gemfibrozil, however, should not be added to statins because of an unacceptable risk of myopathy attributable to the inhibition of the glucuronidation pathway involved in statin metabolism, leading to raised statin levels. The most common patient-reported side effect with statins is myalgia; however, unless the burden of discomfort is atypical, this does not usually necessitate discontinuation. If necessary, up-titration of statin therapy should occur about every 6 weeks. Modest liver function test (LFT) and/or creatine phosphokinase (CPK) abnormalities should not trigger

The metabolic syndrome is considered by some to be a pre-diabetes equivalent.

premature discontinuation of statins; statin therapy should, however, be re-evaluated and/or discontinued if LFTs rise to ≥ 3 -fold or if CPK rises to ≥ 5 - to 10-fold of normal.

Conclusions

The approach to treating both BP and dyslipidemia in persons with pre-diabetes is recommended to be identical to the treatment of these risk factors in DM. The metabolic syndrome, more easily diagnosed in clinical practice than complete ascertainment of pre-diabetes, is considered by some to be a pre-diabetes equivalent. Effective management of nonglycemic risk factors is an integral step in protecting individuals with pre-diabetes from micro- and macrovascular complications as well as organ failure (eg, heart failure).

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and Novartis; and is on the speaker bureau for Daiichi Sankyo, Novartis, and Pfizer.

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LITERATURE CORNER

IS FRUCTOSE IN BEVERAGES A PROBLEM IN DIABETES AND OBESITY?

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Dietary fructose is the molecule that makes the fruit we eat sweet. From an evolutionary perspective, this “sweetness” was a good guide to humans that the food had other important nutritional vitamins, minerals, and fiber. Fructose is also present in table sugar as well as in high-fructose corn syrup (HFCS).

Fructose has, from time to time, been recommended for people with diabetes because it is sweet and has a very low-glycemic index (Table 1), as it is primarily metabolized by the liver before being converted to glucose. Fructose does not stimulate insulin secretion because, among other reasons, β -cells do not have the necessary transporter (GLUT-5). For the same reason, fructose does not readily enter other tissues. A potential disadvantage of fructose is that, within the liver, it becomes the backbone of triglyceride more readily than does glucose.

Recently, questions have been raised about fructose, stemming as much from obesity as from diabetes. Fructose, from sucrose or HFCS, is used to sweeten soft drinks, fruit drinks, sport drinks, and many other food items. The high consumption of these beverages in the United States has led to an increase in the daily intake of fructose (Figure 1) and has been implicated as one factor in the epidemics of obesity and diabetes.

Obesity has become an epidemic problem, and diabetes has followed in its wake. Both adults and children are developing type 2 diabetes mellitus in increasing numbers in the United States and worldwide. Recent National Health and Nutrition Examination Survey

(NHANES) data showed that the prevalence of obesity in children has continued to rise and is now 18%; the prevalence of diabetes has also risen.

Storage of extra fat in the body requires the intake of more food energy over time than is needed—thus, any form of energy we ingest may play a role in the development of obesity and may enhance the risk of diabetes. The possibility that calorie-containing beverages might have a strong relationship to the development of obesity was highlighted in a paper that showed that the growing use of HFCS between 1970 and 1990 paralleled the rising prevalence of obesity in the period between 1970 and 2000 (Click on the PubMed ID number to read the article/abstract: [PMID 15051594](http://pubmed.ncbi.nlm.nih.gov/15051594/)).

Acute Studies

The effect of single doses of fructose versus glucose on energy expenditure, serum lipids, and blood pressure has been examined in several studies. From these studies, it is clear that fructose increases thermogenesis more than glucose, increases triglycerides, and increases blood pressure.

In one study, a 75-g oral load of glucose or fructose was given to 17 healthy volunteers and their metabolic changes

Table 1. Glycemic index (GI) of selected sweeteners

The GI compares a food's postprandial glucose response to an equivalent amount of a control carbohydrate (usually glucose or white bread).

Sweetener	GI
Fructose	15
Lactose	47
Honey	61
High-fructose corn syrup	63
Sucrose	65
Glucose	103

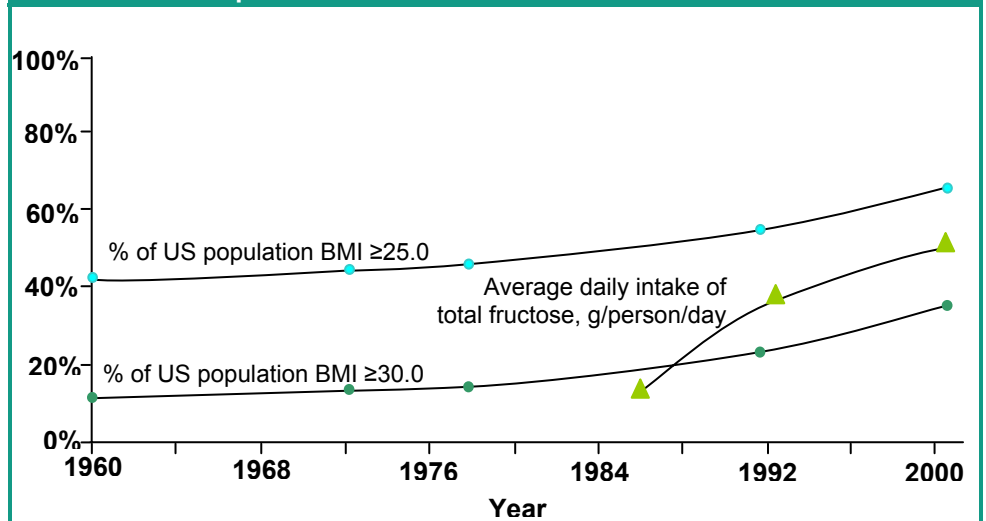
From Atkinson FS, et al. *Diabetes Care*. 2008;31:2281-2283 and online appendix, and <http://www.mendosa.com/gilists.htm> (both accessed August 12, 2009).

followed for 4 hours. Fructose stimulated oxygen consumption to a greater degree than glucose but produced a much smaller stimulation of insulin. It also increased the respiratory quotient more than glucose, a finding that might imply increased de novo lipogenesis. Blockade of the sympathetic nervous system with propranolol, a β -adrenergic blocking drug, reduced oxidation of both fructose and glucose by about 40%.

A second study ([PMID 19208729](http://pubmed.ncbi.nlm.nih.gov/19208729/)) evaluated the effect of fructose on lipids. Obese volunteers (9 male, 8 female;

Continued

Figure 1. Increases over time in percentage of US population that is overweight (BMI ≥ 25.0 kg/m²) or obese (BMI ≥ 30.0 kg/m²), and total fructose consumption



BMI data from National Health and Nutrition Examination Survey (NHANES) published reports; fructose intake from Glinsmann WH, et al. *J Nutr*. 1986;116:S1-216; Park YK, Yetley EA. *Am J Clin Nutr*. 1993;58:737S-747S; and Marriott BP, et al. *J Nutr*. 2009;139:1228S-1235S.

BMI >30 kg/m²) were admitted for a 24-hour crossover study in which mixed nutrient meals, with 30% of total calories from fructose- or glucose-sweetened beverages, were provided. Periodic blood samples were drawn to measure insulin, leptin, and triglyceride areas under the curve. The rise in plasma glucose was lower after fructose, but the rise in triglycerides and lactate larger. Insulin and leptin both showed less response to fructose than to glucose.

Another study of fructose in healthy volunteers (8 male, 8 female) used a hyperglycemic clamp to assess the metabolic effects of a 6-day fructose overfeeding. Each subject underwent a control test and then a repeat test supplemented with 3.5-g fructose/kg fat-free mass/day for 6 days. The short-term fructose overfeeding produced hypertriglyceridemia and hepatic insulin resistance in men but small or no responses in women (PMID 18332156).

Finally, the blood pressure response to fructose was examined in a randomized crossover study of 15 healthy, normal weight volunteers (9 male, 6 female). Each subject participated in all three study arms: water, water containing 60-g glucose, or water containing 60-g fructose. Each drink contained 10-mL lemon juice for uniform taste and had distilled water added for a total of 500 mL. Blood pressure, metabolic rate, and autonomic nervous system activity were measured for 2 hours following each drink. Fructose administration was associated with an increase in both systolic and diastolic blood pressure; blood pressure did not rise following ingestion of either glucose or water (PMID 18199590).

Intermediate-Length Studies

Two 10-week studies investigated the metabolic effects of sweeteners. First, a parallel-arm study examined the difference on body weight in response to sucrose and artificially sweetened beverages in 41 overweight adults (6 male, 35 female; BMI 25 to 30 kg/m²). One group (n=21) received sucrose-containing beverages and foods (averaging 813 calories and 152 g of

sucrose/day); the other 20 received beverages and foods sweetened with aspartame (averaging 240 calories and 0-g sucrose/day). In addition to the assigned consumption, subjects were free to eat until they felt pleasantly satisfied and instructed to keep dietary records. During weeks 0, 5, and 10, 24-hour urine collections were taken. After 10 weeks, the subjects who consumed relatively large amounts of sucrose (~28% of calories) had increased energy intake, body weight, fat mass, blood pressure, and inflammatory activity (Table 2) (PMID 12324283, 16087988).

In another study, fructose and glucose were separately compared. Following a 2-week inpatient baseline phase with an energy-balanced diet (15% protein, 30% fat, 55% carbohydrate), participants (16 male, 16 female; BMI 25 to 35 kg/m²) entered an 8-week outpatient intervention and were assigned to consume either fructose-sweetened (n=17) or glucose-sweetened (n=15) beverages that provided 25% of their energy requirements, along with self-selected ad libitum diets. They then returned for a final 2-week inpatient phase where the assigned beverages were continued as part of the energy-balanced diet. Visceral fat increased by 14.0% in the fructose-consuming group compared with about 3.2% in

the glucose group, with no significant change in body weight or subcutaneous fat. De novo lipogenesis increased and postprandial triglycerides (particularly nocturnal) increased with fructose, but not glucose, consumption (PMID 19381015).

Meta-analyses of Beverage Consumption

A number of meta-analyses have been published on the effect of soft-drink consumption on changes in energy intake or body weight.

Vartanian and colleagues examined 88 studies of sweetened soft drink beverages (HFCS is the sole sweetener in most US soft drinks) (PMID 17329656). The researchers noted that

- There was a consistent link between soft drink intake and increased energy consumption: 10 of 12 cross-sectional studies, 5 of 5 longitudinal studies, and all 4 of the long-term experimental studies examined showed an increase in energy intake concurrent with increased soft drink consumption.
- Cross-sectional and longitudinal studies showed only small positive associations between soft drink consumption and BMI; however, a moderate effect size ($r = 0.24$) was observed for experimental studies

Continued

Table 2. Effect of 10 weeks of elevated sucrose versus artificial sweetener* consumption

	Sucrose (n=20)	Artificial sweetener (n=21)
Energy intake	+384 calories/d	-105 calories/d ($P=0.03$)
Sucrose intake	27% of calories	4% of calories ($P=0.0001$)
Protein intake	-3 g/d	No change
Carbohydrate intake	+93 g/d	-12 g/d ($P=0.0001$)
Fat intake	No change	-7 g/d
Body weight	+1.6 kg	-1.0 kg ($P<0.001$)
BMI	+0.5 kg/m ²	-0.4 kg/m ² ($P<0.001$)
Physical activity	-0.4 h/wk	+0.1 h/wk
Blood pressure	+3.8/4.1 mm Hg	-3.1/1.2 mm Hg ($P<0.01, 0.05$)
Haptoglobin	+13%	-16%
Transferrin	+5%	-2%
C-reactive protein	+6%	-26%

* 54% from aspartame, 22% from acesulfame K, 23% from cyclamate, and 1% from saccharin.

Adapted from Raben, et al. *Am J Clin Nutr.* 2002;76:721-729.

that controlled for multiple extraneous variables.

- Increased soft drink intake was related to decreased consumption of milk and calcium, but mean effect sizes were small. One study showed that a 1-oz decrease in soft drink intake increased milk intake by 0.25 oz. In cross-sectional, longitudinal, and longer-term experimental studies, increased soft drink intake was also related to a higher carbohydrate intake and a lower intake of fruit, dietary fiber, and variety of macronutrients.

Two other meta-analyses of studies of calorically sweetened beverages are noteworthy. Olsen and Heitmann ([PMID 18764885](#)) reported that most prospective studies reviewed found a positive association between beverage intake and obesity, while three experimental studies found positive effects between intake and body fat changes. The authors concluded that a high intake of sweetened beverages is a determinant for obesity.

Most prospective studies found a positive association between beverage intake and obesity.

Finally, Forshee and associates ([PMID 18541554](#)) reviewed two prospective and eight longitudinal studies of calorically sweetened beverage intake in children and found that the association between intake and BMI changes approached zero (0.004); although this change/day was very small, converting it to an annual change of 1.46 BMI potentially provides adequate information to explain much of the current epidemic of childhood obesity.

Conclusion

Both fructose/HFCS and sucrose in the diet appear to be related to a number of health concerns. In addition to the issues already discussed, there is a report that consumption of calorically sweetened soft drinks is associated with the metabolic syndrome and also

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with gout in men; further, there is a suggestion that it is associated with development of diabetes.

There are several potential mechanisms for these effects of fructose from either HFCS or sucrose.

- Inadequate reduction in total caloric intake when calorie-sweetened beverages are ingested has been proposed as part of the mechanism for increased energy intake and obesity. In acute feeding studies, calorically sweetened beverages failed to reduce energy intake.
- The metabolic pathway for fructose may account for the observed increase in de novo lipogenesis and higher triglycerides—fructose is metabolized primarily in the liver where it is converted to fructose-1-phosphate (which can readily become a substrate for the backbone of the triglyceride molecule).
- The metabolism of fructose in the liver generates adenosine 5'phosphate, a substrate for conversion to uric acid through a process that alters nitric oxide generation. The enhanced production of uric acid by the liver may contribute to any association that exists between cardiovascular disease and elevated uric acid levels.

A rising tide of consumption of calorically sweetened beverages provides an increasing amount of dietary fructose to US residents. Based on my review of the literature, I conclude that, in the amounts now ingested, this added

fructose (in the form of HFCS or sucrose) is likely to be hazardous to the health of some people.

Dr. Bray has no commercial relationships to disclose related to the content of this article.

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DIABETES TACTICS

CAN LIFESTYLE INTERVENTION TRUMP GENETIC RISK FOR TYPE 2 DIABETES?

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Case Presentation

At 48 years of age, Bob learned he had impaired glucose tolerance, or pre-diabetes. His identical twin brother had been diagnosed with type 2 diabetes mellitus (T2DM) 3 years earlier. Based on this, Bob's doctor told him he was highly likely to develop diabetes within 5 years because the brothers had the same genes. Bob decided to join the Diabetes Prevention Program (DPP) because he wanted to do everything possible to prevent diabetes.

When Bob joined the DPP, he was 5 feet 10 inches tall and weighed 200 lb (BMI 28.7 kg/m²). He was excited to learn he was randomly assigned to the lifestyle intervention program and that his goals would be to lose 7% of his body weight (to ≤186 lb) and increase

his activity to at least 150 minutes per week. He rated his motivation to change his lifestyle at a "9" out of "10" and his self-confidence to do so at a "5" out of "10" (the latter because he had never been on a weight loss program before).

Bob's wife attended most of his individual coaching sessions to learn how she could support him. Based on his initial weight, he was assigned goals of 42 g fat/day and 1500 calories/day (Table 1). At first, Bob and his wife found keeping food records and learning about the sources of fat and extra calories in their diet to be time-consuming. They also found it difficult to adjust the traditional Italian recipes they enjoyed. With practice, feedback, and support, Bob found he could change his eating habits and lose weight while still enjoying his favorite foods. Over time, he found that the process became easier, and the lifestyle changes became his new eating routine.

After 6 months in the DPP, Bob had lost 15.5 lb (a weight of 184.5 lb) and was exercising 200 to 400 minutes per week. For the remainder of the program, he continued to have individual follow-up visits every 4 to 6 weeks but did not attend any of the group classes offered. Over the next 3 years, Bob's weight remained between 182 and 186 lb, and his activity level remained over 200 minutes per week.

Table 1. DPP lifestyle intervention fat and calorie goals

Starting weight (lb)	Fat goal (g)	Calorie goal
120-170	33	1200
175-215	42	1500
220-245	50	1800
250-300	55	2000

From the Diabetes Prevention Program (DPP) Research Group. *Diabetes Care*. 2002;25:2165-2171.

At study end, Bob weighed 184 lb (BMI 26.4 kg/m²). When he was debriefed on his results, he learned that, after 4 years of lifestyle intervention, he had reverted to normal glucose tolerance based on both fasting and 2-hour blood glucose (BG) criteria at that time (Table 2).

During the DPP Outcomes Study (the DPP continued follow up), Bob participated in study visits every 6 months and met with a lifestyle coach once or twice a year; he continued to decline the group programs offered. His weight gradually increased to a range of 192 to 197 lb (1.5% to 4% weight loss from baseline). His activity level was ~150 minutes/week, mainly through jogging and walking. He was on a statin for lipid lowering prior to the DPP and currently takes simvastatin 20 mg, omeprazole 20 mg for gastroesophageal reflux disease, and ramipril 5 mg for blood pressure (BP) control.

Continued

Table 2. Bob's vital statistics

Visit	Weight (lb)	FPG (mg/dL)	2-h BG (mg/dL)	A1C (%)	TC (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	TG (mg/dL)	BP (mm Hg)
Baseline	200	112	157	5.2	225*	146*	33*	228*	113/69
6 mo	184	94	—	5.2	174	98	41	171	120/69
1 y	183	100	117	4.0	153	90	39	118	112/74
2 y	182	93	119	5.1	162	96	37	141	118/78
3 y	185	108	119	5.2	202	129	38	173	127/84
4 y (study end)	184	103	117	5.4	216	140	36	195	121/72
5 y	182	111	142	5.2	163	105	42	76	125/76
6 y	185	99	142	5.5	142	85	35	103	119/68
7 y	192	112	158	5.2	190	122	42	132	124/79
8 y	193	107	188	5.2	170	85	37	241	121/82
9 y	197	115	143	5.1	162	84	38	199	107/72
10 y	192	108	170	5.1	170	105	47	91	128/79
11 y	196	109	150	5.3	170	101	45	118	131/72 [#]
12 y	192	108	196	5.2	191	91	38	310	119/72

BP: blood pressure; FPG: fasting plasma glucose; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides; 2-h BG: 2-hour blood glucose post-oral glucose tolerance test

* Lipid-lowering medication at baseline

[#] Started blood pressure-lowering medication prior to this visit

Bob is now 60 years of age. He has delayed diabetes for 15 years beyond his identical twin brother; however, he realizes his recent BG levels are close to the diabetes range and his triglyceride levels are too high. His most recent weight was 192 lb. To further delay diabetes, he is committed to re-focusing on his activity level and losing weight back to his 7% goal of ≤ 186 lb.

Analysis

This case demonstrates the powerful effect of *modest* lifestyle changes on reducing risk for progression to T2DM. DPP results showed that lifestyle intervention aimed at 7% weight loss and 150 minutes of weekly activity was associated with a 58% reduction in diabetes risk (click on the PubMed ID to read the article/abstract: [PMID 11832527](https://pubmed.ncbi.nlm.nih.gov/11832527/)). Mean weight loss for lifestyle intervention participants was 4.5 ± 7.6 kg (~ 10 lb) or $4.9 \pm 7.4\%$ of initial body weight, and the mean activity level was 227 ± 212 minutes/week ([PMID 16936160](https://pubmed.ncbi.nlm.nih.gov/16936160/)). Bob's weight loss and activity exceeded these averages during the DPP, and in the long-term follow-up he sustained weight losses between 1.5% and 4% without yet converting to diabetes.

This case also illustrates that *modest* lifestyle changes can modify or trump the expression of high-risk diabetes genes. DPP research has shown that lifestyle intervention participants who had the transcription factor gene TCF7L2, which is associated with susceptibility to T2DM due to impaired β -cell function, did not develop diabetes at the same rates as metformin or placebo group participants with the same high-risk gene ([PMID 16855264](https://pubmed.ncbi.nlm.nih.gov/16855264/)). At 1 year, the lifestyle intervention participants also had the greatest improvements in insulin sensitivity and β -cell function compared with metformin and placebo group participants ([PMID 16046308](https://pubmed.ncbi.nlm.nih.gov/16046308/)). These results suggest that lifestyle intervention can mitigate the risk conferred by genetic background. Bob's lifestyle changes have thus far prevented/delayed T2DM, despite his strong genetic predisposition.

This case further demonstrates that without follow-up and accountability, there

is a tendency to regain weight, and that weight regain is associated with increases in BP, lipids, and BG levels. DPP data demonstrated that among the three treatment groups, those who progressed from normal glucose tolerance toward diabetes trended toward higher BP and triglycerides and lower high-density lipoprotein cholesterol and low-density lipoprotein peak particle density compared with those who had improved glucose tolerance. Bob's results demonstrate this pattern, as his most recent 2-hour BG was 196 mg/dL and his triglycerides bumped up to 310 mg/dL. He was also started on a medication for BP just prior to his 11-year follow-up visit, when his weight regain was at its highest (Table 2).

Recommendations

We now understand that compared with placebo, metformin 850 mg twice daily can reduce the risk of developing diabetes by 31%, while lifestyle intervention aimed at a 7% weight loss combined with 150 minutes of weekly activity can reduce that risk by 58%. In the DPP, the effectiveness of a modest lifestyle change was approximately double that of the medication intervention. The 7% weight loss goal was achieved by 49% of lifestyle participants at the end of the first 6 months and 37% of participants at study end when follow-up was less frequent. Even in those who did not achieve the weight loss goal, there was a 16% reduction in risk of developing diabetes for every kilogram of weight loss achieved. Moreover, lifestyle participants who did not meet the weight loss goal at year 1, but achieved the physical activity goal of 150 minutes of brisk activity per week, had a 44% lower incidence of diabetes. This case and these research results can help health care providers tailor treatment goals and expectations for patients at risk for developing diabetes.

Take-Home Messages

- In patients at risk for diabetes or who have pre-diabetes, it is important to convey that having a strong family history of T2DM does not mean they are fated to develop the

disease, if they are willing to commit to a lifestyle change program.

- Losing as little as 8 to 10 lb may be sufficient to reduce risk of developing T2DM.
- If a patient is not ready to lose weight or does not experience immediate success with weight loss, then encouraging increased activity may confer some diabetes prevention benefits. Adding activity bouts of 10 minutes at a time can help most people feel that increasing their activity is doable.
- Once a patient loses weight and increases activity, it is critical that he or she self-monitors weight and activity so that weight gain trends can be reversed immediately before discouragement develops.
- Patients need to understand that ongoing follow-up and support are critical to sustain behavior changes and maintain weight loss. A dietitian or lifestyle coach can provide the necessary follow-up and support so that patients receive the reinforcement and accountability they need to sustain progress over time.

For further information on the Diabetes Prevention Program lifestyle session, materials, and learning objectives, see <http://www.bsc.gwu.edu/dpp/manuals.html/vdoc>.

Ms Delahanty is a consultant for Eli Lilly, Pfizer Inc, and Tethys Bioscience, Inc.

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