Evidence for the Prevention of Type 2 Diabetes Mellitus

Jay H. Shubrook, DO; William Chen, DO; Alegria Lim, OMS IV

From the Touro University California College of Osteopathic Medicine in Vallejo.

Disclaimer: Dr Shubrook, a *JAOA* associate editor, was not involved in the editorial review or decision to publish this article.

Financial Disclosures: None reported.

Support: None reported.

Address correspondence to Jay H. Shubrook, DO, 1310 Club Dr, Mare Island, Vallejo, CA 94592-1187.

Email: jay.shubrook@tu.edu

Submitted February 26, 2018; revision received May 28, 2018; accepted July 2, 2018.

Type 2 diabetes mellitus (T2DM) is a common chronic metabolic condition. Before receiving this diagnosis, persons typically have a long period of prediabetes. There is good evidence that T2DM can often be prevented or delayed by means of lifestyle interventions (39%-71%), medications (28%-79%), or metabolic surgery (75%). However, despite consistent data demonstrating their efficacy, these tools are underused, and knowledge about them among primary care physicians is limited. In an effort to engage physicians in addressing this public health crisis more effectively, the authors reviewed the evidence that T2DM can be prevented or delayed in persons at risk.

J Am Osteopath Assoc. 2018;118(11):730-737
doi:10.7556/jaoa.2018.158

Keywords: bariatric surgery, lifestyle medicine, obesity, prediabetes, type 2 diabetes mellitus

Obesity and obesity-related diseases have reached epidemic proportions in the United States. It is estimated that more than 70% of adults are overweight or obese.[1] In 2017, the Centers for Disease Control and Prevention reported that if the trend continues, more than half of children today will become obese as adults.[2] We expect, therefore, that the obesity epidemic will continue into the foreseeable future, along with many chronic diseases. Type 2 diabetes mellitus (T2DM) is a common metabolic complication of obesity in the United States.[3] It is therefore not surprising that, in 2016, nearly 1 in 10 adults in the United States had diabetes.[3] Furthermore, 1 in 3 adults and 1 in 2 older adults (>65 years) had prediabetes.[3] If nothing changes, it is predicted that, by 2050, 1 in 3 people in the United States will have diabetes.[4]

The American Association of Clinical Endocrinologists (AACE) and the American Diabetes Association (ADA) state that screening for diabetes and prediabetes is critically important because prediabetes has no classic signs or symptoms; without effective screening programs, persons with prediabetes are unlikely to take the necessary steps to prevent progression to T2DM. Without knowledge of their prediabetes status, people not only miss out on the opportunity to delay or prevent progression of the disease, but they also put themselves at risk for diabetes-related complications. There are simple and affordable tests that can be used for screening, and there is enough time between the appearance of risk factors and disease development to make such screening an effective tool for prevention. There is strong evidence that T2DM can be prevented or delayed in persons at risk.[5]

Evidence for Prevention or Delay of T2DM

Lifestyle Interventions

Several randomized controlled studies have evaluated the effects of lifestyle intervention compared with placebo to prevent or delay the progression of prediabetes to T2DM

Table 1.
Lifestyle Interventions to Prevent or Delay Type 2 Diabetes Mellitus

Study	Country	Patients, No.	Baseline BMI	Intervention Period, y	RRR, %	NNT
The DPP Research Group (DPP)[6,7]	United States	3234	34.0	2.8	58	21
Eriksson et al (DPS)[8]	Finland	523	31	4	39	22
Pan et al (Da Qing)[9]	China	577	25.8	6	51	30

Abbreviations: BMI, body mass index; DPP, Diabetes Prevention Program; DPS, Diabetes Prevention Study; NNT, number needed to treat; RRR, relative risk reduction.

(Table 1).[6-9] Common lifestyle interventions include a focus on nutrition and increases in physical activity to ultimately achieve a weight-loss goal. The programs prioritized providing a supportive group environment to help participants reach their goals. Follow-up studies[10-12] showed that many participants continued to benefit from overall decreased rates of progression to T2DM several years after starting the interventions.

In the US National Diabetes Prevention Program (NDPP), 3200 participants were randomly assigned to routine care, metformin treatment, or an intensive lifestyle intervention.[6] The lifestyle intervention focused on reducing caloric intake by reducing fat calories and increasing physical activity to a goal of at least 150 minutes per week to achieve a mean goal of 7% weight loss. By creating a constant, regular, and supportive group environment, the NDPP helped participants continuously rethink their choices regarding peer support in the prevention of diabetes. Results showed that the incidence of T2DM was reduced by 58% in the lifestyle intervention group, by 31% in the metformin group, and by 17% in the routine care group, after an average of 2.8 years.[6] A 10-year follow-up study reported a 34% decreased incidence of diabetes in the original NDPP group and an 18% decrease in the metformin group.[9]

In Finland, the Diabetes Prevention Study investigated the role of an individualized lifestyle intervention in the prevention of T2DM.[7] The treatment goals included the following: weight reduction of at least 5% relative to baseline, specific dietary modifications (total fat <30% and saturated fat <10% of total calories, dietary fiber intake of 15 g/1000 kcal), and at least 4 hours per week of physical activity. The sessions included visits with a nutritionist as well as supervised gym exercise sessions (free to participants). More than 500 people participated in the study.[7] Seven years after the original study was conducted, a follow-up study[11] revealed a 43% relative risk reduction for new-onset T2DM in the intervention group. A median follow-up of 9 years after the original study showed a 38% relative risk reduction for diagnosed T2DM in the intervention group.[11] Lifestyle interventions in this study were implemented with group sessions that provided individualized support from nutritionists and dieticians. Participants were encouraged to reach out to familial and peer support groups to help maintain the lifestyle changes gained throughout the study.

In China, the Da Qing study[9] analyzed more than 500 men and women with prediabetes from local clinics to study the effects of diet, exercise, or both. The diet intervention groups focused on increasing vegetable intake while lowering alcohol, sugar, and caloric intake. The exercise intervention group focused more on increasing physical activity during otherwise leisure time. At the end of the 20-year follow-up, those assigned to a lifestyle intervention group had a 43% lower incidence of diabetes than those with no intervention.[12] On average, the onset of diabetes was delayed by an average of 3 to 6 years.[12] The 23-year follow-up in the Da Qing study[13] showed a lower

mortality rate in the lifestyle intervention group compared with the placebo group: 28.1% vs 38.4%, respectively.[13] Overall, these studies corroborate the claim that a peer-supported lifestyle intervention is highly successful in preventing T2DM and its consequences.

Medications

Numerous medications have been studied for their effectiveness in preventing or delaying the onset of T2DM, with many showing decreased morbidity rates.[9,14-18] However, only metformin and metabolic surgery have been studied sufficiently to show a decrease in mortality rate.[9,19] To date, metformin has been the most-studied medication for at-risk populations. Metformin was less effective than lifestyle interventions but still showed a substantial decrease in the incidence of T2DM at 10 years (18% decrease compared with placebo). This finding shows that metformin may not merely be treating patients with diabetes earlier in the disease spectrum but may also provide legacy benefits beyond the treatment period.[9] Metformin was most effective in younger and obese populations, as well as in persons with gestational diabetes mellitus, and less effective in older and nonobese populations. The additional benefits of metformin are well documented and include reduced levels of fasting plasma glucose, low-density lipoprotein, and triglycerides; modest weight loss; and increased high-density lipoprotein cholesterol levels.[20-22]

A number of other pharmaceutical interventions have been effective in reducing new-onset T2DM. α-Glucosidase inhibitors inhibit the enzymes that degrade carbohydrates into simple sugars. The Study to Prevent NIDDM (non–insulin-dependent diabetes mellitus) showed that the use of acarbose reduced new-onset T2DM by 25% (relative hazard, 0.75; 95% CI, 0.63-0.90; P=.0015).[14] Furthermore, acarbose also significantly increased the likelihood that impaired glucose tolerance would revert to normal glucose tolerance (P<.001).[14] Another short-term study (<1 year) demonstrated that voglibose was associated with a decrease in the incidence of T2DM compared with placebo (5.6% vs 12.0%, respectively).[23] A third study using acarbose was unable to reproduce the same findings in terms of T2DM prevention or delay.[24]

Thiazolidinediones (troglitazone, rosiglitazone, and pioglitazone) are peroxisome proliferator–activated receptor ɣ nuclear transcription gene promoters that increase insulin sensitivity and levels of adiponectin through glucose regulation and fatty acid breakdown. Troglitazone, the first available drug in this class, was shown in the Troglitazone in the Prevention of Diabetes study[25] to reduce new-onset T2DM by 65% in Hispanic women with a history of gestational diabetes. This study was terminated early when troglitazone was taken off of the market because of hepatic toxicity. More recently, rosiglitazone was shown to have strong clinical significance in decreasing the incidence of T2DM by 50.5% compared with 30.3% in the placebo group.[16] Pioglitazone also showed strong clinical significance, with conversion to normoglycemia in 48% of patients, compared with 28% in the placebo group.[15] The lasting positive benefits from thiazolidinediones after discontinuation of treatment differ between rosiglitazone and pioglitazone. Even 5 years after treatment was discontinued, the cumulative incidence of T2DM continued to be lower in the pioglitazone than in the placebo group (10.7% vs 22.3%); in contrast, rosiglitazone conferred no significant lasting clinical benefit after its discontinuation.[26,27]

The benefits of these medications are offset by their adverse effects, including weight gain and fluid retention leading to edema or worsening heart failure. Women of childbearing age must use effective contraception, because these agents are teratogenic. These adverse effects should be considered before starting thiazolidinedione treatment. However, a 2016 review suggested that the increased incidence of heart failure with thiazolidinediones is probably due to the exacerbation of existing heart failure and not new-onset heart failure.[28] Considering all of these data, pioglitazone seems to be effective in reducing the incidence of new-onset T2DM during its use and continues to have a legacy effect even after its discontinuation.

Pioglitazone may therefore be the most effective agent for preventing T2DM, and the protection it affords seems to be even stronger in older adults.[27]

Two categories of incretin agents, dipeptidyl peptidase 4 inhibitors and glucagon-like peptide 1 agonists, both work to reduce glucose by influencing the incretin gastrointestinal glucose axis. There is evidence that liraglutide (3.0 mg/d), prescribed for weight loss, is effective in reducing the incidence of new-onset T2DM by 66% after 3 years of treatment.[29] However, a 2017 Cochrane review found the evidence to be too weak to conclude that these medications produce a clinically significant decrease in the incidence of T2DM.[30] Specifically, there was no evidence of benefit from the dipeptidyl peptidase 4 inhibitors, and the evidence from the liraglutide trial[29] was too weak to support issuing guidance for diabetes prevention with this class of medications.[30]

Weight loss is a central treatment target for most chronic diseases because the benefit is spread across numerous conditions. Various pharmacologic and surgical approaches to obesity have also provided benefit for T2DM prevention (**Table 2**).[9-19] These methods include orlistat, sympathomimetic, and anticonvulsant drugs (phentermine-topiramate) and metabolic (bariatric) surgery. Orlistat works by inhibiting gastric and pancreatic enzymes. Studies have shown that it induces more weight loss than placebo (6.7 vs 3.8 kg) and a decrease in the cumulative incidence of diabetes (3.0% vs 7.6% for placebo). A follow-up study demonstrated increased efficacy when orlistat was combined with an intensive lifestyle intervention; at 4 years, the cumulative T2DM incidence was 6.2% for this combination vs 9.0% for lifestyle intervention plus placebo.[17,31]

Phentermine is classified as a sympathomimetic drug, and topiramate as an anticonvulsant. Neither medication has a primary indication for weight loss, but both have off-label indications based on their natural adverse effect profiles. The combination of phentermine (15 mg) and topiramate (92 mg) with lifestyle intervention yielded a weight loss of 12.1%, compared with 2.5% for lifestyle intervention only. Patients receiving this combination medication should be closely monitored for depression or suicidal ideation.[18,32]

Physicians have been slow to adopt the use of weight-loss medications for a number of reasons. They are very costly and are not covered by many insurance programs. Furthermore, they have potential adverse effects, including effects on heart rate and blood pressure, that are problematic for many persons with diabetes. It is also hard to determine how much of their benefit is from weight loss and how much is an incremental benefit from the medications themselves. Conversely, given the overwhelming public health threat of obesity-related disease, including T2DM, insurance coverage for treatments for patients with obesity may have value.

Metabolic Surgery

Surgical procedures such as Roux-en-Y and gastric bypass are among the most effective options for patients at increased risk for T2DM. In a study of lifestyle vs surgical management in obese adults at risk for T2DM, surgery was more effective and its benefits longer lasting.[19] The incidence of T2DM was 28.4 cases per 1000 person-years in the control group (lifestyle intervention) compared with 6.8 cases per 1000 person-years in the metabolic surgery group, with a relative risk reduction of 78%. There were also significant differences between the 2 groups, with the metabolic surgery cohort having a higher mean body mass index (BMI) and incidence of T2DM risk at baseline.[19] Although metabolic surgery may be the most effective way to prevent T2DM in persons at risk, its benefits are somewhat offset by the potential for serious adverse events during and after surgery and the requirements for long-term nutritional maintenance and observation for nutritional deficiencies.

Recommendations for Diabetes Prevention

Health care professionals have the tools to help patients change the trajectory of prediabetes to T2DM. The

Table 2.
Pharmacologic and Surgical Approaches to Prevent or Delay Type 2 Diabetes Mellitus

Intervention	Follow-up Period, y	RRR, % (*P* Value vs Placebo)	Pregnancy Risk Category[a]	Adverse Effects
Antihyperglycemic Agents				
Metformin[9]	2.8	31 (<.001)	B	GI distress, infection, lactic acidosis, Nausea, Vomiting, diarrhea
Acarbose[14]	3.3	25 (.0015)	B	GI distress/pain, diarrhea, high LFT results
Pioglitazone[15]	2.4	72 (<.001)	C	HF, weight gain, HLD, edema, hepatotoxicity, bladder cancer
Rosiglitazone[16]	3.0	60 (<.0001)	C	HF, weight gain, HLD, edema, hepatotoxicity
Weight-Loss Interventions				
Orlistat[17]	4	37 (.0032)	X	Headache, GI distress or pain, URTI, hepatotoxicity
Phentermine plus topiramate[18]	2	79 (<.05)	Phentermine: X; topiramate: D	Phentermine: hypertension, palpitations, GI distress, dysphoria, restlessness; topiramate: paresthesias, diarrhea, URTI, drowsiness, dizziness
Bariatric surgery[19]	10	75 (<.001)	…	Dumping syndrome, malabsorption, infection, stenosis

[a] B, animal reproduction studies show no risk to fetus, and there are no well-controlled studies in pregnant women OR animal studies have shown a risk, but well-controlled studies in pregnant women show no risk to the fetus; C, risk has not been ruled out; D, positive evidence of risk, but potential benefits may warrant use of drug in pregnant women; X, contraindicated in pregnancy.

Abbreviations: GI, gastrointestinal; HF, heart failure; HLD, hyperlipidemia; LFT, liver function test; NNT, number needed to treat; RRR, relative risk reduction; URTI, upper respiratory tract infection.

ADA recommends a screening tool (http://main.diabetes.org/dorg/PDFs/risk-test-paper-version.pdf) for use in all adults and children at high-risk for diabetes and prediabetes.[33] The 2018 ADA standards of care recommend testing all adults who are overweight or obese (BMI >25 or >23 in Asian patients) or who have at least 1 of the following risk factors: first-degree relative with T2DM, membership in a high-risk ethnic group (black, Hispanic, Asian, Native American, or Pacific Islander), history of cardiovascular disease, hypertension (>140/90 mm Hg), dyslipidemia (high-density lipoprotein cholesterol level <35 mg/dL or triglyceride level >250 mg/dL), physical inactivity, or polycystic ovary syndrome.[33] Furthermore, all adults older than 45 years should be screened for diabetes or prediabetes.[33]

All persons with these risk factors should be screened at 3-year intervals as long as test results are normal.[33] For patients with prediabetes, both the ADA and the AACE recommend entry into an evidence-based program, such as the NDPP, with annual screening for diabetes after that point.[33,34]

Persons with prediabetes, according to the 2018 ADA standard of care, "should be referred to an intensive lifestyle intervention program modeled on the NDPP to achieve and maintain 7% weight loss of initial body weight and increase moderate-intensity physical activity to at least 150 minutes per week."[33] Furthermore,

metformin should be prescribed for diabetes prevention in persons with prediabetes, especially those with a BMI above 35, those younger than 60 years, and women with a history of gestational diabetes. The AACE recommends that therapeutic lifestyle programs, medications (based on evidence, even without indications approved by the Food and Drug Administration), and metabolic surgery may all have a role in the prevention of T2DM.[34,35]

Cost-Effectiveness of Diabetes Prevention

A cost-effectiveness modeling study was completed to evaluate the potential benefit of broad NDPP intervention for Medicare recipients. The results showed that widespread implementation for Medicare recipients with a 37% reduction in new-onset diabetes led to a savings of $1.3 billion over 10 years.[36,37] The results of the NDPP and the Diabetes Prevention Program Observational Study confirmed that both lifestyle intervention and metformin were cost-effective.[38] As a result, Congress passed into law designating the NDPP a mandated covered benefit for all eligible Medicare recipients (once-in-a-lifetime benefit).[39] Furthermore, some states, such as California, have made this a covered benefit for its Medicaid beneficiaries.[40] Many private insurance plans also now cover the NDPP.

Effectiveness of Community-Based DPPs

Community-based DPPs are also effective. The 2018 ADA guidelines give an "A" recommendation (highest level of evidence) for referral of patients to an intensive behavioral lifestyle intervention program modeled on the NDPP, with the goal of achieving and maintaining a 7% weight loss (based on initial body weight) and increasing moderate-intensity physical activity to at least 150 minutes per week.[33] Given the data suggesting that lifestyle interventions are effective in preventing the progression to T2DM from prediabetes, several studies are evaluating the feasibility of implementing widespread community-based preventive programs.

Community-based programs like those offered by the YMCA are prototypical local implementations of the NDPP. The Translating the Diabetes Prevention Program Into the Community study[41] showed that the YMCA, given its large numbers of facilities across the United States, could broaden access to DPPs. The group nature of YMCA classes, the organization's commitment to including participants unable to pay, and the effectiveness of its group instructors using NDPP materials show promise in implementing the DPP nationwide. Similar studies in Australia and Spain also showed the effectiveness of community-based DPPs.[42,43]

In the United States, efforts are underway to increase access to DPPs through insurance coverage. Programs undergo yearly evaluations by the Centers for Disease Control and Prevention (CDC) early in the recognition process to help ensure that programs meet all pertinent requirements.[44] Patients whose weight-loss goals are achieved may qualify for insurance coverage of ongoing DPP maintenance. The Centers for Medicare & Medicaid Services (CMS) announced that the Medicare Diabetes Prevention Program, which started in April 2018, will be a covered benefit for all Medicare recipients.[45] This coverage is intended to offset substantial current Medicare expenses for persons with T2DM. The CMS estimated that, in 2016 alone, $42 billion more would be spent on persons aged 65 years or older with diabetes who qualify for the Medicare parts A, B, and D combined than would be spent on those without diabetes.[45]

Referring Patients to a DPP

The CDC maintains a national registry of DPPs that meet national standards. They can be found at the CDC NDPP website (https://www.cdc.gov/diabetes/prevention/index.html), which also provides important information about the NDPP, how to start a DPP at an institution, and testimonials from participants.

Future Directions

Despite very good evidence that T2DM can be prevented, the health care system has been slow to engage such efforts. There are many reasons for this hesitation, the most common being physicians' belief that they lack the education or the time to provide extensive lifestyle prescriptions. Moreover, most of these interventions require substantial time and resources, and, unless patients are fully engaged, their value may not be fully realized. Most of the medications that delay the onset of diabetes are very expensive, and many are not covered by insurance because they have no Food and Drug Administration–approved indication. The CMS has taken a major step to address some of these barriers by making the NDPP a mandated covered benefit for all eligible Medicare recipients (those who have confirmed diagnosis of prediabetes),[39] and many private insurers have followed suit. The American Medical Association, the ADA, and the CDC have engaged in large public health campaigns to raise awareness and support DPPs such as the NDPP.

Conclusion

High-level data support the claim that T2DM can be delayed or prevented in persons with prediabetes. The evidence is the strongest for intensive therapeutic lifestyle programs like the NDPP and for metformin, pioglitazone, and metabolic surgery. Consequently, all physicians should have a working knowledge of how to screen for diabetes and prediabetes, should know which interventions delay new-onset T2DM, and should provide access to these interventions for their patients.

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