The risk of adverse cardiac events is substantially higher in patients with diabetes, with cardiovascular disease accounting for 65% of deaths among this patient population. People with diabetes have a 2- to 4-fold increased risk of stroke and coronary heart disease, as well as a 2- to 5-fold increased risk of heart failure.1

Some of the cardiometabolic risk factors that contribute to development of diabetes cannot be modified, such as age, race/ethnicity, gender, and family history.2 However, many risk factors—overweight and obesity, tobacco use, physical inactivity, abnormal lipid metabolism, hypertension, insulin resistance, and inflammation—are modifiable through lifestyle changes and therapy.3

A number of studies have demonstrated the correlation between diabetes and cardiovascular risk. For example, the Nurses’ Health Study4 included 117,629 women aged 30 to 55 years who were followed for 20 years. In a demonstration of the so-called “ticking clock” hypothesis of diabetes and heart disease, it was found that glucose abnormalities increase cardiovascular risk even before the diagnosis of diabetes. In women who were not diagnosed as having diabetes at the beginning of the study, the relative risk of myocardial infarction or stroke was 2.8; this relative risk increased to 3.7 after the diagnosis of diabetes.4 Regarding the 1500 women who had diabetes at commencement of the study, the relative risk of myocardial infarction or stroke during the 20 years of follow-up was 5.0.4 In addition, a study from two hospitals in Sweden5 observed that, of 181 consecutive patients admitted with acute coronary syndrome, 31% had undiagnosed diabetes, and 35% had impaired glucose tolerance.

These findings underscore the importance of examining glucose tolerance in all cardiac patients. Furthermore, given the fact that cardiovascular risk increases before the diagnosis of diabetes is made, it is imperative that every patient who walks into a physician’s office is evaluated for cardiometabolic risk.
mass index, waist circumference, or both should be measured, blood pressure should be checked, and lipids should be analyzed. Lifestyle factors, such as diet, physical activity, and cigarette smoking, should also be assessed. If there is any suspicion of impaired glucose tolerance, fasting and postprandial glucose levels should be evaluated. Patients must understand that by changing some of their habits and that by losing even a small amount of weight, they will be able to prevent the progression to diabetes.

**Diagnosing Prediabetes and Diabetes Glucose Levels**

Prediabetes, defined as either impaired fasting glucose (8-hour fasting plasma glucose levels of 100 to 125 mg/dL) or impaired glucose tolerance (2-hour postprandial glucose level between 140 and 199 mg/dL) is an important risk factor for diabetes and cardiovascular disease (CVD) (Figure 1). Studies have shown that lifestyle modification can reduce the rate of progression from prediabetes to diabetes.

Patients with an 8-hour fasting plasma glucose level of 126 mg/dL or higher, or a plasma glucose level of 200 mg/dL or higher 2 hours after an oral glucose tolerance challenge of 75 g carbohydrate test are diagnosed as having prediabetes and should be identified. The ADA recommends that the diagnosis be made on the basis of the most abnormal test, as long as it is repeated and confirmed.

**Glycated Hemoglobin Levels**

As stated previously, the international expert committee that advocates use of the glycated hemoglobin (HbA1c) test to diagnose diabetes recommends that a diagnosis should be made when HbA1c levels are 6.5% or higher. These tests should also be repeated if they indicate a diagnosis of diabetes. Confirmation is not required, however, in symptomatic patients or in patients with glucose levels greater than 200 mg/dL. If HbA1c testing is not possible, a previously recognized diagnostic method, such as fasting plasma glucose or 2-hour postprandial glucose, may be used, with confirmation using the same assay. HbA1c, as a diabetes diagnostic test may not currently be reimbursable by insurers.

Patients with HbA1c levels below 6.5% but more than 5.7% should be diagnosed as having prediabetes and should receive effective preventive interventions. They should be counseled on lifestyle modification and be administered treatment, as appropriate. However, physicians and patients should understand that the US Food and Drug Administration (FDA) has not approved any agent for the prevention of diabetes. Therefore, this type of use would be off-label.

Patients with HbA1c levels below 5.7% may still be at risk and may benefit from prevention efforts, depending on the presence of other diabetic risk factors.

If initiated early, tight glycemic control can prevent or delay serious complications. Every 1% point drop in HbA1c levels reduces the risk of microvascular complications, such as kidney and nerve diseases, by 40%. Patients with T2DM should have HbA1c goals of between 6.5% and 7%. The American Association of Clinical Endocrinologists recommends HbA1c levels of 6.5% or less, while the American Diabetes Association (ADA) recommends that patients achieve HbA1c levels that are as close as possible to 6% without risking hypoglycemia.

**Natural History of T2DM**

There are three major defects in the pathophysiology of T2DM. First, T2DM usually begins with insulin resistance. With insulin resistance, tissue does not respond properly to circulating insulin, creating a demand for increased insulin secretion. The pancreas attempts to keep up with this increased demand of the body. Eventually, however, pancreatic β cells can no longer compensate, and excess glucose builds in the bloodstream. Moreover, defects in the islets of Langerhans lead to excess production of glucagon by α cells. The excess glucagon and diminished insulin exacerbate the hyperglycemia.

Hyperglycemia can be continuous or occur in spikes. When it occurs in spikes postprandially, it leads to acute glucotoxicity. When hyperglycemia is continuous, it can lead to chronic glucotoxicity. This effect causes to asymptomatic complications, which renders...
treatment difficult because patients often do not understand why they must take so many medications when there is no evidence of disease. Physicians must educate patients on the importance of glucose control and the risk of developing complications later in life. Patients should understand that the higher their HbA1c levels are, the greater the risk of complications. Patients with diabetes also need to understand the value of both fasting and postprandial readings of their blood glucose levels, which will give information about the type of glucose variability. For example, if a patient’s hyperglycemia is primarily postprandial, then checking only their fasting plasma glucose will not help in determining which treatment to administer or whether a particular treatment is effective.

The contribution of postprandial plasma glucose to hyperglycemia increases as HbA1c improves. If a patient’s HbA1c level is below 8.4%, the hyperglycemia is most likely due to postprandial glucose levels. Postprandial glucose levels generally become elevated first. If a patient is examined in the afternoon, the glucose levels should be tested, with a notation made about the time and quantity of the last meal.

Effects of Intervention Strategies on Diabetes Risk Reduction

Many studies have examined and compared the abilities of treatment strategies to reduce the relative risk of diabetes. In the largest such study, the US Diabetes Prevention Program (DPP), researchers found a 58% relative risk reduction with lifestyle intervention alone. The Finnish DPP, which was a similar study but with fewer patients, observed similar results. The US DPP also examined the effects on risk reduction of two pharmacologic agents: metformin and troglitazone. At the beginning of the US DPP, troglitazone seemed to have good results but was terminated prematurely because it was associated with an increased risk of hepatic adverse events. Metformin was associated with a 31% relative risk reduction according to the US DPP. Other studies, such as the UKPDS 10-year follow-up study, found that metformin was associated with a greater risk reduction than other agents, including insulin and sulfonylureas. Thiazolidinediones are useful, but, unlike metformin, they are associated with weight gain caused by fluid retention, and rosiglitazone is now under FDA investigation for increase MI and stroke risk.

The UKPDS 10-year follow-up study examined intensive glucose lowering in patients with T2DM. Investigators reported that long-term sustained glycemic control provided the following beneficial effects:

- risk reduction of any diabetes-related endpoint: 9% with sulfonylurea (SU) or insulin and 21% with metformin 21
- microvascular disease: 24% risk reduction with SU or insulin
- myocardial infarction: 15% risk reduction with SU or insulin, 33% with metformin
- death from any cause: 13% risk reduction with SU or insulin, 27% with metformin

Again, metformin was found to be superior to insulin and SU. However, this finding depends on β-cell function. If there is already significant β-cell deterioration, insulin will need to be administered.

The VADT, ACCORD, and ADVANCE trials found significant benefit of intensive glycemic control in patients with a shorter duration of diabetes, lower HbA1c level at study entry, or absence of known CVD. Again, these studies highlight the importance of aggressively treating patients with diabetes at the time of diagnosis.

Comprehensive, Individualized Therapy

When determining therapy and setting glycemic goals for patients with diabetes, key concepts must be kept in mind. For example, the treatment regimen must be tailored to each individual patient. Treatment should be individualized based on the patient’s age, duration of disease, and comorbidities. Also, specific populations require special consideration. For example, Hispanic and African American populations are at a higher risk of diabetes and physicians should be alert to diagnose and manage the disease aggressively in these patients. Furthermore, achieving lower glycemic goals will improve microvascular complications, but care must be taken to ensure hypoglycemia does not occur. Every patient with diabetes should have a meter to measure their glucose readings. As stated previously, measuring postprandial glucose levels is critical. They may be targeted if the fasting plasma glucose levels are normal, but the patient has not achieved his or her HbA1c goals (Table).

In addition to hyperglycemia, other cardiometabolic risk factors in patients with diabetes must be addressed (Figure 2). The ADA recommends that patients with diabetes should also be treated for elevated blood pressure and dyslipidemia.

Hypertension

The ADA recommends that the target blood pressure for patients with T2DM should be no greater than 130/80 mm Hg, or 125/75 mm Hg if there is end-organ damage. For patients who have a systolic blood pressure of 130 to 139 mm Hg or a diastolic blood pressure of 80 to 89 mm Hg, lifestyle therapy is recommended. If blood pressure targets are not achieved within 3 months, then pharmacotherapy should be implemented along with lifestyle intervention. Patients who have a systolic blood pressure of 140 mm Hg or greater or a diastolic blood pressure 90 mm Hg or greater at diagnosis should receive pharmacotherapy along with lifestyle therapy. Pharmacotherapy for patients with T2DM and hypertension should include an angiotensin converting enzyme inhibitor or an angiotensin II receptor blocker. Thiazide or loop diuretics can be adjunctive to these agents as multiple agents are commonly needed to achieve blood pressure targets. Kidney function and serum potassium levels should be closely monitored.

The ACCORD blood pressure study has recently been published. Overall, there was no evidence that targeting systolic blood pressure less than 120 mm Hg compared to less than 140 mm Hg reduced cardiovascular events. In a subgroup analysis, stroke risk was reduced in the intensive group, but this effect needs to be confirmed in future trials.
Dyslipidemia

Target low-density lipoprotein cholesterol (LDL-C) is 100 mg/dL, or 70 mg/dL for people who smoke, have experienced a cardiovascular event, or have renal insufficiency. Lifestyle modification is recommended by the ADA for management of dyslipidemia in low-risk patients with T2DM. However, in patients with clinical CVD who are older than 40 years and have cardiovascular risk factors, treatment with a statin should be added to lifestyle intervention regardless of baseline lipid levels.6 Glycemic control can also improve lipid levels.27,28

Hyperglycemia is associated with an increase in lipolysis and fatty acid levels as products of insulin resistance. Several antihyperglycemic agents positively affect lipids. For example, metformin, an insulin-sensitizing agent, decreases total cholesterol, LDL-C, triglycerides, and high-density lipoprotein cholesterol (HDL-C). Exenatide also increases HDL-C and decreases total cholesterol, LDL-C, and triglycerides. Pioglitazone, another insulin-sensitizing agent, increases HDL-C and LDL-C and decreases triglycerides. Despite treatment with statins, the majority of adverse cardiovascular events cannot be prevented. It is this residual risk of CVD that must be safely and effectively addressed to reduce the significant morbidity and mortality associated with CVD, particularly in patients with T2DM. Agents that raise HDL-C levels and reduce elevated triglycerides are recommended by the ADA, the Adult Treatment Panel III, and the American Heart Association (AHA).29

The ACCORD lipid study has been recently published. Addition of fenofibrate was not associated with reduced risk for the primary outcome compared

<table>
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<tr>
<th>Class</th>
<th>% HbA1c Reduction</th>
<th>Fasting or PPG</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>Dosing, times/day</th>
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<tr>
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<td>Gain</td>
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<td></td>
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</tr>
<tr>
<td>Repaglinide</td>
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<td>Y</td>
<td>Gain</td>
<td>3</td>
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<tr>
<td>Nateglinide</td>
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<td>PPG</td>
<td>Rare</td>
<td>Gain</td>
<td>3</td>
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<tr>
<td>Alpha-glucosidase inhibitors</td>
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<td>N</td>
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<td>3</td>
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<tr>
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<td>Loss</td>
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<tr>
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<td>Loss</td>
<td>2, injected</td>
</tr>
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<td>DPP-4 inhibitors</td>
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<td></td>
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<td>Both</td>
<td>N</td>
<td>Neutral</td>
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</tr>
</tbody>
</table>

Abbreviations: DPP-4, dipeptidyl peptidase-4; PPG, postprandial glucose.

Figure 2. Beyond lifestyle: aggressive medical therapy in diabetes. Source: Adapted from Beckman JA et al. JAMA. 2002,287(19):2570-2581.
to statin therapy alone. In subgroup analysis, there was heterogeneity in treatment effect according to sex—with benefit for men but possible harm for women. Although much has been made for apparent benefit in the prespecified lipid subgroup with both high triglycerides (>240 mg/dL) and low HDL-C (<34 mg/dL) levels, the interaction here was of only borderline significance.30

Platelet Activation and Aggregation

Patients with diabetes should also undergo therapy targeting platelet activation and aggregation. The ADA and the AHA have, in the past, jointly recommended that low-dose aspirin therapy be used as a primary prevention strategy in individuals with diabetes who are at increased cardiovascular risk.31 However, these recommendations were based on several older trials that included small numbers of patients with diabetes. The current ADA recommendations are to use aspirin therapy (75-162 mg/day) as a secondary prevention strategy in patients with T2DM and a history of CVD. For patients with CVD and documented aspirin allergy, clopidogrel (75 mg/day) should be used. Combination therapy with aspirin and clopidogrel is reasonable for up to 1 year after an acute coronary syndrome.6

Barriers to Treatment

There are a variety of barriers in the treatment of patients with T2DM and its associated comorbidities (Figure 3). For example, barriers may comprise patient factors such as lack of necessary knowledge and information and difficulty with lifestyle changes. Educating patients on the progressive nature of diabetes is extremely critical to overcoming these barriers. Furthermore, the messages delivered to these patients must be communicated in a clear manner so the patient will fully comprehend the seriousness of the disease. The involvement of office staff in educating patients is helpful as well.

Adherence is an important issue. For example, patients may hear about side effects of cholesterol medications and stop taking them. Also, patients often will discontinue a medication if it causes weight gain. These obstacles can also be overcome with patient education. However, medication cost and difficulty with insurance reimbursement also contributes to poor adherence. The progressive nature of the disease can cause patients to become disheartened when they find out they need to begin taking insulin and blame themselves. The physician should explain to the patient at diagnosis that their treatment will begin with one agent, and the number of medications they take will increase over time, and eventually they could need insulin because their β-cell insulin production will generally decrease by approximately 4% each year. If these expectations are set early in the process, patients will not become discouraged when they need insulin.

Treatment Selection

Proper selection of pharmaceutical agents is essential to improve insulin resistance and to control other cardiovascular risk factors, such as dyslipidemia. Early and aggressive treatment is vital and will decrease the long-term risk of cardiovascular events. Several factors should be considered when choosing an anti-hyperglycemic agent for treatment of patients with T2DM, such as their HbA1c levels, the duration of their disease, their cardiovascular risk factors, their risk of gaining weight, their risk of hypoglycemia, and their β-cell health. Therapy must be advanced when HbA1c levels are not improving and staying at goal. Special circumstances in which therapy does not need to be advanced must be documented. For example, a patient with an HbA1c level of 10% who has had diabetes for 40 years and has a high risk of hypoglycemia may not be given advanced therapy. Whether the fasting plasma glucose levels or the postprandial plasma glucose levels should be targeted will also affect treatment selection. In other words, the advantages and disadvantages of each medication must be weighed against each patient's individual needs.

A medication's effects on weight gain must also be considered when selecting a treatment. Dipeptidyl peptidase-4 inhibitors, glucagon-like peptide-1 receptor agonists, metformin, and pramlintide are considered “weight-friendly” antihyperglycemic medications, while glinides, insulin, sulfonylureas, and thiazolidinediones are considered “weight-unfriendly.”32 Treatment with insulin has been found to increase mean weight 3.2 kg to 4.4 kg per 1% reduction in HbA1c with about two-thirds of the weight gain occurring in adipose tissue and one-third in lean body mass.33 Some of the weight gain associated with T2DM medications also can be the patient’s fear of hypoglycemia, an increased appetite,

![Figure 3. Barriers to achieving optimal outcomes in patients with type 2 diabetes mellitus.](image-url)
or catch-up from weight loss pre-treatment. Weight gain can increase systolic blood pressure, making weight an important issue in diabetes treatment.34

Conclusion
In summary, improving glycemic control while decreasing cardiometabolic risk requires an integrated approach to treatment that goes beyond control of blood glucose. The comorbidities of T2DM, such as dyslipidemia, hypertension, and obesity, should also be addressed. Clinicians should assess the cardiometabolic risk of each patient, because cardiovascular risk is increased even before diabetes is diagnosed. Aggressive treatment should be initiated at the time of diagnosis to reduce the risk of microvascular and macrovascular complications.

Physicians should involve patients in the decision-making processes. The clinicians and medical staff should educate diabetic patients on the progressive nature of the disease. Notifying patients early in the disease process that they will progressively need more medications and eventually insulin will prevent patients from feeling disheartened when the time comes for therapy advancement. Medical staff must also be available to discuss the treatment regimens, provide instructions for self-testing of blood glucose levels, and outline the importance of compliance with the recommended therapies.

References


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**Partnership to Fight Chronic Disease**

The American Osteopathic Association has been an active member of the Partnership to Fight Chronic Disease (PFCD) since 2007. This supplement promotes the ideals of this partnership.

The PFCD is a national and state-based coalition of hundreds of provider, patient, community, business, and labor groups committed to raising awareness of the leading causes of death, disability, and rising healthcare costs in the United States—chronic diseases such as diabetes, asthma, cancer, and heart disease. In addition, the PFCD has worked to ensure that prevention and wellness measures were incorporated into healthcare reform legislation passed by Congress in 2010. For additional information, visit www.fightchronicdisease.org.