

Type 2 Diabetes Mellitus

WHAT IS TYPE 2 DIABETES MELLITUS?

Type 2 diabetes mellitus (T2D) is a disease characterized by the progressive worsening of glycemic control, which often starts with mild elevations in blood glucose levels after eating, and, over time, leads to an increase in fasting plasma glucose. Cardiovascular disease is the main cause of morbidity and mortality among diabetic patients, but other complications include nephropathy, neuropathy, and retinopathy, as many types of tissues are damaged by hyperglycemia and the resultant oxidative damage.

It is well-established that hyperglycemia is the result of two major defects: a loss of hepatic and peripheral insulin sensitivity, and defective pancreatic β -cell function. As β -cell function declines, insulin production is not sufficient to keep up with rising blood glucose levels, and hyperglycemia occurs even when fasting.

Hepatic insulin resistance is marked by an inappropriately high rate of hepatic glucose production, despite elevated insulin concentrations. The inability of endogenous insulin to increase plasma glucose uptake by peripheral tissues indicates peripheral insulin resistance. It is estimated that by the time of diagnosis with T2D, β -cell function may already be reduced by 50%, marked by an earlier phase of gradual decline and decompensation preceding overt diabetes. This is followed by a phase of rapid acceleration of impaired insulin secretion and β -cell apoptosis, perhaps due to glucose and lipotoxicity.¹ (See Figure 1).

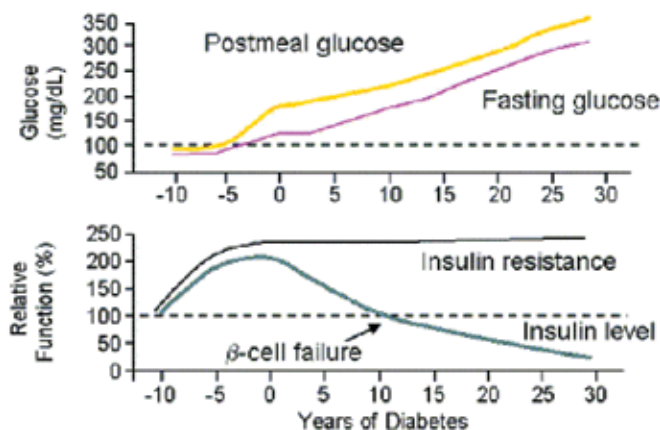


Figure 1* Beta-cell dysfunction and insulin resistance in Type 2 diabetes.

HOW COMMON IS IT?

The NHANES 1999-2004 found that 7.8% of the total US adult population had diabetes mellitus, and approximately 90-95% of those individuals have been estimated to have T2D.² In 2005-2006 this estimate had reached 12.9% among people aged ≥ 20 years, of which $\sim 40\%$ was undiagnosed.³ The total health care costs attributed to diabetes and related complications reached \$174 billion (USD) for the year 2007.⁴

What may be just as alarming is the increasing prevalence of prediabetes, which is an intermediate stage between normal glucose levels and T2D, defined as either an elevated fasting blood glucose or impaired glucose tolerance that falls short of the criteria for diabetes. The NHANES 2005-2006 found that in people aged $> \text{or} = 20$ years, the crude prevalence of impaired fasting glucose was 25.7% and of impaired glucose tolerance was 13.8%, with almost 30% having either. Thus, over 40% of individuals had diabetes or pre-diabetes.

WHY DOES IT OCCUR?

Although there are genetic components to T2D, it is largely thought to occur as a result of poor food choices and physical inactivity. Obesity has been well-established as a risk factor for T2D, with both body mass index (BMI) and waist circumference positively associated with the incidence of T2D, with a risk increase of 1.6 to 2.66 fold.⁵ Given the importance of central adiposity to insulin resistance, it is no surprise that the waist-to-height ratio may also be the best discriminator of cardiovascular disease.⁶

A diet that is high in refined carbohydrates, with low intakes of fruits, vegetables, legumes, whole grain, and fiber is the pattern associated with the greatest risk.^{7,8,9} Consistent with this pattern is a diet low in antioxidants that is calorie-rich and nutrient-poor, with a high-glycemic index. Although a number of genes have been identified that increase the risk of T2D, the importance of lifestyle is clearly shown by the example of the Pima Indians. This population has the highest known rate of T2D, with a strong genetic component. However, Pima Indians living in Mexico have a prevalence of T2D of 6.9%, less than one-fifth of that in the US Pima Indians (38%), due to differences in lifestyle.¹⁰

HOW IS IT DIAGNOSED AND MONITORED?

The diagnosis of T2D can be made in one of three ways—a fasting plasma glucose ≥ 126 mg/dL, symptoms of hyperglycemia with a random glucose ≥ 200 mg/dL, or a 2-hour plasma glucose ≥ 200 mg/dL during an oral glucose tolerance test (See Table 1).

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1.	FPG \geq 126 mg/dL (7.0 mmol/l). Fasting is defined as no caloric intake for at least 8 h.*
OR	
2.	Symptoms of hyperglycemia and a casual plasma glucose \geq 200 mg/dL (11.1 mmol/l). Casual is defined as any time of day without regard to time since last meal. The classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss.
OR	
3.	2-h plasma glucose $>$ 200 mg/dL (11.1 mmol/l) during an OGTT. The test should be performed as described by the World Health Organization using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
* In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing on a different day.	

Table 1* Criteria for the diagnosis of diabetes.

Although fasting glucose alone is often used as a screen for diabetes, it is thought to miss approximately 30% of cases.¹¹ It is an insensitive screen because it does not reflect the earlier rises in postprandial glycemia associated with poor glucose tolerance. Only after the β -cell function has declined enough for an elevated fasting glucose will these patients be detected, after the disease has progressed. Additionally, patients with both impaired fasting glucose and impaired glucose tolerance develop diabetes twice as often as those with only one of these abnormalities, emphasizing the importance of these tests for prognosis.

Monitoring of T2D patients is primarily done in two ways, by measurement of glycosylated hemoglobin (HbA1c), and by self-monitoring of blood glucose (SMBG). The HbA1c gives an estimate of the average value for blood glucose over the last several months, and is often used to measure the effectiveness of therapy. Very recently, an International Expert Committee has also recommended the use of HbA1c for the diagnosis of diabetes, with a level $>$ or $=$ to 6.5% to be used as the cut-off for diabetes. However, an HbA1c does not give good data for the daily fluctuation of blood sugar—it misses the sharp rises and drops in

blood sugar associated with meals that more close monitoring measures.¹²

What has emerged is the importance of SMBG for better metabolic control in diabetic patients. Additionally, newer technologies have also created the ability to monitor glucose continually, known as continuous glucose monitoring (CGM). It has been shown to have the following benefits compared to SMBG:

- The ability to detect postprandial glucose excursions.
- Detection of nocturnal hypoglycemia or hyperglycemia not previously detected by SMBG, even in patients whose HbA1c values suggest reasonably good control (See Figure 2).¹³
- Allows for patients to have better metabolic control, because the data generated by CGM show the effect of meal choices, missed medication, and the effect of lifestyle on glucose control.

COMPLICATIONS

Because patients with diabetes are at high risk for a number of other complications, regular evaluation of kidney function, cardiovascular risk factors, neurological and retinal health exams should be done. For example, ~40% of T2D patients have hypertension at diagnosis. Elevated pressure is a risk factor for both T2D development and complications.¹⁴

T2D increases the risk for peripheral vascular disease, stroke, and periodontal pathologies. Diabetes is also the leading cause of end-stage renal failure, visual impairment and blindness, and of non-traumatic lower limb amputations.^{15, 16}

Generalized endothelial dysfunction in diabetes can result from disparate metabolic insults that include hyperglycemia, dyslipidemia, hypertension, hyperinsulinemia, elevated levels of fatty acids, increased production of reactive oxygen species, hyperleptinemia, and cytokine-mediated inflammation.

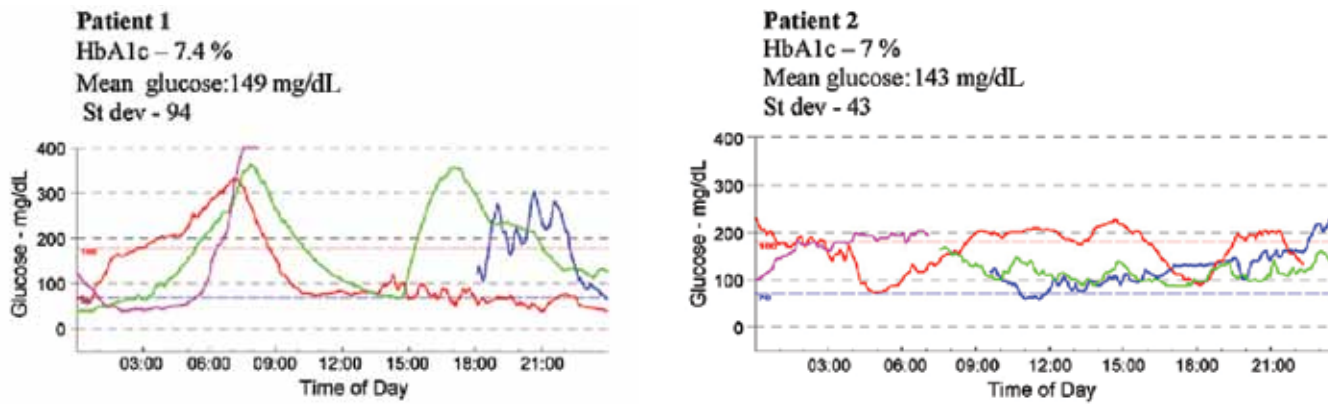


Figure 2 Continuous glucose monitoring of two patients at HbA1c target.

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TREATMENT

The primary goal of diabetes treatment and prevention is to normalize plasma glucose levels, which, in turn, reduces the many complications of hyperglycemia, and reduces the risk of developing T2D for those with prediabetes. To achieve these goals, improving food choices and increasing physical activity may have the greatest impact, along with targeted nutritional supplementation.

Dietary choices that consistently have the greatest benefit resemble a Mediterranean diet. They are comprised of whole foods with a low-glycemic index; they are also high in fiber, are plant-based, and are composed mainly of fruits, vegetables, whole grains, and legumes. This type of diet has been shown to

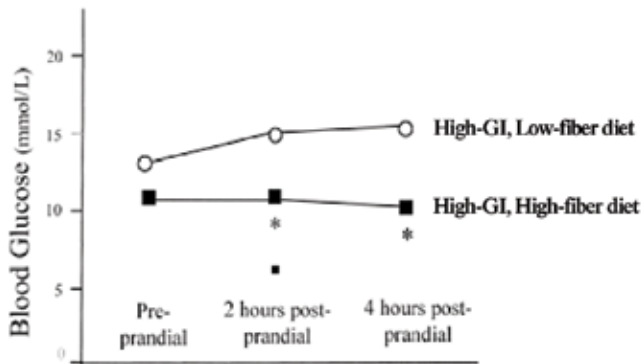


Figure 3 Postprandial blood glucose concentrations in patients with Type 1 diabetes treated with a low-glycemic index (GI), high-fiber diet or with a high-GI, low-fiber diet (a long-term, 24-wk, randomized controlled study; $n = 63$ patients).

reduce glycemia in T2D patients, as well as prevent the risk of developing T2D in those with prediabetes^{17, 18, 19, 20} (See Figure 3). Also, the higher the dietary fiber, the lower the fluctuations seen postprandially.

When combined with an increase in physical activity, dietary changes have been shown to prevent diabetes more effectively than metformin, particularly among older adults (See Figure 4).

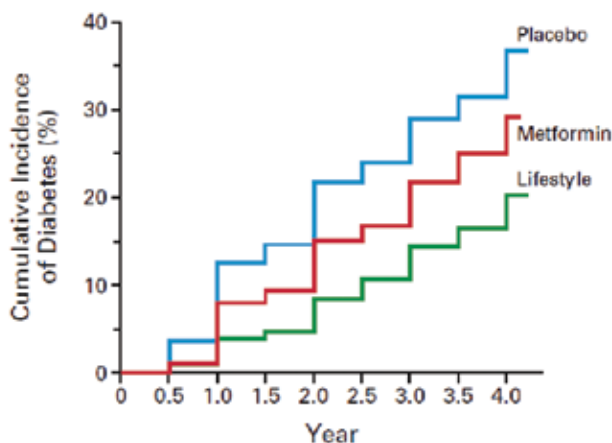


Figure 4 Reduction in the incidence of Type 2 diabetes with lifestyle intervention or metformin.

In addition to diet and lifestyle changes, the use of PolyGlycoPlex (PGX) is a powerful component in the prevention and treatment of T2D. Because PGX has the highest viscosity of any fiber available, and a fiber's viscosity has been shown to be directly proportional to postprandial glycemia, PGX effectively eliminates the fluctuations in blood glucose levels following a meal seen in many diabetic patients.²¹

PGX exerts the following benefits:

- Reduces postprandial (after-meal) blood glucose levels
- Increases insulin sensitivity
- Reduces appetite and promotes effective weight loss
- Improves diabetes control
- Lowers blood cholesterol

PGX typically lowers after-meal blood glucose levels by approximately 35 to 70% and also lowers insulin secretion by approximately 40%, producing a whole body insulin sensitivity index improvement of nearly 60%—a phenomenal accomplishment that is unequalled by any drug or natural health product.²²

For more information, see the PGX Product Monograph.

Other supportive therapies include:

- **Omega-3 Fatty Acids** – have been shown to have significant benefit for cardiovascular disease prevention, the major cause of morbidity and mortality in diabetic patients.²³
- **Broad Antioxidant Support** – vitamins C & E (mixed tocopherols) have been shown to improve endothelial function, glycemic control, arterial stiffness, hypertension, oxidation status, and to reduce inflammation.^{24, 25, 26}
- **Chromium** – improves insulin sensitivity, and may assist with reducing central obesity and weight loss.²⁷
- **Magnesium** – in a review of nine randomized trials with T2D patients, raised HDL cholesterol and lowered fasting plasma glucose in T2D patients.^{28, 29}
- **CoQ10** – improves blood pressure, oxidative status, HbA1c, and glycemic control in diabetic patients.³⁰
- **Botanical Support** – a number of herbs have been shown to improve insulin sensitivity, reduce postprandial glucose elevations, and restore β -cell function.^{31, 32, 33, 34}
- **Vitamin D** – deficiency has been clearly associated with insulin resistance and inflammation, and the pathogenesis of both Type 1 and 2 diabetes.³⁵
- **Alpha-Lipoic Acid** – has been found to reduce oxidative damage, improve glycemic control and insulin resistance, as well as symptoms of polyneuropathy.^{36, 37, 38}

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TABLES

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