

# Prediabetes: The importance of early diagnosis and intervention

Case Study Series with Commentary by:

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## Case: 43-Year-old obese male with impaired fasting glucose.

### Overview

Diabetes is a worldwide epidemic. It is believed that 17.9 million Americans have diagnosed diabetes, with a further 5.7 million remaining undiagnosed.<sup>1</sup>

Diabetes-related morbidity and mortality have become major healthcare problems. The disease is the leading cause of renal failure, nontraumatic lower-limb amputation, and new onset blindness.<sup>1</sup> Diabetes also approximately doubles the risk of developing cardiovascular disease (CVD).<sup>2</sup> In 2006, it was the 7th leading cause of death.<sup>1</sup>

Because the pathologic changes leading to diabetes-related complications begin early in the progression to frank diabetes, early detection and treatment are critical. The Diabetes Prevention Program (DPP) was a large, multicenter clinical research study charged with the task of discovering whether modest weight loss plus regular exercise could prevent or delay the onset of type 2 diabetes (T2DM).<sup>3</sup> Also evaluated was the effect of early use of pharmacologic therapy (metformin) on progression to diabetes. Over an average follow-up of 2.8 years, lifestyle intervention and pharmacologic therapy reduced progression to diabetes by 58% and 31%, respectively. During longer-term (10-year) follow-up, the cumulative incidence of diabetes remained lower in the group assigned to lifestyle intervention.<sup>4</sup> Thus, the challenge that physicians and other primary care providers face is identifying and motivating those at greatest risk for development of diabetes, to help these individuals implement significant lifestyle changes as outlined by the DPP.

## Case: 43-Year-old obese male with impaired fasting glucose.

MM is a 43-year-old white male who presents for an annual physical. He weighs 337 pounds and is 6 feet in height. He denies proper eating habits and regular exercise. His fasting glucose was 118 mg/dL. Total cholesterol was 197 mg/dL. Blood pressure was 129/79 mm Hg. Renal and liver panels were normal. Urinalysis was normal and negative for glucose.

MM does not take any regular medications. He does not have a family history of diabetes.

The patient's current weight is the most he has weighed in his adult life. The least he has weighed was 170 pounds. He recalls a much more active lifestyle at that weight involving skiing, cycling, and running. Since gaining his weight, he has tried and failed many weight-loss programs.

In adults, T2DM accounts for 90% to 95% of all cases of diabetes,<sup>1</sup> and the most important risk factor for T2DM is excess adiposity.

## What is this patient's approximate risk of developing T2DM?

- a. <5%
- b. 5%-10%
- c. >10%-20%
- d. >20%

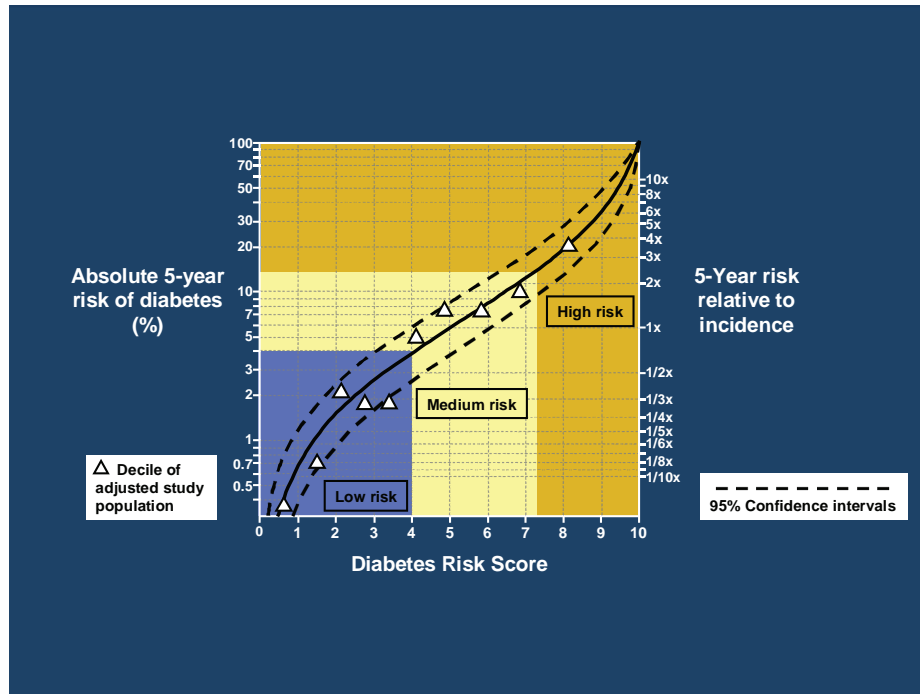
(b) Data suggest that patients with impaired fasting glucose (IFG, 100-125 mg/dL) have an absolute risk of progression to diabetes of 5% to 10% per year.<sup>5</sup>

The risk for diabetes based on levels of glycemia is a continuum. Therefore, there is no threshold at which risk clearly begins. The intermediate state termed “prediabetes” is currently defined as an IFG of 100-125 mg/dL, an impaired glucose tolerance (IGT, measured by the oral glucose tolerance test) of 140-199 mg/dL, or both.<sup>6</sup> There are an estimated 57 million individuals with prediabetes in this country.<sup>1</sup>

The specificity of IFG is poor. IGT is better for risk assessment but requires 2 hours to perform and, consequently, is underused in primary care practice. Several other indices have been developed using combinations of routine clinical information and laboratory measurement; however, these measurements are also underused. Therefore, what further assessment can be done to determine if this patient is one of the 10% of prediabetic Americans at risk?

The Pre-Dx risk assessment test is a novel method of identifying patients at greatest risk for diabetes.<sup>7</sup> It is based on the observation that dysregulation of many biological pathways precede the development of T2DM. Of 260 candidate biomarkers involved in pathways associated with metabolic or cardiovascular disorders, obesity, cell death, or inflammation, 7 were ultimately selected for inclusion in the Pre-Dx test. These biomarkers are glucose (fasting glucose and glycated hemoglobin [A1C]), insulin, high-sensitivity C-reactive protein (hsCRP), ferritin, interleukin-2 receptor alpha (IL2RA), and adiponectin. With the exception of adiponectin, these biomarkers are elevated in patients at risk for diabetes, while adiponectin levels are decreased. These biomarkers are also modifiable, which means that individuals can lower their overall score and, thereby, their risk for developing diabetes.

The 7 biomarkers are combined in an algorithm to provide a diabetes risk score (DRS) score of 1-10. MM’s DRS score was 7.3, corresponding to an 8.6% chance of developing T2DM in the next 5 years (Figure 1).



**Figure 1.** Incorporation of multiple biomarkers into single risk estimate (diabetes risk score [DRS]) using the Pre-Dx test.<sup>7</sup>

## What is the 5-year risk of developing diabetes in the general population?

- a. 2.5%
- b. 3.4%
- c. 4.3%
- d. 5.5%

(b) The Inter99 study was a population-based primary CVD prevention study in 61,301 Danish subjects aged 30 to 60 years.<sup>8</sup> The 5-year rate of progression to diabetes in this study was 3.4%. Data from the Inter99 study

were used to develop and validate the Pre-Dx DRS score. Based on Inter99, MM has a >2-fold higher risk of developing T2DM than the average patient.

## Prescription: Lifestyle modification

A combination of a weight-loss diet plus increased physical activity is the fundamental, first-line approach to preventing progression of prediabetes to diabetes.<sup>6</sup> The patient's diet should include caloric restriction

and increased fiber intake. A program of moderate-intensity physical activity for 30-60 minutes on at least 5 days per week is also recommended (Figure 2).<sup>9</sup>

Daily life	Sports	
Washing car, 45–60 min	Walking 3 mph, 35 min	Less vigorous
Washing windows or floors, 45–60 min	Bicycling 10 mph, 30 min	↑ ↓
Gardening, 30–45 min	Dancing, 30 min	
Raking leaves, 30 min	Water aerobics, 30 min	
	Swimming, 20 min	
	Jogging 1 mile, 15 min	
		More vigorous

**Figure 2.** Examples of moderate-intensity physical activities (equivalent to approximately 150 calories of energy).<sup>9</sup>

## What is the evidence?

The DPP randomized 3234 individuals with a BMI  $\geq 24$  mg/kg<sup>2</sup> plus IFG and IGT to placebo, lifestyle intervention, or metformin 850 mg twice daily. The lifestyle intervention included achieving and maintaining a weight loss of 7% of body weight (at study entry) with diet and  $\geq 150$  minutes weekly of moderate-intensity exercise.<sup>3</sup> The percentage of patients in the lifestyle intervention group

who attained the weight-loss goal was 50% at 24 weeks and 38% at the final visit. The percentage who met the activity goal was 74% at 24 weeks and 58% at the final visit. Despite a less-than-optimal adherence to lifestyle modification, this group had a significantly lower rate of progression to diabetes than either of the other two groups (P < 0.001 for each comparison) (Figure 3).

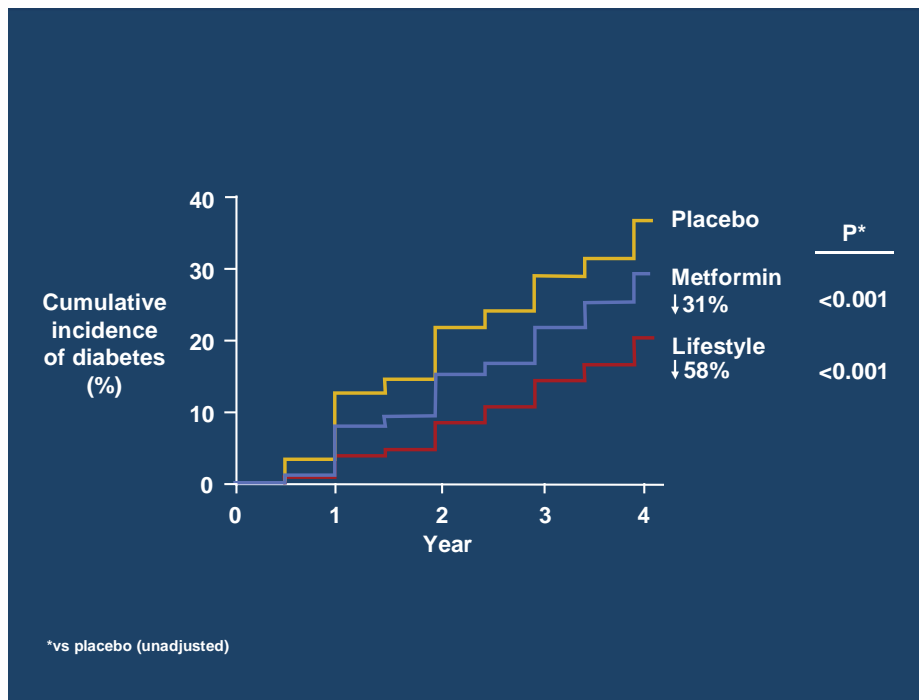


Figure 3. DPP results: Benefit of diet plus exercise in diabetes prevention.<sup>3</sup>

## Results of lifestyle modification

MM was called into his physician's office and notified of his test results. He relayed concern for developing diabetes and told his physician that this test result would motivate him to alter his dietary habits and start exercising. He enrolled in a hospital-sponsored weight-loss program based on the DPP. He was also started on fish oil capsules, multiple vitamins, and 81 mg aspirin daily. After 3 months, he lost 38 pounds. A repeat DRS score 3 months later dropped to 3.2, corresponding to a 1.6% chance of developing diabetes. MM continues to participate in regular exercise classes and he follows a dietary regimen based on the South Beach Diet. He is slowly but steadily losing weight. His goal is to get his weight <200 pounds within the next 12 months.

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