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Prediabetes at the GP office

Is diagnosis worth it?

Prediabetes is defined as an asymptomatic dysglycemia characterized by blood glucose levels that are higher than normal but not high enough to be categorized as type 2 diabetes mellitus (T2DM). This condition is an important precursor to the development of T2DM and other cardiometabolic diseases, with an alarming global prevalence affecting a significant percentage of the population.

According to the International Diabetes Federation (IDF), in 2021, 464 million people worldwide had prediabetes, representing 9.1% of the adult population.

It is estimated that this number will increase to 638 million by 2045, reflecting how big this problem is for public health. Regional variations in prevalence are notable, with studies reporting values as high as 38% in the United States and as low as 17% (1) in a Dutch cohort (2). Between 10% and 50% of people with prediabetes will develop T2DM within 5 to 10 years, with the risk being higher in those who have both impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) simultaneously.

Early identification allows for the implementation of intervention strategies to prevent or delay progression to T2DM, with a significant impact on public health (3).

This piece of information is important enough to consider whether we should take action. But how should we diagnose prediabetes? The following table ***(Table 1)*** presents various methods for diagnosing prediabetes.

PATHOPHYSIOLOGY AND RISK FACTORS

The known pathophysiological defects underlying T2DM are increasingly recognized in the prediabetic state. It is often associated with insulin resistance predominantly in peripheral tissues (skeletal muscle, adipose tissue), which reduces glucose uptake and utilization, leading to elevated blood glucose levels.

Several factors contribute to this resistance:

- Low-grade inflammation: release of pro-inflammatory cytokines that interfere with insulin action.
- Oxidative stress: cellular damage from reactive oxygen species that alters insulin signaling.
- Mitochondrial dysfunction: reduced oxidative capacity of skeletal muscle, decreasing glucose uptake.
- Changes in adipogenesis and lipolysis: accumulation of visceral adipose tissue, releasing hormones and adipokines that impact insulin sensitivity.

The increased demand for insulin due to peripheral resistance leads to compensatory hyperinsulinemia. Over time, this results in β-cell pancreatic exhaustion and reduced insulin production capacity.

Prediabetes is often associated with non-alcoholic fatty liver disease, dyslipidemia, hypertension, and other cardiovascular risk factors, which promote the development of atherosclerotic lesions and premature cardiovascular mortality (6). Early signs of diabetes-related morbidities, such as retinopathy, have also been identified in pre-

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TABLE 1. Criteria for the diagnosis of prediabetes

	ADA* 2024[4]	WHO**	Spanish Council on Prediabetes[5]
Impaired fasting glucose (IFG)	Fasting blood glucose: 100 mg/dL - 125 mg/dL	Fasting blood glucose: 110 mg/dL - 125 mg/dL	Fasting blood glucose 110 mg/dL - 125 mg/dL
Glucose intolerance (GI)	PG *** 2 hours after OGTT****: 140 mg/dL - 199 mg/dL	PG *** 2 hours after OGTT****: 140 mg/dL - 199 mg/dL	PG *** 2 hours after OGTT****: 140 mg/dL - 199 mg/dL
Elevated risk of diabetes	HbA1c 5.7–6.4%		HbA1c 6–6.4%

*ADA (American Diabetes Association) **WHO (World Health Organization) ***PG (plasma glucose)
****OGTT (oral glucose tolerance test)

» diabetes. Additionally, hyperinsulinemia contributes to renal hyperfiltration and early glomerular damage, which precedes chronic kidney disease commonly found in T2DM.

But which factors increase the risk of having prediabetes?

Table 2 explains the factors that would suggest a high risk of developing prediabetes.

Additionally, the PREDAPS trial demonstrated a strong association between abdominal obesity and prediabetes. Waist circumference is a simple and practical measure that can be used to identify individuals at high risk of developing prediabetes. It is recommended to measure waist circumference in all adults, especially those with overweight or obesity. Waist circumferences > 88 cm in women and 102 cm in men are associated with a higher risk of prediabetes and other cardiometabolic diseases (7).

IS IT WORTH DIAGNOSING AND TREATING?

Prediabetes has been associated with an increased relative risk of all-cause mortality and a higher incidence of cardiovascular events, coronary artery disease, stroke, heart failure, atrial fibrillation, chronic kidney disease, cancer, and dementia (8).

Early intervention can significantly reduce the risk of these complications, improving the quality of life and long-term health of affected individuals.

So, what are the appropriate measures for treating it? There are currently several ways to address it: either through hygienic-die- »

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TABLE 2. Criteria for screening diabetes or prediabetes in asymptomatic adults

1. Testing should be considered in adults with overweight or obesity (BMI ⩾ 25 kg/m² or ⩾ 23 kg/m² in Asian Americans) who have 1 or more of the following risk factors:
   - First-degree relative with diabetes
   - High-risk race and ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
   - History of cardiovascular disease
   - **Hypertension** (⩾ 130/80 mmHg or on treatment for hypertension)
   - **HDL cholesterol level < 35 mg/dL** (< 0.9 mmol/L) **and/or triglycerides levels > 250 mg/dL** (> 2.8 mmol/L)
   - Individuals with polycystic ovary syndrome
   - **Physical inactivity**
   - Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
2. Individuals with prediabetes (A1C ⩾ 5.7% [⩾ 39 mmol/mol], IGT, or IFG) should undergo annual testing.
3. Individuals diagnosed with gestational diabetes should be tested for life, at least, every 3 years.
4. For all other individuals, testing should start at the age 35.
5. If results are normal, testing should be repeated at a minimum interval of 3 years, considering more frequent testing based on initial results and risk status.
6. Individuals with HIV, exposure to high-risk drugs, or a history of pancreatitis

*Adapted from Standard Care 2024

» tary measures alone or by adding drugs to these recommendations. Various studies evaluate these interventions, highlighting that the incidence of diabetes was reduced by 58% with lifestyle interventions, by 31% with metformin, and by 56% with pioglitazone (11). Pharmacological treatment achieves a temporary reduction in glucose alteration but does not modify the pathophysiological anomalies of insulin resistance and progressive β-cell dysfunction, which explains the lack of long-term effect when these drugs are discontinued. Although new pharmacological therapies for obesity (GLP-1 and GIP) could have an impact on prediabetes treatment, this treatment is not yet justified today (12).

Currently, lifestyle interventions are the main recommendation, aiming to achieve and maintain a weight reduction of, at least, 7% of the initial body weight through a healthy, calorie-reduced diet and 150 minutes of moderate-intensity physical activity on a weekly basis.

Dietary changes are a fundamental strategy for preventing prediabetes and T2DM. Various studies have shown that diets promoting weight loss, reduced calorie intake, and the choice of nutritious foods are effective in preventing these diseases.

Mediterranean diet (MD) has stood out as one of the healthiest options for preventing prediabetes and T2DM. In this regard, some meta-analyses of prospective studies and clinical trials have found improvements with the Mediterranean diet vs others. Although the exact mechanism of action is not fully understood due to the action of multiple components, possible mechanisms include improved insulin sensitivity resulting from reduced inflammation, as well as beneficial effects of fatty acids and phenolic compounds on the beta cell (13). **D**

CONCLUSIONS

Considering all the above, it is valuable to diagnose prediabetes with the aim of addressing dysglycemia early and striving to delay (or even prevent) the onset of T2Dm, as well as reducing the above-mentioned morbidity and mortality and the associated macro- and microvascular complications (even during the prediabetes stage) (14). Lifestyle interventions remain the primary approach for treating prediabetes. Although new obesity drugs could be beneficial, further research is needed to understand their impact on this condition. Therefore, ongoing reevaluation of treatment strategies will help optimize the prevention of T2DM in the future.

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