Prediabetes or intermediate hyperglycemia: history, criteria, variability, controversies, and updates

Pré-diabetes ou hiperglicemia intermediária: histórico, critérios, variabilidades, controvérsias e atualizações

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Abstract

Prediabetes, or intermediate hyperglycemia, represents a heterogeneous metabolic condition associated with an increased risk of type 2 diabetes mellitus (T2DM) and cardiovascular events. Minor variations in the cut-off points of laboratory markers significantly influence prevalence estimates and eligibility for preventive interventions. This review aims to synthesize the history, diagnostic criteria, prevalence, analytical and biological variability, main complications, and treatments of prediabetes. Current diagnostic guidelines employ fasting plasma glucose (FPG), the oral glucose tolerance test (OGTT), and glycated hemoglobin (HbA1c), while recent recommendations have included 1-hour glucose during the OGTT (1-h OGTT). Concordance among these markers is partial, and the combined use of FPG and HbA1c may increase screening sensitivity, although it is not formally recommended as a universal approach. Biological variability differs among parameters, being higher for 2-hour post-load glucose (CVi ≈17%), intermediate for FPG (≈5%), and lower for HbA1c (≈1–2%), which affects reclassification near diagnostic thresholds. Age-adjusted global prevalence estimates vary widely depending on the criteria used, and Brazilian studies demonstrate substantial discrepancies when reference ranges for HbA1c and FPG are modified. The mean annual progression rate to T2DM ranges from 5% to 10%, potentially reaching up to 70% over the long term, in addition to associations with cardiovascular disease, nonalcoholic fatty liver disease, nephropathy, and early retinopathy. The lack of consensus on diagnostic cut-offs and the impact of analytical and biological variability hinder cross-study comparisons and population estimates, underscoring the need for standardization and the judicious use of laboratory markers.

Keywords: Prediabetes; intermediate hyperglycemia; HbA1c; OGTT; biological variability.

Resumo

O pré-diabetes, ou hiperglicemia intermediária, representa um estado metabólico heterogêneo associado ao risco aumentado para *diabetes mellitus* tipo 2 (DM2) e eventos cardiovasculares. Pequenas variações nos pontos de corte dos marcadores laboratoriais influenciam a prevalência e a elegibilidade para intervenções. Esta revisão objetiva sintetizar histórico, critérios diagnósticos, prevalência, variações analíticas e biológicas, principais complicações e tratamentos do pré-diabetes. As diretrizes diagnósticas utilizam a glicemia de jejum (GJ), o teste de tolerância à glicose via oral (TTGO) e a hemoglobina glicada (HbA1c); recomendações recentes incluíram a glicemia de 1 hora no TTGO (TTGO-1h). A concordância entre os marcadores é parcial, e a associação GJ e HbA1c pode ampliar a sensibilidade de triagem, embora não seja formalmente recomendada como estratégia universal. A variabilidade biológica difere entre os parâmetros: mais elevada para a glicemia 2 horas após sobrecarga de glicose (CVi ≈17%), intermediária para GJ (≈5%) e menor para HbA1c (≈1–2%), o que impacta reclassificações próximas aos limites diagnósticos. Estimativas globais ajustadas por idade variam amplamente conforme o critério empregado; estudos brasileiros evidenciam discrepâncias quando se alteram os intervalos de referência para HbA1c e GJ. A taxa média anual de progressão para DM2 situa-se entre 5% e 10%, podendo alcançar 70% em longo prazo, além de associações com doença cardiovascular, doença hepática gordurosa não alcoólica, nefropatia e retinopatia incipientes. A ausência de consenso nos critérios de corte e a influência das variabilidades analíticas e biológicas dificultam comparações e estimativas populacionais, reforçando a necessidade de padronização e do uso criterioso dos marcadores laboratoriais.

Palavras-chave: Pré-diabetes; hiperglicemia intermediária; HbA1c; TTGO; variabilidade biológica.

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INTRODUCTION

The concept of prediabetes originated in the late 1970s, aiming to characterize individuals who did not meet the diagnostic criteria for diabetes mellitus (DM) but could not be classified as normal or as being at low risk for the condition.[1,2]

The evolution of diagnostic criteria for DM, which initially used fasting plasma glucose (FPG) and the oral glucose tolerance test (OGTT) as markers, led to the establishment of the concepts of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).[3,4] Subsequently, the determination of glycated hemoglobin (HbA1c) was incorporated into these tests.[5]

Prediabetes is characterized by laboratory parameters related to plasma glucose concentration, such as FPG, HbA1c, or glucose measured 1 or 2 hours after a 75-g glucose load during the oral glucose tolerance test (1-h OGTT or 2-h OGTT). Prediabetes is associated with an increased risk of several conditions, particularly type 2 diabetes mellitus (T2DM), cardiovascular disease, and stroke. The term prediabetes is also frequently referred to as "intermediate hyperglycemia" and, less commonly, by the synonyms described in Figure 1,[6-8] which shows the main characteristics that support the concept of prediabetes, as well as terms used over the years for this category.

From a clinical perspective, individuals classified as prediabetic present a higher risk not only of progression to T2DM, with mean annual rates of 5% to 10%, but also of cardiovascular disease, nonalcoholic fatty liver disease, early nephropathy, and early-stage retinopathy.[9,10] The heterogeneity of this group, together with the influence of analytical and biological variability, reinforces the challenge of establishing robust and comparable diagnostic criteria.[11]

In this context, the present integrative review aims to synthesize the historical evolution and current criteria for the diagnosis of prediabetes, discuss the advantages and limitations of the biomarkers used, explore the impact of biological and analytical variability on prevalence, and finally present the main associated complications, with emphasis on recent recommendations. The search was conducted in medical databases, including Medline, Lilacs, and Scopus, among others, without chronological restriction, using the following descriptors in English and Portuguese: glycemia, prediabetes, intermediate hyperglycemia, analytical variability, biological variability, diagnosis of prediabetes, prevalence of prediabetes, and treatment of prediabetes.

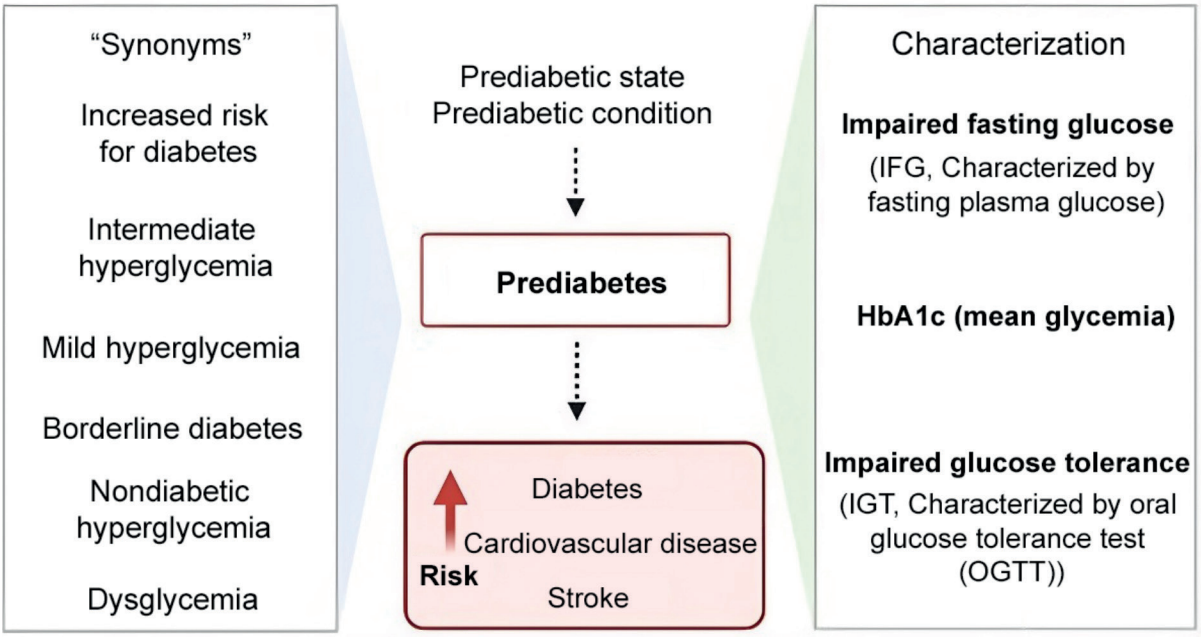


Figure 1
Main characteristics of prediabetes.

Source: Authors.

DEFINITIONS OF PREDIABETES

The concept of prediabetes has been developed over the last five decades, with continuous evolution, progressively incorporating epidemiological, metabolic, molecular, and laboratory findings in the characterization of this group.[2,12,13]

- Prediabetes is defined as glucose levels above the "normal" reference range but below the criteria required to establish the diagnosis of diabetes.[7]
- The terms prediabetes and intermediate hyperglycemia are used to describe impaired glucose tolerance or impaired fasting glucose.[7]
- Individuals with prediabetes have an increased risk of developing T2DM, cardiovascular disease, and stroke.[7]
- Prediabetes characterizes individuals with mild hyperglycemia who do not meet the criteria for diabetes, defined by mild dysglycemia occurring in impaired fasting glucose (IFG) or in the presence of mild hyperglycemia after OGTT, designated impaired glucose tolerance (IGT), without fulfilling the criteria for diabetes.[8]
- Prediabetes is an intermediate state of hyperglycemia with glycemic parameters above normal but below the criteria for diabetes.[14]

Table 1 summarizes the historical evolution of the concept of prediabetes through its main milestones.

LABORATORY CRITERIA FOR THE CHARACTERIZATION OF PREDIABETES

Guidelines published by different scientific societies that define criteria for the diagnosis of prediabetes show relevant divergences. Table 2 presents the diagnostic criteria for the characterization of prediabetes adopted by international guidelines, highlighting that the World Health Organization (WHO) prefers the term "intermediate hyperglycemia" rather than "prediabetes".

Table 1

Chronology of the main events associated with the concept of prediabetes.

Year	Comments	Ref
1970	Term used to identify glucose dysregulation	(12)
1979	**NDDG**: Used the term prediabetes to designate impaired glucose tolerance (**IGT**) defined by **2-h OGTT** plasma glucose between 140 mg/dL and 199 mg/dL	(15)
1997 1998	**ADA, WHO**: The definition of impaired fasting glucose (**IFG**) was accepted based on fasting plasma glucose between 110 mg/dL and 125 mg/dL	(16,17)
2003	**ADA**: New criterion for **IFG** with expansion of the range to 100 mg/dL to 125 mg/dL	(3)
2009	**IEC**: Recommended the definition of prediabetes using HbA1c (6.0% to 6.4%)	(5)
2010	**ADA, WHO**: Introduction of HbA1c in the definition of prediabetes	(18,19)
2025	**ADA, SBD**: Introduction of **1-h OGTT** glucose (75-g load) as an additional diagnostic criterion (155 mg/dL to 208 mg/dL)	(8)

ADA: American Diabetes Association; **HbA1c**: glycated hemoglobin (HbA1c); **IEC**: International Expert Committee (committee composed of members of the ADA, the European Association for the Study of Diabetes, and the International Diabetes Federation – IDF); **IFG**: impaired fasting glucose; **IGT**: impaired glucose tolerance; **NDDG**: National Diabetes Data Group; **SBD**: Brazilian Diabetes Society; **OGTT**: oral glucose tolerance test with a 75-g glucose load; **WHO**: World Health Organization.

Table 2

Diagnostic criteria for prediabetes in different guidelines.

Biomarkers	SBD	ADA KDA	DCCPG	NICE	WHO	IDF
Year	**2025**	**2025**	**2018**	**2012**	**2006**	**2025**
FPG, mg/dL	100 to 125	100 to 125	110 to 125	110 to 125	110 to 125	110 to 125
HbA1c, %	5.7 to 6.4	5.7 to 6.4	6.0 to 6.9	6.0 to 6.4	6.1 to 6.9	5.7 to 6.4
1h-OGTT 75g, mg/dL	155 to 208	-	-	-	-	-
2h-OGTT 75g, mg/dL	140 to 199	140 to 199	140 to 199	140 to 199	140 to 199	140 to 199

The presence of only one biomarker within the defined criteria is sufficient to characterize prediabetes. **SBD**: Brazilian Diabetes Society – Brazil[8]; **ADA**: American Diabetes Association – United States[13]; **KDA**: Korean Diabetes Association[20]; **DCCPG**: Diabetes Canada Clinical Practice Guidelines – Canada[21]; **NICE**: National Institute for Health and Care Excellence – United Kingdom[22,23]; **WHO**: World Health Organization – Global[24]; **IDF**: International Diabetes Federation – Global(7); **FPG**: fasting plasma glucose; HbA1c: glycated hemoglobin (HbA1c); **OGTT**: oral glucose tolerance test with a 75-g glucose load. Source: Adapted from Davidson MB.[22]

BIOMARKERS FOR THE CHARACTERIZATION OF PREDIABETES

As mentioned above, the biomarkers used in the characterization of prediabetes according to the main guidelines are:

- Fasting plasma glucose: useful for the characterization of impaired fasting glucose (IFG);
- Plasma glucose measured 1 hour after a 75-g oral glucose load, used in some guidelines as an additional marker of abnormal glucose tolerance;
- Glucose measured 2 hours after oral administration of a standard glucose dose, usually 75 g: useful for the characterization of impaired glucose tolerance (IGT);
- Glycated hemoglobin (HbA1c).

Among the biomarkers used in the characterization of diabetes and prediabetes, the OGTT is the oldest laboratory procedure, with approximately one century of use. Over this period, the test has undergone successive revisions regarding sampling times, glucose dose, and interpretation of results.[25] HbA1c, the most recently incorporated parameter for the diagnosis of prediabetes, became feasible only after methodological standardization.[26]

The combination of fasting plasma glucose (FPG) and HbA1c has been described as a more sensitive and specific screening tool for identifying diabetes and prediabetes in early stages.[27,28] The combined use of FPG and HbA1c in screening for prediabetes provides the benefits of the individual tests and reduces the risk of systematic bias inherent in the isolated use of HbA1c.[29] However, major guidelines do not formally recommend the combined use of biomarkers as a universal screening strategy, maintaining recommendations based on individual parameters, as previously shown in Table 2.

Biomarkers of glycemic status such as fructosamine, glycated albumin, and 1,5-anhydroglucitol are not recommended in current guidelines for the diagnosis of prediabetes.[6,8]

Although capillary glucose obtained by fingertip puncture may be used in screening settings and population studies, particularly when access to laboratory methods is limited, it does not replace plasma glucose obtained from venous samples.[30] Glucometers, although widely used for glycemic control in individuals living with diabetes, generally show inadequate precision and variability for diagnostic purposes.[31]

Guidelines emphasize that the diagnosis of prediabetes should be based on venous samples, preferably plasma, obtained using antiglycolytic agents, and on the measurement of biomarkers performed in clinical laboratories with an established quality-control system.[32]

Advantages and disadvantages of biomarkers for prediabetes

Biomarkers of glycemic status used in the diagnosis of prediabetes present different characteristics in multiple aspects. The concentrations of these biomarkers change continuously over time and according to glycemic fluctuations, without a clear threshold separating normal from pathological values. The correct interpretation of these tests requires knowledge of the advantages and limitations of these parameters. A broader discussion of the characteristics of the main biomarkers can be found in Anghebem et al., 2024,[33] in which the authors discuss the criteria for the diagnosis of diabetes with emphasis on the oral glucose tolerance test. Table 3 presents a summary of these characteristics.

The definition of cutoff values for biomarkers has a significant impact on estimates of prediabetes prevalence. These diagnostic limits contain arbitrary components and have been modified over time, reflecting advances in pathophysiological understanding and international recommendations.[36] Regardless of the criterion adopted, different cutoff points identify groups with only partial diagnostic agreement.[6,12]

Figure 2 shows that the adoption of different HbA1c criteria has a marked impact on the prevalence of prediabetes. The use of the interval from 6% to 6.4%, recommended by the National Institute for Health and Care Excellence (NICE) in the United Kingdom, when compared with the broader limits of 5.7% to 6.4% adopted in the United States[6] and Brazil,[8] increases the prevalence of prediabetes by approximately threefold. A similar effect is observed for FPG in Figure 2 (FPG columns), in which the adoption of 100 mg/dL as the lower limit, instead of 110 mg/dL, also increases by about threefold the proportion of individuals classified as having prediabetes.

It is important to highlight that when all criteria are required simultaneously (Figure 2, ALL column), prevalence decreases substantially to 2.5%, compared with the requirement of only one biomarker meeting the criteria (Figure 2, ONLY-1 column; 51.3%), representing more than a twenty-fold difference in prevalence.

The marked variation in prediabetes prevalence associated with the criteria used makes long-term epidemiological studies difficult, since prevalence will be affected not only by the characteristics of the population studied but also by the diagnostic criterion applied.[6,12]

Table 3

Characteristics of biomarkers for the diagnosis of prediabetes.

Characteristics	FPG	OGTT	HbA1c
Test cost and availability	Low cost and widely available in all laboratories	Higher cost and may not be available in all laboratories	Higher cost and not available in all laboratories
Detection of hyperglycemia	Acute measurement; Few hours	Minutes	Chronic mean glycemic exposure ~2 to 3 months earlier
Biological variability; CVi (within-subject biological variation)	High	Very high	Low
Fasting requirement	Fasting required and timed samples required		No fasting or special patient preparation required
Pre-analytical stability	Poor; requires immediate plasma separation or glycolysis inhibition		Good; sample is stable
Acute factors that may affect results	Food intake, stress, recent illness, physical activity		Not affected by acute glycemic fluctuations
Other individual factors that may affect results	Diurnal variation, medications, alcohol, smoking, bilirubin		Changes in erythrocyte lifespan (e.g., anemia, iron metabolism disorders, splenectomy, blood loss, transfusion, hemolysis, G6PD deficiency, erythropoietin therapy), HIV infection, cirrhosis, renal failure, dialysis, pregnancy
Analytical interferences	Method-dependent: sample handling/processing time, hemolysis, severe hypertriglyceridemia, severe hyperbilirubinemia		Method-dependent: hemoglobin variants (e.g., HbS, HbC), severe hypertriglyceridemia, severe hyperbilirubinemia

FPG: fasting plasma glucose; **HbA1c**: glycated hemoglobin (HbA1c); **OGTT**: oral glucose tolerance test with a 75-g glucose load. Source: American Diabetes Association Professional Practice Committee[6], Selvin E[34], Sacks DB.[35]

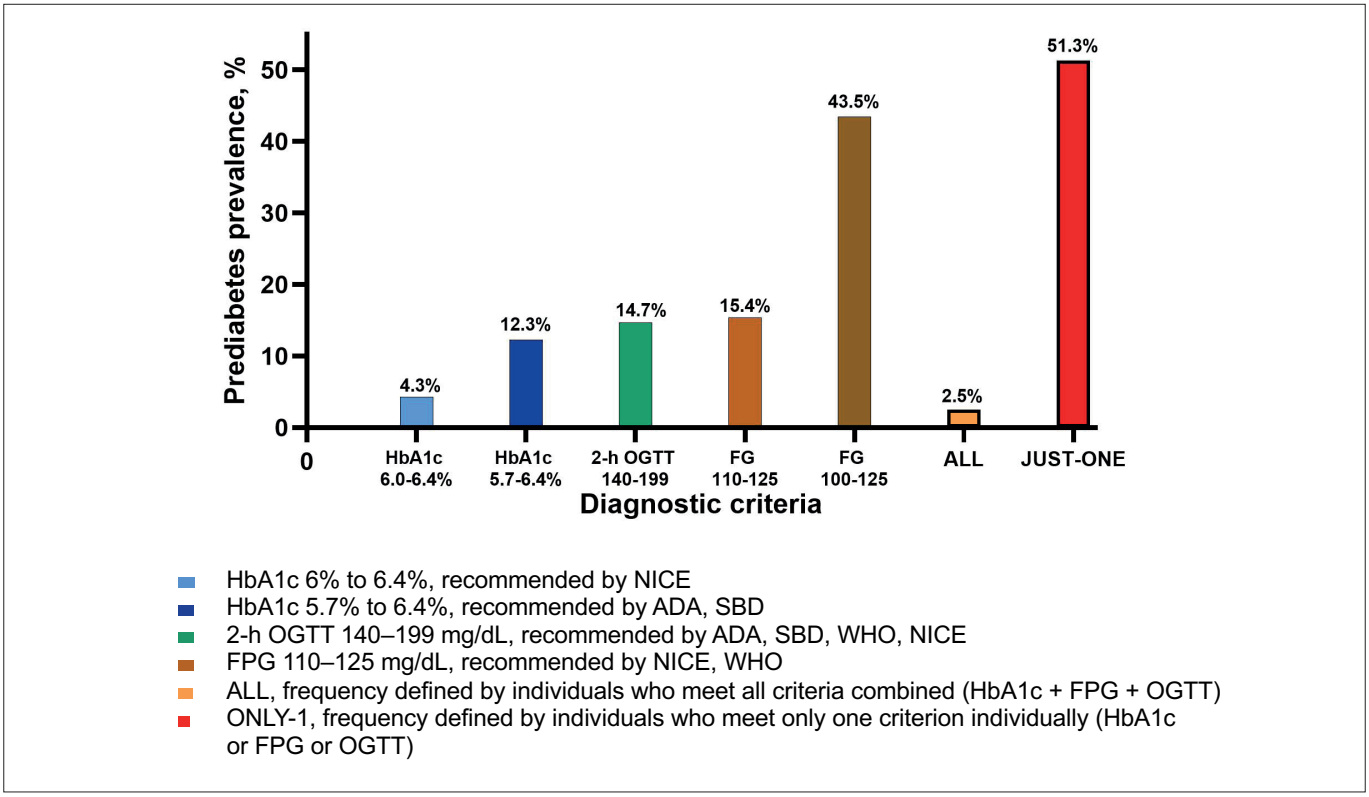


Figure 2

Prevalence of prediabetes according to different criteria.

HbA1c: glycated hemoglobin (HbA1c); **2-h OGTT**: glucose measured 2 hours after oral glucose load (75-g OGTT); **FPG**: fasting plasma glucose; **NICE**: National Institute for Health and Care Excellence – United Kingdom; **ADA**: American Diabetes Association – United States; **SBD**: Brazilian Diabetes Society – Brazil; **WHO**: World Health Organization – Global; **OGTT**: oral glucose tolerance test with a 75-g glucose load. Source: NHANES – National Health and Nutrition Examination Survey 2015–2016, as described by Echouffo-Tcheugui and Selvin, 2021.[12]

PREVALENCE OF PREDIABETES

The International Diabetes Federation (IDF), in its 2025 Atlas, presents global estimates of prediabetes prevalence stratified according to country income level classification.[7] Brazil is classified by the World Bank as an upper-middle-income economy.[37] As previously mentioned, prediabetes is traditionally defined based on two main diagnostic criteria, and prevalence depends on the cutoff values of these biomarkers, as shown in Table 4.

The Brazilian Longitudinal Study of Adult Health (ELSA-Brazil), conducted between 2008 and 2020 in six Brazilian capitals, included 15,105 participants aged 35 to 74 years.[38] The prevalence of prediabetes observed in this study, according to different diagnostic criteria, is shown in Table 5.

When HbA1c between 5.7% and 6.4% is used, as recommended by ADA and SBD, the prevalence of prediabetes ranges from 5.5% in Ireland to 40.5% in Nigeria.[7] In Brazil, Iser et al. (2020)[40] reported an overall prevalence of 18.5%, with no significant differences between sexes, using the HbA1c criterion of 5.7% to 6.4% (Table 6). The same study showed that when the interval of 6% to 6.4%, recommended by NICE and WHO, was adopted, the prevalence of prediabetes decreased by more than half, to 7.5% (95% CI: 6.7% to 8.3%).

Table 4

Age-adjusted prevalence of prediabetes in adults (20–79 years) according to country income level classification.

	Fasting glycemia (100 mg/dL to 125 mg/dL)		2-h OGTT glycemia (140 mg/dL to 199 mg/dL)	
Country income*	**Prevalence, % (age-adjusted)**	**Number of people (millions)**	**Prevalence, % (age-adjusted)**	**Number of people (millions)**
Total	9.2	487,7	12.0	634,7
High	8.4	83,9	10.4	108,6
Medium	9.5	381,3	12.3	491,3
Low	6.7	22,5	11.6	34,8

*World Bank income classification (https://datatopics.worldbank.org/world-development-indicators/the-world-by-income-and-region.html). Criteria used to characterize prediabetes were impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

Table 5

Prevalence of prediabetes based on data from the ELSA-Brasil study.

Criteria	Prediabetes prevalence, %	95% CI
Impaired glucose tolerance (IGT) (2-h OGTT, 140 mg/dL to 199 mg/dL)	20.3	19.7 to 20.9
Impaired fasting glucose (IFG) (FPG, 100 mg/dL to 125 mg/dL)	52.6	51.8 to 53.4
Impaired fasting glucose (IFG) (FPG, 110 mg/dL to 125 mg/dL)	19.1	18.5 to 19.7
HbA1c (5.7% to 6.4%)	16.1	15.5 to 16.7
HbA1c (6.0% to 6.4%)	7.0	6.5 to 7.4

Impaired glucose tolerance (IGT), criteria recommended by ADA, SBD, and WHO.

Impaired fasting glucose (IFG) between 100 and 125 mg/dL, according to ADA and SBD.

Impaired fasting glucose (IFG) between 110 and 125 mg/dL, according to NICE and WHO.

HbA1c between 5.7% and 6.4%, according to ADA and SBD.

HbA1c between 6% and 6.4%, according to NICE and WHO.

Source: Schmidt MI et al.[39]

Prediabetes prevalence increases with age and with higher body mass index, as shown in Table 6, a result consistent across several studies.[7,40,41] Ethnic characteristics of the population also represent determining factors influencing the prevalence of prediabetes in multiple investigations.[7,42-44]) In this context, different regions of Brazil reflect ethnic and cultural variation, which translates into differences in prediabetes prevalence, as shown in the "regions" column of Table 6.

EFFECTS OF ANALYTICAL AND BIOLOGICAL VARIABILITY ON PREDIABETES PREVALENCE

The correct interpretation of biomarkers associated with prediabetes must consider variability in results. The main elements affecting biomarker results are:

A. Preanalytical variability
   a1. Sample stability for glucose measurement or the "glycolysis effect"
   a2. Biological variability: intraindividual (CVi) and interindividual (CVg)
B. Analytical variability
   b1. Analytical imprecision (CVa) or test repeatability

Table 6

Prevalence of prediabetes in the Brazilian population using SBD and ADA criteria based on HbA1c concentration.

Variables	Criterion: HbA1c 5.7% to 6.4%	
	Prevalence, %	95% CI
Total (n= 7548)	18.5	17.4 a 19.7
Age group		
18 to 39	7.8	6.6 a 9.2
40 to 59	20.4	18.5 a 22.4
>60	37.6	34.7 a 40.5
BMI		
Underweight/normal weight	12.4	11.0 a 14.0
Overweight	19.8	17.9 a 21.8
Obesity	20.2	17.5 a 23.2
Regions		
North	14.6	13.0 a 16.3
Northeast	16.4	15.0 a 17.9
Southeast	20.6	18.5 a 22.9
South	16.7	14.4 a 19.3
Central-West	20.2	17.5 a 23.2

Source: Laboratory data obtained from the National Health Survey (PNS) 2014–2015, as reported by Iser et al., 2021.[40]

Preanalytical variability: glucose stability — glycolysis

Blood samples for glucose measurement in the characterization of prediabetes must be obtained after fasting (8–10 hours), 1 hour after glucose load (1-h OGTT), or 2 hours after glucose load (2-h OGTT), and preferably collected in the morning, since glucose shows circadian variation.[33,35]

As blood cells, especially erythrocytes and leukocytes, continue to use glucose in the collection tube after sample withdrawal, a continuous decrease in glucose concentration occurs in the sample, referred to as the "glycolysis effect." In a whole-blood tube without additives that inhibit glycolysis, this loss reaches approximately 5% to 7% (about 10 mg/dL) of the initial glucose concentration per hour.[35] Therefore, blood samples collected for the determination of fasting plasma glucose (FPG) and those obtained during the oral glucose tolerance test (OGTT) must be collected using antiglycolytic agents or undergo rapid plasma/serum separation within less than 30 minutes.[35] Among the anticoagulants routinely used to inhibit glycolysis are sodium fluoride and its combinations with EDTA or oxalate, as well as iodoacetate associated with heparin. These additives do not inhibit glycolysis immediately, allowing the metabolic process to continue for approximately 2 to 4 hours before complete stabilization of glucose concentration, which then remains stable for up to 72 hours after collection.[35,45]

Vacuum collection systems that combine citrate buffer, fluoride, and EDTA inhibit glycolysis immediately and stably and have been recommended for routine laboratory use.[35,46] The rapid acidification of plasma by citrate buffer inhibits glycolysis immediately, and fluoride stabilizes this inhibition.[47] Although these tubes are available on the market, they are not currently used in most laboratories.

Preanalytical variability: Biological variability

Biological variability is defined as the natural fluctuation in the concentration of an analyte within the same individual around a physiological equilibrium point, reflecting homeostatic regulatory mechanisms.[48] Biological variability is expressed statistically by the coefficient of variation (CV), which represents the relationship between the standard deviation (SD, standard deviation) and the mean, calculated by the formula CV = (SD/mean) × 100, expressed as a percentage.

Intraindividual biological variability (CVi) represents the average fluctuation in the concentration of an analyte within the same individual around his or her equilibrium point in response to physiological, hormonal, and environmental stimuli. Interindividual biological variability (CVg), in turn,

expresses the extent of variation observed among different individuals in a population.[48]

Table 7 describes the coefficients of variation for analytical and biological variability of prediabetes biomarkers, combining data from different meta-analyses.

When the effect of the intraindividual biological coefficient of variation (CVi) is applied to the lower cutoff values used to characterize prediabetes, it is possible to determine the magnitude of this factor in test interpretation. Figure 3 highlights this effect.

Considering a 95% probability and applying CVi values to the concentrations of 100 mg/dL (FPG), 140 mg/dL (2-h OGTT glucose), and 5.7% (HbA1c), variations of 20 mg/dL, 94 mg/dL, and 0.2%, respectively, are observed. This analysis shows that 2-h OGTT glucose presents the greatest range of variation, followed by FPG, whereas HbA1c demonstrates the lowest fluctuation. Thus, 2-h OGTT glucose exhibits a high degree of biological variability, making it more susceptible to oscillations that may affect the clinical interpretation of results.

Analytical variability

Glucose in plasma/serum is quantified in most laboratories by methods using the enzymes glucose oxidase/peroxidase (colorimetric) or hexokinase/glucose-6-phosphate dehydrogenase (ultraviolet). Both methodologies can be automated and are suitable for the characterization of prediabetes and diabetes.[35]

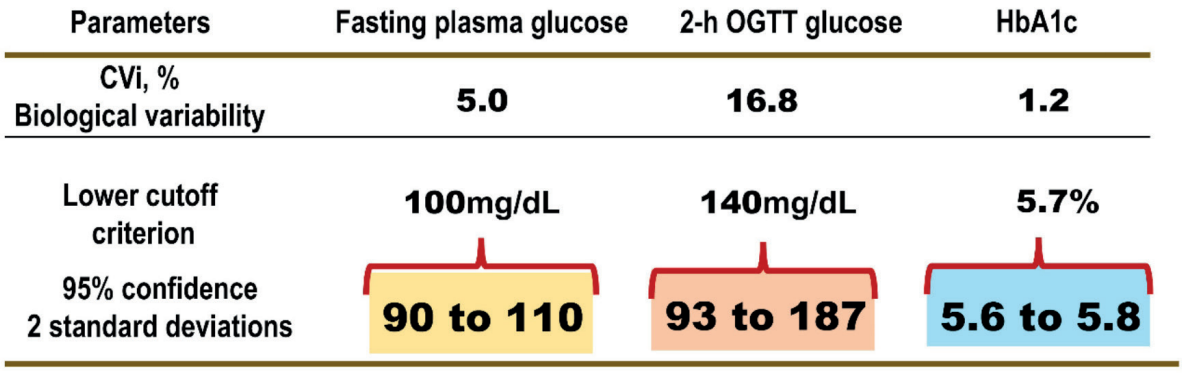
The analytical methodology must be able to accurately reflect the true glucose concentration in the sample. The systematic deviation between the measured value and the true value is referred to as bias and is expressed as a percentage. This parameter can be assessed under actual laboratory conditions using control materials, generally lyophilized or liquid sera, whose reference values are previously established by the manufacturer for different laboratory methods. Bias is

Table 7

Analytical and biological variability of biomarkers for prediabetes.

Parameters	Fasting glycemia	2-h OGTT glycemia	HbA1c
Methodology	Automated enzymatic method		Ion-exchange HPLC
CVa, % (recommended)	≤2.4 [a]		<2.5 [a]
CVa, % (observed) [range]	2.0 [1.5 a 2.5]		1.6 [1.1 a 3.0]
CVi, % (95% CI)	5.0 (4.1 a 12) [b]	16.8 (12 a 18.3) [c]	1.2 (0.3 a 2.5) [b]
CVg, % (95% CI)	8.1 (2.7 a 10.8) [b]		5.4 (3.3 a 7.3) [b]

Values are presented as coefficients of variation (95% confidence interval). **CVa**: analytical coefficient of variation (between runs); **CVi**: intraindividual biological coefficient of variation; **CVg**: interindividual biological coefficient of variation; **95% CI**: 95% confidence interval. Sources: [a]Sacks DB et al[35], [b]Ricós C et al[49,50], [c]Jagganathan R et al.[25]



Application of CVi (intraindividual biological coefficient of variation) to the lower cutoff concentrations for the diagnosis of prediabetes recommended by ADA, 2025,[6] and SBD, 2025.[8] CV = (standard deviation/mean) × 100. Two standard deviations encompass 95% of the data in a normal distribution. Sources: Sacks DB[35]; Ricós[50]

Figure 3

Effect of intraindividual biological variability on cutoff values for the diagnosis of prediabetes.

calculated from the difference between the true concentration provided by the manufacturer of the control material and that obtained in measurements performed by the laboratory, as illustrated below.

$$\text{Bias (\%)} = \left[\frac{\text{Mean control} - \text{Mean laboratory measurement}}{\text{Mean control}} \right] \times 100$$

The analytical coefficient of variation (CVa), also referred to as analytical imprecision, is determined in the laboratory from daily internal quality control results, preferably using samples with concentrations close to diagnostic decision points (e.g., 100 mg/dL for glucose) and with at least 20 measurements obtained on different days. Recommendations for acceptable CVa values for glucose and HbA1c (Table 7 – recommended CVa) were established based on intraindividual biological variability (CVi).[51]

Total error (TE), also referred to as total allowable error (TAE), integrates the components of bias and analytical imprecision (CVa), plus the statistical factor 1.65, which corresponds to a 95% confidence level.

$$\text{TE (\%)} = \text{bias (\%)} + 1.65 \times \text{CVa (\%)}$$

Recommendations for the analytical performance of methodologies used for glucose quantification are presented in Table 8.

Figure 4 describes the central elements for understanding the effect of analytical and biological variability and the statistics applied to describe these effects.

Table 8

Recommendations for analytical performance in glucose quantification.

Analyte: Glycemia	CVa, %	*Bias*, %	TE, %	Ref.
Recommended	≤2.4	≤2.1	≤6.1	(35, 52-54)
Plasma	≤2.3	≤1.8	≤5.5	Westgard*
Serum	≤2.8	≤2.34	≤6.96	Westgard*

CVa, analytical coefficient of variation; Bias, difference between the true value and the obtained value; TE, total error (TE = bias (%) + 1.65 × CVa, %).

*https://westgard.com/clia-a-quality/quality-requirements/biodatabase1.html

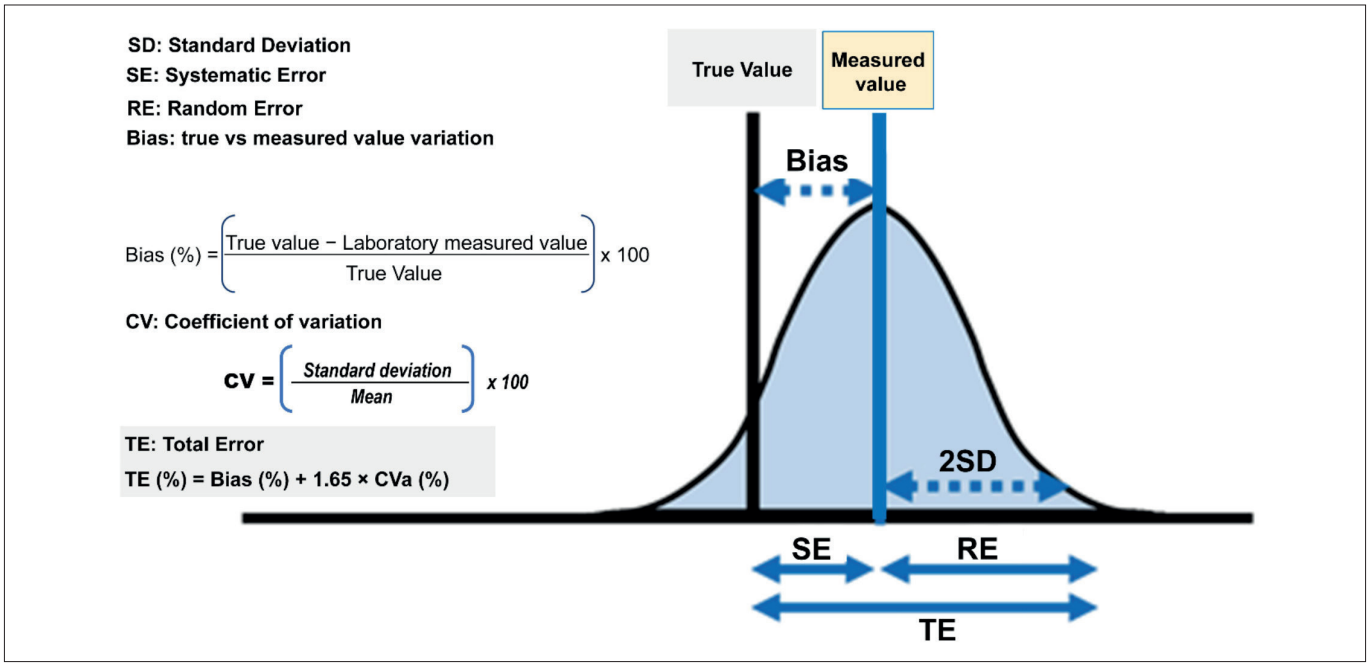


Figure 4

Representation of the main types of variation and statistics associated with biomarker assays.

Source: Adapted from James O. Westgard, Sten A. Westgard. https://myadlm.org/cln/articles/2013/september/total-analytic-error

MAIN COMPLICATIONS ASSOCIATED WITH PREDIABETES

Progression to Type 2 Diabetes

Several studies have evaluated the increased risk of individuals classified as prediabetic progressing to type 2 diabetes mellitus (T2DM). Factors such as older age, male sex, family history of DM, arterial hypertension, and obesity influence the speed of this progression.[55]

Despite the overall consistency of the findings, considerable variation is observed in the quantification and timing of progression. Examples include:

a) It is estimated that 5% to 10% of individuals with prediabetes progress to T2DM annually;[56]
b) Approximately 25% of individuals with prediabetes progress to T2DM over a period of 3 to 12 years;[6,57]
c) Up to 70% of individuals with prediabetes may progress to diabetes over their lifetime;[55]
d) The rate of progression varies according to ethnicity: in Asian Indians, a phenotype with greater predisposition to T2DM, annual progression is 18.3%, higher than that observed in Chinese individuals (11.3%), Finns (6%), and Americans (11% per person-year).[58]

Zhang et al. (2010), in a systematic study of HbA1c concentration, demonstrated the association between levels of this marker and the risk of developing type 2 diabetes mellitus. The study indicated that HbA1c concentrations between 5.5% and 6.5% are associated with a substantial increase in the risk of progression to diabetes.[59] In the study, the authors reported:

- HbA1c 5% to 5.5%: low risk of diabetes incidence, less than 9% over five years;
- HbA1c 5.5% to 6%: moderate risk of diabetes incidence, between 9% and 25% over five years;
- HbA1c 6% to 6.5%: high risk of diabetes incidence, between 25% and 50% over five years.

A risk criterion for estimating the probability of individuals with prediabetes progressing to T2DM, based on the number of altered biomarkers in each individual, has recently been proposed.[36] Table 9 presents the details of this proposal.

In North American and European cohort studies, individuals with abnormalities in two prediabetes biomarkers (2 criteria; Table 9) present an annual risk of progression to T2DM of approximately 5% to 10%, whereas in those with three altered criteria the risk is greater than 10%.[36] This rate of progression may vary according to the population studied.

Insulin resistance is present in 94% of individuals with simultaneous abnormalities in FPG and 2-h OGTT glucose, in 76% of those with isolated abnormality in 2-h OGTT glucose, and in only 57% of individuals with abnormal FPG.[36]

Other complications associated with prediabetes

Prediabetes is not limited to representing a state of increased risk for the development of T2DM. Several cardiovascular and metabolic complications may already be present at this stage, even before the onset of overt hyperglycemia. Prediabetes represents an intermediate condition between normoglycemia and type 2 diabetes mellitus (T2DM), characterized by metabolic alterations that increase the risk of several systemic complications, summarized below:

- Cardiovascular disease: Individuals with prediabetes are at increased risk of coronary artery disease, stroke, and cardiovascular mortality. Longitudinal studies indicate that the presence of IFG or IGT doubles the risk of cardiovascular events compared with normoglycemic individuals, a risk partially explained by its association with hypertension, atherogenic dyslipidemia, and chronic

Table 9

Proposed risk criterion for progression from prediabetes to T2DM.

Risk for T2DM	Normal	Elevated	High	Very high
Number of criteria present	0	1	2	3
Prediabetes phenotypes		IFG **or** 2-h OGTT **or** HbA1c	IFG + HbA1c **or** IFG + 2-h OGTT **or** 2-h OGTT + HbA1c	IFG + 2-h OGTT + HbA1c

Criteria: IFG (impaired fasting glucose) 100 mg/dL to 125 mg/dL; 2-h OGTT (impaired glucose tolerance) 140 mg/dL to 199 mg/dL; HbA1c, glycated hemoglobin (HbA1c), 5.7% to 6.4%. Source: Adapted from Kim SH[36].

low-grade inflammation.[60] In addition, prediabetes has been associated with decreased heart rate variability[61]—a marker of parasympathetic function,[62-65]—reduced postural changes in heart rate,[61] increased prevalence of erectile dysfunction in men,[66] and a worse profile in tests of sympathetic and parasympathetic function.[67] Prediabetes is associated with increased risks of important manifestations of vascular disease, but it remains unclear whether the increased disease risk depends on the development of clinical diabetes.[68,69] Cross-sectional studies provide evidence supporting the vascular risk effects of mild or moderate hyperglycemia, since an excess prevalence of coronary artery disease has been reported in individuals with fasting or post-load hyperglycemia below the diabetic threshold.[70] Compared with coronary artery disease, there is less certainty regarding cerebrovascular disease and aortic aneurysm.[70] Diabetes is a known risk factor for ischemic and hemorrhagic stroke, but it has not yet been established whether this risk increases before the development of diabetes, during the prediabetic state.[68]

- Early kidney disease: Prediabetes has been associated with an increased risk of early forms of nephropathy and chronic kidney disease, characterized by microalbuminuria and reduced glomerular filtration rate.[1,71,72] These early renal changes may progress silently, reinforcing the need for screening in at-risk groups.
- Nonalcoholic fatty liver disease (NAFLD): Insulin resistance and metabolic dysfunction present in prediabetes contribute to fat deposition in the liver. Meta-analyses have demonstrated a high prevalence of NAFLD in individuals with prediabetes, with an increased risk of progression to nonalcoholic steatohepatitis (NASH) and fibrosis.[73,74]
- Cognitive impairment and dementia: Increasing evidence indicates that prediabetes is associated with an increased risk of mild cognitive impairment, vascular dementia, and Alzheimer's disease. Chronic hyperglycemia, even at intermediate levels (prediabetes), may affect cerebral perfusion, neuronal energy metabolism, and promote β-amyloid deposition.[75-77]
- Early microvascular complications: Studies show that retinopathy and neuropathy may be detected in some individuals still classified as prediabetic, suggesting that vascular injury begins before the diagnostic threshold for T2DM.[9,10] Prediabetes may be associated with an increased risk of diabetic retinopathy, although the magnitude of this association varies according to the detection method used.[1,78-82] Recent evidence also points to an increased prevalence of idiopathic polyneuropathy, including sensory or painful neuropathy and small-fiber neuropathy, in individuals with prediabetes.[83-88] In individuals with prediabetes, impaired glucose tolerance (IGT) appears to be more strongly related to painful neuropathy than to nonpainful neuropathy.[83,85,88]

In summary, prediabetes should be regarded not only as a risk phase for T2DM, but also as a clinical condition already associated with multiple metabolic, vascular, and organ complications, as illustrated in Figure 5. This perspective reinforces the relevance of early diagnosis and immediate preventive intervention to reduce the metabolic and vascular impact of this condition and, consequently, the public health burden.

Reversion to normoglycemia

Return to normoglycemia in individuals with prediabetes, or "reversion of prediabetes," is common and varies across populations, diagnostic criteria used, and other factors that may be associated with studies, such as nutritional counseling and lifestyle guidance.[89]

As an example, in the Whitehall II population-based cohort study, which included more than 10,000 English participants with a mean follow-up of 6.7 years, the 5-year rate of reversion to normoglycemia varied according to the criterion used: 45% for FPG, 37% for 2-h OGTT glucose, and 17% for HbA1c. The authors observed that most prediabetic individuals defined by HbA1c remained in this condition or progressed to T2DM over the 5-year follow-up. Reversion to normoglycemia occurred more frequently among those with prediabetes characterized by abnormalities in FPG or 2-h OGTT glucose. It is worth noting that only reversion according to the 2-h OGTT criterion was associated with a significant reduction in the future risk of cardiovascular disease and mortality.[89]

Another relevant study, conducted by Kowall et al., evaluated an elderly population from southeastern Germany, with a mean age of 69 years, considering changes in body mass index (BMI) and waist circumference (WC).[90] During a mean follow-up of 6.5 years, 27.3% and 9.2% of prediabetic individuals, respectively classified according to ADA criteria for HbA1c and for glycemic parameters (FPG and 2-h OGTT glucose), returned to normoglycemia. Reduction in BMI and WC, even when modest, was associated with a greater probability of reversion to normoglycemia and maintenance of this state over time.

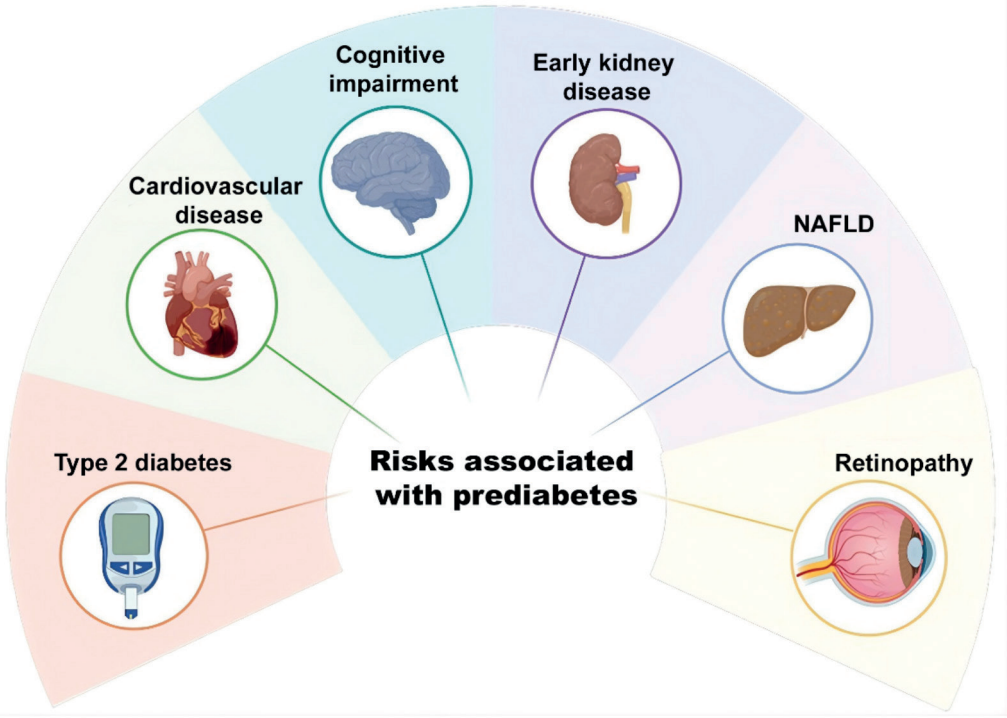


Figure 5

Risks associated with the prediabetic state.

NAFLD: Nonalcoholic fatty liver disease.

Source: Authors.

NONPHARMACOLOGICAL AND PHARMACOLOGICAL THERAPIES FOR PREDIABETES

The management of prediabetes is primarily focused on lifestyle changes, including weight loss, adoption of a balanced diet, and regular physical activity.

Large studies conducted worldwide have shown that these measures are effective in reducing progression to T2DM and are considered the main recommended intervention for individuals with prediabetes. Among the classic clinical trials, the Finnish Diabetes Prevention Study (DPS) included overweight or obese individuals with prediabetes undergoing interventions aimed at achieving ≥5% reduction in body weight, moderate-intensity physical activity for at least 150 minutes per week, reduced fat intake, and increased fiber intake. After three years, the intervention group showed a 58% reduction in progression to diabetes compared with the control group.[91] Similar results were observed in the Diabetes Prevention Program (DPP), in which a 5% to 7% reduction in body weight combined with at least 150 minutes per week of moderate physical activity reduced the risk of progression to T2DM by up to 58%.[92]

Clinical trials conducted in individuals with impaired glucose tolerance (IGT) have shown that metformin can reduce the risk of developing type 2 diabetes mellitus (T2DM) by up to 45%.[93] In the Indian DPP-1 study,[26] the effect of metformin was comparable to that of intensive lifestyle intervention, although in the American DPP study it was less effective than behavioral changes.[94] The benefit of metformin was more pronounced in prediabetic individuals with higher body mass index (BMI) and higher baseline fasting plasma glucose (FPG), compared with leaner individuals and those with lower FPG concentrations.[92]

Current evidence reinforces the potential role of pharmacotherapy in the prevention of T2DM, especially among individuals at higher risk of progression. Biguanides,

particularly metformin, remain the most studied drugs and show moderate efficacy in preventing the progression of prediabetes, although inferior to that achieved with lifestyle-based interventions.[95,96] Its main mechanism of action is the reduction of hepatic glucose production,[97] in addition to beneficial effects on BMI and lipid profile. Metformin has a favorable safety profile, with no reports of serious adverse events, and gastrointestinal side effects are generally mild to moderate.[92,98,99]

In addition to metformin, several randomized placebo-controlled clinical trials have evaluated the efficacy of different medications, including troglitazone, acarbose, orlistat, pioglitazone, rosiglitazone, ramipril, voglibose, nateglinide, valsartan, and liraglutide, in preventing progression from prediabetes to T2DM.[100] Although some studies have shown favorable results, prediabetes is still not universally recognized as a disease per se, which limits the formal approval of pharmacological or surgical interventions in many countries. Furthermore, the cost-effectiveness and sustainability of these therapies remain uncertain.[14,36,101,102]

In summary, most evidence for the management of prediabetes focuses on lifestyle modification with or without medication in overweight or obese individuals with impaired glucose tolerance, as summarized in Figure 6. It is still unclear whether these interventions are beneficial in individuals with impaired fasting glucose and in those with normal body weight, as well as the cost-effectiveness and sustainability of pharmacotherapy for the treatment of prediabetes. The field remains in evolution, with a need for long-term trials evaluating not only diabetes prevention, but also the impact on cardiovascular, hepatic, and renal complications.

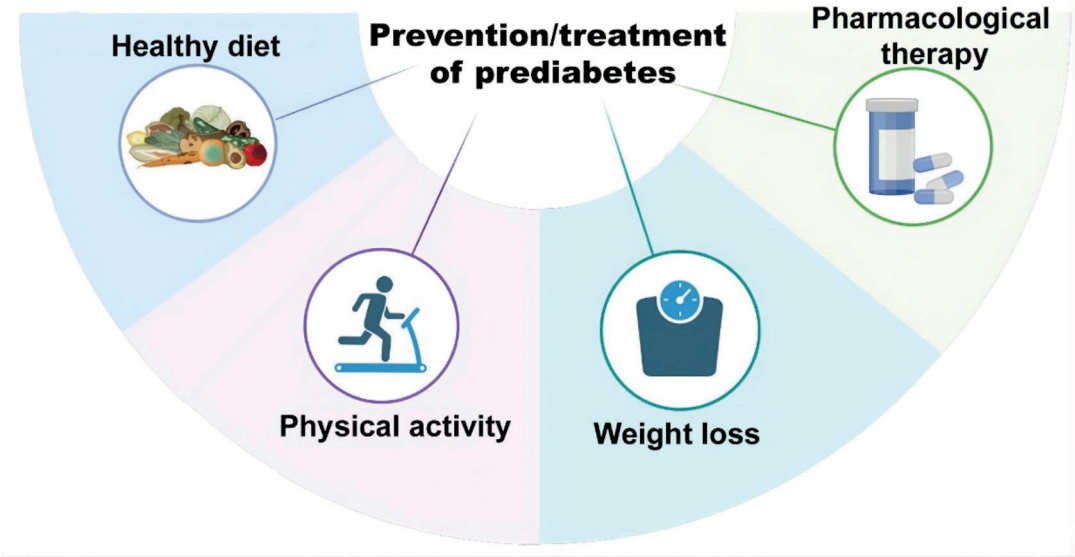


Figure 6

Strategies for the prevention and treatment of prediabetes.

The prevention and management of prediabetes involve lifestyle interventions and, in some cases, the use of pharmacological therapies. The main strategies include adoption of a healthy diet, regular physical activity, and weight reduction, which contribute to improved insulin sensitivity and glycemic control. When behavioral changes are not sufficient, pharmacological therapy may be indicated to delay or prevent progression to T2DM.

Source: Authors.

FINAL CONSIDERATIONS

Prediabetes represents a heterogeneous and dynamic metabolic condition situated along a continuum between normoglycemia and T2DM. More than a simple intermediate phase, prediabetes constitutes an early marker of metabolic dysfunction, reflecting a state in which insulin secretion and action are already altered, thereby signaling an increasing risk of progression to T2DM and of cardiovascular and microvascular complications.

The laboratory biomarkers used to characterize prediabetes—fasting plasma glucose (FPG), plasma glucose during the oral glucose tolerance test (OGTT), and glycated hemoglobin (HbA1c)—present different sensitivities and specificities, reflecting distinct aspects of glycemic homeostasis. These differences, together with their biological and analytical variability, lead to the identification of distinct phenotypic subgroups within the prediabetes spectrum. Among the tests, 2-h OGTT glucose, considered the oldest method and still a diagnostic reference, exhibits the highest intraindividual biological variability, a factor that affects reproducibility and interpretation of the results.

The global prevalence of prediabetes is estimated at 12% when criteria based on the 2-h OGTT are applied and 9.2% when based on fasting plasma glucose (FPG). In Brazil, prevalence varies according to the biomarker used: 20.3% by OGTT (140 mg/dL to 199 mg/dL), 52.6% by FPG (100 mg/dL to 125 mg/dL), and 18.5% by HbA1c (5.7% to 6.4%). These variations demonstrate the influence of diagnostic criteria and population characteristics on epidemiological estimates.

Progression from prediabetes to T2DM occurs at different rates and speeds, depending on genetic, metabolic, and behavioral factors. Conversely, reversion to normoglycemia is a frequent phenomenon, particularly associated with weight reduction, regular physical activity, and the adoption of healthy lifestyle habits. These strategies remain the basis of clinical management, supported by robust scientific evidence of effectiveness.

Pharmacological therapy, notably with metformin, may be considered in specific higher-risk situations, such as in individuals with obesity, impaired glucose tolerance, or a strong family history, although its use is not universally recommended in current guidelines.

Therefore, prediabetes should be understood as a critical window for intervention, in which early identification and preventive action have the potential to interrupt the trajectory toward overt diabetes, representing a decisive opportunity to reduce the global burden of metabolic disease.

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