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Clinical Practice Guidelines

Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome

Canadian Diabetes Association Clinical Practice Guidelines Expert Committee

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KEY MESSAGES

- The chronic hyperglycemia of diabetes is associated with significant long-term microvascular and macrovascular complications.
- A fasting plasma glucose level of ≥7.0 mmol/L, a 2-hour plasma glucose value in a 75 g oral glucose tolerance test of ≥11.1 mmol/L or a glycated hemoglobin (A1C) value of ≥6.5% can predict the development of retinopathy. This permits the diagnosis of diabetes to be made on the basis of each of these parameters.
- The term "prediabetes" refers to impaired fasting glucose, impaired glucose tolerance or an A1C of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications.

Definition of Diabetes and Prediabetes

Diabetes mellitus is a metabolic disorder characterized by the presence of hyperglycemia due to defective insulin secretion, defective insulin action or both. The chronic hyperglycemia of diabetes is associated with relatively specific long-term microvascular complications affecting the eyes, kidneys and nerves, as well as an increased risk for cardiovascular disease (CVD). The diagnostic criteria for diabetes are based on thresholds of glycemia that are associated with microvascular disease, especially retinopathy.

"Prediabetes" is a practical and convenient term referring to impaired fasting glucose (IFG), impaired glucose tolerance (IGT) (1) or a glycated hemoglobin (A1C) of 6.0% to 6.4%, each of which places individuals at high risk of developing diabetes and its complications.

Classification of Diabetes

The classification of type 1 diabetes, type 2 diabetes and gestational diabetes mellitus (GDM) is summarized in Table 1. Appendix 1 addresses the etiologic classification of diabetes. Distinguishing between type 1 and type 2 diabetes is important because management strategies differ, but it may be difficult at the time of diagnosis in certain situations. Physical signs of insulin resistance and autoimmune markers, such as anti-glutamic acid decarboxylase (GAD) or anti-islet cell antibody (ICA) antibodies, may be helpful, but have not been adequately studied as diagnostic tests in this setting. While very low C-peptide levels measured after months of clinical stabilization may favour type 1 diabetes (2), they are not helpful in acute hyperglycemia (3). Clinical judgement with safe management and ongoing follow-up is a prudent approach.

Diagnostic Criteria

Diabetes

The diagnostic criteria for diabetes are summarized in Table 2 (1). These criteria are based on venous samples and laboratory methods.

A fasting plasma glucose (FPG) level of 7.0 mmol/L correlates most closely with a 2-hour plasma glucose (2hPG) value of ≥11.1 mmol/L in a 75 g oral glucose tolerance test (OGTT), and each predicts the development of retinopathy (5–11).

The relationship between A1C and retinopathy is similar to that of FPG or 2hPG with a threshold at around 6.5% (5–7,11,12). Although the diagnosis of diabetes is based on an A1C threshold for developing microvascular disease, A1C is also a continuous cardiovascular (CV) risk factor and a better predictor of macrovascular events than FPG or 2hPG (13,14). Although many people identified by A1C as having diabetes will not have diabetes by traditional glucose criteria and vice versa, there are several advantages to using A1C for diabetes diagnosis (15). A1C can be measured at any time of day and is more convenient than FPG or 2hPG in a 75 g OGTT. A1C testing also avoids the problem of day-to-day variability of glucose values as it reflects the average plasma glucose (PG) over the previous 2 to 3 months (1).

In order to use A1C as a diagnostic criterion, A1C must be measured using a validated assay standardized to the National Glycohemoglobin Standardization Program-Diabetes Control and Complications Trial reference. It is important to note that A1C may be misleading in individuals with various hemoglobinopathies, iron deficiency, hemolytic anaemias, and severe hepatic and renal disease (16). In addition, studies of various ethnicities indicate that African Americans, American Indians, Hispanics and Asians have A1C values that are up to 0.4% higher than those of Caucasian patients at similar levels of glycemia (17,18). The frequency of retinopathy begins to increase at lower A1C levels in American blacks than in American whites, which suggests a lower threshold for diagnosing diabetes in black persons (19). Research is required

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Table 1
Classification of diabetes (1)

- Type 1 diabetes* encompasses diabetes that is primarily a result of pancreatic beta cell destruction and is prone to ketoacidosis. This form includes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.
- Type 2 diabetes may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.
- Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy.
- Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use (Appendix 1).

* Includes latent autoimmune diabetes in adults (LADA); the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells (4).

to determine if A1C levels differ in African Canadians or Canadian First Nations. A1C values also are affected by age, rising by up to 0.1% per decade of life (20,21). More studies may help to determine if age- or ethnic-specific adjusted A1C thresholds are required for diabetes diagnosis. Also, A1C is not recommended for diagnostic purposes in children, adolescents, pregnant women or those with suspected type 1 diabetes.

The decision of which test to use for diabetes diagnosis (Table 2) is left to clinical judgement. Each diagnostic test has advantages and disadvantages (Table 3). In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of 2 different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed. When the results of more than 1 test are available (among FPG, A1C, 2hPG in a 75 g OGTT) and the results are discordant, the test whose result is above the diagnostic cutpoint should be repeated and the diagnosis made on the basis of the repeat test.

Table 2
Diagnosis of diabetes

FPG ≥7.0 mmol/L
Fasting = no caloric intake for at least 8 hours
or
A1C ≥6.5% (in adults)
Using a standardized, validated assay in the absence of factors that affect the accuracy of the A1C and not for suspected type 1 diabetes (see text)
or
2hPG in a 75 g OGTT ≥11.1 mmol/L
or
Random PG ≥11.1 mmol/L
Random = any time of the day, without regard to the interval since the last meal

In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of 2 different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed.

2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *FPG*, fasting plasma glucose; *OGTT*, oral glucose tolerance test; *PG*, plasma glucose.

Table 3
Advantages and disadvantages of diagnostic tests for diabetes* (22)

Parameter	Advantages	Disadvantages
FPG	• Established standard • Fast and easy • Single sample • Predicts microvascular complications	• Sample not stable • High day-to-day variability • Inconvenient (fasting) • Reflects glucose homeostasis at a single point in time
2hPG in a 75 g OGTT	• Established standard • Predicts microvascular complications	• Sample not stable • High day-to-day variability • Inconvenient • Unpalatable • Cost
A1C	• Convenient (measure any time of day) • Single sample • Predicts microvascular complications • Better predictor of macrovascular disease than FPG or 2hPG in a 75 g OGTT • Low day-to-day variability • Reflects long-term glucose concentration	• Cost • Misleading in various medical conditions (e.g. hemoglobinopathies, iron deficiency, hemolytic anaemia, severe hepatic or renal disease) • Altered by ethnicity and aging • Standardized, validated assay required • Not for diagnostic use in children, adolescents, pregnant women or those with suspected type 1 diabetes

2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *FPG*, fasting plasma glucose; *OGTT*, oral glucose tolerance test.

* Adapted from Sacks D. A1C versus glucose testing: a comparison. Diabetes Care. 2011;34:518–523.

Prediabetes

The term "prediabetes" refers to IFG, IGT or an A1C of 6.0% to 6.4% (Table 4), each of which places individuals at high risk of developing diabetes and its complications. Not all individuals with prediabetes will necessarily progress to diabetes. Indeed, a significant proportion of people who are diagnosed with IFG or IGT will revert to normoglycemia. People with prediabetes, particularly in the context of the metabolic syndrome, would benefit from CV risk factor modification.

While people with prediabetes do not have the increased risk for microvascular disease as seen in diabetes, they are at risk for the development of diabetes and CVD (23). IGT is more strongly associated with CVD outcomes than is IFG. Individuals identified as having both IFG and IGT are at higher risk for diabetes as well as CVD. While there is no worldwide consensus on the definition of IFG (24,25), the Canadian Diabetes Association defines IFG as an FPG value of 6.1 to 6.9 mmol/L due to the higher risk of developing diabetes in these individuals compared to defining IFG as an FPG value of 5.6 to 6.9 mmol/L (25).

While there is a continuum of risk for diabetes in individuals with A1C levels between 5.5% and 6.4%, population studies demonstrate that A1C levels of 6.0% to 6.4% are associated with

Table 4
Diagnosis of prediabetes

Test	Result	Prediabetes category
FPG (mmol/L)	6.1–6.9	IFG
2hPG in a 75 g OGTT (mmol/L)	7.8–11.0	IGT
A1C (%)	6.0–6.4	Prediabetes

2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OGTT*, oral glucose tolerance test.

Table 5
Harmonized definition of the metabolic syndrome: ≥3 measures to make the diagnosis of metabolic syndrome* (29)

Measure	Categorical cutpoints	
	Men	Women
Elevated waist circumference (population- and country-specific cutpoints):		
• Canada, United States	≥102 cm	≥88 cm
• Europid, Middle Eastern, sub-Saharan African, Mediterranean	≥94 cm	≥80 cm
• Asian, Japanese, South and Central American	≥90 cm	≥80 cm
Elevated TG (drug treatment for elevated TG is an alternate indicator†)	≥1.7 mmol/L	
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	<1.0 mmol/L in males, <1.3 mmol/L in females	
Elevated BP (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg	
Elevated FPG (drug treatment of elevated glucose is an alternate indicator)	≥5.6 mmol/L	

BP, blood pressure; *FPG*, fasting plasma glucose; *HDL-C*, high-density lipoprotein cholesterol; *TG*, triglycerides.
Three or more criteriaare required for diagnosis.
* Adapted from Alberti KGMM, Eckel R, Grundy S, et al. Harmonizing the metabolic syndrome. Circulation. 2009;120:1640-1645.
† The most commonly used drugs for elevated TG and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high TG and reduced HDL-C. High-dose omega-3 fatty acids presumes high TG.

a higher risk for diabetes compared to levels between 5.5% and 6.0% (26). While the American Diabetes Association defines prediabetes as an A1C between 5.7% and 6.4%, the Canadian Diabetes Association has based the definition on a higher risk group and includes an A1C of 6.0% to 6.4% as a diagnostic criterion for prediabetes (1). However, A1C levels below 6.0% can indeed be associated with an increased risk for diabetes (26). The combination of an FPG of 6.1 to 6.9 mmol/L and an A1C of 6.0% to 6.4% is predictive of 100% progression to type 2 diabetes over a 5-year period (27).

Metabolic syndrome

Prediabetes and type 2 diabetes are often manifestations of a much broader underlying disorder (28), including the metabolic syndrome—a highly prevalent, multifaceted condition characterized by a constellation of abnormalities that include abdominal obesity, hypertension, dyslipidemia and elevated blood glucose. Individuals with the metabolic syndrome are at significant risk of developing CVD. While metabolic syndrome and type 2 diabetes often coexist, those with metabolic syndrome without diabetes are at significant risk of developing diabetes. Evidence exists to support an aggressive approach to identifying and treating people, not only those with hyperglycemia but also those with the associated CV risk factors that make up the metabolic syndrome, such as hypertension, dyslipidemia and abdominal obesity, in the hope of significantly reducing CV morbidity and mortality.

Various diagnostic criteria for the metabolic syndrome have been proposed. In 2009, a harmonized definition of the metabolic syndrome was established, with at least 3 or more criteria required for diagnosis (Table 5) (29).

RECOMMENDATIONS

1. Diabetes should be diagnosed by any of the following criteria:
   - FPG ≥7.0 mmol/L [Grade B, Level 2 (11)]
   - A1C ≥6.5% (for use in adults in the absence of factors that affect the accuracy of A1C and not for use in those with suspected type 1 diabetes) [Grade B, Level 2 (11)]
   - 2hPG in a 75 g OGTT ≥11.1 mmol/L [Grade B, Level 2 (11)]
   - Random PG ≥11.1 mmol/L [Grade D, Consensus]

2. In the absence of symptomatic hyperglycemia, if a single laboratory test result is in the diabetes range, a repeat confirmatory laboratory test (FPG, A1C, 2hPG in a 75 g OGTT) must be done on another day. It is preferable that the same test be repeated (in a timely fashion) for confirmation, but a random PG in the diabetes range in an asymptomatic individual should be confirmed with an alternate test. In the case of symptomatic hyperglycemia, the diagnosis has been made and a confirmatory test is not required before treatment is initiated. In individuals in whom type 1 diabetes is likely (younger or lean or symptomatic hyperglycemia, especially with ketonuria or ketonemia), confirmatory testing should not delay initiation of treatment to avoid rapid deterioration. If results of two different tests are available and both are above the diagnostic cutpoints, the diagnosis of diabetes is confirmed [Grade D, Consensus].

3. Prediabetes (defined as a state which places individuals at high risk of developing diabetes and its complications) is diagnosed by any of the following criteria:
   - IFG (FPG 6.1–6.9 mmol/L) [Grade A, Level 1 (23)]
   - IGT (2hPG in a 75 g OGTT 7.8–11.0 mmol/L) [Grade A, Level 1 (23)]
   - A1C 6.0%–6.4% (for use in adults in the absence of factors that affect the accuracy of A1C and not for use in suspected type 1 diabetes) [Grade B, Level 2 (26)].

Abbreviations:
2hPG, 2-hour plasma glucose; *A1C*, glycated hemoglobin; *FPG*, fasting plasma glucose; *IFG*, impaired fasting glucose; *IGT*, impaired glucose tolerance; *OGTT*, oral glucose tolerance test; *PG*, plasma glucose.

Other Relevant Guidelines

Screening for Type 1 and Type 2 Diabetes, p. S12
Reducing the Risk of Developing Diabetes, p. S16
Type 1 Diabetes in Children and Adolescents, p. S153
Type 2 Diabetes in Children and Adolescents, p. S163

Relevant Appendix

Appendix 1. Etiologic Classification of Diabetes Mellitus

References

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012;35(suppl 1):S64–71.
2. Patel P, Macerollo A. Diabetes mellitus: diagnosis and screening. Am Fam Physician 2010;81:863–70.
3. Unger RH, Grundy S. Hyperglycemia as an inducer as well as a consequence of impaired islet cell function and insulin resistance: implications for the management of diabetes. Diabetologia 1985;28:119–21.
4. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cell cytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. Lancet 1997; 350:1288–93.
5. McCance DR, Hanson RL, Charles MA, et al. Comparison of tests for glycated hemoglobin and fasting and two hour plasma glucose concentrations as diagnostic methods for diabetes. BMJ 1994;308:1323–8.
6. Engelgau MM, Thompson TJ, Herman WH, et al. Comparison of fasting and 2-hour glucose and HbA1c levels for diagnosing diabetes. Diagnostic criteria and performance revisited. Diabetes Care 1997;20:785–91.
7. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 1997;20:1183–97.

8. Ito C, Maeda R, Ishida S, et al. Importance of OGTT for diagnosing diabetes mellitus based on prevalence and incidence of retinopathy. Diabetes Res Clin Pract 2000;49:181–6.
9. Miyazaki M, Kubo M, Kiyohara Y, et al. Comparison of diagnostic methods for diabetes mellitus based on prevalence of retinopathy in a Japanese population: the Hisayama Study. Diabetologia 2004;47:1411–5.
10. Tapp RJ, Zimmett PZ, Harper CA, et al. Diagnostic thresholds for diabetes: the association of retinopathy and albuminuria with glycaemia. Diabetes Res Clin Pract 2006;73:315–21.
11. The DETECT-2 Collaboration Writing Group. Glycemic thresholds for diabetes specific retinopathy. Diabetes Care 2011;34:145–50.
12. International Expert Committee. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32: 1327–34.
13. Sarwar N, Aspelund T, Eiriksdottir G, et al. Markers of dysglycaemia and risk of coronary heart disease in people without diabetes: Reykjavik Prospective Study and systematic review. PLoS Med 2010;7:e1000278.
14. Selvin E, Steffes MW, Zhu H, et al. Glycated hemoglobin, diabetes, and cardiovascular risk in nondiabetic adults. N Engl J Med 2010;362: 800–11.
15. Report of a World Health Organization Consultation. Use of glycated haemoglobin (HbA1C) in the diagnosis of diabetes mellitus. Diabetes Res Clin Pract 2011;93:299–309.
16. Gallagher EJ, Bloomgarden ZT, Roith D. Review of hemoglobin A1c in the management of diabetes. J Diabetes 2009;1:9–17.
17. Herman WH, Ma Y, Uwaifo G, et al. Differences in A1C by race and ethnicity among patients with impaired glucose tolerance in the Diabetes Prevention Program. Diabetes Care 2007;30:2453–7.
18. Ziemer DC, Kolm P, Weintraub WS, et al. Glucose-independent, black-white differences in hemoglobin A1c levels. Ann Intern Med 2010;152: 770–7.
19. Tsugawa Y, Mukamal K, Davis R, et al. Should the HbA1c diagnostic cutoff differ between blacks and whites? A cross-sectional study. Ann Intern Med 2012; 157:153–9.
20. Davidson MB, Schriger DL. Effect of age and race/ethnicity on HbA1c levels in people without known diabetes mellitus: implications for the diagnosis of diabetes. Diabetes Res Clin Pract 2010;87:415–21.
21. Pani L, Korenda L, Meigs JB, Driver C, Chamany S, Fox CS, et al. Effect of aging on A1C levels in persons without diabetes: evidence from the Framingham Offspring Study and NHANES 2001-2004. Diabetes Care 2008;31:1991–6.
22. Sacks D. A1C versus glucose testing: a comparison. Diabetes Care 2011;34: 518–23.
23. Santaguida PL, Balion C, Morrison K, et al. Diagnosis, prognosis, and treatment of impaired glucose tolerance and impaired fasting glucose. Evidence report/technology assessment no. 128. Agency Healthcare Research and Quality Publication No 05-E026-2. Rockville, MD: Agency for Healthcare Research and Quality; September 2005.
24. Shaw JE, Zimmet PZ, Alberti KG. Point: impaired fasting glucose: the case for the new American Diabetes Association criterion. Diabetes Care 2006;29:1170–2.
25. Forouhi NG, Balkau B, Borch-Johnsen K, et al, EDEG. The threshold for diagnosing impaired fasting glucose: a position statement by the European Diabetes Epidemiology Group. Diabetologia 2006;49:822–7.
26. Zhang X, Gregg E, Williamson D, et al. A1C level and future risk of diabetes: a systematic review. Diabetes Care 2010;33:1665–73.
27. Heianza Y, Arase Y, Fujihara K, et al. Screening for pre-diabetes to predict future diabetes using various cut-off points for HbA1c and impaired fasting glucose: the Toranomon Hospital Health Management Center Study 4 (TOPICS 4). Diabetic Med 2012;29:e279–85.
28. Reaven GM. Banting Lecture 1988. Role of insulin resistance in human disease. Diabetes 1988;37:1595–607.
29. Alberti KGMM, Eckel R, Grundy S, et al. Harmonizing the metabolic syndrome. Circulation 2009;120:1640–5.