Therapeutics Initiative
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What to do about borderline hyperglycemia?

Case vignette: *A 55-year-old male with a BMI of 32 kg/m² has been your patient for 2 years. At an annual health review, you order laboratory tests including fasting plasma glucose (FPG) and A1c to screen for diabetes. The FPG of 6.3 mM and A1c of 6.2% are flagged as abnormal; he has already seen the results. What should you do?*

People characterized as borderline hyperglycemic by laboratory tests are at higher risk of progressing to confirmed type 2 diabetes (T2DM) than those who are normoglycemic.[1] **But for those who will not develop T2DM, is recognition and treatment of a "prediabetes" phase beneficial?** A 2020 summary of available evidence suggests that about two-thirds of people characterized as "prediabetic" **do not develop diabetes** when followed for up to 12 years,[2] and a 2010 systematic review reached similar findings.[1] One cohort study followed 6,241 people for 5 years after discovery of "prediabetes": **20–30% reverted to normoglycemia.**[3]

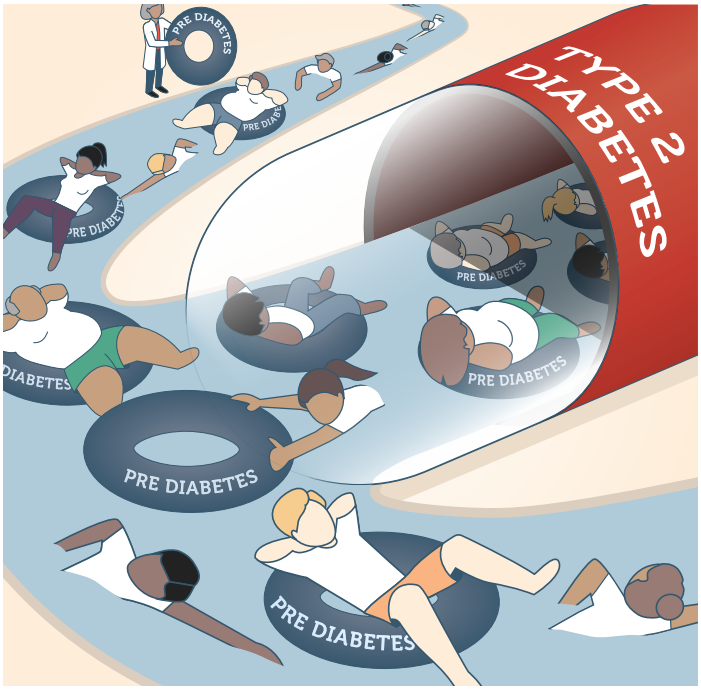
The term "prediabetes" has been used to describe screening test results that are higher than normal but do not meet diagnostic criteria for T2DM.[4] There is debate as to whether there is long-term benefit from identifying "prediabetes." As with other laboratory tests, concerns raised by an abnormal glycemic result can be hard to shed. Unwelcome consequences (testing and monitoring, stigma, potentially costly or harmful treatments, eligibility for life insurance or cost) should be balanced against potential benefits before applying this diagnostic label.[5–7]

Definitions of borderline hyperglycemia

Thresholds for borderline hyperglycemia are based on expert interpretation of studies that rely on surrogate outcomes (e.g. future hyperglycemia or diabetes diagnosis) or on predicted risk (e.g. Framingham Risk Score).[1,8–10]

Diabetes Canada defines "prediabetic" glycemia as either impaired fasting glucose (FPG 6.1–6.9 mM), impaired glucose tolerance (glucose of 7.8–11.0 mM at 2 hours after 75g oral glucose), or an A1c between 6.0 and 6.4%.[4] The American Diabetes Association defines as "prediabetic" any one of: fasting plasma glucose (FPG) of 5.6 to 6.9 mM, 2-hour postprandial glucose 7.8 to 11.0 mM, or A1c 5.7 to 6.4%.[8] **The World Health Organization (WHO) considers evidence insufficient to use A1c levels to define "prediabetes."** WHO accepts either impaired FPG or 2-hour postprandial glucose, using the same ranges as Diabetes Canada.[8]

Using its own criteria, Diabetes Canada estimates that approximately 20% of Canadians are at elevated risk of developing diabetes.[4] Prevalence and incidence of borderline hyperglycemia are not well documented in Canada. But trends likely mirror T2DM, which is more prevalent in people with lower educational attainment or socioeconomic status; women with prior gestational diabetes; and among people who are physically inactive, overweight, or obese.[11,12] Rates also vary by ethnicity.[11,13] Moving from a neighbourhood



with a high level of poverty to one with less poverty reduced diabetes and extreme obesity in a housing subsidy experiment in Chicago in the 1990s.[14]

Choosing lower thresholds and accepting any of 3 criteria (rather than a combination) identifies more people who may progress to T2DM; but it also increases the number of false positives.[15] And individual plasma glucose and A1c vary over time.

Further, whether intensive glycemic control itself reduces important clinical outcomes of T2DM remains at issue.[16] In recent clinical trials of SGLT-2 inhibitors and GLP-1 receptor agonists **for T2DM**, clinical benefits accrued at A1c levels somewhat greater than 7%. These drugs may work by mechanisms other than glucose lowering.[17–19]

Implications for health

The most important clinical issue is to reduce or delay long-term outcomes, primarily cardiovascular (CV) disease, in people who progress to T2DM. A 2020 meta-analysis applied the WHO and Diabetes Canada criteria for "prediabetes" to 129 cohort studies including over 10 million people followed for a median of 9.8 years.[20] The Table shows the authors' relative risk estimates for all-cause mortality and CV events. They estimate absolute risk differences from "prediabetes" vs normoglycemia for all-cause mortality as 7.36 per 10,000 person years, and for composite CV disease as 8.75/10,000 person years.

Glycemic criterion	Outcome	Relative Risk (RR)	95% CI
Impaired FPG	All-cause mortality CV events	1.13 1.20	1.05-1.20 1.09-1.34
Impaired 2h glucose tolerance	All-cause mortality CV events	1.25 1.23	1.17-1.32 1.13-1.32
A1c 6.0-6.4%	All-cause mortality CV events	1.21 1.15	1.06-1.38 0.98-1.35

Whether "prediabetes" causes microvascular complications is less studied.[21]

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Is this a key predictor of future health problems?

Hyperglycemia in "prediabetes" is not independently associated with CV disease, but is associated with co-existing non-glycemic risk factors such as smoking, hypertension, inactivity, or obesity.[2] So, as with T2DM, the association between "prediabetes" and future CV disease is multifactorial.[8] Hyperglycemia may be one indicator of increased CV risk, but not the major driver.

How should we manage borderline hyperglycemia?

The US Diabetes Prevention Program trial (DPP) compared metformin 850 mg twice/day (plus standard lifestyle recommendations) with intensive lifestyle intervention alone, or standard lifestyle recommendations (control). Between 1996 and 2001, DPP followed 3,234 "prediabetic" Americans (mean age 51 years, mean BMI 34 kg/m^2) for a mean of 2.8 years to evaluate their risk of progression to T2DM.[22] **Enrolment criteria were elevated FPG (5.3–6.9 mmol/L) *and* impaired glucose tolerance (2h-PPG 7.8–11.0 mmol/L).** The intensive lifestyle intervention involved 150 minutes of physical activity/week and a meal plan (reduced calories and fat) aiming to achieve >7% weight loss. Compared with standard lifestyle recommendations, the intensive lifestyle intervention (NNT: 7 for 3 years) and metformin (NNT: 14 for 3 years) each reduced progression to T2DM. *Therapeutics Letter 137* recommended exercise prescriptions to facilitate such change.

A 2019 Cochrane systematic review of 20 RCTs (N = 6,774 people) found that both metformin and lifestyle interventions reduced progression to T2DM and were similarly efficacious but not additive.[23] No medications are currently approved to treat "prediabetes" in Canada. A recommendation of metformin to reduce risk of developing T2DM among people with impaired FPG or A1c 6.0 to 6.4% is considered Grade D evidence by Diabetes Canada.[4]

Does treating people with borderline hyperglycemia reduce bad clinical outcomes important to patients? This is less clear. Two long-term observational follow-up studies of the DPP trial (about 20 years each) found no difference in future risk of major CV events, CV death, or total mortality between people originally randomized to receive metformin (continued open label), or intensive lifestyle intervention (offered metformin post-trial) compared with standard lifestyle advice only.[24,25]

Evidence that newer drugs (SGLT2 inhibitors and GLP-1 agonists) improve patient-important clinical outcomes in T2DM at achieved A1c >7% suggests that large RCTs combining lifestyle interventions with these drug classes could potentially identify more promising drug treatments.[26,27]

The health context, values and goals of individual patients (age, life expectancy, co-morbidities, treatment burden) pose an essential question: will acting on borderline hyperglycemia make sense for your patient?

Conclusions

- **Many people with borderline hyperglycemia will not progress to type 2 diabetes.**
- **Borderline hyperglycemia is associated with adverse health outcomes, but other risk factors for cardiovascular disease may be more important.**
- **Use borderline hyperglycemia as a "wake up call": an opportunity to discuss options. Emphasize lifestyle optimization with improved diet and physical activity.**

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