1 "Is Prediabetes a Risk Factor or Is It a Disease?"

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LEARNING POINTS

- Prediabetes is a heterogeneous condition with variable risk of progression to type 2 diabetes
- In addition to diabetes risk, it is associated with an increased risk of vascular disease.
- To date, lifestyle modification is the single most important tool for altering the natural history of prediabetes and progression to type 2 diabetes.

What is prediabetes?

Prediabetes is defined as an elevated fasting plasma glucose (FPG), and/or an elevated 2-hour plasma glucose (2-h PG) during a 75-gram (g) oral glucose tolerance test (OGTT), and/or an elevated Hemoglobin A1c (HbA1c), without meeting diagnostic criteria for overt diabetes mellitus (DM) [1]. The 2020 American Diabetes Association (ADA) Guidelines define prediabetes as impaired fasting glucose (IFG) with a FPG of 100–125 mg/dL, and/or impaired glucose tolerance (IGT) with a 2-h PG during a 75-g OGTT of 140–199 mg/dL, and/or a HbA1c of 5.7–6.4% [1]. In contrast to the ADA, the 2016 World Health Organization (WHO) Guidelines define intermediate hyperglycemia as IFG between 110–125 mg/dL and/or IGT with a 2-h PG during a 75-g OGTT between 140–199 mg/dL [2]. Unlike the ADA, the WHO does not include HbA1c as a diagnostic criterion for prediabetes.

The definitions of both prediabetes and DM have evolved in recent decades. The WHO first defined the "borderline state" in 1965 as a 2-h PG during a 50 or 100 g OGTT between 110–129 mg/dL [3]. The ADA has long recognized IGT, and its definition has undergone little change since its inception. First adopted by the ADA in 1997 and WHO in 1999, the term IFG was originally defined as FPG 110–125 mg/dL [4]. However, in 2003, the ADA revised the criteria for IFG to 100–125 mg/dL based on data from multiple studies showing that the risk of DM increases markedly at a FPG concentration > 100 mg/dL [5]. In 2010, the ADA added HbA1c as a diagnostic criterion for prediabetes because the relationship between HbA1c and the risk of retinopathy was similar to corresponding FPG and 2-h PG thresholds [6].

Rationale for the diagnostic criteria for diabetes mellitus and prediabetes

Individuals with prediabetes have abnormal glucose regulation and increased risk for developing DM type 2 (DM2) and its complications [6]. The diagnostic thresholds for DM are based on [1] the bimodal distribution of FPG and 2-h PG during an OGTT and [2] the glycemic thresholds

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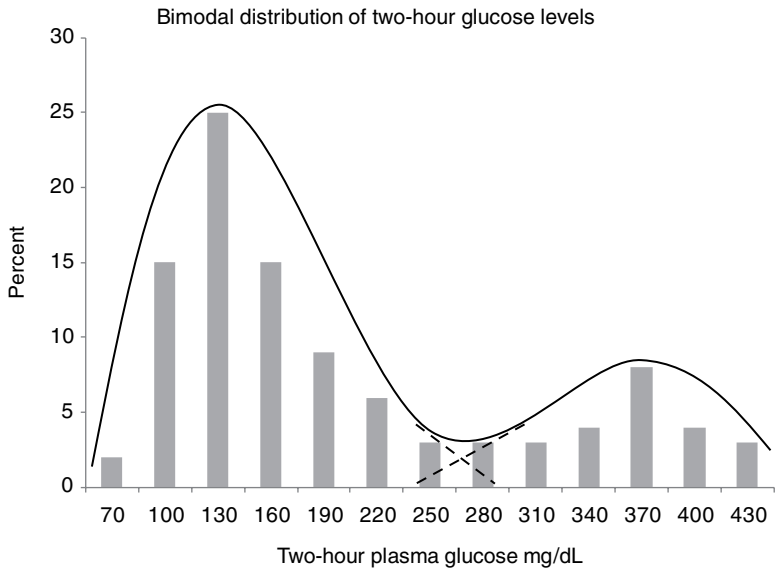

FIG 1.1 Histogram with superimposed composite and component curves to describe the distribution of two-hour plasma glucose levels following an oral glucose load. Glucose concentrations and frequencies were arbitrarily chosen to illustrate a bimodal distribution. The bimodal glucose distribution can be used to separate individuals into two groups, those with normoglycemia and those with hyperglycemia. Intermediate glucose concentrations between normoglycemia and hyperglycemia helped define the diagnostic thresholds for prediabetes.

for the development of microvascular complications, specifically retinopathy (Figure 1.1). The bimodal distribution and glycemic thresholds for the development of microvascular complications have been demonstrated in many populations including the Pima, Nauruans, South Africans, Americans, Chinese, and Egyptians [7–15]. The bimodal distribution of glucose has been used to separate individuals into two groups: those with normoglycemia and those with hyperglycemia. IFG and IGT were defined as intermediates between normoglycemia and hyperglycemia. The diagnostic thresholds for FPG, 2-h PG during a 75-g OGTT, and HbA1c are relatively concordant in discriminating between the two components of a bimodal frequency distribution and their associations with microvascular complications [4]. It is important to note that defining a lower limit of an intermediate category of FPG, 2-h PG during a 75-g OGTT, and HbA1c is somewhat arbitrary because the risk of developing DM is a continuum that extends into the normoglycemic range [6].

Epidemiology of prediabetes

The 2020 National Diabetes Statistics Report published by the Centers for Disease Control and Prevention estimated the prevalence of prediabetes (defined by 2020 ADA criteria) to be 38.0% (95% confidence interval (CI) 35.2–40.8) among adults in the United States (U.S.) [1, 16]. Overall, the prevalence of prediabetes has not changed significantly from 2005–2016. However, the number of U.S. adults who are aware that they have prediabetes increased from 6.5% (95% CI 5.3–7.9) in 2005–2008 to 13.3% (95% CI 11.0–16.0) in 2013–2016. Further, the prevalence of prediabetes increases with age: 29.1% (95% CI 25.2–33.3) of adults 18–44 years of age; 46.3% (95% CI 43.5–49.1) of adults 45–64 years of age; and 51.0% (95% CI 46.5–55.5) of adults ≥ 65 years of age. Prediabetes is also more common in men, whose prevalence is 42.3% (95% CI 38.1–46.5), compared to women, whose prevalence is 33.7% (95% CI 30.7–36.8). The prevalence of prediabetes is similar among racial/ethnic groups and among individuals of different education levels [16].

Pathogenesis of impaired fasting glucose and impaired glucose tolerance

In epidemiologic studies, isolated IGT consistently has a higher prevalence than isolated IFG [17]. The prevalence of IFG and IGT increases with age [17]. In adults less than 55 years of age, IGT is more common in women and IFG is more common in men [17]. This suggests that these two states have different pathophysiologic mechanisms.

Genetics and lifestyle influence the pathogenesis of DM [18, 19]. Although more than 400 genetic signals have been identified as influencing risk for DM2, single polymorphisms add only small degrees of risk [20]. Polymorphisms in the Transcription factor 7-like 2 (*TCF7L2*) locus have the largest-known effect on risk for DM [20, 21]. Compared with non-carriers, heterozygous and homozygous carriers of the at-risk *TCF7L2* variants have relative risks of developing DM of 1.45 and 2.41, respectively [20, 21].

The relationship between genetics and lifestyle on the pathogenesis of DM was emphasized by a study comparing the prevalence of DM2 in the Pima population in Mexico versus the Pima population in the U.S. [22]. The prevalence of DM2 in the Pima population in Mexico was 6.9%, compared to 38% in the Pima population in the U.S. The prevalence of obesity in the Pima population in Mexico was significantly lower than that in the Pima population in the U.S. By comparison, the latter group also had significantly lower physical activity levels.

Overall, islet cell function is the primary regulator of glucose metabolism, but multiple additional factors contribute. Postprandial and fasting glucose concentrations are determined by insulin secretion, hepatic extraction, insulin action, glucagon suppression, glucose effectiveness, and the rate of gastric emptying (Figure 1.2) [23–29].

Studies using the minimal model to quantitate insulin secretion and insulin action demonstrated that both indices are lower in subjects with NFG/IGT and IFG/IGT than in subjects with NFG/NGT [25, 26]. However, there was no significant difference in insulin secretion and insulin action between subjects with IFG/NGT and those with NFG/NGT. This implies that insulin secretion declines in concert with insulin action across the spectrum of prediabetes; however, subjects with isolated IFG may have an altered glucose threshold for insulin secretion without other intrinsic defects in β-cell function.

Using human pancreatic tissue obtained at autopsy, obese individuals with IFG have a 40% deficit in relative beta-cell volume compared to obese individuals with NFG [30]. Additionally, the diabetes-associated genetic variation in *TCF7L2* is associated with impaired insulin secretion [31–33]. The inability of insulin secretion to compensate for a decline in insulin action results in hyperglycemia.

It is also essential to consider the role of hepatic extraction in the pathophysiology of prediabetes and DM [26]. The peripheral insulin concentration reflects portal insulin secretion, hepatic extraction, distribution, and degradation [34]. Hepatic extraction of secreted insulin has a direct relationship with disposition index. Reduced hepatic extraction in prediabetes and DM may be a compensatory measure to increase circulating insulin. Interestingly, insulin pulse characteristics influence hepatic extraction of insulin, and the diabetes-associated genetic variation in *TCF7L2* is associated with abnormal insulin pulse characteristics [33].

Furthermore, lack of glucagon suppression contributes to hyperglycemia in subjects with impaired insulin secretion [24]. The diabetes-associated genetic variation in *TCF7L2* is associated with impaired glucagon suppression [31, 35]. In a longitudinal study, defects in α-cell function with elevated fasting glucagon concentrations were associated with a subsequent decline in β-cell function [36].

Screening recommendations for prediabetes

The 2020 ADA Guidelines recommend screening asymptomatic overweight or obese adults for DM or prediabetes if at least one of the following risk factors is present: first-degree relative with DM; high-risk race/ethnicity (e.g. African American, Latino, Native American, Asian American, Pacific Islander); history of cardiovascular disease; hypertension; high-density lipoprotein cholesterol < 35 mg/dL; triglyceride level > 250 mg/dL; presence of polycystic ovary syndrome; physical inactivity; or other clinical considerations associated with reduced insulin action such as acanthosis nigricans [1]. The 2020 ADA Guidelines further recommend that patients with prediabetes be tested yearly and that women with a history of gestational diabetes be tested lifelong at least every three years. For all other

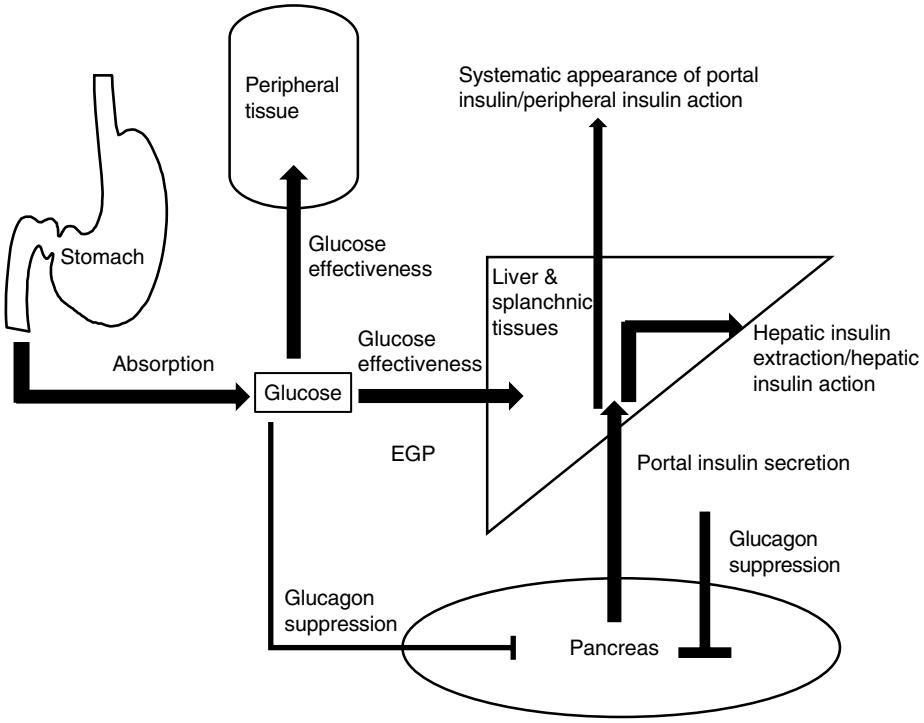

FIG 1.2 Postprandial and fasting glucose concentrations are determined by insulin secretion, hepatic insulin extraction, insulin action, glucagon suppression, glucose effectiveness, endogenous glucose production, and the rate of gastric emptying [23–29]. EGP = Endogenous Glucose Production.

patients, screening should begin at age 45, and if results are normal, should be repeated at least every three years.

Reproducibility, sensitivity, and specificity of glycemic measurements and the role of oral glucose tolerance testing in clinical practice

A study that analyzed data from the Second Examination of the Third National Health and Nutrition Examination Survey (NHANES) found that the within-person coefficient of variation was 16.7% (95% CI 15.0–18.3) for 2-h PG, 5.7% (95% CI 5.3–6.1) for FPG, and only 3.6% (95% CI 3.2–4.0) for HbA1c [37]. A study of non-diabetic adults reported a reproducibility rate of 65.6% for a 75-g OGTT repeated twice over a six-week period [38].

HbA1c, FPG, and 2-h PG during a 75-g OGTT have different sensitivities and specificities in the diagnosis of prediabetes and DM [39]. An analysis of NHANES data from 2005–2010 examined adults without self-reported DM at baseline with available measurements for HbA1c, FPG, and 2-h PG [40]. Prediabetes and DM were defined according to the current ADA Guidelines [1]. Using HbA1c thresholds of ≥ 6.5% for DM and ≥ 5.7% for prediabetes resulted in low sensitivity (24.9% and 35.4%, respectively) and high specificity in identifying patients diagnosed with FPG and 2-h PG. When FPG and HbA1c were used together for diagnosis, the false-negative rate was 45.7% for DM and 9.2% for prediabetes.

Similar findings were reported in the Insulin Resistance Atherosclerosis Study (IRAS), which examined 855 subjects and defined DM and prediabetes in accordance with the 2020 ADA Guidelines (Tables 1.1 and 1.2) [1, 41]. HbA1c ≥ 6.5%, FPG ≥ 126 mg/dL, and 2-h PG ≥ 200 mg/dL identified 32.3%, 44.8%, and 86.8% of individuals with

TABLE 1.1 The sensitivity of various indices of glycemia used to diagnose type 2 diabetes mellitus in the Insulin Resistance Atherosclerosis Study. Diabetes mellitus was defined according to the 2020 American Diabetes Association criteria. This data illustrates that omitting an oral glucose tolerance test leads to under-diagnosis of diabetes mellitus, even when both fasting plasma glucose and hemoglobin A1c are measured concurrently. HbA1c = Hemoglobin A1c. FPG = Fasting Plasma Glucose. 2-h PG = 2-hour Plasma Glucose [41].

	Sensitivity
HbA1c ≥ 6.5%	32.3%
FPG ≥ 126 mg/dL	44.8%
2-h PG ≥ 200 mg/dL	86.8%
HbA1c ≥ 6.5% and/or FPG ≥ 126 mg/dL	52.2%
FPG ≥ 126 mg/dL and/or 2-h PG ≥ 200 mg/dL	97.1%

TABLE 1.2 The sensitivity of various indices of glycemia used to diagnose prediabetes in the Insulin Resistance Atherosclerosis Study. Prediabetes was defined according to the 2020 American Diabetes Association criteria. This data illustrates that omitting an oral glucose tolerance test leads to under-diagnosis of prediabetes, even when both fasting plasma glucose and hemoglobin A1c are measured concurrently. HbA1c = Hemoglobin A1c. FPG = Fasting Plasma Glucose. 2-h PG = 2-hour Plasma Glucose [41].

	Sensitivity
HbA1c 5.7–6.4%	23.6%
FPG 100–125 mg/dL	69.1%
2-h PG 140–199 mg/dL	59.5%
HbA1c 5.7–6.4% and/or FPG 100–125 mg/dL	75.6%
FPG 100–125 mg/dL and/or 2-h PG 140–199 mg/dL	95.8%

DM, respectively. The combination of HbA1c ≥ 6.5% and/or FPG ≥ 126 mg/dL detected 52.2% of all individuals with DM. HbA1c between 5.7–6.4%, FPG between 100–125 mg/dL, and 2-h PG between 140–199 mg/dL identified 23.6%, 69.1%, and 59.5% of all non-diabetic subjects with prediabetes. The combination of HbA1c 5.7–6.4% and/or FPG 100–125 mg/dL detected 75.6% of all non-diabetic subjects with prediabetes.

Despite the limitations of the OGTT – including lower reproducibility and reduced patient convenience compared to FPG and HbA1c – the aforementioned studies suggest that the OGTT continues to have a role in clinical practice. An individual eating three daily meals will be in a postprandial state for 6–9 hours per day [42]. Therefore, it is logical that the knowledge gained from a standardized glucose load is clinically informative. The 2020 ADA Guidelines state that FPG, 2-h PG during a 75-g OGTT, and HbA1c are equally appropriate to test for prediabetes and DM [1]. Many clinicians screen with both a FPG and HbA1c. However, the omission of an OGTT leads to a significant under-diagnosis of both DM and prediabetes.

Risk of progression from prediabetes to diabetes mellitus

The transition from prediabetes to DM2 is variable and influenced by heredity and lifestyle [18, 19, 43]. Multiple variables have been used to estimate the risk of progression to DM2, including glycemic indices, anthropometric data, comorbidities, metabolomics, and genetic variants. Numerous prediction models have been created based on these variables [43–51].

Baseline FPG is a significant predictor of an individual's risk for developing DM [43]. In nondiabetic adults residing in Minnesota, baseline FPG levels < 100 mg/dL, 100–109 mg/dL, and 110–125 mg/dL were associated with a 7%, 19%, and 39% risk, respectively, with progression to DM over a median of 9 years. A discrete gradient of risk for progression to DM was also observed among subjects with a baseline FPG < 100 mg/dL.

During a 75-g OGTT, 30-minute, 60-minute, and 120-minute PG concentrations were all significant predictors for future risk of DM [49, 52]. One-hour plasma glucose during a 75-g OGTT has been shown to be a better predictor of future DM than FPG, HbA1c, and PG at 30 minute and 120 minutes during a 75-g OGTT [50]. In one study, the hazard ratio for the development of DM was 9.5 (7.90–11.43) for those with combined IFG-IGT at baseline, 4.5 (4.03–5.02) for those with isolated IGT at baseline, and 3.98 (3.16–5.02) for those with isolated IFG at baseline [45].

Baseline HbA1c is also a strong predictor for risk of future DM, and the risk of incident DM significantly increased across the HbA1c range of 5.0–6.5% [46]. A systematic review found that the 5-year incidence of DM was

25–50%, 9–25%, and 5–9% among those with a baseline HbA1c of 6.0–6.5%, 5.5–6.0%, and 5.0–5.5%, respectively.

Numerous studies have shown that demographic data, anthropometric data, and comorbidities are associated with progression to DM. Factors positively associated with progression to DM include: family history of diabetes, former or active smoking, higher BMI, abdominal obesity, increased waist circumference, hypertension, elevated triglycerides, low HDL cholesterol, and elevated high sensitivity C-reactive protein [45, 53, 54]. Increasing age has also been shown to be a predictor of DM in some studies.

Metabolomics profiles have been investigated as a tool to estimate the risk of developing DM. Numerous metabolites have been found to be positively and negatively associated with progression to DM [51]. More than 400 distinct genetic signals that affect the risk of developing DM2 have been identified [20, 44]. Polygenic scores have been used to estimate the combined genetic risk for the development of DM.

Microvascular complications associated with prediabetes

Retinopathy

In a large cohort of Pima individuals, the frequency of retinopathy – defined as the presence of at least one hemorrhage, one microaneurysm, or proliferative retinopathy – was directly related to baseline FPG and 2-h PG [55]. Beginning at a baseline FPG threshold of 6.0–6.4 mmol/L and 2-h PG threshold of 9.0–10.6 mmol/L, there was a significant increase in period prevalence (10-year interval) of retinopathy. Additional data from the Pima individuals illustrated that beyond a HbA1c threshold of 6.2% there was a significant increase in the prevalence of retinopathy [12]. Similar glycemic thresholds for an increase in the prevalence of retinopathy were observed in a cross-sectional study of Egyptians and data from the Third National Health and Nutrition Examination Survey [13, 14]. Additionally, in the Diabetes Prevention Program (DPP), diabetic retinopathy was detected in 7.9% of the subjects with IGT and in 12.6% of the subjects who developed DM [56]. The prevalence of retinopathy is significantly higher in subjects with DM, but retinopathy can develop in subjects with prediabetic range dysglycemia.

Pooled data analysis of nine studies from five countries examined glycemic thresholds for diabetes-specific retinopathy (defined as moderate or more severe retinopathy) in 44 623 subjects [57]. A curvilinear relationship was found to exist for FPG and HbA1c when diabetic retinopathy was plotted against continuous glycemic measures. Diabetes-specific retinopathy began to increase from a FPG of 6.0–6.4 mmol/L and from a HbA1c of 6.0–6.4%. Based on vigintile distributions, glycemic thresholds for diabetes-specific retinopathy were observed over the range of 6.4–6.8 mmol/L for FPG, 9.8–10.6 mmol/L for 2-h PG, and 6.3–6.7% for HbA1C. Compared with the first vigintile, the odds ratios for diabetes-specific retinopathy for the above vigintile distributions were 2.5 (95% CI 1.2–5.2) for FPG, 10.1 (95% CI 1.3–79.4) for 2 h PG, and 4.5 (95% CI 1.4–15.2) for HbA1c.

A major limitation of many studies that examine the prevalence of retinopathy is the diagnostic criteria used to define diabetes-specific retinopathy [57]. The use of an overly broad definition for retinopathy leads to the inclusion of subjects with mild retinopathy, which may have etiologies other than hyperglycemia. Overall, the rate of retinopathy increases with the degree and duration of hyperglycemia [56, 57]. Subjects with prediabetes have a higher prevalence of retinopathy than subjects with NFG/NGT, although the prevalence remains relatively low. In many populations, the glycemic threshold for retinopathy occurs in the prediabetic range of dysglycemia [57, 58].

Nephropathy

Analysis of NHANES data from 1999–2006 revealed that chronic kidney disease (CKD), defined as either reduced kidney function or elevated albuminuria (urinary albumin-creatinine ratio ≥ 30 mg/g), was present in 17.1% of prediabetics compared to 11.8% of individuals with normoglycemia [59]. A multiethnic study found that 16.1% of subjects with IGT had microalbuminuria, compared to 4% of subjects with NGT [60]. After adjusting for multiple variables, glycemic status was found to be the most significant determinant of urinary albumin concentration. A systematic review and meta-analysis including 9 studies with 185 452 subjects reported that prediabetes was modestly associated with an increased risk of CKD [61]. After adjusting for established risk factors, the relative risk of CKD was

1.11 (95% CI 1.02–1.21) for subjects with FPG between 6.1–6.9 mmol/L.

The prevalence and five-year incidence of nephropathy increases as FPG, 2-h PG, and HbA1c rise [12, 58]. Of note, the association of glycemia with nephropathy is weaker than the association between glycemia and retinopathy. When plotting prevalence of microalbuminuria against FPG, 2-h PG, and HbA1c, there is a visible inflection point and subsequent increase in microalbuminuria prevalence beyond a FPG of 5.5 mmol/L, 2-h PG of 5.5 mmol/L (and again at 9.3 mmol/L), and HbA1c of 5.8%. In summary, multiple studies suggest that prediabetic-range hyperglycemia is associated with higher rates of nephropathy.

Neuropathy

Although neural dysfunction is associated with hyperglycemia, clinicians should be mindful that neurologic deficits can be attributable to non-glycemic causes in individuals with prediabetes and DM [62]. Subjects with isolated IGT were shown to have subclinical neural dysfunction that was generally asymptomatic and characterized by small-fiber neuropathy and mild impairment of cardiovascular autonomic function [63]. Erectile dysfunction has also been shown to be independently associated with IFG, with an odds ratio of 1.26 (95% confidence interval 1.08–1.46) [64]. Prediabetic-range hyperglycemia is also associated with chronic idiopathic axonal polyneuropathy (CIAP) [65]. In a study of 100 subjects with CIAP, 36 individuals were found to have IFG, 3 had FPG ≥ 126 mg/dL, 38 had IGT, and 24 had 2-h PG ≥ 200 mg/dL. Overall, the prevalence of dysglycemia in this cohort was approximately 2-fold higher than in an age-matched general population group.

Macrovascular complications and mortality associated with prediabetes

There is an increased prevalence of cardiovascular disease (CVD) in individuals with prediabetes, but this relationship is confounded by common-risk factors present in CVD and prediabetes [66–68]. However, after accounting for non-glycemic cardiovascular risk factors, both IFG and IGT are still associated with a modestly increased risk of developing CVD. It is possible that much of this risk is due to the increased risk of ultimately progressing to DM.

Approximately 25% of first myocardial infarctions (MIs) are unrecognized, which are predictive of future major cardiovascular events including death [69]. In a multi-ethnic population-based cohort study adjusted for cardiovascular risk factors, it was shown that subjects with IFG have a higher prevalence of unrecognized MIs than those with NFG, with an odds ratio of 1.60 (95% CI 1.01–2.48).

In the Whitehall Study, after 5–10 years of follow-up, survival by baseline glucose tolerance status diverged among the groups, and median survival differed by approximately 4 years between the normoglycemic and glucose intolerant groups [70]. Overall, all-cause mortality, cardiovascular mortality, and respiratory mortality were higher among participants with glucose intolerance. The hazard of coronary mortality rose beginning at a 2-h PG of 83 mg/dL; however, the graded relationship diminished after adjusting for multiple variables including baseline CVD.

A systematic review and meta-analysis incorporated 53 prospective studies with 1 611 339 subjects who were followed for a median of 9.5 years for cardiovascular and mortality outcomes [68]. IFG and IGT diagnostic criteria were in accordance with 2020 ADA guidelines [1]. Compared to individuals with normoglycemia, those with IGT or IFG had an increased risk of composite CVD (relative risk (RR) 1.13 for IFG and 1.30 for IGT), coronary heart disease (RR 1.10 for IFG and 1.20 for IGT), stroke (RR 1.06 for IFG and 1.20 for IGT), and all-cause mortality (RR 1.13 for IFG and 1.32 for IGT). One limitation of this systematic review and meta-analysis is that some of the included studies did not adjust for progression to DM during the follow-up period.

A separate meta-analysis examined 102 prospective studies with 698 782 subjects and showed that FPG was modestly and non-linearly associated with vascular disease, with hazard ratios for coronary heart disease of 1.11 for FPG of 5.6–6.09 mmol/L and 1.17 for FPG of 6.1–6.99 mmol/L [71]. Another meta-analysis that included 97 prospective studies with 820 900 subjects calculated hazard ratios for cause-specific death according to baseline FPG [72]. After adjusting for multiple variables and excluding subjects with known CVD at baseline, FPG was found to be nonlinearly related to risk of death. Compared with

subjects with NFG, subjects with IFG had hazard ratios of 1.13 for cancer deaths, 1.17 for vascular deaths, and 1.12 for non-cancer and non-vascular deaths.

Management of prediabetes

The goals of prediabetes management include preserving β-cell function, delaying or preventing the onset of DM, delaying or preventing the developing of microvascular and macrovascular complications associated with hyperglycemia, and reducing the cost of diabetes care.

Diabetes prevention program

The Diabetes Prevention Program (DPP) enrolled 3234 nondiabetic adult subjects at 27 centers in the U.S. [18]. Eligibility criteria included FPG of 95–125 mg/dL and a 2-h PG during a 75-g OGTT 140–199 mg/dL. Subjects were assigned to one of three groups: (1) intensive lifestyle modification (goal ≥ 7% weight loss of initial body weight and ≥ 150 minutes of moderate intensity physical activity/week); (2) metformin 850 mg twice daily plus standard lifestyle recommendations; or (3) placebo plus standard lifestyle recommendations. Standard lifestyle recommendations were provided in writing and through annual brief individual sessions [73]. In contrast, the intensive lifestyle modification provided comprehensive instruction in a structured 16-lesson curriculum.

The original DPP results were published after an average follow-up of 2.8 years. The estimated cumulative incidence of DM at three years was significantly different among all groups: 28.9% in the placebo group; 21.7% in the metformin group; and 14.4% in the intensive lifestyle group. Weight loss was the main predictor of reduced DM incidence, with a hazard ratio per five-kilogram (kg) weight loss of 0.42 (95% CI 0.35–0.51). Further, for every one kg of weight loss, there was a 16% reduction in risk of progression to DM [74].

Following randomization, DPPOS followed subjects for 15 years and metformin continued to be provided to the group originally assigned to it [75]. Over 15 years of follow-up, the cumulative incidence of DM was 62% in the placebo group, 56% in the metformin group, and 55% in the intensive lifestyle group. At the end of DPPOS, the aggregate prevalence of microvascular outcomes – which included nephropathy, retinopathy, and neuropathy – did not differ among the 3 treatment groups. However, for women, intensive lifestyle intervention significantly reduced aggregate microvascular disease at 15 years compared to metformin and compared to placebo. Additionally, for those subjects with a baseline BMI ≥ 35 kg/m^2, the RR for the development of aggregate microvascular disease was significantly lower in the intensive lifestyle intervention group compared to the placebo group. Among participants whose most recent HbA1c was ≥ 6.5%, the intensive lifestyle intervention group showed statistically significant reductions in the aggregate microvascular outcome, retinopathy, and neuropathy compared with placebo and metformin.

Other benefits of intensive lifestyle changes were seen in DPP subjects [76]. From baseline to year three after randomization, hypertension increased in the placebo and metformin groups but decreased in the intensive lifestyle group. From baseline to year three, dyslipidemia progressed in all three groups but the progression was less in the intensive lifestyle group compared to the metformin and placebo groups. After a mean follow-up of 3.2 years in the DPP, there were significant improvements in quality of life measures for the intensive lifestyle group, but not for the other two groups [77]. From a payer perspective, 10 years after randomization in DPP, intensive lifestyle changes were cost-effective, and metformin was marginally cost-saving compared to placebo [78].

Da Qing study

In 1986, a population-based survey identified subjects in Da Qing, China with IGT [79]. These subjects were then randomized into four groups: control group, diet only, exercise only, and diet plus exercise. At six years post randomization, the mean rate of DM was significantly higher in the control group at 66%, compared to 47% in the diet group, 45% in the exercise group, and 44% in the diet plus exercise group.

The original Da Qing participants were followed for up to 30 years after randomization to assess the effects of intervention of DM incidence, microvascular and macrovascular complications, and mortality [80]. Active intervention occurred for the first six years after randomization until 1992, after which subjects were informed of the study

results and asked to continue with normal medical care. No specific interventions were offered after the initial six years, and the three intervention groups were combined into one group for analysis purposes.

Over the 30-year follow-up period, the intervention group had a median delay in DM onset by four years (NNT 10) compared to the control group and a significantly lower cumulative incidence of DM onset (HR 0.61) [80]. At 30 years, there were 26% fewer CVD events in the intervention group compared to the control group. The difference between the two groups continued to increase over time.

At 30 years, the incidence of retinopathy was 40% lower in the intervention group than in the control group, and incidence of nephropathy and neuropathy were numerically lower in the intervention group but not significantly different [80]. The median delay of composite microvascular disease outcome was 5.2 years in the intervention group (NNT 10). Cardiovascular and all-cause mortality were also significantly lower in the intervention group (25.6% and 35.2%, respectively) than in the control group (45.5% and 56.3%, respectively). The median delay in CVD death and all-cause mortality in the intervention group were 7.3 years and 4.8 years, respectively, with NNT of 10 for both outcomes.

Pharmacologic therapy for the prevention or delay of diabetes mellitus

A systematic review that included 20 randomized controlled trials examined the efficacy of metformin for the prevention or delay of DM [81]. The overall conclusion was that for at-risk subjects, metformin compared with placebo reduced or delayed the risk of progression to DM. The incidence of DM was not significantly different when comparing metformin plus intensive diet and exercise and identical intensive diet and exercise alone.

In addition to metformin, other medications have proven efficacy in reducing progression to DM. Once-daily subcutaneous liraglutide 3.0 mg as adjunct therapy to lifestyle modifications reduced progression to DM compared to placebo after 160 weeks [82]. In adults with elevated CVD risk and prediabetes or newly established DM, a once-daily insulin glargine injection reduced progression to DM compared to placebo [83]. Several thiazolidinediones also have proven efficacy in reducing the progression to DM, including pioglitazone, rosiglitazone, and troglitazone [84–86]. Additionally, combined hormone replacement therapy in post-menopausal women, glipizide, valsartan, orlistat, and acarbose also significantly reduced the progression to DM compared to placebo [87–92]. Interestingly, during the Study to Prevent Non-Insulin Dependent Diabetes Mellitus (STOP-NIDDM), acarbose was associated with a 49% relative risk reduction in cardiovascular events compared to placebo with a HR 0.51 (95% CI 0.28–0.95). However, the methodology of STOP-NIDDM has been heavily criticized and the validity of the results has been questioned [93]. Many pharmacologic therapies have also been studied and shown to be ineffective in preventing progression to DM, including vitamin D, nateglinide, glimepiride, and ramipril [94–97].

Bariatric surgery for the prevention or delay of diabetes mellitus

A Swedish study enrolled a large cohort of adult nondiabetic subjects who had already chosen to undergo various bariatric surgeries including banding (19%), vertical banded gastroplasty (69%), or gastric bypass (12%), and matched them with a nonrandomized control group [98]. At the time of enrollment, 17.2% of the control group had IFG, compared to 16% of the surgical group. After a median follow-up time of 10 years, bariatric surgery compared with usual care reduced progression to DM by 87% among subjects with IFG. Another study reported that 98.6% of subjects with prediabetic range dysglycemia had normal FPG following gastric bypass [99].

Exercise and diet for the prevention or delay of diabetes mellitus

A systematic review and meta-analysis included 28 studies with 1 261 991 subjects and investigated the role of physical activity in reducing progression to DM [100]. Overall, for those who achieved 11.25 metabolic equivalent of task (MET) hours/week (equivalent to 150 minutes/week of moderate activity) there was a risk reduction of 26% for DM. Further risk reductions occurred at greater MET hours/week. The Health Professionals Follow-up Study showed that engaging in weight training or aerobic exercise for at least 150 minutes/week was independently associated with a lower risk of DM of 34% and 52%, respectively

[101]. The greatest reduction in DM risk was seen in men who engaged in both aerobic exercise and weight training for at least 150 minutes/week, with a risk reduction of 59%.

The Prevención con Dieta Mediterránea (PREDIMED) study enrolled older adult subjects at high risk for but without baseline CVD and randomized participants to either a Mediterranean diet supplemented with extra-virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet based on general advice to reduce fat intake [102]. Compared to the control group, the Mediterranean diet supplemented with extra-virgin olive oil group had significantly lower progression to DM with a HR of 0.60 (95% CI 0.54–0.85). The beneficial effect seen in this study was thought to be due to dietary composition itself and not attributed to calorie restriction, increased physical activity, or weight loss.

American diabetes association 2020 guideline recommendations for the management of prediabetes

The 2020 ADA guidelines recommend that patients with prediabetes participate in an intensive behavioral lifestyle intervention program modeled on the DPP to achieve and maintain 7% weight loss and to achieve ≥ 150 minutes/week of moderate intensity physical activity (such as brisk walking) [103]. Additionally, the ADA recommends that a variety of eating patterns are acceptable for patients with prediabetes including the Mediterranean diet and a low-calorie, low-fat diet. Regarding pharmacologic therapy, the 2020 ADA guidelines state that metformin for prevention of DM should be considered in patients with prediabetes, especially those with BMI ≥ 35 kg/m^2, those aged < 60 years, and women with prior GDM.

Conclusion

In summary, patients with prediabetes have abnormal glucose regulation mediated by impaired insulin secretion and reduced insulin action, as well as an increased risk of progression to DM [18, 25, 26]. Many clinicians screen for diabetes and prediabetes using the combination of FPG and HbA1c. However, even when used together, the combined sensitivity for diagnosing DM and prediabetes is poor [41]. Therefore, omission of a 75-g OGTT results in both misclassification and under-diagnosis of DM and prediabetes. The following question then arises: are there clinical consequences to misclassifying diabetes as only prediabetes or prediabetes as normal glucose metabolism?

We conclude that the answer is yes. There is a clear association of increasing microvascular complications with rising glucose concentrations, and patients with prediabetes have an increased prevalence of retinopathy, nephropathy, and neuropathy compared to individuals with normal glucose metabolism [13, 14, 55, 57, 59–61, 63, 104–106]. There is also an increased prevalence of CVD, cardiovascular mortality, and all-cause mortality in patients with prediabetes compared to those with normal glucose metabolism [66–68, 70].

Therefore, recognition and treatment of prediabetes is essential to minimize morbidity and mortality. Intensive lifestyle changes emphasizing weight loss and physical activity have been shown to prevent or delay progression to DM, potentially decrease microvascular complications, potentially reduce macrovascular complications, improve comorbidities, improve quality of life, reduce medical costs, and decrease mortality [18, 75–80]. In addition to lifestyle changes, numerous medications are also effective in preventing or delaying progression to DM including metformin, glipizide, liraglutide, insulin glargine, several thiazolidinediones, orlistat, acarbose, valsartan, and estrogen/progestin [18, 82–85, 87–92, 107].

The totality of available evidence suggests that prediabetes is not only a risk factor, it is in fact a disease. Perhaps the term "prediabetes" should be changed to "early diabetes" and managed as such clinically.

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