PART I

Prediabetes and the Diagnosis of Diabetes

1 Is prediabetes a risk factor or is it a disease?

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LEARNING POINTS

- The diagnostic criteria for prediabetes and diabetes are based on the relationship of hyperglycemia with microvascular disease.

- Defects in insulin secretion and action occur in people with impaired fasting glucose and impaired glucose tolerance.

- An oral glucose tolerance test may help to better characterize patients at higher risk of progression to type 2 diabetes.

- Intervention may delay the progression to diabetes.

Prediabetes, as previously defined by the American Diabetes Association (ADA), includes subjects with fasting plasma glucose (FPG) >100 mg/dl and <126 mg/dl and/or 2-hour plasma glucose following a 75-g oral glucose load >140 mg/dl and <200 mg/dl. The rate of progression to diabetes without any intervention is about 28.9% over a 3-year period as seen in the placebo arm of the Diabetes Prevention Program [1]. A 9-year longitudinal study from Olmsted County, Minnesota, reported a similar rate of diabetes progression of 34% [2]. The prevalence rate of prediabetes in the American adult population, as reported by CDC from 2003 to 2006, was 25.9% [3]. This represents 57 million American adults, a significant number of whom are predisposed to developing diabetes if adequate intervention is not undertaken. Therefore, understanding the definition of prediabetes, its implications, pathogenesis, and appropriate management becomes critical to any clinician.

Prediabetes includes two categories, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Examining the evolution of these criteria will help us understand not only the basis of the current definitions, but also provide us guidance for the necessary evaluation and management.

Prediabetes, diabetes, micro- and macrovascular disease

Impaired glucose tolerance (IGT) is defined by a plasma glucose 2 hours after a 75-g oral glucose load >140 mg/dl and <200 mg/dl, while impaired fasting glucose (IFG) is defined by a fasting plasma glucose >100 mg/dl and <126 mg/dl.

IGT is a terminology that has been long known and has been a part of the ADA classification since 1979 [4]. IFG as a separate entity was established in an ADA report published in 1997 [5] and was later adopted by an expert WHO panel in 1999 [6]. These categories were intended to be seen as risk factors for future diabetes and cardiovascular disease rather than distinct clinical groups. The definition for IGT has undergone little change since its inception. IFG was initially defined as fasting plasma glucose >110 mg/dl and <126 mg/dl. This classification was rather arbitrary and reflected the then available evidence suggesting an insulin secretory defect and an increased risk of cardiovascular disease.

Brunzell et al. performed intravenous glucose tolerance tests in 66 subjects with a wide range of fasting glycemia [7]. Acute insulin response and glucose disappearance rate were markedly lower in subjects with fasting plasma glucose above 115 mg/dl in comparison to those with a fasting glucose below 115mg/dl. The main limitation of this data was

the relatively small number of patients in the fasting plasma glucose group 115–149 mg/dl ($n = 3$). The Paris Prospective Study noted an increasing risk of diabetes with incremental fasting plasma glucose, despite normal glucose tolerance (2-hour-value after a 75-g oral glucose tolerance test <140 mg/dl). The relative risk of developing subsequent diabetes in the IGT and IFG (fasting plasma glucose >109 mg/dl) groups was 9.6 and 5.6, respectively [8]. The impact of hyperglycemia on cardiovascular mortality was also examined in this study, with the age-adjusted relative risk for coronary heart disease death noted to be 1.32 (1.04–1.67) in subjects in the fasting plasma glucose category of 104–124 mg/dl in comparison to the group <104 mg/dl [9]. A similar increase in risk was observed with increased post-challenge glucose in the Whitehall study that followed 18,403 male civil servants for a total of 7.5 years [10].

The microvascular effects of prediabetes were investigated in a few studies with mostly uniform results. Subjects with a capillary blood glucose between 120 and 200 mg/dl, following a 50-g oral glucose load did not have any discernible difference from controls in the prevalence of retinal abnormalities over a 10-year follow-up period [11]. Klein et al. evaluated the effect of impaired glucose tolerance, with plasma glucose between 140 and 200 mg/dl after a standard 75-g oral glucose load [12]. Age-adjusted frequency of visual impairment as measured by visual acuity of $\leq 20/40$ was higher in the IGT group when compared to men with diabetes and normoglycemic women. However, the rates of retinopathy were uniformly low across all groups with no significant intergroup differences. In another report from two different groups of patients, including Pima Indians and male civil servants, development of retinopathy was mostly confined to subjects with 2-hour plasma glucose exceeding 200 mg/dl, without any marked change in the intermediate groups [13].

Following these earlier studies, one of the important debates that ensued was the comparability between IGT and IFG with regard to outcomes. Data from a longitudinal study of Pima Indians showed greater prevalence of IGT over IFG among nondiabetic subjects [14]. However, the 5-year cumulative incidence of diabetes was much higher for IFG at 31% in comparison to 19.9% for subjects with IGT. The combination of these two risk factors was better than either alone with an incidence of 41.2%. A receiver operating characteristic (ROC) curve analysis showed that, by defining IFG using a fasting glucose ≥ 102 mg/dl, the prevalence in the two groups was mirrored. This might not have necessarily led to identifying the same set of subjects, as these two cohorts might have included subjects who were mutually exclusive. However, the sensitivity and specificity of diabetes prediction was equaled in the IFG and IGT groups when using a definition of IFG >103 mg/dl as opposed to 110 mg/dl. In a Mauritian [15] cohort of 3,229 nondiabetic subjects, 148 had IFG alone in comparison to 489 with isolated impaired post-challenge glucose. A combination of IFG and IGT was present in 118 subjects. The sensitivity, specificity, and positive predictive value for prediction of progression to diabetes were 50, 84, and 24%, respectively, for IGT. Although IFG was less sensitive, it had a better specificity and positive predictive value at 26, 94, and 29%, respectively. These data would suggest that IFG defines a smaller, yet a more extreme category of glycemia that progresses to diabetes more predictably. However, from a population perspective, IFG identifies a lesser percentage of people progressing to diabetes, making it difficult to successfully implement diabetes prevention measures based on fasting plasma glucose alone. In this study, the optimal definition of IFG that gave the best combination of sensitivity and specificity for diabetes prediction was a fasting glucose >99 mg/dl [16]. These data formed the basis for the revised IFG criteria of plasma glucose >100 mg/dl and less than 125 mg/dl, in a follow-up report in 2003 [17].

It is important to remember that in clinical practice, the risk of progression to diabetes follows a gradient across a seamless continuum of glucose levels [16]. While scrutinizing the evidence to decide the optimal definitions of IGT and IFG and their individual value, it is critical to understand if IGT and IFG act as risk factors for micro- and macrovascular disease independently of diabetes.

It is generally accepted that microvascular disease, such as retinopathy, neuropathy, and nephropathy, is a function of the degree and duration of hyperglycemia. Contrary to the earlier studies that did not reveal an increased frequency of retinopathy among people with prediabetes, some recent studies demonstrated an elevated risk of microvascular disease even in subjects with hyperglycemia less than the diabetic range. A subset of the Diabetes Prevention Program cohort was investigated with fundus photographs at a mean 5.6 years of follow-up [18]. Changes of diabetic retinopathy were reported in 7.9% of the impaired glucose group and in 12.6% of the group that developed diabetes on follow-up. Although the subjects who developed retinal changes were not significantly different from those without these changes in the impaired glucose group, they tend to have a higher baseline prevalence of hypertension, lower HDL, higher triglycerides, and a history of gestational diabetes.

The rates of retinopathy and nephropathy were higher in individuals with impaired fasting glucose in comparison to those with impaired glucose tolerance on 10 years of follow-up of a group of Pima Indians, also supporting the previous evidence that IFG might denote a metabolically advanced state [19]. As opposed to these results, the incidence of diabetic retinopathy was reported to be very low at 28–31/10,000 person-years of follow-up in a large Japanese cohort of atomic bomb survivors with impaired glycemia [20]. A steep rise in the incidence and prevalence of fundus changes were noted only when the fasting plasma glucose was >125 mg/dl and the 2–hour post-challenge glucose >198 mg/dl. A similar threshold for retinopathy also evolved in the AusDiab study [21]. A clear threshold effect was not evident for microalbuminuria and the relation to rise in glucose was more gradual. Subjects with neuropathy were more likely to have retinopathy and microalbuminuria in the AusDiab cohort with impaired glucose metabolism [22]. Collectively, although there is evidence for increased prevalence and incidence of microvascular changes before the onset of diabetes, these changes predominantly occur with higher levels of glycemia.

In summary, the recently proposed definitions of prediabetes are dependent on their ability to identify individuals with a high risk of progression to diabetes. Defining IFG using a fasting glucose >100mg/dl increased the prevalence of prediabetes from 19.3% to 36.3% on evaluation of the NHANES III data [23]. Whether this definition portends true benefit or places a higher societal burden for preventive measures has been questioned [24]. We also have to factor in the behavioral impact of this labeling on individuals [25]. Strong antagonistic opinions to the new cutoff cite the lack of net proven benefit based on a detailed decision analysis [26].

Most recently in 2010, the title "Prediabetes" was renamed as "Categories of increased risk for diabetes" to reflect the risk of progression to diabetes rather than the subsequent micro- and macrovascular outcomes. An equivalent intermediate category for A1C was also identified, with values between 5.7% and 6.4% indicating a heightened risk for diabetes development [27–29].

Prediabetes and atherosclerosis: Why do they associate and how to best predict the risk?

A progressive increase in cardiovascular risk has been shown with rising blood sugars, across a spectrum ranging from normal to significant hyperglycemia. The DECODE study group showed a J-shaped relationship between all-cause mortality and plasma glucose, whether fasting or post-challenge [30]. A plausible and intuitive explanation for the increased cardiovascular risk is the clustering of other well-known traditional risk factors in patients who develop prediabetes [31]. The San Antonio Heart Study followed 614 nondiabetic Mexican American individuals and demonstrated that subjects who developed diabetes had a more atherogenic profile at baseline, including higher triglycerides, LDL and total cholesterol, BMI, blood pressure, insulin, and lower HDL than the group that did not develop diabetes [32]. The clustering of risk variables explained all the observed metabolic features rather than a single underlying etiology [33]. Low cardiorespiratory fitness had a significant impact on all-cause mortality in women with IFG in the 16-year follow-up in the Aerobic Center Longitudinal Study (ACLS) [34].

Studies that examined the ability of IGT and IFG to predict cardiovascular risk and mortality suggest that IGT is a better predictor of all-cause mortality [35, 36] and cardiovascular disease [37–39]. In contrast, data from Norwegians followed over 22 years showed that fasting plasma glucose was an important predictor of cardiovascular death [40]. Adding to these already varied results, a Chinese study showed equivalent performance of IGT and IFG in predicting cardiovascular disease risk [41]. The Atherosclerosis Risk in Communities Study (ARIC) also showed that both IGT and IFG were associated with an increased prevalence of cardiovascular risk factors with none being worse than the other [42]. It is also important to remember the important role of other cardiovascular risk factors in the development of atherogenesis. In agreement, the Framingham Offspring and San Antonio Heart Studies have shown that the knowledge we gain from post-challenge hyperglycemia might add little to what we might already know from traditional cardiovascular risk factors [43, 44].

Is there a role for OGTT in clinical practice?

This has been a topic of considerable debate, which was fueled by the 1997 ADA recommendation to favor the use of fasting plasma glucose over OGTT. The huge influx of data that followed in favor and disfavor of this recommendation has helped shape the definition of prediabetes as reviewed earlier. Prevalent use of OGTT has been limited by its inconvenience, cost, and poor reproducibility. Marked

intra- and interindividual variation in postload glucose has been demonstrated in multiple studies [45–48]. McDonald et al. showed that the standard deviation for fasting glucose was about 5 mg/dl, whereas it was substantially higher for 1- and 2-hour postload glucose where the deviation around the mean was 20–30 mg/dl [46]. This degree of fluctuation leads to misclassification, with nearly 39% of people diagnosed with IGT found to be normal on a repeat OGTT within 2–6 weeks [49].

Given that individuals spend at least 6–9 hours on a given day in the postprandial state, knowledge gained from a standardized glucose load cannot be ignored [50]. As discussed earlier, IGT is a better predictor of diabetes and macrovascular risk than fasting glucose. Although in practice clinicians almost never use the OGTT except in special situations such as pregnancy, it continues to remain a valuable epidemiological tool.

What is the underlying pathogenesis and natural history of IGT and IFG?

Hyperglycemia develops when, in response to impaired insulin sensitivity, the secretion of insulin declines. As we would expect, the spectrum of disorders with disturbed glucose metabolism en route from normoglycemia to development of diabetes would encompass defects of insulin action and β-cell secretion. Butler et al., using pancreatic tissue obtained from autopsy, showed that β-cell volume is decreased by 40% in IFG compared to normoglycemic individuals [51]. It has also been shown that the usual 0.7% per year rate of β-cell deterioration is doubled in IGT with accelerated progression to diabetes [52]. There have been attempts to dissect IGT and IFG to denote specific defects in glucose homeostasis, but these have yielded contrasting results. Most studies reported increased insulin resistance in IGT [53–55] and decreased β-cell function in IFG [53, 54, 56] as the predominant metabolic derangements, using data from insulin clamps and glucose tolerance tests. In contrast, the Botnia study concluded that IFG is more characterized by insulin resistance and IGT by impaired insulin secretion with decreased I/G ratio (Insulin/glucose ratio) [57]. The amplitude of insulin secretion and its response to oscillations in glucose were blunted in IGT [58]. Bock et al. reported both defective insulin secretion and action with meal ingestion in IGT, whereas in individuals with isolated IFG the postprandial glucose metabolism was completely normal but they had an inappropriately elevated fasting

endogenous glucose production [59]. Understandably, a combination of IGT and IFG presents a morphologically advanced group with more severe metabolic impairments than isolated presentation of either [56].

In the progression from normoglycemia, it is not imperative that both IGT and IFG develop before transition to diabetes, as we have learnt from the Baltimore Longitudinal Study of Aging [60]. During a 10-year follow-up, only 37% with IFG went on to develop IGT and only 15% with IGT developed IFG. The progression from baseline IGT/IFG to diabetes happened at an accelerated rate of 39.3%. This has also been confirmed in a cohort of Pima Indians, where one-fourth of the subjects with IGT developed diabetes in 5 years and two-thirds in 10 years [61]. The best predictors of this progression were age, male gender, BMI, and central obesity [60, 61]. The progression from normoglycemia to diabetes is more slow and gradual with a 10-year cumulative incidence of 7.01% by 2-hour glucose and 1.48% by fasting glucose.

Management of prediabetes

Relatively few studies have addressed the role of intervention in people with prediabetes. In the Diabetes Prevention Program (DPP) [1], lifestyle intervention in affected individuals decreased the incidence of diabetes by 58% and by 31% when treated with metformin in comparison to the control group. The average weight loss achieved was 0.1, 2.1, and 5.6 kg in the placebo, metformin, and lifestyle groups, respectively. Similar studies have been replicated in different populations, with the Finnish Diabetes Prevention Study demonstrating a comparable weight loss of 4.2 kg with lifestyle modification and a 58% reduction in diabetes incidence over 3.2 years [62]. In the Indian Diabetes Prevention Programme and the Da Qing IGT and Diabetes Study, in accordance with the impression that the South Asians represent a metabolically disadvantaged group for a given weight, the BMI of the subjects with prediabetes was lower in comparison to Caucasians; 25–26 kg/m^2 [63, 64]. They experienced a more rapid rate of progression to diabetes of 55% and 67% in their control groups, respectively, over 3–6 years. Despite minimal or no weight loss with lifestyle intervention, they still had a 28% and a 46% reduction in diabetes progression.

Apart from metformin, the pharmacologic agents that have been utilized in this setting include troglitazone in several studies, and acarbose in STOP-NIDDM. Troglitazone,

during its short span of use in DPP before the drug discontinuation in 1998 due to concerns of liver toxicity, lowered the diabetes incidence rate more significantly in comparison to the other groups [65]. Two short-term studies concluded that the ability of this drug to prevent progressive secretory dysfunction and improve insulin action contributed to its effect on slowing diabetes progression [66, 67]. The increased glycemic durability of rosiglitazone in the ADOPT trial and the decreased incidence of diabetes in the rosiglitazone subgroup in the DREAM trial suggests that this is a class effect for the thiazolidinediones [68, 69]. On the other hand, there are potential risks associated with thiazolidinedione use that must be considered—including an increased risk of hospitalization for heart failure, edema, and fracture.

Acarbose, although successful in decreasing the incidence of diabetes in the STOP-NIDDM study, had a 31% discontinuation rate due to gastrointestinal side effects [70]. Blockade of the renin angiotensin system did not offer any significant advantage, as noted in the DREAM trial, but a modest 3.7% absolute risk reduction in the incidence of diabetes by valsartan was reported in the recently published NAVIGATOR trial [71]. The nateglinide arm in the NAVIGATOR trial did not show any benefit, despite the association of postprandial hyperglycemia with diabetes and cardiovascular risk [72]. Collectively, despite variable glycemic effects, none of the therapeutic agents have been shown to have micro- or macrovascular benefit in the prediabetes population.

One of the commonly cited criticisms of DPP is the replicability of the aggressive lifestyle intervention in their protocol, in common practice. The support and the education offered to the subjects were individualized and included a total of 22 visits in the first year. This is in sharp contrast to current practice, even in the diabetic population. Despite these challenges, we should note that the moderate weight loss achieved in these trials had significant beneficial effects on blood pressure and cholesterol [1, 73]. Risk factor reduction in this population is highly desirable given the high incidence of cardiovascular disease and mortality with diabetes development. Lifestyle modification also resulted in an overall change to healthier habits in this cohort with reduction in smoking. The 10-year follow-up of the DPP cohort confirms that the glycemic benefits of lifestyle intervention are long lasting [74]. One of the key points to be addressed is, if successful intervention at this stage, apart from lowering glycemia, would also lower the risk of future macrovascular disease. The emergent macrovascular and mortality benefits noted from early glycemic intervention in the 10-year follow-up of the UKPDS cohort, in comparison to the ADVANCE and ACCORD trials that included subjects with advanced diabetes, mandate further investigation in the prediabetic population. The beneficial effect in the UKPDS cohort was most pronounced in the metformin arm. The strongest intervention trial in individuals with prediabetes, DPP, has established the superior efficacy of lifestyle intervention over metformin in the short term. This further strengthens our argument to favor behavior and lifestyle modification over early initiation of drugs. The cost–benefit analysis of this approach in people with prediabetes is sparse [75]. Further research into the long-term cost-effectiveness of early lifestyle intervention is needed.

In conclusion, prediabetes identifies a group of individuals at high risk of progression to diabetes and who have increased cardiovascular mortality compared to the normoglycemic population. Clustering of other cardiovascular risk factors might explain the increased macrovascular events in this group. Early lifestyle intervention is needed to decrease the risk of progression to diabetes and potentially offer protection against accelerated atherogenesis.

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