"Prediabetes": Are There Problems With This Label? No, We Need Heightened Awareness of This Condition!

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The category of "prediabetes" defined by the American Diabetes Association comprises a range of intermediate hyperglycemia based on fasting or 2-h postload glucose or on HbA_{1c}. Over the recent past, the "cut points" identifying this stage have changed, i.e., a lower fasting glucose level is used. On one hand, it can be argued that the change to a lower cut point identifies a group of individuals still at higher risk and provides heightened awareness for a condition associated with higher risk for cardiovascular disease. In addition, identification of individuals at this stage may represent a chance of earlier intervention in the disease. However, the argument against this definition of prediabetes is that it disguises the differences in the three subcategories and creates problems in interpreting observations on interventions and outcomes. In addition, it can be argued that the enormous numbers of people identified with the criteria far exceeds the capacity of health care systems to respond through individual care, particularly without evidence that interventions benefit any category other than impaired glucose tolerance. Thus, there does not appear to be consensus on the definition using the cut points identified. Controversy also remains as to whether there are glycemic metrics beyond HbA_{1c} that can be used in addition to HbA_{1c} to help assess risk of an individual developing diabetes complications. Given the current controversy, a Point-Counterpoint debate on this issue is provided herein. In the preceding point narrative, Dr. Yudkin provides his argument that there are significant problems with this label. In the counterpoint narrative below, Dr. Cefalu argues that the cut points are appropriate and do provide useful and important information in trying to reduce the future burden of diabetes.

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The natural history of type 2 diabetes involves a progressive deterioration in physiologic factors (i.e., insulin secretion, peripheral insulin action) that is observed many years before the diagnosis. Trajectories of the metabolic factors suggest that insulin secretion and insulin action may be in the normal range until 2–6 years before diagnosis (1). As currently understood, abrupt changes occur during this "prediabetes" phase, and continued progression of the pathophysiologic abnormalities leads to the clinical states defined as impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and ultimately type 2 diabetes. Recently, the International Diabetes Federation estimated that 415 million adults worldwide now have diabetes and that 318 million have IGT and are considered as having prediabetes. These

numbers are expected to increase to 642 million and 482 million, respectively, by 2040 (2). Of great clinical interest is the observation that the prediabetic states that encompass the categories of IFG, IGT, and combined IFG/IGT may represent different pathophysiologies (3). Individuals in all three categories labeled as having prediabetes have been shown to have increased diabetes risk, although it is understood that individuals at the lower ends of the glycemic ranges are at lower risk for progressing to diabetes than the individuals at the higher ends. Thus, if one does use the lower criteria to diagnose prediabetes (as suggested by the American Diabetes Association [ADA], i.e., fasting plasma glucose [FPG] 100–125 mg/dL and HbA$_{1c}$ 5.7–6.4%), there is no question that the global prevalence rates will increase dramatically. Therefore, one of the main questions I will propose with this counterpoint will be at what diagnostic "cut point" are we comfortable dismissing this "lower risk" group from intervention despite the fact that these categories of dysglycemia still suggest increased risk for developing diabetes? When one is labeled as having prediabetes, what additional information do we need or what strategies need to be put in place to warrant heightened awareness and further evaluation? Hence, in our goal to devise highly translational programs to address the prevention of diabetes, we need consensus on the best approach to screen and identify people at risk for developing diabetes. In this counterpoint narrative, points to argue will be

1. The risk for progression of diabetes is present at the lower cut points suggested for diagnosing prediabetes.
2. There are significant clinical implications for prediabetes for microvascular disease.
3. Prediabetes identifies a cohort for which there needs to be a heightened awareness of cardiovascular disease risk and, therefore, further evaluation.
4. Lifestyle interventions to prevent type 2 diabetes are effective among persons at increased risk.

ARE THE LOWER CUT POINTS FOR DIAGNOSIS OF PREDIABETES APPROPRIATE?

Given the different trajectories for the metabolic and physiologic factors (i.e., FPG, postprandial glucose, and insulin levels) prior to diagnosis and given that they are continuous variables, at what cut point does one agree that it is most appropriate to intervene? The ideal cut point should be one that, if exceeded, readily identifies a high-risk cohort for proposed intervention. If the glucose level falls below the ideal cut point, the cohort identified should be one that will have a much lower risk for development of diabetes and would represent a population less likely to benefit from a prevention intervention or one that would not justify the use of valuable resources as required for such an intervention.

Currently, we rely on FPG, 2-h plasma glucose on oral glucose tolerance test, or HbA$_{1c}$ to diagnose diabetes (1,4). Whereas there may be general agreement on the levels required for the diagnosis of diabetes, the controversy arises for the label of prediabetes and the use of the lower cut points for FPG (i.e., 100 mg/dL) and HbA$_{1c}$ (i.e., 5.7%) as suggested by the ADA's *Standards of Medical Care in Diabetes—2016* (4). This controversy is fueled further by the observation that most if not all of the prevention studies evaluated subjects at high risk having IGT and a 2-h plasma glucose on oral glucose tolerance test between 140 and 200 mg/dL and not those identified with an HbA$_{1c}$ level. Thus, given the current recommendations from many organizations (World Health Organization, International Diabetes Federation, ADA), there remains difference of opinion as to the appropriate criteria required to diagnose prediabetes (1,4,5). However, one of the concerns for the multiple definitions of prediabetes is the less-than-optimal overlap and concordance between FPG, 2-h postprandial glucose, and HbA$_{1c}$. Another issue is that these criteria should be considered in the context of other factors that can help stratify the higher risk group. As an example of this approach, and as outlined in the ADA's Standards, it is stated that "it is important to take age, race/ethnicity, and anemia/hemoglobinopathies into consideration when using the A1C to diagnose diabetes" (4). Therefore, determining the most appropriate criteria for intervention is not a trivial matter, and failure to recognize a high-risk group has tremendous clinical implications. Thus, this counterpoint argues that the lower criteria suggested to identify prediabetes are appropriate for initial evaluation and need to be evaluated with the "company they keep" (i.e., risk factors, age, ethnicity, etc).

RISK OF PROGRESSION OF IFG TO DIABETES?

The fact that most of the prevention trials evaluated individuals with IGT is not in question. However, in moving forward in the effort to address the diabetes epidemic, can we intervene even earlier in the process and consider using the lower criteria for initial evaluation? It is clear that even at the lower cut points, there are individuals who do progress to diabetes. Specifically, when one observes physiologic ranges of a continuous variable as noted for glucose, there is no argument that risks will be lower at the lower ends of the ranges than at the higher ends. This was clearly shown in the work by Forouhi et al. (6) when determining the incidence of type 2 diabetes and examining the effect of different cut points for IFG on diabetes incidence. When adjusting for confounding factors, and compared with normoglycemia, the hazard ratio (HR) for incident diabetes was greatest, as would be expected, for the IFG-original category (110–125 mg/dL [6.1–6.9 mmol/L]) when compared with IFG-lower (101–109 mg/dL [5.6–6.0 mmol/L]) and all-IFG, with HRs of 4.4, 1.9, and 2.9, respectively. In the 10-year follow-up of the Chennai Urban Rural Epidemiology Study (CURES), Anjana et al. (7) evaluated individuals with isolated IFG (i-IFG) (100–125 mg/dL), isolated IGT (i-IGT), or prediabetes defined as those with i-IFG or i-IGT or both. Among those with prediabetes, 58.9% progressed to diabetes (52.8% among i-IGT, 47.8% among i-IFG, and 84.1% among those with combined IGT and IFG). Gerstein et al. (8) when considering IFG (≥110 to <126 mg/dL [≥6.1 to <7.0 mmol/L]) reported a meta-analysis of prospective studies and evaluated individuals with IGT, IFG, i-IGT, i-IFG, and combined IGT and IFG. They reported that "every category of dysglycemia was associated with a high relative risk for future diabetes" and reported annualized relative risks that ranged from 4.7 to 12 with absolute annual risks generally varying from 5 to 10%.

Rasmussen et al. (9) reported on the value of a very comprehensive and thought-provoking stepwise screening program that stratified diabetes risk. In

addition to the other categories, they also used a lower cut point for IFG defined as ≥5.6 mmol/L but <6.1 mmol/L (100–110 mg/dL) and 2-h blood glucose <7.8 mmol/L (140 mg/dL). They reported that diabetes incidence rates were two to four times higher in individuals with intermediate diabetes risk compared with those with low diabetes risk. However, even in those with IFG, the rate ratios were markedly higher (14.9) when compared with IGT and one diabetes glucose value, 29.1 and 53.1, respectively. Heianza et al. (10) provided data on progression to diabetes over an approximately 5-year period based not only on the lower cut point of glucose to define IFG (100–125 mg/dL [5.6–6.9 mmol/L]) but also on the lower cut point for HbA$_{1c}$ (5.7–6.4%). They reported that diagnosis of prediabetes by both criteria identified an increased risk of progression to diabetes (10). Finally, Tirosh et al. (11) analyzed data from 13,163 apparently healthy men with FPG levels of <100 mg/dL and demonstrated that higher FPG values within the normal range independently predict type 2 diabetes. Thus, there does appear to be considerable evidence that risk for progression to diabetes does indeed exist at the lower cut points that currently define prediabetes.

CLINICAL IMPLICATIONS OF THE PREDIABETES DIAGNOSIS

Another major consideration when considering an intervention for prediabetes is the clinical implications of the disease. In this regard, there are a number of reports that suggest that individuals with prediabetes may have complications (e.g., nephropathy, retinopathy, neuropathy) traditionally considered to be complications of diabetes (1,12–15). For example, Plantinga et al. (15) used data from the National Health and Nutrition Examination Survey (NHANES) where prediabetes was defined as an FPG ≥100 to <126 mg/dL. They reported that the prevalence of chronic kidney disease was 17.7% in individuals with prediabetes compared with 10.6% in those with no diabetes and 39.6% and 41.7% in individuals with diagnosed or undiagnosed diabetes, respectively.

The other major consideration is whether individuals defined as having prediabetes have an increased risk of cardiovascular complications and, if so, whether prevention strategies would

ultimately reduce cardiovascular disease. As previously stated, the risk of glycemia is a graded continuum, and one would expect these values to confer some level of increased risk as reported. The U.S. MESA (Multi-Ethnic Study of Atherosclerosis) trial (16) defined IFG as no type 2 diabetes and an FPG of 100–125 mg/dL (5.6–6.9 mmol/L). In MESA, IFG was associated with an increased incidence of cardiovascular events in univariate analysis compared with those with normal FPG and after adjusting for age, sex, race/ethnicity. The association was reported to be attenuated in the full multivariable model (P = 0.30). Data from the Emerging Risk Factors Collaboration (ERFC) (17) suggested that "there are generally continuous associations between fasting glucose levels greater than 100 mg per deciliter and risk of death, supporting the view that hyperglycemia (or some factor closely related to it) may be directly relevant." Finally, Xu et al. (18) provided a meta-analysis on the risk of coronary heart disease (CHD) when using different criterion of IFG. They concluded that "...IFG was associated with an increased risk of CHD. The risk increased in people with FPG as low as 100 mg/dL. These results reaffirm the importance of screening for prediabetes using the ADA criteria" (18).

Some of the more compelling data relating the prediabetes state to cardiovascular risk comes from data assessing glycated hemogloblin levels with outcomes. Selvin et al. (19) measured glycated hemoglobin in whole-blood samples from 11,092 black or white adults who did not have a history of diabetes or cardiovascular disease as part of the Atherosclerosis Risk in Communities (ARIC) Study. For glycated hemoglobin values of <5.0%, 5.0 to <5.5%, 5.5 to <6.0%, 6.0 to <6.5%, and ≥6.5%, the multivariable-adjusted HRs (with 95% CI) for diagnosed diabetes were 0.52 (0.40–0.69), 1.00 (reference), 1.86 (1.67–2.08), 4.48 (3.92–5.13), and 16.47 (14.22–19.08), respectively (Fig. 1). For CHD, the HRs were 0.96 (95% CI 0.74–1.24), 1.00 (reference), 1.23 (1.07–1.41), 1.78 (1.48–2.15), and 1.95 (1.53–2.48), respectively. The HRs for stroke were similar. In contrast, glycated hemoglobin and death from any cause were found to have a J-shaped association curve (Fig. 1). All these associations remained significant after adjustment for the baseline FPG level. They concluded that people with a glycated hemoglobin value of 6.0% or

higher (considered in the prediabetes range) are at high risk for the development of diabetes even after adjustment for other risk factors and independently of baseline FPG levels. They also observed that glycated hemoglobin in the prediabetes range is a marker of cardiovascular risk. In another analysis of the ARIC cohort, Matsushita et al. (20) investigated the association of HbA$_{1c}$ with incident heart failure among individuals without diabetes or heart failure (11,057 participants) at baseline and estimated HRs of incident heart failure by categories of HbA$_{1c}$ (<5.0, 5.0–5.4 [reference], 5.5–5.9, and 6.0–6.4%) and FPG (<90, 90–99 [reference], 100–109, and 110–125 mg/dL). After the adjustment for covariates including FPG, the HRs of incident heart failure were higher in individuals with HbA$_{1c}$ 6.0–6.4% (1.40 [95% CI 1.09–1.79]) and 5.5–6.0% (1.16 [0.98–1.37]) as compared with the reference group. They concluded that "elevated A1C (≥5.5–6.0%) was associated with incident heart failure in a middle-aged population without diabetes, suggesting that chronic hyperglycemia prior to the development of diabetes contributes to development of heart failure" (20).

Collectively, these studies indicate the clinical implications of the continuum of excess risk for microvascular complications, macrovascular complications, mortality, and type 2 diabetes, even at the lower values within the glycemic range that defines prediabetes, and make a compelling argument for better identification and management.

THE VALUE OF DIABETES PREVENTION

There is no longer any question regarding the value and benefit of lifestyle intervention as an effective strategy for prevention of type 2 diabetes. Recently, we provided a comprehensive analysis of all the prevention studies to date that convincingly support lifestyle modification focusing on healthful eating and increased physical activity as viable strategies for preventing type 2 diabetes (21). Further, a recent review (22) also found that "diet and physical activity programs are cost-effective among persons at increased risk." These findings combined with findings from other reviews (23) "add to the growing body of evidence that diet and physical activity promotion programs using group sessions delivered by trained personnel
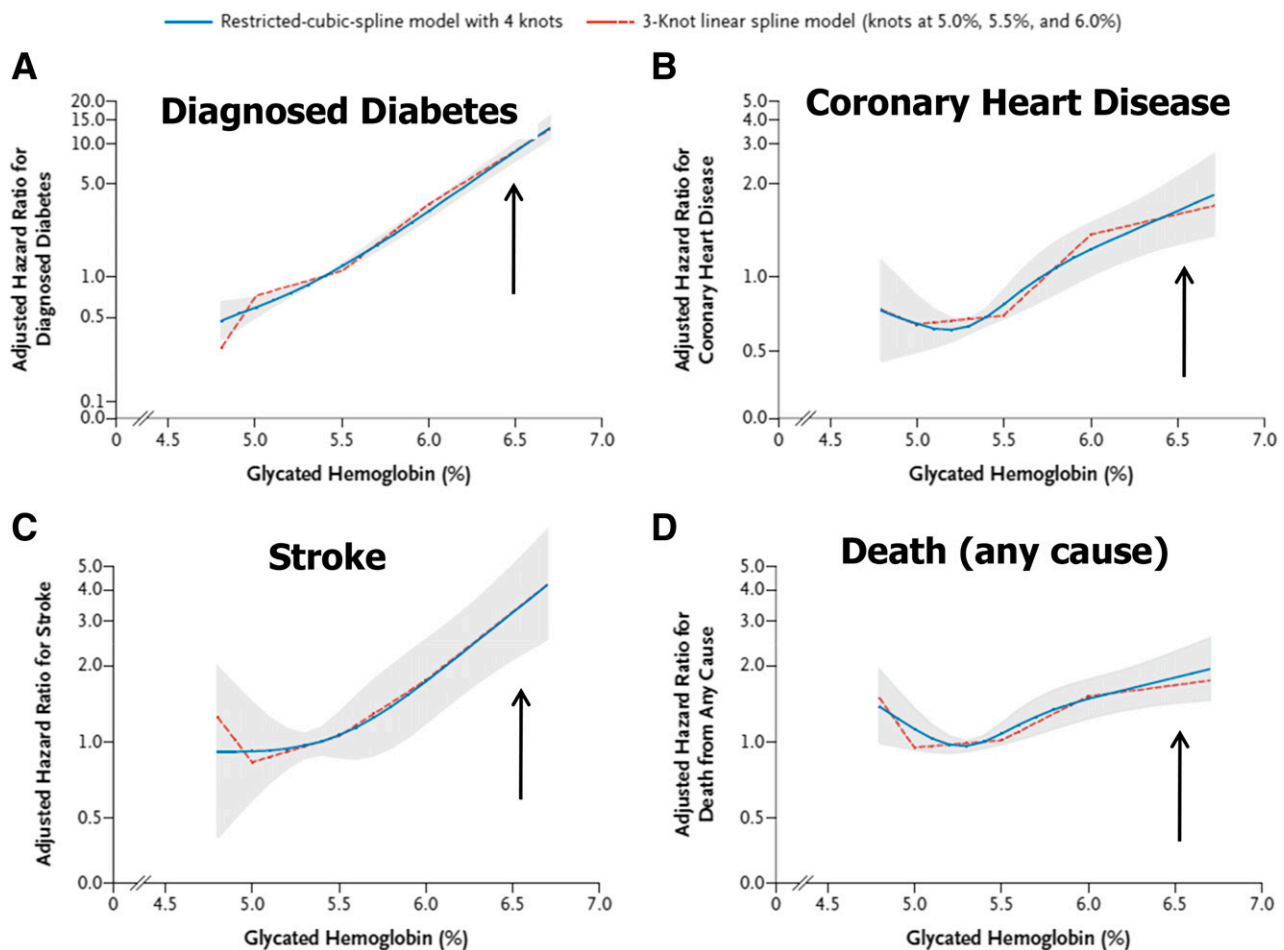
Figure 1—Adjusted HRs for self-reported diagnosed diabetes, CHD, ischemic stroke, and death from any cause, according to baseline HbA$_{1c}$ level. Arrow signifies current definition of diabetes at HbA$_{1c}$ of 6.5%. Adapted with permission from Selvin et al. (19).

are both effective and cost-effective" (22). An additional argument for now is that all the prevention studies to date are only delaying the incidence of type 2 diabetes and not preventing disease. However, it is not feasible at the current time to suggest that an intervention has "prevented" diabetes over a lifetime as the studies can only determine the fraction of the study population that progresses to diabetes. But the fact remains that even delaying the onset of the disease will have substantial benefits. For example, the projection of the Diabetes Prevention Program (DPP) intervention's effects over a lifetime yielded estimates that diabetes may be delayed by 11 and 3 years by lifestyle and metformin interventions, respectively (Fig. 2) (24).

Another argument made against implementing widespread prevention studies is that the current prevention studies have not shown results for reduction in long-term complications.

But the data from the Da Qing Diabetes Prevention Study that evaluated 94% of the original cohort at the 20- and 23-year follow-ups (25,26) showed a durable 43% lower diabetes incidence rate, a 47% reduction in severe diabetic retinopathy (26), and, by year 23, significant reductions in cardiovascular (41%) and all-cause (29%) mortality. We also recognize that the Study to Prevent NIDDM (STOP-NIDDM Trial) reported that treating IGT patients with acarbose was associated with a significant reduction in the risk of cardiovascular disease and hypertension (27). Finally, the DPP lifestyle intervention demonstrated improvements in all traditional, as well as many nontraditional, cardiovascular risk factors (28).

LOGICAL NEXT STEPS

We recognize that the interventions to date have focused on lifestyle modification and pharmacologic interventions on prevention of type 2 diabetes in

high-risk individuals with IGT. Given the information presented above, the logical next steps will be to consider individuals at lower thresholds and determine efficacy and benefit of the intervention. In this regard, ascertaining which individuals will progress from prediabetes to diabetes and when will need to be determined, and we will need to understand how best to identify the most appropriate target populations for intervention. We will also need to know how to disseminate lifestyle interventions most cost-effectively. In this regard, there are a number of national and community campaigns that are occurring throughout the world showing encouraging results (21).

CONCLUSIONS: DOING WHAT IS "NECESSARY"

The global burden of diabetes is enormous, and the projections are staggering. We simply cannot wait until the
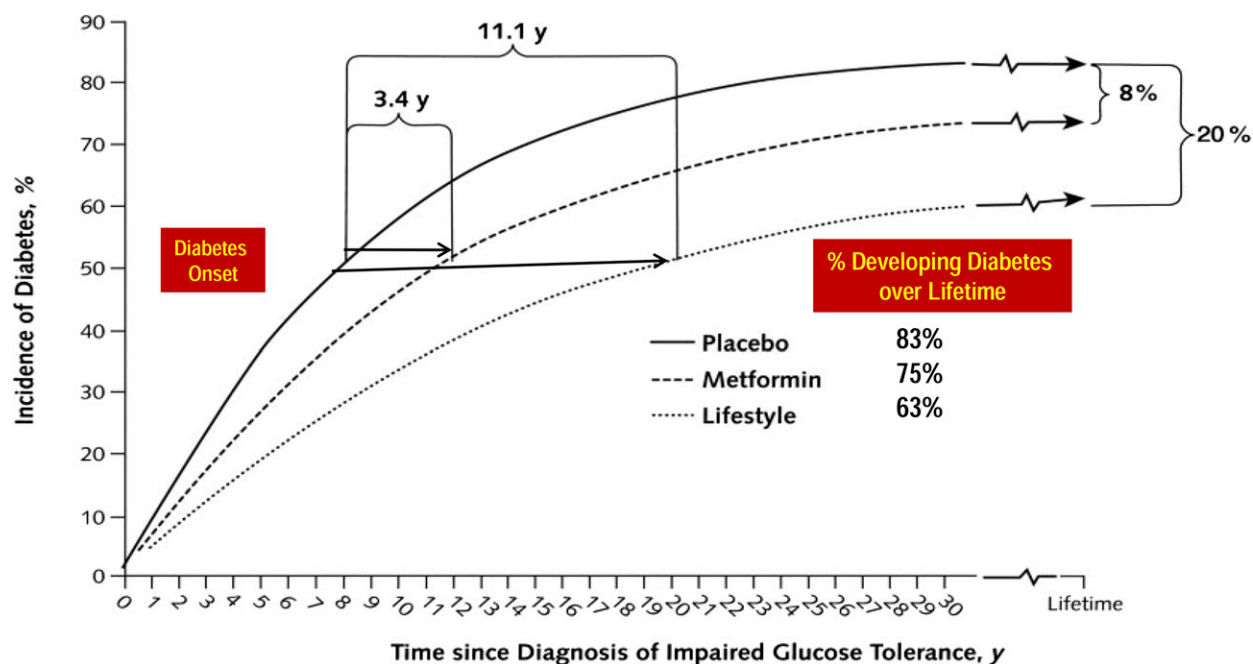
Figure 2—Simulated cumulative incidence of diabetes among adults with IGT in the DPP treatment group. Adapted with permission from Herman et al. (24). y, years.

disease is diagnosed before intervening. We know that prevention interventions (i.e., lifestyle, pharmaceutical agents) work to delay the disease in individuals at high risk. However, with this narrative, I fully recognize that using the lower criteria will greatly increase the prevalence of those identified as prediabetes. I also provide evidence that individuals identified with the lower criteria for FPG and HbA$_{1c}$ are at risk for progression to type 2 diabetes and at risk for microvascular and macrovascular outcomes. Thus, the issue is not with the label of prediabetes. The issue relates to our inability at the current time, both as a medical community and as a society, to deal with the enormity of the global burden. The concern may be that many may feel we have already done our best with the prevention studies and taking the next step in the process, given the huge global burden, is simply too hard at this time to effectively deal with the situation. I think the best way to state our current situation with the label of prediabetes and diabetes prevention would be a quote from Winston Churchill who stated, "It is no use saying, 'We are doing our best.' You have got to succeed in doing what is necessary." Thus, to simply dismiss the label of prediabetes is not the solution! What is now "necessary" is to truly understand the challenge before us and then work to identify the appropriate

candidate for intervention, thereby providing a low-cost, scalable, widespread intervention that is effective. This is even more important in areas of the world that lack resources to address the disease. I remain encouraged by the early results of the translational prevention programs currently being evaluated and urge us to not simply accept that we have done well to date. In addition, we must also accept the fact that the next "necessary" step will be hard!

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