"Prediabetes": Are There Problems With This Label? Yes, the Label Creates Further Problems!

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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 point narrative below, Dr. Yudkin provides his argument that there are significant problems with this label. In the counterpoint narrative that follows Dr. Yudkin's contribution, 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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As a term to describe people at elevated risk for type 2 diabetes, "prediabetes" has taken on and defeated all-comers in the battle for supremacy. Until the millennium, impaired glucose tolerance (IGT) was the only player in the game, but new criteria based on impaired fasting glucose (IFG) (two sets) and then on glycated hemoglobin (HbA_{1c}) (also two sets) arrived on the scene. The American Diabetes Association (ADA) in 2010 deemed that "prediabetes" should encompass the combination of IGT with the wider band of each of the other criteria (1). And it is this term and this classification that dominates the discourse, both scientific and popular.

The results of the Diabetes Prevention Program (DPP) (2,3), based as they are on an intensive program of lifestyle interventions in a highly selected population at very high risk of developing diabetes, have been overinterpreted and used to justify implementing such approaches in the community across populations of millions

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POINT-COUNTERPOINT

of people at substantially lower risk. In this Point-Counterpoint series, I will take the "pro" position and will

- explore what this landmark study has shown and suggest that "diabetes prevention" is conceptually different from prevention of yes/no conditions such as tuberculosis or stroke;
- argue, as have the DPP trialists, that "the ultimate worth of diabetes prevention is in the reduction of long-term morbidity or mortality, compared with waiting for the disease to develop and then treating it" (3) and that by this criterion evidence is still wanting;
- show that assuming equivalence between the high-risk DPP subjects and the 86 million U.S. adults with "prediabetes" (4) risks disease-labeling of many lower-risk people for whom no evidence exists;
- suggest that studies of community-based diabetes prevention programs, generally achieving less than half the impact of the DPP on weight and glycemia, provide little support for implementation, particularly for the entire population with "prediabetes"; and
- point out that in people with "prediabetes," recourse to metformin, and by implication to other glucose-lowering agents, is likely to impact deterioration to diabetes only in people at the very highest level of risk.

Given that I am providing the point position in this debate that the label causes problems, I will suggest that for several reasons the term is doing more harm than good. When the landmark DPP (2) and its Diabetes Prevention Program Outcomes Study (DPPOS) (3) are not convincingly able to show benefit after 15 years on even surrogate markers of microvascular disease, there are questions as to whether the potential problems of the "prediabetes" label might outweigh its benefits.

"PREDIABETES"—WHAT IS IT?

The term "prediabetes" as defined by the ADA (1) comprises borderline glycemia measured by any of three measures—fasting plasma glucose (FPG) 100–125 mg/dL (5.6–6.9 mmol/L), 2-h plasma glucose 140–199 mg/dL (7.8–11.0 mmol/L), or HbA_{1c} 5.7–6.4% (39–46 mmol/mol). Applying the term "prediabetes" to an individual implies that person is at elevated risk for diabetes. Such an individual is also at higher risk of developing cardiovascular disease, although here the different component definitions of the condition do not share similar degrees of risk (5).

In the past it was thought that the cut point for diabetes represented a precise threshold of risk for microvascular complications, but it is clear that no such thresholds exist (6). Glucose intolerance is at the right tail of a distribution curve, so expanding the category by even a small degree will include substantially larger numbers of people. Moreover, because there are three different scales for glycemia with little concordance, the resulting category of "prediabetes" comprises a heterogeneous ragbag of individuals in terms of demography and pathophysiology (7). All three measures tend to deteriorate over time when these people are followed up. But individual studies, or meta-analyses, need rigorous analyses before drawing conclusions that are then applied to everyone with "prediabetes."

WHY PREVENT DIABETES?

The main justification for prevention, as for glucose lowering in people with diabetes, is to reduce the risk of future complications. But preventing diabetes is also worthwhile because of its economic burden, individual and societal, and also because the diagnosis comes with additional problems of self-perception and drug side effects. But a new clinical category of "prediabetes" that itself engenders costs (8), treatment side effects, and disutilities related to self-image (9) is justified only if there are longer-term advantages. There needs to be a persuasive case for creating a disease label for over one-third of the U.S. adult population (7).

WHAT HAS BEEN SHOWN?

The landmark study of diabetes prevention was the DPP (2) and its DPPOS (3,10). The headline results were that the 2.8-year lifestyle intervention in high-risk people resulted by the study end in a 58% relative risk reduction of incident diabetes, a figure that after 15 years still represented a 27% reduction. The intervention was in a highly selected group of overweight people with both IGT and elevated FPG and aimed at a weight reduction of 7% and 150 min of exercise per week. A number of similar diabetes prevention studies have been published, and these are summarized in a meta-analysis in a recent Community Preventive Services Task Force (CPSTF) report (11). In 15 studies of lifestyle intervention lasting between 1 and 23 years, there was a 41% reduction in incident diabetes at study end.

There are four points that are worth flagging. First, nearly 80% of subjects in this meta-analysis had IGT at baseline. Only one study has explored the effects of lifestyle interventions on people with IFG, and it has not found a significant benefit (12). Second, the CPSTF meta-analysis concluded that there was no convincing evidence that these programs reduced the incidence of long-term diabetes complications or of mortality. It noted reductions in retinopathy (13) and in cardiovascular and total mortality (14) in certain intervention subgroups in a small Chinese intervention study but also noted that problems of study design and analysis meant that these findings needed replicating. These reservations appear justified in light of the 15-year follow-up of the DPP/DPPOS, which has shown no clear impact of the interventions on even surrogate markers of microvascular complications (3). Third, following the 2009 report of the International Expert Committee (15), the HbA_{1c} test has become the main method of diagnosing both "prediabetes" and diabetes. But evidence about "prediabetes" and its management based on glycated hemoglobin does not exist. An analysis of the DPP/DPPOS in which HbA_{1c} was used both for classification and outcome (16) showed that 13% of DPP recruits already had diabetes ($HbA_{1c} \geq 6.5\%$) at baseline and that a sizeable proportion had levels of HbA_{1c} below the "prediabetes" threshold. Finally, the expansion of the criteria for "prediabetes" to encompass people with elevated FPG and borderline raised levels of HbA_{1c} raises the prevalence around threefold in the U.S. (37% of adults) (4) and sixfold in China (over 50% of adults) (17). Of the 86 million U.S. adults with "prediabetes," around 1.7 million develop diabetes each year (4), making the annual risk around 2% rather than the 11% seen in the placebo group of the DPP (2). So in summary, studies to date suggest that intensive lifestyle interventions, largely in overweight people with IGT (around 14% of the U.S. adult population) (7), can reduce or delay the incidence of diabetes but not its long-term complications. It is unclear whether

similar effects would be found in people with IFG or with borderline abnormal levels of HbA_{1c} who comprise the majority of U.S. adults with "prediabetes."

The results of the DPPOS were presented as showing that even after 15 years, the 2.8-year period of lifestyle intervention maintained some benefit, with a 27% reduction in incidence of diabetes (3). Yet DPPOS data show a progressive increase in mean levels of FPG in both lifestyle and placebo groups from 12 months into the study (10) (Fig. 1), as well as similar, parallel rates of incident diabetes with time (3,10). So put another way, lifestyle intervention on average delayed the incidence of diabetes by 3–4 years and metformin by somewhat less. But while "diabetes" is a category, glycemia is a continuous variable. Analyzed in this fashion, lifestyle intervention produced a mean reduction in glycated hemoglobin concentration of 0.12% during the 10 years of follow-up (10). This compares to the mean reduction of 0.9% over 10 years in the UK Prospective Diabetes Study (UKPDS) (18), perhaps helping to modulate the expectations from the DPP. Furthermore, rolling out DPP-type lifestyle programs for implementation in community settings has been shown to result in only one-third to one-half of the reduction in weight and glycemia seen in the DPPOS (19), leaving substantial doubt about the value of such programs.

"PREVENTING DIABETES"—THE RISKS OF EXTRAPOLATION

It might be worth considering what benefits might be expected by a 3- to 4-year delay, or a longer-term prevention, of newly developed diabetes. The downside of diabetes includes reduced quality of life, costs, and the risks of complications. How would these factors differ in someone with an HbA_{1c} concentration of, say, 6.4% as a result of an intervention and someone who has developed diabetes with an HbA_{1c} of 6.6%? Neither would have symptoms. The lifetime risk of either end-stage renal failure or blindness for someone aged 60 years with new-onset diabetes would be well below 1% (20), and there would be little expected impact on microvascular or macrovascular risks from the degree of HbA_{1c} reduction achieved during the DPP/DPPOS (3,10,21). Diabetes health care needs and costs are likely to be dependent upon the duration of the condition and its severity and so are unlikely to differ greatly between the patient with newly diagnosed diabetes and someone with "prediabetes." The problem of treating "prediabetes" and diabetes as transition states—separate categories, each with its own disutility and cost—also applies to many of the modeling studies summarized in the CPSTF report (22), with the notable exception of those from the DPP. If someone is considered in a mathematical model as having developed diabetes and is thus assumed to share the average health disutility (23) and the annual costs (24) assessed for a population with diabetes, this may exaggerate the apparent benefits of prevention.

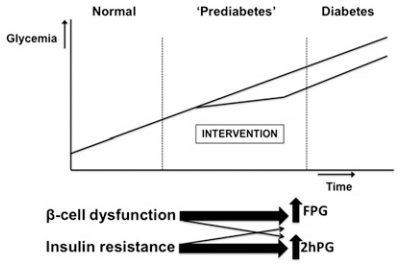

Figure 1—Trends in glycemia with time and the effects of lifestyle interventions. These interventions target insulin resistance and are likely to be less effective in subjects with elevated concentrations of FPG. 2hPG, 2-h plasma glucose.

THE HAZARDS OF A "GLUCOCENTRIC" DEFINITION

One hazard of the concept of "prediabetes" is its reliance on glycemia. Type 2 diabetes is a complex metabolic state. Glycemia is a major determinant of eye, kidney, and nerve damage but a relatively small player in the increased cardiovascular risk of diabetes (18,21). The overall benefit of metformin in the DPP in terms of prevention or delay of diabetes was around half that of lifestyle intervention but with marked heterogeneity—only in the DPP subjects in the highest quartile of diabetes risk did metformin show any benefit (25). So it is wrong to extrapolate the findings even to suggest that this drug, or any other, will benefit all overweight subjects with IGT and elevated FPG, let alone everyone with "prediabetes." Were future results to show macrovascular benefits in the DPPOS with either lifestyle intervention or metformin, in neither case could it be assumed that this was related to glucose lowering. Weight loss and physical activity have numerous nonglycemic benefits on cardiovascular risk, and the findings of cardiovascular benefit from metformin in the UKPDS seemed independent of glycemia (26). Yet the "prediabetes" agenda remains one of preventing glucose-defined diabetes. In consequence this is already driving a powerful pharmacotherapy discourse going way beyond any evidence (9). If opinion leaders and guidelines committees can argue that it is worthwhile to treat people with "prediabetes" using glucose-lowering agents that have not been shown to reduce anything other than glucose concentrations, there is a risk that one-third of the U.S. and U.K. populations and possibly one-half of the adult Chinese population will be considered as possible targets.

CONCLUSIONS—WHAT DO WE NEED?

This author suggests that the main transformation needed in this debate is a considered appraisal of the evidence. Statements such as those suggesting that "programs that achieve a mean weight loss at 1 year of just 2.5% confer a 60% reduction in diabetes development at 6 years" (27) inflate expectations. Type 2 diabetes is generally an asymptomatic risk factor for future disease. For the overweight subjects in the DPP, with both IGT and IFG, the chance of crossing that cut point was around 50% over a 10-year period (10). But among the 86 million people with ADA-defined "prediabetes," the proportion who develop diabetes is around 2% per year (4). If someone is given this diagnosis, it increases their consultations with an endocrinologist by 78% (8), although to what benefit is unclear. Almost all studies on diabetes prevention antedated use of glycated hemoglobin in defining diabetes and in analyses of outcomes. The potential is there for a powerful synthesis of evidence. This needs to combine rigorous meta-analysis of the DPP/DPPOS and other diabetes prevention studies, testing different cut points for diagnosis of intermediate hyperglycemia and diabetes. It also needs to explore the relationship of these to patient-relevant outcomes, or their surrogate markers, and not just to glycemia. Until this is done, there is a

risk that the "prediabetes" agenda will remain dominated by lobbying and hyperbole rather than by science.

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