Lowering the Cut Point for Impaired Fasting Glucose

Where is the evidence? Where is the logic?

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First a disclaimer, neither of us is a diabetologist, endocrinologist, or internist. We do not provide chronic care to people with diabetes. Our only credential relevant to the diagnosis of diabetes is our willingness to think logically and our conviction that the goal of guidelines and policies must be to optimize patient outcomes. From this perspective we are befuddled by the Expert Committee’s (1) decision to lower the cut point for impaired fasting glucose (IFG) from 110 to 100 mg/dl. In this commentary we explain why.

With the publication of the Expert Committee’s report (1) in Diabetes Care in November 2003, the number of 25- to 74-year-olds in the U.S. with IFG instantly tripled from 10 to 35 million people (see Appendix for all methods). We might expect that a decision affecting over 25 million people would be based on some type of explicit modeling that established the benefits of the new cut point. Unfortunately, the Expert Committee’s report contains no such analysis. In fact, the committee states “we do not yet know the total benefit or the total cost to an individual who is designated at risk for diabetes by either test, by any criteria” (1). Given this, the Expert Committee might have concluded, “and we therefore have insufficient evidence to newly label 25 million people with IFG” (1).

Instead, the committee offers two forms of justification for its decision: 1) epidemiological data that suggest that those with an FPG of 100–109 mg/dl may be at higher risk for developing diabetes than those with a level below 100 mg/dl; and 2) the desire to have the IFG population have greater homology to the impaired glucose tolerance (IGT) population. The first argument fails because identifying those at higher risk in no way insures that their health will be improved (there might not be an effective treatment). The second fails because there is no biological or epidemiological reason why IFG should match IGT. Thus, the Expert Committee fails to offer compelling justification for lowering the cut point to 100 mg/dl since they do not establish that the lower cut point will improve the health of the population. The committee’s belief that the beginnings of abnormal glucose metabolism start with a fasting blood glucose of 90–110 mg/dl may be dead on physiologically speaking, but this has no relevance in determining cut points that will have public health implications.

What if we try to perform the kind of formal decision analysis that the Expert Committee should have performed? Such an analysis requires that each outcome that could result from a decision be assigned a probability and a value. For example, consider the decision of whether to buy a $1 lottery ticket for a lottery in which 100 $1 tickets will be sold and a single winner will get $80. The choice to “buy” produces the outcome “lose,” with a probability of 0.99 and a net benefit of minus $1, and the outcome “win” with probability 0.01 and a net benefit of $79. A little math [(0.99 × −1) + (0.01 × 79) = −0.20] produces a net expectation for the choice to “buy” of minus 20 cents. The choice “don’t buy” has a single outcome that has a probability of 1.0 and a net benefit of zero dollars. Thus, if the decision to buy the ticket was purely economic, the rational decision maker would not buy a ticket. One could expand this analysis to account for other values—the thrill of participating in the lottery, the knowledge that the proceeds of the lottery would benefit a charity—but the principles remain the same; one cannot choose a preferred option unless one knows both the probability that each outcome will occur and the value of each outcome.

Expert Committee members were confronted with a similar choice. Should they lower the cut point for IFG to 100 mg/dl or leave it at 110 mg/dl? (They could have changed it to other values, but we consider this binary choice in the name of simplicity.) We can further simplify the problem by noting that only subjects with values of 100–109 mg/dl are affected by the change since all other subjects are treated the same way under both cut points. The decision model has two options, each with two outcomes (Table 1).

As in the lottery example, if we can determine the probability and value of each outcome we can determine the optimal cut point. We start with the probabilities by asking, “what percentage of those with FPG values of 100–109 mg/dl truly have a problem with glucose metabolism?” Because there is no accepted definition of “glucose problem,” we must make indirect arguments. In the past decade, five studies evaluating more than 2,000 patients with both type 1 (2–4) and type 2 (5,6) diabetes over 6–10 years have demonstrated that development or progression of retinopathy and microalbuminuria were minimal or absent if HbA1c levels were maintained <7%, increased only slightly if the HbA1c levels were 7–8%, but increased markedly at values >8%. In the National Health and Nutrition Education Study (NHANES)-III dataset (in which the upper limit of nor-
mal for HbA1c was 6.1%), 0.05% of subjects with FPG levels of 100–109 mg/dl had HbA1c levels of >7.1%, 6% had levels of 6.1–7.1%, and 94% had normal levels. Thus, <1 in 200 patients had a degree of hyperglycemia that is associated with development or progression of the microvascular complications of diabetes.

How many of the 99.5% of subjects whose HbA1c levels are not associated with the microvascular complications of diabetes are at risk of having their FPG or 2-h oral glucose tolerance test levels rise above the cut point for diabetes? In the Diabetes Prevention Program Research Group trial, subjects with an FPG of 95–109 mg/dl who also had IGT and a BMI >24 kg/m² were randomized to placebo, metformin, or an intensive program of diet and exercise and followed for an average of 2.8 years (7). The incidence of diabetes was 6.4 cases per 100 patient-years in the placebo group, 5.5 in the metformin group, and 2.9 in the diet and exercise group. If these rates are constant over time, then left untreated, 50% of subjects will have diabetes in ~12 years. Treatment with metformin delays the 50% threshold until 14 years and diet and exercise until 24 years. These estimates might be high for our purposes because all study subjects had IGT, and their average BMI of 34 kg/m² was considerably higher than the 28-kg/m² average of those with an FPG of 100–109 mg/dl in the NHANES III database. These data provide some tentative estimates of how patient outcomes might be improved if labeling someone with a FPG of 100–109 mg/dl as having “IFG” resulted in effective treatment.

For virtually all patients affected by the change in cut point, the only currently justifiable treatment is diet and exercise. We must now consider what percentage of such subjects would be eligible for such treatment. From the NHANES III data we can determine that ~89% of 25- to 75-year-olds with an FPG of 100–109 mg/dl have another indication (high BMI, hypertension, or dyslipidemia) for diet and exercise and therefore could be identified and treated without being labeled as having IFG. Thus, of all those who will be newly labeled as “IFG,” only 11% have no other indication for diet and exercise. These subjects are likely to be false positives (in the absence of other signs of the metabolic syndrome, it is unlikely that they truly have a problem with glucose metabolism) and are less likely to benefit from the labeling. The 89% with other risk factors will only benefit if the addition of the IFG label to a problem list that includes hypertension, obesity, or dyslipidemia increases their adherence to their diet and exercise regimen. We could find no evidence that it does.

Thus, while it is impossible to accurately quantify the percentage of subjects who are true positives and false positives, we can state with some certainty that only a minority of subjects with FPG in the 100–109 mg/dl range have any chance of being helped by being labeled as having IFG. The converse of this is that the health status of the majority of subjects will either remain unchanged (because they are receiving diet and exercise therapy for another reason) or will suffer as a result of mislabeling. Since neutral or harmful events will occur more frequently than positive ones, the net benefit of a positive event must be greater than the net harm of a harmful event if the balance sheet is to favor lowering the cut point.

We must now consider the benefits and harms. We can simplify the problem by quantifying the net difference in health outcomes between strategies rather than the absolute health outcomes of each strategy. In other words, we can attempt to measure the difference between outcomes 1.1 and 2.1 (what is the benefit of labeling someone who truly has a glucose problem as IFG?) and between outcomes 1.2 and 2.2 (what is the harm of labeling someone who does not have a glucose problem as IFG?) (Table 1).

The first difference will depend on the effectiveness of the early treatment intervention. To create improved outcomes, the identified subjects must be provided an intervention that leaves them healthier than they would have been had their disease progressed until their FPG was >109 mg/dl (at which time they would have been identified as having IFG and treated). For this to occur, two things have to happen. First, the patient can’t already be receiving the intervention for other reasons (if they are, then the knowledge that they have IFG does not result in any new intervention). Second, the knowledge that they have “IFG” must increase their adherence to treatment. While there is some evidence that diet and exercise can delay the onset of diabetes in high-risk patients with IGT and IFG, we know very little about how treatment affects lower-risk subjects (7–9). We know even less about how the long-term outcomes achieved with this early treatment will compare to the outcomes achieved by deferring treatment until the fasting glucose has risen to >110 mg/dl. There is nothing to suggest that the magnitude of the net benefit is large. It is likely quite small.

We also need to quantify the difference in value between outcomes 1.2 and 2.2. This difference will likely be valued negatively, since telling someone she has a problem with glucose metabolism when she doesn’t will create anxiety, increase health care costs, and may produce complications from unnecessary treatment. We could find no research about the magnitude of harm due to false positive cases.

So, despite our best efforts, we are left with very uncertain probabilities and very uncertain valuations of health outcomes. We can say that the majority of people will not be helped, that it is unlikely that the health benefit to the minority who are helped is large, and that many may suffer psychological or physical harm from being labeled as having “IFG” when they are already receiving maximal therapy for other reasons (and therefore cannot benefit from the labeling) or do not have a problem with glucose metabolism. We cannot say with any certainty whether the combined effect of these considerations

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### Table 1—Options and outcomes for subjects with an FPG of 100–109 mg/dl (inclusive)

<table>
<thead>
<tr>
<th>Option 1</th>
<th>Lower the cutpoint to 100 mg/dl</th>
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<tbody>
<tr>
<td>Outcome 1.1</td>
<td>True positive: subject has a glucose problem* and is diagnosed with IFG</td>
</tr>
<tr>
<td>Outcome 1.2</td>
<td>False positive: subject does not have a glucose problem and is diagnosed with IFG</td>
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<table>
<thead>
<tr>
<th>Option 2</th>
<th>Leave the cutpoint unchanged at 110 mg/dl</th>
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<tbody>
<tr>
<td>Outcome 2.1</td>
<td>True negative: subject does not have a glucose problem and is not diagnosed as IFG</td>
</tr>
<tr>
<td>Outcome 2.2</td>
<td>False negative: subject has a glucose problem but is not diagnosed with IFG</td>
</tr>
</tbody>
</table>

*The term “glucose problem” denotes some disturbance of glucose metabolism that will decrease the subject’s longevity or decrease the quality of the subject’s life at present or at some future time.
will produce net benefit or harm. Until we have reasonable numbers for these values, it is pure conjecture to state what the cut point should be. Anyone arguing forcefully for any particular cut point is vested in something other than the available facts.

Here is one such argument. Most of the subjects with an FPG of 100–109 mg/dl can be motivated to lose weight and exercise by citing the general benefits of these activities and by pointing to any hypertension, obesity, or dyslipidemia the subject may have. The evidence that the knowledge that one has IFG increases the motivation to exercise and diet just isn’t there. Alternatively, the IFG label may harm the subject by tarnishing his or her health record and insurability and by creating anxiety about something that may never happen. Furthermore, there is little evidence that early detection of these patients will improve long-term outcomes, even in those who successfully diet and exercise. Thus, our take is that lowering even in those who successfully diet and exercise by citing the general benefits confuses rather than improves, and patients will improve long-term outcomes.

APPENDIX

Methods used to analyze NHANES III

These analyses were carried out using the NHANES III conducted from 1988 to 1994. The NHANES III is a national health survey that includes historical, physical, and laboratory examination of subjects selected through a stratified multistage, probability-cluster sampling design. It is designed to provide data representative of the U.S. population. All analyses were performed using STATA 7.0 (STATA, College Station, Texas) using methods described by Harris et al. (10) and Peters et al. (11).

Step 1) We determined the distribution of HbA1c levels in subjects with fasting glucose measurements of 100–109.9 mg/dl using all subjects in NHANES III who did not report a history of diabetes; were between 40 and 74 years of age (inclusive); were in the morning session sampling; had valid FPG, 2-h oral glucose tolerance test, and HbA1c levels; and had a proper weighting variable (WTPFSD6). A total of 2,853 subjects met these inclusion criteria, of whom 747 had FPG levels of 100–109.9 mg/dl. These subjects were stratified into three categories based on their HbA1c levels: >7.1%, 6.1–7.1%, and <6.1% (normal) [see text and ref. (11) for the rationale for these intervals]. A weighted analysis was then performed using variable WTPFSD6 to render HbA1c distributions representative of the U.S. population in our study population (10). Altogether, 0.045% were found to have HbA1c >7.1%, 5.63% were found to have HbA1c levels of 6.1–7.1%, and 94.3% were found to have normal HbA1c levels.

Step 2) We determined the total number of people in the U.S. with an FPG of 100–109 mg/dl and 110–125 mg/dl using all subjects aged 25–74 years in NHANES III who did not self-report a history of diabetes and had a valid morning session fasting glucose, using the WTPFSD6 weights to account for the number of subjects represented by each subject. We determined the average BMI in this group using the syvenmean command in STATA.

Step 3) We determined the percent-age of subjects with an FPG of 100–109 mg/dl who had elevated BMI, blood pressure, or dyslipidemia as follows. We began with all 25–74-year-olds in the database who did not report a history of diabetes (n = 13,037). Exclusion and inclusion criteria were the same as in step one except that valid 2-h and HbA1c levels were not required. In total, 5,193 nondiabetic subjects comprised this final NHANES III study population. Of the 5,193 subjects in this sample, 1,087 had FPG levels of 100–109 mg/dl (inclusive) (a larger number of subjects than the 747 in step 1 because we did not require valid 2-h OGTT and HbA1c levels). Three risk factors were then analyzed including dyslipidemia, high blood pressure, and BMI. Subjects were considered to have dyslipidemia if they had any one of the following: total cholesterol >200 mg/dl, LDL cholesterol >130 mg/dl, triglyceride level >200 mg/dl, HDL cholesterol <35 mg/dl (men) or <45 mg/dl (women), or evidence of prior diagnosis of dyslipidemia via oral interview. Subjects were considered to have high blood pressure if they had a mean systolic blood pressure >140 mmHg or mean diastolic blood pressure >90 mmHg as averaged over at least three temporally separated measurements. Subjects were considered to have elevated BMI if this variable was calculated to be >27 kg/m². A weighted analysis was then performed using variable WTPFSD6 to determine what percentage of the U.S. population with an FPG of 100–109 mg/dl had these risk factors. Of the subjects, 76.8% had dyslipidemia as a risk factor, 40.0% had blood pressure as a risk factor, 50.9% had BMI as a risk factor, and 89.3% had at least one of the three risk factors; 20.9% had all three.

References

2. The Diabetes Control and Complications Trial Research Group. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. Diabetes 44:968–983, 1995