Identifying glucose thresholds for incident diabetes by physiological analysis: a mathematical solution

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Ferrannini E, Manca ML. Identifying glucose thresholds for incident diabetes by physiological analysis: a mathematical solution. Am J Physiol Regul Integr Comp Physiol 308: R590–R596, 2015. First published December 31, 2014; doi:10.1152/ajpregu.00325.2014.—Plasma glucose thresholds for diagnosis of type 2 diabetes are currently based on outcome data (risk of retinopathy), an inherently ill-conditioned approach. A radically different approach is to consider the mechanisms that control plasma glucose, rather than its relation to an outcome. We developed a constraint optimization algorithm to find the minimal glucose levels associated with the maximized combination of insulin sensitivity and β-cell function, the two main mechanisms of glucose homeostasis. We used a training cohort of 1,474 subjects (22% prediabetic, 7.7% T2DM) in whom insulin sensitivity was measured by the clamp technique and β-cell function was determined by mathematical modeling of an oral glucose tolerance test. Optimized fasting glucose levels were ≤87 and ≤89 mg/dl in ≤45-yr-old women and men, respectively, and ≤92 and ≤95 mg/dl in >45-yr-old women and men, respectively; the corresponding optimized 2-h glucose levels were ≤96, ≤98, ≤103, and ≤105 mg/dl. These thresholds were validated in three prospective cohorts of nondiabetic subjects (Relationship Between Insulin Sensitivity and Cardiovascular Disease Study, Botnia Study, and Mexico City Diabetes Study) with baseline and follow-up oral glucose tolerance tests. Of 5,593 participants, 452 progressed to diabetes. Similarly, in the three cohorts, subjects with glucose levels above the estimated thresholds had an odds ratio of 3.74 (95% confidence interval = 2.64–5.48) of progressing, substantially higher than the risk carried by baseline conventionally defined prediabetes [odds ratio = 2.32 (95% confidence interval = 1.91–2.81)]. The concept that optimization of glucose concentrations by direct measures of insulin sensitivity and β-cell function identifies gender- and age-specific thresholds that bear on disease progression is proven in a physiologically sound, quantifiable manner.

glucose thresholds; β-cell function; insulin sensitivity; incident diabetes

TYPE 2 DIABETES MELLITUS (T2DM) is diagnosed on the basis of fasting (≥126 mg/dl) and/or 2-h (≥200 mg/dl) plasma glucose (FGP and 2-HG, respectively) concentrations during a standard oral glucose tolerance test (OGTT) (1, 31). Prediabetes, encompassing impaired fasting glycemia and impaired glucose tolerance, also is diagnosed on the basis of FGP and/or 2-HG concentrations (1, 31). These threshold values hinge on epidemiological evidence of risk for the presence or future development of retinopathy (1, 31), as well as some evidence for a bimodal distribution of plasma glucose values (25). However, use of outcomes to set diagnostic cutoff points is an inherently ill-conditioned approach, as the choice strongly depends on quality of outcome ascertainment, sample size, duration of observation, and identification of point(s) of inflection. For example, a recent analysis of three large population-based, cross-sectional studies yielded no evidence for a clear glycemic threshold for prevalent or incident retinopathy (30).

In longitudinal surveys, plasma glucose levels as continuous variables, along with other risk factors (e.g., positive family history of diabetes, obesity), are consistent predictors of incident T2DM in nondiabetic individuals (24, 26, 29). A common approach to improving diabetes prediction is to include additional biomarkers, such as HbA1c (24) or multiple other biomarkers (13, 17), in the prediction model.

A radically different approach is to consider the mechanisms that control the level of the biomarker, rather than its relation to an outcome. If the relation between mechanism and biomarker can be described quantitatively (in the form of a so-called objective function), one can determine the best level of control mechanism that optimizes the biomarker, which can then be tested as a threshold. In applied mathematics, this approach is known as an optimization problem. Optimization programs are ubiquitous in engineering (20) and science (12); to our knowledge, they have not been proposed for plasma glucose. In the case of glucose, it is well established that β-cell function and insulin sensitivity are strong independent determinants of plasma glucose concentrations (7, 10, 15). Therefore, by using measures of insulin secretion or insulin action, one can find the minimal plasma glucose level, or threshold, above which the risk of incident diabetes becomes clinically significant.

In the present work, we took advantage of a very large database in which both insulin sensitivity and β-cell function were measured by gold-standard methodology across the full range of glucose tolerance. These data were used to build a “bi-objective” optimization problem, i.e., to estimate the best combination of these two control variables that simultaneously minimizes FGP and 2-HG levels. The value of these thresholds was then assessed in three longitudinal cohorts of incident T2DM.

MATERIALS AND METHODS

Clinical data. The training cohort consisted of 1,474 adult subjects (22% prediabetic, 7.7% T2DM) in whom insulin sensitivity was measured by the euglycemic clamp technique and β-cell function was determined by mathematical modeling of a standard (2-h, 75 g) OGTT. This cohort included nondiabetic participants of the Relation-ship Between Insulin Sensitivity and Cardiovascular Disease (RISC) Study (8), as well as subjects and patients studied at our center as part of a different project. As in previously published methods, insulin sensitivity was indexed as the steady-state whole body glucose utilization rate (M) normalized by the steady-state plasma insulin concentration (M/I, μmol·min−1·m−2·mM−1) (5), while β-cell function was indexed as β-cell glucose sensitivity (βGS, pmol·min−1·m−2·mM−1),...
i.e., the mean slope of the dose-response function of insulin secretion rates (recomputed by deconvolution of plasma C-peptide levels) vs. plasma glucose levels during the OGTT (18). The anthropometric and clinical characteristics of the training cohort, grouped by sex and glucose tolerance status [normal glucose tolerance (NGT), prediabetes (encompassing impaired fasting hyperglycemia and impaired glucose tolerance), and T2DM according to the criteria of the American Diabetes Association (11)] are given in Table 1.

Three prospective, observational studies in which the participants received a standard OGTT at baseline and at follow-up (with measurement of FPG and 2-hG levels) were used as validation cohorts. In the RISC Study (8), nondiabetic participants were recruited at 19 centers in 13 countries in Europe, according to the following inclusion criteria: men or women, 30–60 yr of age (stratified by sex and age), and clinically healthy. Initial exclusion criteria were as follows: treatment for obesity, hypertension, lipid disorders, or diabetes; pregnancy; cardiovascular or chronic lung disease; ≥5 kg weight change in the last 6 mo; cancer (in the last 5 yr); and renal failure. Exclusion criteria after screening were as follows: arterial blood pressure ≥140/90 mmHg, prediabetes or known diabetes, total serum cholesterol ≥7.8 mmol/l, serum triglycerides ≥4.6 mmol/l, and ECG abnormalities. Baseline examinations were completed in July 2005; 1,048 subjects [503 women (44 ± 14 yr of age) and 545 men (47 ± 12 yr of age)] participated in the follow-up examination 3 yr later. Subjects were classified as progressors (n = 130) if they advanced from NGT to prediabetes, from NGT to T2DM, or from prediabetes to T2DM between baseline and follow-up.

The Botnia Study, a family-based, observational study started in 1990 on the west coast of Finland, aimed at identifying diabetes susceptibility genes (16). The prospective part included 2,585 nondiabetic family members and/or their spouses [1,186 men (46 ± 13 yr of age) and 1,399 women (46 ± 14 yr of age)], who were followed for 9.5 yr. Progressors (n = 152) were those nondiabetic participants who had developed T2DM by the end of the study.

The Mexico City Diabetes Study (MCDS) is a population-based cohort participating in a longitudinal survey of incident diabetes and cardiovascular risk factors (6). Among the 15,532 inhabitants of low-income neighborhoods in Mexico City, 2,282 randomly selected subjects were examined between 1990 and 1992 and invited to return for two follow-up examinations, at 3.25 and 7 yr. Among the 1,960 nondiabetic subjects [1,146 men (46 ± 8 yr of age) and 814 women (47 ± 8 yr of age)] who were seen at the 7-yr follow-up, progressors (n = 170) were those found to have T2DM.

The studies of the three validation cohorts (RISC Study, Botnia Study, and MCDS) had been approved by the respective ethics committees (6, 8, 16). The present analysis of data from those cohorts was approved by the Ethics Committee of the University of Pisa.

### Optimization modeling

Optimization refers to a branch of applied mathematics concerned with the maximization or minimization of certain functions (objective functions), possibly under constraints (11, 21). On the basis of an optimization problem with constraints, we aimed to maximize insulin sensitivity and glucose sensitivity, expressed as simultaneous functions of fasting (FPG) and postglucose plasma glucose concentrations (2-hG). In other words, in the training dataset we searched for the values of the independent variables, FPG and 2-hG, that correspond to maximum levels of βGS and M/I. First, we used the IBM SPSS 20 software to construct the two-objective functions. The training dataset was divided into four subgroups based on sex and age (≤45 or >45 yr of age). From a preliminary investigation of the data, nonlinear interactions emerged between the dependent variables (M/I and βGS) and the independent variables (FPG and 2-hG); therefore, these variables were transformed into their natural logarithms for use in linear modeling. After each transformation, we used an automatic data preparation to maximize the predictive power of the model by excluding values of variables outside 3 SDs from the mean (n = 21). Next, the best-subsets method was applied. This method checks all possible models, or at least a larger subset of the possible models than the forward step-wise method, to choose the best model as judged by the adjusted $R^2$.

The mathematical procedure for determining Pareto optima and their range by sensitivity analysis, described in the Appendix and in Table 2, yields an upper boundary for FPG and 2-hG in the four subsets of individuals and the “minimal” value of the associated control variables (M/I and βGS). All subjects with both FPG and 2-hG values below the optimized (Opt) threshold could then be compared

### Table 1. Anthropometric and metabolic characteristics of the training dataset by glucose tolerance status

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
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<tbody>
<tr>
<td>NGT (n = 551)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prediabetic (n = 178)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2DM (n = 54)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, +/− yr</td>
<td>44 ± 14</td>
<td>45 ± 13</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.0 ± 4.1</td>
<td>28.0 ± 4.4</td>
</tr>
<tr>
<td>Waist-to-hip ratio, cm/m</td>
<td>0.85 ± 0.10</td>
<td>0.90 ± 0.09</td>
</tr>
<tr>
<td>Glucose, mg/dl</td>
<td>88 ± 8</td>
<td>102 ± 10</td>
</tr>
<tr>
<td>Fasting</td>
<td>96 ± 20</td>
<td>128 ± 31</td>
</tr>
<tr>
<td>2-hG</td>
<td>146 ± 83</td>
<td>114 ± 88</td>
</tr>
<tr>
<td>M/I</td>
<td>131 ± 94</td>
<td>75 ± 58</td>
</tr>
<tr>
<td>βGS</td>
<td>0.12 0.85</td>
<td>0.05 0.12</td>
</tr>
</tbody>
</table>

Values are means ± SD. NGT, normal glucose tolerance; BMI, body mass index; T2DM, Type 2 diabetes mellitus; M/I, whole body glucose utilization rate (M) normalized by steady-state plasma insulin concentration (I); βGS, β-cell glucose sensitivity. *P ≤ 0.01 for sex; †P ≤ 0.05 for glucose tolerance status; ‡P < 0.001 for gender × glucose tolerance interaction by 2-way ANOVA.

### Table 2. Coefficients of constrained linear programming

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤45 yr old</td>
<td>&gt;45 yr old</td>
</tr>
<tr>
<td>Coefficients of single-objective function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right-hand-side range of 1st and 2nd constraints</td>
<td>−0.76, −1.86, 14.08</td>
<td>−1.94, −1.73, 15.97</td>
</tr>
<tr>
<td>Right-hand-side range of ln(FPG) constraints (d, e)</td>
<td>−1.38, −2.98</td>
<td>−2.15, −4.05</td>
</tr>
<tr>
<td>Right-hand-side range of ln(2-hG) constraints</td>
<td>0.99, 2.78</td>
<td>1.28, 2.80</td>
</tr>
</tbody>
</table>

FPG, fasting plasma glucose; 2-hG, 2-h glucose.
with those nonoptimized (non-Opt) glucose values in the validation cohorts.

Statistical analysis. Values are means ± SD. Group comparisons were carried out using the Mann-Whitney or Kruskall-Wallis test. Adjustment for covariates was done by multiple regression analysis. Univariate and multivariate logistic analysis was used to relate end points, i.e., incident dysglycemia (RISC Study) or overt diabetes (Botnia Study and MCDS), to baseline predictors; results are given as odds ratio (OR) and 95% confidence interval (CI). Relative risk (and 95% CI) and population-attributable risk were calculated by standard formulas.

RESULTS

In the training dataset, prevalence of prediabetes and T2DM was typical of a European population (28). While body mass index (BMI) and FPG and 2-hG increased, insulin sensitivity and βGS decreased across glucose tolerance status, in women as well as men (Table 1). Both M/I and βGS were inversely related to age (P < 0.0001) after adjustment for sex, BMI, and glucose tolerance status.

The results of the optimization procedure are given in Table 3. In the four subgroups, optimized FPG levels were 87 mg/dl (4.83 mmol/l) and 89 mg/dl (4.94 mmol/l) in ≤45-yr-old women and men, respectively, and 92 mg/dl (5.11 mmol/l) and 95 mg/dl (5.28 mmol/l) in >45-yr-old women and men, respectively. Optimized 2-hG levels were 96 mg/dl (5.33 mmol/l) and 98 mg/dl (5.44 mmol/l) in ≤45-yr-old women and men, respectively, and 103 mg/dl (5.72 mmol/l) and 105 mg/dl (5.83 mmol/l) in >45-yr-old women and men, respectively. All these optimized values were considerably lower than the actual mean values of the four subgroups. Correspondingly, the minimal values of M/I and βGS were generally higher than the observed mean subgroup values.

Among the three longitudinal validation cohorts, baseline age did not differ significantly, but BMI was significantly higher in MCDS than RISC or Botnia Study participants (P < 0.0001 for both comparisons). In contrast, Botnia Study subjects had higher FPG (100 ± 10, 92 ± 11, and 84 ± 12 mg/dl for Botnia Study, MCDS, and RISC Study, respectively) and 2-hG (112 ± 28, 105 ± 32, and 106 ± 32 mg/dl for Botnia Study, MCDS, and RISC Study, respectively) levels (all P < 0.0001). As a consequence, 30% of the subjects had Opt values of both FPG and 2-hG in the RISC Study and MCDS, while only 10% of the subjects in the Botnia Study fulfilled the criteria (Table 4). Within each cohort, Opt subjects had a more favorable metabolic profile than non-Opt subjects (Table 4). At follow-up, non-Opt subjects had a higher probability of progressing to dysglycemia (RISC Study) or T2DM (Botnia Study and MCDS) than Opt subjects, with an overall (n = 5,593) OR of 3.74 (CI = 2.64–5.48) [OR = 3.42 (CI = 2.43–5.12) after adjustment for sex, age, and BMI]. As shown in Fig. 1, non-Opt glycemias carried an increased risk of incident dysglycemia/T2DM in each of the three cohorts, both in univariate association and multivariate analyses adjusted for sex [OR = 1.40 (CI = 1.14–1.71) for men], age [OR = 1.23 (CI = 1.11–1.36) for 1 SD], and BMI [OR = 1.57 (CI = 1.44–1.72) for 1 SD]. Furthermore, even in the adjusted model, Botnia Study participants had a significantly (P < 0.0001) lower OR than either RISC Study or MCDS participants.

To further characterize the performance of Opt glucose levels in the pooled validation set, we calculated the relative risk of progression to T2DM for “threshold” glucose values within ±30% of the Opt value. For FPG (Fig. 2) and 2-hG (Fig. 3), relative risk (of above-threshold values) was not a monotonic inverse function of glycemias, but leveled off (or declined) at low glucose values (and CIs widened), while population-attributable risk declined rapidly with progressively higher glycemias.

DISCUSSION

The present analysis demonstrates that the plasma glucose levels associated with the best individual combination of insulin sensitivity and glucose sensitivity are substantially lower than the conventional diagnostic thresholds for FPG and 2-hG and that subjects with non-Opt glycemias are at increased risk of progressing to diabetes. This conclusion requires specification.

First, several previous studies (3, 9) and our training dataset show that, when directly measured, insulin sensitivity declines with age, mostly as a result of increments in BMI and waist-to-hip ratio (Table 3). Similarly, and in a more pronounced

### Table 3. Optimized parameters by sex and age

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤45 yr old (n = 438)</td>
<td>&gt;45 yr old (n = 360)</td>
<td>≤45 yr old (n = 382)</td>
<td>&gt;45 yr old (n = 273)</td>
</tr>
<tr>
<td>Age, yr</td>
<td>38 ± 5</td>
<td>53 ± 5</td>
<td>37 ± 5</td>
<td>53 ± 5</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>25.1 ± 5.4</td>
<td>26.3 ± 4.9</td>
<td>26.3 ± 3.9</td>
<td>27.3 ± 3.9</td>
</tr>
<tr>
<td>Waist-to-hip ratio, cm/cm</td>
<td>0.83 ± 0.11</td>
<td>0.84 ± 0.09</td>
<td>0.90 ± 0.09</td>
<td>0.93 ± 0.08</td>
</tr>
<tr>
<td>Glucose concentration, mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>49–290</td>
<td>65–295</td>
<td>56–324</td>
<td>65–325</td>
</tr>
<tr>
<td>Optimal</td>
<td>49–87</td>
<td>65–92</td>
<td>56–89</td>
<td>65–95</td>
</tr>
<tr>
<td>2-h Actual</td>
<td>45–500</td>
<td>45–477</td>
<td>41–403</td>
<td>49–488</td>
</tr>
<tr>
<td>Optimal</td>
<td>45–96</td>
<td>45–103</td>
<td>41–98</td>
<td>49–105</td>
</tr>
<tr>
<td>M/I, μmol·min⁻¹·m⁻²·mM⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>139 ± 89</td>
<td>130 ± 93</td>
<td>113 ± 73</td>
<td>90 ± 75</td>
</tr>
<tr>
<td>Minimal</td>
<td>&gt;211</td>
<td>&gt;142</td>
<td>&gt;201</td>
<td>&gt;136</td>
</tr>
<tr>
<td>βGS, μmol·min⁻¹·m⁻²·mM⁻¹</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actual</td>
<td>123 ± 101</td>
<td>106 ± 93</td>
<td>105 ± 71</td>
<td>87 ± 68</td>
</tr>
<tr>
<td>Minimal</td>
<td>&gt;142</td>
<td>&gt;124</td>
<td>&gt;131</td>
<td>&gt;120</td>
</tr>
</tbody>
</table>

Age, BMI, waist-to-hip ratio, and actual M/I and βGS values are means ± SD.
fashion, βGS falls with age independently of sex and BMI (14, 18). Therefore, it seemed logical to split our training dataset at around the median age, i.e., 45 yr, which is also perimenopausal age (42% of women were menopausal in the ≤45-yr age subgroup). As a result, the Opt FPG and 2-hG levels differed by age cut in men as well as women, as did the actual plasma glucose concentrations, demonstrating the ability of the optimization procedure to translate the age dependence of the mechanisms into an age-specific output. The algorithm also retrieved the sex difference, which was evident in the actual glucose levels (Table 3). Consequently, if diagnostic glucose thresholds are to be used, our analysis indicates that they should be sex- and age-specific. Application of cutoff values derived from younger groups of individuals to an elderly population may result in an overestimation of prevalence rates and an increased risk of adverse effects of treatment.

Second, in the combined validation cohorts, 46% of progressors had categorical NGT at baseline; the remainder of progressors emerged from the prediabetic pool of individuals. In contrast, 100% of the Opt subjects were NGT at baseline, and only 2.7% of them progressed (as opposed to 9.5% of the non-Opt individuals). Viewed in another way, the risk of progression was higher for the non-Opt category [OR = 3.74 (CI = 2.64–5.48)] than for the conventionally defined prediabetes category [OR = 2.32 (CI = 1.91–2.810)], the difference being maintained in the adjusted logistic model. Thus, Opt glucose thresholds perform better than conventional glucose tolerance categories in predicting T2DM. Also, in the multivariate logistic model, the non-Opt criterion was associated with two- to three-times-higher risk of progression than was sex or age (1 SD of ~12 yr) or BMI (1 SD of 4.3 units or ~12 kg).

Third, the predictive power of Opt glucose values was similar for progression to dysglycemia (RISC Study) and development of T2DM (MCDS) (Fig. 1), confirming that the set of predictors for prediabetes and overt T2DM is essentially the same (4, 27). This finding is especially notable, inasmuch as all RISC Study participants were European while MCDS subjects were natives of Mexico City, where T2DM prevalence is much higher (~12%) than in Europe (~7%) (28). The somewhat lower OR for progression in the Botnia Study may be due to its very high prevalence of familial T2DM (80%, by selection) compared with the other two prospective cohorts. This was likely tracked by the higher baseline plasma glucose levels in the Botnia Study (Table 4), resulting in a smaller percentage of people with Opt plasma glucose values.

Fourth, we tested whether optimization of only one of the FPG and 2-hG categories would still contribute useful predictivity. As shown in Table 5, optimization of either FPG or 2-hG was still associated with significant predictivity for progression, although with lower ORs [OR = 1.71 (CI = 1.39–2.11) and OR = 2.50 (CI = 1.97–3.19), respectively] than that obtained upon optimization of FPG and 2-hG jointly [OR = 3.74 (CI = 2.64–5.48)]. However, it was of interest that Opt 2-hG performed better (in the same range as the prediabetes category) than Opt FPG. Because insulin sensitivity physiologically is a stronger determinant of 2-hG than FPG (19), the superiority of optimization of the former over the latter may be interpreted as evidence that insulin sensitivity plays a major role in the optimization problem. In fact, the “minimally optimal” levels of M/I estimated by the algorithm (Table 3) are far above the actual mean M/I values, particularly in the <45-yr-old groups, whereas the corresponding minimally op-
Optimal βGS values are closer to the observed mean values. Coherent with this, we found that Opt FPG values were closer to the measured fasting levels (an average difference of 8 mg/dl) than Opt 2-hG values were to measured 2-hG values (an average difference of 20 mg/dl). This suggests that the current diagnostic threshold for NGT (2-h glucose > 140 mg/dl) may be too high to effectively protect against incident diabetes.

On the other hand, when trying to optimize both glucose values using only one of the controlling variables (M/I or βGS), the sensitivity analysis could not exclude the upper boundaries of glucose concentrations, i.e., the highest observed plasma glucose levels (Table 5). This result strengthens the posit that although other factors (glucagon, neural input) affect glycemia, prompt release and robust action of insulin are absolute requirements for effective plasma glucose control.

Counterintuitively, lowering plasma glucose “thresholds” below the Opt values did not result in capture of proportionally more progressors, suggesting that the relationship between glycemia and diabetes risk may be J-shaped [as is the case for HbA1c and incident cardiovascular disease (23)].

Clearly, the output of the optimization procedure is as good as are the physiological measures. Our training set has the advantage of a large collection of direct measurements of insulin sensitivity and β-cell function; nevertheless, enriching the database with older people or younger obese adults, both at-risk categories, or multiple ethnic groups would enhance the applicability of the algorithm.

Table 5. Optimized glucose values obtained using only one independent variable or only one objective function

<table>
<thead>
<tr>
<th></th>
<th>Women</th>
<th></th>
<th>Men</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤45 yr old</td>
<td>&gt;45 yr old</td>
<td>≤45 yr old</td>
<td>&gt;45 yr old</td>
</tr>
<tr>
<td>( \ln(\beta_{GS}) ) and ( \ln(M/I) )</td>
<td>( \ln(FPG) )</td>
<td>≤89</td>
<td>≤92</td>
<td>≤90</td>
</tr>
<tr>
<td>( \ln(2-hG) )</td>
<td>( \ln(2-hG) )</td>
<td>≤97</td>
<td>≤102</td>
<td>≤103</td>
</tr>
<tr>
<td>( \ln(FPG), \ln(2-hG) )</td>
<td>( \ln(FPG) ), ( \ln(2-hG) )</td>
<td>≤290</td>
<td>≤295</td>
<td>≤324</td>
</tr>
<tr>
<td>( \ln(FPG) ), ( \ln(2-hG) )</td>
<td>( \ln(FPG) ), ( \ln(2-hG) )</td>
<td>≤501</td>
<td>≤477</td>
<td>≤403</td>
</tr>
</tbody>
</table>
Perspectives and Significance

When the optimization problem is solved for glucose concentrations using direct measures of insulin sensitivity and glucose sensitivity, it is possible to identify sex- and age-specific thresholds that bear on disease progression in a physiologically sound, quantifiable manner. Also, it should be understood that our analysis is a proof-of-concept, and not a clinical recommendation; the latter requires careful consideration of a number of other factors (4).

APPENDIX

The mathematical formulation of the constrained optimization problem (21) was as follows

\[
\begin{align*}
\max f_1(x_1, x_2) &= a_1 x_1 + b_1 x_2 + c_1 \\
\max f_2(x_1, x_2) &= a_2 x_1 + b_2 x_2 + c_2 \\
x_1 &\geq d_1 \\
x_1 &\leq e_1 \\
x_2 &\geq d_2 \\
x_2 &\leq e_2
\end{align*}
\]

where \(f_1\) and \(f_2\) are the objective functions \([\ln(M/I) \text{ and } \ln(BGS)]\) and \(x_1\) and \(x_2\) are the independent variables \([\ln(FPG) \text{ and } \ln(2-hG)]\). The coefficients \(a_i, b_i,\) and \(c_i\) \((i = 1, 2)\) were estimated by linear modeling separately for each subgroup. \(d_i\) and \(e_i\) \((i = 1, 2)\) are the maximum and minimum values of \(\ln(FPG)\) and \(\ln(2-hG)\) for each subset. The four inequality constraints represent the feasible region of the problem. The optimization problem \((13, 14)\) belongs to the class of constrained linear programming, both objective functions and constraints being linear. For a single-objective function, there are efficient algorithms that can be used to look for the solution. Our problem with two-objective functions requires a prior clarification of the concept of optimum and the criterion used to classify optimum. In multiobjective problems, it is infrequent to find the ideal optimal solution, i.e., the solution that maximizes all the objective functions. Generally, at least two optimal solutions are not comparable, i.e., the first optimum is better than the second for some, but not all, objective functions. Among the criteria aimed at distinguishing between “optimal” and “nonoptimal” feasible solutions, we adopt the Edgeworth criterion, developed by Pareto, and the concept of the Pareto optimum (30). The Pareto criterion excludes the dominated solutions; i.e., it finds another feasible solution that is better than the current one in some objective function. A Pareto optimum solution, therefore, is a nondominated solution. Although the Pareto optimum was developed more than a century ago, the resolution of multiobjective problems is uncommon, because it is computationally onerous.

In the present work we have approached the multiobjective problem \((14)\) by using a recent method \((21)\) whereby the problem is transformed into a single-objective optimization problem involving two additional constraints. The single-objective function is a linear combination of the two original functions, i.e., choosing a pair \(P = (p_1, p_2)\)

\[
\max \sum_i p_i f_i(x_1, x_2), \quad i = 1, 2
\]

We chose the values \(p_1 = p_2 = 1; p_i\) \((i = 1, 2)\) can be considered as weights associated to the objective functions. So, a value equal to 1 is equivalent to assign the same weight to the objectives. Then we chose a vector \(x_i = (x_{1i}, x_{2i})\) in the feasible region of Problem 1 and added the following constraints

\[
\begin{align*}
f_1(x_1, x_2) &\geq f_1(x_{1i}, x_{2i}) \\
f_2(x_1, x_2) &\geq f_2(x_{1i}, x_{2i})
\end{align*}
\]

The components of the selected vector were the median of \(\ln(FPG)\) and \(\ln(2-hG)\) data for each subgroup. We have obtained the following constrained linear programming

\[
\begin{align*}
\max \sum_i p_i f_i(x_1, x_2), \quad i = 1, 2 \\
(c_1 f_1(x_1, x_2) &\geq f_1(x_{1i}, x_{2i}) \quad (c_2 f_2(x_1, x_2) \geq f_2(x_{1i}, x_{2i}) \\
c_3 x_1 &\geq d_1 \\
c_4 x_1 &\leq e_1 \\
c_5 x_2 &\geq d_2 \\
c_6 x_2 &\leq e_2
\end{align*}
\]

The coefficients of Problem 2 are given in Table 2. This problem can be easily solved by implementation of one of the available algorithms. Furthermore, we can show that the solution of the single-objective problem \((2)\) is a Pareto optimum of the multiobjective problem \((1)\). The method we used can yield the entire Pareto optimal set by varying the vector \(x_o\). At this stage, additional information would be required from a “decision maker” about her/his preference for solutions. In order not to bias the choice, we calculated a Pareto optimum and then performed postoptimality (sensitivity) analysis to determine the feasible interval of this optimum. For all computations presented here, a LINDO LINGO 13.0 Demo version is used to determine the optimal solution and to perform postoptimality analysis. Optimal solutions were obtained by the linear solver, which uses the algebraic technique called the simplex algorithm.

As far as the sensitivity analysis is concerned, we have utilized the following approach: after an optimal solution \(z_1\) was found, we changed the right-hand side of the constraint \((c_1)\), in the range measured by the software, and calculated the optimal solution \(z_2\) of the perturbed problem. Then we iterated this procedure by modifying the right-hand side of the constraint \((c_i)\), in the range estimated by Lingo, and determined the optimal solution \(z_i\). We considered as the optimal solution set the interval between the minimum and maximum values among \(z_i\), \(i = 1, \ldots, 3\). The maximum \(z_i\), \(i = 1, \ldots, 3\) was interpreted as a threshold.

When the optimization procedure was carried out by using both dependent variables \((M/I \text{ and } BGS)\) but only one independent variable \((FPG \text{ or } 2-hG)\), the optimized glucose values were not greatly different from those obtained by using of both independent variables (Table 5). However, optimization of only FPG yielded an adjusted OR for progression from 1.71 (CI = 1.39–2.11), while optimization of only 2-hG resulted in an adjusted OR of 2.50 (CI = 1.97–3.19); both of these risk estimates are substantially lower than that obtained upon optimization of both FPG and 2-hG [3.74 (CI = 2.64–5.48)]. On the other hand, when only the objective function \((M/I \text{ or } BGS)\) was used, glucose values drift toward the upper boundary of the observed range in the sensitivity analysis (Table 5).

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

E.F. developed the concept and designed the research; E.F. and M.L.M. analyzed the data; E.F. and M.L.M. interpreted the results of the experiments; E.F. prepared the figures; E.F. drafted the manuscript; E.F. and M.L.M. edited and revised the manuscript; E.F. and M.L.M. approved the final version of the manuscript.

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