Bimodality of 2-h Plasma Glucose Distributions in Whites

The Rancho Bernardo Study

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OBJECTIVE — Several studies have shown a bimodal curve in the distribution of glucose in populations with a high prevalence of type 2 diabetes, but bimodality has not been reported among whites of Northern European ancestry. It is not clear whether this difference reflects the lower prevalence of diabetes, obscuring a second mode, or implies a more fundamental difference between whites and nonwhites. We investigate this issue by studying glucose distributions in older white patients.

RESEARCH DESIGN AND METHODS — A study of diabetes was conducted among older community-dwelling white residents of a suburban Southern California community between 1984 and 1987. Two-hour plasma glucose data were collected from 2,326 older white men and women aged 23–92. To investigate bimodality of glucose distributions, we fit unimodal and bimodal normal models to 2-h plasma glucose concentrations transformed by the Box-Cox family of transformations.

RESULTS — We found that the bimodal normal mixture model fit the data significantly better than the unimodal skewed distribution model for both sexes and all age-groups except those ≥80 years. The cut points separating the two modes were generally within the 11.1- to 13.6-mmol/l range.

CONCLUSIONS — The bimodality of glucose distributions among whites, combined with previous findings, indicates that this phenomenon may be universal. A smaller second mode in our study compared with other studies suggests that whites have diabetes susceptibility but may require more obesity to demonstrate it. With increasing obesity in the U.S., the predicted epidemic of diabetes may affect all ethnic groups including whites.

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A bimodal distribution of plasma glucose concentrations in a population was first described in a 1971 study on Pima Indians, who have the highest prevalence of type 2 diabetes in the world (1). A bimodal curve showing two distinct distributions of plasma glucose concentrations, instead of a single skewed distribution, is compatible with a genetic condition (diabetes) manifest by hyperglycemia and a second population without diabetes (without hyperglycemia). Subsequently, bimodality was reported in other populations with a high prevalence of diabetes, including Nauruans from Micronesia (2), Samoans (3), Asian Indians who had migrated to South Africa (4), and Mexican Americans who were ~50% white (5). The diversity of populations with glucose bimodality suggests that this may be a universal phenomenon, readily detected in populations with a high prevalence of diabetes. To our knowledge, no studies have reported a bimodal glucose distribution among whites of Northern European ancestry, suggesting either genetic/environmental differences or a prevalence of diabetes too low to detect a second mode (6,7).

We hypothesized that statistically significant bimodality might be detectable in older white patients because the prevalence of diabetes increases to nearly 20% in old age (8) and because most genetically susceptible people might be expected to develop diabetes if they live long enough. To investigate the bimodality of the plasma glucose distributions in whites, we used data from a diabetes study conducted among older community-dwelling white residents of a suburban Southern California community.

RESEARCH DESIGN AND METHODS — Residents in the planned development of Rancho Bernardo, California, were invited to participate in a study of diabetes conducted between 1984 and 1987. The population was white and middle to upper-middle class. Approximately half were retirees. Participants were asked to come to a research clinic visit between 7 A.M. and 11 A.M. after a 12-h fast. The procedure was explained, and written informed consent was obtained from all participants. During the visit, the following relevant characteristics were recorded: age, sex, weight, height, personal history of diabetes, and the presence of any diabetes or hormone medication within the past 2 weeks. A 75-g oral glucose tolerance test was performed in the morning after a requested overnight (at least 10-h) fast. Venous blood was obtained with the participants seated and the tourniquet removed before and 2 h after a 75-g oral glucose load. Plasma glucose was mea-
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Table 1—Sample summary statistics and statistical tests of unimodal and bimodal fit of 2-h log-transformed glucose concentrations by age

<table>
<thead>
<tr>
<th></th>
<th>20–49 years</th>
<th>50–59 years</th>
<th>60–69 years</th>
<th>70–79 years</th>
<th>≥80 years</th>
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<tbody>
<tr>
<td>n</td>
<td>84</td>
<td>372</td>
<td>576</td>
<td>917</td>
<td>377</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>3.6</td>
<td>7.3</td>
<td>10.5</td>
<td>16.8</td>
<td>22.5</td>
</tr>
<tr>
<td>Unimodal normal model (mmol/l)</td>
<td>5.9 ± 2.0</td>
<td>6.6 ± 2.4</td>
<td>7.3 ± 3.0</td>
<td>8.2 ± 3.4</td>
<td>8.7 ± 3.3</td>
</tr>
<tr>
<td>Test of normality</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
<td>0.6</td>
</tr>
<tr>
<td>Bimodal normal model</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First mode (mmol/l)</td>
<td>5.7 ± 1.4</td>
<td>6.3 ± 1.8</td>
<td>6.9 ± 2.0</td>
<td>7.5 ± 2.3</td>
<td>—</td>
</tr>
<tr>
<td>Second mode (mmol/l)</td>
<td>19.4 ± 1.4</td>
<td>16.5 ± 1.4</td>
<td>17.5 ± 4.8</td>
<td>17.2 ± 3.7</td>
<td>—</td>
</tr>
<tr>
<td>Percent in second mode</td>
<td>3.2</td>
<td>7.9</td>
<td>10.8</td>
<td>18.1</td>
<td>—</td>
</tr>
<tr>
<td>Cut point (mmol/l)</td>
<td>11.1</td>
<td>13.6</td>
<td>13.2</td>
<td>13.3</td>
<td>—</td>
</tr>
<tr>
<td>LRT</td>
<td>34.2</td>
<td>16.4</td>
<td>34.7</td>
<td>15.9</td>
<td>—</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>&lt;0.01</td>
<td>0.01</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise indicated. LRT, likelihood ratio test.

Participants were asked by trained interviewers about their use of insulin in the past 2 weeks. Because insulin treatment for type 2 diabetes was uncommon in 1984–1987, those who were using insulin (n = 11) were excluded from these analyses, as were participants with missing postchallenge glucose concentrations (n = 140). Diabetic participants taking oral agents were not excluded. After the exclusions, a total of 2,326 participants aged 23–92 years (median 71) were included in these analyses.

Height in inches and weight in pounds of participants in light clothing without shoes were measured and converted to meters and kilograms; BMI was then calculated as a measure of obesity. The definition of diabetes included both known diabetes based on disease history and new cases of diabetes based on a fasting plasma glucose level ≥7.8 mmol/l or a 2-h postchallenge plasma glucose level ≥11.1 mmol/l, or both, according to the 1985 diagnostic criteria recommended by the World Health Organization (9).

Statistical methods

To test whether the glucose concentration data follow a bimodal distribution, we fit a normal model \( N(\mu, \sigma^2) \) and a mixture normal model \( \pi N(\mu_1, \sigma_1^2) + (1 - \pi) N(\mu_2, \sigma_2^2) \) to properly transformed glucose concentration data. Here, \( \pi \) represents the proportion of plasma glucose values from the first normal distribution and \( 1 - \pi \) represents the proportion from the second normal distribution. Two transformations were considered: the natural logarithm transformation and the Box-Cox transformation (10), as discussed in more detail below. The normal model gives rise to a unimodal distribution and was fit using the maximum likelihood method. The mixture normal model provides a flexible bimodal distribution and was fit by the expectation-maximization algorithm. The fitting of both models was implemented through the NOCOM (11) program. A likelihood ratio test can be used to compare \( H_0 \) (unimodal normal model) versus \( H_2 \) (mixture normal model). When the two normal components in the mixture distribution have equal variance, the likelihood ratio test statistic can be approximated by a \( \chi^2 \) distribution with 2 degrees of freedom (df). Note that the \( \chi^2 \) distribution is approximate. The P value provided by this test has been shown to be liberal (12), and an improved approximation by a \( \chi^2 \) distribution with 2.5 df has been suggested (13). When the two normal components in the mixture distribution have unequal variances, simulation results have indicated that the limiting distribution is bounded by \( \chi^2 \) distributions with 4 and 6 df (14,15). In this study, results for bimodal models are based on mixture distributions with unequal variances for two normal components, and P values are based on a \( \chi^2 \) distribution with 6 df. Thus, the P values presented are conservative.

Although the logarithm transformation seems a natural choice for making the plasma glucose distribution more normal, there may be residual skewness. To ensure that there is indeed a mixture of two distributions rather than one skewed distribution, it is important to remove any remaining skewness before fitting the unimodal and bimodal models (14,16). Following MacLean et al. (16), we also applied the Box-Cox family of transfor-

Table 2—Sample summary statistics and statistical tests of unimodal and bimodal fit of 2-h log-transformed glucose concentrations by sex

<table>
<thead>
<tr>
<th></th>
<th>Male (20–79 years)</th>
<th>Female (20–79 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>836</td>
<td>1,113</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>15.2</td>
<td>10.4</td>
</tr>
<tr>
<td>Unimodal normal model (mmol/l)</td>
<td>7.6 ± 3.4</td>
<td>7.4 ± 2.9</td>
</tr>
<tr>
<td>Test of normality</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Bimodal normal model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First mode (mmol/l)</td>
<td>6.6 ± 1.9</td>
<td>7.1 ± 2.1</td>
</tr>
<tr>
<td>Second mode (mmol/l)</td>
<td>14.9 ± 3.6</td>
<td>18.1 ± 4.2</td>
</tr>
<tr>
<td>Percent in second mode</td>
<td>17.6</td>
<td>8.9</td>
</tr>
<tr>
<td>Cut point (mmol/l)</td>
<td>11.3</td>
<td>13.6</td>
</tr>
<tr>
<td>LRT</td>
<td>28.3</td>
<td>40.6</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.01</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Data are means ± SD unless otherwise indicated. LRT, likelihood ratio test.
mations, of which the natural logarithm transformation is a member, to the standardized glucose concentration data before fitting and testing for unimodal versus bimodal normal models.

RESULTS — There were 1,025 men and 1,301 women in this sample. The median age was similar: 72 years for men (range 23–91) and 71 years for women (range 23–92). Nine percent of men and 8% of women were obese (BMI ≥30 kg/m²), and 49% of men and 28% of women were overweight (BMI 25–29.9 kg/m²). The median 2-h plasma glucose levels were 6.94 mmol/l for men and 6.99 mmol/l for women. In all, 16% of men and 12% of women had diabetes, based on disease history and World Health Organization 1985 diagnostic criteria (9).

Table 1 presents sample summary statistics and hypothesis testing results for log-transformed plasma glucose concentrations. The grouping is based on 10-year age intervals, with all participants <50 years combined in one group. As shown, the prevalence of diabetes increased with age, from 3.6% in those <50 years to 22.5% in those ≥80 years. It can be seen from summary statistics that the mean plasma glucose concentration also increases with age. P values from the test of normality indicate that we reject the hypothesis that the distribution of the log-transformed glucose concentration is normally distributed for all age-groups, except for the participants ≥80 years. Therefore, the bimodal normal model was not fit for the oldest participants (age ≥80 years). From the bimodal summary statistics, we see that the sample mean of the first mode matches closely the overall sample mean for each age-group and that the sample mean of the second mode is similar for all age-groups. The percent-

Figure 1—Distributions of 2-h plasma glucose concentrations from oral glucose tolerance tests for ages 20–49, 50–59, 60–69, and 70–79 years. ——, estimated densities; ——, density curves of the two normal components.
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Figure 2—Distributions of 2-h plasma glucose concentrations from oral glucose tolerance tests for males (ages 20–79) and females (ages 20–79). — — , estimated densities; – – – , density curves of the two normal components.

ages of participants in the second mode are similar to the percentages in the corresponding groups with diabetes. The cut points, determined by the intersection of the two normal density curves plotted in appropriate proportions, are in the range of 11.1–13.6 mmol/l. The likelihood ratio test statistics comparing the bimodal to the unimodal model fits are large, indicating that the bimodal normal model fits the log-transformed glucose data significantly better than the unimodal model for age-groups 20–49, 50–59, 60–69, and 70–79 years.

We repeated model fitting and hypothesis testing for Box-Cox–transformed standardized plasma glucose concentrations. The results (not presented) were similar to the results presented in Table 1. For age-groups 50–59, 60–69, and 70–79 years, the bimodal model is a significant improvement over the unimodal model (P < 0.01). The only difference is that we fail to reject the test of normality for the age-group 20–49 years and thus do not fit a bimodal model to the youngest age-group (≤49 years). In this group, the prevalence of diabetes was low (3.6%), and the sample size was small (n = 84), limiting our ability to detect a deviation from the unimodal normal model.

For participants <80 years of age, model fitting and testing was repeated for men and women separately. The results are presented in Table 2. For both sexes, we reject the hypothesis that the log-transformed glucose concentrations are unimodal normal and conclude that the bimodal normal model is a significant improvement over the unimodal normal model. Additional likelihood ratio tests (not presented) based on Box-Cox–transformed standardized data were also statistically significant for both men and women (P < 0.01).

The figures show the distributions of 2-h plasma glucose concentrations for men and women and four age-groups. The histograms are based on the observed frequencies of plasma glucose concentrations and the superimposed smooth curves are based on estimated frequencies (densities) of the fitted bimodal normal models. The solid smooth curves denote the overall density for the mixture model with the dashed curves depicting the densities of the two components, graphed in appropriate proportions. Figure 1 presents 2-h plasma glucose distributions for age-groups 20–49, 50–59, 60–69, and 70–79 years, and Fig. 2 presents 2-h plasma glucose distributions for men (aged 20–79) and women (aged 20–79). Note that these plots were made using glucose concentrations in the original scale (without transformations) to enhance the visibility of the two modes and the recognition of the nadir in familiar glucose levels.

CONCLUSIONS—In this older white cohort, the distribution of log-transformed 2-h postchallenge glucose was bimodal in all age-groups except for those ≥80 years. Even in the smallest group (n = 84) who were <50 years of age, a mixture model of two normal distributions fits the data significantly better than a model of a single normal distribution. Also note that diabetic individuals taking oral agents were included in our analysis. The fact that bimodality is demonstrated with these treated individuals who have lowered 2-h glucose values strengthens the case for bimodality.

The World Health Organization criteria for diabetes are based in part on the nadir of the 2-h glucose in the Pima Indians. According to these criteria, values above the nadir are indicative of diabetes, whereas values below the nadir are not. In the present study, the nadir of postchallenge glucose (the cut point that separates the two components) was in the range of 11.1–13.6 mmol/l, which was slightly higher than the diabetes diagnostic criteria recommended by the World Health Organization in 1985 (9), but similar to the 2-h glucose nadirs found in a recent Malaysian study of four ethnic groups (17) and in Egyptians (18).

Studies of diabetes complications suggest that the upper mode of the two distributions is a distinct entity. For example, in the Pima Indians, there was a marked increase in the prevalence of vascular complications of diabetes in persons whose postchallenge glucose or glycosylated hemoglobin levels were in the upper component of the bimodal distribution (19). In the Egyptian study, the intersection between the upper and lower components of the bimodal distribution for...
the 2-h glucose best distinguished those with diabetic retinopathy (18). Only one recent article reported that retinopathy was common in persons with impaired glucose tolerance (20), most of whom would not be in the upper mode of a bimodal distribution.

The prevalence of diabetes (known + unknown) was higher among men (15.2%) than among women (10.4%), but the 2-h glucose concentrations were comparable, with a median of 6.94 mmol/l for men and 6.99 mmol/l for women. For both sexes, a bimodal model fit the glucose data significantly better than a unimodal model. The nadir for women (13.6 mmol/l) was slightly higher than that for men (11.3 mmol/l), possibly because women were leaner. Obesity is a strong predictor of diabetes, and men in this cohort had a BMI similar to that in U.S. men, whereas Rancho Bernardo women were thinner than average U.S. women (21,22).

Although our hypothesis was that age would increase the prevalence of diabetes sufficiently to detect significant bimodality, in this cohort statistically significant bimodality was not observed in the oldest age-group (≥80 years). Absent bimodality in the oldest could be caused by poorer survival among those with hyperglycemia (23) or by an effect of age or illness-related weight and muscle loss on glyce mia. It is also possible that the insulin resistance common in the elderly is of a different etiology. In this cohort, the average plasma glucose concentration in the second mode was similar across age-groups, whereas the average glucose concentration in the first mode increased with age, possibly making it more difficult to discern the two distributions for the oldest age-group.

Failure to find bimodality in prior studies of whites with northern European ancestry may reflect too small a sample when the prevalence of diabetes is low. Other biases that could obscure bimodality of type 1 and type 2 diabetes or admixture in white cohorts include the exclusion of persons with known diabetes who refuse or are not offered a glucose tolerance test (17).

The finding of a bimodal distribution has been interpreted as evidence of two genotypes, one without and one with diabetes. A second mode in a white cohort is compatible with genetic studies showing replication of candidate genes for type 2 diabetes in ethnically diverse populations (24). The size of the second mode probably represents both genetic and environmental factors. With aging and changing body composition and fat distribution, more susceptible persons move into the second mode. The presence of bimodality with a smaller second mode implies that whites have diabetes susceptibility but may require more obesity to demonstrate it. In contrast, some very high-risk groups may require little overall obesity, only central adiposity. For example, none of the participants in the four ethnic groups in the Malaysian study showing bimodal postchallenge hyperglycemia were obese by Western standards (17). Increasing obesity in the U.S. suggests that the predicted epidemic of diabetes will affect all ethnic groups (25).

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