Evaluation of Age-adjusted Criteria for Potential Diabetes

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SUMMARY

Data from Oxford, Massachusetts, indicate that one to two-hour postprandial blood sugar levels rise 4 mg. per 100 ml. per decade. In order to test whether postprandial data used for screening or diagnostic standards should be correspondingly adjusted for age, two criteria, comparable except that one resulted in a sliding scale age-adjustment, were applied to blood sugar levels obtained in Oxford in 1946-1947. The development of diabetes over the next twenty-two years provided no justification for raising these standards for increases in age. These data are considered to provide a pragmatic solution to the rise in glucose levels that occur with age, but are insufficiently precise to resolve its pathophysiologic meaning. The discussion emphasizes that the conclusion reached does not necessarily apply to data obtained following glucose ingestion. DIABETES *20*:811-15, December, 1971.

Whether the rise in blood sugar levels with advancing age should be accepted as a normal physiologic change is a question of current practical importance. Should standards for interpreting blood sugar levels be modified for each age group, or are the age effects related to an actual increase in the frequency of prediabetes or diabetes? Prospective data from the long-term Oxford epidemiological study were used to explore the problem.[1,2]

MATERIAL AND METHODS

Subjects

In 1946-1947, venous blood samples were obtained between one and two hours postprandially on 1,424 persons fifteen years of age and over in the town of Oxford, Mass.[1,2] It was not in the study design to follow 100 per cent of the initial screenees, but three groups totalling 923 persons were requested to return. All persons without known diabetes and with Folin-Wu blood sugar levels of 140 mg./100 ml. and greater, and an age-matched sample of those below 140 mg./100 ml. contributed a total of 287 persons for continuing study. The age matching favored a somewhat older group than would have been obtained by a simple random sample, since persons with blood sugar levels in the upper range of the population's distribution are older than average. Additional young persons with blood sugar levels below 140 mg./100 ml. were obtained by retesting a third group of Oxford residents. They comprised all persons who were aged seventeen to thirty-eight years during the 1946 survey, and they were retested primarily for other purposes.[3]

For comparison with previous reports from this long-term study, the selective aspects of this current analysis should be restated. In order to confine to a minimum the multiple variables inherent in these data, persons with venous blood sugars outside the one to two-hour postprandial interval and those with capillary values were not included for analysis. Examination of the excluded data revealed no trend in the development of diabetes throughout the study that might be a biasing factor. The three study groups described are summarized in table 1. At least one subsequent follow-up examination was obtained in 726 individuals (79 per cent) out of the total of 923 selected for observation, although the number of blood sugar tests varied (up to seven tests per individual) depending on response and survival rates.

Methods

Blood sugar levels were initially determined by the Folin-Wu method. After 1950, the Somogyi-Nelson or AutoAnalyzer (Hoffman) macro whole-blood methods

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TABLE 1

Oxford screenees selected for follow-up study

Category in 1946-47	Median age	Number of persons	Total followed	Response rate (per cent)
I. Total population with blood sugar ≧ 140 mg./100 ml.*	52	118	100	85
II. Age-matched sample of those < 140 mg./100 ml.*	47	169	148	88
III. Total population aged 17 to 38 years	29	636	478	75

*Venous one to two-hour postprandial blood sugar levels.

were also used, for consistency with previous publications; values were converted to Folin-Wu equivalents by the addition of a constant of 20 mg./100 ml. Patients who had migrated from the Oxford area were periodically retested and their blood samples mailed to our laboratory for processing. A diagnosis of diabetes was made when a person was found with hyperglycemia who was receiving insulin treatment, or with repeated hyperglycemia as judged when two or more blood sugar values met or exceeded the postprandial level of 200 mg. or fasting level of 140 mg./100 ml. These definitions correspond to Class A and B diabetes as described previously.[4]

Study design

The study is based on the assessment of two blood sugar criteria calculated in an identical way except that one set is adjusted for age. Equivalent percentile levels seemed appropriate for setting the criteria. The 92nd percentile was chosen since it had proved of value in predicting future diabetes.[4] This percentile was calculated for each of seven age groups separately, using ten-year census intervals, by ranking the blood sugar levels in order from highest to lowest. Each age-specific level was found by counting back through the upper 8 per cent of the distribution, calculated as (0.08) (N + 1) where N is the sample size.[5] In this way, age-adjusted (sliding scale) criteria were thus determined.

Choice of the single 92nd percentile (140 mg./100 ml.) for the seven combined blood sugar distributions as the comparison criterion does not eliminate an age bias. For example, a sample composed of a higher proportion of older people would have a different blood sugar distribution than one in which younger people were the preponderant group. To eliminate dependence on the age composition of the 1946 respondents, equal weight was given to the percentile of each age group by using the average of the seven percentiles to give 147 mg./100 ml. for the age-adjusted population. This adjustment is known as the method of equivalent average rates.[6] Both levels (140 and 147 mg./100 ml.) however, were tested in the final analyses since they reflect different assumptions. This design is specifically aimed at producing strict comparability of two criteria, albeit in a restricted sense. For example, in one set of comparisons, equal numbers of potential diabetics are identified in the Oxford population by both criteria. The development of diabetes throughout the subsequent years from both groups of potential diabetics then, should indicate whether the age-adjusted, sliding scale criterion has greater merit than the single blood sugar criterion. Alternative study designs may eventually prove superior but were not tested here since it was judged that greater numbers and a higher yield of diabetes would be required to allow such further explorations.

The study design chosen is illustrated schematically in figure 1 where the diagonal line represents the age-specific sliding scale criteria, while the horizontal one indicates the uniform blood sugar criterion for potential diabetics. Although there is overlap between the persons considered abnormal by the two criteria, the areas represented by the two wedges in the diagram are

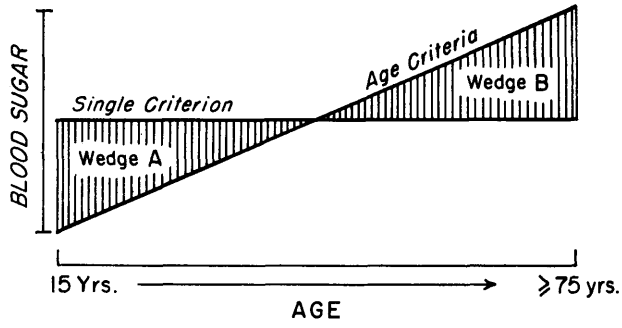

FIG. 1. Study Design: The diagonal line represents postprandial criteria based on age-adjusted normal limits and the horizontal line, the traditional single criterion. Both were calculated using their respective 92nd blood sugar percentiles. Persons in wedge areas A or B would be classified normal by one and abnormal by the other set of standards.

unique, and essential to judging the value of an age adjustment of the criteria. The initial blood sugar levels of persons falling into these two areas would have been considered normal by one, and abnormal by the alternative set of blood sugar standards. The incidence of later diabetes for persons who in 1946 had blood sugar levels in the two wedge areas will then decide which of the two criteria is preferable and consequently whether a sliding scale age adjustment of criteria is necessary.

RESULTS

Figure 2 shows that the median initial blood sugar levels of the 1,424 respondents from the Oxford population rose approximately 25 mg./100 ml. with age, comparing the fifteen and seventy-five-year age groups.

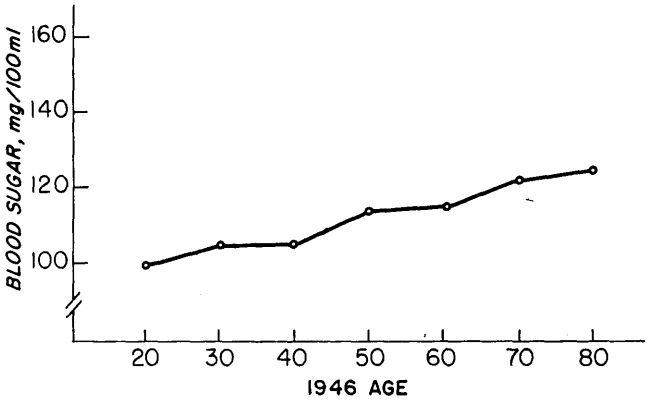

FIG. 2. Median venous blood sugar levels obtained one to two hours postprandially. The figure includes 1,424 specimens obtained in the town of Oxford, Massachusetts in 1946-1947, plotted by age.

The linear regression of blood sugar on age was found to be statistically significant, with a regression coefficient of 0.4 mg./100 ml. per year of age. The effect which this rise (in blood sugar levels with increasing age) had on blood sugar standards was explored by setting up two comparable criteria differing only in that one set was age adjusted (see "Study design").

The relative merits of the two criteria were judged by applying them to the initial blood sugar levels of Oxford population groups. The development of diabetes mellitus among the groups of patients categorized normal and abnormal by these criteria in 1946, was then studied in the subsequent twenty-two years. In figure 3 the number within each segment represents the percentage of persons developing diabetes over this time span.

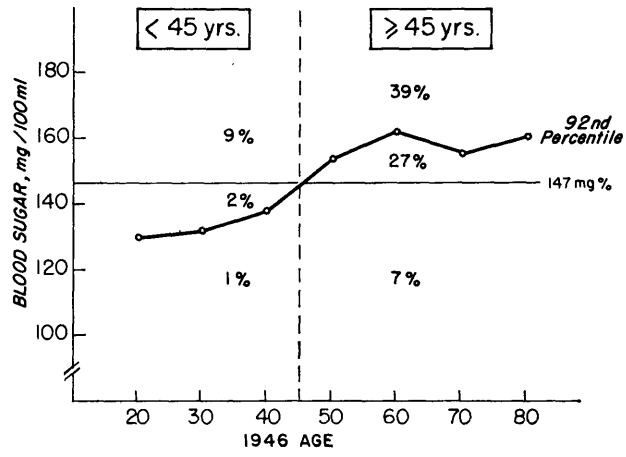

FIG. 3. The estimated proportion of persons developing diabetes over a period of twenty-two years related to initial age and blood sugar level. The specific numbers in the three segments below forty-five years are 2/23, 1/47, and 4/508, and for those forty-five years and over 15/38, 3/11, and 7/99.

From persons considered abnormal by the sliding scale age-adjusted criteria and normal by the uniform criterion (wedge A equivalent), 2 per cent were found to develop diabetes. Alternatively, of persons judged normal by the age-adjusted sliding scale and abnormal by the uniform criterion (wedge B equivalent), 27 per cent developed diabetes. These contrasting areas meet at forty-five years of age. The proportion of persons developing diabetes from wedge B is significantly greater ($P < .05$) than that for persons within the same age group whose blood sugar levels were lower. The corresponding statistical test for the younger patients in wedge A is not significant. The median ages for persons in the three segments below 45 years, were, from above, 31, 30 and 29 years, and for those 45 years and over, 54, 58, and 55 years, respectively. Repeating this analysis, changing the level of the horizontal line to 140 mg./100 ml. confirmed this statistical conclusion.

Table 2 shows an exploration of the effect of age on the development of diabetes for a variety of alternative initial blood sugar levels. The risk of future diabetes is shown to be related generally to the height of the initial blood sugar level, and the graded relationship is primarily confined to those aged forty-five years and older. It is also evident from this table that the selection of comparison levels other than the 92nd percentile would not result in any advantage for a sliding scale age-adjusted criterion for the younger of the two age groups.

TABLE 2

Initial blood sugar levels and age related to subsequent diabetes (1946 to 1969)*

Initial blood sugar (mg./100 ml.)	< 45 years			≧ 45 years		
	Number followed	Subsequent no.	Diabetes (per cent)	Number followed	Subsequent no.	Diabetes (per cent)
<140	542	5	1	84	4	5
140-169	28	0	0	46	10	22
≧170	8	2	25	18	11	61

*Excluding diabetics known in 1946.

DISCUSSION

The evidence from the population study in the town of Oxford, Massachusetts, runs counter to suggestions to alter criteria in keeping with the age-related mean rise in blood sugar values. Among older patients, significant numbers of potential diabetics could be lost by an upward adjustment of criteria. Alternatively, downward adjustment in critical blood sugar levels for the younger patients would greatly increase the number of false positive tests. The results, then, support the use of a single postprandial blood sugar criterion as a pragmatic solution for all ages, rather than separate criteria for each age group. Examination of a variety of blood glucose levels support this general conclusion although no attempt has been made in this presentation to specify which levels can be recommended for use. This information has been discussed elsewhere.[4,7]

The findings in this study can be accepted with reasonable assurance because the median age and the duration of follow-up for each of the groups were found to be similar. In addition, no bias was apparent when the death certificates of non-respondents were examined for diabetes. Finally, the study has particular advantages because of its duration which provided a sufficiently long observation period to make the end-point diagnoses of diabetes mellitus meaningful.

Since both early diabetes and aging are associated with a gradual rise in blood sugar levels, certain practical and philosophical problems arise. If the gradual rise in blood sugar level with age is physiologic, then a seventy-year-old man might not be expected to have the blood sugar level of a twenty or thirty-year old. The position should then be taken that the change in blood sugar levels with age should be discounted by altering the diagnostic criteria. Alternatively, if the rise in blood sugar levels is related to diabetes, a more specific health problem is involved and no such change should be instituted. Data from the Oxford population study tentatively support the latter view extending the earlier findings from the study, that subdiagnostic blood sugar elevations are associated with hypertension, electrocardiographic abnormalities and a higher-than-expected mortality rate.[8] However, a final resolution of the pathophysiologic meaning of the age-related rise in blood sugar levels awaits further evidence. This study can provide no more than a pragmatic clinical solution because of the small number of persons with diabetes in each category and the variability in single blood sugar levels used for initial classification. The resulting imprecision blunts this investigative approach and prevents a more detailed conclusion with respect to the true meaning of the rise in blood sugar levels that occur with age. For clinical use, in similar circumstances, this study simply indicates that criteria do not have to be correspondingly adjusted for the rise in blood sugar levels that occur with age.

These results apply specifically to blood sugar data obtained following a meal. Despite the potential imprecision of postprandial data, such values do not show any greater variability than standardized blood sugar levels obtained following a carefully timed glucose challenge.[9] The rise in postprandial blood sugar levels with age was found to average 4 mg./100 ml. per decade. Data obtained one hour following a glucose challenge, however, show the age-related rise to average 8 mg./100 ml. per decade.[10] Additional studies will be necessary to evaluate the rise in blood sugar levels with age for data obtained following glucose ingestion. The necessity for this further evaluation is emphasized by the suggestion that postprandial and postglucose blood sugar levels are giving qualitatively different information when evaluated by their relationship to blood pressure and electrocardiographic findings.[8]

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Enhancement of Liver Glucose-6-phosphate Dehydrogenase by Dietary Carbohydrate and Insulin

The rate of synthesis of glucose-6-phosphate dehydrogenase in the livers of rats fed carbohydrate increases in proportion to the caloric consumption, but is not related to release of insulin. Metabolic changes including that in the level of glucose-6-phosphate dehydrogenase, have been noted to occur upon alteration of the feeding pattern in rats (see Nutrition Reviews 28:234, 1970). H. M. Tepperman and J. Tepperman (Adv. Enzyme Reg. 1:121, 1963) reported that there is a dramatic increase in the level of glucose-6-phosphate dehydrogenase in the livers of rats who were fasted and then fed a diet high in carbohydrate. The increase observed was found by H. F. Sassoon, J. Watson, and B. C. Johnson (J. Nutrition 94:52, 1968) to be proportional to the caloric consumption, but Y. Yugari and T. Matsuda (J. Biochem. (Tokyo) 61:541, 1967) demonstrated that the final enzyme level is decreased by including fat in the diet. Several studies had indicated that there may be a hormonal involvement in the regulation of glucose-6-phosphate dehydrogenase. The ability of insulin to augment the effect of high carbohydrate diets on the level of the enzyme in liver was reported by G. Weber and H. J. H. Convery (Life Sci. 5:1139, 1966) and by R. A. Freedland, T. L. Cunliff, and J. G. Zinkl (J. Biol. Chem. 241:5448, 1966).

Experiments designed to elucidate the nature of the interaction between high carbohydrate diets and insulin on the rates of glucose-6-phosphate synthesis and degradation in vivo now have been reported by D. Rudack, E. M. Chisholm, and D. Holten (J. Biol. Chem. 246: 1249, 1971). In this study, young male rats of the Sprague-Dawley strain were maintained on a pelleted diet and, usually after a forty-eight-hour fast, fed ad libitum synthetic diets that contained specified amounts of carbohydrate. Glucose or fructose diets contained in per cent: hexose, 60; cellulose, 3; casein, 30; salt mixture, 5; vitamins, 2. The "sucrose" diet contained in per cent: glucose, 48; sucrose, 15; casein, 30; salt mixture, 5; vitamins, 2. When administered, insulin was injected subcutaneously twice a day.

Rudack, Chisholm, and Holten calculated their results following the general procedures delineated by C. M. Berlin and R. T. Schimke (Molec. Pharmacol. 1:149, 1965). The half life for degradation of glucose-6-phosphate dehydrogenase in vivo was calculated by following the time course of the specific activity of the enzyme from one steady state to a new one imposed by experimental design. The activity of enzyme measured at steady state is equal to the ratio of rate constants for synthesis and degradation of the enzyme.

When rats were fasted for two days and then given the 60 per cent glucose diet for seven days, the level of glucose-6-phosphate dehydrogenase activity rose over a few days to a new, markedly higher steady-state level after a lag of nearly one day. The initial and final specific activities were 0.039 and 0.537 (micromoles of NADPH formed per minute per milligram of protein), respectively. Treatment of animals in the same way but with the 60 per cent fructose diet led to a generally

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