*Special Topics in Diabetes*

# Age Gradient in Blood Glucose Levels

## Magnitude and Clinical Implications

*John B. O'Sullivan, M.D., Boston*



Population studies confirm the finding that average blood glucose levels in the fasting state increase with age. This blood glucose gradient is statistically significant even when confounding factors, such as obesity, are considered.[1] The order of magnitude of the increase, however, may be considered of questionable clinical significance since it amounts to no more than 2 mg. per 100 ml. per decade through the adult years. And yet, it reflects a problem that continues to puzzle both investigators and clinicians alike.

The small change in blood glucose levels with advancing years is magnified to a considerable extent in conditions other than fasting. Postprandial values change at the rate of 4 mg. per 100 ml. per decade,[2] and those following a glucose challenge at 8 to 13 mg. per 100 ml. per decade.[1,3,4] In circumstances which affect carbohydrate metabolism, such as steroid administration, the age gradient following a glucose challenge is even more impressive—up to 18 mg. per 100 ml. per decade during cortisone-glucose tolerance tests.[5] The magnitude of the change in blood glucose levels attributable to age, then, appears to be related to the metabolic environment, size, character and proximity of the carbohydrate challenge.

These changes pose formidable problems for the clinician in situations of diagnostic uncertainty. For example, failure to adjust critical screening or diagnostic blood glucose levels may give rise to an uncomfortably high proportion of older persons being diagnosed diabetic. In this regard, data from the National Center for Health Statistics can be used to calculate the difference in numbers of persons rating positive at 150 mg. as compared to 160 mg. following the ingestion of 50 gm. of glucose.[4] The resulting total is in excess of six million persons. Although a 10 mg. difference in blood glucose levels may have little meaning in the control of overt diabetes, this fact often obscures the major influence of such small differences on the outcome of screening and diagnostic tests. Yet, the effect attributable to aging that is under consideration is between 40 and 70 mg. per 100 ml.

It has been argued that with age the decline in tolerance to glucose is reflecting an increasing number of potential diabetics in the population. In this case one would expect to find evidence of increasing skewness to the right in blood glucose distributions since the potential diabetics have been shown to arise from persons in the upper end of the distribution.[6] Alternatively, the age gradient could result from relatively benign physiologic changes, in which case the whole blood glucose distribution would be uniformly shifted to the right. Although these hypotheses are presented in an oversimplified form, they serve the purpose of focusing attention on the primary changes that occur with age. Review of the data from the major population studies leaves little doubt that age is influencing the whole distribution, and the rising trend in glucose levels can be demonstrated in the lower as well as in the upper end of the blood glucose spectrum.[3,4,7] Nevertheless, the changes are greater in the upper end as evidenced by the plots of blood glucose against age for persons comprising the extreme quintiles of the distribution.[3,7] In such graphs the rising blood glucose trends with age diverge, the change in glucose concentration over the entire age span being some two to three times greater for persons above the eightieth as for those below the twentieth percentiles.[3] Further, the blood glucose variation increases with age resulting in larger standard deviations in successive

From the Diabetes and Arthritis Unit and the Section on Preventive Medicine and Epidemiology, Department of Medicine, Boston University, Boston, Massachusetts.

Accepted for publication May 28, 1974.

age groups. Both these characteristics, the shift in whole glucose distribution and the increasing variance with age, are also apparent in populations with a high prevalence of diabetes. The Pima Indians, for example, show strong evidence of bimodality in all but the youngest of their age groups suggesting age activation of a separate population of hyperglycemics. They also show, however, an age gradient in the first or "normoglycemic" component of the distribution.[7] From these facts, then, it seems reasonable to infer that elements of both hypotheses are at least in part correct. With this assumption, then, proponents of age-adjusting should be concerned only with the first of the two components of the blood glucose rise with age. However, even here, no evidence exists to suggest that the philosophically acceptable physiologic first component represents a benign change that should be factored out by appropriate adjustment of blood glucose standards.

Regardless of genetic or other implications in these findings, their assessment in terms of clinical diagnoses arises constantly in clinical practice. The magnitude of the effect of small changes in blood glucose levels combined with the prominent rise in these levels with aging would appear, through the force of numbers, to preclude any approach other than the adjustment of blood glucose standards for age. However, if diagnoses on the basis of single laboratory determinations are avoided, then alternatives that are practical and even desirable are available. A diagnostic algorithm requiring a repeat blood glucose evaluation and/or an abnormal glucose tolerance test can furnish results that have clinical significance and provide an acceptably conservative prevalence rate for diabetes mellitus. The effect of repeat tests can be seen within the standard glucose tolerance test as shown in a random sample from the Sudbury study.[8] Here it was demonstrated that when the tests were judged by the presence of one abnormal value (Fasting: 110, One Hour: 170, Two Hour: 120, Three Hour: 110 mg./100 ml.; venous, whole blood, AutoAnalyzer-Hoffman values post 100 gm. glucose) a total of 13.8 per cent would have been considered abnormal, while requiring three or more elevations reduced the prevalence of abnormal tests to 1.2 per cent.[8] Thus the role of diagnostic standards takes precedence over age effects for their contribution to the frequency of abnormal tests. It should be stressed, however, that there is no valid reason available for discounting the influence of age on blood glucose standards simply because they might give rise to "unacceptably" high prevalence rates. What is needed is the documentation of the health significance of the standards adopted.

In a seventeen year follow-up, the prospective study of the New England town of Oxford demonstrated that subdiagnostic postprandial blood glucose levels are clinically important. In addition to a high yield of subsequent diabetics, the ninety-second percentile blood glucose levels were found to be related to a shortening of life expectancy and an increased incidence of hypertension, ECG abnormalities and retinopathy.[9] A further analysis of the Oxford data found no justification for adjusting *postprandial* blood glucose standards for age.[2] It is also of interest that data from the Framingham Heart Study reveal no diminution, in fact an increase, in the incidence of mortality, cardiovascular and cerebrovascular events by fixed postprandial blood glucose levels across different age groups.[10]

Unfortunately, no comparable long-term prospective data exist for the assessment of blood glucose elevations following a glucose challenge. Cross-sectional data from the Tecumseh and Bedford studies show a significant relationship between postglucose levels and vascular disease even when age and sex were fully taken into consideration.[11,12] A haphazard subset of the Oxford data showed that for comparable postprandial and postglucose levels the relationship to hypertension and ECG abnormalities could be demonstrated in both instances, but was clearly stronger for the values obtained following glucose ingestion.[9] This relationship persisted only for the postglucose values when persons subsequently developing diabetes were excluded from the analysis. The tentative conclusion is that *postglucose* values have, in addition to their relationship to overt diabetes, a separate relationship to hypertension and ECG abnormalities. Alternatively, these clinical features are being identified through this form of testing at a point in time more remote from the development of diabetes than postprandial tests are capable of doing. A related aspect was observed in a study of chemical diabetes, a term which in one sense refers to persons with confirmed hyperglycemia inasmuch as the diagnosis was based on three or more elevated glucose tolerance test values by the standards indicated in parentheses in an earlier paragraph. Some ten years later it was observed that a surprising 74 per cent had shown improvement or had not deteriorated in terms of reducing their tolerance to glucose, in effect countering any inordinate impact of age on the diagnosis of diabetes based on confirmed intolerance to glucose.[13] It is of particular interest that the same patients exhibited more hypertension and ECG abnormalities than age-matched controls.[14]

The evidence available to date, therefore, supports the clinical importance of asymptomatic blood glucose elevations following a glucose challenge, and any system which would have contributed to discounting their initial diagnoses on the basis of age adjustments would have overlooked the presence of an important health risk factor.

To conclude, the moderate rise in postprandial blood glucose values that occur with age is insufficient to warrant a modification of operational standards on this basis. The much greater rise seen after a glucose challenge appears to result from two sources: the first of the two from an upward blood glucose trend with increasing age seen across the whole spectrum of blood glucose levels, and the second component arising from a progressive exaggeration of the disproportionately greater numbers in the upper end of the blood glucose distribution. A case could be made for adjusting blood glucose standards for the first component of the age gradient on the basis of excessively large numbers of older persons found with an abnormal value. However, the relative infrequency of *confirmed* hyperglycemia and the demonstrable relationship between asymptomatic elevations of postglucose values to cardiovascular problems argue against such adjustments. The large number of individuals with single postglucose elevations who do not confirm on repeat testing should, until more specific data become available, be considered at high risk for diabetes and cardiovascular diseases. A considerable accumulation of prospectively collected data is still needed in order to clarify the true relationship between age and blood glucose levels. Fundamental to this endeavor will be a precise clinical definition of the significance of subdiagnostic blood glucose levels, substantiation of the proposed qualitative differences for postprandial as compared with postglucose blood glucose levels, and our ability to produce acceptable and reproducible definitions of cardiovascular disease endpoints for study. Only then can the rise in blood glucose levels with age be placed in proper perspective and the complex interrelationships between blood glucose levels, cardiovascular disease and diabetes mellitus become meaningful to the practicing physician.

ACKNOWLEDGMENT

Supported by Grant HL 16662, National Heart and Lung Institute.

REFERENCES

[1]O'Sullivan, J. B., Mahan, C. M., Freedlender, A. E., and Williams, R. F.: The effect of age on carbohydrate metabolism. J. Clin. Endocrinol. Metab. *33*:619-23, 1971.

[2]O'Sullivan, J. B., and Mahan, C. M.: Evaluaton of age-adjusted criteria for potential diabetes. Diabetes *20*:811-15, 1971.

[3]Hayner, N. S., Kjelsberg, M. O., Epstein, F. H., and Francis, T., Jr.: Carbohydrate tolerance and diabetes in a total community, Tecumseh, Michigan. I. Effects of age, sex and test conditions on one-hour glucose tolerance in adults. Diabetes *14*:413-23, 1965.

[4]National Center for Health Statistics: Glucose Tolerance Tests of Adults, 1960-1962, U.S. Public Health Service publication 1,000, series II, no. 2, 1964.

[5]Pozefsky, T., Colker, J. L., Langs, H. M., and Andres, R.: The cortisone-glucose tolerance test: Influence of age on performance. Ann. Intern. Med. *63*:988-97, 1965.

[6]O'Sullivan, J. B., and Mahan ,C. M.: Blood sugar levels, glycosuria, and body weight related to development of diabetes mellitus. JAMA *194*:587-92, 1965.

[7]Miller, M., Bennett, P. H., and Burch, T. A.: Hyperglycemia in Pima Indians: A preliminary appraisal of its significance. Biomedical Challenges Presented by the American Indian. Scientific Publication no. 165 (Sept. 1968), Pan American Health Organization, Washington, D.C.

[8]O'Sullivan, J. B.: Problems in comparing population studies of diabetes. *In* Sixth Congress of the International Diabetes Federation, Stockholm, Sweden, J. Ostman and Milner, Eds. Amsterdam, Excerpta Medica Foundation, 1969, pp. 696-700.

[9]O'Sullivan, J. B., Cosgrove, J., and McCaughan, D.: Blood sugars, vascular abnormalities and survival. Postgrad. Med. J. *44*:(Suppl.): 955-59, 1968.

[10]The Framingham Study. An epidemiological investigation of cardiovascular disease. Sections 10-22, U.S. Government Printing Office, Washington, D.C., Sept. 1968.

[11]Keen, H., et al.: Blood sugar and arterial disease. Lancet *2*:505-08, 1965.

[12]Ostrander, L. D., et al.: Relationship of cardiovascular disease to hyperglycemia, Ann. Intern. Med. *62*:1188-98, 1965.

[13]O'Sullivan, J. B., and Mahan, C.M.: Prospective study of 352 young patients with chemical diabetes. N. Engl. J. Med. *278*:1038-41, 1968.

[14]O'Sullivan, J. B., Mahan, C. M., and McCaughan, D.: Identification of evolving diabetes. *In* 7th Congr. IDF, August, 1970, R.R. Rodriguez, and J. Vallance-Owen, Eds. Amsterdam, Excerpta Medica Foundation *231*:256-60, 1971.