Ten-Year Prognosis of Impaired Glucose Tolerance in Siblings of Patients with Insulin-dependent Diabetes

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SUMMARY

We traced 105 of 140 siblings of children with insulin-dependent diabetes (IDD) who had had oral glucose tolerance tests (OGTT) 10–12 yr earlier. Siblings with abnormal tests by screening criteria (8.3 mmol/L at 1 h, 7.2 at 2 h, N = 44) included all 6 who subsequently developed IDD after 3 mo to 7 yr (5.7% of entire group, 13.6% of abnormal screenees). The National Diabetes Data Group criterion for children (7.8 mmol/L at 2 h) identified 19 siblings, including 5 of the 6 who later developed IDD (26% of abnormals). Subsequent full 4-h OGTT, including analysis of insulin responses, did not improve predictability for subsequent IDD. Thus, siblings of IDD were identified at high risk (14–26%) or at low risk (0–1%) for subsequent IDD by a simple 2-h OGTT. The prolonged latency in the development of IDD indicates that, among siblings of IDD, this disorder may be already chronic for years by the time of clinical onset. DIABETES *31*:385–387, May 1982.

In 1979 the National Diabetes Data Group (NDDG) assembled international experts to improve classification and terminology for the various hyperglycemic states.[1] The term impaired glucose tolerance (IGT) was adopted as more appropriate and less stigmatizing than chemical diabetes, particularly for pediatric patients.[2] The absence of long-term studies of cohorts of youngsters with impairment was noted; estimates of risk for the development of insulin-dependent diabetes have varied from 0 to 10%.[2,3]

This report provides a follow-up study of a group of young persons at increased risk for insulin-dependent diabetes (IDD), the siblings of children with IDD who had been tested for glucose intolerance 10–12 yr earlier.

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MATERIALS AND METHODS

The subjects were 140 siblings (2–25 yr old) of 67 children with IDD attending Florida's Camp for Children and Youth with Diabetes from 1969 to 1971. Two-hour oral glucose tolerance testing (OGTT) was carried out at camp in the morning after an overnight fast. The glucose load was 1.75 g/kg body wt to a maximum of 75 g (Glucola). Venous plasma specimens obtained fasting and 1 and 2 h post-glucose ingestion were assayed for glucose by the ferricyanide method on an Auto-Analyzer. Screening criteria for IGT were levels at 1 h of 8.3 mmol/L (150 mg/dl) or at 2 h of 7.2 mmol/L (130 mg/dl). Those who exceeded either of these criteria were invited to the Clinical Research Center of the Shands Teaching Hospital for a 4-h OGTT, which included insulin determinations and measurement of calcium, magnesium, and phosphate in response to glucose loading. The results of these measurements have been reported elsewhere, together with data from subjects ascertained in other ways.[4,5] To assess whether this follow-up testing improved risk prediction and to test the hypothesis that insulinopenia is a clue to progression to IDD,[4] glucose and insulin areas were calculated for the first full (4 h) OGTT following screening. The results from the four subjects thus tested who later developed IDD were compared with data for sibs who underwent 4-h OGTT and who did not develop IDD. Glucose and insulin areas and the ratio of insulin area to glucose area for each of these subjects were compared with age-specific normal data from our studies.[4]

Five of the six sib pairs who became concordant for IDD were HLA typed by established methods.[6]

Initial glucose tolerance screening data were analyzed using screening criteria as noted above, as well as the National Diabetes Data Group criteria for impaired glucose tolerance (less than 7.8 mmol/L fasting and greater than 7.8 mmol/L at 2 h).[1] The chi-square test was used to analyze the predictability of the initial screening tests, applying these two sets of criteria.

RESULTS

We were able to trace nearly identical proportions of the original groups classified by the screening criteria as abnormal ($^{44}/_{58}$, 76%) and normal ($^{61}/_{82}$, 74%). This follow-up represented 53 out of the entire cohort of 67 sibships (79%). Thus there did not appear to be ascertainment bias for IDD outcome in those siblings whom we were able to follow up in these studies.

Six individuals developed IDD during the decade of follow-up, 1 within 3 mo (age 15 yr), 2 after 2 yr (ages 9 and 16 yr), 1 after 3 yr (age 14 yr), and 2 after 7 yr (ages 13 and 20 yr). None of the persons who had a normal screening test developed IDD. Thus, 5.7% ($^{6}/_{105}$) of the siblings developed diabetes during the 10–12-yr observation period, a figure remarkably close to the prediction of Hansen and Degnbol[7] of 5.9% developing IDD by age 30 yr if the affected sibling had diabetes before age 20. However, the screening test selected the sibling population in which all diabetes developed, resulting in 13.6% ($^{6}/_{44}$) predictability for a positive test and 100% predictability for a negative screening test ($^{61}/_{61}$). The sensitivity of the screening test was 100% (no false negatives) and the specificity 61.6% (many false positives).[8] The NDDG criteria provided a greater predictability for a positive test of 26.3% ($^{5}/_{19}$) but decreased predictability for a negative test to 98.8% ($^{85}/_{86}$). These standards resulted in a sensitivity of 83% (one false negative) and a specificity of 86% (fewer false positives than with screening criteria). Both these criteria (screening and NDDG) yielded highly significant differences between the frequencies of diabetes in the abnormal and normal screened groups ($P < 0.001$).

Only 4 of the 6 siblings who subsequently developed IDD were retested with 4-h OGTT; three had glucose areas outside the mean +2 SD value of age-specific controls (Table 1) but so did 8 of the other 36 siblings who were retested. None of the 4 who later developed IDD had absolute insulinopenia compared with age-matched control groups. The ratios of insulin area to glucose area were below the mean −1 SD level of controls in 3 who later developed IDD (Table 1). Five of the other 36 sibs retested also had ratios below the mean −1 SD for control groups. Thus, relative insulinopenia during the 4-h OGTT was found in 75% of those who developed IDD during the subsequent 10 yr, but in only 14% of those who did not.

HLA typing of concordant siblings showed HLA-identicality in 4 (80%) of 5 sibships studied (expected 25%) and haploidenticality in one (20%) of the pairs (expected 50%).

DISCUSSION

The NDDG report, in setting criteria for IGT in children, noted the paucity of information on the relationship of IGT to the later development of diabetes.[1] This study indicates that the NDDG criterion of 7.8 mmol/L 2 h following glucose loading will identify those siblings of children with IDD who have a 1 in 4 risk of developing overt IDD during the subsequent decade. This is a 4.5-fold increase in the risk prediction based only on sibship, $^{6}/_{105}$ or 1 in 18. These criteria did not identify one of the siblings who developed IDD 7 yr after the screening study. Our own (screening) criteria identified all siblings who were destined for subsequent IDD, but at the expense of decreased specificity.

Further glucose tolerance testing did not improve predictability for the development of IDD. One subject had overt diabetes at the time of retesting and another who developed overt diabetes 2 yr after screening did not return for retesting. Of the remaining 4 who were given 4-h OGTT, 3 had abnormal tests ("chemical" or IGT by NDDG criteria), but so did 8 others among the 36 retested by 4-h OGTT who did not go on to develop IDD. Thus, for this subset, despite preselection by the screening OGTT, the risk prediction using a full OGTT ($^{3}/_{11}$ or 27.3%) was no greater than for the group as a whole using the 2-h screening glucose tolerance test with NDDG criteria (26.3%).

Comparison of ratios of insulin area to glucose area during the 4-h OGTT between siblings who developed IDD and normal controls suggested insulinopenia in 3 of 4 who developed IDD. Five other siblings who did not go on to develop IDD during the decade of follow up had similar relative insulinopenia. Thus this finding is common during OGTT in those who go on to develop IDD (75%) and uncommon (14%) in those who do not during the subsequent decade. Only one of the 4 who eventually developed IDD did not show hypoinsulinism and he was also the only subject excluded by NDDG criteria applied to the initial 2-h OGTT.

HLA-typing of concordant pairs of siblings with IDD has demonstrated that the absence of HLA-haplotype sharing is rare, in contrast to 25% random expectation. HLA-identity has been present in the majority of affected siblings (55–65% versus a random expectation of 25%) and the sharing of a single haplotype (random expectation 50%) found in

TABLE 1
Glucose and insulin areas during 4-h OGTTs and ratios of insulin area to glucose area in four siblings of IDD who developed IDD 2–7 yr later, compared with age-group controls[4]

Age at testing (yr)	Glucose area (mmol/L × h)		Insulin area (mmol/L × h)		Insulin area/glucose area	
	Sibling	Controls	Sibling	Controls	Sibling	Controls
7	40.2†	22.8(2.5)*	19.4	22.2(8.4)*	0.482‡	0.974(0.360)*
14	34.8†	23.6(2.8)	26.1	37.9(19.2)	0.750‡	1.578(0.693)
4.5	29.3†	22.4(2.1)	10.0	14.9(5.7)	0.340‡	0.665(0.253)
5.5	25.9	22.4(2.1)	23.3	14.9(5.7)	0.900	0.665(0.253)

* Mean (SD).
† Above mean + 2 SD for control group.
‡ Below mean − 1 SD for control group.

the rest.[6,9,10] We found HLA-identity in 80% and haploidentity in 20% of five pairs studied. Had we HLA-typed all the propositi and siblings in this study, we could have excluded 25% of the sibs (N = 26) from risk for IDD because they did not share an HLA-haplotype with the affected sibling. The 25% of siblings HLA-identical to the propositi would have been expected to include 4 or 5 of the 6 siblings who went on to develop IDD. However, the 50% expected siblings sharing a single haplotype with the affected proband would include one or two destined for subsequent IDD during this study. Thus, HLA-typing would have identified the 75% (N = 79) of siblings sharing at least one HLA haplotype with the proband, a highly sensitive, though costly, device. Specificity of such a method for identifying siblings at risk is only 26% (high rate of false positivity) and predictability of a positive test only 7.5%. The efficiency of HLA typing to identify those sibs at risk (true positives + true negatives ÷ N) would be $^{32}/_{105}$ or 30.5% whereas the efficiency of the 2-h OGTT in this study was 64% ($^{66}/_{105}$) using our screening criteria and 86% ($^{90}/_{105}$) applying NDDG criteria.

The 2-h oral glucose tolerance test identified a subset of the sibling cohort at increased risk for the development of IDD. However, without promise of preventative treatment, the knowledge of increased risk would appear to serve no useful purpose to the individual and might, indeed, be a harmful stress.[2] The prolonged latency in the development of IDD after detection of abnormal glucose tolerance indicates that, in siblings of IDD, this disorder may be already chronic at the time of clinical onset.

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REFERENCES

[1] National Diabetes Data Group: Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance. Diabetes *28*: 1039–57, 1979.

[2] Rosenbloom, A. L., Kohrman, A., and Sperling, M.: Classification and diagnosis of diabetes mellitus in children and adolescents. J. Pediatr. *98*: 320–23, 1981.

[3] Rosenbloom, A. L., Drash, A., and Guthrie, R.: Chemical diabetes mellitus in childhood: report of a conference. Diabetes *21*:45–50, 1972.

[4] Rosenbloom, A. L., Wheeler, L., Bianchi, R., Chin, F. T., Tiwary, C. M., and Grgic, A.: Age adjusted analysis of insulin responses during normal and abnormal oral glucose tolerance tests in children and adolescents. Diabetes *24*:820–28, 1975.

[5] Rosenbloom, A. L.: Serum calcium and magnesium decline during oral glucose tolerance testing (OGTT) in pre-clinical diabetes less than in normals. Metabolism *26*:1033–39, 1977.

[6] Maclaren, N. K., Rosenbloom, A. L., McLaughlin, J. V., Krupp, B., Bruck, E., and Lezotte, D.: HLA in insulin dependent diabetes mellitus (IDDM): *dominant susceptibility plus heterogeneity*. IRCS MEd. Sci. *9*:631–32, 1981.

[7] Hansen, A. G., and Degnbol, B.: Prevalence of diabetes mellitus among relatives of patients with juvenile diabetes. Diabetologia *12*:396, 1976.

[8] Thorner, R. M., and Remein, Q. R.: Principles and procedures in the evaluation of screening for disease. Publ. Health Monogr. 67 (PHS Publication No. 846), 1961.

[9] Barbosa, J., Chern, M. M., Noreen, H., Anderson, V. E., and Yumis, E. J.: Analysis of linkage between the major histocompatibility system and juvenile insulin-dependent diabetes in multiplex families. J. Clin. Invest. *62*:492–95, 1978.

[10] Spielman, R. S., Baker, L., and Zmijewski, C. M.: Gene dosage and susceptibility to insulin-dependent diabetes. Ann. Hum. Genet. *44*:135–50, 1980.