Diabetes Mellitus in Familial Hyperlipoproteinemia

YOSHIKUKE MARUHAMA

The First Department of Internal Medicine, Iwate Medical University, Morioka 020, Japan

MARUHAMA, Y. Diabetes Mellitus in Familial Hyperlipoproteinemia. Tohoku J. exp. Med., 1983, 141, Suppl., 593-597 — The relationship between a certain form of type 2 diabetes mellitus and familial endogenous hyperlipoproteinemia still remains confused. Therefore, we examined glucose tolerance and insulin secretion in 133 members (6-80 years old) of 15 families with a history of endogenous hyperlipoproteinemia. A segregation study was carried out to compare the prevalence of diabetes in hyperlipoproteinemic and normolipoproteinemic relatives, and the results seemed to support the recent concept that diabetes and hyperlipoproteinemia are inherited independently. However, the age-group analysis revealed that insulin secretion was progressively impaired with aging and about a third of the elderly group was significantly insulinopenic. Diabetes thus occurred in 0-2.6% of subjects under 40 years of age, 9.8% of those of 41-60 years of age and in 26.3% of those over the age of 61 years, occasionally complicated by diabetic retinopathy. Interestingly, insulinopenic diabetes was not accompanied by hyperlipoproteinemia, but hyperinsulinemic cases remained hyperlipoproteinemic. Therefore, the possibility arises that the independent occurrence of diabetes mellitus and hyperlipoproteinemia suggested by this crosssectional segregation study may result from bidirectional deviations in individuals who started out with uniform familial disorders such as insulin resistance.

The relationship between familial endogenous hyperlipoproteinemia and a certain form of type 2 diabetes mellitus has not yet been elucidated. Fredrickson et al. (1967) and Glueck et al. (1969) previously suggested that both disorders are inherited together. In contrast, Brunzell and colleagues (1975) concluded that genetic hypertriglyceridemia (endogenous hyperlipoproteinemia) and diabetes mellitus are separate entities and that both are transmitted independently. However, the analysis by Brunzell et al. (1975) might be incomplete since no glucose tolerance test (GTT) was performed, and therefore the figures on the prevalence of diabetes mellitus remain uncertain.

In this study, we attempted to re-analyse the diabetes-hyperlipoproteinemia interrelationship on the basis of actual data for the blood glucose curve and plasma insulin response during GTT in members of families with familial hyperlipoproteinemia.
SUBJECTS AND METHODS

Fifteen pedigrees of familial endogenous hyperlipoproteinemia, consisting of a total of 133 relatives (72 males and 61 females, aged 6-80 years), were investigated. The relatives were maintained on a regular Japanese diet and examined for plasma lipids and lipoproteins after an overnight fast as described previously (Maruhama et al. 1978). Subsequently, a GTT using 50 g of glucose (1.75 g/kg of glucose for children aged under 10 years) was performed and blood glucose and plasma insulin were measured before, and 30, 60, 90 and 120 min after glucose loading. The sum of 5 half-hourly plasma insulin or blood glucose values in GTT was used as an index of insulin secretion or glucose tolerance. The variables were judged as abnormally increased when they exceeded the corresponding mean +2 s.d. of the age- and sex-matched controls, and as abnormally decreased when they were below mean −1 s.d. of the matched controls. The data on 93 relatives of endogenous hyperlipoproteinemic family lines and 90 matched controls have been published previously (Maruhama et al. 1978). Glucose intolerance and diabetes mellitus were also judged by the new WHO criteria (WHO Expert Committee 1980) after adjusting the glucose value of 50 g GTT obtained in this study to that of 75 g GTT.

RESULTS AND DISCUSSION

Prevalence of diabetes mellitus

The overall prevalence of diabetes mellitus was as high as 7.5% in members of these hyperlipoproteinemic pedigrees including the probands. In the present analysis, 6 pedigrees of hyperlipoproteinemic and diabetic probands and 9 pedigrees of hyperlipoproteinemic and nondiabetic probands were then segregated, and the prevalence of diabetes mellitus in the hyperlipoproteinemic and normolipoproteinemic relatives excluding the probands was compared in these 2 pedigree groups. Excluding the probands, the total prevalence of diabetes mellitus was 2.5% (1/40) in the hyperlipoproteinemic relatives while it was 3.8 (3/78) in the normolipoproteinemic relatives. Thus, no direct link between diabetes mellitus and hyperlipoproteinemia was indicated in the relatives excluding the probands. These results appear to be very close to those of Brunzell and colleagues (1975).

However, the effectiveness of the above cross-sectional segregation analysis might be limited since the abnormal phenotypes, such as diabetes mellitus and hyperlipoproteinemia, of the affected relatives might not be fixed but modified under the influence of aging or other factors.

Background analysis of diabetes mellitus

Firstly, we reconfirmed the close correlation between hyperlipoproteinemia and hyperinsulinism in the subjects of this study by multivariate regression analysis. The stepwise changes in the multiple correlation coefficients indicated that plasma insulin sum in GTT showed the greatest effect on plasma triglyceride levels. Thus, the insulin value by itself could account for 23% of the total variance of plasma triglyceride. In fact, hyperlipoproteinemia and hyperinsulinism are usually coupled in the affected relatives of each pedigree. Either elevated insulin or insulin resistance could be the causal factor of endogenous
hyperlipoproteinemia (Reaven et al. 1967; Olefsky et al. 1974; Maruhama et al. 1975).

Secondly, we analysed the age-related alteration in the insulin secretory function since we previously noticed the significant decrease in insulin response in GTT with aging in hyperinsulinemic families (Maruhama et al. 1978; Maruhama 1981). As shown in Fig. 1, hyperinsulinemic relatives are predominant in each age group, but it is obvious that the prevalence of cases with decreased insulin response becomes higher in the elderly groups. Since the affected relatives in younger age groups all show insulin hypersecretion, the insulinopenia in the elderly may be due to so-called B cell exhaustion.

Thirdly, we analysed blood glucose curves during GTT in the relatives including the probands. Although the prevalence of borderline GTT abnormality is almost constant among all age groups, the prevalence of impaired glucose
Fig. 2. Prevalence of abnormal glucose tolerance and diabetes mellitus in the relatives of familial hyperlipoproteinemia grouped by age. Impaired glucose tolerance and diabetes mellitus were judged according to the WHO criteria (WHO Expert Committee 1980).

Tolerance increases with age, as shown in Fig. 2. The ratio of relatives judged as diabetic is 2.6% in the under 20 age group and 9.8% in the group aged 41-60 years, while the ratio reaches 26.3% in the group aged over 61 years. Interestingly, insulinopenic and diabetic relatives did not develop hyperlipoproteinemia while the relatives with hyperinsulinism, even if they were senile, were complicated with hyperlipoproteinemia. Funduscopic examination revealed diabetic retinopathy in 3 of 10 diabetic relatives. The lesions were all of mild background retinopathy without proliferation.

In this study, we emphasized the age-related alterations in the profiles of the affected relatives. A longitudinal study is obviously warranted to establish the actual aging process. However, the possibility arises that the independent occurrence of hyperlipoproteinemia and diabetes mellitus suggested by this analysis or by Brunzell et al. (1975) results from bidirectional deviations in the individuals who started with a uniform familial disorder such as insulin resistance. It seems to be possible for one relative to show hyperinsulinism coupled with mild glucose intolerance and hyperlipoproteinemia but for the other elderly relative to show diabetes mellitus without hyperlipoproteinemia. Finally, this form of type 2 diabetes mellitus produces only subclinical retinopathy.
Acknowledgments

This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture, Japan (Nos. 777117, 877132, 967048 and 257170).

References


