Glycation and the Development of Diabetic Retinopathy

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SUMMARY The levels of advanced-stage products of the Maillard reaction in lens proteins are considered to reflect the sum of accumulated glycation over time, because there is little turnover of lens crystallins.

Thus, we investigated the relationship between the degree of diabetic complications, i.e. diabetic retinopathy and levels of advanced-stage products accumulated in the lens proteins prior to the surgical resection.

The level of advanced-stage products in the lens proteins increased with the progression of diabetic retinopathy. The differences among the level in the groups of each diabetic retinopathy were significant.

These results suggest that glycation measured by advanced Maillard product in the lens protein plays an important role in the etiology of diabetic complications.

Introduction

Recent studies had demonstrated that glycation, which is a nonenzymatic binding reaction between proteins and reducing sugars and is termed the Maillard reaction\(^1\), occurs in various tissues\(^3\) such as crystallins, collagen, myelin and glomerular basement membrane etc. other than hemoglobin (Hb). The early-stage products in the Maillard reaction have been found in tissue proteins, such as Hb\(^4\), plasma protein\(^5\), nail\(^6\) and hair protein\(^7\) and can be used as a clinical indicator of blood glucose control in diabetic patients.

In the Maillard reaction, early-stage products, prior to the formation of Schiff bases and the Amadori rearrangement, are converted into advanced products through gradual multiple rearrangements and dehydrations.\(^9\) Advanced-stage products are cross-linked and exhibit fluorescence.\(^10\) The accumulation of these products in the tissue has attracted attention in relation to the assessment of the progression of diabetic complications and aging.\(^10\) We measured the advanced-stage products of the Maillard reaction in the lens nucleus of cataracts from diabetic patients and found that levels of advanced-stage products are related to
Glycation and the Development of Diabetic Retinopathy

It appears that there is little turnover of lens crystallins. Thus, glycation in the lens nucleus may result in formation and accumulation of advanced-stage products over the course of years. There have been few reports on the relationship between the etiology of diabetic complications and advanced-stage products of the Maillard reaction. We have investigated the relationship between the progression of diabetic retinopathy and levels of advanced-stage products accumulated prior to surgery in the lens nucleus, which can be regarded as the sum of glycation over time, i.e. an indicator of blood glucose levels over time. The advanced-stage products were determined by fluorescence high-performance liquid chromatography as described previously.

**Materials and Methods**

Thirty-five patients with non-insulin-dependent diabetes mellitus were included in this study. The patients were divided, by grade of diabetic retinopathy after the resection of their cataracts, into three groups, i.e. those without retinopathy, those with background retinopathy, and those with preproliferative and proliferative retinopathy.

Of the thirteen diabetic patients without retinopathy (mean age, 66.1±7.4 yr; duration of diabetes, 8.1±6.6 yr; mean±S.D.), two received injections of insulin, 6 received oral hypoglycemic drugs, and 5 received diet therapy. Of the twelve patients with background retinopathy (mean age, 70.6±3.6 yr; duration of diabetes, 10.9±7.5 yr), 6 received injections of insulin, 5 received oral hypoglycemic drugs, and 1 received diet therapy. Of ten patients with preproliferative and proliferative retinopathy (mean age, 65.2±12.7 yr; duration of diabetes, 12.5±9.8 yr), 4 received injections of insulin, 5 received oral hypoglycemic drugs, and 1 received diet therapy.

The surgically isolated cataractous lens was divided into three parts: capsule, cortex, and nucleus. The inner third of the lens was regarded as the nucleus.

Levels of the advanced-stage product, which is designated as peak late No. 1 (peak $L_1$) were measured by fluorometry after fractionation by high-performance liquid chromatography (excitation wavelength, 370 nm; emission wavelength, 440 nm).

The levels of HbA1c (HbA1c) were determined prior to the resection of cataracts.

HbA1c was measured by high-performance liquid chromatography using the column chromatograph system (Auto A1c, Kyoto Daiichi Chemical Co., Ltd., Kyoto, Japan).

Student's t-test was used for statistical analysis.

**Results**

The peak $L_1$ levels were $7.0±2.0\times10^3 \mu V\cdot sec$ in the retinopathy-free group, $9.9±2.6\times10^3 \mu V\cdot sec$ in the background retinopathy group, and $13.2±4.0\times10^3 \mu V\cdot sec$ in the preproliferative and proliferative retinopathy group (Table 1).

The differences among the level in the three groups were significant. The level of HbA1c immediately prior to surgery tended to be slightly higher in the background and preproliferative and proliferative groups than in the retinopathy-free group. However, there was no statistically significant difference among the three groups.
Fig. 1 Relationship between the grade of diabetic retinopathy and the level of peak L₁ in the nucleus of diabetic cataract and of HbA₁c at the time of surgery.

The horizontal bar represents the mean ± S.D. Figure in parenthesis represents number of cases. N.S. = not significant.

Discussion

Although there was no difference in mean age among the three groups of patients, the members of the retinopathy-free group tended to have had a slightly shorter duration of illness and had slightly lower levels of HbA₁c. However, the differences were not statistically significant. Thus, there was no remarkable difference in blood glucose levels in the three groups in the present study. Considering that the level of HbA₁c reflects the blood glucose level during the previous one to two months or so, it does not reflect the total sum of blood glucose levels over the long period of duration of the diabetes. Since lens protein is a long-lived protein, glycation, and in particular the levels of advanced products of the Maillard reaction, in cataracts are considered to reflect the sum of accumulated glycation which is formed to an extent dependent on long-term blood glucose levels. If we assume that glycation is involved in the etiology of diabetic retinopathy, it is possible that levels of advanced products in the lens may to some extent reflect the severity of retinopathy. On this assumption, we investigated the levels of advanced products in diabetic patients classified by the severity of retinopathy. The results of the present study suggest that glycation plays an important role in the etiology of diabetic complications. Given the life span of lens protein, the advanced products of glycation in a cataract, if present in lens protein, may be a new indicator, collectable from the body, of the sum of glycation or the sum of blood glucose levels up to the time of extraction of the cataract.

References

2) H. F. Bunn : Diabetes, 30, 613 (1981)
Glycation and the Development of Diabetic Retinopathy


