Increased Serum Levels of Advanced Glycation End Products in NIDDM Patients With Diabetic Complications

Advanced glycation end products (AGEs) are produced by a nonenzymatic reaction between proteins and sugar in patients with long-term hyperglycemia (1). AGEs accumulate with time and are irreversibly deposited in various tissues of the body, contributing to the development of diabetic complications, arteriosclerosis, and aging (1–3).

The results of the Diabetes Control and Complications Trial have shown that long-term hyperglycemia is the cause of various diabetic complications. However, the mechanisms responsible for development of these complications arising from persistent hyperglycemia have not yet been elucidated. The idea that AGEs are the ultimate causative factor of diabetic complications is highly convincing.

Histopathological studies using an anti-AGE antibody have suggested that AGEs play an important role in the development of nephropathy in diabetic animals and patients, as seen, for example, in AGE accumulation on the basement membrane in streptozocin rats (4) and AGE staining in nodular lesions of diabetic patients with nephropathy (5). In addition, an injection of the AGE-modified albumin into normal rats was reported to induce glomerulosclerosis, as manifested by basement membrane widening and an increase in mesangial extracellular matrix (6). In an in vitro investigation, exposure of mesangial cells to AGEs promoted the production of matrix protein (7). These findings strongly suggest that AGEs are associated with nephropathy.

We determined serum AGE levels in patients with NIDDM and evaluated the relationship between these levels and diabetic complications. A total of 125 patients (mean age 59.2 ± 11.1 years, duration of diabetes 11.6 ± 8.9 years, mean HbA_{1c} 6.8 ± 1.0%) and 63 healthy volunteers were studied. Serum AGEs were measured by a newly developed enzyme-linked immunosorbent assay method using anti-AGE keyhole limpet hemocyanin.

Serum AGE levels were significantly higher in the diabetic group compared with the normal control group (7.2 ± 14.6 vs. 3.3 ± 1.0 mU/ml, $P < 0.05$). Significant correlations were seen between serum AGEs and the degree of diabetic nephropathy. Serum AGE levels of diabetic patients with proliferative retinopathy were significantly higher than those of patients without retinopathy ($P < 0.05$).

Serum AGE levels reflected the severity of diabetic complications, including nephropathy and retinopathy; therefore, this method may prove to be a very useful tool for patient evaluation and follow-up, as well as for monitoring the effects of treatment in clinical practice.

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Making Things Easier Is Not So Easy

The 1997 American Diabetes Association criteria and glucose intolerance

The 1997 American Diabetes Association (ADA) diagnostic criteria for diabetes were recently compared with the criteria proposed by the World Health Organization (WHO) by applying the data from the Third National Health and Nutrition Examination Survey. Harris et al. (1) conclude that although the number of people with undiagnosed diabetes was lower when the new ADA fasting criteria were used, their extended use may result in the detection of a greater number of people with undiagnosed diabetes in clinical practice because of the simplicity and greater use of a fasting plasma glucose value versus the glucose tolerance test.

Other conclusions obtained from their results need to be emphasized. First, a poor concordance (38%) was observed between the ADA "impaired fasting glucose" category and the WHO "impaired glucose tolerance" status. In fact, 18% of the subjects with ADA impaired fasting glucose were diabetic according to the WHO criteria, and 43% had a normal glucose tolerance. These data suggest that the 2-h postchallenge plasma glucose is a complementary test needed to be done in these subjects to avoid under- or overcategorization of the cases. Second, 70% of the WHO impaired glucose tolerance cases were considered normal using the ADA criteria. These data suggest that the main purpose of the new criteria, an earlier diagnosis of diabetes and glucose intolerance (2), will not be achieved without complementary actions. Clearly, in a subset of the subjects (fasting plasma glucose <126 mg/dl), the information obtained from the fasting plasma glucose is not the same as that obtained by the 2-h postchallenge plasma glucose. We cannot leave without a proper diagnosis a large number (10.5 million according to Harris) of the glucose-intolerant subjects, knowing that they have increased cardiovascular