Advanced Glycosylation End Products (AGE) and Diabetic Nephropathy

MAKITA Z, RADOFF S, RAYFIELD EJ, YANG Z, SKOLNIK E, DELANEY V, FRIEDMAN EA, CERAMI A, VLASSARA H: ADVANCED GLYCOSYLATION END PRODUCTS IN PATIENTS WITH DIABETIC NEPHROPATHY. *N ENGL J MED* 325:836–42, 1991

OBJECTIVE — To elucidate the relationship of advanced glycosylation end products (AGE) to diabetic nephropathy.

RESEARCH DESIGN AND METHODS — Using a radioreceptor assay, AGEs were measured in serum and arterial wall collagen from patients with insulin-dependent and non-insulin-dependent diabetes and nondiabetic patients with varying levels of renal function.

SETTING — Laboratory of Medical Biochemistry, Rockefeller University, New York, New York, and State University Hospital Department of Medicine, Downstate Medical Center, New York, New York.

PATIENTS — Tissue samples were obtained from autopsy specimens from 9 diabetic patients and 18 nondiabetic patients. Serum samples were obtained from 38 patients: 20 diabetic patients (6 undergoing hemodialysis, 14 not), 10 nondiabetic patients with end-stage renal disease requiring hemodialysis, and 8 nondiabetic nondialysis subjects. The diabetic patients were divided into three groups: those with normal renal function and no proteinuria, those with persistent proteinuria and elevated serum creatinine concentrations but no symptoms of uremia, and those with end-stage renal disease requiring hemodialysis.

INTERVENTION — None.

PRIMARY OUTCOME MEASURES — Serum concentrations of AGE; AGE content of arterial wall collagen.

RESULTS — The mean AGE content of the arterial wall collagen in the 16 samples from the 9 diabetic patients was 14.5 ± 5.2 AGE U/mg collagen compared with 3.6 ± 1.5 AGE U/mg from the 18 nondiabetic patients. Among the patients with end-stage renal disease, the levels of AGE in arterial tissue were higher in the samples from the 3 diabetic patients than in those from the 2 nondiabetic patients (21.3 ± 2.8 vs. 6.3 ± 1.4 AGE U/mg). Within the group of 9 diabetic patients, the AGE levels in arterial collagen in the 3 patients with end-stage renal disease were higher than those in the 6 patients without end-stage renal disease (21.3 ± 2.8 vs. 11.5 ± 1.9 AGE U/mg). The mean AGE content of serum from the diabetic patients who required hemodialysis was higher (82.8 ± 9.4) than the serum levels in each of the other groups. When the diabetic patients without end-stage renal disease were divided according to the degree of loss of renal function, those with normal renal function had serum levels of AGE peptide (16.8 ± 6.1) similar to those in the nondiabetic subjects (15.6 ± 3.4). The diabetic patients with elevated serum creatinine concentrations and persistent proteinuria had serum levels of AGE peptide (30.2 ± 4.8) nearly twice as high as those of both the nondiabetic subjects and diabetic patients with normal renal function.

CONCLUSIONS — AGEs accumulate at a faster-than-normal rate in arteries and the circulation of patients with diabetes; the increase in circulating AGE peptides parallels the severity of renal functional impairment in diabetic nephropathy.

COMMENTARY — As noted by Brownlee et al. (1), the central pathophysiological features of diabetic vascular complications are an abnormal leakage of protein and a progressive constriction of the luminal area in both large and small vessels. The proximate cause of these processes is high concentrations of blood glucose for many years. The glucose in the circulation is known to form chemically reversible early glycosylation products with protein at a rate proportional to the glucose concentration. These Schiff bases then rearrange to form more stable early glycosylation products. Such products are reversible and as such return to lower levels when blood glucose concentrations normalizes. However, some of the early glycosylation products on collagen and other long-lived proteins do not dissociate. Instead, they undergo a complex series of rearrangements to form irreversible AGEs. The rate of accumulation of such end products is proportional to the time-integrated blood glucose level over long periods of time. Consequences of accumulation of AGE include increase in vascular permeability (e.g., proteinuria in diabetic nephropathy) and thickened, inelastic vessel walls. Thus, it is tempting to speculate that these products contribute to the pathogenesis of diabetic vascular disease.

The studies of Makita et al. pro-

vide evidence that such AGE products may contribute to the progression of diabetic nephropathy. Furthermore, their data indicate that normal renal function is an important component in clearing AGE from the circulation. However, as Steffes and Mauer (2) caution, whether such AGE products are responsible for the vascular complications of diabetes has not been proved. Thus, studies need to determine whether reducing the level of AGE can, without other changes, reduce or prevent the development of diabetic microvascular complications.

One such agent that has been used to prevent the formation of AGE is aminoguanidine, a hydrazine that has been shown to react with the early glycosylation products and form a substitute glycosylated product. Studies of diabetic rats suggest that pharmacological inhibition of the formation of AGE may prevent the late and early structural lesion of diabetes (1). Confirmation of these findings has come from the work of Ellis and Good (3) who demonstrated a decrease in glomerular basement membrane thickness in diabetic rats treated with aminoguanidine. Unfortunately, no functional data were presented in these two preliminary studies to indicate that the correction of structural abnormalities was accompanied by decreased proteinuria. Clearly, association does not prove causation, but the work of Makita provides another avenue of research worthy of further exploration to elucidate the pathogenesis of the microvascular complications of diabetes.

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An Artificial Pancreas: 14 Yr of Progress

SULLIVAN SJ, MAKI T, BORLAND KM, MAHONEY MD, SOLOMON BA, MULLER TE, MONACO AP, CHICK WL: BIOHYBRID ARTIFICIAL PANCREAS: LONG-TERM IMPLANTATION STUDIES IN DIABETIC PANCREATECTOMIZED DOGS. *SCIENCE* 252:718–21, 1991

OBJECTIVE— To incorporate islet tissue onto a selectively permeable membrane that isolates this tissue from the immune system of the recipient.

RESEARCH DESIGN AND METHODS— Implantation of biohybrid pancreas devices containing canine islets and bovine islets into pancreatectomized dogs requiring exogenous insulin.

SETTING— Research laboratories of BioHybrid Technologies, Inc, Shrewsbury, MA, The New England Deaconess Hospital and Harvard Medical School, Brookline, MA, and W.R. Grace and Company, Lexington, MA.

ANIMALS— Pancreatectomized dogs were treated with insulin therapy to maintain the fasting glucose concentrations below 12.5 mM (250 mg/dl). Islets were prepared from either adult mongrel dogs or bovine calves.

INTERVENTION— The islets were seeded into the artificial pancreas device. This device uses a selectively permeable membrane with a nominal molecular mass cutoff of 50,000 M_r. The tubular membrane is coiled inside a protective housing that provides the compartment for the islet cells. The membrane is connected at each end to a standard terminal polytetrafluoroethylene graft that extends beyond the housing and is used to connect the device to the vascular system as an arteriovenous shunt. Blood flow through the graft and tubular membrane results in exchange of glucose and insulin across the membrane between the circulating blood and the cell compartment. Antibodies and lymphocytes responsible for immune rejection are excluded from the cell compartment. The output of insulin from one such device was 15–20 U/day; thus it was necessary to use two devices per dog.

PRIMARY OUTCOME MEASURES— Fasting blood glucoses, glycemic response to a meal, or intravenous glucose tolerance test.

RESULTS— Of the 10 original animals, 2 animals showed no response due to a high percentage of nonviable