Commentary on “Protein Glycosylation and AGEs Accumulation: An Avian Solution?”

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DIABETES affects up to 25% of Americans over age 65 and is even more common among minority populations. Long-term complications of diabetes include coronary, cerebral, and peripheral vascular disease as well as abnormal function of the renal, retinal, and nervous systems. These complications are somewhat duration dependent and also appear to be related to the degree of hyperglycemia. The Diabetes Control and Complications Trial (1) has provided data that indicate near normalization of plasma glucose results in prevention or at least delay in onset and progression of complications.

The mechanisms by which hyperglycemia ultimately results in impaired cellular function have been long debated and include production of advanced glycosylated endproducts (AGEs). These are glycosylated proteins with extensive crosslinking and include both short- and long-lived proteins. Because the reactions occur nonenzymatically, AGE production is believed to be due, at least in part, to ambient glucose levels. AGEs have been found in increased amounts in diabetic compared to nondiabetic subjects and in old compared to young animals. AGEs may alter both the structure and function of various important proteins and thereby contribute to diabetic complications. They may also interfere with gene expression as well as intracellular function.

Although hyperglycemia may contribute to AGE formation, other factors have also been postulated to contribute. The formation of various reactive oxygen species (ROS) as a result of metabolic processes may also potentiate AGE formation. AGEs may be removed by receptor or nonreceptor mediated processes and are also excreted by the kidneys (2).

In this issue, Iqbal and colleagues have examined some of these factors in the chicken (pages B000–B000). Birds are naturally hyperglycemic with plasma glucose levels over 200 mg/dl compared to human levels of 80–100 mg/dl, yet they have less accumulated pentosidine, an AGE, than expected. The authors have proposed that this is due, in part, to an amelioration of ROS effects by either endogenous uric acid, dietary restriction, or administration of aminoguanidine. Uric acid was increased in the diet restricted and aminoguanidine groups.

Aminoguanidine has been studied as an inhibitor of protein crosslinking. This has been its postulated mechanism of decreasing AGE accumulation and improving nerve conduction velocity in diabetic rats. Aminoguanidine has recently been shown to have effects on vascular endothelial production of nitric oxide and has been shown to decrease oxidant-induced apoptosis (3). Thus the effects of aminoguanidine are extensive and the observed effects may be due to factors other than impaired crosslinking of proteins. The article by Iqbal and colleagues has not addressed physiologic correlates of AGE accumulation. Aminoguanidine is not FDA approved and clinical trials in humans with diabetes have not been published. Neither short- nor long-term adverse effects are known.

Their proposal would be strengthened by demonstration of an effect on luminescence during the course of aging, rather than at a single time point. Measurement of malondialdehyde (MDA), a lipid peroxidation byproduct, would provide additional evidence of the effect of ROS. Measurement of other antioxidants such as ascorbic acid and vitamin E may further define ROS status. Dietary restriction in rats and humans is associated with a decrease in plasma glucose unlike the increase noted in chickens. This may represent only one recognized difference in the chicken model for diabetes.

Another factor that may account for the protection from hyperglycemia afforded birds is their habitual level of physical activity. The activity level of most birds that fly is much greater than that of mammals. The hummingbird is an extreme example with its rapid wing beat and thousands of miles of migration. It may be that this high level of "aerobic" fitness is in part responsible for the apparent absence of deleterious effects of hyperglycemia. The effect of regular exercise is obviously absent in the caged chicken so one would have to postulate that inherited avian metabolic machinery would confer protection. Exercise has been shown to decrease all-cause mortality as well as specific cardiovascular mortality in humans (4). It may delay the onset of diabetes and ameliorate the effects of hypertension and hyperlipidemia.

Although an acute bout of exercise increases free radical production, those with a high level of physical fitness have increased levels of catalase and superoxide dismutase (SOD) in muscle (5). These are important defenses against oxidants and resting MDA levels are inversely related to fitness. In the horse, repeated bouts of exercise also increased plasma uric acid (6).

Dietary restriction has been shown to increase both the maximum and mean life span of laboratory rodents. This occurs in association with reduction in MDA and increased activity of SOD, catalase and glutathione peroxidase activity. MDA is even lower if exercise is added to dietary restriction. Despite exercise-induced oxidative stress, exercise does not affect the increased life span associated with dietary restriction (7). It is therefore apparent that compensatory effects occur. Exercise training increases mitochondrial number and utilization of oxygen. The trained animal may, therefore, produce less ROS with each activity and defend against ROS more completely because of increased antioxidants, with an end result of less oxidative tissue damage such as impaired nitric oxide production and AGE accumulation.
Clinical studies of diabetic patients show that not all patients with poor glycemic control develop complications and others with apparent excellent control develop severe complications. It is evident that factors other than hyperglycemia are involved. Dietary restriction to the degree employed in Iqbal and colleagues’ study would not be feasible in a free-living population for an extended period of time. Aminoguanidine is unavailable for potential use. Perhaps physical fitness is an important factor that confers protection against complications.

REFERENCES