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STUDY OF SUPEROXIDE DISMUTASE ACTIVITY IN PLASMA OF DIABETIC PATIENTS WITHOUT NEPHROPATHY – A Review

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ABSTRACT

Superoxide excess plays a central role in tissue damage that results from diabetes, but the mechanisms of superoxide overproduction in diabetic nephropathy (DT) are incompletely understood. In the present study, we investigated the enzyme superoxide dismutase (SOD), a major defender against superoxide, in the kidneys with nephropathy.

Key words: Diabetic nephropathy, DT, Enzyme superoxide dismutase, Diabetes mellitus.

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INTRODUCTION

Diabetic nephropathy (DN) is the leading cause of end-stage renal disease. Although hyperglycemia is clearly a prerequisite for the development of DN, alone it is insufficient for its development. Epidemiologic studies demonstrate only 10% to 40% of all diabetic patients get DN, despite comparable levels of glucose control in those subjects developing DN versus spared. In addition, sibling studies show a strong familial component for the risk of developing persistent proteinuria, suggesting a genetic basis for DN risk. However, the molecular or cellular mechanisms coupled with the genetic susceptibility to DN are incompletely understood.

There is compelling evidence that superoxide excess induced by diabetic hyperglycemia plays a central role in diabetic vascular cell damage. High glucose flux increases the production of superoxide anion ($O_2^{\bullet-}$) by mitochondrial electron-transport chain, and the overproduced superoxide enhances the major pathways of hyperglycemic vascular cell damage, including protein kinase C, advanced glycation end (AGE) products, and hexosamine pathways. In addition, superoxide is produced by multiple pathogenic pathways of diabetes. These include increased nicotinamide adenine dinucleotide phosphate [NAD(P)H] oxidase activity, uncoupled endothelial nitric oxide synthase (eNOS), and enhanced signaling of AGEs, angiotensin II, and oxidized-LDL receptors. Excessive production of superoxide anion results in the formation of secondary reactive oxygen species (ROS) including peroxynitrite and hydroxyl radicals, leading the damage of DNA, proteins, and lipids, and causes vascular cell injury. Thus, superoxide overproduction is considered as a major pathogenic pathway in diabetic vascular complication. Animal and human studies and in vitro experiments suggest a role for oxidative stress, via an increased formation of free radicals, in the pathophysiology of diabetic complications. Increased generation of reactive oxygen metabolites, such as superoxide anion and hydrogen peroxide, has been shown to occur in diabetes in response to hyperglycemia. Previous studies have demonstrated that exposure to high glucose concentrations increases the levels of oxygen radical–scavenging enzymes in cultured endothelial cells and in the kidney of rats with streptozotocin-induced diabetes. High glucose concentrations can induce formation

of free radicals and activation of oxidative stress through nonenzymatic glycation of protein, auto-oxidative glycation, activation of protein kinase C, and increased polyol pathway. Excessive generation of reactive oxygen metabolites may also play a role in the pathophysiology of a variety of renal diseases. In the kidney, as in other organs, endogenous antioxidant enzymes protect cells against the toxic effect of free radicals and are an essential defense system against oxidative injury. Indeed, oxygen-derived free radicals are associated in different tissues with an elevation of antioxidant enzyme activity, and an imbalance between antioxidant enzyme productions during exposure to free radicals may lead to tissue injury.

DISCUSSION

High glucose concentrations in vitro and hyperglycemia in vivo are well-known stimuli for the production of free radicals and the generation of oxidative stress, with a consequent increase in the expression and activity of antioxidant enzymes which act as a defense system against cell damage. Hyperglycemia is also a necessary factor for the development of the glomerular lesions of diabetes. The observation that, despite hyperglycemia, only a portion of the population of type 1 diabetic patients will progress to diabetic nephropathy indicates that there is individual diversity in cell response to high glucose concentrations. It is therefore of great relevance that a disturbance in the mechanisms of protection from oxidative stress was found only in the cells of patients with nephropathy. By contrast, in long-term type 1 diabetic patient with normal buminuria, a group that appears protected from renal complications, the defense mechanisms against high glucose–induced oxidative stress were intact, or similar to those of nondiabetic individuals. Although we cannot categorically refute that the abnormalities described in this report may be secondary to renal failure, this scenario seems unlikely, because fibroblasts from nondiabetic subjects with nephropathy reveal an antioxidant enzyme response to hyperglycemia similar to that of both control subjects and diabetic subjects without nephropathy. Because culture in normal glucose concentrations did not reveal any difference among the groups, it would be surprising that nephropathy would spare the basal antioxidant status of skin fibroblasts while impairing their response to glucose. The hypothesis that renal impairment is

secondary to oxidative damage and not the cause of an altered antioxidant enzyme response is also supported by a study in rats with acutely induced reduction in GFR and proteinuria, in which the animals with a better inducible tissue antioxidant enzyme response were more resistant to renal functional deterioration

Also, we do not believe that our findings may be due to worse glycemic control or to a high glucose memory in the group of diabetic subjects with nephropathy, because cells of all groups were exposed in vitro to the same glucose concentration, and, as far as we were able to assess, there had been no difference in glycemic control between the two groups of diabetic patients in the previous four years. It is conceivable that memory of high glucose may be retained differently by cells of patients with nephropathy compared with those without nephropathy, but this would imply a specific intrinsic difference between the two sets of cells in response to hyperglycemia.

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