Review Article

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DIABETES, DYSLIPIDEMIA, ANTIOXIDANT AND STATUS OF OXIDATIVE STRESS

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ABSTRACT

The cluster of lipid abnormalities associated with type 2 diabetes is defined by increases in triglyceride (TG) and small, dense low-density lipoprotein (LDL) concentrations and decreases in high-density lipoprotein (HDL) cholesterol. Plasma LDL cholesterol levels are generally normal because the increase in the number of small, dense LDL particles is accompanied by a reduction in large LDL particles. Each of the features of diabetic dyslipidemia has been associated with increased risk of cardiovascular disease, the leading cause of death in type 2 diabetics. Increasing evidence in both experimental and clinical studies suggests that oxidative stress plays a major role in the pathogenesis of both types of diabetes mellitus. Free radicals are formed disproportionately in diabetes by glucose oxidation, nonenzymatic glycation of proteins, and the subsequent oxidative degradation of glycated proteins. Abnormally high levels of free radicals and the simultaneous decline of antioxidant defense mechanisms can lead to damage of cellular organelles and enzymes, increased lipid peroxidation, and development of insulin resistance. These consequences of oxidative stress can promote the development of complications of diabetes mellitus. Changes in oxidative stress biomarkers, including superoxide dismutase, catalase, glutathione reductase, glutathione peroxidase, glutathione levels, vitamins, lipid peroxidation, nitrite concentration, nonenzymatic glycosylated proteins, and hyperglycemia in diabetes, and their consequences, are discussed in this review. In vivo studies of the effects of various conventional and alternative drugs on these biomarkers are surveyed. There is a need to continue to explore the relationship between free radicals, diabetes, and its complications, and to elucidate the mechanisms by which increased oxidative stress accelerates the development of diabetic complications, in an effort to expand treatment options.

KEY WORDS- Diabetes mellitus, Dyslipidemia, Oxidative stress, Free radicals, Antioxidants

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INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia and insufficiency of secretion or action of endogenous insulin. Although the etiology of this disease is not well defined, viral infection, autoimmune disease, and environmental factors have been implicated[1–5]. While exogenous insulin and other medications can control many aspects of diabetes, numerous complications affecting the vascular system, kidney, retina, lens, peripheral nerves, and skin are common and are extremely costly in terms of longevity and quality of life. Increased oxidative stress is a widely accepted participant in the development and progression of diabetes and its complications[6–8]. Diabetes is usually accompanied by increased production of free radicals[7–10] or impaired antioxidant defenses[11–13]. Mechanisms by which increased oxidative stress is involved in the diabetic complications are partly known, including activation of transcription factors, advanced glycated end products (AGEs), and protein kinase C. This review focuses on recent experimental studies of diabetes and drug interventions done within the context of in vivo assay systems. There are also myriad in vitro experiments and clinical studies which deserve a review of their own.

Each of the features of diabetic dyslipidemia has been associated with increased risk of cardiovascular disease, the leading cause of death in type 2 diabetics. Although attempts at decreasing cardiovascular disease morbidity and mortality have usually been focused on lowering LDL cholesterol, it is important to consider other features of the abnormal lipid profile typical of type 2 diabetes that may contribute to the disease process, particularly TG rich remnants and small, dense LDL. These factors are not detected by standard lipid testing, but part of the benefits observed in coronary artery disease-prevention trials may be because of improvements of these parameters. The cluster of lipid abnormalities associated with type 2 diabetes is defined by increases in triglyceride (TG) and small, dense low-density lipoprotein (LDL) concentrations and decreases in high-density lipoprotein (HDL) cholesterol. Plasma LDL cholesterol levels are generally normal because the increase in the number of small, dense LDL particles is accompanied by a reduction in large LDL particle[14].

Importantly, insulin resistance and type 2 diabetes often occur along with other metabolic abnormalities such as obesity, hypertension, and hypercoagulability This grouping of abnormalities has been referred to as the metabolic syndrome or ‘‘syndrome X’’ and has been associated with an increased risk for atherosclerosis[15,16]. Other abnormalities may be associated with poorly controlled diabetes, for example, glycosylation of lipoproteins and other proteins involved in lipoprotein metabolism.

OXIDATIVE STREES IN DIABETES MELLITUS

Oxidative stress depicts the existence of products called free radicals and reactive oxygen species (ROS) which are formed under normal physiological conditions but become deleterious when not being quenched by the antioxidant systems[17]. There are convincing experimental and clinical evidences that the generation of reactive oxygen species is increased in both types of diabetes and that the onset of diabetes is closely associated with oxidative stress[18,19]. Free radicals are formed disproportionately in diabetes by glucose autoxidation, polyol pathway and non-enzymatic glycation of proteins[20]. Abnormally high levels of free radicals and simultaneous decline of antioxidant defense systems can lead to the damage of cellular organelles and enzymes, increased lipid peroxidation and development of complications of diabetes mellitus[21]. Free radicals may play an important role in the causation and complications of diabetes mellitus[22]. In diabetes mellitus, alterations in the endogenous free radical scavenging defense mechanisms may lead to ineffective scavenging of reactive oxygen species, resulting in oxidative damage and tissue injury. Oxidative stress is currently suggested as mechanism underlying diabetes and diabetic complications[23]. Enhanced oxidative stress and changes in antioxidant capacity, observed in both clinical and experimental *diabetes mellitus*, are thought to be the etiology of chronic diabetic complications [24].

In recent years, much attention has been focused on the role of oxidative stress, and it has been reported that oxidative stress may constitute the key and common event in the pathogenesis of secondary diabetic complications[25]. Free radicals are continually produced in the body as a result of normal metabolic processes

and interaction with environmental stimuli. Oxidative stress results from an imbalance between radical-generating and radical-scavenging systems, i.e. increased free radical production or reduced activity of antioxidant defenses or both. Implication of oxidative stress in the pathogenesis of diabetes is suggested, not only by oxygen free-radical generation, but also due to nonenzymatic protein glycosylation, auto-oxidation of glucose[26], impaired glutathione metabolism[27], alteration in antioxidant enzymes[28], lipid peroxides formation and decreased ascorbic acid levels[29]. In addition to GSH, there are other defense mechanisms against free radicals like the enzymes superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase (CAT) whose activities contribute to eliminate superoxide, hydrogen peroxide and Hydroxyl radical[30]. The level of these antioxidant enzymes critically influences the susceptibility of various tissues to oxidative stress and is associated with the development of complications in diabetes. Also this is particularly relevant and dangerous for the beta islet, which is among those tissues that have the lowest levels of intrinsic antioxidant defenses[31, 32, 33,34].

BIOMARKERS OF OXIDATIVE STRESS

Lipid Peroxidation

Diabetes produces disturbances of lipid profiles, especially an increased susceptibility to lipid peroxidation[35], which is responsible for increased incidence of atherosclerosis[36], a major complication of *diabetes mellitus*[37]. An enhanced oxidative stress has been observed in these patients as indicated by increased free radical production[38], lipid peroxidation and diminished antioxidant status. Hydroperoxides have toxic effects on cells both directly and through degradation to highly toxic hydroxyl radicals. They may also react with transition metals like iron or copper to form stable aldehydes such as malondialdehydes that will damage cell membranes. Peroxyl radicals can remove hydrogen from lipids, producing hydroperoxides that further propagate the free-radical pathway[39].

Glutathione Peroxidase and Glutathione Reductase

Recent studies of the effects of various antioxidants on glutathione concentrations found that glutathiobne are decreased in the liver[40], kidney[41], pancreas[42], plasma, red blood cells[43], nerve, and precataractous lens[44] of chemically induced diabetic animals. However, there is also some contradictory evidence of increased glutathione concentration in diabetic rat kidney and lens[45]. Levels of glutathione are reported to be normalized by vanadyl, dehydroepiandrosterone (DHEA), oil of *Eruca sativa* seeds, nicotinamide, L-arginine or nitroprusside[46], melatonin, and melatonin plus desferrioxamine, when these antioxidants are given prior to or at the same time as the diabetogen. However, antioxidants that fail to reverse the effects of established diabetes on glutathione levels include coenzyme Q10, quercetin, piperine, isoeugenol, DHEA, melatonin[47], and taurine.

Catalase

Catalase, located in peroxisomes, decomposes hydrogen peroxide to water and oxygen. Catalase activity is consistently found to be elevated in heart and aorta, as well as brain of diabetic rats. In contrast to decreased renal, hepatic and red blood cell catalase activity, in liver and kidney of diabetic animals is increased[48].

These alterations of catalase activity due to diabetes are normalized by treatment with captopril, aminoguanidine, melatonin (in liver), acetylsalicylic acid, DHEA, probucol, lipoic acid, and stobadine, all of which were administered before or at the same time as the diabetogen. By contrast, treatment of established diabetes of 4 weeks or more does not reverse or normalize diabetic effects. For example, no reversals are seen after treatment with melatonin, quercetin, coenzymeQ10, piperine, isoeugenol, gemfibrozil, or combined vitamin C, vitamin E, and carotene[49]. Finally, effects of diabetes on cardiac catalase activity are exacerbated by treatment with quercetin[50] or coenzyme Q10 .

Superoxide Dismutase (SOD)

SOD converts superoxide anion radicals produced in the body to hydrogen peroxide, thereby reducing the likelihood of superoxide anion interacting with nitric oxide to form reactive peroxynitrite. The effect of diabetes on the activity of SOD is erratic, with no discernable pattern based on gender or species of animal, or duration of diabetes, or tissue studied. Renal activity, for example, is within normal levels at 3 and 6 weeks after STZ, lower than normal at 6 weeks post-STZ, but also elevated after 6 or 12 weeks of diabetes[51]. In liver, SOD activity is depressed by the third or fourth week of diabetes, but is either normal or elevated 8 weeks after STZ. Kaul *et al*. found cardiac SOD activity decreased after 4 or 8 weeks of diabetes, but Stefek *et al*. reported elevated cardiac activity at 32 weeks, and activity in aorta seems to be unaffected by diabetes. Likewise, activity may be elevated or decreased in red blood cells, decreased in retina and plasma, and increased in pancreas. Alterations of SOD activity in diabetic animals are normalized by probucol, captopril[52], DHEA, lipoic acid, melatonin, boldine, nitecapone, and stobadine , all of which were administered prior to or concomitant with the diabetogen. When treatment is initiated in animals with well established diabetes, coenzyme Q10 and piperine normalize renal activity, but no reversal of diabetic effects is seen with melatonin, aminoguanidine or desferrioxamine, or gemfibrozil. Treatment with vitamin C, vitamin E, and beta carotene for 8 weeks elevates hepatic SOD activity in diabetic rats, which is normal without treatment[53].

Vitamins

Vitamin E, a component of the total peroxyl radical-trapping antioxidant system, reacts directly with peroxyl and superoxide radicals and singlet oxygen and protects membranes from lipid peroxidation. The deficiency of vitamin E is concurrent with increased peroxides and aldehydes in many tissues. There have been conflicting reports about vitamin E levels in diabetic animals and human subjects. Plasma and/or tissue levels of vitamin E are reported to be unaltered, increased, or decreased[54] by diabetes. Discrepancies among studies in terms of preventive or deleterious effects of vitamin E on diabetes induced vascular aberrations may arise from the variety of examined blood vessels or the administered dose of vitamin E.

Nitrite Level

Increased oxidative stress and subsequent activation of the transcription factor NF-kappa B have been linked to the development of late diabetic complications. NF-kappa B enhances nitric oxide production, which is believed to be a mediator of islet beta-cell damage. Nitric oxide may react with superoxide anion radical to form reactive peroxyl nitrite radicals. A number of studies are continuing to examine the role of nitric oxide in diabetes mellitus. For example, subnormal hepatic nitric oxide concentrations in STZ-diabetic rats are restored after melatonin treatment to levels significantly higher than normal. And, although elevated levels of nitric oxide levels in kidneys of 3 week diabetic rats are further enhanced by *S*-methyl-L-thiocitrulline treatment, administration of losartan along with *S*-L-thiocitrulline for 3–5 weeks normalizes the nitric oxide levels implying that angiotensin II is an important modulator of nitric oxide pathway in diabetes[55]. On the other hand, nitric oxide levels in plasma are decreased in alloxan-diabetic rats, an effect that can be abrogated by prior and simultaneous administration of L-arginine, a precursor of nitric oxide[56].

DIABETIC DYSLIPIDEMIA

Association of Insulin Resistance and Hepatic Very Low-Density Lipoprotein Secretion

Resistance to insulin may contribute to the atherogenic dyslipidemia of diabetes by increasing the hepatic secretion of very low-density lipoprotein (VLDL). Metabolic tracer studies have documented overproduction of VLDL TG in insulin-resistant patients with hypertriglyceridemia[57]. Additionally, several recent studies demonstrate increased secretion of apolipoprotein (apo) B in type 2 diabetes[58]. The increased secretion of apoB-containing lipoprotein particles may be the result of increased free fatty acid (FFA) flux to the liver[59]. Also, insulin-resistant persons have been shown to lack sensitivity to the suppressive effects of insulin on

apoB secretion[60]. This resistance to insulin may be at the level of the regulation of apoB degradation or inhibition of microsomal triglyceride transfer protein activity, a protein identified as a key component of the VLDL assembly process[61]. Because of increased endogenous secretion of apoB-containing lipoprotein particles, the increased plasma levels of TG can drive a metabolic process that results in reduced HDL cholesterol levels and LDL particles that are smaller and more dense. In a substrate-driven reaction, cholesterol ester transfer protein (CETP) exchanges VLDL TG for HDL cholesterol. TG-rich HDL particles are hydrolyzed by hepatic lipase (HL) and, as a result, are rapidly catabolized and cleared from plasma[62]. HDL particles are heterogeneous and are classified by particle sizes that range from small, dense HDL3 to larger HDL2 particles[63]. Typically, the reduced plasma levels of HDL in patients with type 2 diabetes manifest as reductions in the HDL2 subspecies with relative or absolute increases in HDL3. Increased concentrations of VLDL in plasma also result in the increased production of small, dense LDL particles. As many as seven distinct LDL subspecies, which differ in metabolic behavior and pathologic roles, have been identified (Fig. 1) [64]. Plasma VLDL levels correlate positively with increased density and decreased size of LDL, and increased concentrations of small, dense LDL in turn have been shown to be associated with reduced plasma HDL levels. Importantly, the residence time of small, dense LDL in plasma may be prolonged, given their relatively reduced affinity for the LDL receptor[64].

Effects of Insulin Resistance on Lipid and Lipoprotein Clearance

Impaired clearance of lipid and lipoprotein particles represents another important mechanism by which insulin resistance can lead to abnormal lipid profiles. Insulin resistance has been associated with impaired lipoprotein lipase (LPL) and increased HL activity[65]. LPL is synthesized in muscle and adipose tissue and interacts with TG-rich lipoproteins in capillary endothelial cell beds where it hydrolyzes TG into FFA. The resultant lipoprotein particles are reduced in core volume and surface and are either cleared through remnant removal pathways or moved along the delipidation pathway where they are converted into less buoyant LDL particles. HL is responsible for the hydrolysis of phospholipids in LDL and HDL particles; its increased activity in the setting of insulin resistance has been associated with smaller and denser LDL particles and a decrease in HDL2 particles because the latter are more rapidly cleared from plasma. Lipid effects on insulin sensitivity Insulin resistance and type 2 diabetes mellitus are often characterized by increased plasma FFA concentrations because of increased adipose tissue efflux or impaired insulin-mediated skeletal muscle uptake[66]. The fact that FFA levels are elevated in individuals with impaired glucose tolerance suggests that insulin resistance associated with increased FFA levels occurs before the onset of hyperglycemia. Elevations of plasma FFA concentrations may interfere with glucose metabolism by impairing glucose uptake and by use in muscle[67]. In addition, infusion of lipid emulsions and heparin to increase ambient FFA concentrations has been shown to increase gluconeogenesis in patients with insulin resistance and type 2 diabetes; however, glycogenolysis was simultaneously dampened in these patients so that net glucose production remained unchanged. Increased FFA concentrations in plasma may also impair hepatic insulin extraction, thereby contributing to peripheral hyperinsulinemia in insulin resistance. At the level of the pancreatic b-cell, FFA acutely increases glucosestimulated insulin secretion, whereas chronic exposure has been associated with relatively impaired insulin secretion[68]. Finally, in the presence of insulin resistance, FFA in the form of TG is deposited in muscle and the liver, heart, and pancreas where it may impair organ function. Notably, agents that lower elevated FFA, such as the thiazolidinediones (TZDs), have been shown to improve insulin sensitivity in muscle, liver, and adipose tissue[69].

CONCLUSIONS

STZ- or alloxan-induced diabetes in rats represents well-established animal models of type 1 insulin dependent, diabetes mellitus. Increased production of high levels of oxygen free radicals has been linked to glucose oxidation and nonenzymatic glycation of proteins which contribute to the development of diabetic complications. Protective effects of exogenously administered antioxidants have been extensively studied in animal models within recent years, thus providing some insight into the relationship between free radicals,

diabetes, and its complications. In vitro and clinical studies may provide additional useful ways to probe the interconnections of oxidant stress and diabetes, and there is a need to continue to explore the mechanisms by which increased oxidative stress accelerates the development of complications in diabetes.

Abnormal lipid metabolism often presents in patients with type 2 diabetes. Resistance to insulin likely underlies the changes that occur in lipid parameters. Increased FFA vailability can drive the secretion of TG rich lipoproteins from the liver, and this increased TG substrate can lead to reductions in HDL cholesterol as well as the conversion of LDL particles into particles that are smaller and denser. The combination of elevated TG, reduced HDL cholesterol, and smaller and denser LDL particles typifies the dyslipidemia associated with type 2 diabetes and insulin resistance. Each of these lipid changes has been independently associated with increased cardiovascular disease risk. A variety of treatment options exist, and changes in lifestyle and behaviors known to adversely alter lipid metabolism should be key components of any program designed to manage atherogenic dyslipidemia. Effective pharmacologic therapies include lipid-lowering agents, such as statins, fibrates, and niacin, as well as antidiabetic agents, such as the thiazolidinediones and metformin. Treatment with these agents alone or in combination has been shown to correct the lipid abnormalities associated with type 2 diabetes and reduce the risk of cardiovascular disease.

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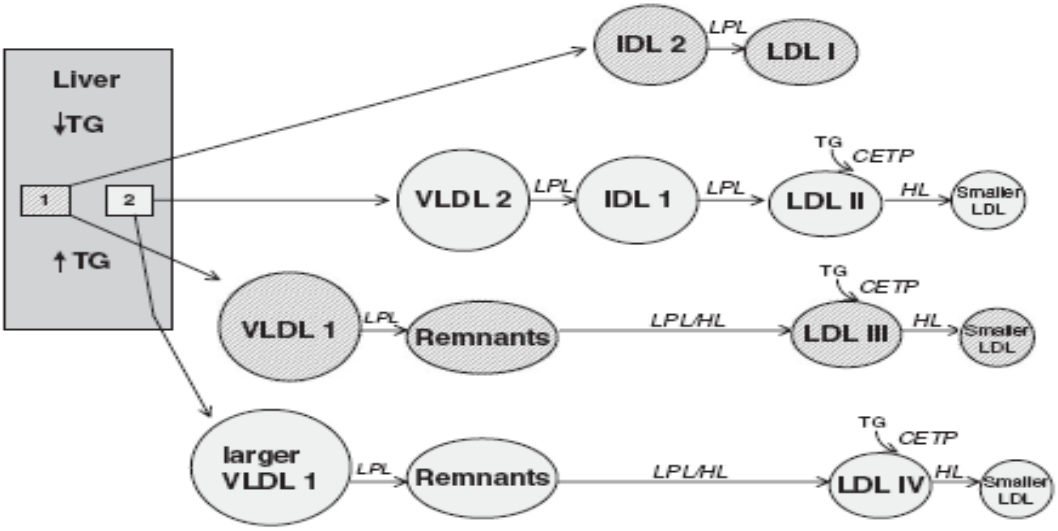

Figure 1. Hypothetical metabolic scheme incorporating proposed pathways for the production of major LDL subclasses I, II, III, and IV. The properties of triglyceride-rich lipoproteins secreted by the liver are determined by the operation of multiple pathways (1 and 2) and by hepatic TG availability. In pathway 1, triglyceride-rich VLDL-1 and triglyceride-poor IDL-2 particles are coordinately produced. VLDL-1 production results from a discrete quantity of lipid on a precursor particle. Lipolysis of VLDL-1 yields remnants, which in turn yield LDL-III by hepatic lipase. Further remodeling of these particles may occur by CETP-mediated triglyceride enrichment and hepatic lipase-mediated lipolysis. Pathway 2, which results in the production of VLDL-2, is distinct from pathway 1 and gives rise to IDL-1 and LDL-II by lipolysis. Further processing by CETP-mediated transfer of triglycerides into LDL-II and lipolysis by hepatic lipase yields smaller and denser LDL products. CE, cholesteryl esters; LPL, lipoprotein lipase. (From Berneis KK, Krauss RM. Metabolic origins and clinical significance of LDL heterogeneity. J Lipid Res 2002;43:1363–79; with permission.)

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