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Forum Review

Oxidative Stress, Glucose Metabolism, and the Prevention of Type 2 Diabetes: Pathophysiological Insights

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ABSTRACT

With the rising epidemic of type 2 diabetes worldwide, including the United States, the death and disability due to the suboptimal control of cardiovascular disease associated with this epidemic has made prevention of type 2 diabetes emerge as a primary strategic intervention. Several modalities have been assessed in large randomized controlled trials for diabetes prevention such as lifestyle interventions and various pharmacologic agents. Included in these agents are metformin, thiazolidinediones, acarbose, angiotensin converting enzyme inhibitors, as well as angiotensin receptor blockers. Abrogation of oxidative stress appears to be a common soil hypothesis that explains the favorable effects of these agents on glucose metabolism, including the prevention of diabetes and its complications. This comprehensive review highlights the role of oxidative stress in the pathogenesis of diabetes, with emphasis on the major clinical trials conducted on prevention of type 2 diabetes. *Antioxid. Redox Signal.* 9, 911–929.

INTRODUCTION

Diabetes mellitus is a major cardiovascular and renal risk factor and is ranked as the fifth leading cause of death worldwide (237). The increasing prevalence of diabetes has led to the increased risk of premature cardiovascular disease and death (31), prompting elaborate strategies to reduce its incidence. Despite public health efforts, diabetes remains a serious cause of morbidity and mortality. In 2002, diabetes was the sixth leading cause of death listed on United States death certificates and a leading cause of blindness and end stage renal disease in adults (42).

Estimates by the American Diabetes Association (ADA) indicate that 21 million people have diabetes and another 41 million are prediabetic, putting them at high risk for developing the disease in the near future. In fact, an estimated 1.5 million Americans develop diabetes every year. ADA also estimates the cost of diabetes, including such expenses as disability payments and lost days at work, to be at least $132 billion a year, as of 2002 (42). The enormity of this epidemic with its associated complications, morbidity, and mortality has initiated evidence-based efforts for its reduction (58, 63, 198).

The World Health Organization (WHO) estimates that >180 million people worldwide have diabetes, with its rate set to increase as childhood obesity rates soar worldwide. WHO estimates that 10% of school age children are overweight and >22 million children under the age of 5 years are obese or overweight. This number is likely to more than double by 2030. WHO also projects that death from diabetes will increase by >50% in the next 10 years without effective preventive strategies (118, 232).

Accumulating evidence indicates that oxidative stress plays a key role in the pathogenesis of diabetic microvascular and macrovascular complications (85), and endothelial dysfunction is an early marker of such damage (36, 85). Several *in vitro* (60, 271) and *in vivo* (19, 44, 178, 278) studies have shown that the acute effects of hyperglycemia can be reversed by antioxidants, thereby suggesting a role of free radicals in producing endothelial dysfunction caused by hyperglycemia (271).

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This is a comprehensive review of oxidative stress and its role in diabetes pathogenesis, highlighting the role of oxidative stress in light of several clinical trials conducted on prevention of type 2 diabetes.

OXIDATIVE STRESS

Oxidative stress is defined as tissue injury resulting from a disturbance in the equilibrium between the production of reactive oxygen species (ROS), also known as free radicals, and antioxidant defense mechanisms (24, 103, 256). Under physiologic conditions, the antioxidant defenses are able to protect against the deleterious effects of free radicals, but under conditions where either the free radical formation is increased or the antioxidant defenses are inactivated, accumulation of free radicals ensues, leading to cellular and tissue damages (24, 96, 103, 256).

Although the history of oxygen toxicity in laboratory animals dates back to 1878 (148), the first description of free radicals came in 1894, when presumably, Fenton reported the first free radical reaction (77). Oblivious to the existence of a moiety called "free radicals" at the time, Fenton described the generation of a hydroxyl free radical as a result of the reduction of hydrogen peroxide with ferrous iron in a solution of tartaric acid—a classic mechanism known as the "Fenton reaction".

$$Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + HO^- + {}^{\bullet}OH$$

The first organic free radical, however, was described by Moses Gomberg, in 1900, when he published the results on the reaction of triphenylmethyl halides with metals leading to the formation of triphenylmethyl radical ($Ph_3C^{\bullet}$) (87).

The role of free radicals in disease processes such as cell injury, cancer, and aging, was originally recognized by Harman (106, 107) who hypothesized the *in vivo* generation of free radicals as a major contributor in the pathogenesis of disease. The discovery of superoxide dismutase, in 1969, established the role of free radicals in biological systems (148). Subsequently, extensive research has established the importance of free radicals in aging (106, 107), as well as several pathological conditions including coronary artery disease (CAD), stroke, ischemic dementia (86, 217, 262), carcinogenesis (8, 45), neurodegenerative disorders (149), pulmonary disease (226), renal disease (181) and diabetes mellitus, which will be discussed in detail.

Free radicals (reactive oxygen species: ROS)

A free radical is defined as any atom or molecule that contains one or more unpaired electrons (101). The presence of unpaired electrons increases the reactivity of an atom or molecule, thereby making it much more reactive than a corresponding nonradical. Free radicals have been known to have deleterious as well as beneficial effects (286).

Free radicals are generated in huge amounts as byproducts of common physiologic reactions, as well as end products for specific defense purposes, such as neutrophil activation. Additional sources of free radical acquisition include ozone, nitrogen dioxide, and electromagnetic radiation (24).

Numerous free radicals are known to perform various functions in the body (Fig. 1). Common examples of free radicals include but are not limited to hydroxyl ($^{\bullet}OH$), superoxide ($O_2^{-\bullet}$), nitric oxide ($NO^{\bullet}$), hydrogen peroxide (H_2O_2), peroxyl ($ROO^{\bullet}$), alkoxyl ($RO^{\bullet}$), thiyl ($RS^{\bullet}$), and peroxynitrite ($ONOO^-$) (24, 148, 292). Superoxide, nitric oxide, and hydrogen peroxide play an important role in normal physiology, but at the same time are well known to be responsible for accelerating the aging process and cell degeneration in disease states (292).

The earliest description of hydroxyl ($^{\bullet}OH$) radical generation comes from the Haber–Weiss reaction (102), described in the1930s, which showed the conversion of superoxide to the hydroxyl radical (Fig. 1). This extremely potent radical has a half-life, in aqueous solution, of less than 1 ns (218). It is generated in the human body by splitting of water molecules as a result of ionizing radiations from the environment and photolytic decomposition of alkylhydroperoxides (101, 286).

Superoxide (O_2^-) is generated in the body by mitochondria when reduced nicotinamide adenine dinucleotide (NADH) is oxidized to nicotinamide adenine dinucleotide $(NAD)^+$. Superoxide (O_2^-) could also be a byproduct of direct reactions of various molecules with oxygen, such as catecholamines and tetrahydrofolates (103, 166, 292) (Fig. 1). Although generally regarded as weakly reactive, superoxide (O_2^-) plays an important role in the immune system, as it is produced by activated phagocytes.

Nitric oxide ($NO^{\bullet}$) is generated through nitric oxide synthase (NOS) and is present in the body in large quantities, acting as a major signaling molecule at the endothelial level in multiple physiological processes (7, 23, 59). $NO^{\bullet}$ is also poorly reactive and has a half-life of only a few seconds in an aqueous environment (50).

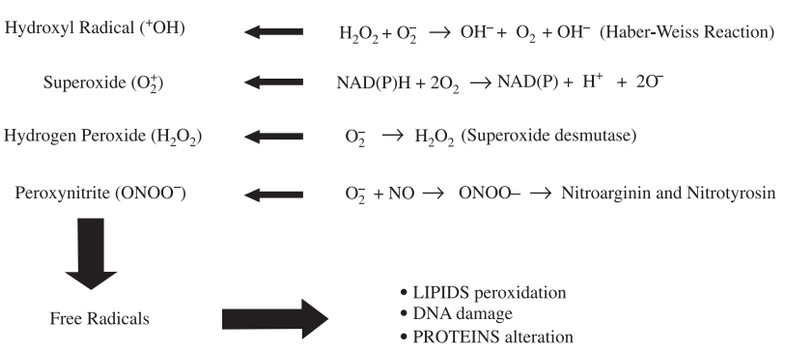

FIG. 1. Origins of main oxygen and organic free radicals and effects on cells.

There is strong evidence supporting the role of metals such as iron, copper, chromium, arsenic, nickel, cadmium, cobalt, and vanadium, causing free radical-induced damage in biological systems, thereby enhancing the process of carcinogenicity (163, 286).

Free radical-induced cell injury

The presence of an odd number of electrons makes free radicals unstable, thereby rendering them highly reactive. Although this reactivity varies between different radicals, free radicals continuously react to the nearby molecules, accepting or donating electrons, in order to achieve a stable state. The majority of these reactions are either between a radical and a nonradical, and a few that occur between two free radicals.

Common examples of reactions between radicals and nonradicals include lipid peroxidation, protein damage (24, 100, 261), and DNA damage that can result from the presence of free radicals in the immediate vicinity of DNA, for example, the conversion of guanine into 8-hyroxyguanine and other products, by hydroxyl radicals (21, 29, 61, 100). The combination of superoxide (O_2^{-}) and nitric oxide (NO$^{\bullet}$), leading to the formation of peroxynitrite ($ONOO^{-}$), however, is an example of a reaction between two radicals (Fig. 1). Peroxynitrite ($ONOO^{-}$), at physiological pH, is injurious to proteins directly and it further decomposes into toxic products like nitrogen dioxide gas ($NO_2^{\bullet}$), hydroxyl radical ($^{\bullet}OH$), and nitronium ion (NO_2^{+}) (20).

Oxidative stress is a state of imbalance between the generation of free radicals and the antioxidant defense mechanisms. Antioxidants enhance the indigenous ability to protect against the free radical damage. These antioxidants are defined as any compound that can donate at least one hydrogen atom to a free radical, resulting in the termination of radical chain reactions (292).

Examples of antioxidants include Vitamin E, beta-carotene, co-enzyme Q, and the enzymes dismutase, peroxidase, and catalase (24). The antioxidants, such as ceruloplasmin, transferrin, and albumin, defend against the harmful effects of free radicals by preventing the initiation of the free radical chain reaction due to their ability to bind metal ions (263, 292).

Measurement of oxidative stress

As discussed earlier, there is strong evidence that oxidative stress plays a role in the pathogenesis of different diseases (8, 45, 86, 106, 107, 149, 181, 217, 226, 262), including diabetes and its complications, but to date there is no direct measure of oxidative stress in biological systems (130). There are several biomarkers that have been identified as measure of oxidative damage at the molecular level, such as isoprostane assays (40, 195), transcriptional activation assays (221), glutathione assays (247), malondialdehyde (MDA), thiobarbituric acid–reactive substances (TBARS) and lipid peroxidation (126), superoxide dismutase, 8-hydroxy-deoxyguanosine (280), catalase (306), 5,5-dimethyl-1-pyrroline-*N*-oxide (94), human myeloperoxidase (144), human plasma lactoferrin (13), among several others. New and improved methods, such as electron spin resonance (ESR) (205), are being developed and perfected to measure oxidative stress more reliably and accurately. Recently, researchers have shown increased levels of xanthine and NADPH oxidase in human coronary artery disease using ESR (260).

A comprehensive discussion on the measurement of oxidative stress is beyond the scope of this review.

Human disease and oxidative stress

Free radical and oxidative stress have become an integral part of understanding the underlying mechanism of disease in today's modern medicine. With the advances in cellular and molecular research, there is considerable and increasing evidence linking oxidative stress and various human diseases. This is hardly surprising given the fact that oxidative metabolism is an indispensable part of cell physiology. In fact, oxidative stress is a well-documented component of several diseases such as acquired immunodeficiency syndrome (AIDS) (78), adult respiratory distress syndrome (ARDS) (89), Alzheimer's disease (169), amyotrophic lateral sclerosis (52), arthritis (285), diabetes mellitus (186), emphysema (294), gastric ulcers (55), glomerulonephritis (254), heart disease (212), hemochromatosis (116), hypertension (141), intestinal ischemia (216), lupus erythematosus (192), multiple sclerosis (279), muscular dystrophy (227), organ transplantation (25, 199), Parkinson disease (52), preeclampsia (120), stroke (15), vasculitis (295), and many others.

OXIDATIVE STRESS AND GLUCOSE METABOLISM

Role of oxidative stress in the etiology of diabetes

Diabetes mellitus is a metabolic disorder characterized by hyperglycemia resulting from absolute or relative deficiency and/or insensitivity to endogenous insulin. Traditionally, it has been classified into two forms, type 1, which is caused by autoimmune destruction of pancreatic β-cells, and type 2, which is known to be multifactorial, resulting from combination of various factors such as impaired fatty acid metabolism, central fat deposition leading to insulin resistance (186), β-cell secretory defect, and obesity (17, 80). This view, however, is currently being challenged by the accelerator hypothesis that argues that type-1 and type-2 diabetes are the same disorder of insulin resistance set against different genetic backgrounds (147).

Evidence has long existed regarding the relationship between oxidative stress and diabetes mellitus (207, 248, 302). The role of oxidative stress in the etiology of diabetes was recognized in the early 1980s, when streptozocin and alloxan (175, 187) were used in experimental animals to induce diabetes. These agents were shown to result in diabetes via mechanisms involving either an increase in the production of free radicals or a decrease in antioxidant defenses (302).

Simoneau and colleagues, in 1995, reported for the first time the relationship between mitochondrial dysfunction and diabetes (258). Since then, research has suggested the role of oxidative stress and mitochondrial dysfunction in the pathogenesis of type 2 diabetes, specifically in intrauterine growth retardation (IUGR) (139, 257). In growth-retarded fetuses, low oxygen levels generate the production of free radicals due to decreased activity of the electron transport chains (46, 70), leading to DNA,

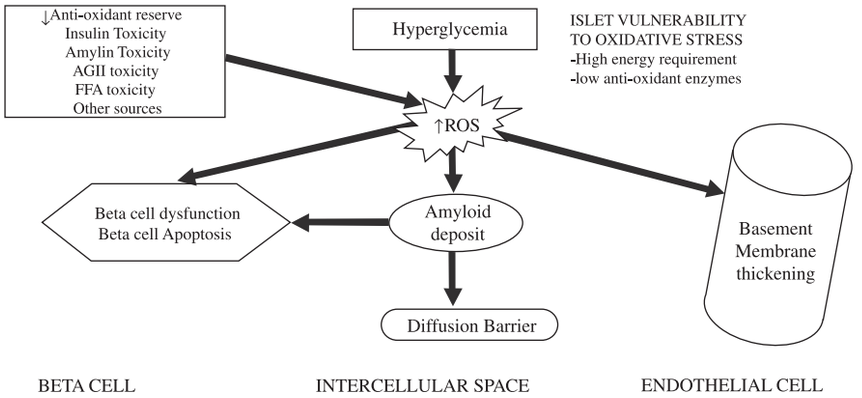

FIG. 2. Effect of oxidative stress on islet beta cells. The islet beta cells are particularly vulnerable to the effect of reactive oxygen species originating from hyperglycemia and other related factors. Oxidative stress may cause an unfolding of the native secondary structure of amylin with subsequent refolding leading to deposit of islet amyloid, creating a secretory and absorptive defect within the islet in addition to space occupying lesion. AGII, angiotensin II; FFA, free fatty acids; ROS, reactive oxygen species.

protein, and mitochondrial damage—decreasing energy production (257). This mitochondrial dysfunction has lethal effects on β-cell function, which has a high energy requirement and depends upon normal ATP production for insulin proliferation and secretion (10, 176, 188, 200, 204, 215, 252). Another reason for the increased β-cell vulnerability comes from the fact that antioxidant enzyme expression is very low in pancreatic islets (162, 275, 276). Furthermore, there is considerable evidence for free radical-induced inhibition of glucose-mediated insulin secretion, apoptosis, and diminished β-cell gene expression (62, 129, 135, 136, 137, 171, 194, 244) (Fig. 2).

Evidence suggests that mitochondrial dysfunction can further lead to oxidative stress via various mechanisms (257). Animal studies have shown that muscle mitochondria in IUGR have chronically decreased ATP production, causing compromised glucose transporter isoform-4 (GLUT-4) recruitment to the cell surface, glucose transport, and glycogen synthesis. This further leads to insulin resistance and hyperglycemia of type 2 diabetes (253). Human studies using $_{13}C$ and $_{31}P$ magnetic resonance spectroscopy in offsprings of parents with type 2 diabetes have suggested mitochondrial dysfunction as a possible contributing factor to the development of diabetes (222).

The polyol pathway is an established contributor to oxidative stress (159). The enzyme aldose reductase, which is responsible for detoxification of aldehydes to alcohols, in the presence of cellular hyperglycemia, reduces glucose to sorbitol, which is oxidized to fructose, consuming large quantities of NADPH, leading to its depletion (Fig. 3). The depletion of NADPH leads to oxidative stress due to the fact that it is a major cofactor for glutathione regeneration and a known antioxidant defense at the cellular level. Additionally,

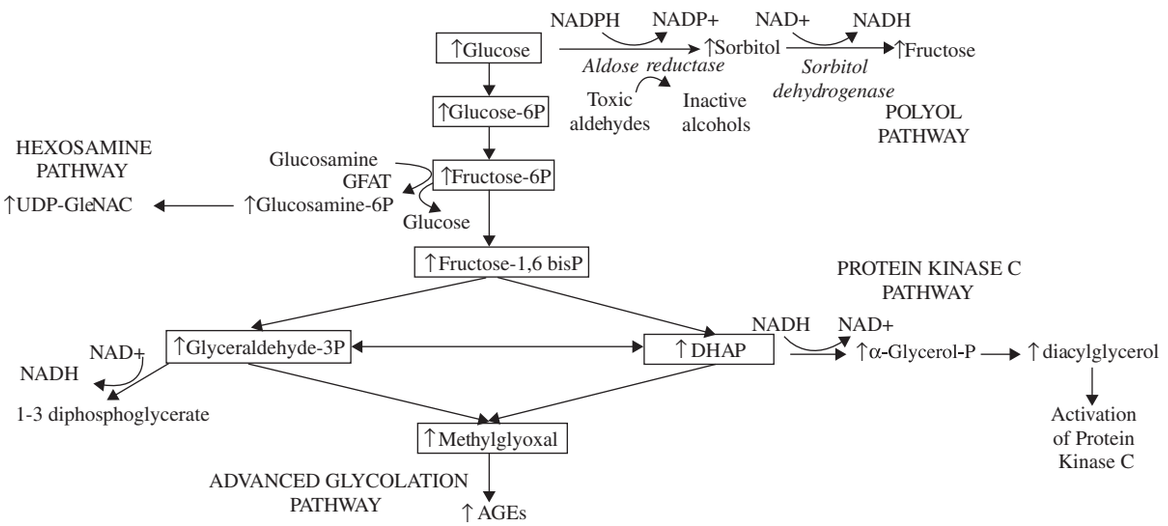

FIG. 3. Major pathways of hyperglycemia-induced oxidative stress. Hyperglycemia leads to increased flux through polyol pathway with subsequent NADPH depletion; increased flux through hexosamine pathway with subsequent gene expression alterations, increased intracellular production of AGE precursors with subsequent direct intra- and extracellular pathophysiologic consequences, and activated protein kinase C affecting genes expression. AGE, advanced glycation end products; DHAP, dihydroxyacetone phosphate; GFAT, glutamine:fructose-6 phosphate amidotransferase; NAD, nicotinamide-adenine dinucleotide; NADH, reduced nicotinamide-adenine dinucleotide; NADP+, oxidized nicotinamide-adenine dinucleotide phosphate; NADPH, nicotinamide-adenine dinucleotide phosphate; UDP Glc-NAC, uridine diphosphate *N*-acetyl glucosamine.

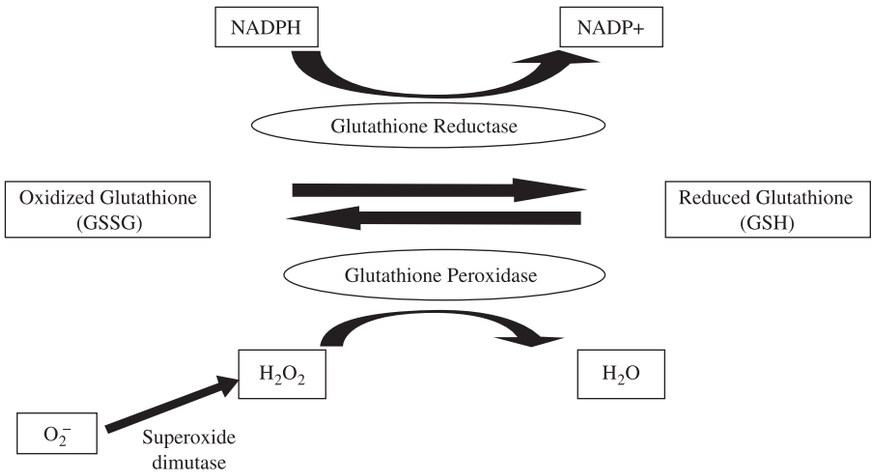

FIG. 4. The glutathione oxidation reduction cycle. H_2O_2, hydrogen peroxide; $NADP^+$, oxidized nicotinamide-adenine dinucleotide phosphate; NADPH, nicotinamide-adenine dinucleotide phosphate; $O_2^{\bullet}$, superoxide.

measures that inhibit the polyol pathway delay the evolution of diabetic complications (67) (Fig. 4).

In addition to the evidence discussed above, implicating oxidative stress as an underlying factor in the pathogenesis of diabetes, there is considerable evidence regarding indirect role of oxidative stress in the etiology of this disease. Chronic hyperglycemia, besides increasing free radical production, is associated with increased production of advanced glycation end products (AGE) and lipid peroxidation products, as well as decreased antioxidant defenses (71, 72) (Fig. 3). Furthermore, animal studies have elucidated a protective role of antioxidants against free radical-mediated injury during short-term hyperglycemic states (97). Numerous nutritional supplements and pharmacologic agents have been shown to improve both insulin resistance and oxidative stress in hyperglycemic states (255).

In diabetes, there is increased generation of pro-oxidants such as cytokines and peroxides (172, 270). Pancreatic islets, having intrinsically low levels of antioxidant enzyme expression (90, 275, 276), are especially susceptible to free radical damage. This, coupled with adverse effects of lipid peroxidation, results in increased islet apoptosis (236) (Fig. 2).

These data collectively highlight the link between diabetes and the imbalance of free radical production and antioxidant defense mechanism. It also provides evidence that oxidative stress plays a key role in diabetic complications (18).

Oxidative stress and metabolic syndrome

Although metabolic syndrome is not included in the defining criteria for diabetes, most people with diabetes have metabolic syndrome and most patients with metabolic syndrome are at risk for developing diabetes.

Metabolic syndrome, initially defined by Reaven in 1988 (229), consists of obesity (abdominal circumference men >40 in and women >35 in), impaired glucose tolerance (fasting plasma glucose ≥100 mg/dL), hypertension (blood pressure ≥130/85 mm Hg), and dyslipidemia characterized by elevated triglycerides (≥150 mg/dL) and low high density lipoprotein (<40 mg/dL) levels (93, 229). All of the individual features of metabolic syndrome are considered to be significant risk factors for cardiovascular disease. This association has recently been termed as cardiometabolic syndrome (CMS), which includes congestive heart failure (CHF), coronary heart disease (CHD), and stroke (108, 110, 158, 202). One of the mechanisms by which CMS results in myocardial injury involves the production of reactive oxygen species and decreased NO resulting from endothelial NO synthase (eNOS) uncoupling (108, 109).

Obesity, one of the key factors of metabolic syndrome, leads to increased oxidative stress caused by reduced availability of NO, thereby leading to increased vascular tone and subsequent hypertension (54). Furthermore, obesity also leads to increased asymmetric dimethylarginine (ADMA) concentrations, which results in eNOS dysfunction as a consequence of its competition for the substrate L–arginine. This causes eNOS uncoupling with increased superoxide production, decreased endothelial nitric oxide, and endothelial dysfunction (111, 165).

Recently it has been shown that there is a positive correlation between body mass index and systemic oxidative stress (140, 211). Furukawa *et al*. demonstrated that a major source of free radicals in plasma is adipose tissue, which subsequently leads to insulin resistance in skeletal muscle and adipose tissue and impaired insulin secretion by β-cells (82). The relationship between obesity and oxidative stress also holds true in nondiabetic subjects (82), making obesity a major player in the pathologic outcomes of metabolic syndrome.

Evidence for the pathogenic role of oxidative stress in essential hypertension is inconclusive (154, 157, 174, 197, 305) despite considerable data supporting the presence of increased free radical production in hypertension. Elevated levels of superoxide, hydrogen peroxide, lipid peroxides, plasma hydrogen peroxide, and decreased superoxide dismutase (SOD) have been observed in hypertensive patients compared to normotensive patients (28, 154, 157, 219).

Free radicals have reactivity with almost all biological substances, the most susceptible of which are polyunsaturated fatty acids which are constituents of cell membranes. These react with the free radicals, leading to lipid peroxidation, a biomarker of oxidative stress (126, 207, 302). Lipid peroxidation is the first step in the generation of oxidized LDL and results in increased production of free radicals and causes platelet activation and increased cardiovascular risk. Oxidized LDL also causes

endothelial damage, macrophage activation and impaired vasodilation (84, 161, 284). Furthermore, in metabolic syndrome, there is impaired antioxidative and anti-inflammatory activity of HDL molecules, leading to elevated systemic oxidative stress as measured by plasma 8-isoprostane levels (105).

The notion that oxidative stress is a major contributor in metabolic syndrome is further supported by the fact that four out of the five criteria (as defined by NCEP/ATP III) are independently associated with increased levels of oxidative stress (14, 140, 207, 230).

Role of oxidative stress in diabetic complications

Hyperglycemia, a characteristic feature of diabetes, predisposes to vascular complications, both microvascular as well as macrovascular, and an early indicator of such damage is endothelial dysfunction (36, 85). These complications result from diverse mechanisms, and oxidative stress has now been suggested to be a common pathway linking these mechanisms to the pathogenesis of diabetic complications (91, 203, 239).

There are four major pathways linking oxidative stress as a contributing factor to the complications of hyperglycemia. These include increased polyol pathway flux, increased advanced glycosylation end (AGE) product formation, activation of protein kinase C, and increased hexosamine pathway flux (33, 64) (Fig. 3). These processes also cause endothelial dysfunction that enhances the development and progression of diabetic complications (60). Furthermore, there is a well-established relationship between diabetes and vascular disease (138). Several clinical trials have established long-term glycemic control as an independent predictor of diabetic vascular complications (156, 272, 283). In addition, insulin has been shown to have anti-inflammatory and antioxidant effects, as evident by its ability to suppress free radical production and p47phox expression—a component of the enzyme complex that produces superoxide free radical (53). These beneficial cardiovascular effects are now being studied in large trials to assess if early insulin therapy would decrease cardiovascular disease in diabetes. Among these is the Outcomes Reduction with Initial Glargine Intervention (ORIGIN) (201).

Cardiovascular disease

Cardiovascular disease is the major cause of morbidity and mortality in diabetes (43). Furthermore, diabetes is now considered a cardiovascular risk equivalent (1, 112, 190). Therefore, diabetic patients who develop myocardial infarctions have poorer prognosis than nondiabetic individuals (79, 98, 119, 125). Diabetes also increases the risk of stroke in diabetic patients by two- to four-fold compared to nondiabetic individuals (99, 177).

The common link in these complications is accelerated atherosclerosis in diabetes (12, 128) where the primary triggers of atherogenesis are insulin resistance and hyperlipidemia, both of which are features of diabetes (12). One of the key mechanisms of premature atherosclerosis in diabetes is the oxidation of low density lipoprotein (LDL) leading to oxidative stress (228) (Fig. 5). Multiple studies have documented the link between diabetes and enhanced LDL oxidative vulnerability (164, 170).

There is increased vascular endothelial free radical production in diabetic subjects, which provides the milieu enhancing the oxidation of LDL (95). As elucidated to earlier, endothelial dysfunction is one of the cardinal features of premature diabetic complications (36, 85, 127). Furthermore, antioxidants have been shown to improve endothelial function, providing indirect evidence for a pathogenic role of oxidative stress in diabetic endothelial dysfunction (224, 259). Increased superoxide production, caused by NADPH oxidase and uncoupled eNOS, is a major contributor to this free radical-mediated injury (128) (Fig. 5).

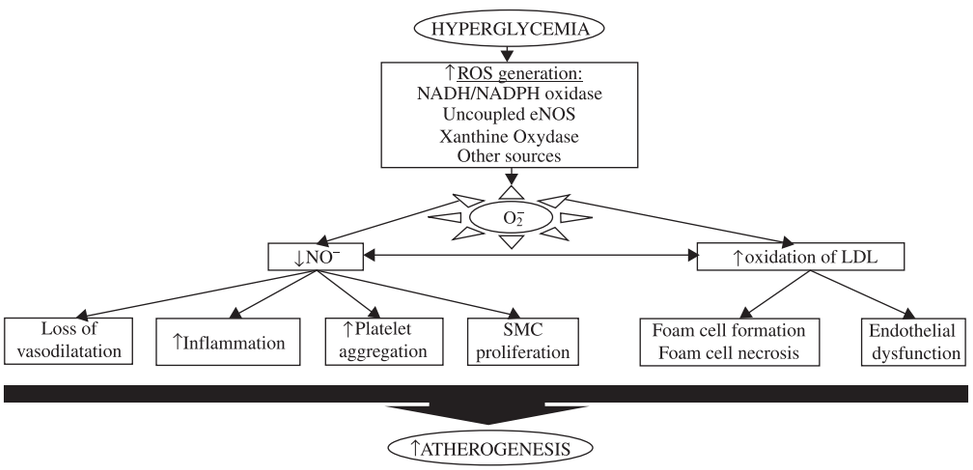

FIG. 5. Role of oxidative stress in diabetes predisposing to atherogenesis. Generation of excess of ROS in diabetes is multifactorial and favors superoxide formation in the superoxide–nitric oxide (NO) balance normally maintaining endothelial function. This oxidative stress will result in increased LDL oxidation and loss of NO beneficial effects resulting in atherosclerosis. eNOS, endothelial nitric oxide synthase; LDL, low-density lipoprotein; NO, nitric oxide; $O_2^{-\bullet}$, superoxide; ROS, reactive oxygen species; SMC, smooth muscle cell.

There is strong evidence linking the increased production of NADPH oxidase in presence of hyperglycemia, oxidized LDL, AGE, and free fatty acids (FFA) (122, 123, 206, 298). Moreover, NADPH oxidase, isolated from vessels of diabetic patients, is more active as evident by increased expression of its subunits, especially p22 phox and p47phox (95). As mentioned earlier, uncoupling of eNOS is an important contributor to the free radical production. Hyperglycemia, like obesity, also results in accumulation of ADMA, which leads to increased eNOS, thereby causing superoxide production (165).

The migration, activation, and release of cytokines by monocytes have a well-documented role in the formation and progression of atherosclerotic plaques. These activated monocytes further develop into macrophages to become foam cells, which are rich sources of inflammatory mediators and free radicals (240). The increased expression of monocyte chemoattractant protein (MCP-1) is known to increase the adhesion of monocytes in hyperglycemic states (269). Dhindsa *et al.* showed that monocyte-mediated free radical generation is increased in healthy volunteers after a single oral glucose dose (57). In addition, monocytes isolated from patients with poorly controlled diabetes, via various mechanisms, increase superoxide production (114, 289).

Dysfunctional vascular smooth muscle in diabetics enhances their susceptibility to premature atherosclerosis (177, 195). Vascular smooth muscle cells (VSMC) produce increased superoxide under hyperglycemic conditions (122, 123, 160). There is enhanced atherosclerotic lesion formation in diabetic patients as a result of the inhibition of vasodilation, caused by production of oxidative stress by VSMC, and increased migration of VSMC into atherosclerotic lesions (128, 267). Oxidative stress, via hydrogen peroxide and oxidized LDL, leads to VSMC necrosis and apoptosis in diabetic patients' coronary arteries and aortas (117, 220). The resultant VSMC death is now suggested to play a vital role in plaque instability and rupture (81).

A distinct but clinically relevant entity, diabetic cardiomyopathy, has been recognized based on clinical, epidemiologic, and pathological data (73, 241). Although the exact cause of diabetic cardiomyopathy remains unclear (27), recent studies suggest a pathogenic role of free radical-mediated apoptosis that leads to the cascade of events eventually causing cardiomyopathy (37, 38). Moreover, considerable similarities exist between cardiomyopathy induced by nitric oxide inhibition and cardiomyopathy induced by the combination of hypertension and diabetes, suggesting an important role of eNOS and eNO in the pathogenesis of diabetic cardiomyopathy (110, 245).

Nephropathy

Diabetic nephropathy is characterized by persistent albuminuria, confirmed on at least two occasions 3–6 months apart, declining glomerular filtration rate (GFR), and hypertension. Diabetic nephropathy develops in ~35% of patients with type 1 diabetes mellitus and 15%–20% of patients with type 2 diabetes mellitus, and is the leading cause of kidney failure, accounting for 44% of new cases in 2002 (41, 111).

Although review of the literature reveals many mechanisms that have been proposed to play a role in diabetic nephropathy, some important pathogenic mechanisms include, but are not limited to, the formation of free radicals, increased formation of AGE, the activation of protein kinase C (PKC), increased growth factor activity, the activation of cytokines, and decreased glycosaminoglycan content in basement membranes (39).

Oxidative stress injury in diabetic nephropathy is potentially mediated by multiple factors, especially free radical generation due to mitochondrial dysfunction and decreased activity of protective mechanisms (22, 257) (Fig. 6). Nitric oxide is excessively active in diabetics with microalbuminuria as compared to nonalbuminuric patients and was found to be related to GFR (49). Mouse studies of inducible nitric oxide synthase (NOS) suggest that NO modulates glomerulosclerosis and tubulointerstitial fibrosis (281).

Additional evidence comes from studies showing increased levels of 8-hydroxy-2′-deoxyguanosine (8-OHdG), indicating oxidative mitochondrial DNA damage and deletion, in rat kidneys (133). Similar studies in humans have

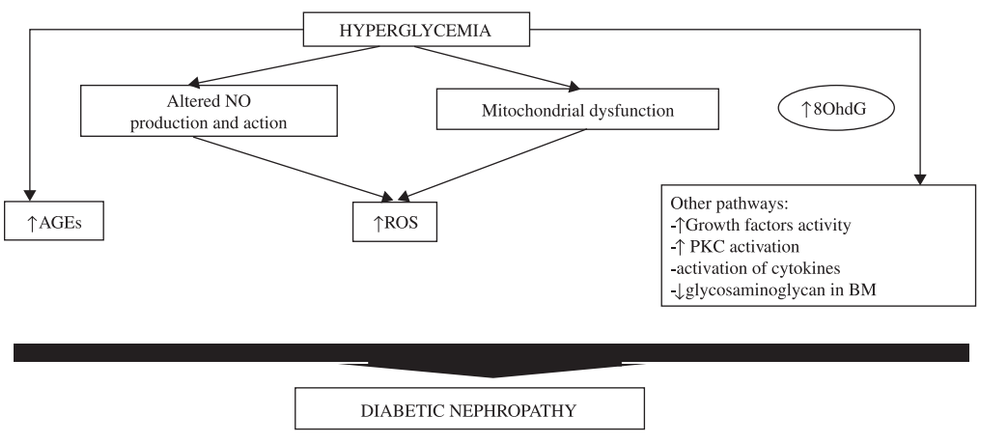

FIG. 6. Implications of oxidative stress in pathophysiology of diabetic nephropathy. AGEs, advanced glycation end products; BM, basement membrane; NO, nitric oxide; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; PKC, protein kinase C; ROS, reactive oxygen species.

demonstrated increased urinary levels of 8-OHdG in type 2 diabetics as compared to controls, and this increase was directly proportional to the severity of glomerular and tubulointerstitial lesions (134). A 5-year prospective Japanese trial, concluded in 2002, documented a urinary 8-oxo-7,8-dihydro-2′-deoxyguanosine level as a strong predictor of the development of diabetic nephropathy in type 2 diabetic patients (113). In addition, antioxidants were found to attenuate oxidative stress and apoptosis in human tubular cells (290).

Over the past few decades, increased production of AGE has been recognized as one of the noteworthy mechanisms that lead to diabetic complications (32, 34, 35). Studies have shown the presence of significantly increased serum and skin levels of AGE in relationship to progression of microalbuminuria to overt nephropathy and severity of renal complications in diabetic patients, respectively (22, 193).

Increased AGE production leads to enhanced free radical generation. Mechanisms responsible for AGE-induced free radical production include creation of catalytic sites for free radical generation, stimulation of NADPH oxidase, and depletion of glutathione peroxidase, a potent cellular antioxidant (297, 303). AGE-mediated mitochondrial dysfunction, in combination with carbonyl intermediates, is a source of superoxide generation, another potent free radical (238).

There is a strong synergistic correlation between oxidative stress and AGE, as indicated by the proportional increase in free radicals and AGE, in diabetic rats (265). Also, strict glycemic control has been shown to attenuate free radical production and AGE accumulation in human diabetic glomeruli (210, 266).

Neuropathy

Diabetic neuropathy represents peripheral and autonomic nerve dysfunction. It is responsible for considerable morbidity and mortality associated with diabetes. More than 50% of diabetics develop neuropathy during their lifetime, making it the most common cause of nontraumatic limb amputations (76, 293). There is a 15% chance for a patient with diabetic neuropathy of undergoing one or more amputations during his/her life (75). Additionally, poor glycemic control and duration of diabetes have been shown to be proportionally related to incidence of diabetic neuropathy (74).

As discussed earlier, hyperglycemia plays a major role in the development and progression of diabetic complications, including neuropathy. The key mechanism, implicated in the neural degeneration induced by hyperglycemia, is increased oxidative stress associated with increased polyol pathway activity, increased PKC activity, and AGE accumulation (Fig. 3). All these converge to mediate apoptosis of neurons and Schwann cells, which are the glial cells of the peripheral nervous system (242, 243, 251).

The role of oxidative stress in neuronal degeneration has been documented in multiple studies (56, 142, 213). Neurons are also vulnerable to free radical-mediated injury due to their reaction with the lipid and protein content of the neurons. This renders the neurons incapable of signaling and axonal transport with increased necrosis and apoptosis (6, 56, 189). Recent *in vivo* and *in vitro* studies have demonstrated the role of mitochondrial dysfunction and oxidative stress as being deleterious to neurons, causing neuronal death (243, 292). Vincent *et al*. demonstrated significantly elevated levels of oxidative stress in the dorsal root ganglia, within 2 h of hyperglycemia, leading to apoptosis. This may explain in part the underlying mechanism responsible for neuropathy in diabetics with good overall control as well as patients with impaired glucose tolerance, who also develop neuropathy (225, 291). Moreover, recovery of damaged neurons in the presence of free radicals, like NO, is much slower and this recovery is accelerated by the administration of NOS inhibitors (268).

Retinopathy

Diabetic retinopathy is a severely disabling microvascular complication and is the most common diabetic eye disease (146). It is clinically manifested by multiple microvascular pathologies, including microaneurysms, hemorrhages, and neovascularization (4). Diabetic retinopathy is the most frequent cause of new cases of blindness among adults aged 20–74 years, and studies have shown that poor glucose control, per se, is the inciting factor in its development (5, 68). During the first 20 years of the disease, >60% of the patients with type 2 diabetes develop retinopathy (5). The strongest predictor for development and progression of retinopathy is the duration of diabetes itself (145).

Poor glycemic control has been consistently shown to be a key risk factor for the development of diabetic complications, including retinopathy. Moreover, tight glucose control delays the onset and progression of retinopathy in the diabetic population (272, 283). As is the case with all other diabetic complications, increased free radical production is seen in the retina of diabetics and oxidative stress is a major contributor in the pathogenesis of diabetic retinopathy (151, 208, 209) (Fig. 7).

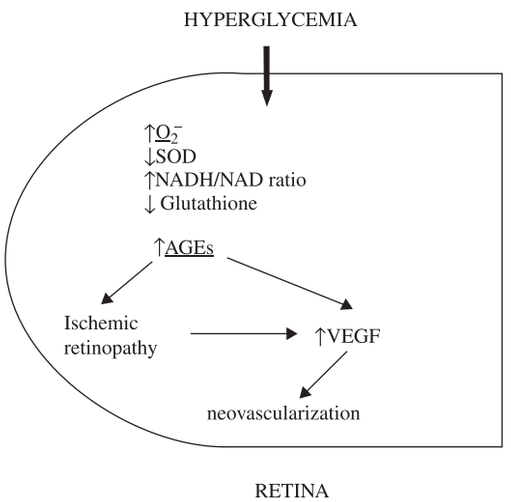

FIG. 7. Oxidative stress and pathogenesis of diabetic retinopathy. AGEs, advanced glycation end products; NAD, oxidized nicotinamide-adenine dinucleotide; NADH, nicotinamide-adenine dinucleotide; $O_2^{-\bullet}$, superoxide; SOD, superoxide dismutase; VEGF, vascular endothelial growth factor.

The retina is highly rich in polyunsaturated lipid membranes, making it extremely vulnerable to free radical-mediated lipid peroxidation (132). Thiobarbituric acid–reacting substances (TBARS) assay (126)—a tool used to measure lipid peroxide levels in oxidative stress, have been found to be increased in type 1 and type 2 diabetic patients (11, 223, 246). The vitreous fluid in diabetic patients with proliferative retinopathy has increased levels of vascular endothelial growth factor (VEGF), which is upregulated and released in response to ischemia and oxidative products (2, 3, 155, 168).

Hyperglycemia causes increased NADH-to-NAD ratio secondary to increased reduction of NAD+ to NADH. This leads to ischemic retinopathy and increased production of the superoxide (287). Moreover, superoxide dismutase (SOD) activity is decreased in the diabetic retina (65), further enhancing the superoxide activity and leading to greater oxidative stress-mediated injury and advanced glycation end (AGE) products. These essentially lead to increased release of VEGF (155, 168) and the risk of neovascularization (2, 104). The accumulation of AGE products is accelerated with advanced age and chronic hyperglycemia and is an established mechanism that mediates tissue damage, including diabetic retinopathy (250).

Further evidence implicating oxidative stress in the pathogenesis of diabetic retinopathy comes from studies showing antioxidants, such as vitamin E, normalize preclinical diabetic retinopathy (51). Additionally, increased expression of mitochondrial SOD leads to decreased superoxide formation leading to prevention of apoptosis in the retina and its capillaries (152). As in diabetic nephropathy, 8-hydroxy-2′-deoxyguanosine (8-OHdG) levels are increased in diabetic retina, and decreased levels in rats have been achieved by administration of alpha lipoic acid—an antioxidant (153). Under hyperglycemic states, glutathione a naturally occurring antioxidant, is significantly decreased in diabetic retina and this decrease is inhibited by administration of antioxidants (153, 196).

Oxidative stress also significantly contributes to the pathogenesis of diabetic cataract, another manifestation of long-standing diabetes (48, 121). The major contributors in the genesis of free radicals in diabetic lens are glycoxidation (9, 301) and impaired antioxidant defense mechanism, resulting from depletion of glutathione reserves (88, 167). Moreover, studies have documented the role of aldose reductase and sorbitol dehydrogenase, enzymes involved in polyol pathway, in the pathogenesis of slowly evolving diabetic cataract. This is thought to occur due to dysequilibrium between free radicals and antioxidant defenses resulting from depletion of NADPH & NAD+, cofactors for aldose reductase and sorbitol dehydrogenase, respectively (277, 300). In short, one of the key mechanisms in the generation of oxidative stress in diabetic cataract is the polyol pathway.

OXIDATIVE STRESS AND PREVENTION OF TYPE 2 DIABETES

In the face of the rapidly growing diabetes epidemic, which is generally perceived as a difficult-to-control disease, and with accumulating data indicating suboptimal control of cardiovascular risk factors in diabetes (182, 249), the need for orchestrated efforts to prevent diabetes has become apparent. In the past two decades, there have been several major trials designed and executed with diabetes prevention as the primary outcome (184) (Table 1). Other studies on diabetes prevention are also ongoing (Table 1). However, it is important to note that the concept of diabetes prevention was first entertained by a pioneer scholar Elliot Joslin as early as the 1920s (131).

Among the major interventions that were tested in several well-designed randomized controlled trials, lifestyle modifications such as diet and exercise consistently yielded significant results. The Swedish Malmo feasibility study showed that men randomized to diet and exercise had less than half the risk of developing diabetes in 6 years (69). The United States Diabetes Prevention Program (DPP) enrolled >3,000 adults with impaired glucose tolerance and studied the effects of standard versus intensive lifestyle intervention, with and without metformin. Although both metformin and lifestyle interventions significantly reduced the incidence of diabetes, this effect was much more pronounced with intensive lifestyle intervention (58). Similarly, multiple international studies, in various cultural, ethnic, and social groups, have shown the benefits of lifestyle modifications for the prevention of type 2 diabetes (150, 214, 282).

Several pharmacological agents have been examined in prospective clinical trials for diabetes prevention in patients with impaired glucose tolerance. Collectively these agents inhibit reactive oxygen species through various mechanisms (Fig. 8). These include metformin, acarbose, thiazolidinediones (TZDs), and angiotensin converting enzyme (ACE) inhibitors, among others. The preventive effects of these therapeutic modalities are primarily attributed to their direct effects on glucose lowering, reduction in triglycerides, and inhibition of the renin angiotensin–aldosterone system (RAAS).

Although lifestyle changes, metformin, acarbose, and TZDs have direct glucose-lowering effects, which may translate into prevention of diabetes and its complications, the fact that diabetes is reduced in patients on statins and ACE inhibitors, albeit inconsistently, raises the possibility of other mechanisms at work. Most of the agents that have been, so far, proven to reduce the incidence of diabetes, are also known to reduce oxidative stress. As discussed earlier in detail, oxidative stress plays a major role in the etiology, pathogenesis, and progression of diabetes and its complications.

One of the most extensively studied strategies for diabetes prevention includes lifestyle interventions such as dietary modification and exercise. These hygienic measures which invariably show improved insulin sensitivity (233) are also known to significantly decrease the levels of oxidative stress (Fig. 8), as measured by 8-isoprostaglandin F2a, superoxide, and hydrogen peroxide production, as well as improve endothelial function in diabetics (16, 173, 235, 274). Moreover, in diabetic patients, the effect of short-term lifestyle interventions has been shown to be long lasting, persisting over a 2- to 3-year follow up (234).

As discussed earlier, hyperglycemia is known to cause enhanced protein kinase C (PKC) activity (33, 124) and metformin, one of the most widely used oral hypoglycemics, not only lowers glucose, but also reduces oxidative stress by inhibiting PKC (143) (Fig. 8). Additionally, metformin reduces oxidative stress-mediated injury by scavenging free radicals and blunting plasma membrane NADPH oxidase—another feature of chronic hyperglycemia (30, 83, 143).

TABLE 1. DIABETES PREVENTION TRIALS

Intervention	*Trial*	*Population (number)*	*NNT*
Completed trials with diabetes prevention as primary outcome			
Lifestyle changes	DPP	IFG/IGT (n = 3,234)	7
	FDPS	IGT(n = 522)	8
Metformin	DPP	IFG/IGT (n = 3,234)	14
Thiazolidinediones	DREAM (Roziglotazone)	IFG/IGT (n = 5,269)	7
Acarbose	STOP-NIDDM	IFG/IGT (n = 1,429)	11
ACE-inhibitors	DREAM (ramipril)	lFG/IGT (n = 5,269)	NS
Xenical	XENDOS	All Obese (n = 3,305)	36
		Obese + IGT (n = 694)	10
Ongoing trials wth diabetes prevention as primary outcome			
Nateglinide	NAVIGATOR		
Thiazolidinediones	ACT NOW (Pioglitazone)		
ARBs	NAVIGATOR (Valsartan))		
	ONTARGET/TRANSCEND (Telmisartan)		
Metformin + Rosiglotazone	CANOE		
Other trials*			
ACE-inhibitors	HOPE (ramipril), CAPP (captopril), ALLHAT (lisinopril)		
ARBs	LIFE (losartan)		
Statins	WOSCOPS		
Bezafibrate	BIP		
Rimobanant	RIO trials		

*Trials with diabetes prevention as secondary outcome or on posthoc analysis. ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; GD: previous gestational diabetes; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NNT, number needed to treat; NS, not significant.

Trials: ACT NOW: ACTos NOW for Prevention of Diabetes; ALLHAT: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; BIP: Bezfibrate Infarction Prevention Study; CAnadian Normoglycemia Outcomes Evaluation (CANOE) trial; CAPP: The CAptopril Prevention Project; DPP: Diabetes Prevention Program; DREAM: Diabetes REduction Assessment with ramipril and roziglotazone Medications; FDPS: Finnish Diabetes Prevention Study; HOPE: Heart Outcomes Prevention Study; LIFE: Losartan Intervention For Endpoint; NAVIGATOR: Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research; ONTARGET: ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial; RIO: Rimonabant In Obesity; STOP-NIDDM: Study TO Prevent Non-Insulin Dependent Diabetes; TRANSCEND: Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular disease; WOSCOPS: West of Scotland Coronary Prevention Study; XENDOS: XENical in the prevention of Diabetes in Obese Subjects.

Thiazolidinedione (TZD) is a class of medication that reduces insulin resistance by reducing plasma glucose, glucose production, and increasing glucose clearance in type 2 diabetes. These agents work primarily by binding to nuclear peroxisome proliferator-activated receptor gamma (PPAR γ) (179, 264). TZDs mediate their antioxidant effects by inhibiting nitric oxide synthase, thereby decreasing peroxynitrite production, and inhibiting superoxide production (185, 231) (Fig. 8). The preventive effects of TZDs were recently validated by the rosiglitazone limb of the Diabetes Reduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial (63) which showed a 60% reduction in the incidence of diabetes in patients with impaired fasting glucose or impaired glucose tolerance. Moreover, there are multiple animal studies showing additional antioxidant properties of TZDs, and researchers are exploring TZD analogues with promising results in ameliorating oxidative stress associated with diabetes (47).

ACE inhibitors have long been known for their cardioprotective and renoprotective effects, but their potential for prevention of diabetes has been a matter of debate. Although post-hoc analysis of the Heart Outcomes Prevention Evaluation (HOPE) trial (304) provided the most persuasive evidence for diabetes prevention with the use of ACE inhibitors, this has not been duplicated in the largest diabetes prevention trial to date: the DREAM trial (273). Even though ramipril, an ACE inhibitor, has not been shown to prevent diabetes, the beneficial effects of these agents on glucose metabolism were confirmed in the DREAM study by a reduction of 6 mg/dl in the 2-h post oral glucose tolerance test plasma glucose level, and by the increased conversion of prediabetes to normoglycemia by 16%. These agents that block RAAS have well-proven effects on the reduction of oxidative stress (26, 115).

Angiotensin II increases intracellular superoxide by the activation of NADPH and NADH oxidase, resulting in oxidative stress (92). This plays a significant role in insulin resistance, and animal studies suggest that abrogation of oxidative stress improves insulin sensitivity (26). Furthermore, it also activates NADPH by enhancing the gene expression of GTPase Rac-1, leading to increased production of peroxynitrite (296). In addition to inhibiting the production of angiotensin II, ACE inhibitors increase the activity of endothelial superoxide

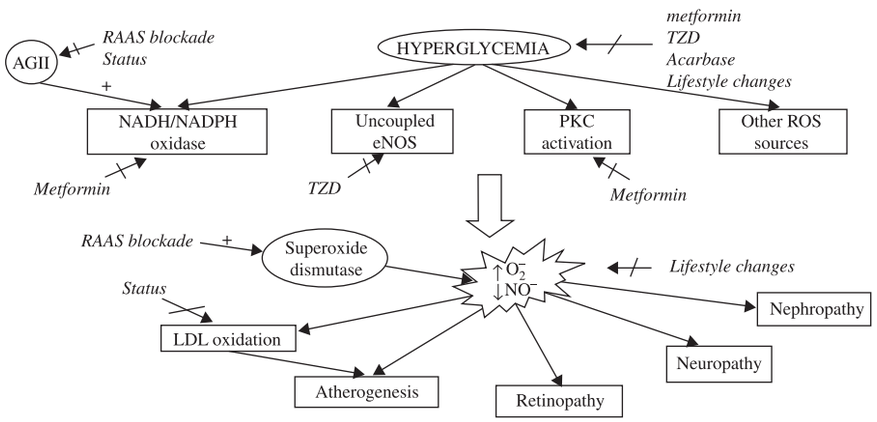

FIG. 8. Effects of diabetes prevention agents on oxidative stress associated with hyperglycemia. AGII, angiotensin II; eNOS, endothelial nitric oxide synthase; LDL, low-density lipoprotein, NADP, oxidized nicotinamide-adenine dinucleotide phosphate; NADPH, nicotinamide-adenine dinucleotide phosphate; NO, nitric oxide; $O_2^{-\bullet}$, superoxide; PKC, protein kinase C; RAAS, renin–angiotensin–aldosterone system; ROS, reactive oxygen species; TZD, thiazolidinediones.

dismutase, a major antioxidant (115) (Fig. 8). Other agents that inhibit the RAAS include angiotensin receptors blockers, which are currently being tested in the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial for primary diabetes prevention (Table 1).

Finally, among other agents that have shown favorable effects on glucose metabolism, statins (Table 1) also reduce oxidative stress independent of LDL reduction (66, 183) (Fig. 8). This reduction in oxidative stress is mediated by various mechanisms such as attenuation of angiotensin II-mediated free radical generation (288) and reduction of LDL oxidation (180).

CONCLUSION

In this article, we have presented a comprehensive review highlighting the evidence that oxidative stress serves as a common soil hypothesis for the various interventions that have been examined in large prospective randomized trials with prevention of diabetes being the primary outcome. These interventions included lifestyle changes as well as pharmacological agents, such as metformin, acarbose, and TZDs, that have been shown to be as effective as lifestyle interventions in the prevention of diabetes, as indicated in the recently published DREAM trial, the largest diabetes prevention trial to date.

The prospect for the use of antioxidants specifically for the prevention of diabetes holds a great promise in the continuing efforts to curb the rapidly growing diabetes epidemic. However, further studies are needed to provide specific answers in this important area of research.

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ABBREVIATIONS

ACE, angiotensin converting enzyme; ADA, American Diabetes Association, ADMA, asymmetric dimethylarginine; AGE, advanced glycation end products; AIDS, acquired immunodeficiency syndrome; ARDS, adult respiratory distress syndrome; ATP, adenosine triphosphate; 13C, carbon isotope; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CMS, cardiometabolic syndrome; DNA, deoxyribonucleic acid; DPP, Diabetes Prevention Program; DREAM, Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication; eNOS, endothelial nitric oxide synthase; ESR, electron spin resonance; FFA, free fatty acids; GFR, glomerular filtration rate; GLUT-4, glucose transporter isoform-4; GTP, guanosine triphosphate; H_2O_2, hydrogen peroxide; HDL, high density lipoprotein; HOPE, Heart Outcomes Prevention Evaluation; $^{\bullet}OH$. Hydroxyl; 8-OHdG, 8-hydroxy-2′-deoxyguanosine; IUGR, Intrauterine growth retardation; LDL, low density lipoprotein; MCP-1, monocyte chemoattractant protein; MDA, malondialdehyde; NAD+, nicotinamide adenine dinucleotide (oxidized form); NADH, nicotinamide adenine dinucleotide (reduced form); NADPH, nicotinamide adenine dinucleotide phosphate; NAVIGATOR, Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research; NCEP/ATP, National Cholesterol Education Program/Adult Treatment Panel; $NO^{\bullet}$, nitric oxide; NO_2^+, nitronium ion; $NO_2^{\bullet}$, nitrogen dioxide gas; NOS, nitric oxide synthase; $O_2^{-\bullet}$, superoxide; $ONOO^-$, peroxynitrite; ORIGIN, Outcomes Reduction with Initial Glargine Intervention; oxLDL, oxidized low density lipoprotein; $Ph_3C^{\bullet}$, triphenylmethyl radical; 31P, phosphorus isotope; PKC, protein kinase C; PPAR γ, peroxisome proliferator-activated receptor gamma; RAAS, renin angiotensin aldosterone system; $RO^{\bullet}$, alkoxyl; $ROO^{\bullet}$, peroxyl; ROS, reactive oxygen species; $RS^{\bullet}$, thiyl; SOD, superoxide dismutase; TBARS, thiobarbituric acid–reactive substances; TZD, thiazolidinedione; VEGF, vascular endothelial growth factor; VSMC, vascular smooth muscle cells; WHO, World Health Organization.

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