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Antioxidant Therapy for Diabetic Kidney Disease

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1. Introduction

Diabetic kidney disease (DKD) is the single most common cause of end stage renal disease (ESRD) with the annual costs of caring for patients with DKD exceeding more than \$9 billion in the United States (Centers of Disease Control and Prevention, 2005). Every diabetic patient has up to a 40% lifetime risk to develop DKD, if the patient does not die prematurely of cardiovascular disease (CVD) (Parving, Osterby, & Ritz, 2000). DKD can present as different phenotypes, progressive and nonprogressive (Figure 1 and 2).

Stages of CKD	GFR (mL/min/ 1.73m ²)	Proteinuria/Albuminuria and/or Hematuria
1	≥90	+
2	60-89	+
3	30-59	±
4	15-29	±
5	<15	±

Stages of DKD	GFR (mL/min/ 1.73m ²)	Albuminuria (mg/g)
1	≥90	-
2	60-89	30-300
3	30-59	>300
4	15-29	>3000 NS
5	<15	±

NS= Nephrotic Range Proteinuria

Fig. 1. A-B. The stages of CKD (A) and DKD (B).

Approximately, a third of patients can have progressive DKD which presents with progressive proteinuria, mainly albuminuria, a subsequent decline in glomerular filtration rate (GFR), and in some patients, progression to ESRD. Clinical studies show that renal

vascular dysfunction can precede the onset of proteinuria in diabetes. Ishimura et al. demonstrated that patients with stage 1 DKD have increased resistive indices in the renal vasculature, indicating a diminished renal vasodilatory blood flow reserve (Ishimura et al., 1997). Furthermore, Frauchiger et al. validated that patients with early DKD have a diminished renal blood flow response to nitroglycerin compared to healthy controls (Frauchiger, Nussbaumer, Hugentobler, & Staub, 2000). In addition, Epstein et al. elegantly demonstrated that renal blood flow oxygenation, as quantified by blood oxygenation level-dependent magnet resonance imaging, is diminished in response to a water load in patients with stage 1 DKD compared to healthy controls, suggesting that oxygen delivery may be impaired in early stages of DKD, at least in part, due to vascular and/or endothelial dysfunction (Epstein, Veves, & Prasad, 2002). The cause for these observations is incompletely understood, but several studies suggest that inactivation of Nitric Oxide (NO) by increased reactive oxygen species (ROS) generation in diabetes may be an underlying mechanism. It has been suggested that increased generation of ROS in diabetes mellitus, namely of superoxide anion (O_2^-), reduces vascular endothelial function. This endothelial dysfunction is characterized by a decreased NO-dependent vasodilation which has been demonstrated in the renal vasculature of early DKD and may also contribute to the increased cardiovascular mortality in these patients (Dai, Diederich, Skopec, & Diederich, 1993; Diederich, 1997; Kanwar et al., 2008). Any form of DKD is associated with a markedly increased cardiovascular mortality and in recent years, even low levels of albuminuria, which were previously thought to be normal, have been shown to be associated with up to 10-fold increased cardiovascular mortality (Rachmani et al., 2000).

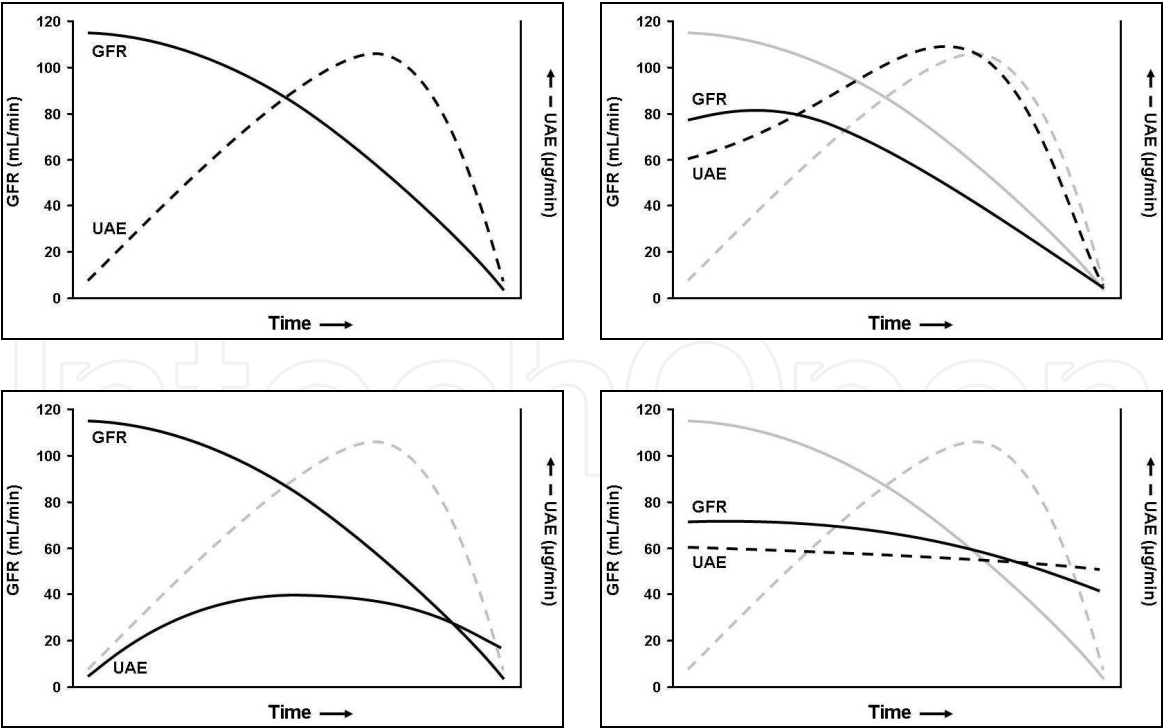


Fig. 2. A-D. Different phenotypes of DKD including progressive (A-C) and non-progressive or slowly progressive DKD (D), GFR, glomerular filtration rate; UAE, Urine albumin excretion.

The therapeutic strategies for DKD are limited due to several factors: (1) Lack of screening for DKD, (2) Lack of implementation of optimal standard therapy for DKD, and (3) Current therapies primarily slow down, but do not halt the progression of DKD. These therapies include: blood pressure, lipid, glycemic, and weight control; diet and lifestyle modifications; antiplatelet aggregation therapy; and initiation of therapy with inhibition of the renin angiotensin system (RAS) by angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and renin inhibitors.

A major role of DKD pathogenesis has been attributed to the increased generation of ROS in diabetes. (Figure 3)

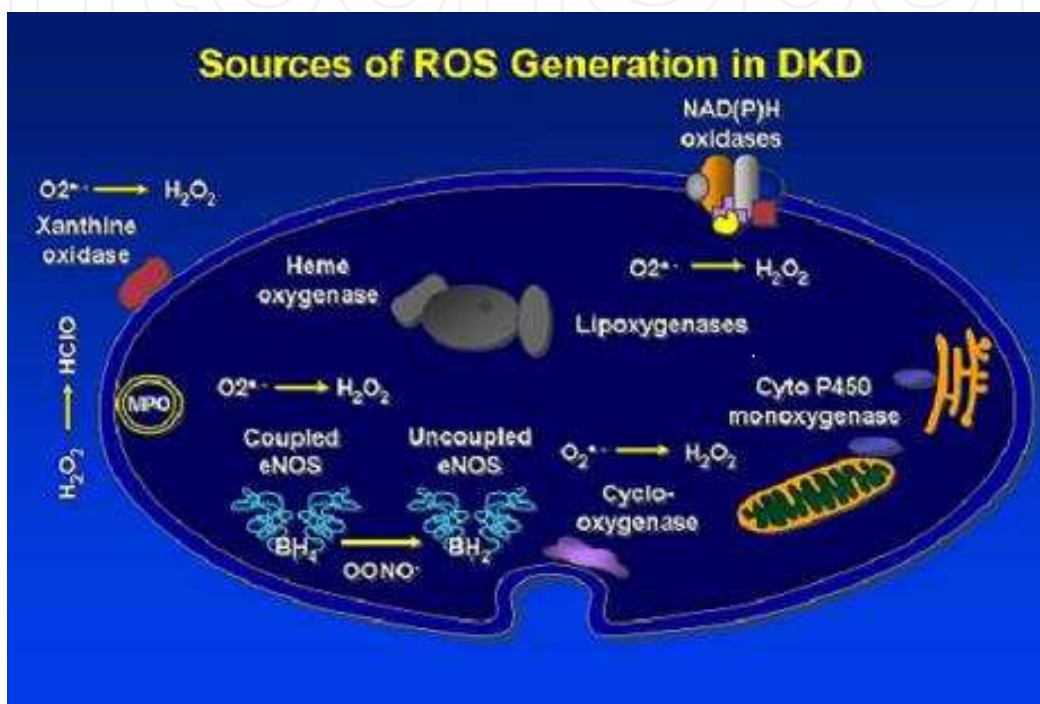


Fig. 3. Sources of ROS Generation in DKD

ROS are natural by-products of oxygen metabolism that are generated during oxidative phosphorylation and play an important role in cell signaling, aging, cancer prevention and degenerative diseases. Oxidative radicals are highly reactive ROS capable of changing the form and function of many cellular components. Under normal conditions, common ROS, including superoxide anion ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), hydroxyl radical (OH^{\bullet}) and hypochlorous acid ($HClO$) are detoxified via electron transfer by cellular antioxidant enzyme systems (superoxide dismutase, catalase, and glutathione peroxidase). However, during periods of stress, including environmental, physical (e.g. radiation, ultraviolet light), and chemical (e.g. hyperglycemia), these free radicals are produced in excess, overwhelming the detoxification capacity of cellular antioxidant enzymes and causing cell damage. This damage is mediated directly by electron shifts or due to cytokine-mediated signal transduction and amplification, DNA damage and structural changes of lipids and proteins.

The overproduction of ROS in the kidney has been demonstrated in both animals (Koya et al., 2003) and humans with DKD (Breznicanu et al., 2007). In addition, the products of increased ROS generation, such as 13-hydroxyoctadecadienoic acid, dimethylarginine,

8-hydroxyguanosine, and oxidized glutathione are increased in DKD (Aslam, Santha, Leone, & Wilcox, 2006). Vascular endothelium is especially prone to ROS-mediated damage (Inoguchi et al., 2003; H. B. Lee, Ha, & King, 2003; H. B. Lee, Yu, Yang, Jiang, & Ha, 2003; Li & Shah, 2003). Superoxide anion generation has been shown to inactivate NO-dependent vasodilation, likely by scavenging NO and generating the very potent ROS peroxynitrite: $\text{NO} + \text{O}_2^- \rightarrow \text{ONOO}$ (Figure 5A) (Hogg & Griffith, 1997).

The challenges antioxidant therapy faces in the clinic are two-fold: (1) prevention of further ROS generation and, (2) achieving an appropriate and constant antioxidant level at the site of injury (mitochondria). Many antioxidant molecules get converted to oxidant radicals during the redox reaction involved in scavenging ROS. Moreover, the mitochondria are the major site of ROS generation and it is questionable if most antioxidants currently in clinical use (e.g. N-acetylcysteine, vitamin C, vitamin E) are reaching their target and acting within the mitochondria in order to effectively decrease ROS generation. Some newer antioxidants, such as ubiquinones, may be more mitochondria-specific and will be discussed later (James, Cocheme, Smith, & Murphy, 2005; James et al., 2007). (Figure 3 & 4)

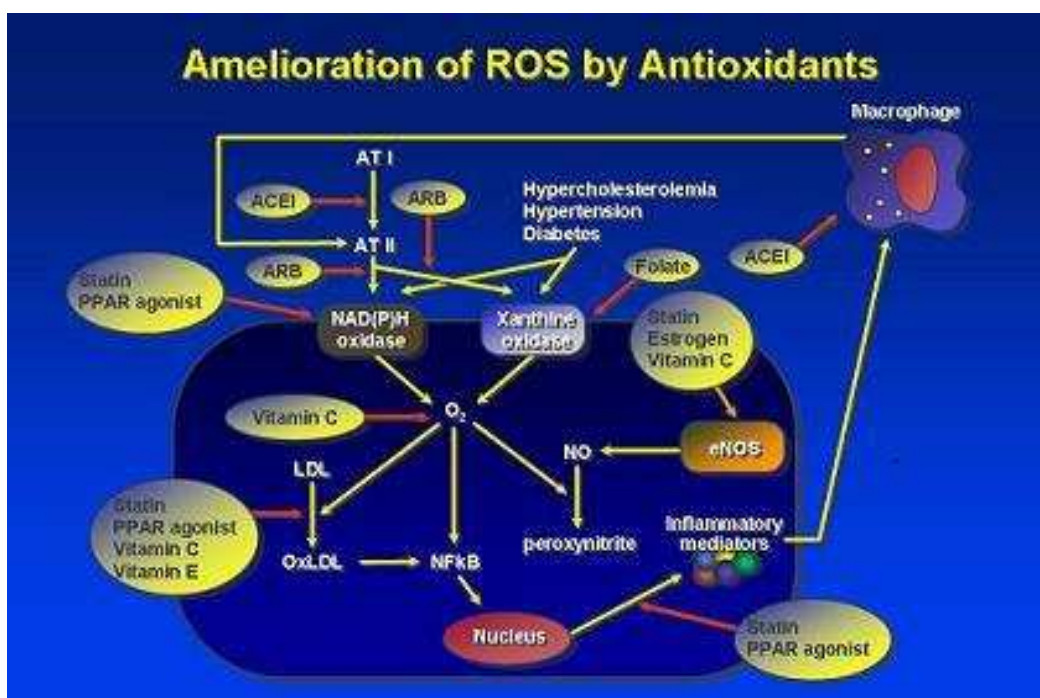
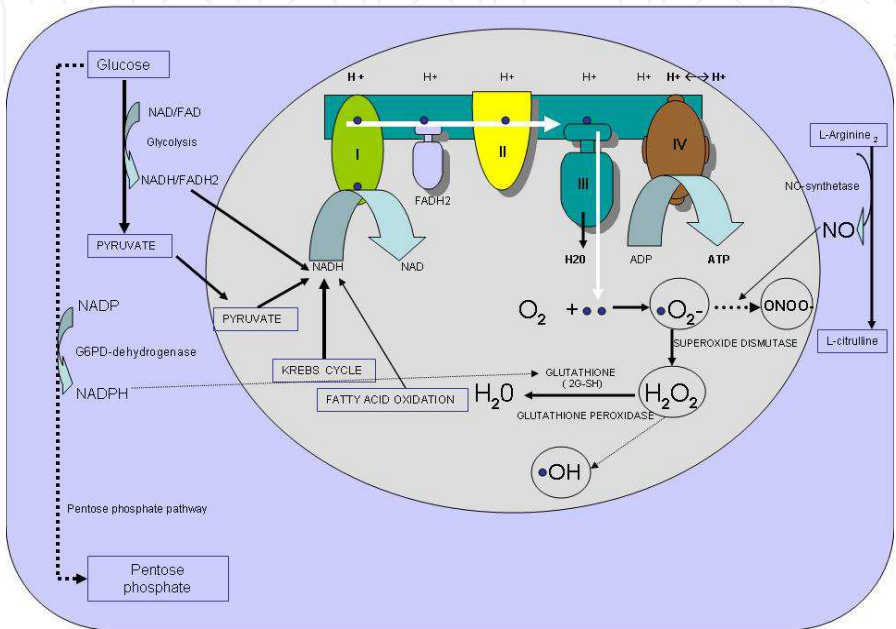


Fig. 4. Amelioration of ROS by Antioxidants

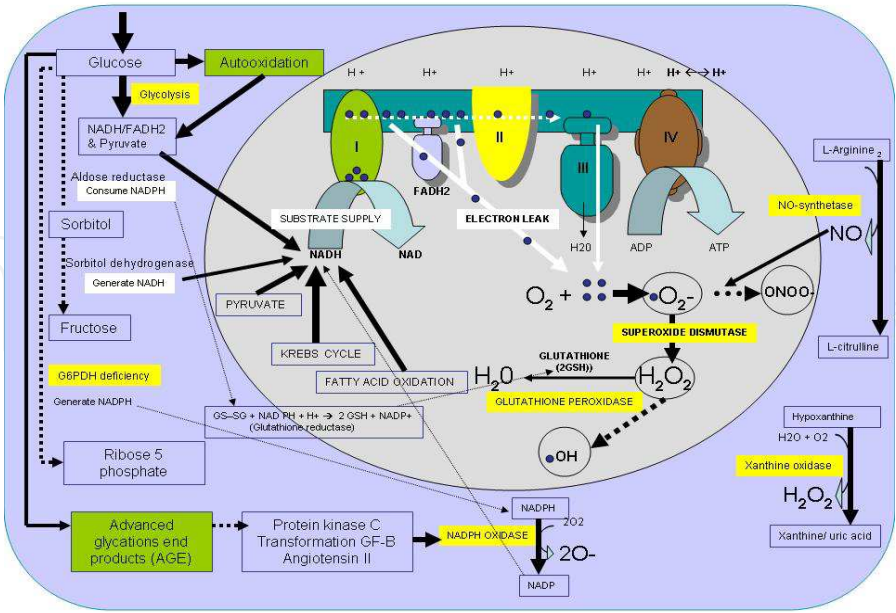
Both enzymatic (NADPH oxidase, G6PDH, xanthine oxidase, NO synthase and glycolysis pathway enzymes) and non-enzymatic reactions (glucose auto-oxidation and advanced glycation) are involved in hyperglycemia-induced overproduction of ROS. Glucose-induced protein kinase C (PKC), advanced glycosylation end-products (AGE), polyol pathways, and nuclear factor kappa B (NF- κ B) activation are the 4 critical pathways involved in DKD. Agents with potential antioxidant effects currently investigated in animals and humans which will be discussed below include renin angiotensin inhibitors, protein kinase C inhibitors, TGF- β inhibitors, pentoxifylline, selective mitochondrial antioxidants, statins, vitamins C and E, sodium bicarbonate, N-acetylcysteine, bardoxolone methyl, omega-3 fatty acids, coenzyme Q10, and tempol.

2. Antioxidant therapy: ROS inhibition for the treatment of DKD

Several studies have demonstrated that inhibition of ROS generation by various therapeutic strategies and targeting different pathways are beneficial in the prevention and/or progression of DKD. An ideal antioxidant agent would be one that targets several ROS-generating pathways, in particular, mitochondrial-derived ROS. Such agents studied for the treatment of DKD are yet to be identified. Potential novel treatment strategies may include the following (see also Figure 5).



(A)



(B)

Fig. 5. A-B. Mitochondrial pathways of ROS generation in non-diabetic (A) and diabetic conditions (B).

2.1 Glycemic control

In hyperglycemia, excess glucose undergoes auto-oxidation and glycolysis to produce large amounts of NADH and FADH₂ which feed into and overwhelm the electron transport chain, causing electron leaks and ROS overproduction in renal and other cells (El-Osta et al., 2008). Currently, standard therapy for DKD includes tight glycemic control, directed by glycosylated hemoglobin A1c (HbA1c) levels to prevent hyperglycemia-induced, ROS-related DKD. Target HbA1c levels of less than 7.0% have been recommended to improve DKD and/or prevent its progression in several trials (National Kidney Foundation, 2010). Generally, elevated HbA1c levels are indicative of chronic hyperglycemia, but insensitive to detect transient hyperglycemic episodes. However, events of transient hyperglycemia (as short as 6 hours of hyperglycemia) have been shown to induce long-lasting activation of NF- κ B (El-Osta et al., 2008) and are now considered a risk factor for diabetic complications independent of HbA1c levels.

2.2 Inhibition or blockade of Renin-Angiotensin System (RAS)

Angiotensin II is a major constituent of the RAS and has been shown to be an important pathogenetic factor in DKD development (Andersen, Tarnow, Rossing, Hansen, & Parving, 2000). Inhibition of the RAS by ACEIs, ARBs, and renin inhibitors have been shown to delay the onset and/or progression of DKD in numerous studies. A meta-analysis by Kunz et al analyzed 110 trials and found that ACEI and ARBs significantly decreased proteinuria, one of the early signs of DKD, in renal disease. No conclusions could be made, however, regarding preservation of kidney function from this analysis due to the variable quality of these studies and their short duration (Kunz et al 2008). Another meta-analysis of 24 studies found that RAS blockers reduce the risks of ESRD and doubling of serum creatinine in diabetic nephropathy patients, but do not affect all-cause mortality (Sarafidis et al 2008). The beneficial effects of RAS inhibitors in DKD may in part be due to their antioxidant properties (Onozato, Tojo, Goto, Fujita, & Wilcox, 2002). However, the use and benefit of these agents is limited by potentially harmful side effects such as hyperkalemia, reduction in the GFR, and failure to completely halt disease progression.

2.3 Inhibition of protein kinase C (PKC)

Hyperglycemia-mediated overexpression of protein kinase C (PKC)- β results in activation of NADPH oxidase, a lysosomal enzyme involved in ROS generation which is also increased in experimental models of DKD (Onozato et al., 2002). Ruboxistaurin, a PKC- β inhibitor, reduced proteinuria in animal models (Inoguchi et al., 2003) and humans (Tuttle et al., 2005). However, larger clinical trials are pending to confirm the safety and validate the prospective benefits of ruboxistaurin. Other PKC- β inhibitors are currently under investigation for possible use in the treatment of DKD.

2.4 Inhibitors of transforming growth factor- β (TGF- β)

Transforming growth factor- β is a family of growth and differentiation factors that includes TGF- β 1, β -2, and β -3, activins, and bone morphogenic proteins (Bottinger, 2007). TGF- β 1 is a pleiotropic cytokine with complex biological activities that depend on cell type and cell context. Cell cycle control, regulation of early development, cell differentiation, angiogenesis, and immune system regulation are all activities ascribed to TGF- β 1 (Schmidt-Weber & Blaser, 2004; Ghosh, 2005 #132). TGF- β is also a major regulator of the extracellular

matrix and tissue repair. A highly validated deleterious action of TGF- β is its contribution to the progressive fibrosis of CKD (Bottinger & Bitzer, 2002) and DKD (Chen et al., 2001). TGF- β 1 appears to be the predominant isotype mediating disease progression. Experimental evidence indicates that TGF- β 1 is the most abundant isoform expressed in the kidney. The TGF- β 2 and- β 3 isoforms have been shown to mediate part of their effect through upregulation of β 1 expression (Chen et al., 2001). In addition, it has been demonstrated in the *db/db* mouse model of DKD that a neutralizing monoclonal antibody (mAb) specific for TGF- β -1 was as effective in reducing renal damage as an mAb against all 3 TGF- β isoforms (Ziyadeh et al., 2000). Thus, modulation of TGF- β 1 activity would be expected to retard DKD progression without interfering with either important regulatory roles of TGF- β 2 and - β 3. Humanized IgG4 mAb that has potent and selective neutralizing activity against active TGF- β 1 (known as CAT-192) is being tested for DKD therapy. Monoclonal antibodies against TGF- β are currently under clinical investigation for DKD.

TGF- β is not only fibrogenic and causes glomerulosclerosis (Sharma, Jin, Guo, & Ziyadeh, 1996) but can also generate ROS by inducing NADPH oxidase (Misra & Rabideau, 2000). Pirfenidone is an inhibitor of fibroblast growth factor, platelet derived growth factor, and TGF- β . Pirfenidone has antioxidant properties, and has been shown to slow the progression of glomerulosclerosis (Misra & Rabideau, 2000; RamachandraRao et al., 2009). Pirfenidone has been clinically used for the treatment of interstitial lung disease, and recently been shown to have beneficial effects for DKD (Sharma et al., 2011).

2.5 Inhibition of non-enzymatic glycation

Advanced glycation end-product (AGE) are endogenous proteins which are non-enzymatically glycated following auto-oxidation of glucose, primarily in diabetes. The interaction between AGE and their receptors (RAGE) in the kidney has been shown to activate expression of NF- κ B which stimulates ROS production, contributing to DKD (Schmidt et al., 1995). Pyridoxamine inhibits glycation of proteins and decreases AGE deposition in animal models of DKD (Degenhardt et al., 2002). One clinical trial in DKD patients who were treated with pyridoxamine demonstrated a reduced progression of DKD defined as the improvement of the serum creatinine; however, a reduction of urinary albumin excretion was not observed (Williams et al., 2007). A multi-center, randomized controlled trial studying the effects of pyridoxamine in DKD is currently being conducted.

2.6 Removal of catalytic iron

Hyperglycemia-induced glycation of proteins increases their affinity for iron, forming glycochelates. Glycochelates, as well as catalytic iron, have also been implicated in DKD (Swaminathan, Fonseca, Alam, & Shah, 2007). Desferoxamine, a commonly used iron chelator (Miller, M.J., 1989), restores endothelial function mediated by inhibition of ROS (Koo, Casper, Otto, Gira, & Swerlick, 2003). The drug has the ability to penetrate cell membranes and chelate intracellular iron species. The role of iron chelators in decreasing ROS in DKD warrants evaluation in randomized controlled clinical trials.

2.7 Role of pentoxifylline

Pentoxifylline has numerous pharmacological roles, including antioxidant and platelet aggregation inhibitor. For example, tissue necrosis factor α (TNF- α) promotes the local generation of ROS in the glomerular capillary wall, increasing albuminuria in DKD (McCarthy et al., 1998). Pentoxifylline decreases TNF- α expression and reduces proteinuria

in DKD (Navarro et al., 1999). Clinical trials have demonstrated that pentoxifylline has additional mild benefits in reducing albuminuria in DKD patients who are already on ACEI or ARB therapy (Harmankaya, Seber, & Yilmaz, 2003; Navarro, Mora, Muros, & Garcia, 2005). However, pentoxifylline has anti-platelet aggregating properties and as such, may increase the risk for bleeding in patients who are already on aspirin therapy (unpublished observations by the authors).

2.8 Selective mitochondrial antioxidants

Some of the newer developed antioxidants are the ubiquinones, and in particular, MitoQ10 has been characterized as an effective mitochondrial antioxidant (Green, Brand, & Murphy, 2004). Furthermore, MitoQ10 is not itself converted to a ROS after it scavenges ROS, making it a safer antioxidant (James et al., 2005; James et al., 2007). Thus, MitoQ10 might be a promising new agent for the treatment of DKD. Idebenone (Hausse et al., 2002), is another safe mitochondrial antioxidant which has a high mitochondrial uptake. Neither the role of Idebenone nor MitoQ10 have been studied yet in the treatment of DKD and remain to be elucidated.

2.9 Statins

Statins have been shown to have multiple antioxidant properties and improve vascular remodeling (Briones et al., 2009). Statins have also been shown to reduce proteinuria (Nakamura et al., 2005) and the progression of DKD (Agarwal, 2007). Therefore, patients with DKD may benefit from intensified statin therapy, even in the setting of an already controlled LDL cholesterol level. In our practice, we have observed a significant reduction in urinary albumin excretion in patients with progressive DKD who are taking statins and are either intolerable for ACEI/ARB therapy or who are already on maximal ACEI/ARB therapy (unpublished findings). Whether these benefits for the treatment of DKD are due to the antioxidant properties of statins, still needs to be determined. Furthermore, the recently published results of the Study of Heart and Renal Protection (SHARP trial) demonstrated the safety of statins in patients with DKD, however, no significant benefits with regard to improved kidney function have been demonstrated (Baigent, C. et al. 2011). However, a population based cohort study demonstrated possible renal toxic effects of statin therapy, in that all statins were associated with acute renal failure over five years, however, the risk of that was extremely low (Hippisley-Cox and Coupland, 2010). For example, in women, the number needed to harm (NNH) for an additional case of acute kidney injury over years was 434 (ranging from 284-783).

2.10 Vitamin C and E

Vitamin C activates vitamin E and each exhibits multiple antioxidant effects, including inhibition of monocyte adhesion. Their effects have been shown in animal models of experimental diabetes mellitus (E. Y. Lee, Lee, Hong, Chung, & Hong, 2007; Nakano et al., 2008; Simsek, Naziroglu, & Erdinc, 2005). Furthermore, vitamin E protected against ROS-induced DKD in diabetic mice with the haptoglobin (Hp) 2-2 genotype (Nakhoul et al., 2009). A small randomized clinical trial of 69, type 2, diabetic patients with DKD, demonstrated a benefit with the administration of vitamin C (200 mg) and E (100 IU) in reducing urinary albumin excretion (Farvid, Jalali, Siassi, & Hosseini, 2005). Larger trials are warranted to further validate these findings.

2.11 Sodium bicarbonate

The administration of sodium bicarbonate for patients with DKD has primarily been utilized for the prevention of contrast-induced acute kidney injury (CIAKI) (Brar et al., 2008; Maioli et al., 2008; Merten et al., 2004). The pathogenesis of CIAKI involves renal ischemia and ROS generation. Therefore, the use of sodium bicarbonate, a pro-oxidant, to counteract an ROS mediated and generated process such as CIAKI, would seem questionable and counter-intuitive. Consistent with these biochemical observations (From et al., 2008), a retrospective cohort study of 7,977 patients undergoing contrast media (CM) procedures found that the administration of sodium bicarbonate for CIAKI prevention was associated with a 3-fold higher risk to develop CIAKI, compared to N-acetylcysteine alone. However, a recent study found a decrease in the progression of chronic kidney disease (CKD) and DKD in patients taking sodium bicarbonate for 2 years (de Brito-Ashurst, Varagunam, Raftery, & Yaqoob, 2009). However, sodium bicarbonate did not change proteinuria in these patients. Further studies are needed to validate these findings and the underlying mechanism.

2.12 N-acetylcysteine (NAC)

NAC has several antioxidant properties, including induction of synthesis of glutathione, which is used by glutathione peroxidase to reduce H_2O_2 . Furthermore, NAC has been successfully utilized for the prevention of CIAKI in patients with DKD, since both DKD and CIAKI are associated with increased ROS generation (A. Pflueger, Abramowitz, & Calvin, 2009).

The first study of NAC for CIAKI prevention was conducted by Tepel and colleagues (Tepel et al., 2000). The investigators used 600 mg orally, twice daily, on the day before and the day of iodine CM administration and 0.45% saline intravenous hydration in comparison to 0.45% saline hydration alone. Forty-eight hours after CM administration, CIAKI tended to occur and the serum creatinine tended to increase from 2.4 to 2.6 mg/dL ($P=0.18$) in the control group, whereas in the NAC group, serum creatinine decreased significantly from 2.5 to 2.1 mg/dL ($P=0.01$). Several studies followed with conflicting results (Fishbane, 2008; Sterling, Tehrani, & Rudnick, 2008). Several factors have been postulated to contribute to these varying results, including different formulations of NAC.

Dose and treatment duration are the most decisive factors in NAC's prevention of CIAKI. NAC is commonly given for only two days (Tepel et al., 2000), and treatment duration may be too brief to effectively counteract CIAKI-induced ROS production. This treatment duration was chosen because ROS production was thought to occur only shortly after CM induction. However, this concept may need to be revised since the effects of ROS-induction may last much longer than previously assumed, particularly in diabetes. Recently, Michael Brownlee and his group (El-Osta et al., 2008) demonstrated that short-term exposure (1 hour) of high glucose induces ROS-mediated, long-lasting activation of NF- κ B subunit p65 in aortic endothelial cells, both in vitro and in vivo. Interestingly, the effects of this short-term ROS-mediated induction on transcription factor activation could be observed for at least six days after the initial induction. Therefore, CIAKI prevention strategies may need to be applied for longer than two days in order to counteract ROS production and induction of other cell signaling mechanisms. In our practice, we have given NAC as long as six days after CM administration with good tolerability and outcome (unpublished observation).

Furthermore, like many antioxidants, NAC has a very short plasma half-life and plasma target levels are difficult to assess. Dosing twice daily may be insufficient to achieve

consistent renoprotective effects. Moreover, the bioavailability of NAC by oral administration is limited by extensive first-pass metabolism, perhaps explaining why studies of intravenous NAC have tended to show greater efficacy in CIAKI prevention (Fishbane, 2008; Sterling et al., 2008).

NAC has been successfully used for the treatment of acetaminophen-induced ROS liver toxicity, typically utilizing 40-fold higher doses than the current recommended dose of NAC (MW: 163.19) for CIAKI prevention, which is 1200 mg daily or 7×10^{-3} moles. The daily physiological production of superoxide anion (MW: 31.99) has been estimated to be 1.75 kg, or 5.5×10^4 moles (Frei, 1994). Furthermore, ROS production is increased in patients with diabetes and CIAKI. Therefore, it may be presumptuous to assume that 7×10^{-3} moles NAC would cause a meaningful reduction in a daily ROS generation of more than 5.5×10^4 moles of superoxide anion, which is a greater than 7 million-fold difference. Marenzi et al. have demonstrated that doubling the dose of NAC (1200 mg twice daily) improves CIAKI prevention rates (Marenzi et al., 2006). Thus, it would seem that higher doses of NAC and longer treatment periods are necessary for more efficacious CIAKI prevention. No clinical trials studying the long-term effects of NAC on DKD have been conducted, though given its low cost and good side-effect profile, they may well be worthwhile.

2.13 Induction of transcription factor Nrf2: Bardoxolone methyl

Bardoxolone methyl, an inducer of transcription factor Nrf2, can induce the generation of over 250 antioxidant enzymes (Dinkova-Kostova et al., 2005). Recently, Bardoxolone methyl has been shown to significantly improve the creatinine GFR and cystatin C GFR in patients with DKD after only 4 weeks (Schwartz, Denham, Hurwitz, Meyer, & Pergola, 2009). However, Bardoxolone methyl did not improve urinary albumin excretion. Moreover, a recent landmark phase 2 trial of 227 adults with CKD and type 2 DM demonstrated that bardoxolone methyl improved GFR by at least 8.2 ± 1.5 ml/min over placebo after 24 weeks of treatment and that this effect was maintained after a year of therapy. (Pergola, et al., 2011). Even though bardoxolone did not effect proteinuria in this trial.

2.14 Role of haptoglobin (Hp) genotype

Hp is a hemoglobin-binding protein that has a major role in protecting against heme-induced ROS (Levy et al., 2010; Nakhoul, Miller-Lotan, Awaad, Asleh, & Levy, 2007). There are three common Hp genotypes: Hp 1-1, Hp 2-1, and Hp 2-2. The antioxidant protection provided by Hp in DKD has been shown to be genotype-dependent in animals (Miller-Lotan et al., 2005) and humans (Burbea et al., 2004), with Hp 1-1 providing superior antioxidant protection compared with Hp 2-2. Diabetic patients with the genotype Hp 2-2 are more likely to develop DKD than those with the Hp 2-1 or Hp 1-1 genotypes (Burbea et al., 2004; Levy et al., 2010; Nakhoul et al., 2007). However, no clinical therapeutic application has been studied in connection with Hp for DKD.

2.15 Plant-derived omega-3 fatty acids: Alpha linolenic acid

Omega-3 fatty acids are incorporated into cell membrane lipids, making them less susceptible to a free radical attack. Additionally, omega-3 fatty acids up-regulate the gene expression of antioxidant enzymes and down-regulate the gene expression of genes associated with ROS production (Takahashi et al., 2002). One of the most important plant-derived omega-3 fatty acids is alpha linolenic acid, found in rapeseed (canola),

chia, kiwifruit seed, soybean oil and in especially high content in flaxseed oil (Kris-Etherton, Harris, & Appel, 2003). Alpha linolenic acid has been shown to prevent the progression of DKD including reduction of proteinuria, glomerular sclerosis, and tubular abnormalities in streptozotocin (STZ)-induced diabetic rats (Barcelli, Weiss, Beach, Motz, & Thompson, 1990).

2.16 Animal-derived omega-3 fatty acids: Fish oil

Important animal-derived fatty acids include eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) found primarily in fish oil. Among their many antioxidant effects, EPA has been shown to inhibit the production of phospholipase A2, an important pro-oxidant enzyme (von Schacky, Siess, Fischer, & Weber, 1985; Zhang et al., 2006), and DHA has been shown to decrease NADPH oxidase activity (Diep et al., 2002). However, these fatty acids are also susceptible to auto-oxidation and may, theoretically, increase ROS and lead to progression of DKD (Nenseter & Drevon, 1996).

The antioxidant effects of fish oil-derived omega-3 fatty acids have also shown promising results in animal models of DKD. Several studies have noted a decrease in albuminuria (Garman, Mulroney, Manigrasso, Flynn, & Maric, 2009; Hagiwara et al., 2006; Zhang et al., 2006) and general proteinuria (Velasquez et al., 2003) in rat and mouse models of diabetes mellitus. The percentage of glomerular abnormalities, defined as either mesangial expansion (Velasquez et al., 2003; Zhang et al., 2006) or glomerulosclerosis (Garman et al., 2009), was less in rodent diabetic models fed omega-3 fatty acids, versus placebo. The extent of tubulointerstitial fibrosis was also less in these animals (Garman et al., 2009; Velasquez et al., 2003; Zhang et al., 2006).

Fish oil-derived omega-3 fatty acid effects on human DKD subjects have been less impressive. Two double-blind, randomized controlled studies, each involving 29 type 1 diabetic patients at a tertiary center, were performed comparing fish oil (4.6 g fish oil/d) with olive oil placebo (Myrup et al., 2001; Rossing et al., 1996). In one of these studies, although triglyceride and VLDL levels were lower in the fish oil group, total and LDL cholesterol were increased in that group, when compared to placebo (Rossing et al., 1996). There was no significant change in albuminuria (Myrup et al., 2001; Rossing et al., 1996) nor in GFR (Rossing et al., 1996) between the fish oil and control groups in type 1 diabetic patients. Currently, the data in vivo concerning the antioxidant effect of omega-3 fatty acids is inconclusive.

2.17 Red wine polyphenols

The antioxidant renoprotective effects of red wine have largely been attributed to their polyphenol constituents, which include resveratrol, quercetin, anthocyanins, gallic acid, catechin, tannic acid and myrcetin. Many other alcoholic beverages as well as tea, garlic, and other plants also are known to contain increased amounts of polyphenols (Rodrigo & Bosco, 2006). Among their antioxidant mechanisms, polyphenols have been shown to increase the activity of glutathione peroxidase and prevent deactivation of endothelial nitric oxide synthase (eNOS). eNOS is an isoenzyme of nitric oxide synthase (NOS) which uses NADPH to generate NO during oxidation of L-arginine and leads to vasodilation. Low starting reagent levels result in uncoupling of NOS and generation of superoxide via NADPH oxidase instead. Decreased NO-dependent renal vasodilation has been demonstrated in early DKD in both animals (Matsumoto, Koshiishi, Inoguchi, Nawata, &

Utsumi, 2003; A. C. Pflueger, Larson, Hagl, & Knox, 1999; A. C. Pflueger, Osswald, & Knox, 1999; A. C. Pflueger, Schenk, & Osswald, 1995) and humans (Frauchiger et al., 2000), also suggesting an uncoupling of the NO signal transduction pathway.

Several studies have also been carried out on rodent DKD models. For example, direct quercetin administration resulted in reduced levels of oxidative stress and attenuation of diabetic proteinuria, polyuria, serum creatinine, and blood urea nitrogen in STZ-induced diabetic rats when compared to STZ diabetic controls (Anjaneyulu & Chopra, 2004). Green tea polyphenol with partially hydrolyzed gaur gum has also been shown to reduce oxidative stress and improve kidney weight, blood urea nitrogen levels, serum creatinine, and creatinine clearance in partially nephrectomized and STZ-induced diabetic rats (Yokozawa, Nakagawa, Oya, Okubo, & Juneja, 2005). Another study on STZ rats led by the Montilla group included administration of red wine four weeks after, as well as two weeks prior to STZ injection. Treatment with red wine significantly prevented changes induced by STZ, including decreased albuminuria, proteinuria, glucosuria, triglycerides, and total cholesterol, when compared with the control STZ rat group (Montilla et al., 2005).

Several studies in humans suggest that chronic exposure to moderate amounts of red wine improve DKD. A large cross sectional study involving 157 type 1 diabetes patients with macroalbuminuria found that those who consume moderate amounts (30-70 g/week) of alcoholic beverages including red wine and beer, had a significantly lower incidence of macroalbuminuria than those who did not (Beulens et al., 2008). A randomized, controlled study involving moderate red wine versus white wine consumption (4 oz/day, for 6 months) in type 2 diabetes patients with DKD showed a statistically significant decrease in proteinuria, as well as in excretion of 8-hydroxydeoxyguanosine and liver type fatty acid-binding protein (markers of tubulointerstitial damage and of CKD, respectively) only in the red wine group (Nakamura, Fujiwara, Sugaya, Ueda, & Koide, 2009). Red wine has a higher content of polyphenols than white wine. Another randomized, controlled trial in diabetic patients showed that the administration of moderate amounts of red wine with a polyphenol-enriched, low-iron-available, carbohydrate-restricted diet was 40-50% more effective in improving renal and overall survival rates than the standard protein restriction diet (Facchini & Saylor, 2003). Further studies need to be conducted in order to investigate the full benefit of these compounds in patients with DKD.

2.18 Berry polyphenols

An important subgroup of polyphenol-containing foods are berries, such as acai berries, bilberries, raspberries, black currants, strawberries, blueberries, lingonberry extracts, and grapes (Pacheco-Palencia, Talcott, Safe, & Mertens-Talcott, 2008; Schauss et al., 2006; Seeram et al., 2008; Spada, de Souza, Bortolini, Henriques, & Salvador, 2008; Sun et al., 2010).

The most beneficial antioxidant molecules in berries are polyphenolic acids, including gallic acid, hydroxybenzoic acids, and flavanoids, including flavan-3-ols along with cyaniding 3-O-rutinoside and cyaniding 3-O-glucoside. One example is the acai fruit berry. Acai is a palm fruit from South America, and the pulp and oil extracts have been studied and shown to inhibit cell proliferation and demonstrate antioxidant properties (Mertens-Talcott et al., 2008; Pacheco-Palencia et al., 2008). Acai extract has been shown to improve endothelium-dependent vasodilatation in the mesenteric vascular bed of rats (Rocha et al., 2007). Furthermore, acai juice and pulp have been shown to increase plasma antioxidant capacity in humans up to threefold, albeit without an elevation in urinary antioxidants (Mertens-

Talcott et al., 2008). The benefits of the acai berry from pulp and oil in vitro have been demonstrated in humans with a dual effect on ROS generation, in that lower concentrations of acai extract may increase ROS generation, whereas higher concentrations have antioxidant properties (Pacheco-Palencia et al., 2008).

The antioxidant capacity of polyphenolics has further been demonstrated in freeze-dried acai extract (Schauss et al., 2006) and in other frozen fruits (Spada et al., 2008), suggesting that processed food items still retain antioxidant properties (Mertens-Talcott et al., 2008).

In one study, the antioxidant property of acai extract, assessed by SOD-induced scavenging of superoxide anion, was remarkably higher than in other reported fruit and vegetables. Seeram and colleagues also compared the antioxidant properties of several polyphenol-rich beverages, including acai juice. Their analyses revealed that the highest antioxidant index and gallic acid equivalence occur in the following order, from highest to lowest antioxidant properties: pomegranate juice, red wine, grape juice, blueberry juice, blackberry juice, acai juice, cranberry juice, orange juice, apple juice, green tea, and black tea (Seeram et al., 2008).

2.19 Role of heme oxygenase (HO)

HO is a heme degradation enzyme which is expressed in several organs, including liver and kidney. It is involved in the production of several molecules known to have antioxidant properties including, carbon monoxide, biliverdin/bilirubin, and iron/ferritin (Stocker, Yamamoto, McDonagh, Glazer, & Ames, 1987). HO-2 is constitutively expressed, while the inducible isoform, HO-1 is generated in response to oxidative stress. HO's specific functions in the kidney include maintaining renal blood flow, vasotonic equilibrium, and sodium and fluid absorption in the Loop of Henle (Abraham, Cao, Sacerdoti, Li, & Drummond, 2009). HO-1 has also been shown to enhance renal mitochondrial transport carriers and cytochrome c oxidase activity (Di Noia et al., 2006). CO, one of the products of heme degradation, has been shown to have both pro-oxidant (via vasoconstriction) and antioxidant (via vasodilation) effects (Abraham et al., 2009; Lamon et al., 2009).

The antioxidant effects of HO-1 have also been demonstrated in rodent DKD models. Goodman, et al. examined the differences between HO-2 (-/-) knockout and HO-2 (+/+) wildtype mice. When diabetes was induced by STZ in both groups, HO-2 (-/-) mice demonstrated increased plasma creatinine levels, acute tubular damage and microvascular pathology when compared to their wildtype HO-2 counterparts. An inverse relationship was demonstrated between HO and superoxide levels. These results clearly indicate that HO activity is essential in preserving renal function and morphology in STZ-induced diabetic mice (Abraham et al., 2009; Goodman et al., 2006).

Although there are studies showing the causative role of pro-oxidants, including endothelin-1, TGF- β and platelet-derived growth factor (PDGF) in DKD patients (Gilbert, Akdeniz, Allen, & Jerums, 2001; Jandeleit-Dahm, Allen, Youssef, Gilbert, & Cooper, 2000; Langham et al., 2003) and HO-1 has been shown to inhibit these pro-oxidants (Abraham et al., 2009; A. Pflueger et al., 2005), no human studies have been performed demonstrating the direct effect of HO on alleviating DKD.

2.20 Role of bilirubin

As noted above, bilirubin is a degradation product of HO and is long known to have antioxidant properties (Stocker, Glazer, & Ames, 1987; Stocker, Yamamoto, et al., 1987). The ROS scavenging properties of bilirubin have been demonstrated in rat tissue samples. In rat

liver tissue exposed to oxidative stresses including UVA radiation, menadione bisulfite, or copper sulfate, the addition of low doses of bilirubin prevented lipid peroxidation and attenuation of glutathione reductase antioxidant enzyme (Ossola, Groppa, & Tomaro, 1997; Ossola, Kristoff, & Tomaro, 2000; Ossola & Tomaro, 1995, 1998). Bilirubin and biliverdin (bilirubin's immediate precursor) inhibit CO-induced superoxide generation in rat renal arteries (Lamon et al., 2009). Bilirubin also demonstrated important effects on angiotensin II (AII) activity: in vitro, AII administration results in vascular smooth muscle contraction and generation of superoxide anion, a powerful ROS. Administration of bilirubin was shown to normalize the pressor and pro-oxidant effects of AII (A. Pflueger et al., 2005).

Despite the aforementioned beneficial properties, high levels of bilirubin have also been associated with adverse effects in cells. In our own experiments, higher bilirubin concentrations ($\geq 100 \mu\text{M}$, $\geq 5.8 \text{ mg/dL}$) were associated with apoptosis (unpublished observations by the authors). Bilirubin has also been shown to inhibit mitochondrial enzymes, cause DNA damage, and inhibit protein synthesis (Chuniaud et al., 1996). Moreover, bilirubin has been shown to have inhibitory effects on ion exchange and water transport in the kidney (Sellinger, Haag, Burckhardt, Gerok, & Knauf, 1990).

A few studies involving bilirubin and renal damage that may mimic DKD have been carried out in animal models. Recently, Adin and colleagues demonstrated that micromolar doses of bilirubin improved renal vascular resistance, urine output, GFR, tubular function, and mitochondrial integrity in rats exposed to ischemia/reperfusion renal injury (which can occur in DKD) (Abraham et al., 2009; Adin, Croker, & Agarwal, 2005). The attenuating effect of bilirubin on AII has also been shown in animal models although AII administration caused a significant decrease in GFR and impairment of both endothelium-dependent and endothelium-independent vasodilators in control rats, hyperbilirubinemic Gunn rats were resistant to such effects (A. Pflueger et al., 2005). Another study by Fujii et al. suggests a protective effect of bilirubin in diabetic animal models via downregulation of NADPH oxidase. Diabetic, hyperbilirubinemic Gunn j/j rats and biliverdin-treated diabetic db/db mice were found to have a lack of progression of mesangial expansion and less albuminuria than the control diabetic, j/+ Gunn rats and non-biliverdin-treated db/db mice, respectively, suggesting a bilirubin- and biliverdin-induced resistance to the development of DKD. In vascular endothelial and mesangial cells cultured from these animals, bilirubin and biliverdin were found to significantly inhibit NADPH-dependent superoxide production, as well as hyperglycemic- and AII-induced production of ROS, suggesting that this bilirubin- and biliverdin-induced protection is mediated by an antioxidant mechanism (Fujii et al., 2010).

Several human studies have recently been conducted studying the antioxidant effects of bilirubin on DKD. A cross-sectional, population-based study of 93,909 Korean subjects found that CKD due to diabetes mellitus was significantly lower in women with higher bilirubin levels, but not in men (Han et al., 2010). However, another cross-sectional study using demographic data from 13,184 US patients found higher serum bilirubin levels to be associated with lower estimated GFR and higher albuminuria, but found no significant associations in diabetic patients (Targher et al., 2009). A recent case control study compared bilirubin levels of 32 type 2 diabetic patients with DKD to those of 32 likewise diabetic patients without DKD, matched for gender, age, and diabetes duration. Bilirubin was $5.5 \pm 2.3 \mu\text{mol/l}$ in cases versus $7.3 \pm 3.3 \mu\text{mol/l}$ in controls ($P = 0.02$), suggesting a protective effect of bilirubin on DKD in humans (Zelle, Deetman, Alkhalaf, Navis, & Bakker, 2011).

2.21 Role of coenzyme Q10

Coenzyme Q10 (also known as ubiquinone, or “Q10”) is a lipid-soluble component of the electron transport chain. In its reduced form (ubiquinol-10), coenzyme Q10 acts as an antioxidant, inhibiting lipid peroxidation and free radical oxidative damage.

Studies involving Q10’s renal effects have thus far been sparse. No rodent studies focusing on DKD have been performed. However, the effects of Q10 on renal function in human diabetics are beginning to be conducted. A 1998 study by Suzuki (Suzuki et al., 1998) and colleagues studied the effect of Q10 on 28 subjects with a rare form of diabetes called maternally inherited diabetes mellitus and deafness (MIDD), caused by a mutation of one of the tRNA genes in the mitochondrial DNA. The subjects were given daily doses of 150mg of Q10 over a period of three years. Results showed that Q10 improved insulin secretory response, post-exercise lactate levels, and progression of hearing loss in these patients. However, Q10 was not shown to improve diabetic complications in these patients, including DKD.

A recent randomized, controlled 8-week trial involving 74 subjects by Mori and colleagues showed that when taken in conjunction with omega-3 fatty acids (4g/d), Q10 (200mg/d) improves systolic and especially diastolic blood pressure in (non-diabetic) moderate-to-severe CKD patients. This effect on diastolic blood pressure using combination therapy was only marginally better than the results of omega-3 fatty acids being used alone (3.4 mm Hg decrease for combination therapy versus 2.9 mm Hg decrease for omega-3 alone), and thus, the effects of Q10 alone on blood pressure need confirmation. When Q10 was used alone on such patients, no benefit on blood pressure was observed; in fact, Q10 demonstrated a slight tachycardic effect. Since hypertension is an important prognostic factor in the progression of CKD, the authors of this study suggested that Q10 may slow down CKD progression when used in conjunction with omega-3 fatty acids (Mori et al., 2009). However, more studies involving Q10 used alone and in combination with omega-3 fatty acids would have to be performed in order to elucidate its effect on CKD. Studies involving Coenzyme Q10 and diabetes-induced CKD and other manifestations of DKD would also need to be performed in order to investigate Q10’s effect on this aspect of diabetes.

2.22 Tempol

Nitroxides, also known as superoxide dismutase mimetics, are a class of potent, synthetic antioxidants. One of the nitroxides, tempol, has been studied extensively for its antioxidant properties. Tempol metabolizes superoxide anion to by a catalase-like action. Furthermore, nitroxides metabolize, detoxify, or prevent the formation or action of a wide range of other ROS (Wilcox & Pearlman, 2008).

In animals, tempol has been shown to prevent the development of hypertension, proteinuria, oxidative ROS, podocyte damage, and upregulation of the aldosterone effector kinase-1 in glomerular podocytes of uni-nephrectomized rats (Ebenezer, Mariappan, Elks, Haque, & Francis, 2009). The authors have suggested that the beneficial effects of tempol on the reduction of proteinuria and glomerular damage are due to its antioxidant properties (Wilcox & Pearlman, 2008). Interestingly, tempol has been shown to improve renal oxygenation in rats and thereby may improve bioavailability of NO. Numerous studies have demonstrated blood pressure-reducing effects of tempol which are outlined in a detailed review article published by Wilcox and Pearlman (Wilcox & Pearlman, 2008). Tempol has also been demonstrated to reduce SOD activity in the renal cortical tissue of diabetic Zucker rats, thereby reducing the expression of numerous pro-

oxidant factors such as TNF, NF- κ B and NADPH oxidase (Ebenezer et al., 2009). Furthermore, the reduction of renal SOD reduced the progression of DKD in the C57 BL/6 Akita diabetic mouse model (Fujita et al., 2009).

However, to date, tempol has never been studied in clinical trials for the treatment of DKD. Although tempol has potential properties to be effective in clinical trials, it can act as a pro-oxidant when used in high doses. Therefore, appropriate dosing regimens have to be determined clinically (Wilcox & Pearlman, 2008).

2.23 Other potential antioxidants for the treatment of DKD

Other potential antioxidant agents for the treatment of DKD include the following, with the potential antioxidant mechanism in parenthesis: selenium (cofactor for glutathione peroxidase), reduced glutathione (reducing agent by virtue of an SH-group), ceruloplasmin (binding iron), transferrin (binding iron), albumin (binding iron and copper), uric acid (binding iron and copper), amino-steroids (e.g. methylprednisolone; inhibit lipid peroxidation by non-glucocorticoid action), metformin (inhibits lipid peroxidation, increases SOD and glutathione levels), thiazolidinediones (inhibit lipid peroxidation, decrease inflammatory mediators, decrease p47^{phox} expression), folate (decreases eNOS and xanthine oxidase-mediated O₂⁻ production), estrogen (decreases eNOS transcription), NOS inhibitors (decrease NO and potentially ONOO⁻), endothelin receptor antagonists, and vitamin B. However, these agents have not been studied systematically to determine their clinical effects in the treatment of DKD and warrant further evaluation.

3. Conclusions

The increased generation of ROS production in diabetes plays a critical role in the pathogenesis of DKD. Appropriate and successful antioxidant therapy for the treatment of DKD will vitally depend on several factors, including: mechanism of action, site of action, auto-oxidation and conversion to ROS while serving as an antioxidant, plasma half-life, mode of delivery, safety, and tolerability. In the past, the benefits of antioxidant therapy have been limited by ineffective targeting of ROS pathways and ROS production at the site of injury or disease process. Antioxidant agents acting directly at the mitochondrial site may promise higher efficacy than non-specific antioxidant agents. However, clinical trials and the development of further appropriate and more effective antioxidant agents are warranted.

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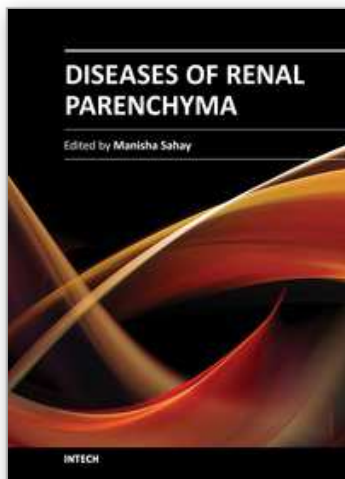
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Clinical nephrology is an evolving speciality in which the amount of information is growing daily. This book gives quick access to some important clinical conditions encountered in nephrology including the diseases of glomeruli, tubules and interstitium. It presents the latest information on pathophysiology, diagnosis and management of important diseases of renal parenchyma. The information is presented in a very user friendly and accessible manner while the treatment algorithms enable the reader to quickly access expert advice on arriving at the most appropriate treatment regimen. The book discusses the renal involvement in various systemic diseases including diabetes and autoimmune diseases. Diabetic nephropathy is fast becoming the commonest cause of end stage renal disease all over the globe and is discussed in this book. The editors believe that this book will be a valuable addition to the reader's library.

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