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THE HEART AND DIABETIC NEPHROPATHY

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BACKGROUND

Diabetic nephropathy represents the most common etiology for stage 5 chronic kidney disease in the United States, resulting in the need for dialysis and transplantation. It is estimated that about one-third of U.S. patients who need renal replacement therapy are diabetics.

Chronic kidney disease (CKD) of any etiology is associated with cardiovascular disease and is more predictable in patients with diabetic nephropathy.[1] Such individuals have an increased incidence of coronary artery disease and hypertension but also can have diabetic cardiomyopathy due to microvascular complications of diabetes.[2] Optimal blood pressure, blood sugar, and blood lipid control as well as cessation of smoking are of utmost importance in preventing progression of cardiovascular, renal, and end-organ damage. Similarly, early recognition and treatment of microalbuminuria (a manifestation of systemic endothelial dysfunction) is extremely important in improving cardiovascular and renal outcomes.[3]

Diabetic Vascular Injury

Diabetes is associated with macrovascular and microvascular complications often worsened by hypertension, with vasculopathy being the major cause of morbidity and mortality in this population.[4] Microvascular complications lead to nephropathy, retinopathy, and neuropathy; macrovascular complications include premature ischemic cardiomyopathy, peripheral vascular disease, and cerebrovascular disease.[5]

Diabetic vasculopathy is due to a combination of humoral factors, hemodynamic abnormalities, and metabolic imbalance leading to multi-organ dysfunction initially resulting from altered glucose homeostasis.[6]

Arterial hypertension present in approximately 70% of diabetics[7] accelerates the microvascular and macrovascular complications of diabetes, resulting in endothelial dysfunction and vascular remodeling; this in turn leads to medial enlargement from vascular smooth muscle cell hyperplasia and cellular matrix accumulation.[8]

Endothelin-1 (ET-1) released from the endothelial cells activates ET_B receptors, causing an initial vasodilatation. This is followed by vasoconstriction resulting from stimulation of ET_A receptors. ET-1 also can cause vascular hypertrophy.[4] ET-1 release is increased in diabetes-associated vascular hypertrophy, and in experimental models, treatment with the ET_A/ET_B receptor antagonist bosentan ameliorated mesenteric vascular hypertrophy.[9]

The renin angiotensin system (RAS) plays an important role in the pathogenesis of diabetic vasculopathy in several ways. The RAS induces vascular hypertrophy by stimulating smooth muscle cell proliferation, increases extracellular matrix (ECM) accumulation, and enhances production of the profibrotic collagen factor IV.[10] Moreover, angiotensin II (ANG II) stimulates the formation of reactive oxygen species by producing superoxide anion from smooth muscle cells. These increased free radical formations result in decreased synthesis of nitric oxide, which leads to endothelial dysfunction, hypertension, and atherosclerosis.[11] Treatment with angiotensin-converting enzyme inhibitors (ACE inhibitors) or angiotensin receptor blockers (ARBs) can alter the RAS and reduce this oxidative stress, which mitigates its atherosclerotic potential. In addition to diminishing ANG II production, ACE inhibitors also decrease degradation of kinins, thus favoring the release of nitric oxide (Figure 1).[12]

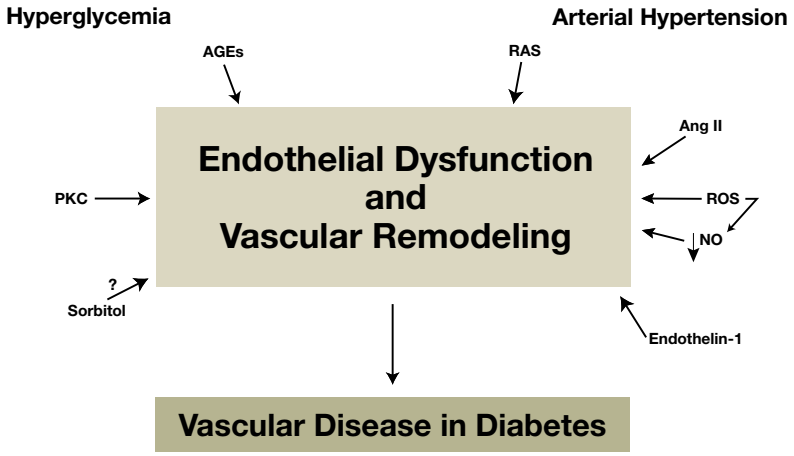

Figure 1. Molecular pathogenesis of vascular disease in diabetes. AGEs: advanced end-glycosylation products; Ang II: angiotensin II; NO: nitric oxide; PKC: Protein Kinase C; RAS: renin-angiotensin-system; ROS: reactive oxygen species.

Hyperglycemia has been directly implicated in accelerated atherosclerosis and microvascular disease.[13] The vascular injury resulting from hyperglycemia occurs from increased formation of advanced glycation end products (AGEs).[14] Direct evidence relating AGEs to atherosclerosis has been shown in experimental normoglycemic rabbits by injecting AGE- modified albumin, resulting in increased atherosclerotic lesions.[15]

Protein kinase C (PKC) appears to be activated by hyperglycemia in several tissues including kidney, heart, retina, and aorta.[16] Increasing levels of PKC β2 isoforms have been described in patients with heart failure, providing further evidence for an etiologic role of this enzyme in heart disease.[17] At the kidney level, in experimental models, ACE inhibitors have been shown to reduce renal PKC activity, perhaps playing an important protective role against PKC-mediated vascular injury.[18]

Another glucose-dependent factor implicated in vascular injury is the polyol pathway.[19] In this pathway, glucose is reduced to sorbitol by the enzyme aldose reductase. The advent of aldose reductase inhibitors has resulted in studies designed to assess the role of the polyol pathway in tissue organ damage, but results of these investigations, specifically on diabetic nephropathy, are conflicting.

Coronary Artery Disease and Diabetic Nephropathy

Diabetic nephropathy with or without decreased kidney function results in accelerated atherosclerosis of coronary and carotid arteries. In fact, cardiovascular mortality is the leading cause of death among the increasing diabetic population.[20]

Asymptomatic coronary artery disease is often present among individuals with diabetic nephropathy. This is an important issue that should be addressed prior to kidney transplantation.[21] Between 25% and 40% of patients without angina and diabetic nephropathy were screened with coronary angiography before receiving a kidney transplant, and one or more coronary arteries were found to have a 50-70% stenosis.[22]

In some transplant centers, coronary angiogram is routinely advised as part of the pre-transplant workup among diabetics; this may not be justified, however, since coronary arteriography could precipitate acute kidney failure in someone with stage 4 or 5 CKD.[23] As such, only high-risk individuals, including those older than 45, smokers, and those with a prior history of myocardial infarction, abnormal echocardiographic studies, or clinical evidence of vascular disease should have coronary arteriograms.

In general, the risk of cardiovascular mortality is increased in patients with microalbuminuria.[24, 25] However, in a prospective study using aggressive therapy with a program designed to control hyperglycemia, hypertension, hyperlipidemia, and microalbuminuria over a seven-year period, a reduction of cardiovascular and microvascular events by 50% was achieved.[3]

When myocardial revascularization is contemplated in patients with diabetic nephropathy, a team effort among nephrologists, cardiologists, and cardiovascular surgeons is imperative in guiding the patient towards the proper treatment, either coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI). In general, diabetes is associated with poorer outcomes for both CABG and PCI. Although there are no specific guidelines in patients with coronary artery disease and diabetic nephropathy, it would appear that with left main lesions, multivessel disease, impaired left

ventricular function, and complex lesions, CABG should be the preferred approach. Individual patient selection should always be the decisive factor.[26]

The issue of sudden death in patients with CKD stage 5D, including those with diabetic nephropathy and coronary artery disease, remains a challenge.[27] Primary preventive measures include the use of β-Blockers such as carvedilol, which showed a reduction of cardiovascular mortality in patients with dilated cardiomyopathy over a two-year period — 29.3% mortality compared to 67.9% in patients receiving placebo.[28] Use of β–blockers is also indicated in patients with sleep-disordered breathing who are at increased risk of sudden death.[29]

In observational studies, blockage of the RAS among patients on dialysis showed no significant improvement in mortality during a prospective controlled trial using the ACE-I fosinopril.[30] Another study showed improved mortality and reduction of cardiovascular events among dialysis patients using an ARB (candesartan).[31]

In general, the use of aldosterone receptor blockade with spironolactone (RALES study) showed a reduction of cardiovascular mortality and sudden death.[32] However, spironolactone or eplerenone can cause severe hyperkalemia among patients with diabetic nephropathy and impaired kidney function, particularly if simultaneously receiving ACE inhibitors or ARBs.

Frequently, patients with diabetic nephropathy have low levels of vitamin D. Active vitamin D, 1,25(OH)2 cholecalciferol, has also been shown to have beneficial effects on the cardiovascular system by causing regression of left ventricular hypertrophy and a reduction in renin production,[33] ANG II, and natriuretic peptide.[34] However, prospective controlled studies are needed to establish the beneficial effects of vitamin D in cardiovascular mortality and sudden death.

Blood Pressure Control and Cardiovascular Events in Patients with Diabetic Nephropathy

Reduction of systolic blood pressure (SBP) to less than 130 mm Hg has been shown to delay progression of kidney disease and also reduce the incidence of cardiovascular complications in patients with diabetic nephropathy.[35] On the other hand, patients over the age of 70 with SBP less than 120 mm Hg had an increased risk of all-cause cardiovascular mortality, making aggressive blood pressure control harmful in these patients.[36]

Table 1. Blood Pressure Goals in Diabetic Kidney Disease

Proteinuria	<1.0 g/day	≥1.0 g/day
BP goal	<130/80 mm Hg	<125/75 mm Hg

The recommended therapeutic approach by the National Kidney Foundation for the treatment of hypertension in patients with diabetes and proteinuria include:

1. Target 130/80 if proteinuria less than 1 gm/day
2. Target 125/75 if proteinuria greater than 1 gm/day

First-line agents:

- Serum creatinine <1.8 mg/dl. ARB or ACE-I +/-HCTZ
- Serum creatinine >1.8 mg/dl. ARB or ACE-I +/- loop diuretic bid

Second-line agents:

- Heart rate >85 per minute. Non-dihydropyridine calcium channel blockers (CCB) (diltiazem/verapamil)
- Heart rate <85 per minute. Dihydropyridine CCB (amlodipine/nifedipine). May use triple combination such as ARB/CCB/HCTZ.

With coronary artery disease or resting tachycardia, add beta blocker and/or clonidine. With prostatic hypertrophy, consider alpha 2 blocker (doxazosin, terazosin). Avoid the combination of ARB/ACE-I/beta blocker as it has been associated with increased cardiovascular mortality.[37]

Glycemic Control in Patients with Cardiovascular Disease and Diabetic Nephropathy

Blood glucose control (HbA_{1c} <6.5%) has been shown to reduce vascular injury, preventing microvas-

Table 2. National Kidney Foundation recommended treatment approach for hypertension in patients with diabetes and proteinuria.

Serum Creatinine	First Line Agents	Second Line Agents
<1.8 mg/dl	ACE I or ARB ±HCTZ	HR<85 bpm: Dihydropyridine CCB (amlodipine/nifedipine) HR>85 bpm: Nondihydropyridine CCB (diltiazam/verapamil) CAD: β-blockers BPH: α-2 blockers (doxazosin, terazosin)
≥1.8 mg/dl	ACE I or ARB ±Loop diuretics	

cular lesions that cause progression of nephropathy and retinopathy.[30]

Many trials have been designed to assess the beneficial effects of glycemic control, most of which agree about the importance of maintaining normoglycemia to prevent further target organ damage among diabetics, but these studies are beyond the scope of this review. It is estimated that diet and weight reduction contribute 50% of blood sugar control, exercise 25%, and medications 25% of diabetes control in both type I and type II diabetes patients.

At present, there are several types of medications available to control blood sugar, all with different mechanisms of action. At times a combination of them is needed to achieve normoglycemia. With impaired kidney function (CKD3 and above), it is probably better to use the short-acting pre-prandial oral hypoglycemic agents (nateglinide/repaglinide) to avoid the risk of prolonged hypoglycemia. Metformin should not be used when the estimated glomerular filtration rate (eGFR) <50 ml/min to prevent potential lactic acidosis. Twice or once a day, long-acting insulin should be used if the patient is unable to reach the HbA_{1c} goal with diet, exercise, and the combination of medications described above.

Blood Lipid Control and Cardiovascular Complications in Diabetic Nephropathy

The importance of controlling hyperlipidemia to prevent cardiovascular complications has been the subject of extensive research in the cardiovascular literature. In regards to diabetic nephropathy, hypercholesterolemia appeared to be an important risk factor in the progressive decline of kidney function in patients with diabetic nephropathy.[38]

A study by Shepherd et al. investigated how intensive lipid-lowering therapy with atorvastatin affected kidney function in 10,000 patients with coronary heart disease. Using the Modified Diet in Renal Disease (MDRD) formula to estimate GFR, the expected decline in renal function was not observed over the 5-year study period; in fact, kidney function was even better maintained in those who received larger doses (80 mg per day versus 10), suggesting a dose-related benefit.[39]

Observational studies showed an increased mortality among CKD stage 5 patients on dialysis when cholesterol levels were low (total cholesterol <150 mg/dL).[40, 41] It is possible that late initiation of statin therapy once patients start dialysis may not be useful, since by then extensive vascular damage has occurred. Moreover, low albumin and low cholesterol levels, a manifestation of malnutrition and inflammation, are markers of poor prognosis. Other studies have reported beneficial effects of statins in terms of reduced mortality among the dialysis population.[42] In a more recent well-designed, randomized, double-blinded, prospective study (AURORA Study Group), initiation of resuvastatin in patients receiving hemodialysis lowered LDL cholesterol but had no significant effect on cardiovascular-related events.[43] At present, it would appear that statins are justified in patients with diabetic kidney disease, and it would be reasonable to continue them once dialysis has begun.[44]

Conclusion

Diabetic nephropathy is a common occurrence in the United States and the leading cause of CKD stage 5. In addition, hypertension frequently is present among these patients, resulting in microvascular and macrovascular damage that leads to ischemic cardiomyopathy aggravated by hyperglycemia and hyperlipidemia — known risk factors for coronary artery disease. Aggressive control of those metabolic abnormalities with the proper drugs, as well as lifestyle modification (smoking cessation, diet and weight reduction, exercise), may slow down the progression of generalized atherosclerosis, coronary artery disease, and kidney failure in patients with diabetic nephropathy.

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