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uring the past few years, it has become apparent that there are factors that place a person at greater risk for the development and progression of renal failure. This has been documented since the early 1980s by the United States Renal Data System that has collected data confirming that end-stage renal disease occurs at a greater rate in certain subpopulations of Americans. It is evident from an examination of the data that African Americans and American Indians have an incidence of end-stage renal disease that is not proportional to their percentage of the total population. In fact, African Americans and American Indians are reported to have at least a 4-fold greater incidence of end-stage renal disease than white Americans. There have been 5 factors identified: hypertension, glucose intolerance, insulin resistance, salt sensitivity, and hyperlipidemia, which may play a greater role in these subpopulations. In addition, as with other populations, lifestyle issues may serve to alter these primary risk factors or may act as direct modulators of renal disease progression. There is also a possibility that interactions between risk factors frequently occur that may modify the development or progression of the disease. This article reviews these risk factors and emphasizes the interaction between hypertension and the other factors. In addition, the effects of antihypertensive agents on risk factors and on renal outcome are emphasized. Where possible, issues specific to African Americans and American Indians are underscored; however, one must accept that the database on these populations is only now developing. This review should help the clinician make appropriate choices when prescribing antihypertensive therapy for patients who may be at risk of developing progressive renal failure.

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RISK FACTORS IN
AFRICAN AMERICANS AND
AMERICAN INDIANS

It is apparent that there is a propensity for African Americans to develop hypertension and diabetes at a greater rate than whites. The reported prevalence of hypertension is double that of whites in both sexes and in all age groups after the second decade of life. In addition, numerous studies have shown a much higher prevalence of type 2 diabetes mellitus in African Americans than in whites. And finally, the combination of hypertension and diabetes is three times more common in African Americans than in whites.

The same predilection for hypertension and diabetes is also present in American Indians. Prior to 1950, the prevalence of hypertension in American Indians was 8% to 10%, compared with the national average of about 25%. Similarly, type 1 diabetes mellitus apparently did not occur in American Indians and the glucose intolerance of type 2 diabetes mellitus was unusual. However, probably as a consequence of dietary and lifestyle changes, hypertension now occurs more frequently in American Indians than in the general American population. The prevalence of type 2 diabetes mellitus has increased dramatically as well. In addition, American Indians who used to have cholesterol levels much lower than the national average now have an increased occurrence of hyperlipidemias. As these risk factors have become more evident in these subsets of the US population during the past several years, so too has there been an increase in the incidence of ESRD. The rates of ESRD in these groups have now increased alarmingly, as noted by the US Renal Data System reports.

RISK FACTORS FOR CHRONIC RENAL FAILURE

Hypertension

Hypertension is a major independent risk factor for the development of renal failure. In addition, it also appears to play a major role in the progression of renal failure in patients who have primary renal disease from other causes. Rosansk and colleagues noted this relationship when they compared the rate of change in renal function in patients who had essential hypertension with that of an age-matched normotensive control group. Renal deterioration was greater in the hypertensive cohort, with the greatest correlation noted with the level of systolic blood pressure.

In a recent analysis of data from the Multiple Risk Factor Intervention Trial, cases of ESRD were identified from the 332,544 men followed up for the 16-year span of the study. This study found a strong correlation between the degree of blood pressure elevation and the occurrence of ESRD, with the level of systolic blood pressure being the better predictor. In addition, the relative risk of ESRD in men with stage 4 hypertension (blood pressure, 210/120 mm Hg) was 22 times that of those with optimal blood pressure (<120/80 mm Hg). This study involved mostly white men and because of the nature of the data retrieved probably underestimates the problem. Earlier studies by Moyer et al and Magee and coworkers also clearly documented that untreated hypertension commonly results in ESRD.

Although hypertension increases the risk of developing renal failure in most populations studied, its effect seems to be enhanced in African Americans and American Indians. The question is whether this occurs because of interactions with other risk factors. Analysis of data collected by the Hypertension Detection and Follow-up Program showed a rate of significant deterioration of renal function between 2% and 22% in African Americans when other risk factors, such as male sex and older age, were present. This risk of the loss of renal function was evident even when blood pressure was adequately controlled. If renal impairment was present at the outset of the study, the risk of the loss of renal function increased 10-fold.

The negative impact of hypertension on renal function in African Americans has been noted in other studies as well. Rostand and coworkers followed the course of 94 patients who had hypertension and normal serum creatinine concentrations at the outset of the study. They found that African American patients had twice the risk (30% vs 15%) of having a significant increase in serum creatinine concentration during the 5-year study. Again, it was found that this increase in risk persisted even if blood pressure was adequately controlled. McClellan et al also concluded that African American patients had a disproportionately higher incidence of ESRD. When their data analysis was corrected for the increased incidence of hypertension in the African American patients (3 times that in whites), the higher risk persisted. When the data from the Multiple Risk Factor Intervention Trial were reanalyzed, it was determined that the decline in renal function was greater for black men than for white men, despite similar control of blood pressure. Other studies have shown this independent correlation between African Americans and ESRD. Thus, there appears to be support for the conclusion that there are racial differences in the propensity to develop renal failure. It also is apparent that hypertension in African American patients may make them more susceptible to ESRD, while other factors may play an additive role.

Type 1 Diabetes Mellitus

Microscopic evidence of diabetic nephropathy is evident in approximately 90% of patients who have had insulin-dependent diabetes for more than 10 years. However, renal insufficiency and persistent proteinuria develop in only about half of the patients in this category. The National High Blood Pressure Education Program’s Working Group on Hypertension in Diabetes has noted that all forms of hypertension may coexist with diabetes mellitus because of the high prevalence of the 2 conditions.

Whether the now documented interaction between hypertension and diabetic nephropathy leads
to an increase in the rate of progression to renal failure is the question. In 1976, Mogensen was the first to note an association between hypertension and loss of renal function in patients with diabetes. He found that a 2-month course of antihypertensive therapy in patients who had both diabetes and impaired renal function resulted in a decrease in proteinuria. He later prospectively treated 6 patients with diabetes for 6 years and found a reduction in the rate of decline of renal function and proteinuria. Parving et al treated hypertension aggressively with metoprolol in 10 patients with type 1 diabetes and found a similar reduction in the rate of progression of renal failure. Subsequent clinical investigations have shown the beneficial effects of therapy with a variety of antihypertensive regimens, including calcium channel blockers and angiotensin-converting enzyme (ACE) inhibitors.

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is the most prevalent form of diabetes. In addition, it has emerged as a major risk factor for the development and progression of renal disease. In 1982, Fabre and colleagues published the results of a study in which they examined the course of renal disease in 510 patients with type 2 diabetes mellitus who were chosen at random from their clinic in Switzerland. When compared with nondiabetic controls, the patients with diabetes had a relatively good prognosis, except when there was coexistent hypertension or proteinuria. Hypertension was twice as prevalent in the patients with diabetes, and the degree of hypertension correlated with the increase in protein excretion and the decrease in renal function. Furthermore, 14% of hypertensive diabetic patients had a glomerular filtration rate below 60 mL/min vs only 4% of normotensive diabetic patients. When protein excretion exceeded 150 mg/d, the risk of having abnormal renal function doubled but control of blood pressure had little effect on protein excretion.

Studies of African American patients have revealed some interesting facts. Tierney et al studied 6880 patients in a general internal medicine clinic and emphasized that type 2 diabetes mellitus and its common comorbidity, systolic hypertension, were the major risk factors in the development and perpetuation of renal failure. However, what was more striking was the finding that the black race was also a risk factor for the development of renal failure. Cowie and coworkers analyzed data from the Michigan Kidney Registry and made the interesting observation that most African American patients who had diabetic renal disease had type 2 diabetes mellitus, whereas most white patients who had diabetic renal disease had type 1 diabetes mellitus. Furthermore, they showed that although the risk of ESRD is higher with type 1 diabetes mellitus, the majority of patients in the population they studied had type 2 diabetes mellitus.

A similar observation was noted in Pima Indians by Nelson et al in 1988. They found a 13-fold greater prevalence of ESRD in their 1137 patients who had type 2 diabetes when compared with a control group of white patients. In addition, the incidence of ESRD correlated with the presence of hypertension and the duration of the diabetes but not with age or age at onset of diabetes. Nielsen and coworkers reached a similar conclusion about the correlation between hypertension and the rate of progression of renal failure in Danish patients with type 2 diabetes for whom systolic blood pressure was the best correlate. Similar results were found by Ravid et al in an Israeli population and Chaien et al in a study of African Americans. Thus, evidence has shown that type 2 diabetes is a major risk factor for the development of renal disease and that the presence of hypertension increases the likelihood for renal failure. Furthermore, the increased prevalence of these risk factors in American Indians and African Americans is associated with progression to ESRD.

Salt Sensitivity

Although there is some controversy, it appears evident that there is a link between salt intake and hypertension in a subset of hypertensive individuals. It is unclear whether there is a direct relationship between salt sensitivity and renal failure, or whether the coexistent hypertension is the risk factor. However, it does appear that certain hypertensive patients who are salt sensitive have abnormal renal responses to a salt load. Williams and Hollenberg studied a group of patients with essential hypertension and normal or high plasma renin activity. Those individuals did not show the normal increase in renal blood flow when given a high-sodium diet, and they had a prolonged sodium excretion time. Campese et al extended these observations when they described a group of African American patients with essential hypertension but low plasma renin activity. These individuals had an abnormal response to a high-sodium diet with a decrease in renal blood flow and an increase in filtration fraction. Those authors surmised that this response reflected an increase in intraglomerular pressure. They suggested the possibility that in a subset of patients, especially those of African American and American Indian descent, more rapid progression to ESRD may result from this abnormal renal response to salt loading, thus resulting in high glomerular pressures and consequent renal injury.

Another question is whether there is a relationship between salt sensitivity and insulin resistance. A recent study involving 28 patients showed that plasma glucose and insulin concentrations were higher in patients with salt sensitivity. Although preliminary, these data suggest that salt sensitivity may exert its influence on renal disease by aggravating glucose intolerance and insulin resistance.

Hyperlipidemia

Increasing evidence has implicated hyperlipidemia as an independent risk factor for the
development and progression of renal failure. In 1981, Edwards et al. reported an inverse correlation between fasting levels of serum triglycerides and glomerular filtration rate. The next year, Moorhead et al. proposed that filtered lipoproteins may lead to chronic renal failure by damaging the glomerular and tubular membranes. During the late 1980s, Maschio and coauthors described 247 patients they had followed up for 1 to 14 years who had chronic renal failure as a result of various causes. They found that there were substantial differences in the serum lipid levels in patients with different nephropathies, despite treatment with a protein- and phosphate-restricted diet with 40% of the energy intake as lipids. In that study, patients with chronic glomerulonephritis and nonnephrotic range proteinuria had higher serum triglyceride levels than those with pycnephritis at comparable levels of renal function. Furthermore, after a 32-year follow-up, the patients with hyperlipidemia lost renal function at twice the rate of the patients with normal lipid levels.

Despite the mounting evidence, it has been difficult to isolate the effects of lipids alone on the progression of renal disease. The clear-cut interaction between lipid disorders and hypertension has led to the suggestion of additive risk when both are present. The possible interaction between abnormal lipid levels and diabetes was studied by Mulec et al., who described a prospective randomized trial of patients with nephropathy secondary to type 1 diabetes. These patients were treated with either enalapril or metoprolol for hypertension, resulting in equivalent blood pressure, urinary albumin, and hemoglobin A1C measurements during the 18-month follow-up period. In the 14 patients who had elevated cholesterol levels, the rate of progression of their renal failure was 3.6 times greater than the rate in the 17 patients with normal serum cholesterol levels.

A recent report by Krolewski and coworkers reviewed the data from the Diabetic Retinopathy Study to determine what variables were responsible for loss of renal function in patients with proliferative retinopathy and proteinuria who were followed up for a 3-year period. Because this study was performed during the 1970s, few of the patients received adequate treatment for their hypertension or hyperlipidemia. Those authors found that only one third of their patients were at risk for rapid progression of nephropathy and that only systolic blood pressure and hyperlipidemia correlated with this decline in function. In those patients who were both normotensive and normcholesterolmic (ie, neither risk factor present), 1 patient in 5 was described as a fast progressor (those who experienced a 50% increase in serum creatinine levels in 3 years). If either risk factor was present, 1 patient in 3 was described as a fast progressor, and if both were present, 1 patient in 2. Similar interactions have been shown by Samuelsson et al. Although there is evidence that treating hyperlipidemias ameliorates the adverse effect on renal function in animal models, adequate human studies have not been conducted.

**Lifestyle**

Lifestyle modification, weight reduction, increased physical activity, and moderation of salt and alcohol intake have been noted by both the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure, and the Working Group on Hypertension in Diabetes as an important adjunct in any hypertension treatment regimen. The question remains whether these lifestyle factors are independent variables in the development and progression of renal disease or whether their role is through the other major factors, such as hypertension, glucose intolerance, or abnormal lipid levels.

The possible role for dietary salt intake in salt-sensitive individuals was discussed earlier. There are some preliminary data that would suggest a role for obesity as either a direct or indirect factor in the initiation or progression of renal disease. Ribstein reported that urinary albumin excretion was enhanced in obese individuals whether or not hypertension was present. A recent study of American Indians by Robbins and coworkers found a high prevalence of diabetes, obesity, and hypertension in this population. When they quantified the amount of albuminuria in these subjects, they found the expected increased prevalence in those individuals with diabetes. However, they also noted a prevalence of microalbuminuria (≥30 to <300 mg albumin per gram of creatinine) of 3.9% to 16.2% and macroalbuminuria (≥300 mg of albumin per gram of creatinine) of 0.6% to 4.2% in those without diabetes. In addition, they found that those subjects with the greatest percentage of American Indian blood had the greatest prevalence of proteinuria, suggesting a possible separate genetic component.

The issue of whether a sedentary lifestyle affects renal function has not been adequately studied. However, it is clear that there is a relationship between the degree of physical fitness and hypertension. That is, sedentary individuals have a 20% to 50% increased risk of developing hypertension than do their fit counterparts. The case for alcohol is probably similar, exerting an effect through its causal relationship to hypertension.

Therefore, in choosing antihypertensive therapy for the individual with multiple risk factors for renal disease, it may be important to consider the effects of antihypertensive medications on other risk factors. As mentioned, some of these factors have been directly linked to renal outcome, while with others the evidence is becoming more suggestive. As an example, human studies have not clearly shown an association between decreases in lipid levels and favorable outcome of renal disease. However, it is likely that when multicenter studies are performed, they will document this association in a similar fashion to the way the Diabetes Control and Complications Trial demonstrated an association between diabetic control and renal outcome.

There is little controversy regarding the benefit of antihypertensive therapy on renal outcome. However, there is disagreement as to
which agent or agents are best in individuals at risk for developing renal disease or those who currently have it. The following sections will attempt to summarize the effects of antihypertensive drugs on glucose and lipid metabolism, and review available data from some of the studies that have looked at the issue of slowing the progression of renal failure with the use of antihypertensive drugs.

**EFFECT OF ANTIHYPERTENSIVE THERAPY ON GLUCOSE Intolerance AND INSULIN RESISTANCE**

Patients with hypertension have been shown to have glucose intolerance. The effects of certain classes of antihypertensive drugs on glucose metabolism are as follows:

<table>
<thead>
<tr>
<th>Antihypertensive Drug</th>
<th>Response</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzothiadiazide diuretics</td>
<td>Decrease in glucose utilization</td>
<td></td>
</tr>
<tr>
<td>β-Adrenergic blocking agent</td>
<td>Increase in insulin resistance</td>
<td></td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>Increase in glucose utilization</td>
<td></td>
</tr>
<tr>
<td>α₁ Peripheral blockers</td>
<td>Decrease in insulin resistance</td>
<td></td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>Variable effect and/or neutral</td>
<td></td>
</tr>
<tr>
<td>Angiotensin II antagonists</td>
<td>Unknown</td>
<td></td>
</tr>
</tbody>
</table>

When Prisant and Carr examined the literature concerning the effects of antihypertensive drugs on insulin resistance and glucose metabolism, they found that benzothiadiazide diuretics and β-adrenergic blocking agents increase insulin resistance and worsen diabetic control. In contrast, α₁-adrenergic blocking agents and ACE inhibitors decrease insulin resistance and improve glucose control. When calcium antagonists have been evaluated, a mixed effect has been observed: nifedipine worsens insulin sensitivity and verapamil has no effect.

It has been shown that the beneficial effect of certain drugs on glucose metabolism may be negated by the concomitant use of agents that have negative effects. Shieh and colleagues evaluated the effects of cilazapril, an ACE inhibitor, alone or in combination with hydrochlorothiazide on the patients’ plasma glucose levels and insulin response to an oral glucose tolerance test. When cilazapril was given alone, the glucose challenge test resulted in reduced plasma glucose and insulin levels compared with those prior to treatment. However, the addition of hydrochlorothiazide with the ACE inhibitor resulted in plasma glucose and insulin levels remaining unchanged from pretreatment values. It is also of interest that in this study the negative effect was observed even though the patients received a low dose of hydrochlorothiazide (12.5-25 mg/d).

**EFFECT OF ANTIHYPERTENSIVE THERAPY ON SERUM LIPID LEVELS**

It has been shown that both pharmacological and nonpharmacological (lifestyle modifications) therapy for hypertension may affect serum lipid levels. In the Treatment of Mild Hypertension Study, one of the parameters evaluated was the effect of lifestyle modifications alone or in combination with the use of a diuretic, β-blocker, α₁-adrenergic antagonist, calcium channel blocker, or an ACE inhibitor on lipid levels in 902 hypertensive men and women with diastolic blood pressures less than 100 mm Hg. It was found that with either lifestyle modifications or pharmacological therapy, total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels decreased and high-density lipoprotein cholesterol levels increased. However, the magnitude of the decrease in total cholesterol, low-density lipoprotein cholesterol, and triglyceride levels and the increase in high-density lipoprotein cholesterol was smaller and equivalent in the groups who modified their lifestyle or who used a diuretic in addition to modifying their lifestyle.

The effects of the various classes of antihypertensive agents on lipid profiles are listed in the table. There is consensus that diuretics and β-adrenergic blocking agents decrease high-density lipoprotein cholesterol levels and increase triglyceride levels. Angiotensin-converting enzyme inhibitors, calcium channel blockers, and α₁-agonists are neutral in terms of their effect on lipids, and there is now mounting evidence that the newer angiotensin II selective blockers are also neutral. In older studies using relatively high doses (50-100 mg/d of hydrochlorothiazide) compared with those recommended today, diuretics were shown to increase total and low-density lipoprotein cholesterol levels and decrease high-density lipoprotein cholesterol levels. When lower doses have been used (12.5-25 mg/d of hydrochlorothiazide), the effect on lipids has been less marked or neutral.

**EFFECT OF ANTIHYPERTENSIVE THERAPY ON PROGRESSION OF RENAL FAILURE**

When the seminal work of Brenner and coworkers was published, it demonstrated a positive effect of the use of ACE inhibitors in preventing the progression of renal failure in the rat. Since that time, there has been interest in examining the re-
nal effect of various antihypertensive medications in patients who have chronic renal failure. Although definitive human studies evaluating the effect of blood pressure control on renal function have not been performed, several studies have suggested that antihypertensive therapy may have a beneficial effect.68,69 “The National High Blood Pressure Education Program Working Group’s Report on Hypertension and Chronic Renal Failure”13 concluded that there is “an association between the rate of decline in renal function and the level of blood pressure control . . . ” Furthermore, the report suggests that whether the patient had mild, moderate, or severe pretreatment hypertension, the reduction of blood pressure was beneficial in protecting renal function.

Beneficial effects have been shown in patients with diabetes when blood pressure is lowered with β-adrenergic blocking agents79,80 and vasodilators.29,31 However, more recently the major focus has shifted to the use of ACE inhibitors, calcium channel blockers and the newest class of antihypertensive agent, the selective angiotensin II–receptor blockers. In addition to lowering blood pressure, the physiological basis for using these agents is that they are likely to affect the potential adverse effects of angiotensin II on the kidney. Angiotensin II has been shown to decrease both renal blood flow and the glomerular filtration rate.70 Because of its preferential constrictive effect on the efferent glomerular arteriole, it may also increase glomerular hydrostatic pressure. In addition, angiotensin II increases macromolecular penetration into the mesangial areas, causing an inflammatory response.51 Release of the cytokine’s transforming growth factor β and platelet-derived growth factor causes increased growth and hypertrophy of mesangial cells.31 Numerous studies have demonstrated a positive effect in preventing one or more of these potentially deleterious effects of angiotensin II by ACE inhibitors,72,74 calcium channel blockers,72 and selective angiotensin II–receptor blockers.73,74 Angiotensin-converting enzyme inhibitors act by blocking conversion of angiotensin I to angiotensin II, calcium channel blockers by antagonizing the vasoconstrictive action of angiotensin II, and the angiotensin II–receptor blockers by selectively and directly blocking the angiotensin II receptor.75

There are currently 2 approved angiotensin II–receptor blockers, losartan potassium and valsartan, with a third, irbesartan, in the final stages of the Food and Drug Administration approval process. Losartan has been the most extensively studied of the 3 and preliminary studies suggest that in many respects losartan acts similar to the ACE inhibitors. In patients with primary glomerular disease, losartan has been shown to reduce blood pressure and proteinuria to the same extent as the ACE inhibitor enalapril.76 Also, losartan is well tolerated in patients who have renal insufficiency77 and has been found to be beneficial in lowering blood pressure in hypertensive patients who have chronic renal insufficiency.78

COMMENT

The process of selecting an appropriate antihypertensive agent for a given patient is complex. This process becomes even more difficult in the case of a patient who belongs to a subpopulation that characteristically has many risk factors for the development and perpetuation of chronic renal failure and ESRD. Even the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure,51 which advocated the use of diuretics and β-blockers as the preferred first-line therapy amid some controversy,79 did not suggest limiting treatment options to these agents when coexistent renal failure, diabetes, or dyslipidemia was present. The report further suggested, in reference to the treatment of African Americans, that because of the greater incidence of severe hypertension in this group, the clinician should not hesitate to use the most powerful agents necessary for control of hypertension, especially if renal failure was also present. Thus, when the clinician is faced with an African American or American Indian patient who has hypertension that requires treatment, it is imperative that an antihypertensive drug be chosen that is free of adverse effects on these factors. Although control of blood pressure is paramount, it is advantageous to control it without adversely affecting glucose or lipid metabolism. If this class of drugs also has demonstrated a probable positive effect on the rate of progression of chronic renal failure and is relatively efficacious, then these features would add to the clinician’s preference for using this class of drugs. From the clinical data available, it appears that the ACE inhibitors, calcium antagonists, and the newest agents, the selective angiotensin II–receptor antagonists, possess many of these positive attributes. Thus, these considerations may make them the preferred drugs for use in the subpopulations of Americans who have a predisposition for the development of renal disease or renal failure.

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