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HYPERTENSION AND DIABETES

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Epidemiological studies and therapeutic trials frequently have used different criteria to define hypertension in diabetic patients. It is not clear which criteria is the most appropriate to define hypertension in these populations. Studies in the general population indicate an increased risk of cardiovascular disease occurs with any increase in blood pressure level, so an increase in diastolic blood pressure of 5 mmHg is associated with an increase in the incidence of stroke of 34% and incidence of coronary disease of 21%[1].

Recently the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure in its sixth report (JNC VI)[2] has recommended criteria for borderline and established hypertension using both systolic (SBP) and diastolic blood pressure (DBP) levels. This new criteria, also categorize individuals into 3 groups according to their risk of hypertensive complications (groups A, B and C). Subjects with established target organ damage and all diabetic patients are categorized in the risk group C (the highest risk group). In these recommendations, treatment decisions are based both on the absolute blood pressure level and on the risk profile of the individual patient. The main consequence of this classification is that diabetic patients with blood pressures between 130 - 139 systolic and 85 - 89 diastolic, that are considered borderline for other groups, are candidates for antihypertensive treatment. The available information from controlled clinical trials, suggests that these goals would result in decreased renal and cardiovascular outcomes.

A clearer understanding of the impact of diabetes and hypertension on the development of cardiovascular disease (CVD) has also emerged over the past two decades. Both are well-established risks alone, but when coexistent, increase the risk two to eightfold for CVD morbidity, and more than double it for CVD mortality.[3,4,5,6] Once nephropathy has developed, the risk for CVD is even greater.[7,8] Heart disease and stroke remain the first and third leading causes of death in the U.S.[9]

A number of clinical studies have established strong support for the positive impact that early detection and aggressive treatment of both diabetes and hypertension can have. Such intervention can delay the onset of diabetic nephropathy and prevent its progression to ESRD. It is presumed that such treatment could also prevent CVD and death. To date, treatment of hypertension had impacted the incidence of strokes and renal disease, at least until a recent leveling,[9] but has not shown a benefit in terms of reducing the morbidity or mortality of CVD,[10,11] perhaps because of the frequently associated metabolic abnormalities which co-contribute to risk for CVD. The need for ongoing intensification and refinement of intervention strategies, and assurance of their availability to all people affected by diabetes and hypertension, cannot be overemphasized, if two of the most deadly complications of diabetes are to be eventually eradicated.

EPIDEMIOLOGY OF HYPERTENSION IN DIABETES

Approximately 16 million Americans have diabetes; the vast majority (> 90%) of those have type 2 diabetes.[12,13] Approximately 60 to 65% of diabetic individuals have coexistent hypertension,[14,12] twice the rate of the general population.[15,16,17] About 20% of End-stage renal disease is caused by hypertension,[18] but diabetes is the leading cause of ESRD in the U.S. and Europe.[19,7,20,21] In the U.S. it accounts for 36% of all diagnosed cases, an increase from 13% in 1982 and 26% in 1992, a threefold rise.[19,12]

The timing and presentation of hypertension is different between type 1 and type 2 diabetes. In type 1 diabetes, hypertension develops after several years of the disease and usually reflects the development of early or advanced diabetic nephropathy. It ultimately affects approximately 30% of individuals with type 1 diabetes [22,23]. In type 2 diabetes, hypertension may be present at the time of diagnosis or even prior to the development of hyperglycemia [22, 24, 25].

Several confounding factors are present in type 2 diabetes that make the assessment of the frequency of hypertension difficult. Type 2 diabetic patients are older and have a greater degree of adiposity than non diabetic patients. The prevalence of hypertension in Western populations increases with age and degree of obesity [26]. Thus, the elevated blood pressure in these individuals may represent the aging or obesity of the population. However, compared with age and weight matched subjects, a higher prevalence (of approximately 1.5 times that of non diabetic groups) of hypertension is still observed in individuals with type 2 diabetes [25]. Approximately 40 - 60% of patients with type 2 diabetes will develop hypertension. In some ethnic groups, diabetic nephropathy may be the primary determinant of hypertension in type 2 diabetic patients, Asians, African Americans, Native Americans, and Mexican Americans have a much higher risk of nephropathy than Caucasian patients,[15,13,27,28-31] and, a much higher likelihood of ESRD.[32,29,31,33] The Pima Indians of Arizona have not only the highest incidence of diabetes in the world (70%),[34] but an incidence of nephropathy of 40-50%,[33] and a prevalence of ESRD 20 times that of the general U.S. population.[33]

Some recent data regarding the incidence of nephropathy are more optimistic, showing a decline at least in some type 1 diabetic populations. The earliest such study appeared in 1989, reporting that the cumulative incidence of clinical nephropathy was significantly lower in patients diagnosed with type 1 diabetes in the U.S. after the 1940s than in those diagnosed earlier.[35] A similar decline in risk for nephropathy was observed in Denmark[36] and Sweden.[37] Moreover, it has been estimated that most future cases of ESRD are preventable. [15,32,38-41]

PATHOGENESIS OF HYPERTENSION IN DIABETES

Although the overall rate of hypertension in diabetic individuals is twice that of the general population, this is largely accounted for by patients with type 2 diabetes. The rate in those with type 1 diabetes, until renal disease is present, is approximately the same as that of individuals without diabetes.[42] The development of hypertension in type 1 diabetes correlates with duration of disease,[43] presence of nephropathy,[16,17,42] and its progression.[44,45] In contrast, elevation of blood pressure commonly occurs before onset of, or even without nephropathy, in type 2 diabetes,[46-49] suggesting that potentially different mechanisms may underlie the development of hypertension in the two types of diabetes. The causes of hypertension in type 2 diabetes potentially are many, including concomitant essential hypertension, insulin resistance, atherosclerotic disease, or nephropathy which is yet undiagnosed. Thus, hypertension in diabetic individuals reflects a complex and heterogeneous pathogenesis, and may include different mechanisms in the two types of the disease.

Genetic Factors

Data suggesting a genetic basis for hypertension, particularly in type 1 diabetes, include those studies which have correlated hypertension in a nondiabetic parent with increased risk of nephropathy in the diabetic offspring.[50,51] Hypertension is also more common in certain ethnic groups with diabetes; for example, African Americans (63%) more than Caucasians (38%) and Mexican Americans (34%).[12,52]

Attempts to identify a hypertensive gene or genes are ongoing. Some recent work has shown that mutations in the angiotensinogen gene are highly correlated with hypertension in several nondiabetic, white, European families.[53] There is, however, no known relationship between mutations at this gene locus and other gene loci associated with diabetes, including HLA loci.[53,54]

Ion Transport Dysregulation

Considerable data in the literature support an association between hypertension and certain alterations in the concentrations of a variety of intracellular electrolytes. For example, in type 2

diabetic/insulin resistant individuals, evidence suggests that increases in intracellular sodium and calcium, and deficiency in magnesium, may play roles.[55-61] Abnormalities in intracellular electrolytes may occur as a result of dysregulation of membrane ion transporter systems, such as the Na^+-K^+-ATPase, the Ca^{2+}-ATPase, $Mg^{2+}Na^+$-exchanger, the Ca^{2+}-H^+ exchanger, the Na^+-Li^+ countertransporter, and the Na^+-H^+ antiporter,[55,56,58,60,62-68] the latter two perhaps particularly operative in diabetic hypertensive individuals.[63,65,67-69] Insulin increases Na^+-H^+ antiporter activity,[70] which stimulates sodium reabsorption.

What is not known is whether disturbances in ion transport predate the development of hypertension and diabetes, or whether hypertension results from an altered diabetic metabolic environment. Disordered cellular calcium transport may also contribute to the development of hypertension in diabetes, and may, in fact, be one of the mechanisms underlying resistance to insulin.[61,65] Insulin can cause intracellular calcium concentration to increase in a number of ways, including enhancing membrane calmodulin and stimulating ATPase affinity for calcium, or by increasing the number of units of calcium per cell via enhanced tissue synthesis.[71,72] Hyperglycemia can also increase vascular smooth muscle cell calcium,[73,74] which can increase vascular tone.[5,75] Studies in both hypertensive animals and diabetic humans have shown that increased intracellular calcium concentrations may be associated with a salt-sensitive form of hypertension.[177,76,77]

Extracellular Sodium And Insulin

Total body exchangeable sodium is increased in diabetic compared with nondiabetic individuals.[177,3,16,78] This occurs in part as a result of hyperglycemia, hyperfiltration of glucose, and alterations in the sodium-glucose exchanger,[79,80] and as a result of stimulation of the Na-K-ATPase[55,56] in the kidney tubule. Insulin (particularly hyperinsulinemia) reduces sodium excretion in normal individuals,[81,82] and this effect may be augmented in hypertensive diabetic patients,[83,84-86] which in theory could, over time, result in the development of hypertension. Other studies have shown, however, that chronic hyperinsulinemia does not cause an expansion of extracellular sodium and volume,[87,88] and is unlikely to be responsible for the development of hypertension. It is possible that insulin contributes to hypertension in multiple ways, either through effects on sympathetic nervous system activation, salt sensitivity, or because of systemic resistance to its action. These mechanisms will be discussed further.

Hyperglycemia per se may contribute to increased body sodium. Studies have demonstrated that a reduction in sodium excretion occurs after salt loading in hyperglycemic subjects,[80] which may result from alterations in the sodium-glucose exchanger.[80] However, the total body sodium pool is increased in diabetic individuals whether normo- or hypertensive,[89] so changes in total body sodium are unlikely to contribute directly to the mechanism of hypertension, unless an individual is salt-sensitive.

Sympathetic Nervous System Activity

A number of studies have demonstrated a direct correlation between increases in plasma insulin concentration and increases in sympathetic nervous system (SNS) activity,[90-93] manifested by increased plasma norepinephrine levels,[90, 91] pulse rates, blood pressures,[90-92] and other cardiovascular measures of sympathetic tone.[92] Hyperinsulinemia is also accompanied by increased sensitivity to pressors such as norepinephrine and angiotensin II.[79,94,95] However, these normal physiologic responses to insulin in humans are accompanied by a paradoxical decrease in both peripheral vascular resistance and blood pressure; i.e., insulin acts as a vasodilator.[87,96] Evidence suggesting a role for the SNS in the relationship between hypertension and insulin can also be surmised from studies of obesity-related hypertension. Insulin resistance and hyperinsulinemia are more closely associated with hypertension in obese individuals than in nonobese individuals.[97,98]

According to this hypothesis, hyperinsulinemia, which is a compensatory mechanism for insulin resistance, stimulates the SNS, producing increased thermogenesis. Plasma insulin concentration and urinary norepinephrine excretion have been shown to be significantly correlated with blood pressure in a cohort of obese individuals,[122] after adjustment for BMI and body fat distribution. There is wide variation, however, in the correlation between insulin resistance and hypertension according to ethnicity.[99]

Insulin resistance in obese subjects is presumed to result from increased fat mass, or conversely, from decreased muscle mass. But insulin resistance has also been demonstrated in nonobese individuals with hypertension,[54,100] and the operative mechanisms are less clear. The fact that insulin resistance has been observed in normotensive relatives of hypertensive individuals suggests a genetic contribution.[54]

Salt-Sensitive Hypertension

Individuals with hypertension manifest variable blood pressure responses to salt-loading and increased dietary salt intake, and can be classified as either salt-sensitive or -resistant.[101-103] Salt-sensitive individuals with essential hypertension have been shown to increase insulin secretion in response to an oral glucose load, suggesting a correlation between salt-sensitivity and insulin sensitivity.[104] A number of investigators have suggested such a relationship among hyperinsulinemia, insulin resistance, and salt-sensitive hypertension, but such a correlation has not been demonstrated in all studies.[97,99,105] Interestingly, salt-sensitive individuals have increased urinary albumin excretion rates, more atherogenic lipid profiles,[104] and a greater propensity to retain salt, a characteristic which could directly aggravate hypertension.

Hypertension And Metabolic Disorders

Hypertension is frequently associated with, and is indeed a component of, a metabolic syndrome which includes insulin resistance, impaired glucose tolerance, dyslipidemia, and obesity.[106-110] Studies have shown that a significant proportion of individuals with hypertension are insulin resistant and/or hyperinsulinemic.[106,111] This finding suggests that the metabolic changes associated with hypertension may, in some cases at least, play a role in the regulation of blood pressure, or, alternatively, that a common underlying mechanism may contribute to the development of hypertension, insulin resistance, glucose intolerance and dyslipidemia.[83,106-110]

PATHOGENESIS OF DIABETIC NEPHROPATHY

Despite some lack of clarity defining the mechanisms underlying the pathogenesis of hypertension in diabetes, the impact of hypertension is all too clear. A self-propagating cycle unfortunately often develops in the diabetic individual, whereby hypertension and hyperglycemia lead to nephropathy, nephropathy to more severe hypertension, and hypertension to accelerate the course of nephropathy toward ESRD. Understanding how hypertension and other factors create an environment for the development and progression of nephropathy opens windows of opportunity for intervention and prevention.

While the pathogenesis of hypertension may differ in type 1 and type 2 diabetes, there is probably less difference in the factors which lead to nephropathy,[13,112,113] including genetic, metabolic and hemodynamic components. Among the risk factors which appear to be most important are hyperglycemia, hypertension, ethnicity, gender, family history, duration of diabetes, and cigarette smoking.

The Natural History Of Diabetic Nephropathy

Mogensen first described the progression of nephropathy in type 1 diabetes[109] as a series of stages or steps on a steadily deteriorating pathway from normal renal function to ESRD, marked by

the appearance of increasing amounts of albuminuria. Data support that these stages are similar in type 2 diabetes.[112,113,114] Increased albumin excretion reflects histological and functional abnormalities in the kidney.[115] Microalbuminuria is the earliest laboratory evidence of diabetic kidney disease,[117,115,116] and occurs 5-8 years prior to the onset of overt proteinuria.[118] Individuals with albumin excretion rates (AER) below 30 mg/day (20 ug/min) have normoalbuminuria, while those above this range, but with less than 300 mg/day (200 ug/min), are designated as having microalbuminuria. An AER of greater than 300 mg/day is termed macroalbuminuria, clinical albuminuria, gross or overt proteinuria.[119,120-123] At this point the urine protein test is generally positive with commercial albumin test sticks.

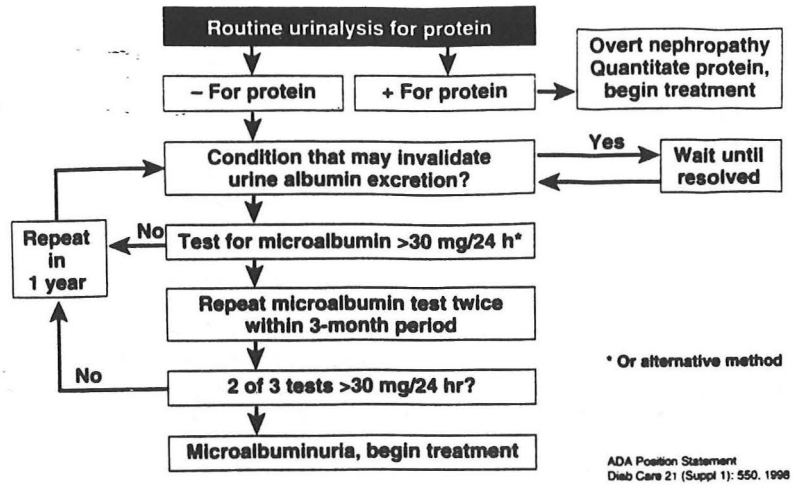
According to Mogensen, stage 1 is defined by hypertrophy of kidney tissue[119,124] and hyperfunction, manifested as an increase in the glomerular filtration rate (GFR).[117,119,116,125] Stage 2, which occurs 2-3 years after the onset of diabetes, is characterized histologically by the presence of specific glomerular lesions, namely expansion of the mesangium, glomerulosclerosis, and basement membrane thickening, but without clinically overt disease.[119,124-128] Stage 3, which occurs 7-15 years after onset, is referred to as incipient nephropathy, and its hallmark is an increase in urinary albumin excretion (UAE)[129] into the range of microalbuminuria.[7,13,119,120,130] It is during this stage that intervention may reverse the microalbuminuria and halt or slow the progression of nephropathy.[131,27,35,119] The GFR at this stage is usually normal or slightly elevated.[119,116] Stage 4 is overt nephropathy, defined by the presence of frank proteinuria with a normal or slightly decreased GFR.[119,116] Glomerulosclerosis continues during stages 3 and 4. Intervention during stage 4 can slow, but not reverse, the progression to renal failure.[37,41,132] Without specific intervention, the rate of decline of renal function occurs at approximately 1 ml/min per month,[44,121,118,133,134-137] but there is wide individual variability.[27,120] During Stage 5, which occurs 20-40 years after onset of diabetes, GFR continues to decline and blood pressure continues to increase. Approximately 50-75% of patients who reach this point will progress to ESRD within 10-18 years.[37]

The development of albuminuria within the first 5 years of diagnosis of type 1 diabetes should trigger an alert to search for another cause of the kidney disease. This is not necessarily true in individuals with type 2 diabetes, in whom the incidence of albuminuria at time of diagnosis of diabetes ranges from 3-30%.[128,121,131-142] The highest incidence of overt proteinuria at the time of diagnosis is in the Pima Indians.[142]

Microalbuminuria And The Progression Of Diabetic Nephropathy

That microalbuminuria predicts risk for progression to overt proteinuria and nephropathy in both type 1 and type 2 diabetes has been appreciated for more than a decade, and its value as such provides a promising opportunity for intervention at a time when future renal damage is preventable. The value of microalbuminuria for predicting the risk of progression of nephropathy in type 2 diabetes is regarded by some to be less certain, but most would agree that its presence still indicates a need for appropriate evaluation and treatment.[7,123,143] A study which compared type 1 and type 2 diabetic individuals reported that, over ten years of followup, the risk of progression of microalbuminuria in the patients with type 2 diabetes was significantly lower (22%), but still not insignificant, compared with that in type 1 (80%) patients.[123] Other studies have demonstrated that in any diabetic individual, once proteinuria occurs, the decline in renal function continues at the same rate whether type 1 or type 2.[144,145,146] From the time of onset of clinical albuminuria, studies have shown that GFR declines at a rate of approximately 1.0 ml/min per month,[144,116,121] and the rate of this progression is increased further if hypertension is present or if the individual is a cigarette smoker.[147-150] The combined analyses of a number of studies have shown the value of microalbuminuria for prediction of progression to proteinuria is in the range of 30-87.5%[135,151,152] for either type of diabetes, with a negative predictive value (the risk of an individual with normoalbuminuria *not* progressing to clinical albuminuria) of 99.5%.[135]

ALGORITHM FOR MICROALBUMINURIA SCREENING



Genetic Risk For Diabetic Nephropathy

The fact that only a portion of patients with diabetes develop nephropathy suggests that there is a genetic susceptibility to do so. Brenner has suggested that the absolute number of nephrons present at birth may predetermine an individuals risk for hypertension and renal disease from multiple causes.[153] Evidence supporting a genetic predisposition to diabetic nephropathy includes the increased risk for nephropathy developing in diabetic siblings of a type 1 diabetic proband with nephropathy,[154] and familial clustering of nephropathy in both types 1 and 2 diabetes.[51,155] Furthermore, ethnicity appears to affect the prevalence and severity of diabetic nephropathy, which is greater in Hispanics and nonwhite groups such as Native Americans and African Americans.[15,28-30,155-157,158] Several mechanisms potentially link genetic susceptibility to nephropathy and are felt to be the same as those which confer susceptibility to hypertension,[75,78] including familial hypertension,[159,160] increases in erythrocyte sodium-lithium countertransport,[67-69] increases in sodium-hydrogen antiporter activity,[62,65,161] polymorphism in the angiotensin converting-enzyme (ACE) gene,[53,162,163] and insulin resistance.[164,76,51,82,83,87]

Interestingly, some type 2 populations, such as Pima and Zuni Indians and Alaskan natives, develop renal disease without hypertension,[47,165,166] suggesting a separate genetic risk for each disease, but possibly also protection against the development of hypertension, but not diabetic nephropathy and ESRD.

THE ROLE OF HYPERGLYCEMIA IN THE INITIATION AND PROGRESSION OF DIABETIC NEPHROPATHY

There is now overwhelming evidence that the onset of microalbuminuria and the progression to nephropathy correlate closely with poor glycemic control, particularly in type 1, but also in type 2, diabetes. The Steno group followed 209 normotensive patients with type 1 diabetes and normoalbuminuria for 10 years and demonstrated that the development of microalbuminuria could be predicted by the level of HbA_{1c}, and that no patient with an HbA_{1c} level below 7.5% developed

microalbuminuria.[118] In another 10 year followup study of 109 patients with type 1 diabetes, of 81 patients who initially had normal albumin excretion, 6 (23%) remained microalbuminuric, fifteen of the initially microalbuminuric patients (58%) developed normoalbuminuria after 10 years, and 5 (19%) developed macroalbuminuria.[167] Those who normalized their albumin excretion had lower HbA_{1c} levels (6.7%) than either those who remained microalbuminuric (7.7%) or who developed macroalbuminuria (8.9%).A large study in 1613 patients with type 1 diabetes followed at the Joslin Clinic demonstrated that the development of microalbuminuria correlated closely with glycemic control, with a gradual rise in rate as the HbA_1 level increased from 8.1 to 10.1% (HbA_{1c}= 6.1 to 8.1%) and with a sharp increase occurring above a HbA_1 level of 10.1% (HbA_{1c}= 8.1%).[168] These findings suggest the possibility of a threshold glycemic level for microalbuminuria, but this has clearly not been demonstrated in other studies.[40]

There is even data to suggest that, contrary to long-held belief, improvement in glycemic control can slow progression of nephropathy in patients with more advanced disease.

The Wisconsin Epidemiologic Study is instructive regarding the impact of glucose control on complications in type 2 diabetes. A 10 year prospective study in 2990 type 1 and type 2 diabetic subjects (1210 younger-onset [< age 30] and 1780 older-onset [> age 30]), it was designed to evaluate the relationship between glycemic control and the incidence and progression of diabetic complications, including nephropathy. Followup at 10 years demonstrated that the higher the glycated hemoglobin level, the greater the incidence of gross proteinuria in both groups of diabetic individuals.[169]

A recent, retrospective study in 123 elderly Japanese with type 2 diabetes lends support to the importance of poor glycemic control on the initiation of diabetic nephropathy.[170] In this study, among the group of 74 normoalbuminuric individuals, those who developed microalbuminuria over the course of the 6 year study (n=24) had significantly higher 6 year HbA_{1c} levels than the group which remained normoalbuminuric, with no differences in mean blood pressures. This study suggests that glycemic control is the most important factor in initiating nephropathy.

THE IMPACT OF HYPERTENSION ON DIABETIC NEPHROPATHY

Hypertension is the other key factor which contributes to the development and progression of diabetic nephropathy. The presence of hypertension is a serious comorbidity in both type 1 and type 2 diabetes, because it either reflects an already ongoing renal impairment, and/or it represents a condition which will adversely impact on future kidney function. If treated aggressively, however, control of hypertension is probably the most critical factor in slowing the rate and extent of decline. By the time albuminuria develops, approximately one-third of type 1 diabetic individuals have some degree of blood pressure elevation;[116,122] by the time ESRD develops, 80-90% have hypertension.[121,171] In type 2 diabetes, hypertension frequently precedes the development of renal disease, suggesting that different mechanisms may be operative, despite similar histological changes.[172, 173] The presence of hypertension developing prior to onset of type 2 diabetes in fact predicts the development of renal dysfunction.[46,173] Whatever the operative sequence, once hypertension has developed, there is an accelerated decline in GFR and an increase in albuminuria.[144]

A retrospective analysis of 103 proteinuric individuals with type 2 diabetes explored potential factors which were felt to have affected the progression of early nephropathy, and observed a close correlation between the rate of progression to proteinuria and systolic blood pressure.[174] Parving, in a now classic prospective study of the clinical course of diabetes, followed 11 type 1 patients for 23-66 months, observing the course of renal function. He found that GFR decreased significantly over this time and correlated closely both with increasing albuminuria and blood pressure.[137] Mogensen, in his early studies, observed similar findings.[175]

Some of the best evidence that hypertension plays a role in the development of nephropathy in type 2 diabetes comes from data collected from the Pima Indians.[80] Although the incidence of renal failure is higher in this population than in others, the risk factors are felt to be similar, and include hypertension, hyperglycemia, microalbuminuria, and hypercholesterolemia.

A significant correlation between hypertension and the rate of progression of albuminuria was reported by Mogensen and colleagues, in a 6 year prospective study of 278 type 2 diabetic individuals.[176] These data are supported by a recent, retrospective study in 123 elderly Japanese with type 2 diabetes.[170] In this study, among a group of 74 initially normoalbuminuric individuals, those who eventually progressed to proteinuria over the course of the 6 year study had significantly higher mean blood pressure levels than the group which remained normoalbuminuric or microalbuminuric, with no differences in mean HbA_{1c} levels. This study suggests that blood pressure control is more important than glycemic control in progression to clinical nephropathy in type 2 diabetes.

RENAL DISEASE AND THE RISK OF CARDIOVASCULAR DISEASE

Increased mortality in individuals with type 1 and type 2 diabetes is largely attributable to CVD, not nephropathy.[177,3,4,5] The reasons for this are not entirely clear. Although glycemic control, blood pressure, and lipid status are certainly contributing factors, they do not entirely explain the excessive risk for, or severity of, CVD.[14]

That microalbuminuria is a marker of risk for development of CVD was independently reported in 1984 by both Mogensen[121] and Jarrett,[178] and their common conclusion, that microalbuminuria predicts cardiovascular and all-cause mortality, has since been confirmed in a number of studies in both type 1 [179,180] and type 2 diabetes.[181-183] This association does not appear to hold true in all populations,[184] but in those individuals in whom albuminuria does herald a potential risk of mortality, its value as a predictor appears to be powerful. An elevation in albumin excretion has even been shown to predict an increase in cardiovascular mortality even in nondiabetic individuals.[185]

In a ten year study Parving and colleagues[186] followed 939 patients with type 1 diabetes of five or more years of duration, 593 of whom had normal albumin excretion, 181 who had microalbuminuria, and 165, macroalbuminuria, at baseline. Outcome measures included all-cause and cardiovascular mortality. The results showed that 15% of patients with initial normoalbuminuria, 25% with initial microalbuminuria, and 44% with initial macroalbuminuria died during followup. Significant predictors of all cause mortality were male gender, age, height, smoking, urinary albumin excretion, hypertension, serum creatinine, and HbA_{1c} level. Age, smoking, microalbuminuria, overt nephropathy, and hypertension were also found to be significant predictors of cardiovascular mortality. Messent and colleagues[187] demonstrated that microalbuminuria predicted cardiovascular mortality in type 1 diabetic individuals over 23 years of followup.

Microalbuminuria has been shown to predict the development of cardiovascular disease in type 2 diabetes as well. In a 10 year followup study of predominantly type 2 diabetic individuals, 265 of 503 participants died. Age, urine albumin excretion, serum creatinine, and duration of diabetes were found to be significant risk factors for mortality, of which 58% was due to CVD.[182] In a large population-based study[188] in 947 patients with type 2 diabetes, albumin excretion was a strong predictor of cardiovascular disease, suggesting that it may represent a marker for more widespread vascular disease.

Why microalbuminuria should be a predictor of serious and widespread vascular disease and mortality is not clear, yet it appears to be so even in nondiabetic individuals.[46,185] A number of hypotheses have been suggested as potential explanations. The Steno group has theorized that microalbuminuria represents a generalized vascular hyperpermeable state, wherein a decrease of the positive charges on the glomerular basement membrane allow leakage of albumin, and that similar changes in blood vessels elsewhere in the body allow potentially atherogenic lipoproteins to penetrate into the vascular walls, causing structural and functional damage to the endothelial cell barrier. [178,115]

Cardiovascular risk factors including obesity, impaired glucose tolerance, type 2 diabetes, hypertension, and dyslipidemia are associated together so frequently that a shared underlying

mechanism is suggested. This clustering of risk factors is, in fact, considered to be a metabolic syndrome,[107] known as Syndrome X, the Insulin Metabolic Syndrome, the Insulin Resistance Syndrome, and a host of other names, and its presence significantly increases risk for atherosclerotic disease, particularly coronary artery disease, in individuals so affected. Insulin resistance has been demonstrated in both type 1 and type 2 diabetic individuals with microalbuminuria, hypertension, and clinical nephropathy,[189,190] although not invariably,[191] and among their first degree relatives.[192] This syndrome could potentially be an explanation for the association between nephropathy and increased cardiovascular disease.

The value of microalbuminuria as a marker of the risk for development of both diabetic nephropathy and cardiovascular disease lies in the fact that it heralds such risk at a point in time when it is possible to intervene and stop, delay, or significantly ameliorate, the onset of such complications.

THE IMPACT OF IMPROVED GLYCEMIC CONTROL ON DIABETIC NEPHROPATHY

One of the most important concepts to appreciate regarding the pathogenesis of diabetic renal disease is that nephropathy does not occur in the absence of hyperglycemia.[193,194] Intensive control of blood glucose has been shown in numerous intervention studies to reduce the risk of microalbuminuria and progression to nephropathy. The data in type 1 diabetes are indisputable, but ample evidence exists to support this tenet in type 2 diabetes as well. It appears from most studies that tight glycemic control must be instituted early, i.e., before the onset of overt proteinuria, to effectively halt the progression of this complication.[40, 195,122, 196,152]

The Diabetes Control and Complications Trial (DCCT),[40] the largest prospective study of the role of glycemic control in the prevention of diabetic complications, followed 1441 individuals with type 1 diabetes for an average of more than 6 years, randomized to conventional versus intensive diabetic management. Two cohorts of subjects were included--a primary prevention cohort, with no retinopathy, and a secondary intervention cohort, with mild retinopathy at baseline. All subjects were followed for development/progression of retinopathy, neuropathy, microalbuminuria, proteinuria, and decline in GFR. The intensively treated group had a mean hemoglobin A_{1c} of 7% compared with 9% in the conventionally treated group and exhibited a reduced risk of development of microalbuminuria--34% in the primary prevention cohort, and 43% in the secondary intervention cohort, and a 56% reduction in risk of albuminuria in the secondary intervention cohort. Additionally, the results demonstrated a *continuous* risk gradient between complications and glycemic control, that is, any reduction in HbA_{1c} from baseline was associated with a reduction in risk of complications. The DCCT results summarily put to rest any debate still lingering regarding the benefit of improved glycemic control on the onset and progression of chronic complications of type 1 diabetes. As a result of this study, intensive treatment of type 1 diabetes has not only become the gold standard of care, but federal and state laws have been passed mandating that insurance carriers and health maintenance organizations provide for the costs of such a level of care, ideally to be accessible to all people with diabetes.

Is there evidence to suggest a benefit of intensive management in type 2 diabetes? A recent 6 year prospective study performed in 110 Japanese individuals with type 2 diabetes[197] was modeled after the design of the DCCT, with primary and secondary treatment cohorts randomized to intensive vs. conventional control. The intensive group achieved a mean HbA_{1c} of 7.1% vs. that of 9.4% in the conventional group. The results demonstrated an overall reduction in risk of nephropathy in the intensive group of 70%, reduction of microalbuminuria of 57%, and complete elimination of clinical grade albuminuria. This study's results certainly should impress with the effects of improved glycemic control in type 2 diabetes. Finally, the United Kingdom Prospective Diabetes Study (UKPDS)[33] is a large ongoing study designed to determine if improved glucose control impacts on the development of long-term complications in type 2 diabetes. The results of this study will be available in 1998.

Evidence for reversal of the pathologic changes characteristic of microalbuminuria has been

demonstrated in a study of diabetic subjects in whom improved glycemic control was associated with a decrease in mesangial matrix expansion, basement membrane thickening, and arteriolar hyalinosis.[198]

Currently there is ample evidence to support the appropriateness of intensive management with the goal of near normalization of blood glucose levels in most patients with diabetes. Accomplishing this goal will help to prevent the development of chronic diabetic complications, including nephropathy.

THE IMPACT OF BLOOD PRESSURE CONTROL ON DIABETIC NEPHROPATHY

Approximately 20% of patients with type 1 diabetes and 10% with type 2 diabetes will develop ESRD [199]. ESRD is the leading cause of mortality in type 1 and the second cause in type 2 diabetes. The purpose of the interventions on diabetic nephropathy is to reduce the morbidity and mortality from this complication. Few interventional studies have looked at the development of ESRD or mortality. Many studies have analyzed the effects on surrogate markers of renal damage mainly glomerular filtration rate, creatinine clearance or excretion of different markers, mainly urinary albumin.

Several long term (more than 5 years of follow up) prospective cohort studies have shown that the progression of diabetic nephropathy can be significantly slowed with the use of aggressive antihypertensive treatment using combinations of diuretics, beta blockers and vasodilators [200-202]. In these studies, the baseline rate of deterioration in GFR has been used as control. Typically, untreated patients with hypertension and diabetic nephropathy show a progressive loss in glomerular filtration rate of approximately 1 ml/min/month. In these cohort studies, aggressive antihypertensives treatment was associated with a reduction in the rate of deterioration of GFR of approximately 50% - 70%. The reduction in blood pressure levels obtained in these studies was in the range of 15 mmHg. A similar effect on the deterioration of renal function was observed with captopril in a long term cohort study (18 patients followed for 10 years)[203].

A large placebo controlled clinical trial using the angiotensin-converting-enzyme inhibitor (ACE inhibitors) captopril (Collerborative Study Group Trial), showed significant decrease in the progression of diabetic nephropathy in subjects with overt proteinuria (urinary albumin levels >500 mg/24hr) in patients with type 1 diabetes and decreased renal function [204]. A total of 400 patients were studied. The patients were randomized to captopril or placebo. Other antihypertensive drugs were allowed to achieve the desired blood pressure level. The blood pressures obtained on the captopril group were 128-134/77-82 and in the placebo group, 129-136/80-84 mmHg. The great majority of patients received diuretics and less than 15% receive beta-blockers. The progression to end stage renal disease or doubling the creatinine was reduced by 50%, compared to standard antihypertensive treatment. The differences in blood pressure levels in the two groups (placebo and captopril) studied was small (3 mmHg lower in the captopril group). This small difference, suggests that ACE inhibitors have a renal protective effect independent of its antihypertensive effect. Based on this evidence, the American Diabetes Association considers that ACE inhibitors should be the first line drug in the treatment of hypertension in patients with overt diabetic nephropathy. There are studies showing that in patients with microalbuminuria (urinary albumin excretion between 30-300 mg/24hr) and hypertension, ACE inhibitors decrease the progression to overt diabetic nephropathy [205,206]. Also, in normotensive patients with microalbuminuria, several small clinical trials suggest ACE inhibitors may be beneficial in preventing progression, [207, 208]. However, the limited number of patients in these studies, makes it difficult to make a recommendation on the routine use of ACE inhibitors in patients with microalbuminuria who are normotensive. There is no evidence that the use of ACE-inhibitors as prophylactic treatment in patients without microalbuminuria can prevent the development of diabetic nephropathy.

EFFECTS OF BLOOD PRESSURE CONTROL ON CARDIOVASCULAR DISEASE

Results from large scale clinical trials in hypertensive populations have clearly shown the benefits of antihypertensive medications on the prevention of stroke and congestive heart failure of approximately 30 - 40% for each 5 mmHg reduction is diastolic blood pressure [209, 210]. Most of these studies used thiazides alone or in combination with adrenergic inhibitors. Several rigorous meta-analyses of placebo controlled, randomized studies involving more than 39,000 patients, have been published. The available information is consistent with a reduction of approximately 20 - 25 % in cardiovascular mortality with antihypertensive treatment resulting in reductions of diastolic blood pressure of 6 mmHg. In most of these studies no report is available on the outcomes of diabetic patients. Since diabetic patients have a higher risk of cardiovascular morbidity and mortality, a reduction in relative risk of a given magnitude will result in greater absolute risk reduction in diabetic groups versus non diabetic groups with otherwise similar characteristics. In one large trial of treatment of systolic hypertension in the elderly (Systolic Hypertension in the Elderly Progression [SHEP]), a reduction in systolic blood pressure with low dose diuretics resulted in a 34 % relative risk reduction in diabetic and non diabetic patients, however, the reduction in absolute risk was two times as high in the diabetic group [211].

MANAGEMENT OF HYPERTENSION IN DIABETES

Initial Evaluation

The initial assessment of a hypertensive diabetic patient should include complete medical history and with special emphasis on cardiovascular risk factors and the presence diabetic and cardiovascular complications.

The measurement of blood pressure should be performed in the supine and standing position. Cardiovascular autonomic neuropathy with significant orthostatic changes in blood pressures are common in diabetic subjects and can cause falsely low or high readings depending on the position of the patient [212]. The physical exam should include height, weight, funduscopic examination and careful evaluation of the arterial system. Initial laboratory examination should include: Serum creatinine, electrolytes, glycated hemoglobin (HbA1c), fasting lipid profile and urinary albumin excretion (this can be measured by semiquantitative methods as screening tests, quantitatively in timed urine samples or as albumin-to-creatinine ratio in untimed samples).

Non-pharmacological treatment of hypertension

Dietary management with moderate sodium restriction has been effective in reducing blood pressure in individuals with essential hypertension [213, 214]. Several controlled studies have looked at the relationship between weight loss and blood pressure reduction [215-217]. Weight reduction can reduce blood pressure independent of sodium intake and also has the benefits of improving blood glucose and lipid levels. The loss of 1 Kg in body weight has resulted in decrease in mean arterial pressure of approximately 1 to 1.5 mmHg [218]. The role of very low calorie diets and pharmacologic agents used to reduce appetite in the management of hypertension in diabetes has not be studied in detail. Since there are reports that some of these agents may actually produce small increases in blood pressure [219], they should be used with caution in diabetic hypertensive patients. Given the present evidence, weight reduction with moderate calorie restriction seems to be an effective treatment for mild to moderate hypertension and the results can probably extrapolated to the diabetic population.

Sodium restriction has not been tested in the diabetic hypertensive population in controlled clinical trials, however results from controlled studies in the general hypertensive population indicate a reduction in systolic blood pressure of approximately 5 mmHg and

diastolic blood pressure of 2 - 3 mmHg [213, 214] with moderate sodium restriction (from 200 to 100 mmol of sodium / day). A dose response effect has been observed with sodium restriction, reductions to levels around 10 - 20 mmol of sodium per day may result in decreases in systolic blood pressure of 10 - 12 mmHg [213].

Supplementation of calcium and magnesium has shown in small, uncontrolled studies to lower blood pressure levels [220-222] and to also improve insulin sensitivity [223]. However, the current evidence for the hypotensive effects of calcium and magnesium come from a limited number of subjects and thus it cannot be recommended as a therapy for individuals with diabetes. The treatment of hypertension in diabetic patients should also include the management of other atherosclerosis risk factors such as hyperlipidemia, smoking and stressful life style.

Pharmacological treatment

The purpose of antihypertensive treatment is to reduce the morbidity and mortality from cardiovascular (congestive heart failure, coronary artery disease and stroke) and diabetic complications (nephropathy and retinopathy). Available studies exploring the effects of pharmacologic agents on the course of diabetic complications will be reviewed. Since the major morbidity and mortality in diabetic patients is due to cardiovascular disease and renal failure, and there are no controlled studies analyzing the effects of hypertension control on other complications, the focus of the pharmacologic agent section will be on the effects of antihypertensive agents on cardiovascular and renal complications in diabetic groups. All antihypertensive drugs available for chronic therapy cause a decrease in systolic or diastolic blood pressure of approximately 10% [224] and the great majority of studies available have used doses of medications that produced similar effects on blood pressure levels. The effects of certain agents on metabolic parameters including lipids, glucose control and insulin resistance will be discussed with the caveat that no relationship between these effects and clinical outcomes has been published to date.

REVIEW OF PHARMACOLOGICAL AGENTS IN THE MANAGEMENT OF HYPERTENSION IN DIABETES

Thiazide Diuretics

The mechanism of action of diuretics, is to reduce total body sodium though its natriuretic action[225]. The efficacy of diuretics in reducing the risk of stroke and congestive failure in randomized clinical trials including subjects with severe, moderate and mild hypertension has been demonstrated. Also, in elderly populations with isolated systolic hypertension, thiazides have resulted in decreased cardiovascular morbidity. There are no studies on long term cardiovascular outcomes in diabetic populations treated with thiazide diuretics. Two retrospective studies comparing diabetic patients with and without nephropathy, treated with diuretics, against other agents, were suggestive of increased cardiovascular mortality in diabetic patients receiving diuretics [226, 227]. Unfortunately, the baseline characteristics of the patients in these studies were not known and differences in baseline risk could have affected the results.

Decreases in insulin sensitivity have been reported in one study in diabetic patients treated with bendrofluazide at 5 mg (conventional dose) for 12 weeks but not when a dose of 1.25 mg was used for the same period of time [228]. In another study using low dose hydrochlorothiazide (25 mg) in 9 patients with type 2 diabetes, no changes in insulin sensitivity or glucose levels where observed compared to placebo [229]. Low dose chlorthalidone (mean dose 18 mg) plus atenolol (mean dose 71 mg) for 12 weeks in type 2 diabetic patients showed a statistically significant decrease in insulin sensitivity and increased triglyceride levels [230]. The clinical significance of these changes in glucose level, lipids, and insulin sensitivity are unknown.

Loop Diuretics

No randomized long term studies examining long term outcomes (cardiovascular or renal) with loop diuretics have been published to date. Loop diuretics like furosemide and ethacrynic acid are effective especially in patients with advanced nephropathy and renal failure. They too produce a significant decrease in total body sodium [231]. Treatment can be associated with hypokalemia, hyponatremia and volume depletion [231]. Their use is recommended for patients with decreased renal function or frank end-stage renal disease, usually in combination with other agents.

Adrenergic Blockers

Centrally acting agents: These drugs effectively lower blood pressure by decreasing central sympathetic outflow [230]. Their metabolic effects have not been studied in detail. In renal studies examining cardiovascular outcomes these drugs were used in combination with diuretics [231, 232]. They are associated with orthostatic hypotension and they should be used with caution in patients with cardiovascular autonomic neuropathy. Common side effects are drowsiness, impotence and dry mouth. Less common effects are depression, Coombs positive anemia (with alpha methyl-dopa) and liver damage [233]. These drugs are inexpensive.

Beta blockers: Beta blockers are competitive inhibitors of the Beta-adrenergic receptors. Non-selective Beta blockers markedly inhibit both the B_1 and B_2 receptors. Selective Beta blockers inhibit predominately the B_1 receptors [234]. Beta blockers are effective antihypertensive agents. Non-selective beta blockers are associated with decreased responses to hypoglycemia, particularly in patients taking insulin [235]. The prevalence of this problem is unknown. The initial cohort studies demonstrating reduction in the declining GFR in patients with type 1 diabetes and nephropathy used combination of hypertensive medications and beta blockers were usually included in the regimens [200-202]. There are no randomized studies examining the effects of non-selective beta blockers on the cardiovascular or long-term renal outcomes of diabetes. In three randomized studies in diabetic hypertensive patients in which proteinuria was examined [236-238], atenolol (a selective Beta blocker) produced similar reductions in proteinuria compared to an ACE inhibitor. In the only long term study (42 months of follow-up, n=43), atenolol and lysinopril produced similar reductions in the declining of glomerular filtration rated in patients with type 2 diabetes and nephropathy [236]. In one cross-over study comparing captopril, metoprolol and hydrochlorothiazide for 8 weeks in 16 patients, similar effects on urinary albumin excretion and glomerular filtration rate were observed [237]. In a 36 month, double blind study, captopril therapy was more effective in decreasing the level or urinary albumin than conventional therapy with metoprolol or hydrochlorothiazide. The number of patients with microalbuminuria in the conventional group, however, was very small (n=12) [239]. Based on the information available, it seems that Beta blockers are useful drugs in the prevention of the deterioration in renal function in patients with nephropathy.

Beta blockers have demonstrated efficacy in patients who have had a myocardial infarction with relative reductions in mortality of approximately 25% [234]. Given the lack of outcome data with non-selective beta blockers in diabetes and the possibility of aggravating hypoglycemic symptoms and peripheral vascular disease with this group of drugs, the use of selective beta blockers seems to preferable.

Alpha Adrenergic blockers

Alpha Adrenergic Beta blockers are inhibitors of the α post-sympathetic adrenergic receptors [240]. The antihypertensive effects of these medications at the doses approved for clinical use, is similar to that of other groups of agents. No long term randomized clinical trials examining cardiovascular or renal outcomes have been published with this family of drugs. They have been associated with improved insulin sensitivity and lipid levels in patients with

insulin resistance in patients with essential hypertension without diabetes [241]. In a recent, non-controlled study, doxazosin significantly increased insulin sensitivity in a group of 17 non-diabetic hypertensive subjects, but not in a group of 13 patients with type 2 diabetes and hypertension [242]. A slight decrease in LDL cholesterol [243] or an increase in the ratio of total-to-HDL cholesterol [242] has been reported with alpha adrenergic blockers in small short term clinical trials, all involving less than 25 patients per group. The clinical significance of these findings is unknown. In a non-randomized clinical trial, a slight decrease in HbA1c was observed in 35 patients with type 2 diabetes receiving doxazozin [244].

A first dose effect, characterized by rapid drops in blood pressure has been reported with alpha blockers in the general hypertensive population, particularly with prazozin [240]. These agents should be used with caution in patients with diabetic autonomic neuropathy or who have orthostatic hypotension.

Calcium Channel Blockers

The mechanism of action of calcium channel blockers' inhibition of calcium influx through membrane-bound voltage-dependent calcium channels , resulting in decreased intracellular calcium levels and vasodilation [245]. The family of the calcium channel blockers is formed by three groups of drugs that have significant differences in their hemodynamic effects [245]. The dihydropyridine group has mainly vasodilatory effects and relatively small effects on cardiac inotropism or atrio-ventricular node conduction. Reflex tachycardia can be seen and edema is the most common side effect. There are many drugs in this group available in the United States and there are significant differences in the pharmacokinetics of different preparations of a given drug. The second group, the benzothiazepines, has moderate vasodilatory effects and a moderate negative inotropic effect. These drugs tend to produce decreases in heart rate. The only available drug in this group is diltiazem. There are several preparations of this drug with different absorption profiles. The third group, the phenylalkylamines, has similar vascular and cardiac effects, as diltiazem. Verapamil is the only drug in this group approved in the United States. It also comes in slow release forms and rapidly absorbed preparations.

Dihydropyridine Calcium channel blockers

The only dihydropyridine approved for treatment of hypertension are the slow release preparations. These drugs are effective antihypertensive agents [245]. There are no studies evaluating the effects of these drugs on the progression of diabetic nephropathy to renal insufficiency or ESRD. There are several studies evaluation the effects of these drugs on proteinuria or the rate of decline in GFR in diabetic nephropathy. One study with nifedipine has shown an initial increase in proteinuria in patients with diabetic nephropathy with further stabilization [206, 247]. Of 6 studies comparing dihydropyridine CCB with ACE inhibitors [247-255] recently published, 2 showed that the ACE inhibitors had a greater antiproteinuric effect than the dihydropyridine CCB [248, 249]. In one of these studies, the effects of nifedipine and captopril on exercise induced albuminuria was assessed in 11 diabetic hypertensive patients with microalbuminuria[248]. Captopril was more effective than nifedipine in this study. In a 6 month randomized clinical trial involving a total of 103 patients, benazepril and nicardipine both reduced microalbuminuria but benazepril was more effective [249]. In two double blind clinical trials, the ACE inhibitor has shown greater antiproteinuric effect than the CCB but the later was more effective in preserving the GFR after 6 months [250] and 12 months [251]. In a 3 year randomized study of 44 patients randomized to the ACE inhibitor, cilazapril, and the CCB, amlodipine, similar effects on urinary albumin and GFR were observed with both drugs [252].

The effects of dihydropyridine CCB on cardiovascular events in diabetic hypertensive patients is currently under study. Several ongoing clinical trials include a significant number of diabetic patients.

Several randomized clinical trials, in patients with established coronary artery disease strongly suggests that short acting nofedipine (a dihydropyridine CCB) increases cardiovascular morbidity and mortality [253]. In a retrospective case - control study, an increase in coronary events due to the use of short acting calcium channel blockers (dihydropyridine and non-dihydropyridine) in patients with hypertension[254]. Short acting CCB's are not approved for treatment of hypertension. The hypothesis that long-acting calcium channel blockers do not increase cardiovascular mortality was tested in a large randomized clinical trial of patients with severe congestive heart failure. Patients were randomized to controlled release amlodipine and placebo. The patients received the standard treatment for congestive heart failure. No significant differences in mortality were observed between the two groups. A small, non-significant decrease in death and hospitalization due to cardiovascular events was observed in the group that received amlodipine. In two recently published small randomized clinical trials comparing the effects of ACE inhibitor and CCB [255, 256] in patients with hypertension and type 2 diabetes, a significant difference in cardiovascular mortality [254] and morbidity [255] was observed between the two groups with ACE inhibitor having the lower number of cardiovascular events or deaths. In these studies, cardiovascular events were secondary endpoints and the studies were originally designed to test other variables as primary end-points. The appropriate Blood Pressure Control and Diabetes study is a prospective study designed to evaluate the effects of different degrees of blood pressure control on the progression of diabetic nephropathy. Four hundred and seventy patients with hypertension were included. All of the patients received nisoldipine (a long-actingdihydropyridine) and half received enalapril. After five years of follow-up, the combined outcome of number of fatal or non-fatal myocardial infarctions was 25 in the nisoldipine group and 5 in the enalapril group (risk ratio 5.5 [95% carfidence ontervals 2.1-14.6]). No significant differences were observed ion cerebrovascular causes or deaths of any cause and they was not designed to have the power to detect differences in these areas.

The other recently published study, compared Fosinopril versus amlodipine in 380 diabetic, hypertensive patients. The primary objective of the study was to compare the effects of these drugs on serum lipids and diabetes control in type 2 diabetes. One hundred and eighty-nine patients received fosinopril and 191 received amlodipine. Cardiovascular events were secondary end points, 14 patients in the fosinopril group and 27 in the amlodipine group developed the combined outcome of acute myocardial infarction, stroke or hospitalized angina (risk ratio 0.49, 96% CI=0.26-0.95). Mean follow-up time was 2.9 years in the fisinopril group and 2.4 years in the amlodipien group. Blood pressure control was similar with both drugs. These studies were not placebo controlled and the baseline risk of the study patients is unknown, however, these studies support the idea that ACE inhibitors may have a more potent cardiac protective effect than the dihydropyridine CCB's on cardiovascular morbi-mortality in diabetic patients with hypertension. If these results apply to non-dihydropyridine CCB's, it is not known. The results of ongoing larger clinical trials using dihydropyridine CCB's in hypertensive populations that include a significant number of diabetic patients will help to clarify this issue. Dihydropyridine treatment should be reserved for use in diabetic patients with severe hypertension in combination with other agents (particularly ACE-inhibitors) and after failure to control the blood pressure with other agents. Some studies [257, 258] suggest that dihydropyridine agents, such as amlodipine, improve insulin sensitivity and reduce LDL-cholesterol levels. Other studies have shown neutral effects of dihydropyridine CCB's on glucose metabolism [248-256].

Non-dihydropyridine (benzothiazepine and phenylalkylamines) Calcium Channel blockers

There are no studies evaluating the effects on non dihydropyridine CCB's on cardiovascular morbidity or martality or long-term renal function ind diabetic patients.

Diltiazem has been associated with decreased proteinuria in patients with overt diabetic nephropathy [259]. Its long-term effects on renal function or cardiovascular events, is not known.

Angiotensin Converting Enzyme Inhibitors

These drugs are useful in the management of hypertension in diabetic patients with or without diabetic nephropathy. They are also effective in decreasing cardiovascular mortality and morbidity in patients with congestive heart failure and post myocardial infarction [260]. As reviewed in previous sections, ACE inhibitors have shown to slow in the progression of overt diabetic nephropathy to ESRD [206], have an antiproteinuria effect and in two studies a strong suggestion of beneficial effects on cardiovascular morbidity in diabetic, hypertensive patients compared to CCB's, has been discussed [255, 256].

The most common side effects of ACE inhibitors include cough, an acute decrease in renal function, hyperkalcemia, especially in patients with renal insufficiency, hyporeninemic hypoaldosteronism and angioedema [261]. ACE inhibitors have been shown to cause an improvement in insulin sensitivity in several studies in essential hypertension and in type 2 diabetes [261, 262].

Currently ACE inhibitors should be considered first line drugs in the management of hypertension in patients with overt diabetic nephropathy or microalbuminuria. They can also be used as first line agents in diabetic hypertensive patients without diabetic nephropathy and can be used safely in combination with other agents.

Angiotensin II receptor blockers

Losartan, ibesartan and vaslartan are effective antihypertensive agents [263]. They are not associated with cough like ACE inhibitors. These agents are new and results of studies evaluating efficacy on long term events, i.e., progression of diabetic nephropathy or cardiovascular disease, are lacking. Their main indication is for use on as for use as a substitute for ACE inhibitors is patients who develop a cough with these agents.

CONCLUSION

The treatment of the patient with diabetes, with or without hypertension, is complex and challenging, because of the heterogeneity of their respective pathogeneses. Hyperglycemia treatment should ideally not only control blood glucose, but prevent the chronic complications and the metabolic derangements associated with it which can lead to increased morbidity and mortality. Hypertensive treatment should not only decrease blood pressure, but reduce the risk of macrovascular and microvascular disease. The use of agents to treat hypertension that worsen insulin resistance, dyslipidemia, glycemic control and nephropathy should be avoided whenever possible. The key to success in managing the care of the hypertensive diabetic patient is adequate evaluation and appropriate treatment targeted toward preventing complications.

End stage nephropathy need not be the inevitable outcome for individuals with early diabetic kidney disease. Interventions which currently are available and are targeted at the known modifiable risk factors underlying the development and progression of diabetic nephropathy offer the best hope for reducing the incidence and severity of this complication. Prevention of all of the complications of diabetes, including nephropathy, must be the goal of future research on behalf of those who now have diabetes; the means to prevent diabetes must be the goal for the future on behalf of the rest of the world.

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