Diabetic Nephropathy and Treatment of Hypertension

Updated: January 1, 2009

Authors: Allen I. Arieff, M.D., F.A.C.P.

Diabetic Nephropathy: General

Diabetic nephropathy is the commonest cause of end-stage renal disease (ESRD) in the USA. The next most common cause is glomerulonephritis, the most important varieties being immunoglobulin A nephritis (IgA), membraneous glomerulonephritis (MGN) and focal sclerosing glomerulonephritis (GSGN). Among all the complications of diabetes mellitus, nephropathy is the diabetes-specific complication with the greatest mortality [1]. Recently, there appears to have been an explosion in the incidence of diabetic nephropathy (DM), which is most often type 2, (previously known as non-insulin dependent diabetes mellitus (NIDDM)). The increased incidence of Type 2 DM appears linked to a virtual epidemic of obesity in the USA. According to a New York Times study, the incidence of diabetes in New York and other large cities in the USA is about 18%. Among all diabetic patients in the USA, the overall incidence of diabetic nephropathy remains small at about 20%. However, it used to be believed that most cases of diabetes mellitus occurred in individuals with Type 1 diabetes. However, recent data establishes that diabetic nephropathy now commonly occurs in patients with type 2 diabetes mellitus.

In the 1970's, the treatment of ESRD secondary to diabetes mellitus was so disappointing that its utility was widely questioned [2]. However, gradual application of the improvements summarized above has greatly improved the quality of life (Q of L) of diabetic patients receiving chronic hemodialysis therapy. Although survival figures lag behind those of nondiabetic patients with ESRD being treated with hemodialysis, the cummulitive survival for diabetic subjects is currently about 22% vs about 37% for nondiabetic subjects [3].

Diagnosis of Diabetic Nephropathy

The diagnosis of diabetic nephropathy is usually based on clinical evidence, most important of which is the appearance and progression of proteinuria from microalbuminuria to macroalbuminuria in a patient with diabetes mellitus, particularly if the subject also has diabetic retinopathy. Typically when a patient who has had Type 1 DM for upwards of 12 years

demonstrates overt urinary protein loss which excedes 0.5 g/24 hr, the probability of diabetic nephropathy is high. In a typical patient, the proteinuria is often associated with hypertension and increasing plasma creatinine (Cr). Although not done routinely, recent evidence suggests that the type of protein excreted, whether high molecular weight (immunoglobulins G and M) or low molecular weight (alpha 1 and beta 1 microglobulins) correlate with the severity of the renal histologic lesion, and may predict the outcome and the response to therapy [4]. It is important to note that even in a patient with Type 1 DM, an increase in plasma creatinine without the presence of nephrotic range proteinuria is very unusual. Such a finding suggests another possible etiology for the rise in creatinine and might suggest performance of a diagnostic renal biopsy [5].

Nephrotic syndrome has been redefined in the last decade. Whereas the definition used to include lipiduria, hyperlcholesterolemia, hypoalbuminemia and edema, most definitions now require only the excretion of 3.5 gm of protein per day in an adult, with a variable tendency towards edema, lipiduria, hypoalbuminemia and hyperlcholesterolemia.

Widespread treatment of ESRD with hemodialysis (HD) has only been established in the USA since about 1975. There are currently (2007) about 400,000 patients with ESRD in the USA who are being treated with chronic hemodialysis. Recent improvements in the management of hemodialysis patients have greatly improved the quality of life among such individuals. These important quality of life (Q of L) improvements include: a) better management of uremic bone disease because of research which has brought to the bedside increased knowledge and use of vitamin D and its derivatives and better control of hyperparathyroidism; b) improved medical control of hyperphosphatemia; c) laser photocoagulation of diabetic retinopathy to prevent blindness; d) improved access to the circulation for hemodialysis, which has resulted in the near replacement of external arteriovenous shunts by either internal arteriovenous anastomosis or an arteriovenous graft (usually with artificial materials), which last much longer and become infected much less frequently; e) aggressive treated of coronary artery disease and its sequelae (myocardial infarction) by CABG, angioplasty, placement of stents, implantable defibrillators and more effective cardiovascular drugs; f) improved management of hypertension, particularly the use of ACE inhibitors, angiotension receptor blockers (ARBs) and multiple drug therapy [6].

In the 1970's, the treatment of ESRD secondary to diabetes mellitus was so disappointing that its utility was widely questioned [7]. However, gradual application of the improvements summarized above have greatly improved the quality of life of diabetic patients receiving chronic hemodialysis therapy. Although survival figures lag behind those of nondiabetic patients with ESRD being treated with hemodialysis. After six years of hemodialysis, the cummulative survival for diabetic subjects is currently about 22%, versus about 37% for nondiabetic subjects [8].

Nephrotic syndrome has been redefined in the last decade. Whereas the definition used to include lipiduria, hypoalbuminemia and edema, most definitions now require only the excretion of 3.5 gm of protein per day in an adult, with a variable tendency towards lipiduria, hypoalbuminemia and edema.

Both type 1 and type 2 diabetic patients are at risk for development of nephropathy. However,

ESRD is less common in type 2 diabetic patients, in part because type 2 diabetic patients with signs of renal dysfunction (microalbuminuria) have a very high cardiovascular mortality rate before ESRD can become manifest. Nonetheless, because the prevalence of type 2 is much greater than that of type 1 diabetes, the total contribution of type 2 diabetes to ESRD far exceeds that of type 1 diabetes. The renal disease often is more dramatic and rapidly progressive in young patients with type 1 diabetes than in patients with type 2 diabetes. However, the clinical picture after the onset of overt diabetic nephropathy in the two types of patients probably is not very different [9]. It can be speculated that severity of diabetes, age, and renal hemodynamic alterations may considerably modify the earlier course, resulting in higher risks and more rapid progression of the preclinical phase in the type 1 diabetic patient [10].

Factors Which May Lead to Impaired Renal Function in Diabetic Patients

Genetic and racial factors

Among first degree relatives of individuals with diabetes mellitus, 10 to 30% have diabetes, while among first degree relatives of nondiabetic subjects, only one to six percent have diabetes [11]. Among diabetic patients, metabolic control of hyperglycemia was not different in individuals with or without diabetic nephropathy [12]. The aforementioned suggest that development of diabetic nephropathy may be an inherited tendency. Among a group with a high incidence of diabetes mellitus, such as the Pima Indians, the progression to diabetic nephropathy is different. Whereas progression to diabetic nephropathy is usually slow and gradual in patients with type 1 diabetes mellitus, studies in Pima Indians suggest that rapid progression to diabetic nephropathy is typical of such patients with type 2 diabetes [13]. The aforementioned suggest that racial factors may play a role in the development of diabetic nephropathy [14]. Although no significant excess incidence was seen among African-American type 2 diabetic patients in this study, other studies suggested that racial or ethnic background also may be an independent risk factor in type 1 diabetes [15]. Diabetes mellitus is more prevalent among African Americans, Hispanics and Pima Indians than among Caucasians [16].

Multiple recent studies show that the incidence of diabetic end-stage renal disease is much higher in blacks and other minorities than in whites [17][18]. Yet there probably are very important genetic differences, which account for the differences in progressive end-stage renal disease, that we have yet to be elucidated [19]. However, at the present time, no specific genetic or racial factor has been identified which explains the development of diabetes mellitus in the majority of such patients [20].

Microalbuminuria

Microalburninuria appears to be a strong predictor of the subsequent development of overt diabetic nephropathy. Microalbuminaria is often defined as the excretion of at least 100 mg of

albumin per day. However, there are flaws with this line of reasoning, as there are causes of microalbuminaria other than impending diabetic nephropathy [21]. There are a number of reasons why diabetic patients may have protein in the urine and even more reasons why patients who do not have diabetes and relatively normal kidney function might have microalbuminuria. These include: a) high blood pressure; b) patients who have donated a kidney for renal transplant; c) loss of a kidney in childhood; d) advanced age. Proponents of the theory that microalbuminuria can be used to predict the development of microangiopathy-diabetic nephropathy have seized upon this finding as universal, but appear to be neglecting some fundamental facts.

For example, after 20 years of hypertension, patients often have significant microalbuminuria, often well over the 200 mg/day said to be high for a diabetic. In such individuals, there is no progression to nephrotic syndrome. More important, kidney donors have now been followed for as long as 28 years, during which time no progression in the range of microalbuminuria (several hundred mg/day) has been observed, nor has there been a change in glomerular filtration rate (GFR) . Furthermore, follow-up of 41 persons in two series who lost a kidney as children — usually in an accident or following surgery for malignancy or congenital abnormalities — for as long as 33 years has revealed stable microalbuminuria of 800 mg/day or more, with no progression or change in GFR. Thus, although microalbuminuria is probably a major prognostic factor for the development of nephropathy in patients with diabetes [22], there are exceptions [23].

Among the 14 million or more diabetics in the United States, from a statistical standpoint, there are going to be a number of patients who will have any of several other causes of proteinuria, such as: a) membranous nephropathy; b) post-streptococcal glomerulonephritis; c) minimal change nephropathy; d) focal segmental glomerulosclerosis. In dificult cases, these ofther causes of proteinuria may require renal biopsy to establish the diagnosis [24].

Hyperfiltration

A concept which is of major importance in the progresion of kidney disease, particularly in diabetes mellitus, is the concept developed by Brenner and coworkers [25] relating to glomerular hyperfiltration in the progression of renal disease [26]. No matter what the original initiating disease process, this theory holds that the progression to ESRD is based primarily upon hemodynamic factors rather than metabolic ones [27]. Glomerular hyperfiltration is a common abnormality of renal function among diabetic patients with either type I or type 2. Studies in rats by Brenner and colleagues demonstrated that insulin-treated diabetic rats have glomerular hyperfiltration along with increased single nephron blood flow and GFR, with increased glomerular capillary pressure [28]. However, the genesis of diabetic nephropathy cannot be explained by hyperfiltration alone. Insulin-treated diabetic rats with hyperfiltration have slower development of diabetic renal lesions than do untreated diabetic rats with worse hypoglycemia and relative hypofiltration. The central lesion associated with hyperfiltration in rats, focal segmental sclerosis, is not an important lesion in human or animal diabetes [29]. There are at least two clinical situations where there is unilateral nephrectomy: a) loss of a kidney in childhood; b) donation of a kidney for transplantation. Both of these groups of patients

are subjected to hyperfiltration for in excess of ten years, and the resultant is no effect upon either GFR or blood pressure. An accumulating body of evidence suggests that this process, as initially described by Brenner, Hostetter and colleagues, may be common to a number of renal diseases [30]. Moreover, proteinuria may lead to tubulointerstitial injury through complex mechanisms leading to further acceleration of loss of GFR. In fact, the magnitude of residual proteinuria after the institution of antihypertensive therapy, especially ACE inhibitors, is a strong predictor of the subsequent rate of decline of GFR in proteinuric diabetic patients.

It is not generally appreciated by non-nephrologists that in early diabetes the GFR is greatly increased, to as high as 180 ml/min/1.73 sq meter versus a normal value of about 120 ml/min/1.73 sq meter, and the kidney is enlarged [31]. It has been postulated that hyperglycemia, by expanding the extracellular volume, may contribute to the increased GFR of type 2 daibetes [32]. Beck-Nielsen has demonstrated that insulin – pump therapy actually reduces kidney size within one year, presumably by retarding hyperfiltration, whereas conventional insulin therapy does not [33]. Others have reported similar results within different time frames [34]. Hyperfiltraton as a pathogenic mechanism in the progression of renal insuffficency is a relatively recent concept. It is well known that once the GFR has decreased to about half the control value from any cause, it proceeds to end-stage renal disease over a period of years, regardless of how the underlying process is treated. Almost all forms of end-stage kidney disease, including that in diabetes mellitus, are characterized by a lesion called focal sclerosis. Brenner and co-workers have theorized and demonstrated in animal models that as nephrons are progressively destroyed, glomerular filtration increases in a compensatory manner in the remaining nephrons, which must thus undergo hyperfiltration, eventually resulting in focal sclerosis [35]. This has been confirmed in laboratory animals with progressive renal ablation (7/8 nephrectomy), experiemental diabetes mellitus and experiemental glomerulonephritis.

Hypertension

Hypertension has been found to be a major factor in the prediction of progression of diabetic nephropathy, along with microalbminuria and hyperglycemia [36]. Hypertension is virtually always present in persons with end-stage diabetic renal disease, and also contributes to focal sclerosis in diabetic laboratory animals. Because the arteriolar vasoconstriction seen in experimental diabetic hypertension is believed to be the result of abnormalities in the renin/angiotensin system of the juxtaglomerular apparatus, angiotensin-converting enzyme (ACE) inhibitors are the treatment of choice. Thus, in laboratory animals, focal sclerosis and end-stage renal disease can be largely prevented by a combination of a low-protein diet and angiotensin converting enzyme inhibitors. Hypertension has been shown to be detrimental in essentially all forms of progressive renal disease, contributing to the progression of renal insufficiency. Control of hypertension is a theoretically attractive modality as a means of preventing progression of nephropathy and has been effectively demonstrated in both laboratory animals and humans.

Improper control of blood glucose

Control of blood glucose with insulin has been the hallmark of the therapy of diabetes mellitus for over 70 years. Despite the intuitiveness of this approach, it is only recently that such therapy has been shown to be of any benefit, other than for the prevention of diabetic coma. It has been anathema to even suggest that control of blood glucose was not a universal good, despite the very high morbidity (brain damage) from hypoglycemia as a consequence of “tight control” of blood glucose [37]. Despite the many cooperative patient studies on the effectiveness of control of blood glucose in prevention of diabetic complications, it still has not been shown that controlling the blood glucose in any manner has any effect in retarding progression of renal insufficiency once a patient has nephrotic syndrome [38]. One should not, however, overlook the many theoretical and biochemical arguments for control of blood glucose in prevention of progressive diabetic renal disease [39][40]. There are several studies on the effect of conventional and vs intensive insulin therapy on the rate of progression of renal insufficiency in patients who already had nephrotic syndrome. No difference has been found in progression. Hyperglycemia has been found to be a major factor in the prediction of progression of diabetic nephropathy, along with hypertension [41]. Whether or not good glycemic control before the development of nephrotic syndrome would be prophylaxis against the development of diabetic nephropathy is a question that has been argued at least since the advent of insulin therapy, and remains unsettled to the present. Despite the lack of objective evidence, because of the beneficial effect of control of hyperglycemia on other complications of diabetes mellitus, most Nephrologists and Diabetologists recommend control of hyperglycemia in patients with diabetes mellitus and proteinuria [42].

Multiple studies which suggest that tight metabolic control (of blood glucose) improves renal function are all lacking in actual assessment of renal function. The most widely cited study is probably the Diabetes Control and Complications Trial [43]. In this study of 1441 patients, conventional therapy versus intensive therapy were compared over 6.5 years. Renal function, in terms of comparative changes in GFR or renal histology, were simply not examined. Creatinine clearance was only “estimated” by the inverse of serum creatinine or the Cockcroft-Gault formula. Neither of these crude methods attains any accuracy when compared to readily available methods for evaluating the GFR, such as the MDRD [44], and none have been compared to iothalamate or inulin clearance, still the “gold standard” [45]. In actuality, this widely quoted study did not actually evaluate the effects of control of blood glucose on renal function. The only actual data showed essentially no difference in the number of patients with increased microalbuminuria, which is probably of questionable clinical significance [46].

Glomerular filtration rate and microalbuminuria

Elevated GFR is a well-established phenomenon in patients with short-term type 2 diabetes [47]. This increased GFR, which can be reduced but is difficult to normalize by glycemic control, has been suggested as a risk factor for the development of diabetic nephropathy. One study showed a 14% increase in GFR in 134 normoalburninuric type 1 diabetic patients versus control values, with a further 5% increase in 50 microalburninuric patients [48]. Another study suggested that GFRs may be falling during the transition from microalbuminuria to overt nephropathy, and yet other studies indicated that reduced GFR can be seen in some normoalbuminuric and microalbuminuric patients with type 1 diabetes in association with more

advanced glomerular lesions. From these studies it may be reasonable to conclude that among diabetic patients, microalbuminuria encompasses a quite wide range of renal structure and function

Microalbuminuria derives its clinical utility as a strong predictor of the later development of overt nephropathy and, indeed, ESRD and death. Combining the initial longitudinal studies, microalbuminuria had a predictive value of approximately 75% to 80%. A recent review suggested that the predictive value of microalbuminuria may be somewhat less. The risk of progression of microalbuminuric patients to proteinuria over the subsequent decade was approximately 40% to 45% in patients with either type 1 or type 2 diabetes, with approximately 30% of microalbuminuric patients reverting to normo-albuminuria over 6 to 10 years of follow-up, whereas the remainder have persistent microalbuminuria.

Only a relatively small percentage of patients who are normoalbuminuric despite 10 or more years of diabetes progress to microalbuminuria and overt proteinuria. Nonetheless, because at initial screening, most long- standing type 1 diabetic patients are normoalburninuric, a sizable proportion of the patients are ultimately at risk for development of diabetic nephropathy.

Combined use of ACE inhibitors and angiotensin receptor blockers in diabetes

It is generally agreed that pharmacological inhibition of the renin-angiotensin system (RAS) with angiotensin converting enzyme (ACE) inhibitors slows the progression of renal disease to end-stage renal failure [49]. This attests to the central role of angiotensin II (Ang II) in the pathogenesis of chronic renal injury [50]. The development of orally active Ang II subtype (AT1) receptor antagonists have provided an alternative system of inhibiting the RAS, thus creating a novel potential therapy for chronic renal diseases. AT1 receptor antagonists differ from ACE inhibitors in their effects on the RAS and on bradykinin metabolism. In general, ACE inhibitors and AT1 receptor antagonists exert equivalent renoprotective effects, which implies that their renoprotective effects are due primarily to inhibition of ANGII-mediated stimulation of angiotensin subtype 1 receptors [51].

It has been suggested that a combination of an Ang II subtype (AT1) receptor antagonist combined with and ACE inhibitor might result in a more complete blockade of the RAS and thus be more effective than either agent alone [52]. This combination does attenuate progression of diabetic nephropathy to end-stage renal disease [53][54].

Use of aldosterone receptor blockers in diabetes

More recently, there has been extensive documentation of the widespread role of aldosterone as an important agent in the pathogenesis of progressive renal disease [55]. In particular, spironolactone has been shown to both reduce proteinuria and retard the progression of renal insufficiency in patients with chronic kidney disease [56]. More specifically, in patients with diabetic nephropathy and albuminuria, the addition of spironolactone to therapy with RAS

blockade results in an additional decrease of blood pressure and proteinuria [57]. Although use of aldosterone blocking agents for the treatment of diabetic nephropathy is not yet routine, data currently available is very encouraging and the therapy is currently widely used in diabetic subjects with proteinuria [58]. Animal studies suggest that in rats with glomerulosclerosis, aldosterone inhibition can lead to regression of the glomerulosclerosis [59].

The most important side effect of the combination of RAS blockade plus aldosterone inhibition is probably hyperkalemia. This most be closely monitored. Spironolactone may also lead to gynecomastia in men.

There are currently three aldosterone inhibitors as pharmacological preparations which are commercially available in the USA. These are spironolactone, eplerone (Inspra) and aliskiren (Tekturna). The latter two drugs have a much lower incidence of gynecomastia in males than spironolactone.

Stages of diabetic nephropathy

Diabetic nephropathy in both type 1 and type 2 diabetic patients characteristically follows a well-described clinical course, but coincident cardiac disease may blur its expression somewhat. Typically, the stages of diabetic nephropathy are as outlined previously. In this section, the stages at which renal functional changes are detectable and the management aspects of these stages are described.

Microalbuminuric Stage

The microalbuminuric stage is a clinically silent period, lasting 10 years or longer, before the first symptoms attributable to diabetic nephropathy appear. Once microalbuminuria has progressed to proteinuria, there is often the appearance late manifestations of renal damage, such as leg edema or generalized weight gain, often associated with hypoproteinemia.

In practice, the diagnosis of diabetic nephropathy is almost always based on clinical grounds, including a history of diabetes for a decade or longer, proteinuria preceding azoterma, and evidence of coincident extrarenal vasculopathy (retinopathy, peripheral vascular disease, coronary artery disease). However, as mentioned earlier, these are circumstances in which a complete nephrologic evaluation, perhaps including a renal biopsy, may be warranted. Patients with syndrome X (in which type 2 diabetes is associated with hyperlipidernia, insulin resistance, hypertension, coronary artery disease, and low levels of high-density lipoproteins) may present with renal dysfunction simulating diabetic nephropathy [60]. The etiology of the renal disease may be hypertensive nephrosclerosis, hyperlipidemic renal artery stenosis, poor renal perfusion due to congestive heart failure, or the synergistic effects of two or more of these factors. Kidney biopsy may be especially helpful in older patients in whom hypertension and degenerative vascular disease may simulate diabetic nephropathy. Illustrating this point is the impressive finding that in a clinicopathologic retrospective clinical kidney biopsy study of 334 patients 65 years of age or older, 33 had diabetes mellitus. Twenty-two of these 33 diabetic patients (67%) had pathologic findings not related to diabetes [61].

Nephrotic stage

The nephrotic stage is defined as a daily urinary protein excretion in excess of 3.5 gm. In recent years, nephritic syndrome in generally defined only as the excretion of 3.5 gm per day of ureine protein, with a tendency towards edema, hypoproteinuria and hyperlipidemia.

The DCCT and other studies in type 1 diabetic patients provide conclusive evidence that strict glycemic control in type 1 diabetes delays the onset of diabetic retinopathy [62]. Although it is often claimed that these studies also demonstrate delay in the progression of diabetic nephropathy, this is simply not the case [63]. A critical reading of the actual data demonstrates that strict glycemic control at the very best may reduce proteinuria or stabilize the rate of its development [64]. There is no evidence that GFR is either increased, or that its rate of decline is lessened by any sort of strict glycemic control [65][66].

The value of careful metabolic control in type 2 diabetes was provided in the UKPDS, which included over 4,000 patients with prolonged diabetes mellitus, some of whom died owing to cardiac failure, sudden unexplained death, or stroke. The UKPDS provided information for cardiac disease, stroke and retinal disease – as in other large studies, examination of renal function was not satisfactorily carried out. Between the start of the study and initiation of dialysis or death, the prevalence of extrarenal disease rose sharply: retinopathy increased from 75% to 100%, cardiovascular disease increased from 45% to 90%, and cerebrovascular disease increased from 30% to 70%. Depression, often profound, results from the cumulative impact of vision loss, limb amputation(s), and cardiogenic limitation of routine daily activites. Withdrawal from dialytic therapy (tantamount to passive suicide) is observed more frequently in diabetic patients than in nondiabetic individuals. There are as yet no evidence-based conclusions are the contributions to diabetic morbidity from smoking, alcohol ingestion, and obesity.

Diabetic proteinuric patients may retain fluid at higher levels of serum albumin than do nondiabetic patients. The explanation for this observation is unclear. However, it is known that glycated albumin-a product of hyperglycemic protein denaturation-moves more freely than does normal albumin across the GBM both in vitro and in diabetic patients, and this could be true of other basement membranes in the body. There is little difficulty in ascribing nephrosis to diabetes in a young proteinuric person with type 1 diabetes, diabetic retinopathy, and no evidence of advanced cardiac or liver disease. By contrast, however, the volume-overloaded older patient with type 2 diabetes often presents a mixture of heart failure and kidney disease. It must be cautioned that the combination of oral metolazone plus furosemide is very dangerous, often inducing severe hyponatremia and hypokalemia in a very short time intrerval [67]. Although aldactone has been shown to be useful in the management of some patients with heart failure, practical experience suggests that use of this agent in diabetic patients should be limited because of the tendency towards hyperkalemia, and the additive effect of type IV RTA, which is often present in diabetic subjects and also often leads to hyperkalemia.

Azotemic stage

The azotemic stage evolves from the nephrotic stage of diabetic nephropathy as renal function

continues to decline. Renal function appears to deteriorate at a slower rate in type 1 than in type 2 diabetes. This distinction may not be real, however, because, according to the natural history of diabetic retinopathy, there often is a delay of 5 to 10 years prior to the diagnosis of type 2 diabetes in its incipient stages. Despite the DCCT and other studies in type 1 diabetic patients, evidence that strict glycemic control in type 1 diabetes delays the onset of nephropathy while also slowing the progression of already established nephropathy is still lacking. The value of careful metabolic control in type 2 diabetes was provided in the UKPDS, (over 4,000 patients). In these patients, many had surgical therapy of such late manifestations of diabetic retinopathy as vitreous hemorrhage and retinal detachment [68]. As a component of the initial evaluation of diabetic patients with nephritic syndrome, direct fundoscopy, retinal photography, and fluorescein angiography should be performed to provide a baseline facilitating interpretation of subsequent eye examinations.

Cardiovascular Disease

Cardiovascular disease is the comorbid condition that most frequently threatens life in diabetic patients with nephropathy. A number of studies have strongly suggested that microalburninuria (the earliest stage of diabetic nephropathy) is an independent predictor for cardiovascular mortality in diabetic patients [69]. Beilin et al. undertook a prospective longitudinal study of 666 type 2 diabetic patients, with a follow-up period from 1986 to 1993 [70]. When those with UAE of less than 30 mg/L were compared with those with urinary albumin levels of 30 to 300 mg per liter, after adjustment for age, sex, and other cardiovascular risk factors, the hazard ratios were 1.77 for all causes, 2.34 for cardiovascular disease, and 1.78 for coronary artery disease [71].

By the time diabetic patients reach ESRD, the relative mortality risk from cardiovascular disease is even higher. Chantrel and associates consecutively evaluated 84 type 2 diabetic patients who began hemodialysis from 1995 to 1996. Cardiovascular disease was highly prevalent at the start of dialysis, with a history of myocardial infarction in 26%, angina in 36%, and acute left ventricular dysfunction in 67%; 32% (27 of 87 patients) died after a mean follow-up of 211 days, mostly from cardiovascular disease. Adding to the difficulty in management of diabetic nephropathy complicated by cardiac disease is the reality that extensive coronary artery disease often is asymptomatic in diabetes. Coronary angiography was perfomed in all regardless of clinical symptoms of coronary artery disease. Coronary artery disease was documented in 38 patients. In 29%, cardiac intervention was thought to be indicated, and 3 patients underwent either coronary artery bypass grafting or angioplasty. In this study, risk factors such as hypertension, smoking, and cholesterol and lipoprotein levels were not significantly different in patients with and without coronary artery disease.

In summary, coronary artery disease and congestive heart failure are the two most common causes of death in diabetic patients being maintained with chronic hemodialysis, making a proactive approach necessary to reduce this risk. Investigation and intervention are warranted even in asymptornatic diabetic patients with ESRD and significant coronary artery disease. Whether treatment with aspirin, ACE inhibitors, ARBs and cholesterol lowering agents, as well as regular cardiac evaluations, will reduce mortality and morbidity caused by cardiovascular disease in diabetic patients with kidney disease is still unclear.

End-stage renal disease

In the USRDS registry, as has been true for a decade, in the United States, Japan, Israel and most of industrialized Europe, diabetes is the leading cause of ESRD [72]. The number of new diabetic patients accepted for renal replacement therapy has increased continuously during the 1990s, from 27% in 1988 to 40.5% in 1998. Although the relative rates of ESRD treatment in Europe and Canada are approximately half that in the United States, a similar progressive increase in the proportion of patients with diabetes is reported.

Survival and medical stabilization of diabetic patients on renal replacement therapy is significantly inferior, from a “numbers” standpoint, to that of other patients with ESRD. The highly prevalent comorbid conditions affecting diabetic patients when renal replacement therapy is initiated account for the greater risk of death and limited rehabilitation potential in these patients. With recognition and efforts to correct the impact of hypertension and metabolic abnormalities, survival of diabetic patients with ESRD has improved yearly since the mid 1980s. This hopefully is the result of a comprehensive team effort by medical professionals in stressing the importance of medical management to treat hypertension, normalize blood glucose levels, and correct hyperlipidemia.

Treatment and Prevention of Diabetic Nephropathy

There are now several approaches to modification of the progression of diabetic nephropathy. While diabetic nephropathy, once developed, probably cannot be “cured”, there are a number of approaches for prevention of the deterioration towards ESRD. Current approaches include a) control of blood glucose; b) low-protein diet; c) control of hypertension; d) control of hyperfiltration, usually through angiotensin-converting enzyme inhibitors or angiotensin-receptor blocking agents.

Regulation of blood glucose

It still has not been determined that control of blood glucose, either by conventional therapy or insulin pump, can have any effect on the development of progressive diabetic nephropathy. What really needs to be determined is whether lowering the blood sugar to normal early in the course of diabetic nephropathy — which has a tendency at least to normalize the GFR and reduce kidney size — will retard the development of proteinuria and eventual decline in GFR. Although this fact in anathema to many Diabetologists, it is nonetheless correct. This of course does not relate to the well-demonstrated beneficial effects of control of blood glucose on the outcome of pregnancy, retinal deterioration and improvement in cardiovascular disease.

It appears doubtful that a study on the effects of proper control of blood glucose on the development of diabetic nephropathy will ever be done. Given the most optimistic estimate of about a third of diabetic patients who eventually develop clinical diabetic nephropathy, any such study would have to involve thousands of diabetic patients kept in tight glycemic control for more than a dozen years, and compared to a concomitant control groups.

Low-protein diet

An early study based on the theory that protein feeding led to increased GFR involved more than 200 patients with various forms of chronic renal failure [73]. One group was treated with a normal high-protein diet and another with an all-pasta diet for two years. The rate of progression of renal insufficiency in the pasta group was significantly decreased when compared to those eating a high-protein diet.

A low-protein diet is the hallmark of preventive therapy for diabetic nephropathy [74]. Such diets have been shown to retard the progression of renal insufficiency in both experimental and other forms of diabetic nephropathy [75]. Protein feeding is a standard test for measurement of renal functional reserve [76] – it increases GFR and would at least theoretically lead to increased hyperfiltration. Several studies suggest that to be the case in humans with diabetes [77]. In a meta-analysis, Pedrini and associates found that protein restriction effectively slows the progession of diabetic nephropathy [78]. However, protein restriction is very difficult in terms of patient compliance, and has not been found to be a practical consideration for long-term management. Other therapeutic modalities to preserve renal function include judicious use of loop diuretics (furosemide), and control of hyperparathyroidism by use of active vitamin D derivatives and Sensipar, which inhibits parathyroid hormone secretion.

Control of hypertension

It is generally believed that the hypertension in diabetes is largely due to intraglomerular or intrarenal efferent arteriolar spasm. Inhibition of this process by ACE inhibitors lowers the intraglomerular hypertension and decreases hyperfiltration, while also lowering systemic blood pressure [79] The angiotensin receptor blocking agents (ARB), which avoid many of the side effects of ACE inhibitors, appear to be at least as effective at retarding the progression of renal insufficiency in patients with diabetic nephropathy [80]. Although not yet tested in patients with diabetic nephropathy, in patients with non-diabetic chronic renal disease, progression of renal insufficiency is retarded by a combination of ACE inhibitor plus an angiotensin receptor blocking agent [81]. Recent data strongly suggest that this combination (ACE inhibitor plus an angiotensin receptor blocking agent) is effective in retarding the progression of diabetic nephropathy [82].

Treatment of hyperfiltraton

Hyperfiltraton as a pathogenic mechanism in the progression of renal insuffficency is a relatively recent concept. It is well known that once the GFR has decreased to about half the control value from any cause, it proceeds to end-stage renal disease over a period of years, regardless of how the underlying process is treated. Almost all forms of end-stage kidney disease, including that in diabetes mellitus, are eventually characterized by a lesion called focal sclerosis. Brenner and co-workers have theorized and demonstrated in animal models that as nephrons are progressively destroyed, glomerular filtration increases in a compensatory manner in the remaining nephrons, each of which must thus be subjected to increasing hyperfiltration, eventually resulting in focal sclerosis [83]. This has been confirmed in laboratory animals with

progressive renal ablation (7/8 nephrectomy), experiemental diabetes mellitus and experiemental glomerulonephritis [84][85][86].

Although still somewhat theoretical, there is substantial evidence suggesting that all subjects with type 2 diabetes should be treated with ACE inhibitors, even if they not yet hypertensive [87]. Recent data from several large scale studies demonstrates that angiotensin receptor blocking agents (ARB) are at least as effective at retarding the progression of renal insufficiency in patients with diabetic nephropathy [88][89]. Presumably, much of the effect of such agents is due to reduction of hyperfiltration [90]. More recent data suggests that in patients with non-diabetic chronic renal disease, progression of renal insufficiency is retarded by a combination of ACE inhibitor plus an angiotensin receptor blocking agent, and these findings may apply to diabetic subjects as well [91]. Current studies demonstrate that such a combination does in fact retard the progression of diabetic nephropathy [92].

When does diabetic nephropathy become end-stage kidney disease?

In general the mainstays of management for diabetic nephropathy can be very briefly stated and are often very effective in maintaining such patients without renal replacement therapy for five years and more. These consists of maintainance of normal blood pressure (or as close to normal as possible), a low protein diet, weight control (difficult but essential), and the simultaneous administration of an combination of ACE inhibitor plus an angiotensin receptor blocking agent [93][94]. The purpose of the ACE inhibitor and angiotensin receptor blocking agent is not just control of blood pressure, although this is certainly a desirerable effect, but is rather a reduction in hyperfiltration. The mainstay of blood pressure control is currently an ACE inhibitor, but addition of an angiotensin receptor blocking agent is becoming more common as data accumulates [95]. A low protein diet also serves to reduce hyperfiltration [96][97].

Unfortunately, in many cases, the above therapy fails. Proteinuria increases to nephrotic levels (over 3.5 gm per 24 hours) and plasma creatinine continues to increase. Although there is individual variation, in general when the plasma creatinine reaches 4.5 mg/dl and there is nephrotic syndrome, dialysis will become necessary. There is an unfortunate tendency to delay referral to a Nephrologist until the patient has developed stigma of end-stage renal disease which are often difficult to reverse. These include wasting, cachexia, uremic bone disease with secondary hyperparathyroidism, anemia and neurological manifestations of renal failure, including tremor and mental clouding. All of the aforementioned are reversible with institution of hemodialysis therapy, but if they have been allowed to progress too far, rehabilitation will often be slow and costly [98]. When the plasma creatinine has reaches level of 4.5 mg/dl, the GFR as estimated by the creatinine clearance will usually be less than about 18 ml/min. When the creatinine clearance (GFR) is below about 20 ml/min, most patients will not be able to survive without renal replacement therapy (dialysis or renal transplantation). Measurement of the glomerular filtration rate (GFR) has in the past involved slow and tedious collection of 24 hour urine specimens. It has now been shown that the GFR can be accurately calculated from the patients weight, gender, race and plasma creatinine. This is done using the modification of diet in renal disease formula (MDRR), which is now widely accepted for clinical use [99]. When the

GFR is below 20 ml/min, an access for dialysis should be surgically placed in the patients arm. The preferred access is an internal fistula (anastamosis internally of an artery to a vein in the upper arm, generally placed by a vascular surgeon). If the blood vessels are not ideal, as is often the case in diabetic subjects, an artery is connected internally to a vein by means of a graft, usually of a synthetic substance such as Dacron or gortex. Either a graft or a fistula generally lasts for several years. The connection increases pressure on the venous side and leads to hypertrophy and muscularization of small veins in the upper arm. The connection (graft or fistula) takes about 6 weeks to develop the hypertrophied smaller veins which are used for dialysis. Placement of an access early (scl emergency dialysis is needed to correct acidosis, hyperkalemia or mental obtundation) prevents the need for emergency dialysis, which generally requires placement of large bore catheters in the neck or groin and emergent institution of hemodialysis. For those patients with diabetic nephropathy blood vessel disease (usually atherosclerosis), peritoneal dialysis may be indicated [100].

Treatment of end-stage kidney disease

When diabetic patients with nephrotic-range proteinuria develop an elevated plasma creatinine along with a tendency towards edema, hypertension, neurological abnormalities, hyperkalemia and circulatory congestion, remaining renal function is insufficient to support life. One of the available renal replacement therapies must be instituted – either dialysis or renal transplantation [101][102].

Dialysis

Dialysis has been used for the treatment of ESRD in diabetic patients for more than 30 years. Initially, complications of diabetes, such as myocardial infarction, blindness, stroke and vascular occlusion and leg amputation were so frequent that the efficacy of such therapy was questionable. A particular problem was that of preserving vascular access to the circulation. Progresive arteriosclerotic vascular disease was so frequent that diabetic patients eventually used up all available sites for construction of and arteriovenous connection, which initially was usually via silicon tubing, which had a high tendency to clot. When all accessable arteries were used up, a femoral site was utilized, and this was often followed by peritoneal dialysis. Blindness was a frequent co-morbid condition, and the combination was often fatal. Recently, multiple advances have served to improve the quality of life for diabetic patients maintained with chronic dialysis. The use of laser photocoagulation of diabetic retinopathy to prevent blindness has greatly expanded with better preservation of vision. Access to the circulation for hemodialysis has greatly improved, which has resulted in the almost complete replacement of external arteriovenous shunts by internal arteriovenous anastomosis, which last much longer and become infected much less frequently. Cardiologists use a much more aggressive approach to the treatment of coronary artery disease and its sequelae (myocardial infarction) by CABG, angioplasty, placement of coronary artery stents, implantable defibrillators and more effective cardiovascular drugs. One of the most important improvements is the improved management of hypertension, particularly the use of ACE inhibitors, angiotension receptor blockers (ARBs) and multiple drug therapy [103][104]. In the 1970's, the treatment of ESRD secondary to diabetes mellitus was so disappointing that its utility was widely questioned [105].

However, gradual application of the improvements summarized above has greatly improved the quality of life in diabetic patients receiving chronic hemodialysis therapy. Although survival figures lag behind those of nondiabetic patients with ESRD being treated with hemodialysis, the cumulative survival for diabetic subjects is currently about 22% vs. about 37% for nondiabetic subjects [106]. Diabetic patients treated with hemodialysis have a higher rate of infection than do non diabetic subjects. As mentioned, there are frequent losses of access, with the useless graft remaining, forgotten, in the body. Subsequently, there may be either infection of undetermined location, combined with erythropoietin-resistent anemia. In such cases, the C-reactive protein (CRP) will be substantially elevated. The source of often occult infection is the inactive graft. Diagnosis is made by indium scan. The only successful treatment is surgical removal of the infacted graft [107]. Unlike the situation in nondiabetic patients with EDRD, renal transplantation is superior to dialysis thrapy in diabetic patients.

Kidney Transplantation

Diabetic nephropathy accounts for approximately 20% of kidney transplantations performed annually in the United States. One- and five -year survival rates of diabetic patients with a kidney transplant, whether from a cadaver or live donor, have been improving consistently. In 1988, the one and 5-year survival rates of diabetic patients after kidney transplantation were 71.2% and 31.5%, respectively; survival rates improved by 1998 to 88.1% and 54.9%, respectively. Although improved survival of diabetic recipients of renal transplants is noted compared with survival on any form of dialysis, the comparison may be flawed because of a selection bias favoring healthier patients for transplantation. The quality of life of a diabetic patient with ESRD is almost certainly improved if the patient has a functioning kidney transplant compared to that available for the same patient treated with either hemodialysis or peritoneal dialysis. More than half of all diabetic kidney transplant recipients, in most series, live for at least 3 years. Many survivors return to occupational, school, or home responsibilities. Almost all diabetic patients with ESRD who have been treated by both dialysis (whether CAPD or hemodialysis) and a kidney transplant request another transplant on loss of the allograft by rejection or other causes. In the patient’s perspective, the vastly enhanced quality of life permitted by a functioning kidney transplant usually makes the choice between dialysis and renal transplantation moot.

Kidney Plus Pancreas Transplantation

Combined pancreas and kidney transplantation in type 1 diabetic patients is no longer an investigational procedure. Some centers have more than 10 years of experience with dual organ transplantation. The major benefit of a combined kidney pancreas transplantation is the improvement in quality of life afforded by freedom from both insulin and dialysis; in this context, the improved patient survival rate is a bonus. The current status of follow-up on type 1 diabetic patients subjected to combined pancreas kidney transplantation, compared with diabetic patients given a kidney transplant alone has been summarized [108]. After 10 years, recipients of a combined pancreas-kidney graft maintain normal glucose control, have improved nerve conduction and autonomic function, experienced better quality of life, and have a significantly lower mortality rate. Unique benefits of combined pancreas-kidney transplantation include

normalization of both fasting glucose and HbA 1 c levels, decreased plasma cholesterol, improved hypertension control, and a slowing of the rate of progression of both microvascular and macrovascular diabetic disease [109]. As already mentioned, neuropathy can improve after combined pancreas and kidney transplantation. Further adding to the positive balance favoring dual-organ transplantation are studies indicating that diabetic retinopathy is stabilized in 75% to 90% of patients after a mean follow up of 10 years. Kidney transplantation offers better survival rates than any form of dialysis for diabetic patients, but combined pancreas-kidney transplantation may often even better survival rates and improved quality of life for type 1 diabetic patients. However, no randomized, controlled studies of dual transplantation versus kidney transplatation alone have been done, and selection bias could affect the studies published to date (2008). Moreover, Manske et al. interjected a cautionary note in a study showing higher mortality rate among cadaver kidney-pancreas versus cadaver kidey-alone recipients [110]. These investigators urged careful selection of dual-transplant recipients. Finally, it may be reasonable to consider a well-matched living related donor kidney as a first step, with a cadaver pancreas transplant some time later. Whether patients with type 2 diabetes will gain biochemical or clinical improvement from either a pancreas or a pancreas plus kidney transplant is unclear. Preliminary reports suggest that pancreas plus kidney transplant may both normalize glycemic regulation and correct renal insufficiency to the same extent in selected type 2 diabetic recipients as has been observed in the type 1 recipient [111]. Sasaki et al. performed 13 simultaneous pancreas-kidney transplants in type 2 diabetic recipients (documented by raised C-peptide levels) [112]. Unexpectedly, the graft survival rate in these type 2 diabetic recipients was 100% after a mean follow-up of 46 months. Data available thus far suggests that pancreas – kidney transplant into patients with type 2 diabetes actually results in a regression of diabetic neuropathy [113] and the lesions of diabetic nephropathy [114].

Other renal and electrolyte complications in patients with diabetic nephropathy

Type IV Renal Tubular Acidosis

Type IV renal tubular acidosis (RTA) is also called hyperkalemic distal RTA, and is manifested by impaired tubular secretion of both hydrogen ion and potassium, which results in hyperchloremic acidosis with hyperkalemia. Distal RTA is an acquired disorder and is almost always accompanied by moderate renal insufficiency (GFR < 50 ml/ml). Some of the conditions associated with type IV renal tubular acidosis are sickle cell disease, gouty nephropathy, pyelonephritis, AIDS, various tubulointerstitial disorders and diabetic nephropathy. In patients with diabetic nephropathy, there is often impaired function of the juxtaglomerular apparatus. This results in aldosterone deficiency, which may be due to either impaired function secondary to involvement of the juxtaglomerular apparatus by diabetic nephropathy, or to aldosterone resistance. There is hyperkalemia with reduced proximal tubule ammonia production, resulting in decreased secretion of hydrogen ion and metabolic acidosis. The urine is often acid because of inadequate ammonia to buffer hydrogen ion in the distal nephron. Plasma levels of both renin and aldosterone are low. Among diabetic subjects with type IV RTA, renal insufficiency with hyperkalemia is a common presenting manifestation. Such a presentation often leads to emergency dialysis for the hyperkalemia. Therapy consists of methods to lower the plasma

potassium without exacerbating a tendency towards congestive heart failure and worsening hypertension. The simplest therapy is an increase in dietary sodium (2 gm/day) plus a loop diuretic (furosemide). Mineralocorticoid supplementation with fludrocortisone will generally improve the hyperkalemia, but because of the usual resistance to mineralocorticoid, the dose will have to be higher than the usual 0.1 to 0.2 mg/day (usually about 0.3 mg bid). It goes without saying that all of the above – mineralocorticoid and increased dietary sodium- will tend to exacerbate heart failure and hypertension. Ion exchange resins such as kayexelate will treat hyperkalemia on an emergency basis, but are not well tolerated for long-term therapy. If all else fails, acute hemodialysis on an emergent basis may be required, and is frequently used.

Hyponatremia and pseudohyponatremia

Hyponatremia (plasma sodium below 130 mmol/L) is often present in patients with diabetic nephropathy, and may be due to a multitude of causes. Many diabetic subjects are taking diuretics, and this can lead to volume and sodium depletion, with increased plasma levels of anti-diuretic hormone (ADH). The volume contraction leads to increased thirst, with increased water intake leading to hyponatremia. Hyperglycemia (as occurs in patients with diabetic coma) can lead to osmotic movement of water from cells to the extracellular space, with dilutional hypontremia. This is often incorrectly called pseudohyponatremia, but is not, because the low measured value for plasma sodium is correct (with pseudohyponatremia the sodium must appear to be low but is in reality normal) . Real pseudohyponatremia occurs in diabetic subjects if there are elevated values for plasma lipids or protein. Sodium is not soluble in lipid – the lipid displaces water from plasma, leaving the sodium in a larger volume of distribution than appears to be the case, with a falsely low value for plasma sodium. Another mechanism for hyponatremia in diabetic patients involvesthe use of oral hypoglycemia agents which enhance or mimic the action of ADH. The most well-studied of these is chlopropamide, which leads to hyponatremia in about 4% of patients who utilize it [115]. The syndrome is that of inappropriate secretion of antidiuretic hormone (SIADH). Such patients have hyponatremia and are unable to properly dilute the urine or excrete a standard water load. The hyponatremia is reversible with withdrawal of the chlorpropamide [116].

Radiocontrast media associated nephropathy

Acute renal failure following intravenous infusion of diagnostic radiocontrast media was described in diabetic patients more than 25 years ago [117]. It was initially felt that diabetic patients were uniquely at risk for the development of acute renal failure following intravenous (IV) infusion of contrast media. The renal failure was related to the volume of radiocontrast media used, was usually reversible, but often required short-term hemodialysis. Radiocontrast media employed in the 1960's often had a very hypertonic osmolality of 1200 to 2100 mOsm/kg, which was felt to be important in the pathogenesis of renal failure. Newer agents have much lower osmolality (570 to 600 mOsm/kg). It appears that renal vasoconstriction leading to ischemia is important in the genesis of radiocontrast media induced renal failure, and that high osmolality contrast media are far more likely to lead to renal insufficiency than are those with low osmolality. Following IV contrast media, the creatinine begins to rise within the initial 48 hours, peaks at 3-5 days, and generally returns to baseline with 1.5 weeks. More recent

information indicates in diabetic patients with normal renal function, the risk of renal failure is rare [118]. Renal failure also occurs in nondiabetic subjects following IV radiocontrast media, but generally only in those who have impaired renal function before the test. Various studies have suggested that contrast media induced renal failure can be prevented by some combination of IV furosemide, IV normal saline, IV mannitol and N-acetylcysteine. However, evidence to support any of these maneuvers is lacking [119]. The possibility of acute renal failure following intravenous infusion of diagnostic radiocontrast media has almost led to the elimination of intravenous urography as a diagnostic tool. Combinations of ultrasound and CT scanning have almost completely substituted for intravenous urography in the diagnosis of obstructive uropathy and assessment of kidney size [120]. Among patients with moderate chronic renal insufficiency who require elective coronary angioplasty, treatment with oral acetylcysteine and intravenous NaHCO3 helps to protect them from deterioration of renal function [121].

Other disorders which are closely associated with diabetic nephropathy include atheroembolic renal disease, renal papillary necrosis, advanced atherosclerosis and neurogenic bladder dysfunction. These disorders are discussed elsewhere [122].

References

1. Nathan DM. Long-term complications of diabetes mellitus. New Engl J Med 1993;328:1676-85.
2. Arieff AI. Kidney, water and electrolyte metabolism in diabetes mellitus. In: Brenner BM, Rector FC, Jr., eds. The Kidney. 1st ed. Philadelphia: W. B. Saunders; 1976:1257-96
3. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.
4. Brenner BM, Cooper mE, DeZeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. New Engl J Med 2001;345:861-9.
5. Preston RA, Stemmer CL, Materson bJ. Renal biopsy in patients 65 years or older: An analysis of the results of 334 renal biopsies. J Am Ger Soc 1990;38:669-78.
6. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of agressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97
7. Arieff AI. Kidney, water and electrolyte metabolism in diabetes mellitus. In: Brenner BM, Rector FC, Jr., eds. The Kidney. 1st ed. Philadelphia: W. B. Saunders; 1976:1257-96
8. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.
9. Kunzelman CL, Knowler WC, Pettit DJ. Incidence of proteinuria in type II diabetes in the Pima indians. Kidney Int 1989;35.
10. Zatz R, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. Proc Natl Acad Sci USA 1985;82:5963-7.
11. Lindner TH, Monks D, Wanner C, Berger M. Genetic aspects of diabetic nephropathy. Kidney Int 2003;63 (suppl. 84):S186-S91.

12. Seaquist ER, Goetz FC, Rich S, Barbosa J. Familial clustering of diabetic kidney disease: Evidence for genetic susceptibility to diabetic nephropathy. New Engl J Med 1989;320:1161-5
13. Kunzelman CL, Knowler WC, Pettit DJ. Incidence of proteinuria in type II diabetes in the Pima indians. Kidney Int 1989;35.
14. Cowie CC. Diabetic renal disease: Racial and ethnic differences from an epidemiologic prospective. Transplant Proc 1993;25:2426-30.
15. Kunzelman CL, Knowler WC, Pettit DJ. Incidence of proteinuria in type II diabetes in the Pima indians. Kidney Int 1989;35.
16. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 1989;321:1074-9.
17. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.
18. Cowie CC, Port FK, Wolfe RA, Savage PJ, Moll PP, Hawthorne VM. Disparities in incidence of diabetic end-stage renal disease according to race and type of diabetes. N Engl J Med 1989;321:1074-9.
19. Lindner TH, Monks D, Wanner C, Berger M. Genetic aspects of diabetic nephropathy. Kidney Int 2003;63 (suppl. 84):S186-S91.
20. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.
21. Arieff AI. Proteinuria and microalbuminuria as predictors of nephropathy. Hospital Practice 1992;27((suppl. 1)):51-4
22. Mogensen CE. Microalbuminuria predicts clinical proteinuria and early mortality in maturity-onset diabetes. N Engl J Med 1984;310:356-60.
23. Arieff AI. Proteinuria and microalbuminuria as predictors of nephropathy. Hospital Practice 1992;27((suppl. 1)):51-4
24. Preston RA, Stemmer CL, Materson bJ. Renal biopsy in patients 65 years or older: An analysis of the results of 334 renal biopsies. J Am Ger Soc 1990;38:669-78.
25. Zatz R, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. Proc Natl Acad Sci USA 1985;82:5963-7.
26. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.
27. Brenner BM. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 1983;23:647-55.
28. Brenner BM. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 1983;23:647-55.
29. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.
30. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.

31. Mogensen CE, Anderson MJF. Increased kidney size and glomerular filtration rate in early juvenile diabetes. Diabetes 1973;22:706-12.
32. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.
33. Beck-Nielsen H, Richelsen B, Mogensen CE, et al. Effect of insulin pump treatment for one year on renal function and retinal morphology in patients with IDDM. Diabetes Care 1985;8:585-9.
34. Wiseman MJ, Saunders AJ, Keen H, Viberti G. Effect of blood glucose control on increased glomerular filtration rate and kidney size in insulin-dependent diabetes. New Engl J Med 1985;312:617-21.
35. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.
36. Breyer JA, Bain RP, Evans JK, Nahman NS, Lewis EJ. Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. Kidney Int 1996;50:1651-8.
37. Malouf R, Brust JCM. Hypoglycemia: Causes, neurological manifestations, and outcome. Ann Neurol 1985;17:421.
38. Adler AL, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: The united kingdom prospective diabetes study (UKPDS 64). Kidney Int 2003;63:225-32.
39. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.
40. Clark CM, Lee DA. Prevention and teatment of the complications of diabetes mellitus. New Engl J Med 1995;332:1210-7.
41. Breyer JA, Bain RP, Evans JK, Nahman NS, Lewis EJ. Predictors of the progression of renal insufficiency in patients with insulin-dependent diabetes and overt diabetic nephropathy. Kidney Int 1996;50:1651-8.
42. Adler AL, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: The united kingdom prospective diabetes study (UKPDS 64). Kidney Int 2003;63:225-32.
43. Adler AL, Stevens RJ, Manley SE, Bilous RW, Cull CA, Holman RR. Development and progression of nephropathy in type 2 diabetes: The united kingdom prospective diabetes study (UKPDS 64). Kidney Int 2003;63:225-32.
44. Levey AS, Bosch JP, Lewis JB, Greene t, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 1999;130:461-70.
45. Rollin HA, III, Hall PM, Wei R. Inaccuracy of estimated creatinine clearance for prediction of iothalamate glomerular filtration rate. Am J Kidney Dis 1984;4(1):48-54.
46. Diabetes D. Retinopathy and nephropathy in patients with Type I diabetes four years after a trial of intensive therapy. New Engl J Med 2000;381-389:977-65.
47. Mogensen CE, Anderson MJF. Increased kidney size and glomerular filtration rate in early juvenile diabetes. Diabetes 1973;22:706-12.

48. Wirta O, Pasternack A, Laippala P, Turjanmaa V. Glomerular filtration rate and kidney size after six years disease duration in non-insulin-dependent diabetic subjects. Clin Nephrol 1996;45:10-7.
49. Chaturvedi N, Barnett AH, Bilous R, Bojestig M. Should all patients with type I diabetes mellitus and microalbuinuria receive angiotensin-converting enzyme inhibitors? Ann Intern Med 2001;134:370-9.
50. Noris M, Remuzzi G. ACE inhibitors and AT1 receptor antagonists: Is two bettter than one? Kidney Int 2002;61:1545-7
51. Chobanian AV. The hypertension paradox – More uncontrolled disease despite improved therapy. New Engl J Med 2009;361:878-87.
52. Jacobsen P, Andersen S, Jensen BR, Parving HH. Additive effect of ACE inhibition and angiotensin II receptor blockade in type i diabetic patients with diabetic nephropathy. J Am Soc Nephrol 2003;14:992-9.
53. Cortinovis M, Cattaneo D, Perico N, Remuzzi G. investigational drugs for diabetic nephropathy. Expert Opin Investig Drugs 2008;10:1487-500.
54. Jacobsen P, Rossing K, Parving HH. Single versus dual blockade of the renin-angiotensin system (ACE inhibitors and/or angiotensin II receptor blockers) in diabetic nephropathy. Curr Opin Nephrol Hypertens 2004;13:319-24.
55. Epstein M. Aldosterone blockade: An emerging strategy for abrogating progressive renal disease. Am J Med 2006;119:912-9.
56. Bianchi S, Bigazzi R, Campese V. long-term effects of spironolactone on proteinuria and kidney function in patients with chronic kidney disease. Kidney Int 2006;70:2051-3.
57. Schjoedt KJ. Beneficial impact of spironolactone in diabetic nephropathy. Kidney Int 2005;68:2829-36.
58. Bombeck AS, Kshirsagar AV, Amamoo MA, Klemmer PJ. Change in proteinuria after adding aldosterone blockers to ACE inhibitors of angiotensin receptor blockers in CKD; A sysemic review. Am J Kidney Dis 2008;51:199-211.
59. Aldigier jC, Kanjanbuch T, Ma LJ, Brown NJ, Fogeo AB. Regression of existing glomerulosclerosis by inhibition of aldosterone. j AmSoc Nephrol 2005;16:3306-14.
60. Haffner SM, Valdez RA, Hazuda HP, Mitchell B. Prospective analysis of insulin-resistence syndrome (syndrome X). Diabetes 1992;41:715-22.
61. Preston RA, Stemmer CL, Materson bJ. Renal biopsy in patients 65 years or older: An analysis of the results of 334 renal biopsies. J Am Ger Soc 1990;38:669-78.
62. Diabetes D. Retinopathy and nephropathy in patients with Type I diabetes four years after a trial of intensive therapy. New Engl J Med 2000;381-389:977-65.
63. Diabetes C. The effects of intensive treatment of diabetes on the development and progression of long-trm complications of insulin dependent diabetes mellitus. New Engl J Med 1993;329:977-65.
64. Richard P, Nisson BY, Rosenquist V. The effect of long term intensified insulin tratment on the development of microvascular complications of diabetes mellitus. New Engl J Med 1993;329:304-11.
65. Diabetes D. Retinopathy and nephropathy in patients with Type I diabetes four years after a trial of intensive therapy. New Engl J Med 2000;381-389:977-65.
66. Richard P, Nisson BY, Rosenquist V. The effect of long term intensified insulin tratment on the development of microvascular complications of diabetes mellitus. New Engl J Med 1993;329:304-11.

67. Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. Amer J Med 1981;70(6):1163-8.
68. UK Prospective Diabetes Study (UKPDS) Group U. Intensive blood glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes. Lancet 1998;352:837-51.
69. Dinneen SF, Gerstein HC. The association of microalbuminuria and mortality in non-insulin dependent daibetes mellitus: A systematic review of the literature. Arch Intern Med 1997:1413-99.
70. Bellin J, Stanton KG, McCann VJ. Microalbuminuria in type 2 daibetes mellitus: An independent predictor for cardiovascular mortlaity. Aust N Z J Med 1996;26:519-26.
71. Bellin J, Stanton KG, McCann VJ. Microalbuminuria in type 2 daibetes mellitus: An independent predictor for cardiovascular mortlaity. Aust N Z J Med 1996;26:519-26.
72. Renal Data System US. USRDS Annual Report, 1999. In: USRDS 1999 Annual Report. Bethesda, MD: NIH, NIDDKD; 1999.
73. Barotti G, Morelli E, Giannoni A, Lupetti S. Restricted phosphorus and nitrogen intake to slow the progression of chronic renal failure: A controlled trial. Kidney int 1983;16, Suppl. 1:S278-S84.
74. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991;324(2):78-84.
75. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991;324(2):78-84.
76. Bosch JP, Saccaggi A, Lauer A, Ronco C, Belledonne M, Glabman S. Renal functional reserve in humans. Am J Med 1983;75:943-50.
77. Zeller K, Whittaker E, Sullivan L, Raskin P, Jacobson HR. Effect of restricting dietary protein on the progression of renal failure in patients with insulin-dependent diabetes mellitus. N Engl J Med 1991;324(2):78-84.
78. Pedrini MT, Levey AS, Lau J, Chalmers TC. The effect of dietary protein restriction on the progression of diabetic and nondiabetic renal disease: A meta-analysis. Ann Intern Med 1996;124:627-32.
79. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. New Engl J Med 1993;329:1456-62.
80. Brenner BM, Cooper mE, DeZeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. New Engl J Med 2001;345:861-9.
81. Campbell R, Sangalli F, Perticucci E, Aros C, Viscarra C. Effects of combined ACE inhibitor and angiotensin II antagonist tratment in human chronic nephropathies. Kidney Int 2003;63:1094-103.
82. Linas SL. Are two better than one? Angiotensin-converting enzyme inhibitors plus angiotensin receptor blockers for reducing blood pressure and proteinuria in kidney disease. Clin J Am Soc Nephrol 2008;3:S17-S23.
83. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.

84. Zatz R, Meyer TW, Rennke HG, Brenner BM. Predominance of hemodynamic rather than metabolic factors in the pathogenesis of diabetic glomerulopathy. Proc Natl Acad Sci USA 1985;82:5963-7.
85. Brenner BM. Hemodynamically mediated glomerular injury and the progressive nature of kidney disease. Kidney Int 1983;23:647-55.
86. Anderson S, Meyer TW, Rennke HG, et al. Control of glomerular hypertension limits glomerular injury in rats with reduced renal mass. J Clin Invest 1985;76:612-9.
87. ACE inhibitors in Diabetic Nephropathy TG. Should all patients with type 1 diabetes mellitis receive angiotensin-converting enzyme inhibitors? Ann Intern Med 2001;134:370-9.
88. Brenner BM, Cooper mE, DeZeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. New Engl J Med 2001;345:861-9.
89. Lewis EJ, Hunsicker lG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbosartan in patients with Nephropathy due to type 2 diabetes. New Engl J Med 2001;345:851-60.
90. Giovanni FM, Strippoli MC, Schena FP, Craig JC. Antihypertensive agents for primary prevention of diabetic nephropathy. J Am Soc Nephrol 2005;16:3081-91.
91. Campbell R, Sangalli F, Perticucci E, Aros C, Viscarra C. Effects of combined ACE inhibitor and angiotensin II antagonist tratment in human chronic nephropathies. Kidney Int 2003;63:1094-103.
92. Linas SL. Are two better than one? Angiotensin-converting enzyme inhibitors plus angiotensin receptor blockers for reducing blood pressure and proteinuria in kidney disease. Clin J Am Soc Nephrol 2008;3:S17-S23.
93. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.
94. Linas SL. Are two better than one? Angiotensin-converting enzyme inhibitors plus angiotensin receptor blockers for reducing blood pressure and proteinuria in kidney disease. Clin J Am Soc Nephrol 2008;3:S17-S23.
95. Linas SL. Are two better than one? Angiotensin-converting enzyme inhibitors plus angiotensin receptor blockers for reducing blood pressure and proteinuria in kidney disease. Clin J Am Soc Nephrol 2008;3:S17-S23.
96. Brenner BM, Meyer TW, Hostetter TH. Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. N Engl J Med 1982;307:652-60.
97. Meloni C, Tatangelo P, Cipriani S. Adequate protein dietary restriction in diabetic and nondiabetic patients with chronic renal failure. J Renal Nutr 2004;14:208-13.
98. Arieff AI. Uremic and Dialysis Encephalopathies. In: McCandless DW, ed. Metabolic Encephalopathy. New York: Springer Verlag; 2009
99. Levey AS, Bosch JP, Lewis JB, Greene t, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Ann Intern Med 1999;130:461-70.
100. Sharad G, Saran R, Nolph KW. Indications, contraindications and complications of

peritoneal dialysis in the critically ill. In: Ronco C, Bellomo R, eds. Critical Care Nephrology. Hingham, MA: Kluwer Academic Publishers; 1998:1373-82.
101. Himmelfarb J, Chuang P, Schulman G. Hemodialysis. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1957-2006
102. Magee CC, Ansari MJ, Millford EL. Renal Transplantation: Clinical Management. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:2138-68.
103. Schrier RW, Estacio RO, Esler A, Mehler P. Effects of agressive blood pressure control in normotensive type 2 diabetic patients on albuminuria, retinopathy and strokes. Kidney Int 2002;61:1086-97.
104. Lewis EJ, Hunsicker lG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbosartan in patients with Nephropathy due to type 2 diabetes. New Engl J Med 2001;345:851-60.
105. Arieff AI, Myers BD. Diabetic nephropathy. In: Brenner BM, Rector FC, Jr., eds. The Kidney. 2nd ed. Philadelphia: W. B. Saunders; 1981:1906-49.
106. Himmelfarb J, Chuang P, Schulman G. Hemodialysis. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1957-2006.
107. Nassar GM, Fishbane S, Ayus JC. Occult infection of old nonfunctioning arteriovenous grafts: A novel cause of erythropoietin resistance and chronic inflamation in hemodialysis patients. Kidney Int 2002;61:S49-S54.
108. Hariharan S, Pirsch JD, Lu CY, Chan L. Panceas after kidney transplantation. J Am Soc Nephrol 2002;13:1109-18.
109. Gruessner AC, Sutherland DER, Dunn DL, Najarian JS, Humar A. Pancreas after kidney transplants in posturemic patients with type I diabetes mellitus. J Am Soc Nephrol 2001;12:2490-9.
110. Manske CL, Wang Y, Thomas W. Mortality of kidney transplantation versus combined kidney-pancreas transplantation in diabetic patients. Lancet 1995;346:1658-61.
111. Fioretto P, Steffes MW, Sutherland DER, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. New Engl J Med 1998;339:69-75.
112. Sasaki TM, Gray RS, Ratner RE. Successful long-term kidney – pancreas transplants in diabetic patients with high C-peptide levels. Transplantation 1998;65:1510-6.
113. Hariharan S, Pirsch JD, Lu CY, Chan L. Panceas after kidney transplantation. J Am Soc Nephrol 2002;13:1109-18.
114. Fioretto P, Steffes MW, Sutherland DER, Goetz FC, Mauer M. Reversal of lesions of diabetic nephropathy after pancreas transplantation. New Engl J Med 1998;339:69-75.
115. DeFronzo RA, Arieff AI. Hyponatremia: Pathophysiology and treatment. In: Arieff AI, DeFronzo RA, eds. Fluid, Electrolyte and Acid-Base Disorders. second ed. New York: Churchill Livingstone; 1995:255-303.
116. DeFronzo RA, Arieff AI. Hyponatremia: Pathophysiology and treatment. In: Arieff AI, DeFronzo RA, eds. Fluid, Electrolyte and Acid-Base Disorders. second ed. New York: Churchill Livingstone; 1995:255-303.
117. Manske Cl, Sprafka JM, Strony JT. Contrast nephropathy in azotemic diabetic pateints undergoing coronary angiography. Am J Med 1990;89:615-20.
118. Parfrey PS, Griffiths SM, Barrett BJ, et al. Contrast material-induced renal failure in patients with diabetes mellitus, renal insufficiency, or both. A prospective controlled study. N Engl J Med 1989;320:143-9.

119. Kelly AM, Dwamena B, Cronin P, Carlos RC. Meta-analysis: Effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008;148:284-94.
120. Boswell WD, Jadvar H, Palmer SL. Diagnostic Kidney Imaging. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:839-914.
121. Kelly AM, Dwamena B, Cronin P, Carlos RC. Meta-analysis: Effectiveness of drugs for preventing contrast-induced nephropathy. Ann Intern Med 2008;148:284-94.
122. Parving HH, Mauer M, Ritz E. Diabetic Nephropathy. In: Brenner BM, ed. Brenner and Rector's The Kidney. 8th ed. Philadelphia: W.B. Saunders; 2008:1265-98.