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Review
The role of calcium channel blockers in the treatment of diabetic nephropathy

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Abstract

Diabetic nephropathy (DNP) is a chronic renal disease (CRD) and a major cause of illness and premature death in people with diabetes mellitus (DM). It is the single most important cause of end-stage renal disease in the Western world and accounts for more than a quarter of all end-stage renal diseases. This article reviews the current development in DNP and the therapeutic challenge with particular reference to the role of calcium channel blockers. Moreover, renal ischaemia hastens the progression of DNP. Diltiazem and amlodipine have a tendency to reverse the changed parameters toward normal values but do not affect the biochemical parameters. Generally speaking, diltiazem is better than amlodipine in reversing biochemical and histopathological changes produced by DNP, and captopril reverses most of the changed parameters with the exception of the histopathological changes. These agents have nephroprotective properties and delay the progression of DNP.

Key words: *Amlodipine, calcium channel blockers, diabetic nephropathy, diabetes mellitus, diltiazem, ischaemia*

Introduction

Diabetes Mellitus

Diabetes mellitus (DM) is a major health problem all over the world. It is defined as a group of syndromes characterized by hyperglycaemia, altered metabolism of lipids, carbohydrate and proteins, resulting from a defect in insulin secretion, insulin action or both. This chronic hyperglycaemic condition is associated with long term damage, dysfunction and failure of various organs especially eyes, kidney, nerves, heart and blood vessels.[1]

Complications of diabetes mellitus include acute complications that are generally a reflection of altered energy homeostasis either from hyperglycaemia (diabetic ketoacidosis and non-ketotic hyperosmolar syndrome) or hypoglycaemia and chronic complications consisting of retinopathy, nephropathy, neuropathy and angiopathy.[2,,3]

Diabetes Mellitus and Diabetic Nephropathy

Diabetes is the single most important disease leading to end-stage renal disease (ESRD) in the western hemisphere contributing to about 33 to 40% of chronic renal failure and new cases of ESRD. Only 5 to 10 % of patients with type II diabetes develop end-stage nephropathy, but they account for nearly two thirds of diabetes related ESRD, in part due to the 20 fold higher prevalence of type II DM in comparison with type I diabetes. In contrast, nearly 25 to 40 % of patients with type 1 diabetes are estimated to enter into ESRD as a result of DNP.[4]

The incidence of DNP peaks after 10 to 15 years of diabetes, however, functional renal abnormalities are often present within 2 years of the onset of type I DM. Because the diagnosis of type II DM is often delayed from the actual onset, renal changes are usually present at diagnosis in this population. Aside from hyperglycaemia, co-morbidities such as hypertension and hyperlipidemia are common in DM and are believed to contribute to the progression of nephropathy in most cases.[5]

Type II diabetes is responsible for more end-stage renal disease in the United State than any other single condition. Until recently, the majority of research in DNP has focussed on patients with type I diabetes despite the fact that type II nephropathy is a more prevalent condition. The notion that there are major differences between the nephropathy of these two types of diabetes is not supported by recent literature. The biggest difference appears to be related to affiliation. Histopathologic differences are now being described as well. Clinical interventional trials in type II DM are few compared to that in type I. However, it seems that manoeuvres that improve renal prognosis with type I diabetes (blood pressure control, blood glucose control and the use of angiotensin-converting enzyme inhibitors) apply to type II population as well.[6]

As alluded to earlier, about half of all diabetics progress completely to ESRD. This fraction is disproportionately high in certain racial groups such as Pima, Native Americans, Hispanic and Asian/Pacific Islanders. Therefore, racial or hereditary factors are believed to influence the likelihood of developing end-stage DNP. In type II DM, DNP appears to be of a complex nature, involving heterogeneous mechanisms in addition to those typical of type I DM.[7]

Diabetic Nephropathy

Diabetic nephropathy is a chronic renal disease (CRD) which can be defined as a persistent or progressive

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deterioration in renal function progressing over several years to a complete loss of renal function and end-stage renal failure. It is associated with a persistent proteinuria of more than 0.5 gm/24h (microalbuminuria = urinary albumin excretion rate, 20-200 µg/min). There is a positive correlation between the level of hyperglycaemia and DNP with a male to female ratio of 1:7.[8,9]

Epidemiology of DNP

Chronic renal disease due to DNP is a major cause of morbidity and mortality in the United States and has been steadily on the rise. The number of individuals suffering from CRD in the United States is estimated at over 1.6 million distributed in the following age groups: 20 to 44 years (25%), 45 to 64 (39%) and 65 years and older (34%). DNP is a common problem that is most likely to occur in patients who have poor glycaemic control, hypertension, glomerular hyperfiltration and who are black, Mexican or Pima Indian.[10-12]

Diabetic nephropathy is the major cause of illness and premature death in people with diabetes. Indeed, diabetic patients are several times more prone to kidney disease than non-diabetic people. It is considered the most common microvascular complication, being present in 30 to 50% of type I and 10% of type II diabetics after 10-20 years of the disease. Diabetic patients represent 35% and 20% of all new end-stage renal disease patients in the USA and Europe respectively.[13] It is considered the single most important cause of ESRD in the western world and accounts for more than a quarter of all ESRD. In New Zealand, Polynesians, in particular Maoris with diabetes, have a very high rate of DNP and develop renal failure at a more rapid rate than European patients with nephropathy.[14-16]

Causes and Risk factors

Secondary renal microvascular complications of diabetes mellitus represent a health problem of enormous social cost. Studies in man and animals strongly support the concept that the primary cause of DNP is the metabolic derangement of the diabetic state. Although these metabolic derangements have complex biological effects it is unlikely that hyperglycaemia *per se* produces all of the nephropathic influences of diabetes. Alterations in micovascular haemodynamics probably contribute to glomerular pathology. These alterations may be based upon disturbed vasoactive central mechanisms regulating angiotensin and prostaglandin secretion and metabolism. Factors other than hyperglycaemia may contribute to the glomerular injury in this setting. Extensive studies in diabetic animals suggest that intraglomerular hypertension and glomerular hypertrophy play an important role, being present early in the disease, as diabetes induces renal vasodilation and often a rise in glomerular filtration rate. This is then exacerbated by the compensatory response to nephron loss.[17-19]

Familial clustering of diabetes and nephropathy suggests that either common environmental or inherited mechanisms are important in the development of DNP. The risk of DNP does not appear to be associated with the degree of familial risk of diabetes itself. Rather, the risk of DNP may be the result of a familial risk of nephropathy from any cause and is associated with diabetes through relative hypoinsulinaemia and long standing hyperglycaemia. The more prolonged and severe the hyperglycaemia, the greater is the risk of DNP. Moreover, genetics plays an important role; patients who have one or two deletions of the angiotensin-converting enzyme (ACE) gene, a defect in the sodium proton pump or a family history of hypertension are at increased risk for progression to DNP. However, in such patients, nephropathy does not occur until type I diabetes develops.[20] In some studies it was shown that diabetic siblings of parents with type I diabetes and DNP had a high prevalence of DNP. This observation, along with the finding that the incidence of diabetic renal disease in siblings of patients with diabetes is significantly greater than (~70% versus 25 %) in siblings of patients without renal disease, supports a possible genetic role for renal disease in patients with diabetes. Several genes have been proposed as biologically interesting candidates for a so-called nephropathy gene. Polymorphisms of the angiotensin-converting enzyme (ACE), the so-called insertion/deletion genotype, have been proposed and the angiotensinogen gene and angiotensin II type I receptor gene have also been mentioned as possible candidates. [21]

A genetic role in type I diabetes was suspected in view of the association of renal disease in the offspring of patients with cardiovascular disease. In addition to this, DNP is associated with a very high risk of cardiovascular morbidity and mortality, which is not abolished by dialysis or renal transplantation.[19,22]

Chowdhury *et al*[23] stated that, only a minority of patients with diabetes develop DNP irrespective of glycaemic control, suggesting that a subgroup of patients are at higher risk of DNP. There is a marked ethnic variation with nephropathy, being more common in certain ethnic groups. Parental history of hypertension, diabetes or cardiovascular disease appears to predispose to DNP in diabetic patients. Luno *et al*[24] showed a clear relationship between hypertension and the microvascular complication of diabetes. Genetic predisposition to hypertension has been correlated to the risk of DNP in type I diabetes, and hypertension is a well known risk factor for developing nephropathy in patients with type II diabetes.

Pathogenesis and Pathological changes

A proposed mechanism for the development of nephropathy in patients with type I diabetes is elevation of growth hormone levels due to poor glycaemic control, resulting in glomerular hypertension. Mesangial cells in the glomerulus respond to glomerular hypertension by producing growth factors, especially tumor necrosis factor, which results in increased glomerular permeability, proliferation of glomerular epithelial cells and excessive production of basement membrane and collagen tissue. These effects eventually lead to glomerular scarring and renal failure. Patients who are prone to excessive production of collagen (e.g. those in whom keloid forms) are at greater risk, which

may explain the higher prevalence of DNP in African Americans. Pathogenesis in patients with type II diabetes differs in that mesangial lymphokine production is associated not only with hyperglyacemia but also with insulin resistance and generalized vascular disease. Thus, albuminuria may occur even before hyperglycaemia develops. Thus, the hallmark lesions of DNP in type I DM include glomerular basement membrane thickening, glomerular hypertrophy, mesangial matrix expansion and hyalinization or sclerosis of glomerular capillaries. Histologic findings in type II DM often include these lesions as well as a mixture of others like the depositions of hyaline, a proteinaceous material that is often seen to be present throughout the nephron causing nephrosclerosis. [25]

Morphologically, the development of DNP is characterized by progressive thickening of the glomerular basement membrane, expansion of the mesangial matrix which correlates with glomerular filtration function, extensive inflammation and tubulointerstitial fibrosis ending in tubular atrophy. Mesangial cells are pericyte like which are found in the glomeruli of the kidney. It is well known that they have important contractile and synthetic properties that regulate the function of the glomerulus. During diabetes, the synthesis of various extracellular matrix (ECM) components by mesangial cells is increased. It has been recognized that degradation of ECM may also be decreased in diabetes, contributing to the process of mesangium accumulation. The major enzymes responsible for ECM degradation are a large group of enzymes collectively known as matrix metalloproteinases (MMPs) which are synthesized as proenzymes. The mesangial cell and its pericellular matrix have a very active plasminogen cascade that can liberate plasmin locally to mediate matrix degradation both directly and indirectly by activating the MMPs. There is evidence that each of these pathways regulating the matrix degradation is affected by the diabetic environment. [26]

There are several possible mediators including the advanced glycation end products (AGEs), carboxymethyllysine and pentosidine whose formation is closely linked to oxidation, which accumulate in the characteristic diabetic glomerular lesions such as the expanded mesangial matrix and nodular lesions.[27]

Choi *et al*[28] proposed that excessive nitric oxide production may also contribute to renal hyperfiltration and hyperperfusion that occur in early diabetes. Anderson *et al*[29] suggested that there were many shunt-like defects early in the course of DNP. Such defects may account for immunoglobinuria in this disorder.

Another factor identified to play a role in the development of DNP as well as in other complications of diabetes, is an alteration in polyol metabolism. Increased polyol pathway activity in diabetes has been demonstrated to result in the elevation of sorbitol concentration in the renal glomerulus and renal medulla. Depletion of myo-inositol pools and decreased Na^+-K^+-ATPase activity has been demonstrated in the renal glomerulus.[30]

Renal hypertrophy has been proposed to be a factor in the pathogenesis of DNP. It develops early in the course of both experimental and human diabetes mellitus. Regression of renal hypertrophy has been demonstrated following insulin treatment in animal models of diabetes but good control of blood glucose with administration of insulin has not been proven to reverse nephromegaly in human diabetes. The temporal development of renal hypertrophy and changes in renal function are well established in the STZ-DM rat. Increased kidney weight has been described as early as thirty six hours after induction of diabetes. The early kidney growth is primarily due to cellular hypertrophy but cellular hyperplasia plays a major role after one week of STZ-induced diabetes mellitus. Insulin treatment results in prevention or regression of renal hypertrophy in experimental diabetes. Studies have demonstrated some regression after one week of insulin and a return to control values after three weeks of insulin administration.[30,31]

Diagnosis

Early diagnosis is of utmost important, since the development of DNP affects the general health and the carbohydrate metabolism of the patient. Furthermore, it aggravates hypertension and accelerates atherosclerosis. In the early stages of DNP there are no clinical signs or symptoms of renal disease. Glomerular changes can be identified only by renal biopsy, which is impractical, or by the presence of microalbuminuria (albumin excretion rate >30 mg/day). Therefore, all diabetic patients should be tested annually for microalbuminuria.[32]

Microalbuminuria is a sensitive but relatively late marker of diabetic kidney disease. Nevertheless, screening of diabetic patients for microalbuminuria is of great importance since there is no other screening test capable of diagnosing DNP at an earlier stage. Without intervention, microalbuminuria will increase by an average of 15% to 20% every year, an observation that is true for patients with both types of diabetes. Albumin measurements include the urine albumin concentration (UAC) and the urine albumin:creatinine ratio (UACR). Once macroalbuminuria occurs (albumin excretion rate >300mg/day), usually after type 1 diabetes has been present for 10 to 15 postpubertal years, renal function declines about 10 % per year, ending in end-stage renal disease. Beside the classical clinical and chemical parameters for evaluation of renal function, the measurement of urinary albumin excretion is now widely used for the detection of developing DNP.[33,34]

The appearance of albumin in the urine is usually considered as a harbinger of incipient nephropathy. In this sense, proteinuria is thought to indicate the presence of intraglomerular hypertension and abnormal glomerular permeability. However, because tubular protein deposits can elicit proteolytic inflammatory responses, proteinuria itself is suspected to contribute independently to renal damage. If microalbuminuria is found, causes other than diabetes like urinaty tract infection, ketosis or use of DHPCCBs, should be ruled out. The appearance or worsening of proteinuria is believed to predict the likelihood for progression of DNP. Therapies that reduce proteinuria such as angiotensin converting enzyme inhibitors (ACEIs) have, in many studies, been associated with a salutary effect on renal

disease progression. For these reasons, proteinuria has been emphasized as a clinical monitoring parameter in those recognized to be at risk of renal disease. Also, the degree of reduction in proteinuria is sometimes assessed as a sure endpoint for adjusting therapies. In general, a 30 to 50% reduction from baseline urinary albumin excretion rate has been targeted clinically. In addition, the presence of microalbuminuria should be confirmed on at least two separate occasions 1 month apart. If microalbuminuria persists, aggressive treatment should be initiated. Tight glycaemic control, keeping glycosylated haemoglobin A1c (HbA1c) levels within or just above the nondiabetic range, undoubtedly is beneficial.[35,36]

Screening for microalbuminuria is not as useful in type II as it is in type I diabetes because it is not as predictive of progression to overt nephropathy as it is in type I diabetes. However, once overt proteinuria occurs, the rate of loss of glomerular filtration rate (GFR) and the deleterious effect of hypertension are equivalent to that seen in type I diabetes, suggesting similar pathogenetic mechanisms. In the absence of aggressive intervention, the time to progression from overt proteinuria to end-stage renal disease in either form of diabetes averages six to seven years. [37]

Classification according to degree of albuminuria, i.e. normoalbuminuria, microalbuminuria and macroalbuminuria, is more or less universally accepted, although there may be a few exceptions in the United States. The strong predictive value of microalbuminuria was recently confirmed in the follow-up study from the Diabetes Control and Complications Trial (DCCT). It should be noted that the development of renal damage according to this system in patients with diabetes is continuous. For example, patients with high normoalbuminuria have a greater risk for disease progression than those with microalbuminuria in the low range. The degree of overt proteinuria is a major risk marker in patients with diabetes, but the risk starts with even the slightest increase in albuminuria and continues to nephrotic-range proteinuria. Therefore, microalbuminuria (as early in the course as possible) is an ideal stage for intervention because loss of organ function (decline in GFR) has not yet occurred.[34,38] Rave *et al*[39] suggested that, primary care physicians must participate in screening and diagnosis of DNP by detection of overt albuminuria. Also, home blood pressure self-monitoring is a better predictor of progression of DNP than office blood pressure measurements.

Watanabe *et al* [40] stated that, there is an increased production and degradation of type IV collagen in DNP. They suggested that augmented turnover of type IV collagen in glomerular basement membrane and tubular basement membrane results in increased concentration of free u-IV collagen. Therefore, measurement of u-IV collagen may be a useful specific indicator of the progression of DNP.

Progression and Psychosocial Aspects

Early recognition of DNP remains one of the greatest challenges to the timely institution of nephroprotective measures. Diabetics are the most obvious target population on which to focus preventive efforts and screening for early evidence of nephropathy. Current World Health Organization (WHO) protocols suggests that we screen yearly for microalbuminuria, beginning at the time of diagnosis in type II diabetics and within 5 years of onset of type I diabetics or at puberty in juvenile onset DM. Because other factors can transiently elevate urinary albumin excretion, positive screens should be confirmed within 6 months and antiproteinuric treatment should be instituted only if two separate evaluations show evidence of microalbuminuria. National Institutes of Health recommends that, women or men exhibiting a serum creatinine of greater than 1.5 or 2 mg/dl (132 or 177 micromol/L) respectively, should be referred to a renal specialist team as pre ESRD candidates. After macroalbuminuria appears, without treatment, renal function declines at a rate of about 1 mL/min per month or 10 % per year; thus, end-stage renal disease occurs after about 7 years. Treatment can prolong the active life of the kidney, but once macroalbuminuria occurs, end-stage renal disease is inevitable. [41]

Numerous studies have shown that the development of DNP is often accompanied by significant losses in quality of life, functional status and autonomy. In turn, impairments in mental status, performance status and quality of life are independently correlated with risk of mortality. Moreover, several barriers, both practical and artificial, exist against employing ESRD patients. Although, these are not insurmountable, fewer than 10 % of ESRD patients below 60 years of age are able to maintain gainful employment. DNP is a costly disease, in United States, medical care of ESRD patients especially those having DNP incurred over $ 11 billion in direct expenditure in 1997 and is projected to approach $16 billion annually (Latham , 1998) [42].

Non Pharmacologic Therapy

Diet

To a great extent, many symptoms and complications of CRD are explained by the imbalance between the dietary intake and urinary excretion of several solutes. Dietary interventions are generally regarded to be of equal importance to pharmacologic therapies for disease and symptoms control. Dietitians are integral members of most specialized renal care teams and can complement the efforts of physicians to educate patients on appropriate use of their treatments like calcium, iron and phosphorus supplements. In the face of mild to moderate renal disease e.g. GFR less than 60 ml/min, restriction of dietary intake to from 0.6 to 0.8 g/kg/d of high biologic value protein is now presumed to diminish the progression of renal disease. Restriction of dietary potassium generally is required once GFR is less than 10 ml/min in order to avoid life-threatening hyperkalaemic episodes. Also, adherence to dietary measures to control diabetes is generally advocated to improve therapeutic outcomes.[43]

Several studies have shown a significant reduction in the rate of GFR decline after 37 months following a low-protein diet compared with a control group following a normal-

protein diet. Interestingly, the rate of GFR decline was only significantly different between the patients following the two diets when those with initial GFRs greater than 45ml/min were considered. This may suggest that dietary intervention should be introduced early in the course of DNP before significant reductions in GFR occurs, but a reduction in dietary protein content is not easy and the effect on albuminuria may be limited. The long-term effect on GFR is not and may never be available.[44,45]

Patient Education

Individuals with DNP are expected to understand and follow complex dietary medication and physical regimens. Data indicated that intense educational effort is associated with increased patient autonomy, improved quality of life, increased compliance with therapies and the medical ability to delay initiation of dialysis. Educational programs generally emphasize patient comprehension of the most common complications of kidney disease (anaemia, bone disease and hypertension), measures to slow progression of renal disease, if still feasible, dietary management (protein, potassium, sodium and fluid restrictions) and medication management (reason for use, manner of use and precautions). Physicians can address several facets of medication use to foster patient acceptance, compliance and safety. Patients should be encouraged to seek advice before using over-the counter products, because even over-the counter products can worsen renal function e.g. NSAIDs, prove dangerous e.g. certain antacids, laxatives or require precautions e.g. H_2 antagonists used in excessive quantity.[42]

Improving outcomes

The median number of maintenance medications prescribed in ESRD exceeds 8 per patient and medications are often prescribed by multiple practitioners who are not fully aware of the patient`s entire medication regimen. Given that the likelihood of drug interactions and drug related misadventures increase with regimen complexity, a role for regular review of medication profiles becomes evident. Patients should be encouraged to communicate and verify information about their actual medication routine on a regular basis, because dosing changes are often communicated verbally from prescriber to patient and medical records or dispensing profiles may not reflect actual practice.[10]

Prevention & Treatment

Options for prevention include optimal glycaemic control, intensive lowering of blood pressure and use of ACE inhibitors even in normotensive patients with microalbuminuria. The prophylactic and therapeutic benefits of these interventions are an appreciation of DNP as a generally preventable disease. In patients with confirmed microalbuminuria, a treatment regimen of the same intensity as that used in patients with macroalbuminuria, including ACE inhibitors, is essential. Adjusting the ACE-inhibitors dose to the maximum allowable normalizes or significantly decreases albuminuria. In patients with type I diabetes and microalbuminuria, the chance of macroalbuminuria developing within 10 years is 80 %. The incidence of macrovascular disease and the mortality rate are also increased in these patients. Presumably, these effects occur because if the glomerulus is permeable to albumin, the intima of the major vessels will also be permeable to lipoproteins.[46]

It has been documented that antihypertensive treatment can reduce the decline in renal function considerably. Without treatment, the decline in GFR is approximately 10 ml/min/y in proteinuric patients but treatment can reduce this by more than 50%, therefore, early treatment of patients with microalbuminuria is advocated because GFR decline seems to be prevented by this early intervention. Good metabolic control is still essential for slowing down disease progression. In patients with type II diabetes, the overall prognosis is generally not optimistic because of the associated cardiovascular disease, although the clinical course of renal disease is not too different from type I diabetes and with similar treatment strategies.[47,48]

Aggressive treatment or elimination of DM can potentially retard or interrupt the progression of DNP to end-stage renal failure. So, early intervention appears to be crucial in maximizing the success of preventive efforts. Intensive control of blood glucose has been shown to reduce or slow the onset of DNP in insulin dependent diabetics and patients with type II diabetes. It has been stated that strict glycaemic control may not slow the rate of progressive renal injury once overt dipstick-positive proteinuria has occurred. Once macroalbuminuria develops, the course of DNP cannot be reversed, therapeutic measures are directed at decelerating the decline in function to extend the kidney's active life. If medical science had the means to totally control diabetes, the process could be reversed even at this stage. Unfortunately, at present, glycaemia cannot be controlled to the degree necessary to stabilize or reverse clinical advancement of DNP.[49,50]

Aggressive control of hypertension in diabetic patients without microalbuminuria and tight glycaemic control in those with microalbuminuria can avoid or delay its onset. Even, when macroalbuminuria is present, treatment can prolong renal function. Also, aggressive antihypertension therapy, especially with combination of ACE inhibitors and CCBs can reduce renal decline by half. Moreover, avoiding circumstances that may damage the kidney e.g. use of radiocontrast materials or nephrotoxic drugs, dehydration, hyperlipidemia and urinary tract infection, is critical and mandatory in prevention policy. Inadequate treatment of hypertension, use of radiocontrast materials or potentially nephrotoxic drugs, overuse of diuretics and urinary tract infection may hasten progression to end-stage renal disease and should be carefully avoided.[33,51]

The plasma lipoprotein profiles become more atherogenic in patients with DNP, including at the sub-clinical stage, compared with diabetes without nephropathy or those with non-diabetic kidney disease. So, it has been suggested that 3-hydroxy-3-methylglutaryl coenzyme A (HMG Co A) reductase inhibitors confer renoprotection via effects on

prosclerotic cytokinase such as transforming growth factor-beta (TGF-beta), and macrophage accumulation is independent of their lipid lowering properties.[52]

Some methods of treatment are controversial (dietary protein restriction) or still under investigation (use of injected or oral heparin) but may help delay renal transplantation or dialysis. Injected or oral heparin can be used to replenish intraglomerular levels of heparin sulfate and other proteoglycans that are underproduced by mesangial cells in DNP. Loss of proteoglycans leads to loss of anionic charge in the basement membrane and proteinuria as well as loss of inhibition of mesangial cell proliferation and glomerulosclerosis. Heparin injections restore heparin sulfate production, lessen albuminuria and stabilize the mesangium. Recently, oral therapy with glycosaminoglycans derived from pig intestines was shown to decrease albuminuria in patients with type II diabetes and nephropathy. Use of danaparoid sodium (Orgaran) which increases levels of glomerular proteoglycans, has also improved exudation in DNP.[53]

Furthermore, pharmacotherapy also focuses on the control of glomerular pressure bearing in mind that control of systemic hypertension can slow the progression of proteinuria and deterioration of renal function. So, ACE inhibitors and calcium channel blockers have been demonstrated to be effective in the management of DNP. [54]

A high protein diet has been found to increase renal blood flow and glomerular filtration rate by several potential mechanisms. One could therefore theorize that excessive protein intake would heighten glomerular hyperfiltration and hence long term risk of renal disease. Conversely, protein restriction might help limitation of hyperfiltration and renal disease in certain individuals. So dietary protein restriction (low protein diet) induces a reversible decline in glomerular filtration and albuminuria in insulin-dependent diabetic patients with DNP.[55]

Levey[56] found that, protein restriction was indeed beneficial in retarding DNP progression, particularly in individuals with moderate disease (GFR 25 to 55 ml/min). Despite that, there is a controversy about the benefit of protein restriction in retarding GFR decline, the optimal level of protein intake, and which types or stages of renal disease are most likely to benefit. In practice, most nephrologists advise CRD patients to avoid excessive protein intake and many advocate dietary protein restriction to 0.6 to 0.8 gm/kg/day.

There are however, potential problems associated with a low protein diet. In addition to the difficulty with compliance due to concurrent fat and simple carbohydrate restriction, diabetics are at an increased risk for protein malnutrition because the reduction in intake may be associated with enhanced protein breakdown induced by insulin deficiency. Recent experimental studies also suggest that restriction of all components of protein intake may limit the potential efficacy of this regimen. The administration of L-arginine, precursor of the vasodilator nitric oxide, to diabetic rats with nephropathy ameliorates both the glomerular hyperfiltration and the degree of proteinuria. Thus, limiting L-arginine intake as part of protein restricted diet may not be desired. [57]

Kidney transplants from living related donors appear to be the best line of treatment. Cadaveric transplants and long term haemodialysis are considered reasonable options in patients with end-stage renal disease.[17]

Several therapies like receptor antagonists of endothelin, an endogenous vasoconstrictor derived from the vascular endothelium, are under clinical development. These "-entans" e.g. bosentan are thought to be promising in the setting of renal disease in which endothelin levels are noted to be elevated and are suspected of perpetuating vascular and target organ damage. Unfortunately, they are not yet clinically available.[58,59]

Finally, the methods of prevention and management of DNP can be summarized in the following items: control blood pressure, encourage smoking cessation, prevent radiocontrast-induced renal shutdown, avoid risk factors (sepsis, hypoxia, dehydration), restrict dietary protein, maintain hydration, avoid renal damage from infection and drugs, control vascular disease and dyslipidemia, assess for renal transplantation and select dialysis method. [60]

The optimal therapy of DNP continues to evolve. It now seems clear in type I diabetes that ACE inhibitors lower protein excretion and slow the rate of disease progression in patients with microalbuminuria and in those with overt nephropathy. It is important to appreciate, however, that these agents do not completely prevent progression. Thus, other modalities may also be required. Probably most important is maintenance of strict glycaemic control early in the course of the disease. In addition, dietary protein restriction may be beneficial in patients with established nephropathy. As a result, the clearly emerging consensus opinion is that the optimal treatment of DNP is not based upon the administration of a single agent or agents to modify only one adverse factor. Rather, the targeting of all possible risk factors such as hyperglycaemia, hypertension, microalbuminuria and hyperlipidemia, is the best management strategy.[61]

Two final points deserve empahsis. First, it has yet to be proven that a fall in protein excretion is an indicator of a better long-term outcome in DNP. Second, proteinuria tends to increase over time in untreated patients. Thus, antihypertensive drugs that produce no or less fall in protein excretion may still be having a beneficial effect when compared to the progressive course in untreated patients. [62]

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