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Nutritional Approach to Diabetic Nephropathy

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Abstract

Diabetes is an important cause of renal disease. Diabetic nephropathy (DN) is characterized by albuminuria, which is usually accompanied by hypertension, progressive rise in proteinuria (albuminuria >0.5 g/24 h), and decline in renal function. Long term complications of diabetes are macrovascular disease (coronary heart disease), cerebrovascular disease, peripheral arterial disease and microvascular disease retinopathy and nephropathy. DN carries a 20- to 40-fold increased risk for cardiovascular (CV) mortality. To delay progression of DN to ESRD following measures are recommended a) good control of blood glucose, b) low-protein diet, c) control of hypertension, d) restriction of dietary salt, phosphorus and potassium in advanced cases and e) control of hyperfiltration, usually through angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocking (ARB) agents. ACE inhibitors reduce proteinuria and glomerulosclerosis. Mangement of proteinuria with diet has shown that antiproteinuric effect is strongly dependent on dietary sodium restriction.

Keywords: Diabetic nephropathy; Diabetes; Renal function; Cardiovascular

Introduction

India among all the SAARC countries has become the diabetes capital of the world. Twenty to forty percent of type 2 diabetes patients having microalbuminuria progress to overt nephropathy i.e., diabetic nephropathy (DN), and ~20% progress to end stage renal disease (ESRD) making it the leading cause of ESRD in the past two decades. Diabetic nephropathy (DN) is characterized by albuminuria, which is usually accompanied by hypertension, progressive rise in proteinuria (albuminuria >0.5 g/24 h), and decline in renal function.

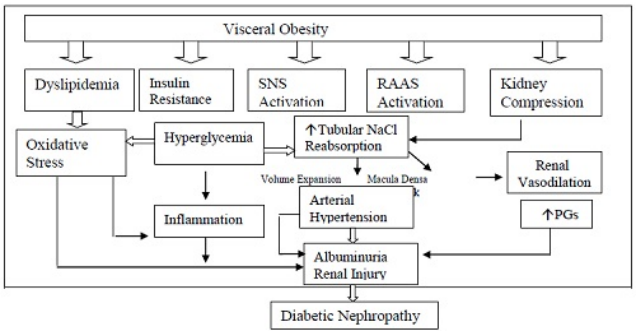

Figure 1: Interaction between metabolic and hemodynamic pathways in the pathophysiology of diabetic nephropathy. SNS: Sympathetic Nervous System; RAAS: Renin Angiotensin Aldosterone System; PGc, intraglomerular capillary pressure (Adapted from Christine Maric and John E. Hall Obesity, metabolic syndrome and diabetic nephropathy Contrib Nephrol. 2011; 170: 28–35).

Long term complications of diabetes are macrovascular disease (coronary heart disease), cerebrovascular disease, peripheral arterial disease and microvascular disease retinopathy and nephropathy. DN carries a 20- to 40-fold increased risk for cardiovascular (CV) mortality. Figure 1 illustrates interaction between metabolic and hemodynamic pathways in the pathophysiology of diabetic nephropathy. To delay progression of DN to ESRD following measures are recommended a) good control of blood glucose, b) low-protein diet, c) control of hypertension, d) restriction of dietary salt, phosphorus and potassium in advanced cases and e) control of hyperfiltration, usually through angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blocking (ARB) agents. ACE inhibitors reduce proteinuria and glomerulosclerosis. Mangement of proteinuria with diet has shown that antiproteinuric effect is strongly dependent on dietary sodium restriction. A low-sodium diet is known to enhance the renoprotective and cardioprotective effect of ACE inhibitors (Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study) and Irbesartan Type II Diabetic Nephropathy Trial (IDNT)) in DM patients with nephropathy. Compared to higher sodium intake groups, the patients in the low sodium group had better renal (by 43%) and cardiovascular (by 37%) outcomes. These studies support low dietary salt intake, particularly in patients with DM and nephropathy treated with angiotensin receptor blockers. Dietary sodium intake of less than 2.4 g/d (one teaspoon salt) is recommended in adults with CKD and hypertension. Studies have shown fall in blood pressure by 2-3 mmHG when sodium intake is lowered from 4.0 g to 2.0 g per day. This fall of blood pressure may lead to a cumulative decrease by 10 mmHg over several years and may eventually lower the risk of heart disease. Target blood pressure should be <130/80 mm Hg. LDL cholesterol should be <100 mg/dl and those with cardiovascular disease should maintain <70 mg/dl [1-8].

Pathophysiology of Diabetic Nephropathy

The exact cause of diabetic nephropathy is unknown, however, it is postulated that

i) hyperglycemia (which causes hyperfiltration and renal injury), ii) advanced glycosylation products (AGEs), and iii) activation of cytokines play key role in causing renal injury. Hyperglycemia increases expression of transforming growth factor-beta (TGF-beta) in the glomeruli and of matrix proteins specifically stimulated by this cytokine. TGF-beta and vascular endothelial growth factor (VEGF) may contribute to the cellular hypertrophy, enhanced collagen synthesis, and vascular changes observed in persons with diabetic nephropathy. Hyperglycemia also may activate protein kinase C, which may contribute to renal disease and other vascular complications of diabetes. Familial or perhaps even genetic factors also play a role. Three major histologic changes occur in the glomeruli in diabetic nephropathy.

The earliest morphologic abnormality in diabetic nephropathy is the thickening of the GBM and expansion of the mesangium due to accumulation of extracellular matrix.

1. Mesangial expansion induced by hyperglycemia via increased matrix production or glycosylation of matrix proteins.

2. Thickening of the glomerular basement membrane (GBM).

3. Glomerular sclerosis caused by intraglomerular hypertension.

Intraglomerular hypertension is induced by dilatation of the afferent renal artery or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli. The key change in diabetic glomerulopathy is augmentation of extracellular matrix.

The severity of diabetic glomerulopathy is estimated by the thickness of the peripheral basement membrane and mesangium and matrix expressed as a fraction of appropriate spaces (eg, volume fraction of mesangium/glomerulus, matrix/mesangium, or matrix/glomerulus). The glomeruli and kidneys are typically normal or increased in size initially, thus distinguishing diabetic nephropathy from most other forms of chronic renal insufficiency, wherein renal size is reduced (except renal amyloidosis and polycystic kidney disease).

Patients with overt diabetic nephropathy generally develop systemic hypertension. The deleterious effects of hypertension are seen in the vasculature and microvasculature. Proteinuria, a marker and potential contributor to renal injury, accompanies diabetic nephropathy. Increased glomerular permeability allows plasma proteins to escape into the urine. Some of these proteins are taken up by the proximal tubular cells, which initiate an inflammatory response that contributes to interstitial scarring eventually leading to fibrosis is present. Tubulointerstitial fibrosis, which is present in advanced stages of diabetic, nephropathy, is a better predictor of renal failure than glomerular sclerosis. Hyperglycemia, angiotensin II, TGF-β, and proteinuria play role in stimulating this fibrosis. There is an epithelial-mesenchymal transition that takes place in the tubules, with proximal tubular cell conversion to fibroblast-like cells. These cells then migrate into the interstitium and produce collagen and fibronectin [9-12].

Hence, medical nutritional management is important for the prevention of DN. The goals of medical nutritional therapy which will be dealt in this article are:

1. Maintenance of near normal blood glucose levels (glycemic control) by controlling food intake and exercise

2. Achieving optimal serum lipids and blood pressure to reduce the risk of cardiovascular disease (CVD)

3. Management of body weight.

4. Maintaining biochemical parameters and fluid status

5. Prevention of long term complications

6. Prevention of malnutrition and strategies to control diabetic gastroparesis.

An important marker of good diabetes therapy is that blood glucose is maintained below the renal threshold (250 mg/dL), so that it is not passed into the urine. Insulin resistance and glucose intolerance are characteristic features in patients with kidney disease. The Diabetes Control and Complications Trial (DCCT 1993) and the United Kingdom Prospective Diabetes Study (UKPDS) have shown that intensive insulin therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy. According to American Diabetes Association (ADA), after five years of diagnosing DM, microalbuminuria must be tested annually as microalbuminuria is also associated with elevated HbA1C levels (>8.1). Target HbA1C should be ≤ 7.0 % (Table 1). However, the values may be falsely elevated or decreased in patients with chronic kidney disease (CKD) because of factors given in Table 2.

Glycemic target	ADA*	ACE**	IDF***
A1c%	<7.0	≤6.5	<6.5
Fasting Glucose mg/dl	90-130	<110	<100
Postprandial glucose mg/dl	<180	<140	<145

Table 1: Target HbA1C for diabetics with kidney disease.

Assessment of Nutritional Status

According to KDOQI guidelines, in chronic kidney disease (CKD) there is no single valid tool for assessment of nutritional status. Tools for assessment of nutritional status are given in Table 3.

Reduced red blood cell life span
Iron deficiency
Blood transfusion
Accelerated erythropoiesis due to administration of erythropoietin stimulating agents
Metabolic acidosis

Comorbid depression which can cause poorer metabolic control, decreased adherence to medication and diet, and reduced quality of life.

Table 2: Factors affecting HbA1C levels in chronic kidney disease.

Tool	Reliability	Frequency
Serum albumin	Negative phase reactant proteins. Affected by hydration status.	Monthly
Serum prealbumin	Negative phase reactant proteins.	Monthly
Serum cholesterol	Good indicator of chronic malnutrition	3 monthly
Subjective global assessment (SGA)	Good assessment of nutritional status	Six months
Anthropometry (edema free body weight, body mass index (BMI), skinfolds, mid upper arm circumference (MUAC)	Reliability varies with hydration status	As and when required (or at six months spacing)
Dietary diaries, and dietary interviews	Reliable	Every visit
nPNA	Good indicator of protein intake	Monthly or 3 monthly

Table 3: Assessment of nutritional status.

Blood Glucose Control

An important marker of good diabetes therapy is that blood glucose is maintained below the renal threshold (250 mg/dl), so that it is not passed into the urine. Insulin resistance and glucose intolerance are characteristic features in patients with kidney disease. Target HbA1C should be ≤7.0 %. However in CKD, the values may be falsely elevated or decreased. Amount and type of carbohydrate (CHO) in food influences blood glucose levels. Glycemic index attempts to classify foods according their impact on blood glucose levels. Foods with GI under 55 are considered as Low GI foods, foods with GI between 56-69 are termed as having moderate GI and high GI foods are foods with GI >70. Hence, patients should be educated on importance of glycemic index (GI) and glycemic load for better control of blood sugar. Fiber intake can reduce blood sugars in diabetic patients. ADA recommends fiber intake of 14g/1000 kcal which can be increased up to 35g. Soluble & insoluble fiber decrease gastrointestinal transit time which improves insulin sensitivity by slowing carbohydrate absorption. Energy requirements vary according to age, sex and activity levels. Energy requirements should be calculated depending upon whether the goal is

i) Weight reduction,

ii) Maintain weight or

iii) Gain weight

Energy intake should not exceed 30kcal/kg/d, out of which 50-60% of total dietary energy should come from carbohydrate, 30% from fat and 20% from protein. Selecting fat-free and low-fat dairy products and cutting back on foods containing partially hydrogenated vegetable oils to reduce trans-fat in diet is recommended. Reduction in saturated fat to no more than 5 to 6 percent of total calories is recommended to lower cholesterol. Consumption of beverages and sugar should be curtailed (ADA). Cholesterol should be limited to <200 mg/day. Polyunsaturated fats of the Omega-3 series are provided naturally in fish and other seafood, and the intake of these foods need not be curtailed in people with diabetes [13-20].

Diabetic Gastro paresis (DGP)

Diagnosis of gastroparesis should clearly establish delayed gastric emptying, in the absence of an obstructing structural lesion in the stomach or small intestine (The American Gastroenterological Association (AGA). Fullness and bloating are suggestive of delayed emptying and hence DG. DGP affects 20% to 50% of the diabetic patients and is usually associated with retinopathy, diabetic peripheral neuropathy (DPN) and DN as well as poor blood sugar control. Management of DGP should be focused on maintaining good control of blood sugar, hydration, nutrition, controlling symptoms of delayed gastric emptying. Prokinetic drugs, antiemetic agents, and analgesics may be required to control symptoms of DGP. Maintaining glucose levels below 180 mg/dL prevents inhibiting gastric myoelectric control and motility. Since hyperglycemia inhibits the action of prokinetic drugs such as erythromycin, therefore, maintaining good glycemic control is important. It is important to maintain proper hydration and nutrition. If patient is able to take orally, prefer enteral route.

Recommendations for Protein and Phosphorus Intake

Dietary protein

Animal studies have shown lower urinary albumin excretion when a soy protein diet or a low casein diet is fed, suggesting a delay in the progression of diabetic nephropathy. Several small studies in humans with diabetic nephropathy have shown that a prescribed protein restricted diet of 0.6 g/ kg day (subjects actually only achieved a restriction of 0.8 g/kg/day) retards the rate of fall of GFR modestly. Protein requirements for dialysis dependent diabetic patients are increased to 1.2 g/kg/d due to dialysis induced hypercatabolism and protein losses. Accumulation of AGE's due to hyperglycemia causes degenerative changes in retina. Low carbohydrate and low protein diet is recommended for diabetics because factors crucial for formation of AGE's are: 1. turnover of protein for glycation, 2. degree of hyperglycemia, and 3. extent of oxidative stress. Exogenous sources of AGE's are tobacco, smoking, diet (meat, cheese, egg yolk) and

prolonged and high cooking temperature that induce glycol-oxidation and lipo-oxidation products ingested with food. Human AGE's are pentosidine and CMI. AGE's effect produces radical oxygen species (ROS). AGE's also change local concentration of cytokines and growth factors. AGE's accumulate in the vessel walls that disturb the cell structure and function. AGEs get absorbed, transported and deposited in retinal pericytes cause apoptosis through basement thickening, pseudo aneurism and hyperpermeability. AGE's also reduce nitric oxide bioavailability. Protein has linear relationship with phosphorus. Phosphorus intake should not exceed 800-1000 mg/day in order to control hyperphosphatemia in predialysis and dialysis patients. Foods with high protein to phosphorus ration should be avoided. Milk and milk products, cola beverages, frozen meat, processed food (cheese) with phosphorus as additives have high phosphorus content. Patients should be advised to take vegetarian protein as only 50-60% of phosphorus from vegetable source is absorbed. Calcium intake should be restricted to <2000 mg/d including supplementation. Ideally it should not exceed 1200 mg if patient is being treated for vitamin D deficiency.

Obesity and Diabetic Nephropathy

Obesity is one of the factors causing DM and metabolic syndrome. These disorders increase the severity of chronic renal disease. Good glycemic control, regular exercise, weight reduction diet and other changes in life style are recommended for overweight and obese patients. Minimizing insulin dose is one strategy to limiting weight gain. In obese patients, restrict energy intake to 20-25 kcal/kg/d.

Pregnancy and Diabetic Nephropathy

It is recommended to liberalize dietary protein intake to 1.0-1. 2 g/kg preconception weight/ day. Energy intake should be 35 kcal/kg/d sufficient enough for protein sparing effect. Insulin should be used to control hyperglycemia. Some patients may require oral nutritional supplements (ONS) to fulfill protein and energy requirement. While prescribing ONS, care should be taken to choose ONS with low glycemic load and it should not be hyperosmolar. Target BP should be <130/80 mm Hg because of CKD. Hypotension should be avoided.

How to Control Diabetic Peripheral Neuropathy (DPN)

The key to preventing DPN is good control of blood sugar through diet, exercise, and weight management. A study has shown that tight blood sugar control yielded hemoglobin HbA1C of 7.2%, compared to an HbA1C of 9.1% in a conventional therapy group which resulted in 60% reduction in the occurrence of peripheral neuropathy. A fasting blood sugar <110 mg/dl prevented these complications. Another study on DM has shown that 1% reduction in HbA1C correlated with a 37% reduction in microvascular complications, and a 43% reduction in amputation or death from peripheral vascular disease.

Severity of neuropathy is associated with serum albumin levels. A Japanese study has shown that serum albumin has independent association with the severity of peripheral neuropathy. Low serum albumin levels are associated with the severity of other microvascular complications, such as nephropathy and retinopathy. Hypoalbuminemia should be corrected by improving protein and calorie intake in diet and by correcting hydration status. Studies have shown that elevated levels of homocysteine are independently associated with the prevalence of peripheral neuropathy either by direct cytotoxic effects on nerve function, or by small vessel occlusions caused by endothelial damage. To control homocysteine levels folic acid, B12, and pyridoxal 5 '- phosphate should be prescribed. In diabetic patients with normal renal function calories from dietary protein should not exceed 15% to 20% of total kilocalories. (ADA). Patients with diabetic nephropathy can take 2 or more servings of fish/ week, minimum intake of fiber should be 14 g/1,000 kcal, and saturated fat should be less than 7% of total calories [21-25].

Nephrotoxicity

Patients with diabetic nephropathy must avoid nephrotoxic agents. The nonsteroidal anti-inflammatory drugs (NSAIDs) can cause a significant drop in GFR, particularly when used with angiotensin-blocking agents. Daily low-dosage aspirin is safe and cardio protective. Cyclooxygenase 2 (COX-2) inhibitors are nephrotoxic. If possible, radio contrast media should be avoided in diabetics. Even with a normal serum creatinine level, patients with diabetes and proteinuria should be well hydrated 12 hours before and after exposure to contrast. Diuretics should be temporarily discontinued, and hyperglycemia should be controlled. Other agents such as dopamine-like agonists and acetylcysteine may help prevent contrast nephropathy in diabetics but require further study.

Dietary Tips

Hyperglycemia plays an important role in the development of DN. Positive family history and poor glycemic control greatly increases the risk for development of DN. It is advisable for patients with diabetic nephropathy to ensure good glycemic control. Diabetics should eat at fixed times and eat several small meals a day because blood sugar level are at peak one to two hours after eating meal, after which levels fall. Snacks in between meals should be preferred. Meals should be well-balanced containing the right proportion of starches, fruits and vegetables, proteins, and fats. Patients should be advised to keep carbohydrate quantity constant at each meal and snack to regulate blood sugar levels. Maintaining food dairies is helpful. Use of measuring cups or a scale to ensure proportion size should be encouraged. Coordination of meals and medications to avoid hyperglycemia and hypoglycemia is important. Too little food in comparison to medications for diabetes may result in low blood glucose levels (hypoglycemia). On the contrary, too large portions of meal taken at a time can cause blood glucose levels to rise (hyperglycemia). Diet prescription for a patient with diabetic nephropathy is given in Table 4 [26-31].

Case: Body weight 82 kg, Height 165 cm ; Hb 10.5 g/dL Creatinine 2.3 mg %, Na: 136, K: 4.2; Ca: 8.2; P: 5.5; Proteinuria: +3	
Energy	25 k cal/kg/d (weight reduction)
Protein	0.6-0.7 g/kg/d + 3g for Proteinuria(If renal function is normal Protein 0.8g/kg/d)
Visible Fat	15-20 g/d
Dietary Fiber	20 g/1000 calories
Serum Na	< 2.4 g/d
Serum K	1mEq ideal body weight.
Serum P	800-1000 mg/d
Serum Calcium	1500 mg

Cholesterol	<150 mg/d (no egg yolk, cream)
Phosphate binders are a must to be taken with meals.	
Folic acid and iron supplements are a must.	

Table 4: Diet Prescription: For A Patient with Diabetic Nephropathy.

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