

Diabetic Nephropathy in Children

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1. Introduction

Diabetic nephropathy (DN) is one of the consequences of a long-term diabetes, typically defined by macroalbuminuria—that is, a urinary albumin excretion of more than 300 mg in a 24-hour collection—or macroalbuminuria and abnormal renal function as represented by an abnormality in serum creatinine, calculated creatinine clearance, or glomerular filtration rate (GFR).¹

2. Prevalence

Long-term microvascular and neurologic complications cause major morbidity and mortality in patients with insulin-dependent diabetes mellitus (IDDM)². The incidence of overt nephropathy rapidly grows 10-15 years after the onset of type 1 diabetes mellitus; the incidence of nephropathy declines after that period and the occurrence of nephropathy after 35 years of duration of type 1 diabetes is uncommon. Diabetic nephropathy rarely develops before 10 years' duration of IDDM. The peak incidence (3% per year) is usually found in persons who have had diabetes for 10-20 years. The increased mortality risk in long-term T1DM may be due to nephropathy, which may account for about 50% of deaths.

Epidemiologic data derived from one of the studies - EDC - showed that in group of patients aged <18 and with the duration of diabetes over 5 years the prevalence of microalbuminuria reached as much as 14%. Long-term diabetes further increased the prevalence of albuminuria, thus 80% of male and 50% of female patients having diabetes up to 30 years of duration had proteinuria in micro- or macroalbuminuric range. (3-4)

3. What is microalbuminuria

Microalbuminuria is a marker for more serious proteinuria followed by azotemia in type 1 diabetic nephropathy⁵. Microalbuminuria develops in 40-60% type 1 diabetic patients and over 50% of patients with microalbuminuria evolve to macroalbuminuric stage e.g. advanced phase of overt diabetic nephropathy.

4. Risk factor for diabetes nephropathy

Reported risk factors for the development of diabetic renal disease include a longer duration of IDDM, an earlier age at the time of diagnosis, onset of puberty, poorer glycemic control

during the first five years of diabetes, smoking, and a family history of diabetic nephropathy.⁶⁻⁷

Some of the factors leading to occurrence of diabetic nephropathy are hereditary predisposition (ACE genotype), poor glycemic control, diabetes - induced hyperfiltration, tissue hypoxia owing to reduction in capillary permeability, and increased postcapillary resistance. The capillary changes are caused by accumulation of glycated proteins and interaction of these proteins with cellular elements in the capillary walls, that effectuate the decrement in capillary ability for dilatation and ultimately, lead to capillary obstruction. In diabetes, morphological changes in type 4 collagen, heparin - sulphat proteoglycane, fibronectin and enectin molecules leads to structural and functional changes in basal membrane of the renal capillary bed.⁸

The theory of a reduction in nephron number at birth indicates that individuals born with a reduced number of glomeruli may be predisposed to subsequent renal injury and progressive nephropathy. This has been shown in animal studies in which the mother was exposed to hyperglycemia at the time of pregnancy. If this linkage is true in humans, that would have important implications concerning the role of maternal factors in the eventual development of kidney disease.¹

Certain ethnic groups, particularly African Americans, persons of Hispanic origin, and American Indians, may be particularly disposed to renal disease as a complication of diabetes.

5. Pathology and patohistologic changes in diabetic nephropathy

The earliest morphologic abnormality in diabetic nephropathy is the thickening of the glomerular basement membrane (GBM) and expansion of the mesangium due to accumulation of extracellular matrix. Light microscopy findings in diffuse diabetic nephropathy show an increase in the solid spaces of the tuft, most frequently observed (by the positive periodic-acid Schiff reaction) as coarse branching of solid material. Large acellular accumulations also may be observed within these areas. These are circular on section and are known as the Kimmelstiel-Wilson lesions/nodules. Three major histologic changes occur in the glomeruli of persons with diabetic nephropathy. First, mesangial expansion which may be directly induced by hyperglycemia, perhaps via increased matrix production or glycation of matrix proteins. Second, a glomerular basement membrane thickening may occur. Third, glomerular sclerosis being caused by intraglomerular hypertension (induced by renal vasodilatation or from ischemic injury induced by hyaline narrowing of the vessels supplying the glomeruli). These different histological patterns appear to have similar prognostic significance.

Hyperglycemia induces diverse metabolic changes which may give birth to variety of microvascular lesions. The glycation (also called non-enzymatic glycosilation) of proteins is a process induced by the incubation of soluble proteins in the solution with a high glucose concentrations. Glucation lead to three-dimensional structural and/or functional alterations of the proteins involved: thus, the glycation of the erythrocyte membrane proteins leads to its increased adherence ability; likewise, the glycation of heparin - sulphate proteoglycans leads to proliferation of mesangial cells.

High glucose level induces activation of polyol metabolic pathway resulting in increased sorbitol production. Sorbitol, in turn, reduces intracellular myoinositol levels leading to increased capillary permeability and structural basal membrane changes.⁹

Hyperglycemia increases the expression of transforming growth factor-beta (TGF-beta) in the glomeruli and of matrix proteins specifically stimulated by this cytokine. TGF-beta may contribute to the cellular hypertrophy and enhanced collagen synthesis observed in persons with diabetic nephropathy.¹⁰ High glucose levels may also activate protein kinase C, which further contribute to renal disease and other vascular complications of diabetes.

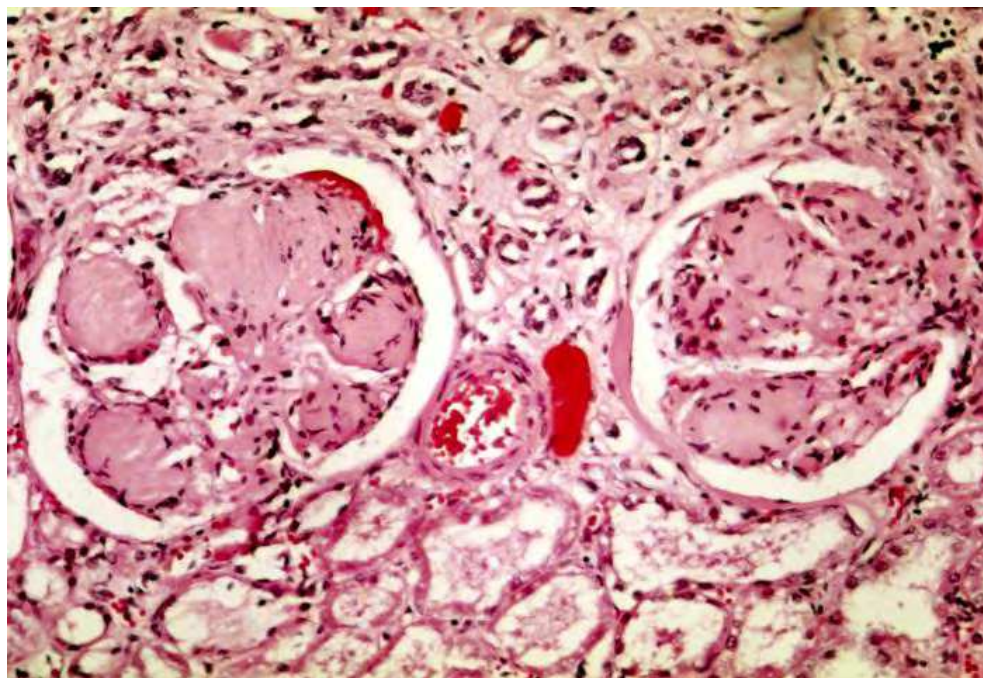


Fig. 1. Nodular glomerular sclerosis - *Nodular glomerulosclerosis in the kidney of a patient with diabetic nephropathy. US Federal Government public domain image. Source: CDC. (This image was copied from wikipedia)*

Tissue hypoxia, augmented capillary permeability and capillary blood flow are the factors which cause increased production of angiotensin II in 45% of diabetics. Angiotensin II might generate precapillary and capillary hypertension. The presence of risk factors for hypertension is particularly important in patients with relatively poor glucose control (hemoglobin A1c concentration above 12 percent). These patients are at increased risk of developing overt nephropathy within 20 years.¹¹ Furthermore, the risk for developing diabetic nephropathy in adolescents with type 1 diabetes whose parents suffered hypertension is threefold increased.¹² The effects of prostaglandin PGI₂ produced by hypertrophic mesangial cells and atrial natriuretic polypeptide may be important in development of microvascular complications including diabetic nephropathy.

In our previous study¹³, performed among the 55 pediatric patients with type 1 diabetes, who had urinary albumin excretion in the range of microalbuminuria was found in almost half (17 of 35 e.g. 48.6%) of children with diabetic ketoacidosis. Furthermore, among the 20 patients with normoalbuminuric UAE only 3 (15.0%) had ketoacidosis.

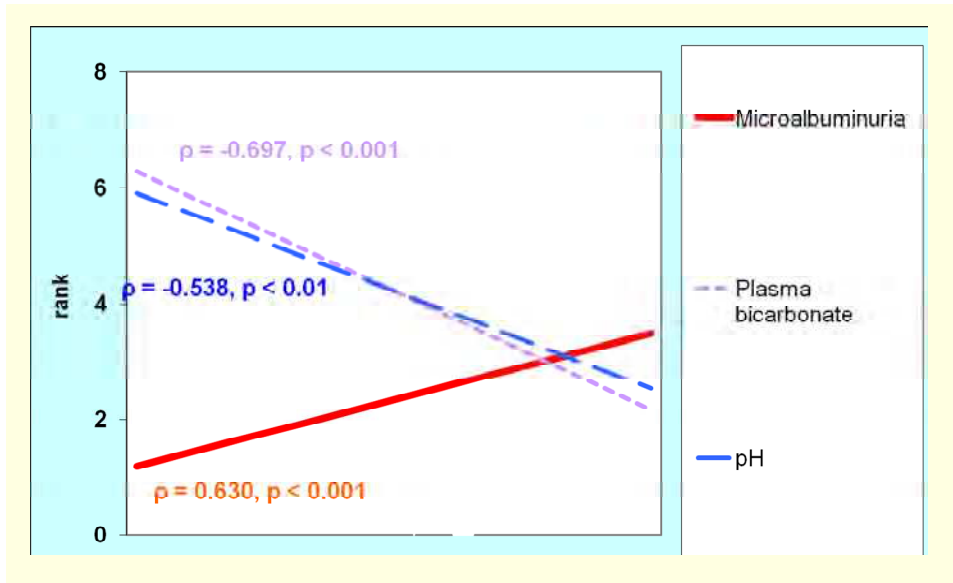


Fig. 2. Showing the correlations between the level of UAE and main parameters of acid-base status.

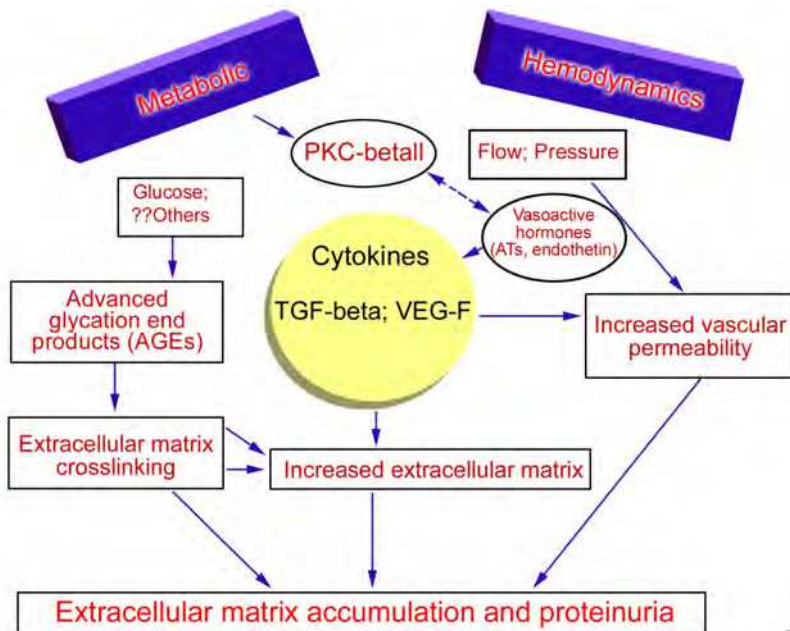


Fig. 3. The pathogenesis of diabetic nephropathy, Soman SS, Soman AS>Diabetic Nephropathy eMedicine Specialities, Endocrinology, Diabetes Mellitus, 2009.

The results of the study¹³ revealed a quite significant correlation between microalbuminuria and plasma pH and bicarbonates; moreover, the level of plasma bicarbonate was a very good predictor of UAE values, depicting the aggravation of urinary albumin excretion in a response to the development of diabetic ketoacidosis

6. Alterations in renal function in diabetic nephropathy

There are 5 clinical stages of diabetic nephropathy. In the first stage, there is the substantial increase of glomerular filtration rate. Hyperglycemia and the lack of insulin along with several other hormones and factors undoubtedly contribute to development of hyperfiltration. The increase in glomerular filtration rate correlates with the enlargement of total filtration surface owing to glomerular hypertrophy; the latter reaches as much as 80% of the values existing prior to diabetes.

In the second ("silent") phase hypofunctional periods alternate the periods of normal function, and vice-versa. The periodicity of these alterations depend on quality of metabolic control. Glomerular filtration rate is, therefore, variable, arterial blood pressure is mainly within the normal range, although a mild hypertension might be present; UAE excretion rate is normal.

The third stage (the incipient nephropathy) is characterized by UAE within microalbuminuric range (30-300 mg/24 h), there is progressive increment of arterial blood pressure, usually 5-15mmHg above the normal values, while the glomerular filtration rate may be normal, increased or reduced.

In our previous study, the total of 40% microalbuminuric children had systolic prehypertension and systolic hypertension (17.1% and 22.9%, respectively) and even 60% had diastolic blood pressure disorders: diastolic prehypertension was found in 35% and diastolic hypertension in 25% patients with microalbuminuria. While the microalbuminuric patients had significantly higher blood pressure comparing to normoalbuminuric group, its noteworthy that the percentage (15% with systolic and 20% with diastolic disturbances) of prehypertensive and hypertensive patients among the type 1 diabetic children with normal UAE was also relatively high (Fig.1 and 2). The level of blood pressure correlated significantly with UAE, but was not proved to be a predictor of microalbuminuria in children with type 1 diabetes.

The fourth stage, also known as manifest nephropathy, a clinically manifest proteinuria ensues, with UAE excretion rate exceeding 300 mg/24h; albuminuria tends to be progressive, possibly leading to the clinical manifestations of nephritic syndrome. As nephropathy evolves to early overt stage with proteinuria (UAE >300 mg/24 hr, or >200 µg/min), it is accompanied by hypertension. The arterial blood pressure is generally raised by 7% per year, followed by the variable reduction in glomerular filtration rate. In the majority of patients, in the midst of this phase a manifest renal insufficiency characterized by overt azotemia occurs. The fourth and fifth stages almost never occur in children and are quite rare in adolescents, mostly being related to the adult population.

The fifth phase (renal insufficiency) is characterized by the general glomerular collapse, followed by overt azotemia, manifest proteinuria and grave hypertension.

Microalbuminuria is also a well-established marker of increased CVD risk¹⁵⁻¹⁶

At the beginning, proteinuria is mild and intermittent and may remain that way during 5-10 years following the first discovery. However, an increase of the amount of excreted protein and of frequency of proteinuric episodes might be expected afterwards. The beginning of retinopathy may precede or follow the occurrence of nephropathy, but in the later stages these two diabetic complications usually have roughly parallel course.

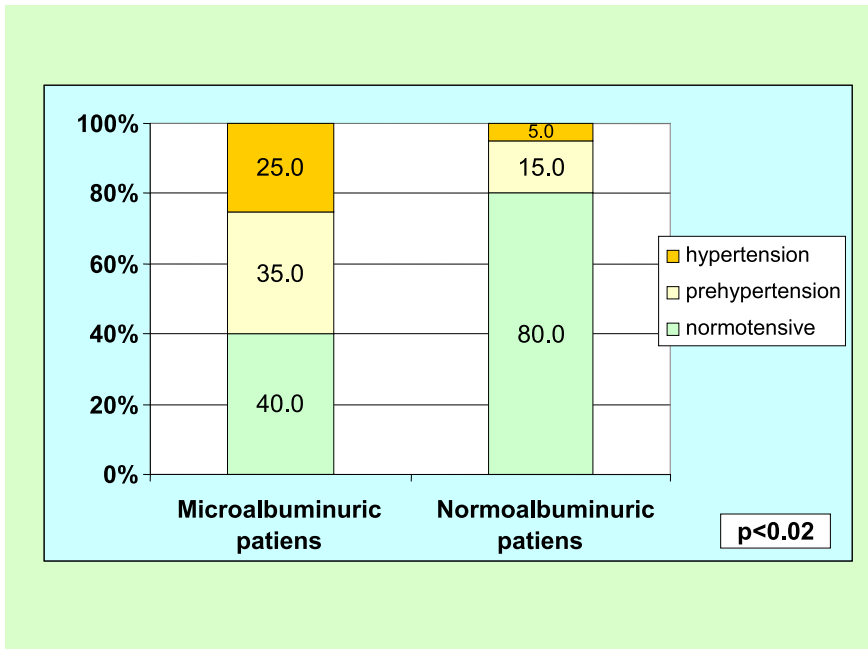
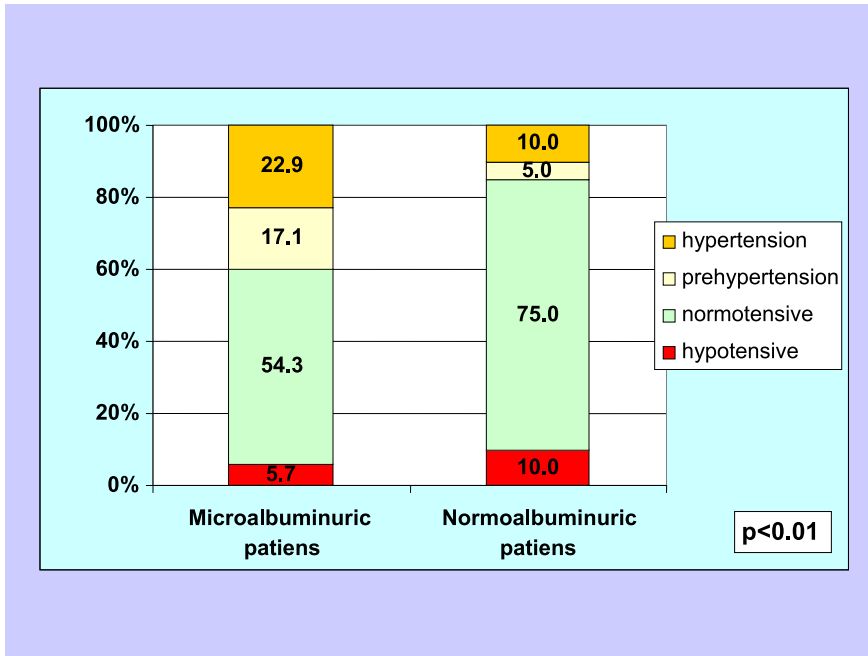


Fig. 4 and 5. Showing the percentage of blood pressure disturbances in microalbuminuric and normoalbuminuric group of children with type 1 diabetes .

Phase of constant and massive proteinuria may follow the stage of intermittent proteinuria. During the period, serum creatinine remains normal or slightly increased. The duration of this stage may be variable. Its course may accelerate leading to terminal renal insufficiency. The first sign of this acceleration is the rise in serum creatinine level.

Advanced stage nephropathy is defined by a progressive decline in renal function (declining glomerular filtration rate and elevation of serum blood urea and creatinine), progressive proteinuria, and hypertension. Progression to end-stage renal disease (ESRD) is recognized by the appearance of uremia, the nephritic syndrome.

Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickened BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>380 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

Fig. 6. Soman SS, Soman AS: Diabetic Nephropathy eMedicine Specialities, Endocrinology, Diabetes Mellitus, 2009.

7. The clinical features and laboratory findings in diabetic nephropathy

The first system manifestation of diabetic nephropathy is the occurrence of **peripheral oedema** usually on ankles. Contrary to the widely accepted conviction that only hypoalbuminemia gives rise to ankle oedema, the direct cause of this symptom is usually not found. It seems that the pathogenesis of this symptom is quite complex. In most of the patients, the frail capillary walls are detected very often and, thus, the oedema might be due to increased capillary permeability.

Regardless of cause, the peripheral oedema always indicate advanced stage of diabetic nephropathy and the occurrence and extent of the swelling is dependent on the duration of clinically manifest proteinuria. Also, the complaints related to lower leg muscle cramps are not unusual.

Hypertension: Incipient to mild structural glomerular lesions do not correlate with the raise in arterial blood pressure. However, in the advanced stage of diabetic nephropathy the arterial hypertension is almost always present and relates with the duration of clinically manifest proteinuria.

Some of our previous results¹³ showed a very good correlation between the level of urinary albumin excretion and the values of systolic and diastolic arterial blood pressure. Still, the

arterial blood pressure level was not predictive for microalbuminuria, judging by the multiple regression analysis, as already stated above.

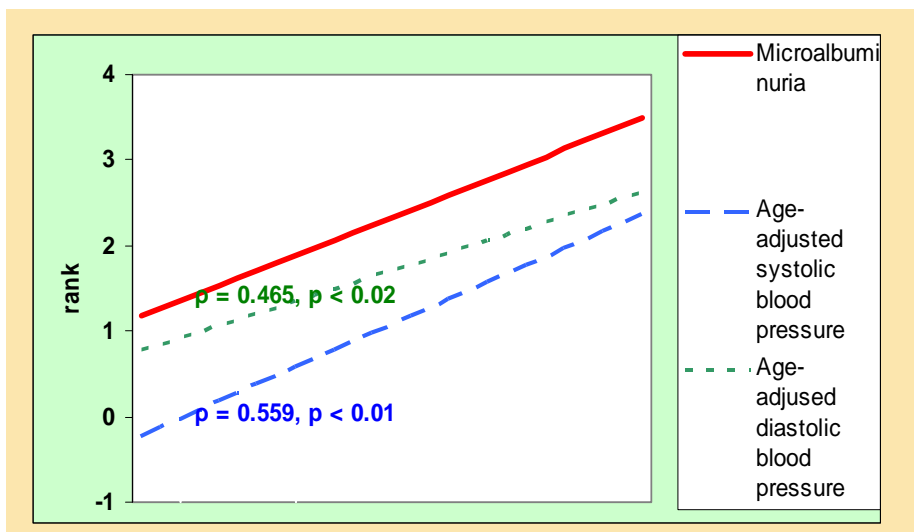


Fig. 7. Showing the relation between the arterial blood pressure level and UAE values

Paradoxically, however, there is no good correlation between the reduction in glomerular filtration rate and the rise in arterial blood pressure¹⁷⁻¹⁸. Yet, most certainly, the therapy aimed at lowering high blood pressure leads to slowing down in reduction of glomerular filtration.

Macroproteinuria: The amount of proteins daily excreted in patients with diabetic nephropathy ranges from the minimal concentrations of 30 mg/day to more than 20g/day. The average excretion is about 2,5g/24h. In about 20% of patients with nephropathy the amount is less than 1g/day and in 15% it exceeds 5g/day (nephritic syndrome). Therefore, although proteinuria is considered a marker of chronic diabetic nephropathy, yet it relatively rarely reach the nephritic range.

Other symptoms of kidney disease include loss of sleep, poor appetite, upset stomach, weakness, and difficulty concentrating. Characteristic signs are:

- Going to the bathroom more often at night
- Less need for insulin or antidiabetic medications
- Morning sickness, nausea, and vomiting
- Weakness, paleness, and anemia
- Itching

8. Differential diagnosis

Other pathological states of potential significance in differential diagnosis are:

- Cholesterol embolization
- Chronic obstruction
- Interstitial nephritis
- Amyloidosis

Disease	Differentiating Signs/Symptoms	Differentiating Tests
Non diabetic kidney disease	<ul style="list-style-type: none"> • Since both diabetes mellitus and chronic kidney disease (CKD) are common disorders, patients with both conditions may or may not have DN. A diagnosis other than DN should be considered if: there is a rapid progression of renal failure, evidence of another systemic disease, or short duration of diabetes (although onset is insidious in type 2, and DN may occasionally be the presenting manifestation of type 2 DM). 	<ul style="list-style-type: none"> • Minimal proteinuria may indicate nondiabetic kidney disease. • Other specific diagnostic tests for other systemic disorders associated with nondiabetic kidney disease may be positive.
Multiple myeloma (MM)	<ul style="list-style-type: none"> • Multiple myeloma (MM) patients also may present with renal failure and proteinuria. • Symptoms of bone pain and anemia are the most common presenting features, affecting 80% of patients with MM. 	<ul style="list-style-type: none"> • The characteristic test results that differ from DN are: the presence of paraproteinemia/paraproteinuria; hypercalcemia; impaired production of normal immunoglobulin; and lytic bone lesions. Bataille R, Housseau JL. Multiple myeloma. <i>N Engl J Med.</i> 1997;336:1657-1664 • Urinalysis with sulfosalicylic acid (SSA) was classically utilized to evaluate for discrepancy between albumin and total protein, as standard urinalysis dipstick detects albumin only. SSA causes precipitation of all of the urinary proteins, including paraproteins (Bence Jones proteins). • Serum protein electrophoresis (SPEP), urine protein electrophoresis (UPEP): paraprotein spike. • Serum and urine free light chains: increased concentrations of free light chain in serum. • Skull x-rays, CT or MRI bone: lytic lesions. • Bone marrow biopsy: plasma cell Proliferation
Renal tract obstruction	<ul style="list-style-type: none"> • Can be caused by stones, cancer, fibrosis, prostate hypertrophy/cancer, neurogenic bladder, or pelviureteric junction obstruction. • Obstruction to urine flow can result in postrenal failure. Symptoms 	<ul style="list-style-type: none"> • Passage of Foley catheter will result in flow of urine and relief of obstruction. • Kidney ultrasound: hydronephrosis, stones. • Prostate ultrasound: hypertrophy, cancer.

Disease	Differentiating Signs/Symptoms	Differentiating Tests
	include trouble passing urine, anuria, oliguria, hematuria, pain (with kidney stones), and urinary leakage/incontinence. Physical examination findings include enlarged prostate on rectal examination, costovertebral angle tenderness, suprapubic tenderness, and bladder fullness.	<ul style="list-style-type: none"> • CT abdomen: hydronephrosis, stones, mass, congenital abnormalities, fibrosis. • PSA: elevated in BPH, prostate cancer. • MRI: not routine but may show hydronephrosis, stones, mass, congenital abnormalities, fibrosis
Glomerulonephritis	Glomerulonephritis, such as lupus nephritis and cryoglobulinemia, is in the differential for DN. Patient presentation and physical examination may be similar to that of DN. However, there may be symptoms and signs of other systemic disease, such as rashes or joint involvement.	Urinalysis: hematuria, proteinuria, RBC casts, dysmorphic red cells. Albuminuria. Positive serology (e.g., ANA, ANCA, hepatitis serology). Complement: decreased in immune glomerulonephritis (e.g., lupus). Kidney biopsy: glomerulonephritis.
Renal artery stenosis	Renal artery stenosis presents either as hypertension refractory to multiple maximized antihypertensives or as renal failure shortly after the initiation of an ACE inhibitor. Physical examination is significant for an abdominal bruit. Safian RD, Textor SC. Renal-artery stenosis. N Engl J Med. 2001;344:431-442	Ultrasound, CT scan, MRI: shrunken kidney, decreased flow through the renal artery. Magnetic resonance angiography (MRA): renal artery stenosis. Renal angiogram: renal artery stenosis.

Table 1. BMJ Group: Diabetic nephropathy, differential diagnosis , eprocates online, 2010

8.1 The diagnosis of diabetic nephropathy ¹⁹

Patients with diabetes should be screened annually for DKD. Initial screening should commence:

- 5 years after the diagnosis of type 1 diabetes; or
- From diagnosis of type 2 diabetes.

Screening should include:

- Measurements of urinary ACR in a spot urine sample;
- Measurement of serum creatinine and estimation of GFR.

An elevated ACR should be confirmed in the absence of urinary tract infection with 2 additional first-void specimens collected during the next 3 to 6 months.

- Microalbuminuria is defined as an ACR between 30-300 mg/g.
- Macroalbuminuria is defined as an ACR > 300 mg/g.
- 2 of 3 samples should fall within the microalbuminuric or macroalbuminuric range to confirm classification.

Using the CKD staging likelihood of DN can be determined as follows:

- Normoalbuminuria in CKD stages 3 to 5 (GFR <60) is unlikely to be DN.
- Microalbuminuria in CKD stages 1 to 3 (GFR >30) is possible DN.
- Microalbuminuria in CKD stages 4 to 5 (GFR <30) is unlikely to be DN.
- Macroalbuminuria at all stages of CKD is highly likely to be DN.

Urinalysis	proteinuria
Urinary albumin for creatinine ratio	microalbuminuria: between 30 and 300 mg/g; macroalbuminuria: >300 mg/g
Blood biochemistry	elevated creatinine
Serum creatinine with GFR estimation	Glomerular filtration rate (GFR) may be raised in CKD stage 1, normal in CKD stage 2, and reduced in CKD stages 3 to 5
Kidney ultrasound	normal-to-large kidneys with increased echogenicity; may show hydronephrosis if vesiculopathy and/or obstruction is superimposed

Table 2. Clinical tests in diagnosis of diabetic nephropathy Clinical tests in diagnostics of diabetic nephropathy:

Test	Results
24 hour urine to collection	microalbuminuria: albumin 30 to 300 mg/24 hours; macroalbuminuria: albumin >300 mg/24 hours
CT-abdomen	hydronephrosis; wedge-shaped areas of low attenuation; loss of the ability to distinguish the corticomedullary border; perinephric stranding; cysts; masses; stones
Magnet resonance angiography	renal artery stenosis
Doppler ultrasound	may show renal artery stenosis
Kidney biopsy	mesangial expansion, fibrosis, Kimmelstiel-Wilson nodules

The source: epocrates online com, 2010

Table 3. Other tests to consider

High blood pressure often goes along with diabetic nephropathy. You may have high blood pressure that develops rapidly or is difficult to control.

9. Treatment and therapy

Annual screening for microalbuminuria, with a random spot urine sample for microalbumin-to-creatinine ratio, should be initiated once the child is 10 years of age and has had diabetes for 5 years.

Confirmed, persistently elevated microalbumin levels on two additional urine specimens should be treated with an ACE inhibitor titrated to normalization of microalbumin excretion if possible

Once albuminuria is diagnosed, a number of factors attenuate the effect of hyperfiltration on kidneys:

1. Control of hyperglycemia- The Diabetes Control and Complications Trial (DCCT)²¹ and the United Kingdom Prospective Diabetes Study (UKPDS)²¹ have definitively shown that intensive diabetes therapy can significantly reduce the risk of the development of microalbuminuria and overt nephropathy in people with diabetes.

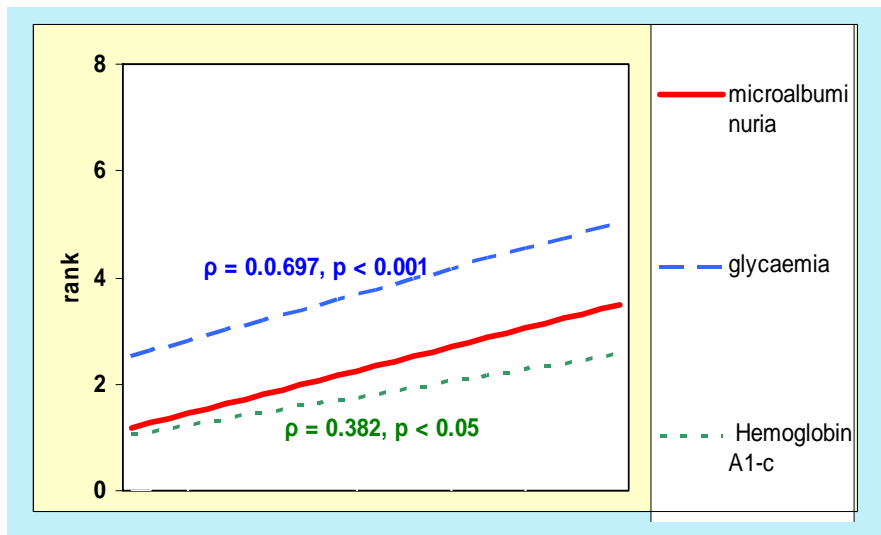


Fig. 8. Showing the relation of the parameters of metabolic regulation and the UAE level in children with type 1 diabetes

Accordingly the earlier study¹³ revealed that hemoglobin A1/c and, particularly, blood glucose level were significantly related to urinary albumin excretion rate. Furthermore, blood glucose was the major predictor of microalbuminuria in children with type 1 diabetes. Lowering A1C to an average of ~7% has been shown to reduce microvascular and neuropathic complications of diabetes and, possibly, macrovascular disease. Preliminary results of the multicenter A1C-Derived Average Glucose (ADAG) Trial, presented at the European Association for the Study of Diabetes meeting in September 2007, confirmed a close correlation of A1C with mean glucose in patients with type 1, type 2, or no diabetes. Final results of this study, not available at the time this statement was completed, should allow more accurate reporting of the estimated average glucose (eAG) and improve patients' understanding of this measure of glycemia²²

Target HbA1c for people with diabetes should be < 7.0%, irrespective of the presence or absence of CKD.²³

Considering the high incidence of overnight hypoglycemias, in children and adolescents during the optimal regulation of blood glucosae levels, the A1C level achieved in the "intensive" adolescent cohort of the DCCT group was >1% higher than that achieved by adult DCCT subjects and above current ADA recommendations for patients in general. Standards of Medical Care in Diabetes—2008 American Diabetes Association Tight glycemic control will delay the progression of microalbuminuria and slow the progression of diabetic nephropathy.

2. Aggressive control of systemic blood pressure- In patients with type 1 diabetes, hypertension is usually caused by underlying diabetic nephropathy and typically becomes manifest about the time that patients develop microalbuminuria . Hypertension in childhood is defined as an average systolic or diastolic blood pressure ≥ 95 th percentile for age, sex, and height percentile measured on at least three separate days. "High-normal" blood pressure is defined as an average systolic or diastolic blood pressure ≥ 90 th but <95th percentile for age, sex, and height percentile measured on at least three separate days.

Treatment of high-normal blood pressure (systolic or diastolic blood pressure consistently above the 90th percentile for age, sex, and height) should include dietary intervention and exercise aimed at weight control and increased physical activity, if appropriate. If target blood pressure is not reached with 3–6 months of lifestyle intervention, pharmacologic treatment should be initiated.

Pharmacologic treatment of hypertension (systolic or diastolic blood pressure consistently above the 95th percentile for age, sex, and height or consistently $>130/80$ mmHg, if 95% exceeds that value) should be initiated as soon as the diagnosis is confirmed.

The principal agents for lowering high blood pressure are angiotensin convertase inhibitors (ACE). The beneficial effect of ACE inhibition on preventing progression from microalbuminuria to overt diabetic nephropathy is long-lasting (8 y) and is associated with the preservation of a normal GFR. ACE-I reduces the risk of progression of overt type 1 diabetic nephropathy to ESRD and in type 1 patients with microalbuminuria to overt nephropathy.²⁵ The results of multicentric studies showed that blood pressure in patients with chronic renal insufficiency should be lowered below normal range (as recommended by WHO) in order to achieve beneficial effect on progression of the disease.

A meta-analysis of several small studies has shown that protein restriction may be of benefit in some patients whose nephropathy seems to be progressing despite optimal glucose and blood pressure control²⁶

Hypertensive people with diabetes and CKD stages 1-4 should be treated with an ACE inhibitor or an ARB (Angiotensin Receptor Blocker), usually in combination with a diuretic²⁷

If needed to achieve blood pressure targets, a thiazide diuretic should be added to those with an estimated glomerular filtration rate (GFR) (see below) ≥ 50 ml/min per 1.73 m² and a loop diuretic for those with an estimated GFR < 50 ml/min per 1.73 m². (E)

Normotensive people with diabetes and macroalbuminuria should be treated with an ACE inhibitor or an ARB. In type 1 diabetes with macroalbuminuria, ACE inhibitors decrease albuminuria and reduce the risk of clinical outcomes regardless of the presence or absence of hypertension. A randomized controlled trial in people with type 1 diabetes and macroalbuminuria found that ACE inhibitors reduced the risk of the combined outcome of doubling of serum creatinine level, CKD stage 5, and death.²⁸ A quarter of the participants were normotensive. There was no significant difference in the treatment effect between the normotensive and hypertensive individuals.

Future agents: Wenzel et al.²⁹ have examined the role of avosentan (endothelin antagonist) on progression of microalbuminuria. Avosentan have demonstrated antifibrotic, anti-inflammatory, and antiproteinuric effects in experimental studies. Wenzel et al conducted a randomized, placebo-controlled, double-blind, parallel-design, dosage-range study on the effect of the endothelin-A antagonist avosentan (SPP301) on urinary albumin excretion rate in 286 patients with diabetic nephropathy, macroalbuminuria, and a blood pressure of $< 180/110$ mm Hg. All dosages of avosentan, administered in addition to standard ACE inhibitor/ARB treatment, were found to reduce the mean relative urinary albumin excretion rate (-16.3% to -29.9%, relative to baseline) in the study's patients.

3. Selective control of arteriolar dilation by use of angiotensin-converting enzyme (ACE) inhibitors (thus decreasing transglomerular capillary pressure) This is particularly significant when lowering of systemic blood pressure is accompanied with concomitant lessening of glomerular capillary pressure. however the optimal lower limit for systolic blood pressure is unclear.³⁰

4. Dietary protein restriction (because high protein intake increases renal perfusion rate). A meta-analysis examining the effects of dietary protein restriction (0.5-0.85 g/kg/d) in diabetic patients suggested a beneficial effect on the GFR, creatinine clearance, and albuminuria. However, a large, long-term prospective study is needed to establish the safety, efficacy, and compliance with protein restriction in diabetic patients with nephropathy. Considering the importance and role of dietary proteins in the process of growth and development, a sharp restriction (<15% of total daily amount of nutrients) of proteins in adolescents with diabetic nephropathy is not justified.

Other standard modalities for the treatment of progressive renal disease and its complications (e.g., osteodystrophy) must also be used when indicated, such as sodium and phosphate restriction and use of phosphate binders. When the GFR begins to decline substantially, referral to a physician experienced in the care of such patients is indicated. Radiocontrast media are particularly nephrotoxic in patients with diabetic nephropathy, and azotemic patients should be carefully hydrated before receiving any procedures requiring contrast that cannot be avoided.³¹

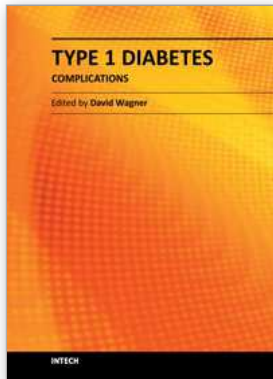
As for any other patient with ESRD, diabetic patients with ESRD can be offered hemodialysis, peritoneal dialysis, kidney transplantation, or combined kidney-pancreas transplantation.

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This book is a compilation of reviews about the complication of Type 1 Diabetes. T1D is a classic autoimmune disease. Genetic factors are clearly determinant but cannot explain the rapid, even overwhelming expanse of this disease. Understanding etiology and pathogenesis of this disease is essential. The complications associated with T1D cover a range of clinical obstacles. A number of experts in the field have covered a range of topics for consideration that are applicable to researcher and clinician alike. This book provides apt descriptions of cutting edge technologies and applications in the ever going search for treatments and cure for diabetes.

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