NATURAL HISTORY AND MANAGEMENT OF DIABETIC NEPHROPATHY

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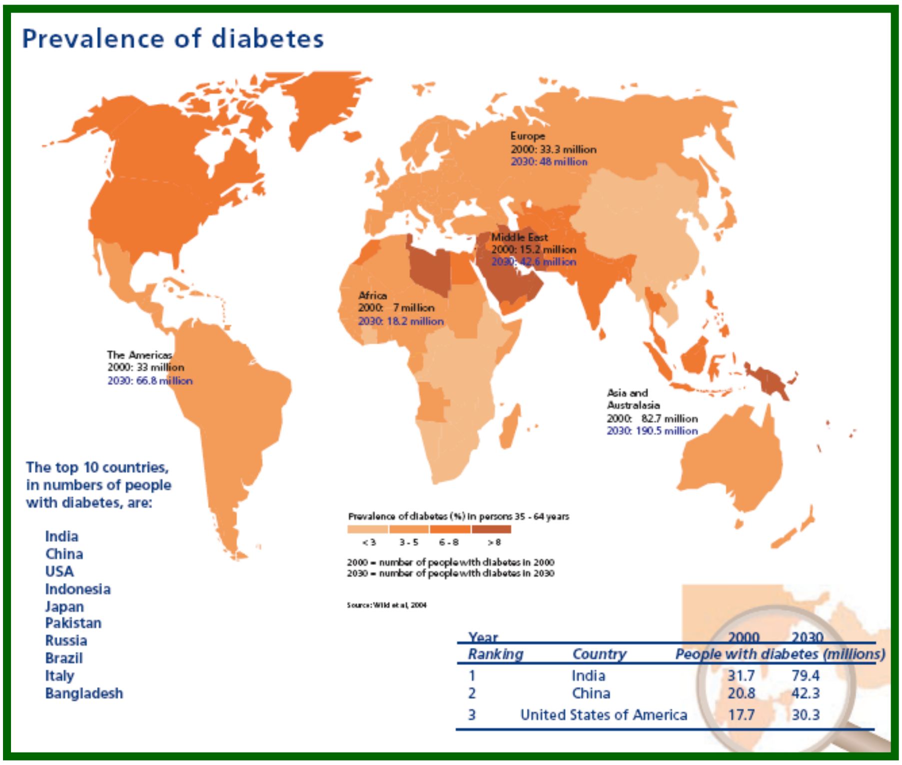
Definitions and Epidemiology

Diabetic kidney disease is the leading cause of chronic and end-stage renal disease (ESRD), and is epidemic worldwide. The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes (picture 1). This number is likely to more than double by 2030 (1). In 2005, an estimated 1.1 million people died from diabetes. Almost 80% of diabetes deaths occur in low and middle-income countries (picture 2). Almost half of diabetes deaths occur in people under the age of 70 years; 55% of diabetes deaths are in women.

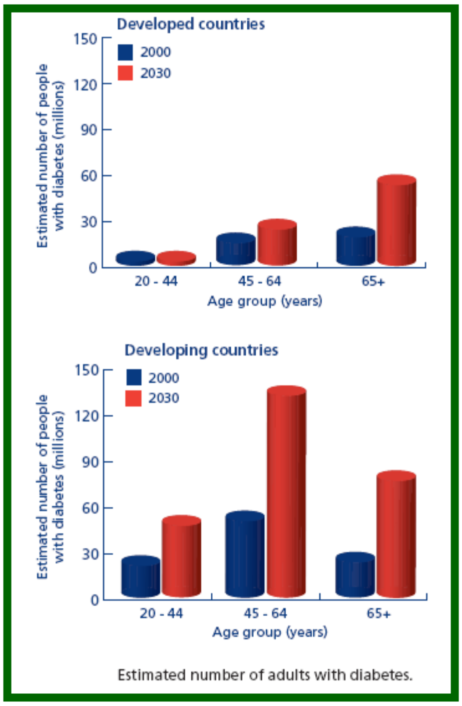
WHO projects that diabetes deaths will increase by more than 50% in the next 10 years without urgent action (picture 3). Most notably, diabetes deaths are projected to increase by over 80% in upper-middle income countries between 2006 and 2015.

In Europid populations during 1998-2002 all-cause ESRD declined by 2% per year in persons aged 0-44 years, and all non-diabetic ESRD by a similar amount in persons aged 45-64 years, in whom diabetic ESRD had increased by 3% per year (2).

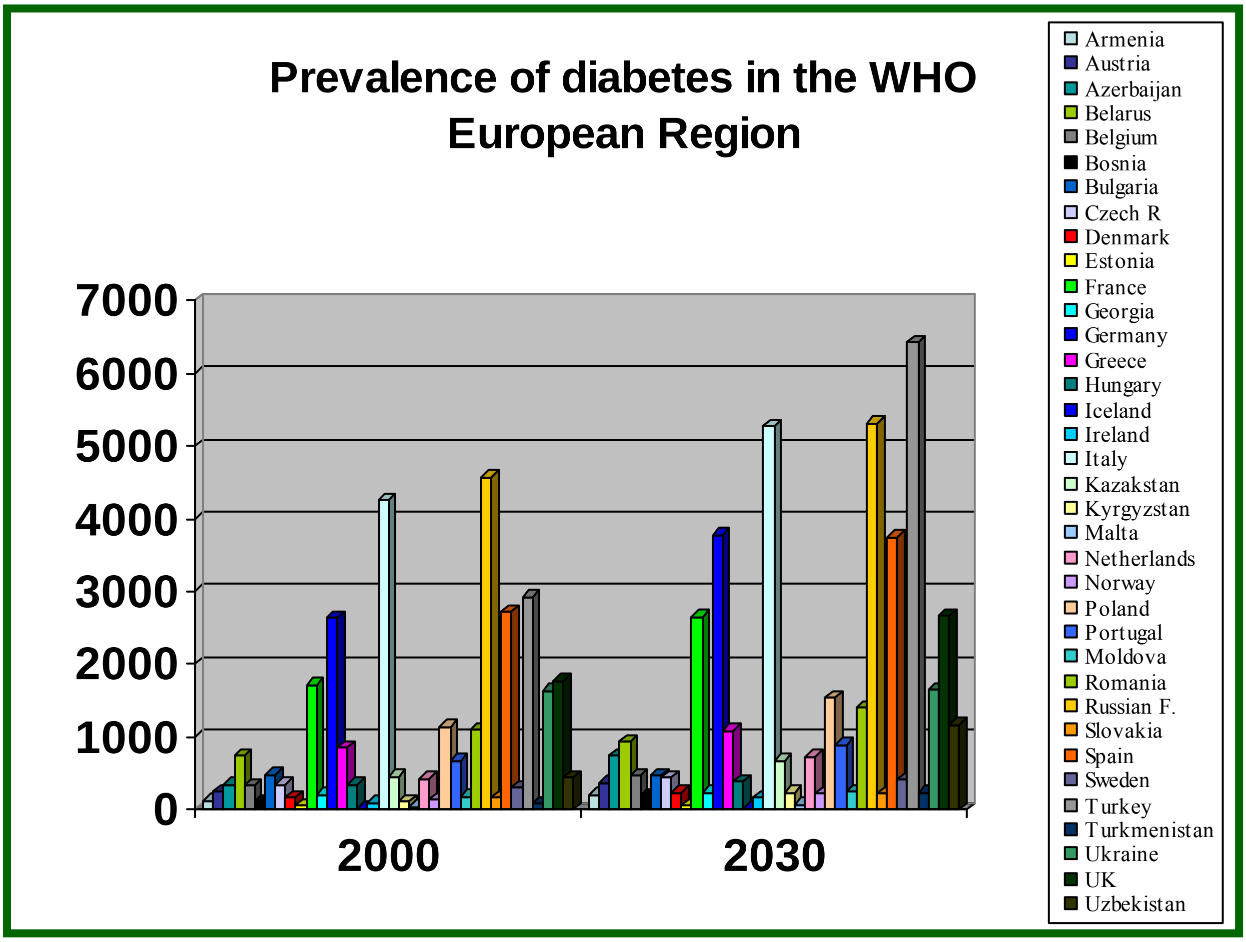
Diabetes mellitus (DM) and chronic kidney disease (CKD) are common and exhibit synergistic associations with premature mortality. Current screening strategies, based on creatitine or albuminuria often fail to identify a considerable number of subjects with CKD caused by DM. Incorporating eGFR into screening for CKD would identify individuals earlier in the natural history of disease and enable early effective treatment to delay progression of CKD (3).



Picture 1. Prevalence of diabetes (WHO, 2008. http://www.who.int/en/)



Picture 2. Diabetes in develepd and developing countries
(WHO, 2008. http://www.who.int/en/)



Picture 3. Prevalence of diabetes in the WHO European Region (http://www.who.int/en/)

Type I DM is an autoimmune disease characterized by antibody and cell-mediated destruction of pancreatic islets. Circulating C-peptide is absent indicating failure of insulin production. Type 1 DM may occure at any age, but is usualy presenting prior to the age of 30 years, and insulin therapy is obligatory.

Type 2 DM is combination of insulin resistance and qualitative or quantitative insulin deficiency. It may represent a component of the metabolic syndrome (insulin resistance, obesity, hypertension, hyperlipidemia). The patients experienced gradual decline in pancreatic β-cell function and 40-50% of the patients need supplemental insulin. This is typically disease of older age, but increasingly is seen in children.

Diabetic nephropathy (DN) is now one of the leading cause of ESRD, and type 2 DM is the largest cause of ESRD in American and European adults. These patients represent one third of all patients beginning renal replacement therapy (RRT). The clinical signature of DN is proteinuria which is a marker of disease severity and is used clinically to guide our therapies. It is also an independent risk factor for cardiovascular disease (4). Diabetic nephropathy is a clinical syndrome with persistent albuminuria (>300mg/24h or 200µg/min) on at least two occasions separated by 3-6 months (equivalent to total proteinuira >500 mg/24h). We register progressive increase in proteinuria, associated hypertension and decline in glomerular filtration rate (GFR).

In type 1 DM, we diagnose DN in 30-40% of the patients after 25-40 years with DM, but statistical data showed decline in this cumulative incidence to about 25%, probably because improved glycemic control and reduced incidence of all chronic microvascular complications. 25% of the patients, 20 years after diagnosis of DM will have DN, and 20% of these patients will develop clinically significant renal disease. Diabetic nephropathy will have 5-10% of the patients at the time of diagnosis of DM.

There is no doubt that glycemic control is the most important factor in predicting the risk of developing nephropathy in both type 1 and 2 DM. In addition, there are other risk factors: genetic, gender and age. The incidence of DM varies widely depending on the ethnic origin of the population. Native, Mexican and African Americans in USA have higher incidence of diabetes and South Asians, African-Caribbian have higher incidence of ESRD than Caucasion population in UK, for example. The causes of these differences are multifactorial with significance role of glomerulonephritis, pyelonephritis, tuberculosis and non-regulated hypertension.

Type 1 DM is 1.5 x more common in females than males, but males have a higher risk of developing DN (1.7:1). Over 40 years the cumulative incidence of DN is 46% in males and 32% in females. Type 2 DM has a higher risk for males also, up to 5:1. The highest long-term incidence of DN is found in those who develop type 1 DM between the ages 11 and 20 years. The median time between onset of proteinuria and ESRD is 8-14 years. Pre-puberty duration of DM appears not to contribute to evolution of renal disease.

After 40 years of DM only 10% with proteinuria are alive compared with 70% without proteinuria, and the main cause of mortality are cardiovascular diseases. Persistent proteinuria in patients with type 1 DM caused 50-fold increase in mortality. These patients have 15 times higher ischemic hearth disease, and mortality is 20-40x higher in patients older than 40 in type 1 DM, but mortality is falling from 80% in the 1950s to 20% in 1990s. Patients with type 2 DM, and with microalbuminuria or proteinuria have the survival rate at 10 years 30% compared to 55% in the patients with normoalbuminuria. United Kingdom Prospective Diabetes Study (5) showed link between varying levels of proteinuira and mortality rates/year: 1.4% – normoalbuminuria, 3% – microalbuminuria, 4.6% - macroalbuminuria and 19.2% - uremia. ESRD patients secondary to DN have 50% greater mortality rate on dialysis.

Pathogenesis od diabetic nephropathy and renal pathology

DN is characterized by excessive contents of extracellular matrix with thickening of glomerular and tubular basement membranes and increased amount of mesangial matrix which ultimately progress to glomerulosclerosis and tubulo-interstitial fibrosis: all kidney cellular elements (endothel, mesangial cells, podocytes, tubular epithel) are targets of hyperglycemic injury. There is an obligatory excessive channeling of glucose intermediaries into various metabolic pathways with generation of advanced glycation products (AGEs), activation of protein kinase C (PKC), increased expresson of transforming growth factor beta (TGFβ), GTP binding proteins and generation of reactive oxygen species (ROS) – common denominator in various pathways and are central to the pathogenesis of hyperglycemic injury. Also, there are marked alterations in intraglomerular hemodynamics (hyperfiltration)(6).

Glucose dependent effect on afferent arteriolar dilatation is mediated by vasoactive hormones and cytokines including insulin-like growth factor 1, nitric oxide, prostaglandins and/or glucagon. Glomerular hydrostatic pressure increases. Measures that reduce the glomerular pressure are systemic blood pressure reduction, low protein diet, ACE inhibitors. They all reduce the development of glomerular damage and proteinuria. Low protein diet blocks the aferent arteriolar dilatation and ACE inhibitors mediated constriction of the efferent arteriole (7). The early hyperfiltration response is associated with both glomerular and tubulointerstitial proliferation and hypertrophy. Kidney size may increase by several cm. Glomeruli enlarge with both an increase in capillary loop number and surface area. There is a stimulation of a variety of growth factors. Glucosis and AGE products stimulate production of TGFβ which stimulates protein synthesis. This early hyperfiltration can be prevented by intensified insulin therapy (7).

Early in the course of DM the glomerular basement membrane (GBM) widens and may reach 3-4 x normal thickness. The increased GBM thickness is associated with a loss of heparan sulfate proteoglycans, the principal negatively charged constituens of GBM that provide the charge barrier to prevent proteins from escaping into Bowman's space. There is a loss of the overlying glomerular epithelial cell (podocyte) which important in restricting protein permeability. Mesangial expansion is the hallmark of DN, culminating in the development of the Kimmelstiel-Wilson nodule which probably correlates better than GBM thickness with the subsequent development of renal failure. Increased deposition of several extracellular matrix components, later cause general loss of mesangial cellularity. As in other renal diseases, the degree of tubulointerstitial fibrosis correlates not only with current renal function, but also with prognosis. Release of growth factors and cytokines from the glomerulus with direct or indirect effects of proteinuria and renal ischemia induced by the progressive hyalinosis of the afferent and efferent arteriole both contribute to tubulointerstitial fibrosis.

Glucose can induce cell hypertrophy, extracellular matrix synthesis and TGFβ production in a variety of cell types. Many of the adverse effect of hyperglycemia have been attributed to activation of PKC (protein kinase C), a family of serine-threonine kinase that regulates diverse vascular functions, including contractility, blood flow, cellular proliferation and vascular permeability (7).

Advanced glycation end products (AGE) are a heterogenous group of protein and lipids to which sugar residues are covalently bound. AGE formation is increased in hyperglycemia (DM), and stimulated by oxidative stress (uremia). Renin-angiotensin system (RAS) activation may contribute to AGE formation. AGEs mediated variety of cellular actions (cell hypertrophy, extracellular matrix synthesis, differentiation of tubular cells and inhibition of nitric oxide synthesis) and induce albuminuria and glomerulosclerosis. The are several inhibitors of AGEs which had been studied for therapeutic purposes: aminoguanidin in animal studies reduces AGE deposition, stabilize diabetic retinopathy and neuropathy; new inhibitor is phenacylthiazolium bromide (7). Glucose nonenzymatically binds to amino residues to become glycated Schiff bases with later "rearrangement" to form a more stable but still reversible Amadori product – HbA1C. Over time these products become irreversible advanced glycation end (AGE) products. Both circulating and tissue proteins as well as lipids and nucleic acids may be glycated. Classic example is hemoglobin that initially forms the HbA1C. AGEs also accumulated in aging and renal failure.

Hyperglycemia induced generation of polyols which also mediated some of the complications od DM. In tissues where glucose uptake is independent of insulin, such as lens, retina and kidney, chronic hyperglycemia results in increased tissue levels of glucose. Sorbinil, tolrestat and ponalrestat (aldose reductase inhibitors) are promising agents in preventing diabetic cataracts and in improving diabetic neuropathy, but not in diabetic nephropathy. Glucose than reduced to sorbitol by NADPH dependent enzyme aldose reductase, the first enzyme in the polyol pathway. Accumulation of sorbitol is accompanied by an icrease in intracellular osmolality, a depletion of free myoinositol, los of NaKATPase activity and increased consumption of the enzyme cofactors NADPH and NAD, leading to changes in cellular redox potential (7).

The pathogenic mechanisms by wich angiotensin II contributes to DN are connected with hemodynamic effects (increase systemic and glomerular pressure, mediate proteinuria and induce renal vasoconstriction) and with nonhemodynamic effects (mediate cell proliferation, hypertrophy, matrix expansion and TGFβ synthesis). ACE inhibitors lowered systemic blood pressure and intraglomerular pressure and increased renal blood flow and reduce proteinuria which all contribute to renoprotective effect of ACE inhibitors.

Central histologic feature of DN is extracellular matrix accumulation in the mesangium and tubulointerstitium. TGF-β has the pivotal role in the extracellular matrix accumulation in DN. Increased TGFβ expression in DM could be a consequence of a direct effect of AGEs to increase its synthesis.

Genomic and proteomics approaches are now used to analyse gene and protein expression profiles that underlie experimental kidney disease, including DN. Some studies have already identified molecular markers that correlate with tubulointerstitial progression of DN in humans (8).

The kidneys in DM are larger than those of non DM control subjects. Following the onset of DM, kidney weight increases by about 15%. This changes can be reversed with induction of early normoglycemia, but not after estbalishment of renal hypertrophy. Renal volumen continues to increase as UAER rises to the level of overt proteinuria.

Light microscopy shows nodular glomerular intercapillary lesions which were described in 1936 by Kimmelstiel and Wilson. One can see diffuse glomerular lesions, exudative lesions (eosinophylic and nonspecific), arteriolar lesions (hyalinization and involvment of efferent vessel is highly specific for diabetes) and tubules and interstitium with variety of nonspecific changes. Afferent arteriolar hyalinization is non specific (hypertension and other conditions). Immunopathology shows linear staining of the GBM, Bowman's capsule and outer aspect of the tubule for IgG, IgM, albumin and fibrinogen, type IV and V collagen, laminin and fibronectin in the mesangium; heparan sulphate proteoglycans are decreased.

Electron microscopy shows thickening of the GBM, a prominent feature in the diabetic kidneys which is evident in two years after diagnosis and associated with nodular renal disease and with no electron-dense deposits (13). Relatively large kidneys persist with progressing renal failure unlike other chronic renal pathologies. Hypertrophied glomeruli causes hyperfiltration. Nodular lesions are of little functional significance. Degree of diffuse glomerulosclerosis with changes in the mesangium and capillaries correlates with the clinical manifestation of worsening renal function.

Albuminuria and clinical manifestations

It has been identifying five distinct stages of renal dysfunction in DM. In the **stage 1**, renal hypertrophy and hyperfiltration are present at the time of diagnosis, urinary albumin excretion rate (UAER) is elevated, GFR also (20-40%), renal plasma flow (RPF) is elevated by 9-14%. Insulin therapy reduces of both GFR and UAER. The earliest clinical renal symptom in untreated or poorly controlled DM, in addition to glucosuria is, in fact, osmotic polyuria (9). The degree of polyuria and the accelerated tubular fluid rate is defined by the glucose concentration – dependent osmotic forces, especially in the distal nephron.

Stage 2 is clinically silent, tipically lasts 5-15 years, GFR remains elevated with normal UAER and blood pressure. One can notice early histologic changes (increase of GBM thickness; increase in mesangial matrix volume). There is a connection between levels of glycemia (> 14 mmol/l) and reduction in GFR. Improving glycemic control reduce the extent of hyperfiltration.

Stage 3 is characterized with albuminuria or incipient nephropathy, usually occurs after 6-15 years of DM. GFR is still elevated or normal, UAER is 20-200 µg/min (30-300 mg/24h). The blood pressure increases, and one can see progression of the histologic changes: increase in GBM thickness and increase of fractional mesangial volumes within the glomerulus. Correct identification of incipient DN by accurate measurement of albuminuria as UAER is crucial to strategies to modify the natural history of DN. Normal UAER is 1.5-20 µg/min, but increase with strenuous exercise, oral proteine intake, fluid loading, urinary tract infection, pregnancy. Albumin excretion is about 25% higher during the day than overnight. An overnight urine sample is simpler and more convinient for patients to collect: 2-3 consecutive collections within 3 months should be in the albuminuric range to make diagnosis. We need to measure the albumin:creatinine ratio (ACR, mg albumin:mmol creatinine). An early morning urine sample is more practicable than collecting timed urine samples. Screening recommendations for albuminuria is as follow:

- All type 1 DM diagnosed for more than 5 years and over 12 years of age and all type 2 DM should have their urine screened for albumin yearly until the age of 70 yrs.

- If the morning ACR is raised and a concurrent urinary tract infection excluded, 3 timed overnight urine collections should be arranged.

- Those with an elevated UAER should than be screened every 6 months.

Albuminuria is the earliest clinically detectable phase of diabetic renal dysfunction. More than 80% of patients progressed to overt nephropathy over 10-15 years. GFR is normal or slightly elevated during the first 6 years of albuminuria before DN develops. Risk factors for developing albuminuria in type 1 and 2 DM are poor glycemic control, genetic predisposition, male sex, age at diagnosis of type 1, mean blood pressure > 95 mmHg, smoking, hyperlipidemia and presence of retinopathy.

Stage 4 represents established or overt nephropathy with proteinuria increase at the rate of 15% to 40%. In these circumastances nephrotic syndrome is common, GFR declines and correlates with blood pressure levels. Hypertension is present in most patients, microhaematuria in 66% of patients with overt DN and we can see clear histologic changes.

In **stage 5,** ESRD develops with median of seven years from the development of persistent proteinuria, if therapeutic intervention are not undertaken.

Hyperfiltration is present in many newly diagnosed type 2 DM compared to age-matched non-DM controls; 30-40% of newly diagnosed type 2 DM patients have an elevated GFR. GFR values not correlate with blood pressure, but correlate with glycemic control, lipid levels higher initial albumin excretion rates and smoking. In these patients the effective RPF is not raised, and one can see an elevation in the glomerular capillary pressure (glomerular hypertension) which is important factor in the development and progression of DN (10).

Albuminuria in type 2 DM have the following characteristics: UAER is 2-3 x higher in new diagnosed patients than in age-matched controls; correlation with disease duration is poorer than in type 1 DM (consequence of delayed diagnosis); the prevalence of albuminuria at diagnosis is 5-20%, with an initial decrease in UAER with treatment of DM. Albuminuria develops as a consequence of hypertension, cardiovascular disease, diabetic and non-diabetic renal disease. Antihypertensive treatment results in normalisation of UAER in 20% of the patients, whilst progression to overt nephropathy was observed in 15% of patients in two-year period.

Conditions associated with albuminuria/proteinuria are diabetic microangiopathy, cardiovascular disease, hypertension and hyperlipidemia. In both type 1 and 2 DM, prevalence of proliferative retinopathy and blindness increases with progressive albuminuria, as well as, peripheral neuropathy with risk of foot ulceration. Albuminuria is a strong predictor of cardiovascular mortality and morbidity in patients with type 1 and 2 DM and in elderly nondiabetic individuals. In a study with type 2 DM patients, there was a 28% mortality rate in those with albuminuria compared with 4% in the normoalbuminuria group over a 3-4 period, or 70% at 10 years (11). In another study, 69% of albuminuric patients died in 10 years, 58% from cardio or cerebrovascular disease and 7% from ESRD (12). Albuminuria is also associated with coronary hearth disease including silent myocardial ischemia and left venticular hypertrophy.

Albuminuria is renal manifestation of generalized vascular endothelial dysfunction. There are incresed incidence of hyperlipidemia, hypertension, obesity and insulin resistance. The positive correlation with UAER indicates that endothelial cell function and coagulation disorders deteriorate with the progression of DN. Blood pressure begins to rise once UAER has increased into the albuminuric range (2.7 mm/Hg/year). A significant increase in extracellular fluid volume with increased sodium retention, due to hyperinsulinemia (with or without insulin resistance), is a significant factor in the rise in blood pressure. Prevalence of hypertension in type 1 DM patients with overt DN is 80% (>140/90) compared to 40% in those with albuminuria and 20% in those without albuminuria. Prevalence of hypertension in patients with type 2 DM is 30-50% at onset of diagnosis of DM, increasing to 90% with the development of abnormal UAER.

Hypertriglyceridemia typically develops once albuminuria has occured and statins are the drug therapy of choice. Fibrate derivatives should be used if hypertryglyceridemia is prominent. HDL cholesterol falls and there are variable increases in LDL cholesterol and lipoprotein (a). Target LDL cholesterol is 120 mg/dL (3 mmol/L) in DM. There is no evidence that lipid lovering may reduce progression of DN, but there is a strong evidence that lipid lovering has a role in primary and secondary prevention of coronary hearth disease, especially in those with increased UAER (type 1 and 2 DM).

Diagnosis and differential diagnosis

The majority of DM patients with proteinuria and retinopathia will have diabetic kidney disease. With prolonged disease duration, most type 1 DM patients develop typical diabetic glomerulosclerosis, but only 1/3 develop clinically apparent DN. 1/3 patients with type 2 DM with proteinuria will have classical diabetic glomerular changes and retinopathy. Others will have nondiabetic or mixed renal disease. Nondiabetic renal disease superimposed on DN occurs more frequently in type 2 DM.

Retinopathy and diabetic nephropathy have a concordance rate of 85-99% in type 1 DM and 63% in type 2 DM. The absence of retinopathy is a strong indication for renal biopsy, particularly in type 1 DM. In DM type 2 (and 1), further investigations, including renal biopsy, should be considered in the absence of retinopathy, sudden and rapid onset of proteinuria, macroscopic hematuria (red cell casts) and rapid decline of renal function without significant proteinuria when renovascular disease has to be considered.

Almost every form of glomerular disease has been reported in association with DM. Membranous nephropathy is the glomerular disease most commonly reported in association with DM. On autopsy, 4% of DM kidneys showed evidence of papillary necrosis; 50% of the patients with papillary necrosis had DM. The incidence and severity of papillary necrosis is decreasing with early antibiotic treatment; tends to occur in patients with long-standing DM. DM patients have an increased incidence of occlusive vascular disease, especially in association with peripheral vascular disease. When diagnosed on urodynamic criteria, autonomic neuropathy has a prevalence of 40% in long-standing diabetes. The incidence of asymptomatic bacteriuria in diabetic women is double that of a control nondiabetic population. DN is associated with an increase in symptomatic UTI during pregnancy. Acute pyelonephritis can causes perinephric abscesses. Urine culture may be negative with flank tenderness and pyrexia. Infection with Gram negative organisms are more common in diabetics. Risk of developing renal tuberculosis is increased, and should be suspected when there is azotemia with modest proteinuria, especially in the case of sterile pyuria.

The use of contrast media increases risk of deterioration of renal function. There is evidences that non-ionic contrast has lower incidence of contrast nephropathy. Type 1 DM patients have greater risk than type 2 DM patients. Patients without pre-existing renal dysfunction have minimal risk. In order to minimize risk of contrast nephropathy it is important good hydration of the patients, avoidance of concomittant non-steroidal anti-inflammatory agents or aminoglycosides, and avoidance treatment with metformin two days prior and following an investigations (14).

In European population, type 1 DM occurs in about 3/1000 pregnancies. During pregnancy GFR increases, tubular absorption of protein decreases. Proteinuria moderate increases during first two trimesters, and rapid increases in third trimester. Blood pressure significant increases and nephrotic syndrome develops in 71% of pregnancies. In most cases, all values return to values of the first trimester, after delivery. Oral hypoglycemic agents should be stopped before the conception (possible teratogenic effects). ACE inhibitors has been associated with fetal morbidity including renal tubular dysplasia, anuria/oligohydramnions, growth retardation, intrauterine death. Agressive treatment of hypertension and insulin therapy are the most important. DN has the greatest impact on fetal outcome: the risk of preterm birth, stillbirth, neonatal death and fetal distress are increased significantly among diabetic women with DN.

Prevention and treatment

Intensive glycemic control, antihypertensive treatment and restriction of dietary protein in the setting of normoalbuminuria, incipient and overt DN, are the major clinical interventions in the patients with DN.

The timing of renoprotective therapy in DM is a subject of current inquiry. Certainly, hypertension, poor metabolic regulation and hyperlipidemia should be addressed in every diabetic individual at discovery. Diagnosis of microalbuminuria is, by consensus, reason to start treatment with an ACE inhibitor in either type of DM, regardless of blood pressure elevation. As is true for other kidney disorders, however, nearly the entire course of renal injury in DM is clinically silent. Medical intervention during this „silent phase" however is renoprotective, as judged by slowed loss of glomerular filtration. In DCCT trial intensive glucose control was associated with a decreased risk for the subsequent development of microalbuminuria in type 1 DM. Patients were randomized to intensive insulin therapy (three injection/day or pump) or conventional therapy (two injection/day). During nine years patients on intensive therapy (mean HbA1c 7%) had a 35-45% lower risk for developing microalbuminuria, compared to the control group (mean HbA1c 9%) (15). Only a small number entering DCCT had microalbuminuria at baseline. Similar findings were reported in another study (16, 17). Poor regulated hypertension may overshadow the benefits of intensive insulin therapy.

United Kingdom Prospective Diabetes Study (UKPDS) has explored more than 10 years the effect of intensification of glycemic control with oral antidiabetic agents or insulin in a large cohort of newly diagnosed type 2 DM patients. HbA1c difference was 7% in intensified and 7.9% in conventionally treated groups. After nine years of treatment there was a 25-30% decrease in the development of microalbuminuria and proteinuria, and over a 50% decrease in the number of patients with a doubling of serum creatinine (18). Framingham Hearth Study lasts seven years with 2398 patients, 53% women, 63% normoglycemic, 29% had impaired fasting glucose or impaired glucose tolerance; 3.4% of the patients were newly diabetic and 4.6% had known DM. By glycemic category mean GFR at follow-up was 87, 85 and 78 ml/min per 1.73m2. The fully adjusted odds of developing CKD were 0.98, 1.71, and 1.93 among those with impaired fasting glucose or impaired glucose tolerance, newly diagnosed DM or known DM, compared with those who were normoglycemic at baseline. Cardiovascular disease risk factors explain much of the relationship between prediabetes and the development of chronic kidney disease (19).

Hypertension classically develops within 2-5 years after the onset of microalbuminuria and is usually associated with volume expansion and salt-sensitivity. Numerous studies have shown that control of systemic hypertension has a major effect on reducing proteinuria and slowing progression to renal failure in both type 1 an 1 DM. According to MDRD study of nondiabetic patients, goal blood pressure of 125/75 mmHg in proteinuric patients was suggested (20).

EUCLID study showed no evidence for a beneficial role for the lisinopril in normoalbuminuric type 1 DM, despite evidence that it reduces retinopathy, but study lasts only two years. Indeed, three years study with ACE inhibitor perindopril retarded the increase of albuminuria that is observed in the placebo group. There is a large number of clinical studies which have clearly documented that ACE inhibitors will decrease microalbuminuria in type 1 DM. Is not allways clear whether the effect is independent of blood pressure (21).

The dual blockade of RAS with low dose ramipril and candesartan was found to be safe and offered additive benefits with respect to reducing proteinuria and urinary TGF-β1 excretion in DM patients with advanced CKD. These benefits were evident as compared with single ramipril and candesartan therapies at doses two-fold greater (22). Angiotensin receptor antagonists (ATRA) may have similar beneficial effects as ACE inhibitors: three landmark studies have demonstrated the utility of ATRA in hypertensive type 2 DM with microalbuminuria (RENAAL with 1513 patients, IDNT with 1715 patients and IRMAII with 590 patients (7). Various combinations of antihypertensive drugs are now being investigated to optimize blood pressure control (23).

Low protein diet (0.6 g/kg/day) was associated with a 75% reduction in the rate of decline of the GFR in type 1 DN compared to patients on a 1.0 g/kg/day protein diet (24). Meta-analysis of of the various trials confirmed these data (25). ADA (American Diabetes Association) recommends that nonpregnant diabetic patients should restrict their protein intake to 0.8 g/kg ideal body weight/day (26). In advanced stages of renal failure there are various, and somewhat contrasting abnormalities affecting glucose and insulin metabolism (27): augmented hepatic gluconeogenesis, diminished renal gluconeogenesis, peripheral insulin resistance, decresed level of degradation of insulin in the peripheral tissues, type 2 patients retain the ability to endogenously secrete insulin and demonstrate an impaired beta cell response to glucose in the pancreas, metabolic derangements in the clearance of insulin.

The most clinicians agreed about strategies and goals for reno and cardioprotection in patients with DN (28):

- ACE inhibitor and/or ARB and low protein diet (0.6-0.8 g/kg/day) with goal in microalbuminuric patients to reduce albuminuria or reverse to normoalbuminuria and stabilize GFR, and in macroalbuminuric patients to reduce protenuria (less than 0.5 g/kg/24 h) and keeping GFR decline less than 2 ml/min/year.
- Antihypertensive agents (blood pressure < 130/80, or 127/75 mmHg)
- Strict glycemic control (HbA1C < 7%)
- Statins (LDL cholesterol ≤ 100 mg/dl)
- Acetyl salycylic acid (thrombosis prevention)
- Smoking cessation (prevention of atherosclerotic progression)

The Bergamo Nephrologic Diabetes Complication Trial (BENEDICT) was a prospective, randomized, double-blind, parallel-group study that was organized in two phases (34). Phase A included 1204 patients and was aimed at assesing efficacy of ACE inhibitor trandolapril, calcium channel blocker (CCB) verapamil, a combination of these two medication, as compared with placebo, in prevention of microalbuminuria in hypertensive patients with type 2 DM and normal UAER. Phase B was aimed at assesing the eficacy of the combination as compared with trandolapril alone in prevention of macroalbuminuria. The BENEDICT Phase A study showed that DN can be prevented by ACE inhibitor therapy. The beneficial effect of ACE inhibition is not enhanced by combined non-dihydropyridine CCB therapy. The apparent adventage of ACE inhibitors over other agents includes a protective effect on the kidney against the development of microalbuminuria, which is major risk for cardiovascular events and death in this population.

Prevention and treatment - ESRD

"Diabetes is one of the biggest health catastrophes the worlds has ever seen. The diabetes epidemic will overhelm health care ressources everywhere if governments do not wake up now and take action"(Dr Martin Silink, President-elect, International Diabetes Federation, July 2006, 29). Hearth failure is a major contributor to poor quality of life, a leading cause of hospitalization and cause of premature death. Both kidney disease and diabetes are major and independent risk factors for the development of hearth failure. Such patients usually have coronary artery disease and hypertension and diabetic cardiomyopathy (microvascular complications of diabetes). It is important to early recognized cardiac dysfunction in DM and the high prevalence of hearth failure with preserved left ventricular systolic function (30).

A multicentric cros-sectional study was performed in Italy to evaluate cardiorenal risk factors and their management in light of international guidelines. 847 type 2 DM patients were recruited. 749 patients had microalbuminuria. GFR less than 60 ml/min was revealed in 41% and anemia in 23.8% of the patients (31). Management strategies are incrisingly focusing on preventive measures following early detection of markers of atherosclerosis to reduce the burden of cardiovascular desease. We all know that albuminuria is predictive, independently of traditional risk factors, of all-cause and cardiovascular mortality and cerebrovascular events within groups of patients with DM or hypertension, and in general population (32).

There are no absolute criteria for abandoning conservative management in favor of initiating maintenance hemodialysis or peritoneal dialysis. As a generalisation, diabetic individuals with progressive renal disease decompensate with uremic symptoms earlier than nondiabetic individuals. A decision to start dialysis is usually the culmination of unsuccessful efforts to regain compensation after episodic dyspnea due to volume overload or nausea and a reversed sleep patern characteristic of renal failure (7). The highest death rate have diabetic dialysis patients (PD and HD), while the best survival is experienced by nondiabetic renal transplant recipients.

Ideally, treatment for ESRD should be selected without stress or urgency on the basis of prior thought and planning. We need to explain treatment options, establish vascular or peritoneal acccess and encourage intrafamilial kidney donation (13).

Comparison of dialysis options for the diabetic patients (7):

- Peritoneal access is easy, but peritoneal dialysis has low technique survival rate, high hospitalization rate and higher rate of infection
- Hemodialysis has better technique survival rate, lower hospitalization rate and lower infection rate, but a lot of diffculties with vascular access.
- Blood pressure control is good with peritoneal dialysis, ultrafiltration is slower and there is fewer episodes of cardiovascular instability
- Blood pressure control is not so good on hemodialysis, frequent hypotensive episodes
- Peritoneal dialysis preserve residual renal function for longer, biochemical parameters are steady-state

– During hemodialysis we obtain efficient solute and water extraction
– Peritoneal dialysis maintains independence, but hemodialysis can be performed at home, also
– Patients need fewer dietary restrictions on peritoneal dialysis, but excessive weight gain, poor nutrition aand hyperlipidemia occurs frequently
– Patients on hemodialysis have difficulties with fluid and dietary restrictions

A total of 114 diabetic CKD patients on HD were surveyed for seven years. In these patients poor glycemic control is an independent predictor of prognosis. This finding indicates the importance of careful management of glycemic control even after initiation of HD (33).

American Diabetes Association recommends Standards of Medical Care in Diabetes in 2008 (position statement, 35):

- To reduce the risk or slow the progression of DN, optimize glucose control (A)
- To reduce the risk or slow the progression of DN, optimize blood pressure control (A)
- Perform an annual test to assess UAER in type 1 DM patients with disease duration of ≥ 5 years, and in all type 2 DM patients, starting at diagnosis (E)
- Measure serum creatinine at least annually in all adults with DM regardless of the degree of UAER. The serum creatinine should be used to estimate GFR and stage the level of CKD, if present (E)
- In the treatment of the nonpregnant patients with micro or macroalbuminuria, either ACE inhibitors or ATRA should be used (A).
- While there are no adequate head-to-head comparisons of ACE inhibitors and ATRA, there is clinical trial support for each of the following statements:
    - In patients with type 1 DM, with hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of DN (A)
    - In patients with type 2 DM, hypertension and microalbuminuria, both ACE inhibitors and ATRA have been shown to delay the progression to macroalbuminuria (A)
    - In patients with type 2 DM, hypertension, macroalbuminuria and renal failure ATRA have been shown to delay the progression of DN (A)
    - If one class of drugs is not tolerated, the other should be substitued (E)
- Reduction of protein intake to 0.8-1.0 g/kg wt/day in individuals with DM and the earlier stages of CKD, and to 0.8 g/kg wt/day in the later stages of CKD may improve measures of renal function (UAER and GFR) and is recommended (B)
- When ACE inhibitors, ATRA or diuretics are used, monitor serum creatinine and potassium levels for the development of acute kidney disease and hyperkalemia (E)
- Continued monitoring of UAER to assess both response to therapy and progression of disease is recommended (E)
- Consider referral to a physician experienced in the care of kidney disease when there is uncertainity about the etiology of kidney disease (active urine sediment, absence of retinopathy, rapid decline in GFR), difficult management issues, or advanced kidney disease (B)

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