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Cost-Effective Screening of Kidney Disease in Families of End-Stage Renal Failure Patients on Dialysis in Serbia

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Abstract
Despite the availability of improved medical therapy to slow the progression of nephropathy, a worldwide epidemic of ESRD exists. Ideally all adults would be routinely screened for evidence of early kidney disease and associated risk factors. Unfortunately this would be a massive and expensive screening. Family members of individuals with chronic kidney disease are disproportionately affected with unrecognized and asymptomatic nephropathy. Screening of these high-risk relatives for early nephropathy, and for risk factors for nephropathy, will probably lead to successful treatment for nephropathy and slow the growing worldwide epidemic of end-stage renal disease. After a cost-effect analysis of the prevention project Serbian nephrologists have decided to start screening of first and second-degree relatives of dialysis and kidney transplant patients. Assuming that each year about 1,000 new patients start ESRD supporting treatment in Serbia, and that preventive programs could delay ESRD for several years, or even, in diabetes mellitus type 2, prevent diabetic nephropathy, the feeling of Serbian nephrologists was strong in favor of prevention. The first decision was to start that program at the University Clinics in Belgrade, Nis, Novi Sad and Kragujevac. Primary health physicians will be trained in screening procedure and preventive measures in kidney disease, diabetes and hypertension.

Kidney disease in the new millennium

Chronic kidney disease (CKD) is a worldwide public health problem. The incidence of patients with end-stage renal disease (ESRD) and diabetes mellitus type 2 as a comorbid condition has increased progressively in the past decades, first in the United States and Japan, but subsequently in all countries with a western lifestyle. End-stage renal failure (ESRF) in type 2 diabetes has become a medical catastrophe of worldwide dimensions [1].

Despite advances in dialysis and transplantation, the prognosis of kidney failure remains bleak. The USRDS reports more than 63,000 deaths of patients with ESRD in 1998, and an annual mortality rate of dialysis patients in excess of 20%. Expected remaining lifetimes of patients treated by dialysis were far shorter than the age-matched general population, varying (depending on gender and race) from 7.1 to 11.5 years for patients aged 40 to 44 years, and from 2.7 to 3.9 years for patients aged 60 to 64 years. Morbidity of kidney failure is also high. The mean number of comorbid conditions in dialysis patients is approximately 4 per patient, the mean number of hospital days per year is approximately 15, and self-reported quality of life is far lower than the general population. Total Medicare and non-Medicare costs for ESRD treatment in 1998 were $12.0 billion and $4.7 billion, respectively. There is an even higher prevalence of earlier stages of chronic kidney disease. Mortality, morbidity, hospitalizations, quality of life, and costs for caring for patients with earlier stages of CKD have not been systematically studied.

Substantial improvements in the dialytic treatment of patients with end-stage renal disease have been made during the past several decades. However, inadequate attention has been given to the problem of CKD as a whole. CKD and its associated complications emerge years before patients develop kidney failure and become dialysis dependent. It now is evident that to improve dialysis outcomes, it is essential for practitioners to recognize the earlier stages of CKD, not only to retard disease progression, but also to prevent and treat its complications and comorbidities long before the need for dialysis arises. The recently published National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines identify the broad-based problem of CKD in the general population and introduce action plans that can be used at the different stages of CKD [2].

Screening of kidney disease

Despite the availability of improved medical therapy to slow the progression of nephropathy, a worldwide epidemic of ESRD exists. Many patients are not diagnosed until the late stages of disease, as early kidney disease may be asymptomatic. Ideally all adults would be routinely screened for evidence of early kidney disease and associated risk factors such as hypertension and diabetes mellitus [3]. Unfortunately this would be a massive and expensive screening. A more practical, cost-effective solution might be to direct screening at those individuals who are known to be at high risk for the development of nephropathy. The familial clustering of ESRD has been reported for many types of renal disease.

Family history of end-stage renal disease is an important risk factor for the subsequent development of nephropathy. Multiply-affected families with members demonstrating end-stage renal disease often contain individuals with disparate etiologies of renal disease. These observations have led to the search for nephropathy susceptibility genes [4]. Genetic loci associated with susceptibility to diabetic (3q, 18q22.3-23) and non-diabetic nephropathy (chromosome 10) have been identified. A mutation in the uromodulin

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gene (16p11-13) has recently been linked to medullary cystic kidney disease type 2 and familial juvenile hyperuricemic nephropathy. Familial focal segmental glomerulosclerosis is linked to the 1q25-31, 11q21-22, and 19q13 loci in different families. Family members of individuals with chronic kidney disease are disproportionately affected with unrecognized and asymptomatic nephropathy. Screening of these high-risk relatives for early nephropathy, and for risk factors for nephropathy, will probably lead to successful treatment for nephropathy and slow the growing worldwide epidemic of end-stage renal disease.

Satko and Freedman have proposed that the routine screening of first- and second-degree relatives of ESRD patients for nephropathy might be an efficient way to detect subclinical renal disease [5]. Early detection and intensive treatment of renal disease may help to curb the current epidemic of ESRD.

The ESRD Network 6 Family History of ESRD database was analyzed to compare dialytic survival among patients with first- or second-degree relatives on dialysis therapy (positive family history) with those lacking relatives with ESRD (negative family history). Study participants included 3,442 adult, black or white, incident patients with ESRD who initiated dialysis therapy in ESRD Network 6 facilities in 1995 and participated in the Network-sponsored Family History of ESRD study. Overall, 730 patients (21.2%) had a positive family history of ESRD [6]. Black patients, those who were younger at the onset of ESRD, patients with greater degrees of functional status, and women were more likely to have a positive family history.

A cross-sectional survey, by way of a voluntary screening of relatives of patients with ESRD in 10 communities in one southeastern state, was performed [7]. Among 769 screened adults, 29.2% with a family history of ESRD were included in the study sample. CKD (CrCl < 90 mL/min) was present in 49.3%, 13.9% had a CrCl less than 60 mL/min, and 9.9% had proteinuria of 1+ or greater. Among those with a CrCl less than 60 mL/min or a proteinuria of 1+ or greater, or both, only 13.0% were aware of their KD. Awareness of CKD was not associated with age, race, sex, education, control of diabetes and hypertension, or physician's visits. Among those who had seen a physician recently, only 7.9% were aware of their KD. Awareness of KD is less than expected among relatives of patients with ESRD considering the high prevalence of CKD in this population. Screening these individuals might help identify people with early KD.

Evaluation of Patients at Increased Risk

Clinical evaluation of patients at increased risk of chronic kidney disease includes assessment of markers of kidney damage, estimated GFR, and blood pressure [3]. Abnormal urinary excretion of albumin and total protein is a highly sensitive indicator of glomerular disease. The results of urine sediment examination and of imaging studies of the kidney, however, can also suggest other types of chronic kidney diseases, including vascular, tubulointerstitial, and cystic diseases of the kidney. In addition, proteins other than albumin in the urine may indicate tubulointerstitial injury. At present, there are no clinically proven markers specific for tubulointerstitial or vascular diseases of the kidney.

Markers of kidney disease

Markers of kidney damage in addition to proteinuria include abnormalities in the urine sediment and abnormalities on imaging studies. New markers are needed to detect kidney damage that occurs prior to a reduction in GFR in other types of chronic kidney diseases.

1. **Proteinuria**
2. **Urine sediment examination or dipstick** for red blood cells and white blood cells should be performed in patients with chronic kidney disease and in individuals at increased risk of developing chronic kidney disease.
3. **Decreased GFR.** Serum creatinine is not a valid measure of kidney function, however, calculated creatinine clearance is very useful.
4. **Imaging studies of the kidneys** should be performed in patients with chronic kidney disease and in selected individuals at increased risk of developing chronic kidney disease.

Proteinuria

Dipstick urinalysis for proteinria and hematuria has been used to screen renal disease, but evidence of the clinical impact of this test on development of ESKD is lacking. Development of ESRD through 2000 in 106,177 screened patients (20,584 men and 55,593 women), 20 to 98 years old, in Okinawa, Japan, who participated in community-based mass screening between April 1983 and March 1984 was assessed [8]. During 17 years of follow-up, 420 screened persons (246 men and 174 women) entered the ESRD program. A strong, graded relationship between ESRD and dipstick urinalysis positive for proteinuria was estableshed; adjusted odds ratio (95% CI) was 2.71 (2.51 to 2.92, $p<0.001$). Similar trends were observed after adding serum creatinine data. In this study proteinuria was found a strong, independent predictor of ESRD in a mass screening setting. Even a slight increase in proteinuria was an independent risk factor for ESRD. Therefore, asymptomatic proteinuria warrants further work-up and intervention.

Proteinuria is a key finding in the diagnosis and differential diagnosis of chronic kidney disease [3]. Proteinuria is a marker of damage in diabetic kidney disease, in glomerular diseases occurring in the native kidney, and in transplant glomerular disease and recurrent glomerular disease in the transplant. On the other hand, proteinuria is usually mild or absent in vascular diseases, tubulointerstitial diseases, and cystic diseases in the native kidney.

Proteinuria is also a key prognostic finding [3]. It is well-known that nephrotic range proteinuria is associated with a wide range of complications, faster progression of kidney disease and premature cardiovascular disease. However, it is now known that elevated urine protein excretion below the nephrotic range is also associated with faster progression of kidney disease and development of cardiovascular disease. Furthermore, the reduction in proteinuria is correlated with a subsequent slower loss of kidney function.

Finally, proteinuria is also a guide to therapy [3]. The benefit of antihypertensive therapy, especially with angiotensin-converting enzyme inhibitors, to slow the progression of kidney disease is greater in patients with higher levels of proteinuria compared to patients with lower levels of proteinuria. In summary, proteinuria is not only a marker of kidney damage, it is also a guide to the differential diagnosis, prognosis, and therapy of chronic kidney disease.

Abnormalities of the Urinary Sediment

Examination of the urinary sediment, especially in conjunction with assessment of proteinuria, is useful in the detection of chronic kidney disease and in the identification of the type of kidney disease [3]. Urinary sediment examination should be considered in individuals at increased risk of developing chronic kidney disease.

Urine dipsticks include reagent pads that are sensitive for the detection of red blood cells (hemoglobin), leukocytes (leukocyte esterase), and bacteria (nitrites). Thus, urine sediment examination is generally not necessary for detection of these formed elements. However, dipsticks cannot detect tubular epithelial cells, fat, or casts in the urine. In addition, urine dipsticks cannot detect crystals, fungi, or parasites. Urine sediment examination is necessary for detection of these abnormalities. The choice of urine sediment examination versus dipstick depends on the type of kidney disease that is being considered.

Unfortunately, these markers do not detect all types of chronic kidney damage. Thus, it may be difficult to detect the onset of some types of chronic kidney disease until GFR is decreased, for example, hypertensive nephrosclerosis and noninflammatory tubulointerstitial diseases.

Decreased GFR

Decrease in GFR of 60 to 89 mL/min/1.73 m^2 is defined as chronic kidney disease only if accompanied by a marker of kidney damage. GFR declines with age in normal individuals; therefore, it can be difficult to distinguish age-related decrease in GFR from chronic kidney disease in the elderly. Other causes of chronically decreased GFR in normal individuals without chronic kidney disease include a habitually low protein intake and unilateral nephrectomy.

Data from NHANES III suggest that almost 75% of individuals ≥70 years old may have GFR <90 mL/min/1.73 m^2, and almost 25% may have GFR <60 mL/min/1.73 m^2. The fraction of elderly individuals with decreased GFR who truly have chronic kidney disease has not been systematically studied. Moreover, the health outcomes of decreased GFR in the elderly, with or without chronic kidney disease, are also not known.

Imaging Studies

Abnormal results on imaging studies (ultrasound) suggest either urologic or intrinsic kidney diseases [3]. Imaging studies are recommended in patients with chronic kidney disease and in patients at increased risk of developing chronic kidney disease due to urinary tract stones, infections, obstruction, vesico-ureteral reflux, or polycystic kidney disease.

Screening recommendations

Members of a working party for the management of CKD have identified several recommendations for the screening of patients at risk of CKD [9].

How to screen for chronic kidney disease ?

Dipstick (untimed spot urine sample) for proteinuria, WBC and RBC

If positive for proteinuria: measure total protein to creatinine ratio in an
untimed spot urine sample

If negative for proteinuria: perform a specific search for microalbuminuria
in patients with diabetes mellitus or hypertension

If positive for WBC or RBC: perform a **sediment analysis** in an untimed
spot urine sample

Estimate creatinine clearance

Use Cockcroft-Gault formula:

$$\frac{(140\text{-age}) \times \text{weight}}{\text{serum creatinine } (\mu\text{mol/l})} \quad (\times 1.23 \text{ for men})$$

When to evaluate screening ?

If screening was negative:

Every 1-3 years, depending on risk factors

If abnormality is evidenced at screening:

Perform *diagnostic and therapeutic work-up*

Screening: Problems to be solved

At present, studies that definitively demonstrate the effectiveness of population-based screening for renal disease are not available. Randomized clinical trials would be the ideal methodology to evaluate the effectiveness of this comprehensive, population-based approach to disease prevention. However, such trials are not generally feasible because of the requirement of large sample sizes of communities and the long period of observation alternative, statistical. As an simulations of screening programs may provide indirect evidence of the cost-effectiveness of such programs.

Clinical Applications

In patients known to have chronic kidney disease on the basis of a decreased GFR, urinalysis and imaging studies may yield important diagnostic information [3].

In patients not previously known to have chronic kidney disease, examination of the urinary sediment may confirm the presence of kidney disease. Abnormalities in the sediment will be present in a large proportion of patients with chronic kidney disease. On ultrasound examination, the presence of a kidney stone and findings of obstruction may help to explain acute flank pain. Radiological assessment may help to clarify other aspects of the nature of the kidney involvement. For example, bilateral small echogenic kid-

neys in a patient presenting with newly detected decreased kidney function can suggest a chronic rather than an acute process.

Examination of the urinary sediment may lead to the detection of kidney disease in patients presenting for evaluation of symptoms related to other organ systems. The evaluation of the urine in patients with signs of vasculitis or with carcinomas may result in detection of associated kidney disease. Findings suggestive of kidney disease may be expected to occur frequently in the evaluation of individuals presenting with hypertension, especially younger individuals.

Cells in urinary deposit may originate from the kidneys or from elsewhere in the urinary tract, including the external genitalia. Casts form only in the kidneys and result from gelling within the tubules of Tamm-Horsfall protein, a high molecular weight glycoprotein derived from the epithelial surface of the distal nephron. Casts entrap material contained within the tubular lumen at the time of cast formation, including cells, cellular debris, crystals, fat, and filtered proteins. Examination of the urinary sediment for casts requires careful preparation. A "fresh" first morning specimen is optimal, and repeated examination may be necessary. The presence of formed elements in the urinary sediment may indicate glomerular, tubulointerstitial, or vascular kidney disease. Significant numbers of erythrocytes, leukocytes, or cellular casts in urinary sediment suggest the presence of acute or chronic kidney disease requiring further work-up. The differential diagnosis for persistent hematuria, for example, is quite broad, including glomerulonephritis, tubulointerstitial nephritis, vascular diseases, and urologic disorders. Therefore, as with proteinuria, specific diagnosis requires correlation of urinalysis findings with other clinical markers. The presence of red blood cell casts strongly suggests glomerulonephritis as the source of hematuria. Dysmorphic red blood cells may also indicate a glomerular disease. Pyuria (leukocyturia), especially in the context of leukocyte casts, may be seen in tubulointerstitial nephritis, or along with hematuria in various forms of glomerulonephritis. Urinary eosinophils have been specifically associated with allergic tubulointerstitial nephritis. Examination of a single urinary sediment may be adequate in most cases. However, the finding of a negative urinary sediment in patients considered to be at high risk for chronic kidney disease should lead to a repeat examination of the sediment.

Application of the newer urinary markers (mononuclear cells and specific proteins such as NAG) must await their validation in more extensive clinical studies [3].

Prevention of kidney damage

Therapeutic interventions at earlier stages of chronic kidney disease are effective in slowing the progression of chronic kidney disease [3]. The major therapeutic strategies that have been tested include strict blood glucose control in diabetes, strict blood pressure control, angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers, and dietary protein restriction. The study of kidney diseases in the transplant population has long focused on prevention and treatment of allograft rejection. Observational studies have demonstrated that non-immunological factors, such as proteinuria and higher blood pressure, appear to be risk factors in diseases of transplanted as well as native kidneys.

Prevention of comorbidities

Patients with CKD have a large number of comorbid conditions. Comorbidity is defined as conditions other than the primary disease (in this case, chronic kidney disease). Complications of chronic kidney disease, such as hypertension, anemia, malnutrition, bone disease and neuropathy, are not considered as comorbid conditions. It is useful to consider three types of comorbid conditions: diseases causing CKD (diabetes, hypertension, urinary tract obstruction), diseases unrelated to CKD (chronic obstructive pulmonary disease, joint disease, malignancies, etc), and cardiovascular disease. CKD is the primary cause of end-stage renal disease. A 5-year study was performed to understand the natural history of chronic kidney disease with regard to progression to renal replacement therapy (transplant or dialysis) and death [10]. A representative population in Oregon of 27 998 patients, with glomerular filtration rates of less than 90 mL/min per 1.73 m^2 was followed. Data showed that the rate of renal replacement therapy over the 5-year observation period was 1.1%, 1.3%, and 19.9%, respectively, for the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) stages 2, 3, and 4, but that the mortality rate was 19.5%, 24.3%, and 45.7%. Thus, death was far more common than dialysis at all stages. In addition, congestive heart failure, coronary artery disease, diabetes, and anemia were more prevalent in the patients who died. Efforts to reduce mortality in this population should be focused on treatment and prevention of coronary artery disease, congestive heart failure, diabetes mellitus, and anemia. Screening and early detection of kidney disease has the aim not only to prevent kidney damage but also to prevent comorbidities associated with chronic kidney disease.

Cost-effective screening in families of ESRF patients

Screening in families of ESRF patients could be cost-effective. Assuming that actually in Serbia there are 6,000 ESRF patients on supportive treatment (HD, PD, Kidney transplants), and that annual increase is about 1,000 of patients, the cost of new dialysis patients is substantial, as there is no robust transplant program. Cost of hemodialysis is mainly for dialyzers and solutions, as there is no money for adequate salaries, and no private dialysis units exist to date. Hemodialysis costs about 6,000 euros/patient/year, but peritoneal dialysis costs more, e.g. 8,000-10,000 euros/patient/year.

Screening costs for 30,000 persons at risk (6,000 patients, each with 5 first and second degree relative) would be around 150,000 euros. This small sum comes from rational testing (kidney disease history, measurement of blood pressure, urinary dipstick or sediment examination, serum creatinine and creatinine clearance calculation), which we estimate to cost about 5 euros per patient. Confirmation testing is necessary for about 20% of screened population, i.e. 6,000 patients. It includes ultrasound examination, other

laboratory tests (urea, creatinine, glycose, electrolytes), and could cost about 25 euros/patient. This clinical estimation for 6,000 patients would cost 150,000 euros. The total cost of screening and clinical estimation of families of ESRF patients will be about 300,000 euros, i.e. 50 hemodialysis patient/years. Assuming that 1,000 new patients start ESRF supporting treatment, and that preventive programs could delay ESRF for several years, or even, in diabetes mellitus type 2, prevent diabetic nephropathy, the feeling of Serbian nephrologists was strong in favor of prevention. The first decision was to start that program at the University Clinics in Belgrade, Nis, Novi Sad and Kragujevac. In June this year, to the Ministry of Health of Serbia a project will be send, with demand for funding a permanent screening which includes all persons with family history of kidney disease, at primary health settings. Primary health physicians will be trained in screening procedure and preventive measures in kidney disease, diabetes and hypertension.

References

1. Ritz E, Rychlik I, Locatelli F, Halimi S: End-stage renal failure in type 2 diabetes: A medical catastrophe of worldwide dimensions. Am J Kidney Dis 1999;34:795-808.
2. Eknoyan G: Meeting the challenges of the new K/DOQI guidelines. Am J Kidney Dis 2003;41(5 Suppl):3-10.
3. National Kidney Foundation: K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 2002;39 (2 Suppl 1):S1-266.
4. Satko SG, Freedman BI: The importance of family history on the development of renal disease. Curr Opin Nephrol Hypertens. 2004;13:337-41.
5. Satko SG, Freedman BI: Screening for subclinical nephropathy in relatives of dialysis patients. Semin Dial 2001; 14: 311-3.
6. Freedman BI, Soucie JM, Kenderes B, et al: Family history of end-stage renal disease does not predict dialytic survival. Am J Kidney Dis. 2001;38:547-52.
7. Jurkovitz C, Franch H, Shoham D, Bellenger J, McClellan W: Family members of patients treated for ESRD have high rates of undetected kidney disease. Am J Kidney Dis. 2002;40:1173-8.
8. Iseki K, Ikemiya Y, Iseki C, Takishita S: Proteinuria and the risk of developing end-stage renal disease Kidney Int 2003; 63: 1468-74.
9. Rossert JA, Wauters JP. Recommendations for the screening and management of patients with chronic kidney disease. Nephrol Dial Transplant: 2002;17 (Suppl 1):19-28.
10. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH: Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med. 2004;164:659-63.