Прилози, Одд. биол. мед. науки, МАНУ, XXXI, 1, с. 249–259 (2010)
Contributions, Sec. Biol. Med. Sci., MASA, XXXI, 1, p. 249–259 (2010)
ISSN 0351–3254
УДК: 616.61-008.64-08

BENEFITS OF SCREENING FOR CHRONIC KIDNEY DISEASE

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A b s t r a c t: The number of patients on renal replacement therapy has doubled every decade since 1980, and prevalence of chronic kidney disease (CKD) in the early stages is also markedly increased. In addition, CKD is a significant risk factor for cardiovascular morbidity and mortality. The only effective approach to this problem is prevention and early detection of CKD.

In recent years, screening studies have been carried out in several countries. The findings have defined the scope of the problem and indicated which population groups are at risk of developing CKD. The most numerous are patients with hypertension and diabetes. Also, these studies have indicated that screening should include measurement of serum creatinine for eGFR as well as urine albumin. Early detection of CKD allows proper management that could slow down CKD progression, prevent cardiovascular and other comorbidities and enable timely initiation of dialysis.

Screening for CKD could be best managed by partnership between primary care physicians and nephrologists. It is necessary to educate primary care physicians about CKD, its risk factors and associated co-morbidities.

Although multiple benefits of screening for CKD are doubtless, the results obtained by screening should be interpreted with caution, bearing in mind that screening detects only markers of kidney disease but not the disease itself

Key words: chronic kidney disease, screening.

Introduction

The number of patients who require renal replacement therapy is increasing all around the world [1–4]. In addition to the steady rise in the incidence of treated ESRD patients, an important characteristic of chronic kidney disease

(CKD) is its asymptomatic course. Thus, many patients with CKD are detected only shortly before the onset of renal replacement therapy, when there is no possibility of influencing the course of the disease and only a few opportunities to prevent different comorbidities and adverse outcomes. It has become obvious that our attention must move from treating only advanced stages of CKD towards therapy during its early stages. Since in most patients CKD is asymptomatic and undiagnosed, early detection of the disease can be achieved only by active screening.

In recent years, a number of screening programmes have been carried out all over the world [5–8]. The results of these studies show the multiple benefits of screening for CKD but also some limitations and mistakes in methodology and interpretation of the results. In this review the benefits of screening for CKD are presented.

Screening studies enable estimation of prevalence of chronic kidney disease

The first benefit and the aim of screening studies is to estimate CKD prevalence in a particular population. The well known Third National Health and Nutrition Examination Survey (NHANES III) was carried out in the United States from 1988 to 1994 and involved 15,488 participants. The results showed that the overall prevalence of CKD among that population was 11%. Prevalence of CKD by stage varied between 3% and 4.3% for stage 1 to 3 and was 0.2% for stages 4 and 5 [9]. In this study the classification of CKD proposed by the NKF/DOQI clinical practice guideline was used [10]. Stages 1 and 2 were defined by the presence of signs of kidney damage (albuminuria, erythrocyturia or abnormalities on renal ultrasound) but only impaired estimated glomerular filtration rate (eGFR) was necessary to classify someone in stages 3 to 5 CKD. That prompted a pro and con debate especially on the classification of subjects in stage 3 of CKD. It is well known that the glomerular filtration rate (GFR) declines with normal ageing [11, 12] and, if age and gender influences on eGFR are not taken into account, the prevalence of stage 3 CKD in the general population will be significantly overestimated. Many persons, mostly elderly and female subjects, with low eGFR will be falsely identified as patients with kidney diseases [13]. Analysis of data from the NHANES study showed that albuminuria was absent in more than two thirds of subjects with stage 3 CKD while, on the other hand, albuminuria was necessary to classify someone in stages 1 and 2 [9]. All these showed that the method of CKD screening should be evaluated.

Evaluation and improvement of the screening method

The above-mentioned analysis of results of the NHANES study as well as some other screening studies have indicated that screening should involve measurement of serum creatinine for eGFR as well as urine albumin [14–16]. Microalbuminuria has been found to be associated with an increased risk of cardiovascular events [17] and this risk is independent of that induced by an impaired GFR [18]. Analysing the results of numerous screening studies, de Jong and Gansevoort [16] underlined that there are far more subjects with elevated albuminuria than with a seriously impaired eGFR, and also most subjects with a seriously impaired eGFR have increased albuminuria. Therefore, they advocated the approach of first screening for the presence of elevated albuminuria, which can be done by a simple dipstick test [16].

It is necessary to stress that the use of an appropriate method in screening for CKD is as important as the correct interpretation of the results. Thus, eGFR calculated from serum creatinine level cannot be "automatically" translated into a K/DOQI-CKD stage. Screening detects only markers of kidney disease but not the disease itself and all persons with detected abnormalities in screening should undergo an additional diagnostic procedure in order to confirm or exclude kidney disease.

The second methodological question is who should be included in screening for CKD. Universal screening of unselected populations not already known to be at risk of CKD has not been shown to be cost-effective and has the potential risk of generating a large number of falsely positive persons [15]. Targeted screening for CKD is likely to be more cost-effective than universal screening. Identification of individuals at risk of CKD is the prerequisite of targeted screening. Diverse populations at risk for CKD have been proposed for screening in different guidelines and examined in various studies (Table 1).

Table 1 – Табела 1

Populations at risk of chronic kidney disease proposed for screening
Ризични популации предложени за скрининг за хронична бубрежна болест

Targeted screening is proposed in persons with:
– diabetes
– hypertension
– age > 55 years
– multisystem disease
– use of nephrotoxic drugs
– family history of chronic kidney disease
– risk of obstructive kidney disease
– cardiovascular diseases

Screening for CKD in patients with hypertension or diabetes is generally accepted. The US KDOQI guidelines also proposed targeting people over 55 years old [10]. The United Kingdom chronic kidney disease guidelines recommend at least an annual screening of all adults at risk of obstructive kidney disease and those with prevalent cardiovascular diseases [19]. Both guidelines highlight the risk associated with multisystem diseases and nephrotoxic drugs. Even wider ranging, the International Society of Nephrology advocates screening for minor renal damage in all patients visiting general practitioners [20]. All these recommendations, however, are based mostly on consensus procedures rather than on hard evidence and the different screening strategies have not been compared for their ability to detect CKD.

As an illustration of the difference in the prevalence of detected signs of CKD depending on the characteristics of the examined population, the data from two of our screening studies are presented in Table 2. The first involved 813 patients with hypertension, while in the second the whole population of a Balkan endemic nephropathy village, both persons with a positive and those with a negative family history, was examined. In the groups at risk of CKD due to the presence of hypertension or a positive family history, 10.8% and 12.7% showed proteinuria with or without haematuria using the urine dipstick test, while this was found in only 3.9% of the remaining 642 inhabitants of the endemic village who had negative family histories.

Table 2 – Табела 2

Prevalence of proteinuria and/or haematuria depending on the presence of risk factors for chronic kidney disease
Преваленција на протеинурија и/или хематурија зависно од присуството на факторите за ризик кај хронични бубрежни болести

	Screening for CKD in patients with hypertension	Screening for CKD in a BEN village	
		persons from BEN families	person from non-BEN families
No (%) with protienuria +/- haematuria	99 (10.9%)	22 (12.7%)	25 (3.9%)
Total number of examined persons	813	173	642

BEN – Balkan endemic nephropathy

Early detection of chronic kidney disease

All screening studies showed that CKD is certainly under-recognized. Analysing the NHANES III data, Coresh and co-workers [9] noted that about 10% of adults with albuminuria and eGFR above 60 ml/min/1.73 m^2 and 18.6% of adults with both moderately decreased kidney function (30 to 59 ml/min/1.73 m^2) and albuminuria (> 30 mg/g) reported previous knowledge of weak or failing kidneys. Detection of undiagnosed and thus untreated CKD, especially detection in its earlier stage, is the main goal and benefit of screening. Numerous studies have shown that subjects with detected proteinuria and impaired eGFR have an increased risk of end stage renal disease (ESRD) but also of cardiovascular disease (CVD) and mortality [7, 21–24]. The PREVEND study demonstrated that the risk of reaching ESRD rose with an increasing CKD stage and patients with stages 4 and 5 of CKD had a 100- to 1000-fold higher chance for developing ESRD compared with patients with CKD stages 1 to 3. Patients with CKD were at a much higher risk of CVD events compared with people without CKD. Furthermore, although the risk of developing a CVD end point in stages 1 to 3 CKD was much higher than that for developing ESRD, it increased much more steeply for renal than for CVD end points [7, 14]. Iseki *et al*. [21] studied the 7-yr cumulative incidence of ESRD in 143,948 individuals from the general population in Okinawa on the basis of baseline creatinine clearance quartile and proteinuria. The presence of proteinuria had a significant impact on the cumulative incidence of ESRD. Thus, 8.5% of individuals with creatinine clearance below 50 ml/min and proteinuria had to start dialysis, while only 0.1% of individuals who had creatinine clearance below 50 ml/min without proteinuria reached ESRD. Patients with proteinuria and with a fairly normal eGFR had a worse prognosis than patients in stage 3 of CKD without proteinuria. The results suggested that proteinuria is a strong indicator of CKD progression. Therefore, early detection of CKD is of the utmost importance and allows more time for the evaluation and treatment of patients. Screening for CKD enables early detection of CKD and the timely initiation of strategies for slowing down its progression, together with prevention of CVD and other comorbidities (Table 3).

Table 3 – Табела 3

Benefits of early detection of chronic kidney disease
Користи од рано откривање на хронична бубрежна болест

Detection of CKD at earlier stages of disease offers the opportunity: • to initiate therapy for slowing down CKD progression and delaying the onset of end-stage renal disease • to carry out preventive strategies for cardiovascular disease strictly and reduce cardiovascular complications and premature death • to prevent, detect and treat early co-morbidities accompanied by CKD • to use eGFR in medication dosing • to avoid drug-induced kidney toxicity and acute changes in effective circulating fluid volume • to reduce late referral of CKD patients to nephrologists

Who should manage screening and subsequent treatment of CKD patients?

If we know that approximately 10% of the general population has CKD, it is obvious that no single country has enough nephrologists to manage such a huge number of patients. This led to the proposal that these patients would be best managed in a partnership arrangement between primary and secondary care [25]. In addition, detection of CKD should not be limited to occasional cross-sectional screening studies but should be carried out continuously. The main role in detection and subsequent treatment of CKD ought to belong to primary care physicians. They could carry out permanent screening of populations at risk of CKD but they should also treat persons at risk to prevent CKD as well as patients with detected CKD (Table 4). The question arises whether general

Table 4 – Табела 4

The main role of primary care physicians in early detection and treatment of chronic kidney disease
Главна улога на лекарите од примарната здравствена заштита во раното откривање и третманот на хроничната бубрежна болест

Primary care physicians could have the main role in: • detection of CKD in populations at high risk for CKD • prevention of CKD in at risk populations • treatment of patients with detected CKD to prevent its progression and comorbidities • referral of CKD patients to nephrologists on time

practitioners are sufficiently well trained to recognize the problems of CKD and to fulfil these tasks. The answer is 'probably not', and nephrologists have the main role in the education of primary care physicians in the prevention and early detection of CKD. The recent initiative of the UK Renal National Service Framework is one example of how this can work in practice [26].

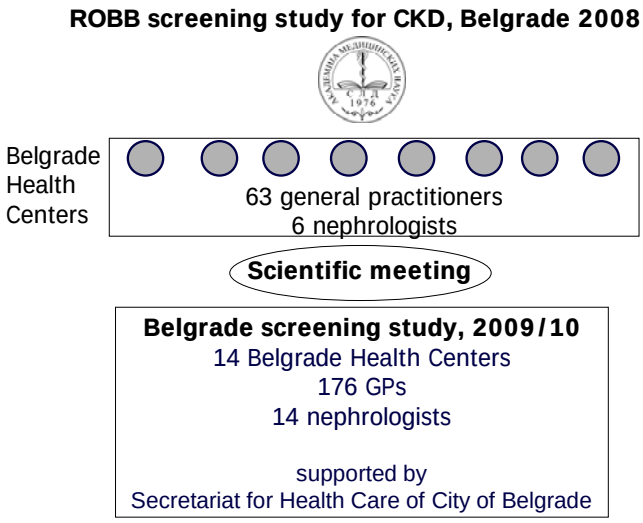

Figure 1 – Collaboration of nephrologists and primary care physicians in two screening studies carried out in Belgrade under the leadership of the Academy of Medical Science SMS and described in the text
Слика 1 – Соработка на нефролози и лекари од примарната здравствена заштита во две студии на скрининг изведени во Белград под водство на Академијата за медицински науки при Српското лекарско друштво и опишани во текстот

We have some experience in collaboration with primary care physicians and the steps of our work are presented in Figure 1. In 2008, under the leadership of the Academy of Medical Science SMS, the "ROBB (Rano Otkrivanje Bolesti Bubrega – early detection of kidney disease) Study" that involved patients with hypertension and persons older than 60 years was carried out in Belgrade. The screening consisted of a questionnaire, urine dipstick analysis, microalbuminuria measurement and eGFR calculation using the MDRD formula. It was carried out by primary care physicians from eight Belgrade Local Health Centres in collaboration with nephrologists from University Clinical Centres. The results were presented at a scientific meeting [27] and aroused great interest both among general practitioners from other Health Centres and also from the

Secretary of Health Care of the City of Belgrade. Financial support from the Secretariat for Health Care enabled a new "Belgrade Screening Study" that is in progress and in which primary care physicians from all 14 Health Centres participate. The goal of these studies is not only to detect the prevalence of CKD in a population at risk of CKD but also to educate primary care physicians in how to include a screening programme in their regular practice and how to interpret the results of screening and manage subsequent treatment alone or in collaboration with nephrologists. The creation of a guideline for early detection and treatment of chronic kidney disease is in progress, too.

Conclusion

The multiple benefits of screening programmes have been shown in many studies carried out in both developed and developing countries. These have established that screening should not be limited to determining eGFR but also to measurement of albuminuria. The results obtained by screening should be interpreted with caution, bearing in mind that screening detects only markers of kidney disease but not the disease itself.

Screening enables early detection of CKD and the timely initiation of strategies for slowing down its progression, prevention of CVD and other comorbidities. This could be best managed by a partnership between primary care physicians and nephrologists.

Acknowledgement

This study was supported by a grant from the Ministry of Science and Technology of the Republic of Serbia. Contract No. 145043.

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Резиме

КОРИСТ ОД СКРИНИРАЊЕ ЗА ХРОНИЧНА БУБРЕЖНА БОЛЕСТ

Ѓукановиќ Љ.

Академија за медицински науки при Српско лекарско друштво, Белград, Србија

Бројот на пациентите на кои им треба заместителна терапија за бубрежна функција се удвојувал секоја декада од 1980 г. и преваленцата на хронични бубрежни болести (ХББ) во раните стадиуми, исто така, забележително се зголемила. Исто така, ХББ е значителен фактор на ризик за кардиоваскуларен морбидитет и морталитет. Единствениот ефективен пристап кон овој проблем е превенцијата и раното откривање на ХББ.

Во последните години, скрининг студии се изведени во неколку земји. Наодите го дефинираа опсегот на проблемот и покажаа кои популациски групи имаат ризик од развивање ХББ. Најбројни се пациентите со хипертензија и дијабетес. Исто така, овие студии покажаа дека скринингот треба да вклучи мерење на креатинин во серумот за eGFR како и албумин во урината. Раното откривање на ХББ овозможува соодветно менаџирање што може да го забави напредувањето на ХББ, да ги спречи кардиоваскуларните и другите коморбидитети и да овозможи навремено започнување со дијализа.

Скринингот за ХББ може најдобро да се менаџира со партнерство меѓу докторите од примарната здравствена заштита и нефролозите. Потребно е да се едуцираат докторите од примарната здравствена заштита за ХББ, за нејзините фактори на ризик и придружните коморбидитети.

Иако е несомнена повеќекратната корист од скринингот за ХББ, резултатите што се добиени со скрининг треба да се интерпретираат внимателно, имајќи предвид дека скринингот ги открива само маркерите на бубрежна болест, но не и самата болест.

Клучни зборови: хронична бубрежна болест, скрининг.

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