

# Why Do We Need Chronic Kidney Disease Screening and Which Way to Go?

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Dialysis and transplantation are life-saving but very expensive treatments. Current increases in the number of hemodialysis centers, machines, shifts, and kidney transplantations cannot keep pace with the increasing number of end-stage renal disease patients globally. The only way to decrease the incidence of end-stage renal disease is identifying patients with low glomerular filtration rate. The risk groups to be targeted, the expected outcomes, and the tests to be ordered are reviewed in this article. The ways that it is possible to make a screening program sustainable and likely cost-efficient model is discussed. It seems the high-risk target population for chronic kidney disease screening in our country can be those with diabetes mellitus, hypertension, hyperlipidemia, age over 40 years, and obesity (possibly abdominal obesity). Macroalbuminuria check in addition to serum creatinine measurement in high-risk population may look a practical approach to initiate a national program.

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## INTRODUCTION

It is a renowned fact that end-stage renal disease (ESRD) is a disabling disease with high mortality rate, and although it affects a very small percentage of the population, its treatment consumes a considerable portion of national health resources.<sup>1-3</sup> All modalities of life-saving renal replacement therapy (RRT) are expensive. Kidney transplantation, the most cost-effective one is again a costly procedure, especially when rehospitalization comes into play. Although the total cost of kidney transplantation in different countries is so diverse, it is so expensive. It has been estimated that the cost of kidney transplantation is US \$ 66 000 in Germany, US \$ 65 000 in China, and US \$ 44 000 to US \$ 60 000 in the United State. This cost in Iran, without the costs of rehospitalization which sometimes equal or exceed surgery itself, is near US \$ 10 000.<sup>4,5</sup> These facts mean that the expenses of this modality in later years of transplantation will stay high, especially with the concern of newer recommendations for longer duration of cytomegalovirus prophylaxis and newer immunosuppressive protocols. Costs

associated with each session of hemodialysis (another modality of treatment), excluding surgical setup, were estimated at US \$ 80 (US \$ 12 500 annually) in Iran and US \$ 21.6 to US \$ 130 in Malaysia (without considering the cost of erythropoietin), US \$ 72.1 in Barbados, US \$ 240 in Greece, and US \$ 209.79 in Chile. In Brazil, an amount of US \$ 46 per session is paid by the ministry of health. Outpatient hemodialysis facilities are paid a fixed amount of about US \$ 187 per treatment as Medicare's reimbursement system in the United States.<sup>3</sup>

On the other hand, the number of patients with ESRD globally continues to grow at an unexpected rate. While, almost 90% of those on RRT live in high-income countries, it has been broadcasted that by 2030, more than 70% of patients with ESRD will be from developing countries with less than 15% of the world economy. Although the statistics from many developing countries may be scarce, it is believed that the average incidence of ESRD in this region is 150 per million in total.<sup>6</sup> Over the past decade, RRT rates have increased in many countries. This rate was 11% in Japan<sup>7</sup> and 12.3%

in Iran. Similarly, ESRD has steadily increased in prevalence and incidence in Latin America (478.2 pmp and 168.7 pmp, respectively) where 300 pmp are on one modality of RRT.<sup>7,8</sup>

### COUNTRIES COPING WITH DISEASE

The main question is how each country copes with the inevitable increase of patients' number and limited healthcare expenditure. Incidence of ESRD for persons aged 20 to 64 years in 18 populations from Europe, Canada, and the Asia-Pacific region, for 1998 to 2002 from registries, were calculated and a small downward trend in all-cause ESRD (-1.7% per year,  $P = .001$ ) was shown. Incidence of type 1 diabetic ESRD fell by 7.8% per year ( $P < .001$ ); glomerulonephritic ESRD, by 3.1% per year ( $P = .001$ ); and "all other nondiabetic" ESRD, by 2.5% per year ( $P = .02$ ). It has been shown that some renoprotective treatments appeared to have been effective for prevention of ESRD.<sup>8,9</sup> Remarkably, nationwide urinalysis screening in Japan from 1983 resulted in declined incidence of ESRD attributable to glomerulonephritis 10 years later.<sup>10</sup> According to the 19th national or regional renal registries participating in the European Renal Association-European Dialysis and Transplant Association Registry 1997 to 2006 (Austria, Denmark, United Kingdom, Finland, Greece, Iceland, Norway, Sweden, the Netherlands, the regional registries of Dutch- and French-speaking Belgium, Calabria, Andalusia, Asturias, Basque, Cantabria, Catalonia, and the Valencian region) the average annual percentage rate (AAPC) of age-adjusted incidence rate of RRT in the period of 1997 and 2000 was 3.3% (95% confidence interval [CI], 0.6% to 6.1%) in males and 2.8% (95% CI, 1.0% to 4.5%) in females.

However, after 2000, the rates increased at a much slower rate (overall incidence, 0.6% per year; AAPC in males, 1.1%; 95% CI, 0.6% to 1.6% and AAPC in females, 0.7%; 95% CI, 0.1% to 1.3%). A similar trend was found in those with ESRD due to type 2 diabetes mellitus (AAPC 1997 to 2002, 8.3%; 95% CI, 6.4% to 10.3% and AAPC 2002 to 2006, 3.2%; 95% CI, 0.6% to 5.8%). In sharp contrast, the adjusted incidence of RRT for ESRD due to type 1 diabetes mellitus decreased during the mentioned period (AAPC -1.1%; 95% CI, -2.0% to -0.2%). This could be due to the increased awareness of the burden of CKD and greater emphasis on early detection and prevention.<sup>11</sup>

### MEASURES IN IRAN

#### Providing Treatment Resources

These experiences may be helpful for other countries. In Iran, as a model of a developing country with a well-defined RRT program and developmental strategic plan, great efforts were done for convincing decision makers to allocate enough resources to improve indexes for all RRT modalities (Table 1): decreasing the patients-machines ratio and increasing the percentage of patients with thrice weekly hemodialysis sessions,<sup>12</sup> massive subsidization of essential immunosuppressive drugs, presenting some amount of money and 1-year health insurance to living donors under the title of "gift for altruism," and provision of operation costs of transplantation in both deceased and living donation.<sup>13-15</sup> Although what has been achieved for RRT in Iran is comparable to that of western countries in some aspects (Table 1) there is a long way to achieve the optimal goals of therapy. Increases in the number of hemodialysis centers,

**Table 1.** Quantitative Indexes of Renal Replacement Therapy in Iran From 2000 to 2006

Index	Changes During 2000 to 2006
<b>Hemodialysis</b>	
Patients-machines ratio	5.1 to 4.7
Bicarbonate-based dialysis sessions	5% to 63%
Patients with thrice weekly sessions	52% to 61%
Increase of dialysis centers	227 to 316
Quality of treatment	100% dialyzers of synthetic membrane 10% coverage with high-flux dialyzer
<b>Peritoneal dialysis</b>	
Increase its ratio to other modalities	0.5% to 3%
<b>Kidney transplant</b>	
Implementation of deceased donation program and increase its rate	32 to 243 case per year
Maintaining its ratio to other modalities	47.5% to 48.5%

machines, and kidney transplantations, which are taking place, cannot keep pace with the increasing number of patients.

### Population-Based Programs to Promote Screening

Is continuing such a strategy the “highest and best” allocation of society’s finite healthcare expenditure? It is confirmed that ESRD is destination of chronic kidney disease (CKD) road. To deal with overwhelming number of patients in coming years it is shown that realistic approaches for early detection and treatment of CKD can decrease the incidence of ESRD and cardiovascular disease,<sup>9,11,16</sup> and the proverb of “prevention is better than cure” is so wise to follow. If we can find cost-effective methods for early detection and intervention, not only there is room for efficiency improvement for those who need RRT, but also higher coverage would be possible. Screening of CKD looks necessary, because CKD’s natural history is progressive without serious symptoms, and ESRD patients are frequently diagnosed as having kidney function impairment in advanced stage. If we can diagnose them earlier, renoprotective measures may be more effective and can help to delay or prevent its progression.<sup>7,16-19</sup>

Screening refers to detecting individuals with unrecognized or early stages of disease in a population. Therefore, the main point is that it should be a continuing process. The only way that it can be sustainable is not only carriage of a greater benefit than risk of harm for the participants, but also its cost-effectiveness from the health economy point of view. An effective screening program finds cases with the minimum number needed to screen. The Norwegian large scale general health survey on 65 000 adults aged over 20 years from 1995 and 1997 found that for finding each case of CKD 5.9 people (5.7 to 6.2) had to be screened, if screening was restricted to hypertensives or diabetics. Nonetheless, this model detected less than half of all cases. In those without known diabetes mellitus or hypertension, the number needed to screen was 34.6 (33.3 to 36.0) per case. Extension of screening to those without diabetes mellitus or hypertension by including other risk factors for CKD, such as family history, previous cardiovascular disease, obesity, or smoking, amplified the detection rate to 81.4% by a number needed to screen close to 19.<sup>20</sup>

Although population-based programs to promote screening for CKD look intriguing, prevention strategies based on screening high-risk populations find more patients and save time and resources better.<sup>8,16,18,21-22</sup>

Although risk factor analysis confirmed that diabetes mellitus, hypertension, cardiovascular disease, and older age are significant associated conditions,<sup>20,23,24</sup> according to differences in causes of ESRD in different countries and some ethnic differences in the rates of CKD progression towards ESRD,<sup>25</sup> the Kidney Disease Prevention Network consensus was that each country should define its own high-risk groups to target for screening programs according to the dominance of CKD risk factors at a local level.<sup>21</sup> It seems that population-based studies may be a prerequisite for developing a coordinated approach to classify a target group of CKD screening programs.

In the 1st national health survey for surveillance of risk factors of noncommunicable diseases in Iran in 2005 on 89 000 persons aged 15 to 64 years, the prevalence of diabetes mellitus was 7.7% (95% CI, 7.5% to 7.9%), higher in older age and urban dwellers, and of hypertension was 25.2% (95% CI, 24.4% to 28.9%) in ages of 25 to 64 years.<sup>26</sup> The second national survey in 2006 on a sample of 29 972 adults between the age of 15 and 64 years found that the odds of hypertension in males were 1.27 times higher than in females after controlling for social set of individual-level variables, and each specified 10-year age interval has the odds of 1.89 times more than its preceding 10-year age interval to prevalence of hypertension. In addition, higher educational level showed lower prevalence of hypertension (odds ratio, 0.76; 95% CI, 0.73 to 0.79). Interestingly, different provinces showed different prevalence of hypertension (Figure 1).<sup>27</sup> It is expected that in those provinces with higher prevalence of hypertension, CKD would be more common, which will be discussed later. Safarinejad, in his all-inclusive well-designed population-based study on nearly 17 000 persons around Iran during 2002 to 2005, showed the prevalence of CKD (estimated glomerular filtration rate [GFR] < 60 mL/min) as 8.3%, which differed from 6% to 17% in different provinces (Figure 2) and was slightly more frequent in males than females (1.2:1). In addition to age, positive associations between CKD and obesity and hypertension were found. It was

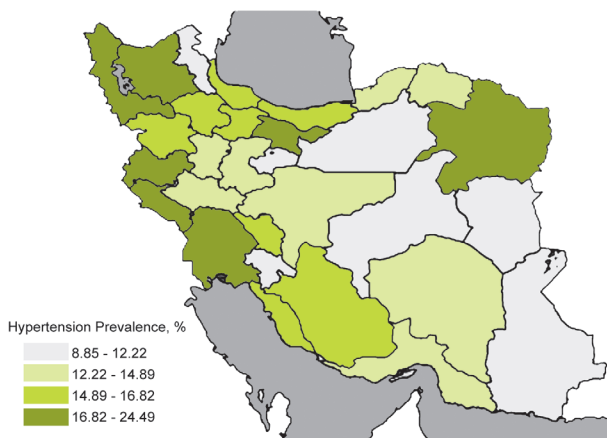


Figure 1. Prevalence of hypertension in Iran.<sup>27</sup>

also shown that the prevalence of CKD in diabetics was 10-fold of those without it. Interestingly, a negative association between CKD prevalence and educational level was revealed (less than high school versus college graduates; odds ratio, 0.80; 95% CI, 0.62 to 1.34,  $P = .02$ ). Family history of kidney disease in siblings (odds ratio, 3.80; 95% CI, 2.64 to 4.66) and lower socioeconomic status (odds ratio, 1.4; 95% CI, 1.22 to 1.58;  $P = .02$ ) were other significant risk factors.<sup>28</sup>

The same risk factors were confirmed in Mahdavi-Mazdeh and colleagues' cross-sectional survey on nearly 32 000 taxi drivers in Tehran in 2007, in which the overall prevalence of an estimated GFR of less than 60 mL/min/1.73 m<sup>2</sup> was found to be 6.5%. The difference between these two studies mainly seems to be due to the younger age of the second one (43.8 ± 11.3 years versus 51 ± 3.6 years) and their healthier situation, as they were able to work. The positive associations between CKD

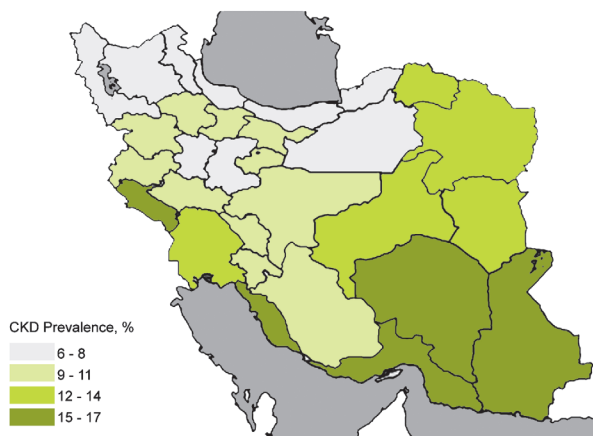


Figure 2. Prevalence of chronic kidney disease (CKD) in Iran.<sup>28</sup>

and risk factors which were found in this study were an age over 40 years, diabetes mellitus, low-density lipoprotein level of 190 mg/dl or higher, hypertension, and high body mass index.<sup>8</sup>

Hosseiniapanah and colleagues analyzed the data of a large cohort of 10 063 participants aged 20 years and over in Tehran; the participants were mostly young and the mean age was 42.7 ± 14.9 years. The overall prevalence of CKD, based on the GFR calculated with the abbreviated Modification of Diet in Renal Disease (MDRD) equation was 18.9% (95% CI, 18.2% to 20.6%), and 33.3% (n = 3349) had abnormal waist circumference, which was more common in women (48.9%, n = 2855) than in men (11.7%, n = 494), recognized as a risk factor for CKD (odds ratio, 1.2; 95% CI, 1.1 to 1.4; Table 2).<sup>29</sup> Similarly, Noori and associates in another cohort of 3107 subjects (1309 men and 1798 women), older than 20 years, without CKD at baseline, showed development of CKD in 7 years' follow-up (GFR < 60 mL/min/1.73 m<sup>2</sup>) in 13.5% of the participants (n = 419). They showed a significant correlation of waist circumference and risk of CKD. The hazard ratios for CKD incidence for waist circumference categories 1 to 4, after multivariable adjustment for age, sex, smoking, physical activity, blood pressure, and diabetes mellitus, were 1.00 (reference), 1.60 (95% CI, 1.06 to 2.42), 1.86 (95% CI, 1.21 to 2.85), and 1.88 (95% CI, 1.17 to 3.01), respectively ( $P$  for trend < .02). It was concluded that abdominal adiposity measured with waist circumference, irrespective of general adiposity, was a more important determinant of CKD risk in adults than body mass index.<sup>30</sup>

In the Framingham offspring cohort (n = 2676; mean age, 43 years), the incidence of CKD during 18.5 years' follow-up was 7.9% (n = 212). Obesity which showed 68% increased odds of developing stage 3 CKD (odds ratio, 1.68; 95% CI, 1.10 to 2.57;  $P = .02$ ) turned into nonsignificant in multivariable models.<sup>31</sup> Viktorsdottir and coworkers, in their cross-sectional study of 19 256 Icelandic population aged 33 to 85 years, found age as a significant risk factor and age-standardized prevalence of low estimated GFR for those aged 35 years.<sup>32</sup> The proportion of subjects with an estimated GFR < 60 mL/min/1.73 m<sup>2</sup> increased with advancing age.

In view of all these studies, it seems the high-risk target population for CKD screening in most countries can be those with diabetes mellitus,

**Table 2.** Characteristics of Population-based Screening for Chronic Kidney Disease in Iran Early Detection Programs\*

Characteristics	Studies		
	Safarinejad <sup>28</sup>	Mahdavi-Mazdeh et al <sup>8</sup>	Hosseinpanah et al <sup>29</sup>
Target population	16 354 individuals Over 14 years old Iran	31 999 Taxi drivers 43.77 ± 11.32 years Tehran	10 063 individuals > 20 years 42.7 ± 14.9 years Tehran
Prevalence of eGFR < 60 mL/min	8.3%	6.5%	18.9%
BMI, kg/m <sup>2</sup> ; OR (95% CI)	≥ 30; 1.80 (1.62 to 2.02)	≥ 25; 1.12 (1.02 to 1.23)	≥ 30; 1.6 (1.3 to 2.0)
Age, OR (95% CI)	5.8 (4.6 to 11.4) for ≥ 70 y	2.0 (1.85 to 2.14)	1.1 (1.0 to 1.2)
Hypertension, OR (95% CI)	2.6; (2.25 to 2.96)	1.2 (1.07 to 1.41)	1.2 (1.1 to 1.4)
Dyslipidemia, OR (95% CI)	...	1.6 (1.43 to 1.81)	1.3 (1.1 to 1.5)

\*eGFR indicates estimated glomerular filtration rate; BMI, body mass index; OR, odds ratio; and CI, confidence interval. Ellipsis indicates not available.

hypertension, hyperlipidemia, age of more than 40 years, and obesity (possibly abdominal obesity), as it is recommended by previously mentioned studies.<sup>8,22,28-30</sup>

### OPTIMAL SCREENING TESTS

There is, thus, the need for a simple method of risk assessment that can be applied to all patients with CKD to identify those few at greatest risk. The 24-hour urine collections are not recommended for screening because of their inconvenience and time. The nominated tests for screening are urine test for proteinuria, urinary albumin-creatinine ratio in a spot urine sample (preferentially obtained in the morning) or urinalysis and serum creatinine level to estimate GFR. Testing for urinary albumin is ideal as albuminuria is a sensitive and specific marker for the most common causes of CKD in adults. Microalbuminuria was associated with the same relative risk for progression to clinical proteinuria in nondiabetic and diabetic kidney diseases.<sup>23,33</sup> In clinical practice, a cutoff value of less than 30 mg/g is used to define microalbuminuria.<sup>23,34</sup> However, confirmation of albuminuria requires 2 positive tests out of 3 tests. Albumin-creatinine ratio in spot urine is more appropriate than urinary albumin concentration (UAC) to avoid variation due to dehydration, diuresis, or lower urinary tract infections.<sup>34</sup>

van der Velde and associates showed that a UAC of 20 mg/L or higher was a significant risk factor for start of RRT during 9 years' follow-up.<sup>33</sup> They compared the hazard ratio of RRT risk in those with a UAC of 20 mg/L to 100 mg/L (lower microalbuminuria category), 100 mg/L to 200 mg/L (high microalbuminuria), and higher

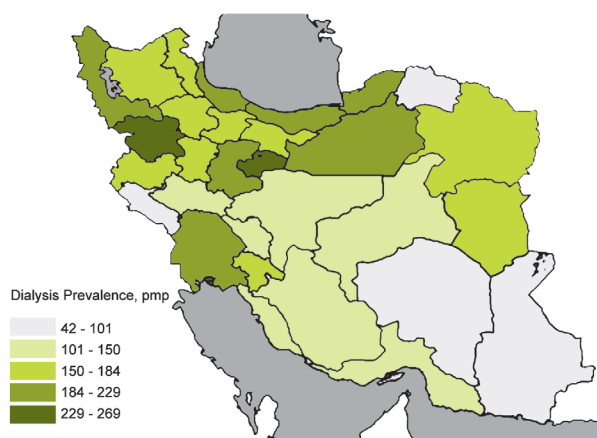
than 200 mg/L (macroalbuminuria category). The hazard ratio increased from relatively small (3.0) in lower microalbuminuria category to 47 (95% CI, 18 to 122) and 120 (95% CI, 58 to 246) in high microalbuminuria and macroalbuminuria categories, respectively; nevertheless, after exclusion of those with diabetes mellitus, the hazard ratios (n = 38) changed to 2.4 (95% CI, 0.7 to 8.3), 44 (95% CI, 15 to 123), and 112 (95% CI, 51 to 247) respectively. They also assessed the rate of decline in estimated GFR during follow-up in each UAC category. The average decline rate of GFR was 0.45 ± 1.6 mL/min/1.73 m<sup>2</sup>/y. The slope of GFR decline in those with lower microalbuminuria category in comparison with those with macroalbuminuria was -0.34 ± 2.10 versus -1.06 ± 1.56 in those without risk factors for CKD, which in contrast to authors' recommendation for screening of all population with or without risk factors, advocates not to screen all is more appropriate. Furthermore, 39 persons out of 15 257 persons with 1 risk factor for CKD needed RRT in the follow-up period. Eighty-eight percent of this group had a UAC higher than 20 mg/L and 15 persons of them needed RRT, but 1.3% had a UAC over 200 mg/L and again 15 patients needed RRT. By measurement of microalbuminuria 9 more cases had the chance of being detected. The PREVEND study data are based on a one-time screening for UAC.<sup>33</sup> If we can develop a sustainable screening program, the process of case finding by annual or longer intervals would be easier and by cheaper tests, it is possible to achieve the same results. It seems limiting the screening test to macroalbuminuria (urinalysis) instead of microalbuminuria looks more realistic in not only our country, but also some

other developing countries, as well, and may be a guarantee for possibility for screening at regular intervals regarding finite resources.

Particularly, we know that CKD patients are a heterogeneous group and only a minority of such patients ever progress to ESRD.<sup>35</sup> The figures on the subject of CKD, hypertension, and dialysis mellitus in Iran in Figures 1 to 3 clearly show that there is no parallel relationship between the prevalence of CKD, hypertension, and ESRD. They do not always go hand in hand. Correspondingly, the relative risk for progression from CKD stages 3 to 4 to ESRD in the American whites compared with Norwegian patients was 2.5. Adjustment for age, gender, and diabetes mellitus did not modify these risks considerably.<sup>36</sup>

Another concern is the method of creatinine measurement: the Jaffe method in comparison with enzymatic assay. It has been revealed in several studies that formula-estimated GFR underestimated kidney function in people without known kidney disease, even more so for Jaffe-related results (about -27%) in comparison with measurements based on enzymatic assay (about -10%).<sup>37</sup>

The next issue is the correlation between formulas used to estimate of GFR. One is based on reciprocal of serum creatinine value. The other well-known formula is the Cockcroft-Gault equation, and the last is the modified MDRD equation. Viktorsdottir and coworkers found that reciprocal of serum creatinine detected more women with higher GFR than men and little change with age. The Cockcroft-Gault equation detected more men with higher GFR than women and marked decline in GFR with age.



**Figure 3.** Prevalence of patients on dialysis in Iran (Ministry of Health 2006 report).<sup>12</sup>

The modified MDRD equation was similar to the Cockcroft-Gault equation, but the decline in GFR with age was not as great.<sup>32</sup> In Mahdavi-Mazdeh and colleagues' study, the Cockcroft-Gault equation overestimated GFR in comparison with the MDRD formula in younger age group with higher GFR, but underestimated lower GFR, especially in the older groups (older than 55 years).<sup>8</sup> Generally, the MDRD and Cockcroft-Gault equations have a correlation of more than 0.8.<sup>8,38</sup> Regardless of the equation used, using a GFR less than 60 mL/min/1.73 m<sup>2</sup> as a cutoff point seems to be rational.

## CONCLUSIONS

The bottom line is that our ability to decrease the incidence of ESRD is based on identifying patients with low GFR and to cut a long story short, the only way to decrease the incidence of ESRD is identifying patients with low GFR. Considering CKD prevention, it may be more cost-effective to consider addition of macroalbuminuria check to creatinine measurement initially in high-risk populations to reduce the number needed to screen and the costs of screening, which may guarantee persistent basis of a national program.

## CONFLICT OF INTEREST

None declared.

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