Screening for renal disease—what can be learned from the Okinawa experience

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Introduction from Editorial office

Screening for renal disease—a lesson from East Asia

There is an ongoing discussion in Europe on whether screening for renal disease is sensible and cost-effective, be it universal screening or targeted screening in specific segments of the general population. Of course, screening for renal disease makes sense, not only with respect to prevention or retardation of end-stage renal disease, but—quantitatively even more so—with respect to prevention of cardiovascular complications.

Even when one considers the substantial demographic and biological differences between Okinawa islands and Western Europe, the unique data of the community-based screening programmes in Okinawa, covering more than 10% of the general population and continuing for more than two decades, are of substantial interest for Europeans, nephrologists as well as public health officials. They are a rich source of information on the benefits, but also the limitations, of screening programmes.

It is for this reason that the editors of Nephrology Dialysis Transplantation (NDT) have asked Dr Iseki to share his findings with the readers of our journal, not least in the hope that political authorities recognize the immense value of such screening programmes.

Prof. N. Lameire
Editor-in-Chief NDT
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Burden of end-stage renal disease in Okinawa

The number of patients with end-stage renal disease (ESRD) requiring chronic dialysis therapy is increasing worldwide [1–3]. In Japan, the Okinawa prefecture has the highest prevalence of ESRD (Figure 1) [4]. Currently, the prevalence is more than 2500 per million population and the mean age at the start of dialysis is more than 65 years [5]. We investigated the renal outcome of the screened population in Okinawa [6–8]. We have published a number of significant predictors of chronic kidney disease (CKD) and ESRD (Table 1), and several other factors are currently under investigation [9–24]. CKD is a cause of ESRD, but many CKD patients contract cardiovascular disease (CVD) before ESRD [25]. Screening for CKD is therefore important, not only for preventing ESRD, but also for preventing CVD and premature death.

In Japan, all employees (≥40 years) and school children, from elementary to high school-age, undergo obligatory routine health examinations, including urine tests [26–28]. Recent progress in pharmacologic therapy for patients with hypertension and diabetes mellitus (DM) indicates that early detection and appropriate treatment might reduce the incidence of CKD and ESRD. Unfortunately, we do not yet have a clear evidence supporting the benefit of the screening programme for preventing ESRD.

Community-based screening programme in Okinawa, Japan

The Okinawa General Health Maintenance Association (OGHMA), a non-profit organization founded in 1972, conducts a large annual community-based health examination [9]. Okinawa consists of subtropical islands that are separated from mainland Japan, so there is relatively little migration of patients. The current population is approximately 1.34 million. Once a year, the staff, doctors and nurses visit the residences and work places throughout the prefecture to perform health examinations. The OGHMA personnel provide mass screening, inform the participants...
of the results and, when necessary, recommend further evaluation or treatment. This process includes an interview concerning health status, a physical examination, and urine and blood tests. A nurse or a doctor measures the blood pressure using a standard mercury sphygmomanometer, with the subject in the sitting position. Dipstick testing using an Ames dipstick (Tokyo, Japan) is performed in spontaneously voided fresh urine. Computer-based registry data for standard analysis are available for the 1983 ($n = 106\,171$), 1993 ($n = 143\,948$), and 2003 ($n = 154\,019$) screenings. Approximately 14% of the total adult population participates in each screening registry. The OGHMA is the largest provider of screening in Okinawa. There are other organizations, both profit and non-profit, that also provide screening programmes. Serum creatinine was measured using a modified Jaffe’s reaction (1983 and 1993) or enzyme assay (2003) in an auto-analyser at the OGHMA laboratory. Subjects already on chronic dialysis are excluded from the analysis.

A subgroup of the screening participants who visited the central OGHMA clinic was examined further. These subjects answered questions about various lifestyle habits, including smoking, alcohol consumption and exercise, as well as their medical history, current medications and whether or not they had been diagnosed with DM [20]. The responses to the questionnaires were verified and all the subjects were interviewed by a physician. Participants in the 1997 OGHMA registry ($n = 9914$) were followed-up until 31 March 2003. The ethics committee of the OGHMA approved the study protocol.

### ESRD patient registry in Okinawa

The details of every ESRD patient treated in Okinawa since 1971 are maintained in an independent community-based registry, the Okinawa Dialysis Study (OKIDS) registry [29–31]. All chronic dialysis patients residing in the prefecture, who survived for at least 1 month on scheduled dialysis were included in the registry. By the end of 2000, there were 46 dialysis units in Okinawa: 9 in the public sector, 17 in private hospitals, and 20 in the clinics. All patients ($n = 5246$) were followed-up until the occurrence of a major medical event or until January 2001, whichever occurred first, and all outcomes were verified [31].

### Predictors of CKD and ESRD

Using the two registries, we identified screening participants who later entered a dialysis programme using the two computer registries [9]. Furthermore, patients were verified by medical records with the

#### Table 1. Summary of the reported risk factors for developing CKD and ESRD in screened subjects in Okinawa, Japan [9–24]

<table>
<thead>
<tr>
<th>CKD</th>
<th>Triglycerides, smoking, obesity, metabolic syndrome(^a)</th>
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<tr>
<td>ESRD</td>
<td>Proteinuria, haematuria, hypertension</td>
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<th>Elevated serum creatinine</th>
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<tr>
<td>Previous history of stroke or acute myocardial infarction</td>
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<tr>
<td>Obesity (men only), low GFR and anaemia (low haematocrit)</td>
</tr>
<tr>
<td>Hyperuricaemia ($\geq 6.0$ mg/dl women only)</td>
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<tr>
<td>High fasting plasma glucose ($\geq 126$ mg/dl)</td>
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\(^a\)Metabolic syndrome was diagnosed using the modified National Cholesterol Education Program (NCEP) criteria (abdominal circumference; men $\geq 85$ cm and women $\geq 90$ cm).
collaboration of colleagues. Among the variables studied, proteinuria was the strongest predictor [11,17]. The dipstick urine test for proteinuria has low sensitivity, but is convenient to use.

The CKD was diagnosed by the KDOQI guidelines [32]. Estimated glomerular filtration rate (GFR) was calculated using the abbreviated modification of diet in renal disease (MDRD) formula. Because there is no known ethnic factor for Japanese, we did not correct the estimated GFR value. We observed significant changes in the participants’ demographics from 1983 to 2003 screenings. While both systolic and diastolic blood pressure decreased, the mean levels of serum cholesterol, triglycerides and fasting plasma glucose, and the prevalence of overweight and obesity increased.

We examined the relationship between the number of components of metabolic syndrome and the prevalence of CKD using a hospital-based registry [24]. The relationship was not linear using the NCEP criteria, but was linear by the modified NCEP criteria [24]. The cut-off levels for obesity might be lower for the Japanese than for the US population [33]. The prevalence of metabolic syndrome (NCEP criteria) and CKD was 12.8 and 13.7%, respectively [24].

Limitations of our study

As in other large-cohort studies, the follow-up was passive. Although all new ESRD patients were accounted for in the data, those subjects who died during the study period were not excluded from the logistic analysis. There is an increased risk of death for individuals with proteinuria [34,35], hypertension and low GFR [36]. The screened subjects were relatively healthy individuals who demonstrated concern about their general health, and should therefore be considered a self-selected population. Individuals who had already been diagnosed with CKD might have been less likely to participate in the screening. Therefore, we might have underestimated the risk of developing ESRD based on dipstick proteinuria, blood pressure and other laboratory variables.

Measurements of proteinuria and other laboratory variables were performed only once. This might result in an underestimation of the strength of the association between the variables studied and the incidence of ESRD. Significant changes in treatment strategy have occurred over the past 30 years, e.g. angiotensin-converting enzyme inhibitors and angiotensin receptor blockers. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers have been available in Japan since 1983 and 1998, respectively. These drugs effectively retard the progression of CKD and reduce the mortality rate due to CVD [19,37], possibly leading to the increase in ESRD with multiple comorbid conditions.

Finally, data on lifestyle-related variables were only available for subgroups of the cohort. Low income/education is an additional potential risk factor for susceptibility to, and the progression of, CKD [32]. Reasons for the high incidence and prevalence of ESRD in Okinawa remain speculative; however, there might be some role of genetic factors. The relative homogeneity of the Okinawa population enhances the internal validity of our results.

Cost and benefits of screening

The progression rate of CKD varies among individuals. Normal results at the screening do not mean that there is no risk of developing CKD or ESRD. We estimated the risk of developing ESRD among those without any risk factors to be very low; one per million per year. The optimal time to offer therapy to asymptomatic subjects with risk factors is not clear [38]. The cost–benefit of the frequency of screening and the extent of tests has been analysed [39]. Boulware et al. [40] reported that the early detection of proteinuria, aimed at slowing the progression of CKD and decreasing mortality, was not cost-effective unless selectively directed towards high-risk groups.

The early detection and treatment of predictors of ESRD might be an effective and inexpensive strategy, particularly for those individuals who are at a high risk of developing ESRD (Table 2). In these high-risk groups, ESRD incidence is more than 1 per 100 patient-year [9,23]. Mean duration from screening to starting dialysis was ~64 months when the serum creatinine level was 2.0 mg/dl [10]. Family members of ESRD patients might have similar risk factors of CKD, such as hypertension, DM and other lifestyle-related factors [41,42].

Perspectives

Given the steady increase in the number of ESRD patients and the economic burden of dialysis therapy, serious efforts need to be made to prevent the development of ESRD. Epidemiologic evidence demonstrating the predictive significance of various factors in the development of CKD and ESRD is important for designing strategies for detecting high-risk individuals and producing follow-up guidelines. The Okinawa screening programme provides valuable opportunities for the detection of CKD in the general population. The actual screening rate, including other providers however, is approximately only 60% of the adult population in Okinawa. Late referral to the

<table>
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<th>Table 2. High risk of ESRD</th>
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<td>Proteinuria (≥2+ by dipstick test)</td>
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<td>High SCr (≥2.0 mg/dl)</td>
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<td>Severe hypertension (JNC-VI)</td>
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<td>Family history of ESRD</td>
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<td>Renal biopsy patient</td>
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<td>ESRD, end-stage renal disease; SCr, serum creatinine.</td>
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nephrology service is common, even among those who participated in the screening [43,44].

Lifestyle-related factors, such as over-nutrition and low levels of exercise, contribute to the prevalence of CKD [24,33,45] and ESRD [14]. Clearly, more public information about CKD and ESRD is needed to ensure the compliance of individuals with screening programmes and intervention strategies. Changes in physician and patient behaviour are needed for better management of CKD [46].

The proportion of elderly people (≥65 years of age) is increasing rapidly in Japan; therefore, the prevalence of low GFR (<60 ml/min/1.73 m²) is also increasing. The clinical significance and outcomes of those screened with CKD remain to be explored.

Conflict of interest statement. None declared.

References

35. Hillege HL, Fidler V, Diereck GH et al. Urinary albumin excretion predicts cardiovascular and
Blood pressure lowering or selection of antihypertensive agent: which is more important?

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**Keywords:** Blood pressure; antihypertensive therapy; cardiovascular risk; renal insufficiency

The relationship between an elevated blood pressure (BP) and cardiovascular (CV) and renal damage has been clearly established. It has remained a matter of debate, however, whether effects beyond BP control force the clinician to prefer certain class(es) of antihypertensive drug(s) beyond what nowadays are considered compelling indications for antihypertensive therapy.

**The ALLHAT study**

After the publication of the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) [1], those defending the idea that only BP control matters have argued that diuretics are the first-choice drugs and this stance has been supported by the Joint National Committee-7, in the absence of real arguments according to the definition of evidence-based medicine [2]. Among the many flaws in the ALLHAT study, we simply point out that probably two-thirds of the patients were on a diuretic before entering the trial; they were then selected as responders to this type of drug and this creates a relevant bias in the final result, because this type of therapy was given many more possibilities to be the winner. Even so, the primary endpoint analysis revealed that there were no significant differences between a diuretic, a dihydropiridine and an angiotensin-converting enzyme (ACE) inhibitor – despite the presence of BP differences, which in the opinion of many experts could explain significant differences in CV outcome [3]. To buttress this argument, the analysis of the Trialist Group [4] revealed that what really matters is BP control.