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Current Situation of Chronic Kidney Disease Management in General Practice in Japan: A Questionnaire Survey for General Physicians

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Total management of chronic kidney disease has been well established, and the screening using dipstick urine test has already been widespread in Japan. Nevertheless, the number of dialysis patients is still rising. While clinical cooperation between general physicians and nephrologists is expected to improve prognoses of chronic kidney disease patients, real situation of the management in general practice has not been obvious. We conducted a questionnaire survey for the doctors of Hyogo Prefecture Medical Association excluding nephrologists to clarify the situation and the issue about chronic kidney disease management in general practice. Total 169 doctors replied to the questionnaire. In 74.0% of medical facilities, estimated glomerular filtration rate was automatically calculated and indicated in the result report with the measurement of serum creatinine. The compliance rates of the chronic kidney disease clinical guideline for Japanese regarding referral to nephrologists were 33.7% in cases of urine abnormality and 57.4% in cases of decreased kidney function. For the patients of diabetes without previous diagnosis of nephropathy, only 30.8% of doctors examined urine albumin at least every 6 months. In general practice, there is still much possibility to improve chronic kidney disease management. We have to continue to advocate the significance of clinical cooperation between general physicians and nephrologists, with high level of evidence.

INTRODUCTION

As it has been more than 10 years since chronic kidney disease (CKD) campaign started in Japan, the increase of dialysis initiation has stopped since 2009, and the increase of dialysis patients has gotten dull [1]. However, the total number of dialysis patients is still rising around 5,000 patients annually in the country [1]. The leading cause of newly initiated dialysis cases was diabetes, accounting for around 43% [1].

The treatment of diabetes and total management of CKD have been well established, and CKD screening using dipstick urine test has already been done nationwide in Japan. Nevertheless, the effect of CKD prevention is not enough. While it is expected that the improvement in clinical cooperation between general physicians and nephrologists reduces the cases of end stage kidney disease (ESKD), real situation about CKD management in general practice has not been obvious.

Thus, we conducted a questionnaire survey for the doctors of Hyogo Prefecture Medical Association to clarify the situation and the issue about CKD management in general practice.

Here, we explain overview of Hyogo prefecture. Hyogo prefecture is located at the center of Japan, ranging from big cities to rural areas, facing both the Pacific Ocean and the Sea of Japan, which is expressed as a miniature of Japan. The data provided by the Japanese Society for Dialysis Therapy (JSDT) indicated that the number of chronic dialysis patients per million population was 2,551 in Hyogo prefecture at the end of 2017, and around middle in the country [1]. Although the population per nephrologist in 2017 was 24,096 people in urban areas (Kobe and Hanshin area), which was very close to the national average value of around 25,000, it was 61,067 in non-urban areas (Harima, Tamba, Tajima, and Awaji area), indicating a large gap in the prefecture.

MATERIALS AND METHODS

We sent question papers to around 8,000 doctors of Hyogo Prefecture Medical Association by post, and asked them to return the answer by FAX or enter it on the website in anonymous name between March 1st and June 30th, 2018. The contents of questionnaire is described in Table I. For each question item, we revealed the overall tendency and analyzed the relation between attributes of doctors and responses. We used the computer software application IBM SPSS Statistics 23 (IBM Corp. USA) for all statistical analyses. For categorical

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variables it was analyzed using Pearson's chi-square test. A p value of less than 0.05 was considered to be statistically significant.

RESULTS

Respondents

Totally 169 doctors of Hyogo Prefecture Medical Association except nephrologists responded to the present survey. Attributes of respondents are shown in Table II. Among respondents, 89.3% of them were working in clinics, the other 10.7% in hospitals. Forty six percent of them were working in urban areas and 53.8% in non-urban areas. The answers were gathered almost in proportion to the population ratio from whole Hyogo prefecture. Regarding to age, the ratio was 1.2%, 13.6%, 33.1%, 37.9%, and 14.2% in 20-30s, 40s, 50s, 60s, and above 70 years, respectively. As for specialties, 78.1% of them were internists, and 21.9% were the others such as pediatrics, surgery, obstetrics and gynecology, dermatology, and etc.

Evaluation of kidney function and diagnosis of CKD

It was possible to measure estimated glomerular filtration rate (eGFR) in routine examination in 89.3% of all medical facilities. And in 74.0% of all the facilities, eGFR was automatically calculated and indicated in the result report with the measurement of serum creatinine. In 57.4% of respondents, eGFR was used as the main indicator for kidney function. The rate was higher among internists than in the other doctors, but there was no statistically significant difference. Serum creatinine, cystatin-c, and creatinine clearance were mainly used in 37.9%, 3.6%, and 1.2% of all respondents, respectively (Figure 1). For the patients of diabetes without previous diagnosis of nephropathy, only 30.8% of doctors examined urine albumin at least every 6 months. Thirty seven percent of doctors did not examine it for those patients at all. Especially, 51.4% of doctors of other than internal medicine and 45.1% of doctors in non-urban areas did not examine urine albumin at all (Figure 2).

Treatment for CKD

Implementation rates of 11 kinds of medication treatments, such as renin-angiotensin system (RAS) inhibitors, other anti-hypertensive drugs, diuretics, statins, uric acid lowering drugs, phosphate binders, activated vitamin D agents, sodium bicarbonate, adsorbent carbon, anti-diabetics, and erythropoiesis stimulating agents, are shown in Figure 3. Among those medication, on average 4.9 kinds of them had been used in general practice. Internists and the other doctors had used 5.4 and 3.2 kinds of them on average, respectively. As for nutrition instruction, 77.5% of doctors had performed it. Forty one percent of them had instructed patients by themselves, 16.6% of them had asked nephrologists, and 19.5% of them had asked registered dietitians.

First referral timing of the patients with urine abnormality to nephrologists is shown in Figure 4. The compliance rate of the CKD clinical guideline was 33.7% (Table III). The rates of the doctors aged below 60 years and those who knew of nephrologists in each area were higher than the others. When judging with only urine protein without considering urine occult blood, the rate was 65.7%.

First referral timing of the patients with decreased eGFR to nephrologists is shown in Figure 5. The compliance rate of the CKD clinical guideline, in case of the patients aged between 40 and 69, was 57.4% (Table III). The rates and attributes of doctors were not significantly associated. In 65.7% of doctors, referral timing of the patients with decreased eGFR aged over 70 was later than that of the patients below 70 years.

Table I. Questionnaire.

<**Attribute**>

Facility	Clinic	Hospital	Others			
Age	20-30s	40s	50s	60s	Above 70	
Area	Kobe	Hanshin	Harima	Tajima	Tamba	Awaji
Specialty	Internal medicine	Pediatrics	Surgery	Others( )		

<**1. Examination & diagnosis**>

1-1 Is the measurement of eGFR possible in routine examination in your facility?

Possible Impossible

1-2 In cases of "yes" in question 1-1, when you examine serum creatinine, is eGFR automatically indicated in the result?

Yes No

1-3 Which indicator do you mainly use for evaluation of kidney function?

Serum creatinine eGFR Serum cystatin-C Others

1-4 How much is the proportion of the patients having abnormal urine findings in your facility?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

1-5 How much is the proportion of the patients with an eGFR value less than 60mL/min/1.73m^2?

0% 10% 20% 30% 40% 50% 60% 70% 80% 90% 100%

1-6 How often do you examine microalbuminuria for diabetic patients without diagnosis of nephropathy?

Every 3 months Every 6 months Once a year Less than once a year Only once Not examined

<**2. Treatment**>

2-1 Which of the following drugs are you using for CKD treatment?

RAS inhibitors Other anti-hypertensives Diuretics Statins Uric acid lowering drugs Phosphate binders
Activated vitamin D Sodium bicarbonate Adsorbent carbon Anti-diabetics Erythropoietin stimulating agents

2-2 How do you provide nutrition instruction?

Do by myself Ask registered dietitians Ask nephrologists Not performed

<**3. Clinical cooperation between general physicians and nephrologists**>

3-1 In which of the following urine findings do you refer the patients to nephrologists?

Protein +/- Protein ≅ 1+ Protein ≅ 2+ Protein ≅ 3+ Protein ≅ 0.5g/gCr Only occult blood Protein and occult blood

3-2 In which of the eGFR, do you refer the patients to nephrologists?

Below 40 years	< 60 mL/min/1.73m^2	< 50	< 45	< 40	< 30	< 15
40-69 years	< 60 mL/min/1.73m^2	< 50	< 45	< 40	< 30	< 15
Above 70 years	< 60 mL/min/1.73m^2	< 50	< 45	< 40	< 30	< 15

3-3 Which medical care style do you desire after consultation to nephrologists, diagnosis, and decision of treatment plan?

Stage G3a	Mainly by general physician	Co-treatment by general physician and nephrologist	Mainly by nephrologist
Stage G3b	Mainly by general physician	Co-treatment by general physician and nephrologist	Mainly by nephrologist
Stage G4	Mainly by general physician	Co-treatment by general physician and nephrologist	Mainly by nephrologist
Stage G5	Mainly by general physician	Co-treatment by general physician and nephrologist	Mainly by nephrologist

3-4 Do you know "CKD notebook" made by Hyogo CKD association and use it?

Use it. Know it but do not use it. Do not know it.

3-5 Do you know any nephrologists whom you can refer CKD patients to?

Yes, and familiar. Yes, but do not know his/her face. No.

3-6 How is satisfaction level about CKD clinical cooperation between general physicians and nephrologists?

6 Very satisfied 5 Satisfied 4 Satisfied a little 3 Dissatisfied a little 2 Dissatisfied 1 Very dissatisfied

3-7 Free description field

Table II. Attributes of the respondents.

		Number	(%)
Type of facility	Clinic	151	(89.3)
	Hospital	18	(10.7)
Age	20-30s	2	(1.2)
	40s	23	(13.6)
	50s	56	(33.1)
	60s	64	(37.9)
	Above 70	24	(14.2)
Area	Urban	78	(46.2)
	Non-urban	91	(53.8)
Specialty	Internal medicine	132	(78.1)
	Others	37	(21.9)

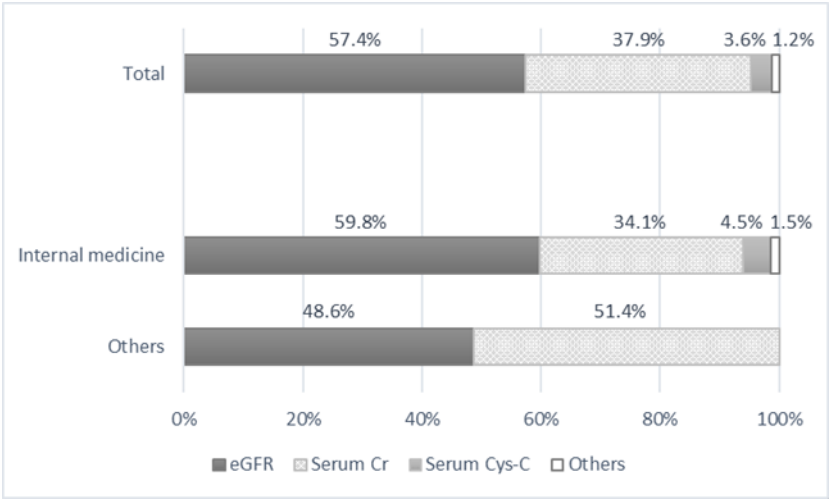


Figure 1. Main clinical indicator of kidney function.
eGFR, estimated glomerular filtration rate; Cr, creatinine; Cys-C, cystatin C.
N.S., not significant.

Clinical cooperation between general physicians and nephrologists

With regard to presence of nephrologists to whom general physicians can refer CKD patients, 45.6% of respondents had familiar nephrologists, 37.9% of them knew of nephrologists but did not know their faces, other 16.6% (21.8% in urban areas) of them did not know of nephrologists at all in each area.

Desirable medical care style after consultation to nephrologists, diagnosis, and decision of treatment plan, for each CKD stage is described in Figure 6. The ratios of the doctors who wanted to continue to see the patients with nephrologists together (co-treatment) were 29.6%, 65.7%, 46.2%, and 10.7% in CKD stage G3a (eGFR; 45-59 mL/min/1.73m^2), G3b (eGFR; 30-44 mL/min/1.73m^2), G4, (eGFR; 15-29 mL/min/1.73m^2) and G5 (eGFR; <15 mL/min/1.73m^2), respectively. And the ratios of the doctors who wanted to entrust the patients to only nephrologists were 3.0%, 8.3%, 49.1%, and 87.6% in CKD stage G3a, G3b, G4, and G5, respectively. In CKD stage G4, the ratios of the doctors who wanted co-treatment were 53.0% in internists and 21.6% in the other doctors, and those who wanted to entrust the patients to only nephrologists were 43.2% in internists and 70.3% in the other doctors.

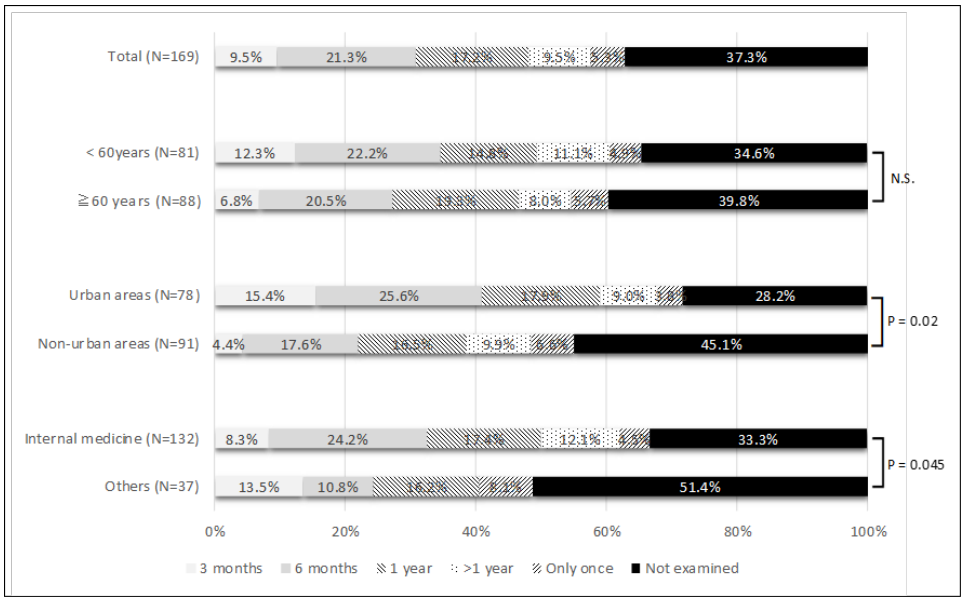


Figure 2. Measurement interval of microalbuminuria for the patients of diabetes without previous diagnosis of nephropathy.
N.S., not significant.

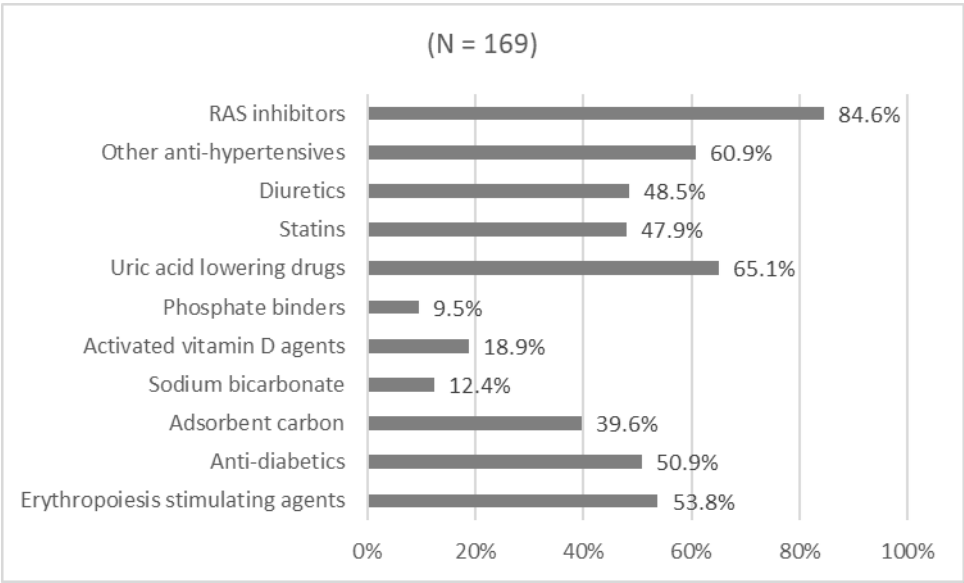


Figure 3. Treatments which had been performed in general practice.
RAS inhibitors, renin-angiotensin system inhibitors.

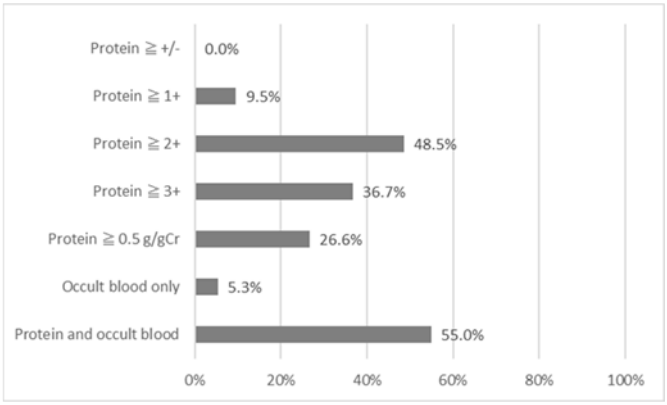


Figure 4. First referral timing of the patients with urine abnormality to nephrologists.

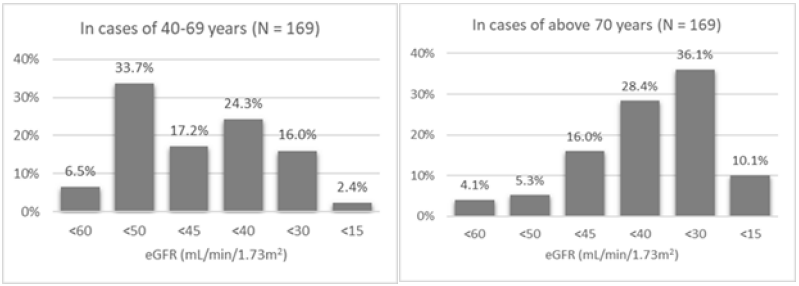


Figure 5. First referral timing of the patients with decreased eGFR to nephrologists.
eGFR, estimated glomerular filtration rate.

Table III. The compliance rates of the CKD clinical guideline regarding referral to nephrologists.

Attributes of respondents	N	The cases with urine abnormality	P value	The cases with decreased eGFR (40-69 years)	P value
Total	169	33.7%		57.4%	
<Age>					
< 60 years	81	42.0%	0.03*	63.0%	N.S.
≧60 years	88	26.1%		52.3%	
<Area>					
Urban areas	78	33.3%	N.S.	53.8%	N.S.
Non-urban areas	91	34.1%		60.4%	
<Specialty>					
Internal medicine	132	34.8%	N.S.	58.3%	N.S.
Others	37	29.7%		54.1%	
<The presence of nephrologists>					
Familiar	77	37.7%	0.017*	58.4%	N.S.
Do not know his/her face	64	37.5%		56.3%	
None	28	14.3%		57.1%	

CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; N.S., not significant.

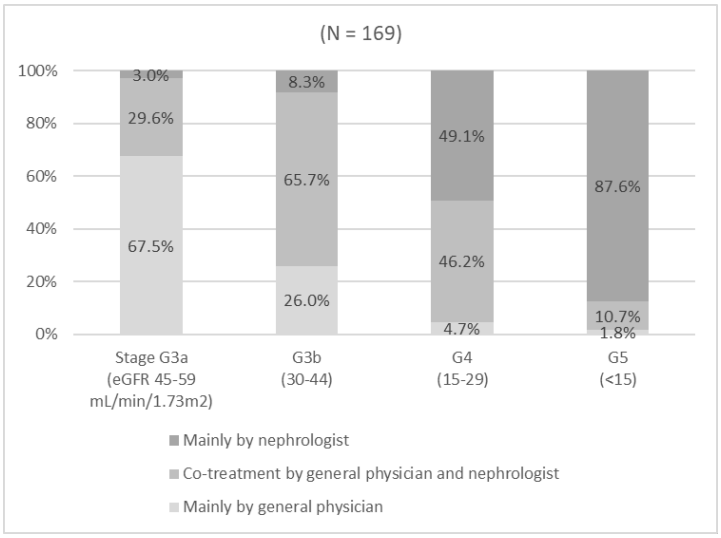


Figure 6. Desirable medical care style after consultation to nephrologists and decision of treatment plan for each CKD stage.
CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

DISCUSSION

In Japan since CKD campaign started in 2004, nephrologists have made an effort to promote the use of eGFR. From the results of this study, the medical facilities, in which eGFR was calculated and indicated in the result report automatically with the measurement of serum creatinine, had reached 74.0%. While, the doctors, who used eGFR as the main indicator of kidney function, were still not high rate as 57.4%. Thirty-eight percent of doctors had mainly used serum creatinine to evaluate kidney function. In order to further spread the use of eGFR, we should continue to explain the limitations of serum creatinine, such as easy to miss the early phase of kidney disease, easy to overestimate kidney function especially in the elderly or women, and difficult to evaluate the change of kidney function.

For the patients of diabetes without previous diagnosis of nephropathy, the doctors, who examined urine albumin at least every 6 months, were only 30.8%. According to a large scale study, kidney lesions could achieve remission with strict glycemic control, until the microalbuminuria period [2]. It was also reported that, in a case of type 1 diabetes in the microalbuminuria period, kidney lesion greatly improved pathologically after normalization of blood glucose level by pancreatic transplantation [3]. In a large scale historical multicenter cohort study, among type 2 diabetes of Japanese, 2.3% of normoalbuminuria cases, 8.3% of microalbuminuria cases, and 47.8% of macroalbuminuria cases reached ESKD or 50% reduction of eGFR during median seven years of follow up. Increased urine albumin levels were closely related to the increase in the risk for renal, cardiovascular events and all-cause mortality [4]. Among type 2 diabetes of Japanese, it was reported that the microalbuminuria period accounted for a very large portion (31.6%) of total cases [5]. Therefore, it is required to control blood glucose level strictly by the microalbuminuria period without missing mild urine albumin. Nevertheless, even in internists 33.3% of them and among the other doctors 51.4% of them had not examined urine albumin in diabetic patients at all. These findings seemed to be a major factor in the delay of countermeasures against diabetic kidney disease, thus further enlightenment is required.

With regard to medication related to CKD treatment, 84.6% of doctors had prescribed RAS inhibitors if necessary. On the other hand, the doctors, who had used diuretics, statins, or erythropoiesis-stimulating agents in necessary cases, remained around half. There were few doctors prescribing phosphate binders and activated vitamin D agents. From the results, it seems that CKD total management is not enough in the present situation, and in other words there is much possibility for improvement of the management by promoting clinical cooperation between general physicians and nephrologists. In addition to medication, nutrition instruction for CKD patients is also important. The rate of the doctors who had been practicing nutrition instruction was very high regardless of doctor's attributes. In "Frontier of renal outcome modification in Japan (FROM-J) study", lifestyle modification including nutrition instruction by registered dietitian retarded eGFR deterioration in the patients of CKD stage G3 of Japanese [6]. But, in the present study, the quality of nutrition instruction was not evaluated, thus further investigation is necessary.

We discussed the timing to refer the patients to nephrologists, which is a key point in CKD clinical cooperation. It is desirable to determine the timing to refer CKD patients of Japanese to nephrologists according to the Evidence-based clinical practice guideline for CKD 2018, which reflected a lot of high-level evidence [7]. It had been indicated that the risk of future cardiovascular death and ESKD was strongly associated with the level of proteinuria as well as eGFR [8]. Based on the results, the clinical guideline recommended referral to nephrologists in cases of CKD stages G3b or more regardless of urine protein, stage G3a with "mild proteinuria (stage A2; dipstick± or 0.15-0.49 g/gCr)", or "overt proteinuria (stage A3; dipstick ≧1+ or ≧0.5 g/gCr)" regardless of eGFR values [7]. A longitudinal 10-year follow-up study in Japan showed that, in the elderly above 70 years, the rate of kidney function decline had been relatively slow until eGFR 40 mL/min/1.73m^2 [9]. After that, a large-scale observational study on annual health check-ups in Japan showed that less than 45 mL/min/1.73m^2 of eGFR was at high risk for total and cardiovascular death in the elderly aged 65-75 [10]. Thus, in the clinical guideline, it is recommended that the elderly above 65 years are referred to nephrologists when eGFR is less than 45 mL/min/1.73m^2 [7].

Prior to the present survey, a similar questionnaire survey was conducted targeting the doctors of Hyogo Prefecture Medical Association in 2011 [11]. Since the question sentences and attributes of the respondents in the previous survey were not the same as those in the present survey, we were not able to compare these two results directly. However, some of the previous results are referenced in this section to grasp rough trend of CKD management in general practice in Hyogo prefecture over the last seven years.

In the present survey, regardless of diabetes, referral timing of the patients, with urine abnormality to nephrologists greatly differed from the result of the 2011 survey [11]. During the period of the present survey, the CKD clinical guideline 2018 was issued by Japanese society of nephrology, and the definition of CKD stage A3, one of the referral criteria to nephrologists, was changed from urine protein ≧2+ to ≧1 [7]. Thus, in this survey, in addition to urine protein ≧2+ or ≧0.5 g/gCr, urine protein ≧1+ was also considered to be compliance with the guideline. Nevertheless, the compliance rate of the guideline regarding urine abnormality was as low as 33.7%. Since, in the previous survey, there was only data focusing on urine protein without considering urine occult blood, we compared the same point this time. The compliance rate regarding only urine protein had tended to decrease from 82.8% in the 2011 survey to 65.7% in the present survey [11]. The deterioration trend was due to the remarkable increase of the doctors who had referred the patients with urinary protein at least ≧3+ to nephrologists. The reason for that is not clear. But considering with the free description reply of the present survey, we speculated as follows. Along with the increase of the elderly with atherosclerosis, the number of the patients is rising who have 1+ or 2+ of proteinuria but whose kidney function decline is not so fast. When general physicians referred those patients to nephrologists, many cases, especially in the elderly, would be returned to general physicians without any useful suggestion. Therefore, there was a possibility that dissatisfaction had accumulated in both general physicians and patients, and as a result, referral timing would be delayed. But further consideration is needed to ascertain whether this speculation is correct. In this point, nephrologists also need to consider carefully. Although it is also true that there are some referral cases whom nephrologists cannot do anything, even in such cases nephrologists should find the point to be corrected in CKD total management even somewhat and provide useful advice to general physicians politely to build a better relationship of trust.

In contrast to the response to urine abnormality, referral timing of the patients with decreased kidney function tended to be earlier than the previous survey regardless of doctor's attributes. Although the doctors who referred the patients whose serum creatinine less than 2.0 mg/dL to nephrologists was only 18.8% in the 2011 survey [11], those who referred the patients by 45 mL/min /1.73m^2 of eGFR at the latest were 57.4% in the present survey. Such improvement seemed to reflect dissemination of the use of eGFR because it was difficult to evaluate precise kidney function by serum creatinine only. As for also the question about desirable medical care style after decision of treatment plan by nephrologists, most respondents wanted to see the patients of CKD stage G3b with nephrologists together (co-treatment). In CKD stage G4, there was a remarkable difference in desirable medical care style according to attributes of doctors. While 53.0% of internists wanted co-treatment with nephrologists and 43.2% of them wanted to entrust those patients to only nephrologists, among the other doctors as many as 70.3% of them wanted to entrust those patients to only nephrologists. In CKD clinical cooperation, it is also necessary to consider the patient's age. It was suggested that the doctors, who had considered patient's age at the referral to nephrologists, tended to increase. Thirty six percent of respondents had decided whether they refer the patients with low eGFR to nephrologists considering patient's age in the 2011 survey [11]. In the present survey, we asked doctors about referral timing of CKD patients by patient's age group. The doctors, who had referred CKD patients aged over 70 at lower eGFR than that of patients aged 40-69, accounted for 65.7%.

As a whole, referral timing regarding decreased eGFR has been remarkably improved, but even now 42.6% of doctors still refer those patients late. It is desired to further promote appropriate referral of the patients with decreased eGFR to nephrologists according to the clinical guideline. In the free description answers of the present survey, there were many comments that the respondents were not able to understand the significance of referral to nephrologists because kidney function in CKD patients could not be improved at all. In order to eliminate those dissatisfaction and misunderstanding, nephrologists have to continue to advocate the significance of referral to nephrologists while providing the evidence. According to the report from Taiwan, referral of the patients with CKD stages G3b or more significantly improved the annual change of eGFR (ΔeGFR) from -7.38 mL/min/1.73m^2/year to -1.02 mL/min/1.73m^2/year regardless of the presence of diabetes or hypertension [12]. Compared to conventional care, multidisciplinary care including nephrologists during pre-dialysis period conducted slow kidney function decline, low catheter usage rate at dialysis initiation, high selection rate of peritoneal dialysis, few hospitalizations due to infectious diseases, and few deaths [13].

In Hyogo prefecture, it is apparent that there are much more nephrologists in urban areas than non-urban areas. But even in urban areas, as many as 21.8% of doctors answered that they did not know of nephrologists to whom they can refer CKD patients. The compliance rate of the CKD clinical guideline regarding referral to nephrologists in cases of urine abnormality was associated with whether the doctors knew of nephrologists, but not with their area. From those results, it was considered that we should make effort to have opportunities for exchange between general physicians and nephrologists to promote clinical cooperation.

The biggest limitation of the present survey was the small number of the respondents. Although the respondents were distributed across a wide range of age groups and the number of those was proportional to the population ratio of each area in Hyogo prefecture, we were not able to deny the possibility of selection bias that the general physicians with relatively high interest in CKD had more tended to respond to this survey. Therefore, the actual compliance rate of the CKD clinical guideline was likely to be even lower than the results of the present survey, and still more, further enlightenment is required. Despite such limitation, the present survey revealed that there was a major barrier for CKD clinical cooperation in the timing of first referral to nephrologists. In addition to building scientific evidence for CKD prevention, we have to disseminate and utilize it in real clinical situation.

In conclusion, in general practice in Hyogo prefecture, it was considered that there had been a lack of awareness among the doctors towards the measurement of albuminuria in diabetic patients. It is necessary to further enlighten about the significance of the strict blood glucose control during the microalbuminuria period in diabetes. With or without diabetes, the compliance rate for the CKD clinical guideline regarding referral to nephrologists in cases of urine abnormality was as low as 33.7%. Although several reasons were speculated, it has not been clear. We have to make an effort to clarify the cause and solve it. Since the compliance rate was associated with whether the doctors knew of nephrologists to whom they could refer CKD patients, making opportunities for exchange between general physicians and nephrologists may be one of useful way in promoting appropriate referral. While, the compliance rate in cases of decreased kidney function seemed to have improved along with the spread of the use of eGFR, but it was still not enough. In CKD total management, only a part of them had been practiced by general physicians. Therefore, it is required to enable better kidney prognoses among CKD patients through the early and appropriate referral to nephrologists and the addition of necessary management.

ACKNOWLEDGEMENTS

We are very grateful to Hyogo CKD Association for discussion on the questionnaire, and Hyogo Prefecture Medical Association for helpful cooperation in sending questionnaire to all the members.

COMPLIANCE WITH ETHICAL STANDARDS

Since the present study was a questionnaire survey targeted for medical doctors, it did not involve invasion or intervention. It was performed in accordance with “Ethical guidelines for medical and health research involving human subjects (the Ministry of Education, Culture, Sports, Science and Technology / the Ministry of Health, Labour and Welfare in Japan, revised in 2017)”, “the 1964 Helsinki declaration”, and its later amendments or comparable ethical standards. All procedures performed in the present study were approved by the Institutional Review Board of Hyogo University (IRB approval number 18014).

As it was an anonymous survey, it was not possible to identify the respondent. All the survey results were processed as a group and analyzed. It was clearly stated in advance that the results of the survey would be

published in the journal, that the cooperation to this questionnaire was free willing and there was no disadvantage even if they did not answer, and that it would be considered as agreed to the survey by submission of the questionnaire.

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

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