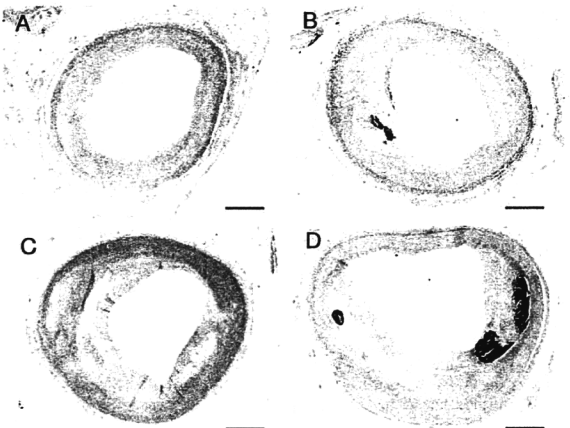

Figure 2. Typical arteries for each classification by glomerular filtration rate (GFR). (A-D) Typical light microscopic views of coronary arteries from respective cases with estimated GFRs (A) ≥60, (B) 45-59, (C) 30-44, and (D) <30 mL/min/1.73 m^2. Stenosis rates of respective arteries were (A) 36.8%, (B) 42.3%, (C) 54.2%, and (D) 58.9%. All sections were stained with hematoxylin and eosin. Scale bars = 1.0 mm.

justed mean values for coronary artery stenosis rate increased significantly with lower eGFRs (mean, 46.7% ± 1.9% [SE], 49.2% ± 1.9%, 51.9% ± 1.9%, and 53.7% ± 2.7% for eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; P for trend = 0.02).

Figure 3 shows proportions of atherosclerotic lesions using the AHA classification according to eGFR level. Prevalences of advanced atherosclerotic lesions defined as types IV-VI were 34.3% for eGFR ≥ 60 mL/min/1.73 m^2, 41.7% for eGFR of 45-59 mL/min/1.73 m^2, 52.3% for eGFR of 30-44 mL/min/1.73 m^2, and 52.8% for eGFR < 30mL/min/1.73 m^2. Individuals in the latter 2 categories had a significantly higher proportion of advanced atherosclerotic lesions on autopsy than those with eGFR ≥ 60 mL/min/1.73 m^2. The risk of advanced atherosclerosis was doubled in individuals with eGFR < 45 mL/min/1.73 m^2 compared with those with eGFR ≥ 60 mL/min/1.73 m^2 after adjustment for potential confounding factors, including age, sex, hypertension, diabetes, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, calcium-phosphorus product, hematocrit, smoking habit, and alcohol intake (Table 2).

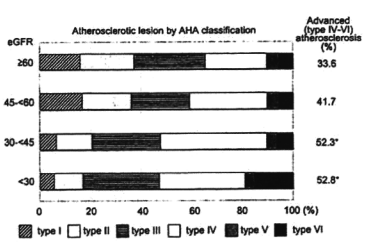

Figure 3. Proportions of atherosclerotic lesion types using American Heart Association (AHA) classification by level of kidney function. Percentages of advanced atherosclerosis (AHA types IV-VI) for each estimated glomerular filtration rate (eGFR) level is shown at the right side of the graphs. *P < 0.05 vs eGFR ≥ 60 mL/min/1.73 m^2.

Prevalence of Calcified Lesion in Coronary Artery According to Kidney Function

In a case of AHA type VI in the subgroup of eGFR < 30 mL/min/1.73 m^2, the arterial intima was thickened and associated with calcified plaque and hematoma (Fig 4).

Many coronary artery samples showed intimal calcified lesions, but there was no medial calcification in any specimen examined. Prevalences of calcified lesions were 36.5% for eGFR ≥ 60 mL/min/1.73 m^2, 37.0% for eGFR of 45-59 mL/min/1.73 m^2, 44.9% for eGFR of 30-44 mL/min/1.73

Table 2. Age- and Sex-Matched or Multivariate-Adjusted Odds Ratios for Advanced Coronary Atherosclerotic and Calcified Lesions According to Kidney Function

eGFR (mL/min/1.73 m²)	No. of Vessels Assessed	Age and Sex Adjusted[a] Matched Odds Ratio	95% Confidence Interval	P	P for Trend	Multivariate Adjusted[b] Matched Odds Ratio	95% Confidence Interval	P	P for Trend
Advanced Atherosclerosis (AHA type IV-VI)									
≥60	107	1.00	Reference		0.006	1.00	Reference		0.01
45-59	108	1.51	0.80-2.87	0.2		1.40	0.76-2.55	0.3	
30-44	107	2.22	1.11-4.43	0.02		2.02	0.99-4.15	0.05	
<30	53	2.38	1.18-4.81	0.02		3.02	1.22-7.49	0.02	
Calcified Lesion									
≥60	107	1.00	Reference		0.02	1.00	Reference		0.009
45-59	108	1.02	0.50-2.08	0.9		0.95	0.46-1.94	0.9	
30-44	107	1.43	0.71-2.89	0.3		1.43	0.69-2.95	0.3	
<30	53	2.75	1.19-6.34	0.02		4.71	1.78-12.50	0.002	

Abbreviations: AHA, American Heart Association; eGFR, estimated glomerular filtration rate.
[a]Odds ratios were adjusted for age and sex.
[b]Odds ratios were adjusted for age, sex, hypertension, diabetes, total cholesterol level, high-density lipoprotein cholesterol level, triglyceride level, calcium-phosphorus product, hematocrit, smoking habit, and alcohol intake.

m^2, and 60.4% for eGFR < 30 mL/min/1.73 m^2 (P for trend = 0.02). Lower eGFR was associated with a higher prevalence of calcified coronary artery lesions. The multivariate-adjusted OR of calcified lesions was 4.71 (95% CI, 1.78-12.50) in individuals with GFR < 30 mL/min/1.73 m^2 compared with those with GFR > 60 mL/min/1.73 m^2 (Table 2).

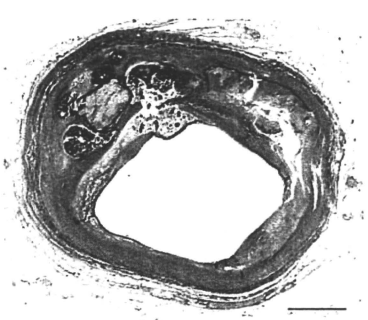

Figure 4. Typical artery of American Heart Association type VI lesion in the category glomerular filtration rate < 30 mL/min/1.73 m^2. (Masson trichrome stain; scale bar=1.0 mm.)

Association of Cardiovascular Risk Factors With Risk of Advanced Atherosclerotic Lesions and Calcified Lesions in Individuals With Decreased eGFR

Next, we assessed the relationship between the prevalence of advanced atherosclerotic lesions and cardiovascular risk factors, such as hypertension, diabetes, and dyslipidemia, in individuals with eGFR < 60 mL/min/1.73 m^2 (Table 3). The risk of advanced atherosclerotic lesions tended to be higher in individuals with hypertension than in those without hypertension (OR, 1.76; 95% CI, 0.93-3.35). Individuals with diabetes had a significantly higher risk of advanced atherosclerotic lesions (OR, 2.57; 95% CI, 1.26-5.24). Likewise, hypertension and diabetes were associated significantly with increased risk of calcified lesions in individuals with eGFR < 60 mL/min/1.73 m^2 (OR, 1.88; 95% CI, 1.04-3.39 for hypertension; OR, 2.91; 95% CI, 1.56-5.45 for diabetes).

Sensitivity Analyses Using the JSN-CKDI Equation to Estimate GFR

We also estimated GFRs using the JSN-CKDI equation.[21] The distribution of JSN-eGFR (median, 49 mL/min/1.73 m^2; Q1-Q3, 35-65) was similar to that of GFR estimated using the MDRD

Table 3. Association of Cardiovascular Risk Factors With Risk of Advanced Coronary Atherosclerotic and Calcified Lesions in Individuals With Decreased Kidney Function

	No. of Vessels Assessed	Frequency of Lesion (%)	Odds Ratio	95% Confidence Interval	*P*
Advanced Atherosclerosis (American Heart Association types IV-VI)					
Hypertension					0.08
No	71	38.0	1.00	Reference	
Yes	197	51.8	1.76	0.93-3.35	
Diabetes					0.01
No	212	43.4	1.00	Reference	
Yes	56	66.1	2.57	1.26-5.24	
Dyslipidemia					0.1
No	143	42.7	1.00	Reference	
Yes	125	54.4	1.61	0.91-2.86	
Calcified Lesion					
Hypertension					0.04
No	71	33.8	1.00	Reference	
Yes	197	48.7	1.88	1.04-3.39	
Diabetes					<0.001
No	212	40.1	1.00	Reference	
Yes	56	62.5	2.91	1.56-5.45	
Dyslipidemia					0.5
No	143	42.0	1.00	Reference	
Yes	125	48.0	1.25	0.71-2.20	

Note: Hypertension defined as blood pressure ≥ 140/90 mm Hg and/or use of antihypertensive agent. Diabetes defined as hemoglobin A_{1c} level ≥ 6.0%. Dyslipidemia defined as total cholesterol level ≥ 220 mg/dL, high-density lipoprotein cholesterol level < 40 mg/dL, and/or triglyceride level ≥ 150 mg/dL. Odds ratios adjusted for age and sex.

Study equation (median, 52 mL/min/1.73 m^2; Q1-Q3, 39-64), and these values correlated well ($r = 0.98$; $P < 0.0001$). Median (Q1-Q3) JSN-eGFR values for each category of GFR estimated using the MDRD Study equation were 77 (71-83), 54 (48-56), 36 (33-39), and 18 (15-21) mL/min/1.73 m^2 for eGFR categories ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively. Sensitivity analyses using the JSN-CKDI equation to estimate GFR made a little difference in the findings. Age- and sex-adjusted mean values for coronary artery stenosis rate increased gradually with lower JSN-eGFR levels (mean, 47.3% ± 1.9% [SE], 49.4% ± 2.1%, 51.7% ± 2.0%, and 52.3% ± 2.6% for JSN-eGFRs ≥60, 45-59, 30-44, and <30 mL/min/1.73 m^2, respectively; P for trend = 0.06). Lower JSN-eGFRs were associated significantly with higher risks of advanced atherosclerosis and calcified lesions after adjusting for age and sex (P for trend = 0.04 for both). Individuals with JSN-eGFRs < 30 mL/min/1.73 m^2 were likely to have greater risks of advanced atherosclerosis (OR, 1.80; 95% CI, 0.70-4.64) and calcified lesions (OR, 3.90; 95% CI, 1.45-10.49) than individuals with JSN-eGFR ≥ 60 mL/min/1.73 m^2 after adjusting for the mentioned confounding factors.

DISCUSSION

This study showed a clear relationship between lower kidney function and severity of coronary atherosclerosis in autopsy samples from a general population. To the best of our knowledge, this is the first histopathologic study showing the gradual progression of coronary atherosclerosis, even in individuals with moderate CKD. Additionally, cardiovascular risk factors, including hypertension, diabetes, and dyslipidemia, were associated with higher risk of advanced coronary atherosclerosis and calcified lesion in individuals with CKD. These findings imply the

importance of the management of cardiovascular risk factors before reaching an advanced stage of CKD to reduce the risk of coronary atherosclerosis.

Several authors have reported the relationship between kidney function and coronary atherosclerosis in people with advanced kidney failure. Lindner et al[26] showed that ~35% of all deaths in patients receiving hemodialysis were caused by coronary heart disease, partly confirmed by autopsy. Cross-sectional studies also showed that more than half the predialytic patients without signs and history of angina or myocardial infarction have had significant coronary artery stenosis, proved by coronary angiography.[27,28] Additionally, uremic patients are more likely to have coronary atherosclerotic lesions with plaque, medial thickness, and calcification than nonuremic patients in an autopsy-based study.[14] In the present study, the prevalence of advanced coronary atherosclerotic lesions increased gradually, even in individuals with moderate stages of CKD. These results emphasize the importance of considering kidney function status before patients reach advanced CKD in trying to reduce the burden of coronary atherosclerosis in the general population.

Several potential mechanisms can explain the association shown. Individuals with CKD often have a higher burden of traditional cardiovascular risk factors, such as aging, increased blood pressure, diabetes, and dyslipidemia.[29] Additionally, decreased eGFR may be associated with increased levels of novel cardiovascular disease risk factors, such as inflammation, oxidative stress, anemia, and abnormal calcium-phosphate metabolism.[29-31] Several experimental findings from uremic apolipoprotein E knockout mice support these results.[32-35] In the present study, the significant association between decreased GFR and severity of coronary arteriosclerosis was observed even after adjustment for all major traditional cardiovascular risk factors and some novel factors, including anemia and abnormal calcium-phosphate metabolism. However, we were unable to assess sufficiently how these other potential confounding factors influenced study findings. Further exploration clearly is needed to map risk factors for coronary atherosclerosis in individuals with CKD.

Several limitations of our study should be discussed. First, this was a cross-sectional study; therefore, it was difficult to infer causality between CKD and risk of progression of coronary atherosclerosis. However, the findings suggested strongly that individuals with CKD should be examined for progressive coronary atherosclerosis. Second, it has been well recognized that GFR estimated using the MDRD Study equation leads to a certain degree of misclassification of eGFR levels. However, this limitation is unlikely to change our conclusions because sensitivity analysis using the JSN-CKDI equation to estimate GFR did not make material differences in the findings. Third, no information was available regarding the severity or duration of hypertension and other cardiovascular disease risk factors. Furthermore, we also have no data available for medication use, such as lipid-lowering agents and phosphate binders. This limitation may reduce the experimental accuracy to some extent. Finally, this study is based on autopsy and the proportion of aged people is extremely high. Thus, these findings might not be applicable to the general living population. Nevertheless, information gained in this study contributes meaningfully toward better understanding the pathogenesis of coronary atherosclerosis in individuals with CKD.

In conclusion, decreased eGFR is associated significantly with severity of coronary atherosclerosis. The findings emphasize that individuals with CKD should be considered a high-risk population for coronary heart disease, and cardiovascular risk factors should be monitored substantially in this population to prevent the progression of coronary atherosclerosis. Further studies are needed to elucidate the precise mechanism mediating the deterioration of atherosclerotic lesions in individuals with CKD.

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Review Article

Renal outcomes in chronic kidney disease

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ABSTRACT:

The prevalence of treated patients with end-stage renal disease (ESRD) has been increasing steadily in Japan. High ESRD prevalence could be explained by multiple factors such as better survival on dialysis therapy, luxury acceptance due to insurance system to cover dialysis therapy, and 'truly' high incidence and prevalence of chronic kidney disease (CKD). The growing elderly population may also contribute to this trend. The Japanese Society of Nephrology estimated the prevalence of CKD stage 3 as 10.4%, 7.6% within the range of 50–59 mL/min per 1.73 m² in a screened population. Strong predictors of treated ESRD shown by using community-based screening programs and an ESRD registry in Okinawa are dip-stick-positive proteinuria and hypertension. Low glomerular filtration rate per se, which is often observed in the elderly population, is not a significant predictor of developing ESRD unless associated with proteinuria. CKD is common in Japan and is expected to increase, particularly in the elderly population. Benefits of proteinuria screening and automatic reporting of estimated glomerular filtration rate on the incidence of ESRD remain to be determined.

According to the annual report of the Japanese Society for Dialysis Therapy (JSDT), the prevalence of treated end-stage renal disease (ESRD) patients has been increasing for the past 20 years (Fig. 1).[1] In the population aged 75 years and over, the prevalence is more than 0.5%. The incidence of ESRD is also increasing, particularly in those aged 75 years and over (Fig. 2). The main causes of ESRD incidence are diabetes mellitus (DM), chronic glomerulonephritis and nephrosclerosis. The incidence of DM is now more than 300 per million populations in those aged 65 years and over (Fig. 3). The mean age at start of dialysis therapy is over 65 years. There is a north (low) to south (high) gradient in the incidence and prevalence of ESRD without obvious explanation.

The CKD prevalence seemed to be increasing in Japan. According to a community-based study in Hisayama, the age-adjusted prevalence of CKD stage 3 and 4 was 4.1% in 1974, 4.8% in 1988 and 8.7% in 2002 in men, and 7.3% in 1974, 11.2% in 1988 and 10.7% in 2002 in women.[2] This secular trend may be related to both genetic and environmental factors. Low birthweight, which is associated with lower nephron number, might develop DM and hypertension and therefore increase risk of ESRD.[3] However, such data is not available in Japan. Lifestyle-related factors that are often associated with obesity and metabolic syndrome may have a role in the development and progression of CKD.[4,5]

PREDICTORS OF ESRD AMONG SCREENED SUBJECTS (Table 1)

Japan has a long history of universal screening systems including urine test for proteinuria and haematuria.[6,7] It is not mandatory, however, so the fraction of people participating has been low at approximately 20–30%. We have been investigating the predictors of ESRD using two independent registries (Okinawa Dialysis Study (OKIDS) for dialysis patients and Okinawa General Health Maintenance Association (OGHMA)) for community-based screenees.[8,9] Screenees who eventually developed ESRD were confirmed by using the two registries and medical records.

Among the commonly measured variables, significant predictors of developing ESRD were dip-stick positive proteinuria and haematuria, and hypertension.[10] We have been reporting the importance of proteinuria and hypertension. Other predictors in Table 1 are also statistically significant, but the clinical significance is less than that of

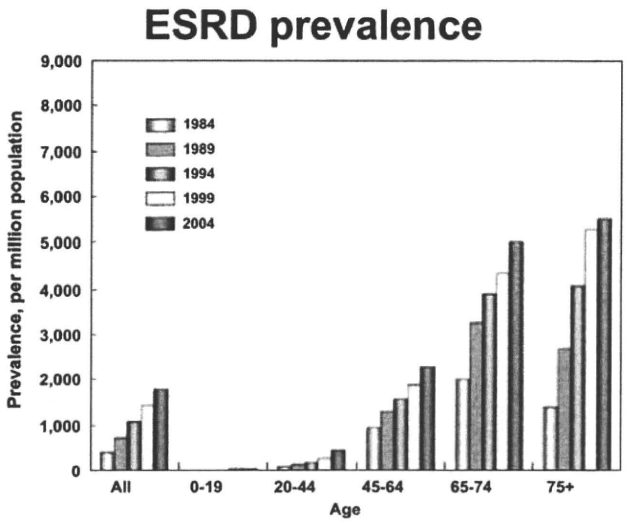

Fig. 1 Prevalence of dialysis patients in Japan. Data are cited from the Japanese Society for Dialysis Society. ESRD, end-stage renal disease.

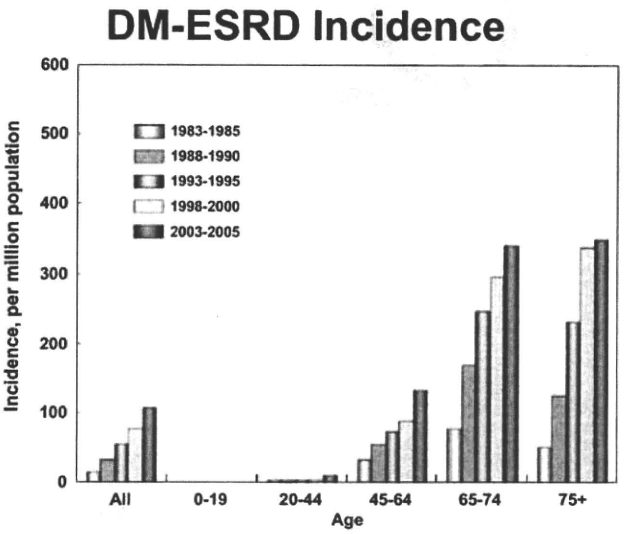

Fig. 3 Incidence of diabetes mellitus (DM) dialysis patients in Japan. Data are cited from the Japanese Society for Dialysis Society. ESRD, end-stage renal disease.

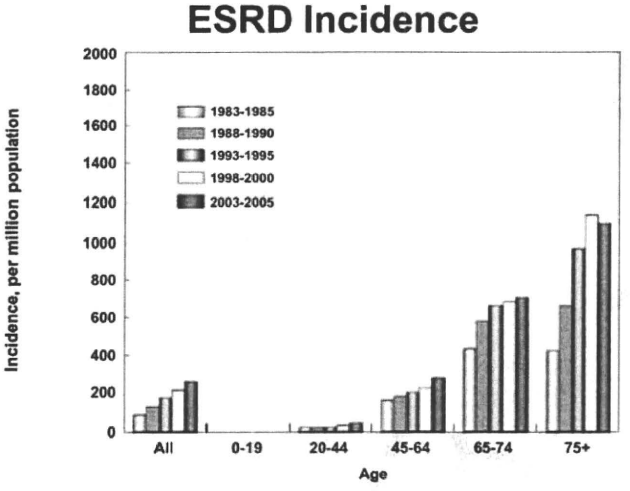

Fig. 2 Incidence of dialysis patients in Japan. Data are cited from the Japanese Society for Dialysis Society. ESRD, end-stage renal disease.

Table 1 Important predictors of end-stage renal disease

1. Proteinuria
2. Hypertension
3. Hyperglycaemia
4. Hyperuricaemia
5. Anaemia
6. Obesity
7. Metabolic syndrome
8. Low glomerular filtration rate

proteinuria and hypertension.[8–13] Effects of obesity on CKD and ESRD were complex and we observed that the decrease in body mass index was a risk factor for developing CKD[14] and ESRD.[15] Low glomerular filtration rate (GFR) per se was not significant, unless otherwise associated with proteinuria.[16] The annual incidence of ESRD was approximately 1% in those with dip-stick 3+ and over and renal biopsy recipients.

The Japanese Society of Nephrology (JSN) has estimated the prevalence of CKD stage 3 to be 10.4%, 7.6% within the range of 50–59 mL/min per 1.73 m^2, in the screened population. The annual GFR decline rate was approximately 0.36 mL/min per 1.73 m^2.[17] Among those who visited twice in 10 years, GFR declined only in the aged group, 60 years and over.[18] Other than high blood pressure and proteinuria, factors related to this age-related GFR decline were not certain. Prevalence of proteinuria, hypertension, DM, anaemia, and metabolic syndrome increased with the decline in estimated GFR (eGFR).

UNIVERSAL OR TARGETED SCREENING FOR CKD?

In April 2008, the Ministry of Health, Labour and Welfare started Tokutei-Kenshin for all residents aged 40–74 years. This strategy is to implement lifestyle modification for those diagnosed with metabolic syndrome. Initially, the urine test was set as optional, not mandatory for this program. This screening program was not originally planned to detect CKD. The cost for measuring microalbuminuria is only covered for DM patients without obvious nephropathy and the test can be repeated every 3 months. The cost is ¥1150 (>$US 10). A

cost–benefit analysis examining the frequency and extent of screening including microalbuminuria is currently under survey in Japan.

ONGOING STUDIES

Both the JSN and JSDT are working together to educate people and collecting evidence for preventing ESRD and related cardiovascular disease (CVD). The JSN has published the GFR estimation equation based on inulin clearance.[19] Using the nationwide registry, Japan Kidney Disease Registry (J-KDR), several cohort studies are underway.

Late referral to nephrologists, which is defined as dialysis started within 1 year after referral is common.[20,21] According to the 2007 annual report of the JSDT, the late referral rate was 69.3%, and that of less than 1 month was 37.7%. Such 'late referral' has a negative impact on survival after starting dialysis. Preliminary result of the JSDT supports the notion that the longer the duration of pre-haemodialysis (HD) treatment, the better the survival. The explanations of such an observation remained speculative. Differences in the control of hypertension, nutritional status and comorbid conditions identified by different nephrologists might play a role.[22] The Japan Incident Dialysis Cohort Study (J-IDCS) has been started to examine the current status of the incidence of Japanese HD patients and how they progress into ESRD.

There are two other ongoing projects in Japan. The Japanese Government (Ministry of Health and Labour) assigned CKD as a national target disease for the strategic medical research in 2007. The Japan Kidney Foundation was asked to launch the investigation: project leader, Professor K Yamagata; Frontier of Renal Outcome Modifications in Japan (FROM-J). The main objective of this research is to observe the CKD progression between two treatment strategies such as intervention A and B, and the target number of total patients is 2500. In both groups, CKD patients are treated by a general physician (Kakarituke doctor) based on the CKD practice guide of the JSN. In intervention B, patients are also followed by a registered dietician and monitored by outside personnel every month. The primary outcomes are: (i) the dropout rate; (ii) the referral rate to registered nephrologists; and (iii) progression rate of CKD to ESRD. The expected difference in the incidence in ESRD is 15% in 5 years between the two groups. This target was set using the following reports. The 2002 DM survey conducted by the Ministry of Heath, Labour and Welfare of Japan stated that only 33.3% of patients had been controlled their HbA1c less than 6.5%; that hypertension is not adequately controlled because less than 50% of subjects with hypertension are taking medications for hypertension in Ibaraki, Japan;[23] and renin angiotensin inhibitors have been used less in the area where the incidence of ESRD is high.[24] Sorensen *et al.* reported that significant decrease (15%) in DM nephropathy was achieved with aggressive management of blood pressure and glucose.[25] In this study, GFR change will also be followed using the JSN original equation.[19] The second is the chronic kidney disease-Japan cohort (CKD-JAC).[26] The natural course of CKD has not been studied in a large cohort of patients. Risk factors of CKD progression with respect to the development of CVD are not known in Japan. The study will enrol 3000 CKD patients, eGFR 10–59 mL/min per 1.73 m^2, in 18 clinical centres around Japan. Each clinical centre will enrol approximately 200 patients over 12 months and monitoring the incidence of ESRD, CVD and all-cause mortality will be determined in 4 years. The study will also examine the relationship between eGFR and quality of life. The enrolment was started in September 2007.

CONCLUSION

Japan is an emerging 'elderly' society. CKD is common in Japan and is expected to increase, particularly in the elderly population. Proteinuria and hypertension are common denominators of CVD, DM, obesity and metabolic syndrome. Further studies are necessary to determine the benefits of proteinuria screening and automatic reporting of eGFR on the incidence of ESRD. More research is needed to determine the natural course of CKD progression, particularly in the elderly population.

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● 総　論

疫学：改訂をせまられる診断基準

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要　旨

2009 年 10 月，ロンドンにて CKD 分類に関する KDIGO のコントラバシー・カンファレンスが開催された．世界中より 58 のコホート（登録数 115 万人）のメタ解析結果が示され，推算糸球体濾過量（eGFR）別の予後との関連（カットオフ値）およびアルブミン尿（および試験紙法によるタンパク尿）を診断基準に加えるべきか否かについて多くの時間が割かれた．本稿では，その議論を踏まえて CKD 分類の問題点を概説する．

はじめに

2002 年 K/DOQI（KDIGO）より推算糸球体濾過量（eGFR）による CKD 分類が提唱され，またたく間に世界中に受け入れられた．これに伴い CKD 関連の論文数も増加し，非専門医・一般医間での腎臓病に対する関心が高まっている．当初は増加し続ける透析導入患者の抑制を目指していたが，CKD は心血管障害のみならず入院，感染症，悪性腫瘍の危険因子であるとの認識，急性腎障害（AKI）まで腎臓病に対する関心が広まりつつある．

腎機能（糸球体濾過量：GFR）の正確な測定（イヌリン・クリアランス）は臨床の現場では実用的でないので，さまざまな推定式

キーワード：糸球体濾過量，タンパク尿，透析導入，心血管障害，肥満

表1　推算糸球体濾過量（eGFR）のみを用いるCKD診断に関するコメント（文献[2]より引用）

臨床家，非腎臓専門医へ推定式自体の限界について啓発が必要である．
確定した腎疾患以外では診断，スクリーニング目的では適さない（CKDの定義の問題，加齢による腎機能低下との区別が難しい）．
真のGFRが必要な例では実測（イヌリン，イオタラム酸ナトリウム，イオヘキソール）が望ましい．
世界的な血清クレアチニン測定の標準化が必要である．
病院や一般外来での血清クレアチニン測定の際，自動的（強制的？）にeGFRを報告するのは公的，専門的立場からは勧められない．

GFR：糸球体濾過量

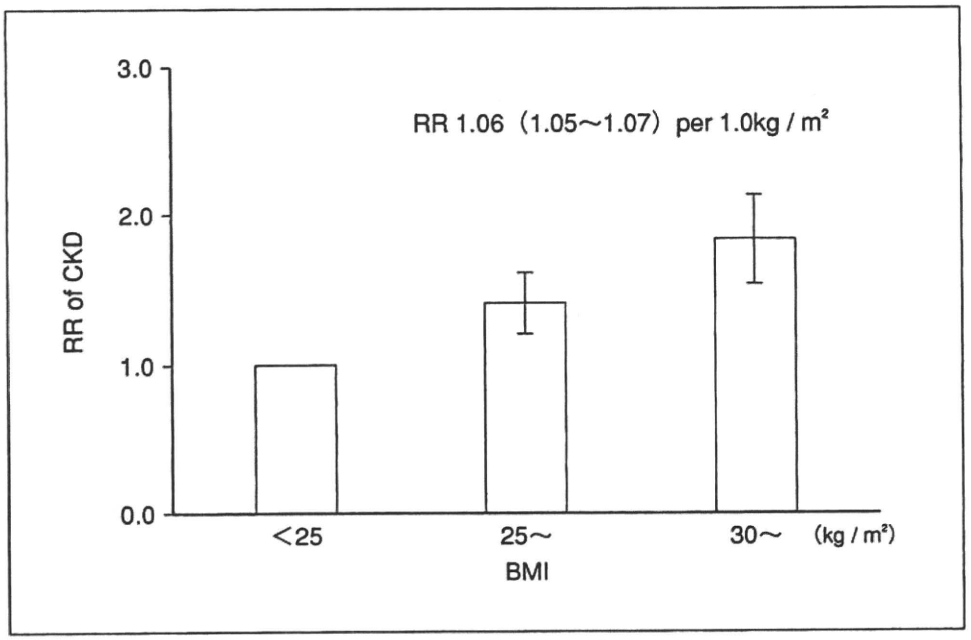
（eGFR）が提唱されている．当然，用いる推定式によってCKDの頻度は異なる．従来用いられてきたCG法はクレアチニン・クリアランスの推定式であり，誤差が大きい[1]．MDRD研究をもとに作成された式は，CKD患者集団において60 m*l* / min / 1.73 m^{2}まではかなり相関が良いが，それ以上では過小評価する．CKDステージ3（eGFR30～59）は，尿所見の異常がなくてもCKDと診断されるためにeGFRの精度が問題となる．eGFRのみで病気（disease）と診断して良いのか，単なる障害（damage）ではないのかという論争が続いている（表1）[2]．

2009年10月，ロンドンにてCKD分類に関するKDIGOのコントラバシー・カンファレンスが開催された．世界中より58のコホート（登録数115万人）のメタ解析結果が示され，特にCKDステージ3について，eGFR別の予後との関連（カットオフ値）およびアルブミン尿（および試験紙法によるタンパク尿）を診断基準に加えるべきか否かについて多くの時間が割かれた．クレアチニンを基本にしたeGFRには限界が明らかとなってきた（健常者，肥満・やせ，腎移植患者などでは適応できない）．シスタチンC値を基本にしたeGFRはより正確であるが，測定法の標準化，コスト面での問題が指摘されている．

透析患者（CKDステージ5D）について

慢性透析患者数は増加の一途をたどり，2008年度には国民450人に1人の割合を超え，人口100万人対で3,000人を超えている県も

図1　体格指数（BMI）別の CKD 発症率（文献[4]より引用）



RR：相対危険度

出現している[3]．腎機能の低下につれて心血管障害が増加することや，透析に要する治療費が医療費全体の約 4 % を占めることから，腎臓病診療は削減を迫られている．透析導入の原因疾患は 1998 年度よりそれまで首位であった慢性腎炎から糖尿病に移行した．前者が減少しつつあるのに対し，後者は直線的に増加し続けている．背景には肥満，メタボリックシンドロームの増加が考えられる．体格指数（BMI）が 1.0 kg / m² 増加するごとに CKD が 6 % 増加することが示されている（図 1）[4]．腎炎による透析導入は実数の低下に加えて，導入時の平均年齢が年々上昇しており予防対策が効を奏していると考えられる．一方，かなり進行して腎臓内科を受診し 1 年以内に透析導入となる，いわゆる手遅れ（late referral）症例も少なくない．現在，日本腎臓学会を中心に多くのコホート研究が進行中である．

透析予備軍（CKD ステージ 1 ～ 5）について

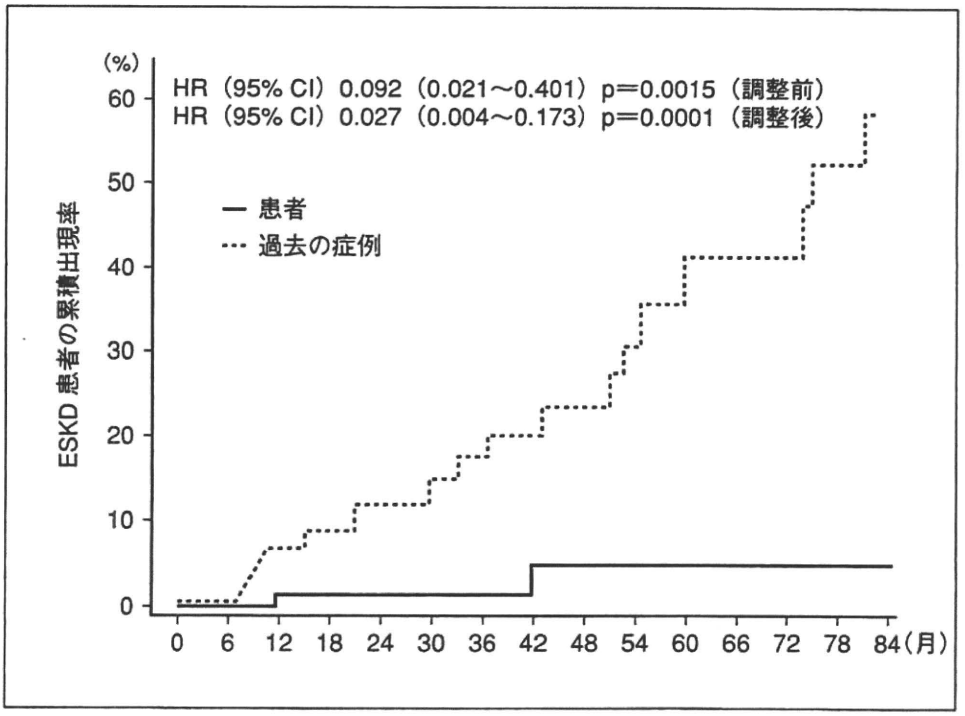
GFR が 60 ml / min / 1.73m² 未満（CKD ステージ 3 以降）の人口は，20 歳以上で全人口の約 10.6 %（約 1,130 万人），50 未満は 2.9 %（約 310 万人）で，ステージ 1 ～ 2（タンパク尿陽性者）を含めると，CKD 患者は約 1,330 万人と推測される（表 2）[5]．5 年後に透析へ移

表2 我が国の健診受診者におけるCKDの頻度（文献[5]より引用）

	総計	タンパク尿（+）	タンパク尿（−）
GFR			
90 ～	27.8 %	0.6 %	27.2 %
60 ～ 89	61.6 %	1.7 %	60.0 %
30 ～ 59	10.4 %	0.8 %	9.6 %
＜30	0.2 %	0.1 %	0.1 %
ステージ3			
50 ～ 59	7.6 %	0.4 %	7.2 %
40 ～ 49	2.3 %	0.3 %	2.0 %
30 ～ 39	0.6 %	0.1 %	0.4 %

GFR：糸球体濾過量

図2 集学的治療（レミッション・クリニック）の効果（文献[6]より引用改変）

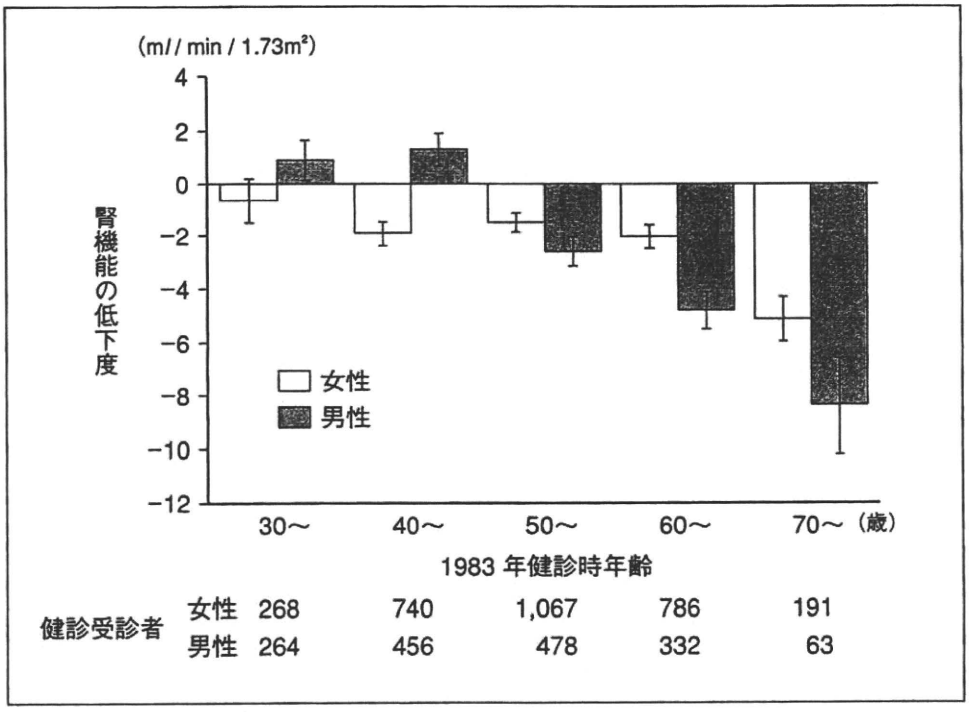


ESKD：末期腎不全，HR：ハザード比，CI：信頼区間

行する血清クレアチニン値2 mg / dl以上の頻度は，健診受診者の約0.2 % 前後（1,000人に2人）である（沖縄県総合保健協会資料）．

CKDは多くの場合，自覚症状がなく検尿異常またはGFR低下で発見され，徐々に進行し末期腎不全に進行すると考えられる．しかし，集学的治療によってかなり進行抑制が可能となってきている（図2）[6]．

図3 加齢による腎機能の低下（文献[9]より引用）



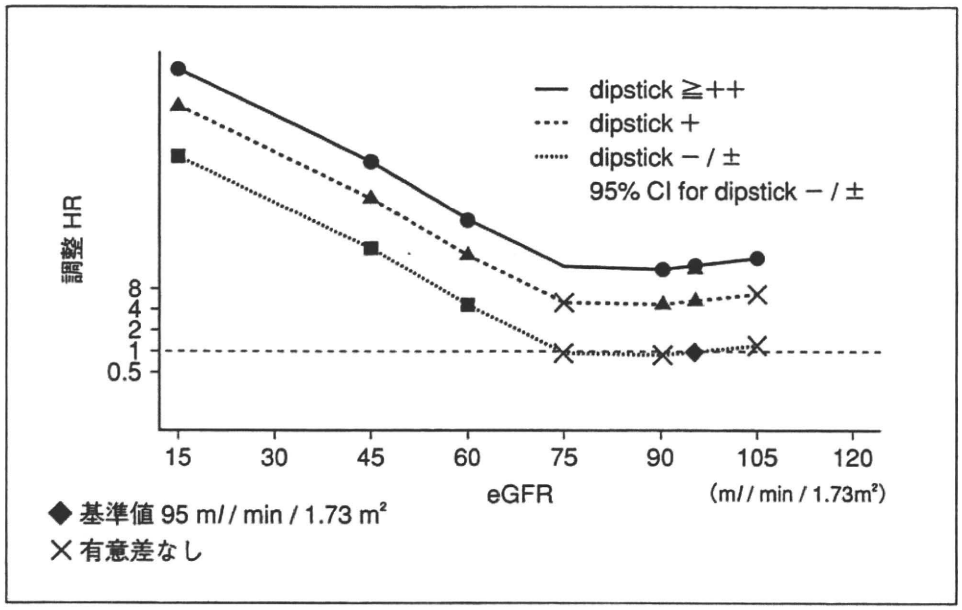
CKD のステージが進むほど，血圧や脂質のコントロールなどが難しくなるので早期に発見し，治療することが重要である．現在，我が国の CKD 患者コホートを対象に治療経過，予後に関する観察研究が行われている[7]．また，非専門医と腎臓専門医との医療連携および栄養・生活指導の介入による腎不全予防効果を検討する戦略研究も実施中である[8]．

加齢に伴い腎機能は低下するが，タンパク尿を伴わなければ透析導入が必要になるほどは低下しない（図3）[9]．eGFR＜60 は高齢者になるほど頻度が高くなるので，高齢者人口の増加に伴い CKD 患者数は増加する．実際，eGFR 50 ～ 59 ml / min / 1.73m² は約 780 万人にのぼると推測されている．しかし，進行しやすいと考えられるタンパク尿陽性者は約 42.5 万人である．KDIGO カンファレンスでのメタ解析結果では，ステージ3を前半と後半（30 ～ 44，45 ～ 59）に分けるべきだという意見が大勢を占めた．

アウトカムとの関連

透析導入の予測因子で最も鋭敏で簡便な検査法は，試験紙法による

図4 健診時のタンパク尿（試験紙法）と累積透析導入率（文献[10]より引用改変）



HR：ハザード比，eGFR：推算糸球体濾過量

検尿（タンパク尿）である．タンパク尿の程度別（マイナスから3+以上までの5段階）に透析導入の発症率をみると，タンパク尿が多いほど高くなる．KDIGO の基準にそって新たな関連図を作成した（図4）[10]．CKD のアウトカムとして末期腎不全以外に死亡（全死亡および心血管障害による死亡），腎機能低下度，AKI が考えられる．

おわりに

CKD は早期に発見すれば少なくとも透析への進行阻止が可能で，心血管障害の予防にもつながる．診断は検尿（タンパク尿），血清クレアチニンの測定（GFR の推定）により容易である．しかし，病態の変化，検査値の変動，誤差を考慮して少なくとも3ヵ月の間隔を空けて確認すべきである．日本腎臓学会の『CKD 診療ガイド』が広く利用されれば，潜在する多くの CKD 患者が早期に発見され，適切な治療を受けることが可能である[11]．「誰でも分かる」，「症状がなくても分かる」CKD の概念の普及により，早期に治療が適切になされ，透析導入率の低下，心血管障害の発症率低下につながることを期待したい[12~14]．

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Epidemiology: Need to Change ?

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特集　CKD（慢性腎臓病）の概念と対策

CKD診断における尿検査の意義

井関邦敏

キーワード　検尿　蛋白尿　血尿　スクリーニング

はじめに

日本透析医学会の調査によると2008年度末の透析患者数は28万人を超え，国民の450人に1人の割合である[1]．透析予備軍であるCKDステージ3,4は全人口の1割弱であるが，65歳以上の高齢者ではさらに頻度が高くなる．CKDでは心血管障害による死亡率が透析導入率よりも高く，社会的，医療経済的影響が大きい．WHOは，感染する疾患ではないが世界的に対策を要する非感染性疾患としてCKDを認知している．

わが国では学童検診，住民健診，老人保健法による基本健康診査などCKDの早期発見には理想的な，対象者全員の検尿（universal screening）を実施してきた．無症候性蛋白尿・血尿が診断のきっかけとなる慢性腎炎（IgA腎症）における透析導入数が減少し，透析開始時年齢が高齢化していることから，これらの施策が功を奏していると考えられる[2]．2008年4月より施行された「特定健診」においては当初，検尿が必須から選択項目へと計画されていたが，日本腎臓学会を中心とした折衝が功を奏し，検尿が必須に戻され，今日に至っている．5年後の見直しまでには「検尿の効果を検証」する責務が腎臓学会に課せられている．「蛋白尿検診」で透析患者が減少するエビデンスは今のところ存在しない．2008年4月より開始されたCKDの「戦略研究」では，かかりつけ医/非専門医と腎臓病専門医の協力を促進する目的で，慢性腎臓病患者の重症化予防のための診療システムの有用性を検討している．

Ⅰ．蛋白尿の臨床的意義

蛋白尿とは尿中に蛋白が1日に150mg以上，持続的に排泄されている状態を指す．生理的（激しい運動，発熱後，ストレス，長時間の起立など）にも尿中に蛋白が出現するが，持続的であれば腎臓から尿路の障害を示唆する．蛋白尿が多いほど生命予後が不良であることは古くより知られている．蛋白尿はGFRの低下速度を規定する因子であり，治療の最大のターゲットである．

透析導入をアウトカムとした沖縄県での疫学的研究では蛋白尿，血尿ともに陽性例（1+以上）は累積透析導入率が10年間で約3%，血尿のみ陽性（特に高齢の女性に多い）は蛋白尿・血尿共に陰性例とそれほど累積透析導入率は差異が認められなかった（図1）[3]．試験紙法による蛋白尿の程度別（−，+/−，1+，2+，3+〜の5段階）に透析導入率をみると，17年間の観察期間中の累積発症率は蛋白尿3+以上で16%，2+では約7%である[4]．蛋白尿陰性者では透析導入に至る率は10年間で100万人当たり1名程度である．高齢者に多い低GFRのみ

Role of Urinalysis on CKD Diagnosis
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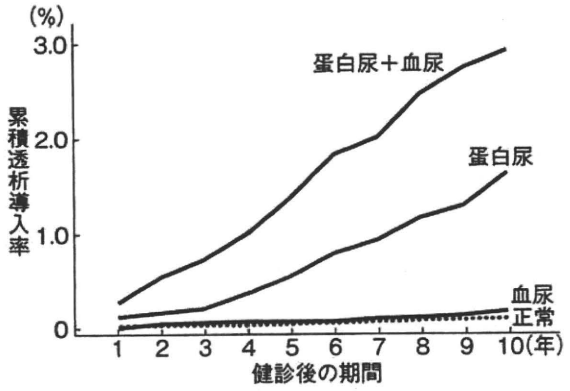

図1　住民健診時の尿所見と累積透析導入率
(Iseki K, *et al* : *Kidney Int* 1996 ; 49 : 800−805 より引用)

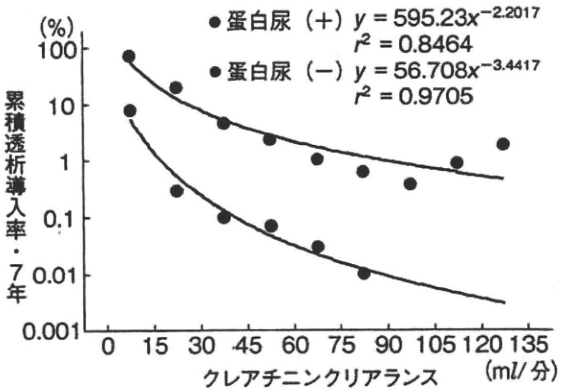

図2　住民健診時の尿所見，腎機能と累積透析導入率
(Iseki K, *et al* : *Am J Kidney Dis* 2004 ; 44 : 806-814 より引用)

では，蛋白尿を伴わない限り，透析導入に至る率は低い（図2）[5]．健診受診者においては加齢による GFR の低下は比較的軽度（＜0.4m*l*/分/1.73m²/年）であり，加齢のみで透析導入に至ることはまれと考えられる[6]．

高齢者人口の増大および肥満，糖尿病の増加に伴い，透析導入時の平均年齢が上昇している．米国では透析導入率が 75 歳以上の年齢層でのみ増加し，ほかの年齢層では低下しつつある．微量アルブミン尿の測定は保険診療で早期の糖尿病性腎症にしか認可されていない．しかし，研究目的で一般住民を対象にした調査では，微量アルブミン尿の頻度は意外に高く，65 歳以上で男女共に 10% を超え，75 歳以上では 20% 以上が微量アルブミン尿陽性であった．

Ⅱ．腎臓専門医への紹介および併診

糖尿病，高血圧，肥満者では，年に 1 回の検尿，可能なら血清クレアチニンの測定が勧められる．そのほか，原因不明の貧血，骨折，心血管障害では CKD の鑑別が必要である．日本腎臓学会の『CKD 診療ガイド』では下記の 3 項目のいずれかの場合，腎臓専門医への紹介を勧めている[7]．

① 0.5g/g クレアチニン以上または 2＋以上の蛋白尿
② eGFR 50m*l*/分/1.73m² 未満
③蛋白尿と血尿が共に陽性（1＋以上）

欧米では，コスト・ベネフィットの面からは，試験紙法による年に 1 回の成人すべてを対象にした蛋白尿検査を疑問視する報告もある[8]．しかし，蛋白尿 1＋以上ではすでにかなりの GFR 低下が存在する可能性を否定できない．微量アルブミン尿測定の保険診療を拡大すべきだという意見もある．

Ⅲ．検尿結果をどう活かすか

1．非薬物療法

最近，肥満腎症という概念が提唱されている．肥満の是正により蛋白尿が陰性化し，予後は比較的良好であるので，生活習慣の是正が勧められる．蛋白異化（筋肉量の減少）を避ける意味から，十分なカロリー摂取（30〜35kcal/kg 標準体重/日）をまず指導する．過度の蛋白質摂取は糸球体高血圧を惹起し，一時的には GFR 上昇に働くが，長期的には糸球体硬化を惹起する．高齢者では GFR の調節が十分ではないので，緩徐に改善する．絶食，脱水（急速，過度の食塩制限）を避け，蛋白制限食の際には十分なカロ

リー摂取を図る.

2. 薬物療法

降圧療法：CKDでは130/80mmHg未満を目標にRA系抑制薬を中心に血圧をコントロールする. 蛋白尿1g/日以上では, さらに125/75 mmHg未満を目標とする. この観点からすると降圧薬よりも腎保護薬という概念に近い. 糸球体濾過圧が上昇している病態（片腎, 糖尿病, 糸球体腎炎, ピューロマイシン腎症など）では, RA系抑制薬の使用によって蛋白尿の減少が認められる.

糖尿病：HbA1c 6.5% 未満を目標に血糖のコントロールを行う.

おわりに

（1）加齢によりGFRは低下するが蛋白尿を伴わなければ透析導入の可能性は低い. しかし最近, 高齢者（75歳以上）で蛋白尿を伴わない透析導入例が増加しており, 注意が必要である. 試験紙法（蛋白尿）と微量アルブミン尿測定の適応区分は明確ではない.

（2）GFR低下により貧血, 骨折, 感染症, および心血管合併症の発症率が増加する. GFRの程度, 蛋白尿の有無との関連は今後の課題である.

（3）血尿は明らかに女性に多く, 蛋白尿, 透析導入率は男性に多い. 西欧人に比し日本人（アジア人）では血尿が多く, IgA腎症が多いので検尿の意義は異なる. わが国独自のCKDスクリーニング策が必要である[9,10].

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