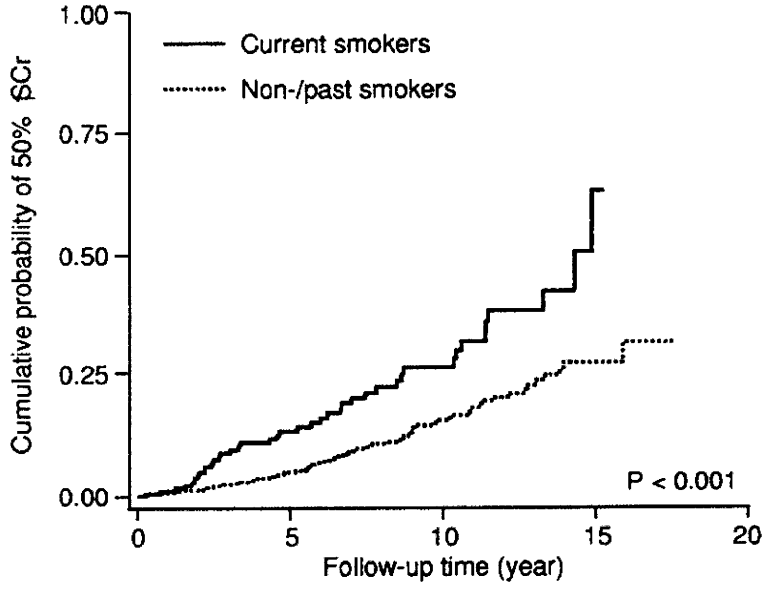

Current smokers (n = 226)

Cumulative probability	0.13	0.26	0.63
95% CI	0.09-0.20	0.19-0.35	0.39-0.86
No. at risk	108	45	4

Non-/past smokers (n = 745)

Cumulative probability	0.05	0.15	0.27
95% CI	0.04-0.07	0.12-0.19	0.21-0.34
No. at risk	410	182	32

Figure 1. Cumulative probability of primary outcome (50% increase in serum creatinine level) for non-/past and current smokers. Death before end-stage renal disease (n = 5) was regarded as censored. Abbreviation: CI, confidence interval.

201 mg/dL [interquartile range, 179-225] vs current smokers, median 211 mg/dL [interquartile range, 185-245]: $P = 0.01$). Multivariate Cox proportional hazards models adjusted for propensity score and stratified on quartiles of propensity score verified that current smokers were significantly associated with primary outcomes (HR, 2.02 [95% CI, 1.32-3.09], $P = 0.001$ in the adjustment model and HR, 2.13 [95% CI, 1.39-3.25], $P < 0.001$ in the stratification model) and also secondary outcomes (Table 4). Even after each current smoker was matched to the non-/past smoker with the closest propensity score, leading to 220 matched pairs with well-balanced clinical characteristics (Table 5), current smokers also were identified as the significant predictor of primary outcomes (HR, 2.18 [95% CI, 1.67-11.6]; $P = 0.003$) and secondary outcomes. All propensity score models confirmed a significant association between current smokers and outcomes.

After identifying smoking status as the significant predictor of outcomes, we further assessed a dose-dependent association between cigarette smoking and outcomes. Number of cigarettes per day as recorded at the time of kidney biopsy was associated significantly with primary and secondary outcomes in univariate models (Table 2) and also multivariate models (HR, 1.21 [95% CI, 1.06-1.39]; $P = 0.005$ for primary outcome; Table 6, multivariate model 1). Individuals smoking more than 20 cigarettes per day at kidney biopsy were significantly associated with outcomes, whereas current smokers reporting 20 or fewer cigarettes smoked per day were not, compared with non-/past smokers (Table 6, multivariate model 2). These results suggested that heavier smokers, especially with more than 20 cigarettes smoked per day, were at increased risk of progression of IgA nephropathy.

To assess whether smoking status was associated with progression in patients at early and advanced stages of IgA nephropathy, effect modification between smoking status and kidney function was examined. Facility-stratified multivariate models adjusted for baseline covariates (age,

Table 3. Predictors of Progression of IgA Nephropathy

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Baseline characteristics			
Age (/10 y)	1.05 (0.89-1.24)	0.85 (0.69-1.04)	0.73 (0.56-0.96)[a]
Male	0.73 (0.46-1.18)	0.80 (0.46-1.40)	0.60 (0.29-1.27)
Body mass index (/1 kg/m^2)	0.99 (0.93-1.05)	1.03 (0.96-1.11)	1.06 (0.98-1.15)
Hypertension[b]	1.42 (0.93-2.17)	1.89 (1.13-3.18)[a]	1.93 (0.93-4.01)
SCr (/0.5 mg/dL)	2.07 (1.68-2.56)[c]	2.74 (2.03-3.71)[c]	3.72 (2.45-5.65)[c]
Urinary protein (/1 g/d)	1.36 (1.21-1.52)[c]	1.38 (1.21-1.57)[c]	1.29 (1.09-1.54)[d]
Total cholesterol (/20 mg/dL)	1.08 (1.00-1.17)[a]	1.13 (1.03-1.24)[d]	1.15 (1.03-1.29)[a]
Uric acid (/1 mg/dL)	1.14 (0.98-1.33)	1.02 (0.84-1.23)	1.07 (0.83-1.37)
Current smokers[e]	2.03 (1.33-3.10)[d]	2.06 (1.24-3.43)[d]	2.73 (1.40-5.34)[d]
Therapeutic interventions within 1 year of kidney biopsy			
RAAS blockers	1.10 (0.72-1.67)	1.07 (0.64-1.79)	1.06 (0.52-2.17)
Immunosuppressants	0.59 (0.37-0.96)[a]	0.55 (0.30-1.00)[a]	0.65 (0.30-1.42)

Note: Analysis based on multivariate Cox proportional hazards models stratified on facilities; values shown are hazard ratio (95% confidence interval).

Abbreviations: ESRD, end-stage renal disease; IgA, immunoglobulin A; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

[a]$P < 0.05$.

[b]Defined as systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or any antihypertensive medication.

[c]$P < 0.001$.

[d]$P < 0.01$.

[e]Non-/past smokers were set as a reference.

sex, body mass index, hypertension, serum creatinine level, urinary protein excretion, serum total cholesterol level, and serum uric acid level) and therapeutic interventions (use of RAAS blockers and immunosuppressants) showed significant interactions between serum creatinine level and current smokers regarding primary and secondary outcomes (P values for interaction in 50% increase in serum creatinine level, a composite outcome of 100% increase in serum creatinine level and ESRD, and ESRD were <0.001, <0.001, and 0.002, respectively). We therefore classified patients into 6 categories: non-/past smokers with CKD stages 1, 2, and 3-5 and

Table 4. Association Between Current Smokers and Outcomes

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Adjustment for propensity score (n = 971)[a,b]	2.02 (1.32-3.09)[c]	2.10 (1.26-3.49)[c]	2.80 (1.43-5.48)[c]
Stratification on quartiles of propensity score (n = 971)[a]	2.13 (1.39-3.25)[d]	2.16 (1.30-3.58)[c]	2.61 (1.33-5.12)[c]
Matching by propensity score (n = 440)	2.18 (1.67-11.6)[c]	2.74 (1.71-14.6)[c]	7.00 (1.59-30.8)[e]

Note: Values shown are hazard ratio (95% confidence interval) for current smokers, with non-/past smokers set as the reference group. Analysis based on propensity score–based multivariate Cox proportional hazards models.

Abbreviations: ESRD, end-stage renal disease; SCr, serum creatinine.

[a]Adjusted for baseline characteristics (age, sex, body mass index, hypertension, SCr level, urinary protein excretion, total cholesterol level, and uric acid level) and therapeutic interventions within 1 year of kidney biopsy (renin-angiotensin-aldosterone system blockers and immunosuppressants).

[b]Stratified on facilities.

[c]$P < 0.01$.

[d]$P < 0.001$.

[e]$P < 0.05$.

Table 5. Clinical Characteristics of 220 Pairs of Non-/Past and Current Smokers Matched by Propensity Score

Smoking Status	Non-/Past Smokers (n = 220)	Current Smokers (n = 220)	P
Baseline characteristics			
Facility A	49 (22.3)	50 (22.7)	0.7
Facility B	129 (58.6)	123 (55.9)	
Facility C	42 (19.1)	47 (21.4)	
Age (y)	37 (23-50)	33 (25-48)	0.7
Men	137 (62.3)	138 (62.7)	0.8
Body mass index (kg/m^2)	22.9 ± 3.3	22.9 ± 3.6	0.9
Hypertension	88 (40.0)	83 (37.7)	0.6
SCr (mg/dL)	0.84 (0.69-1.00)	0.84 (0.70-1.00)	0.4
Urinary protein (g/d)	0.45 (0.21-0.94)	0.51 (0.22-1.14)	0.2
Total cholesterol (mg/dL)	197 ± 38	199 ± 50	0.7
Uric acid (mg/dL)	6.0 ± 1.5	5.9 ± 1.6	0.8
Therapeutic interventions within 1 year of kidney biopsy			
Use of RAAS blockers	101 (45.9)	101 (45.9)	0.9
Use of immunosuppressants	64 (29.1)	62 (28.2)	0.8
Outcomes			
50% ↑ SCr	19 (8.6)	40 (18.2)	0.002
100% ↑ SCr or ESRD	11 (5.0)	28 (12.7)	0.002
ESRD	6 (2.7)	19 (8.6)	0.002
Observational period (y)	6.2 (3.2-10.7)	5.1 (1.7-9.1)	0.02

Note: Continuous variables are expressed as mean ± standard deviation or median (interquartile range). Categorical variables are expressed as number (proportion). Conversion factors for units: SCr in mg/dL to μmol/L, ×88.4; total cholesterol in mg/dL to mmol/L, ×0.02586; uric acid in mg/dL to μmol/L, ×59.48.

Abbreviations: ESRD, end-stage renal disease; RAAS, renin-angiotensin-aldosterone system; SCr, serum creatinine.

current smokers with CKD stages 1, 2 and 3-5, and calculated their multivariate adjusted HRs for primary outcome (Fig 2). When non-/past smokers with CKD stage 1 served as reference, those with CKD stage 2 did not have a significantly increased risk (HR, 0.95 [95% CI, 0.51-1.77]; $P = 0.9$), but those with CKD stage 3 (HR, 3.32 [95% CI, 1.66-6.62]; $P = 0.001$; Fig

Table 6. Dose-Dependent Associations Between Number of Cigarettes Smoked Per Day at Time of Kidney Biopsy and Outcomes

Outcomes	50% ↑ SCr	100% ↑ SCr or ESRD	ESRD
Multivariate model 1			
No. of cigarettes (/10/d)[a]	1.21 (1.06-1.39)[b]	1.29 (1.09-1.53)[b]	1.37 (1.10-1.70)[b]
Multivariate model 2			
Current smoking level			
1-20 cigarettes/d[a]	1.55 (0.91-2.62)	1.41 (0.73-2.71)	1.83 (0.79-4.21)
≥21 cigarettes/d[a]	3.00 (1.68-5.35)[c]	3.89 (1.96-7.73)[c]	5.50 (2.20-13.7)[c]

Note: Analysis based on multivariate Cox proportional hazards models; values shown are hazard ratio (95% confidence interval). Model 1 and 2 are based on data from 954 patients because of the missing number of cigarettes per day at kidney biopsy in 17 current smokers, adjusted for baseline characteristics (age, sex, body mass index, hypertension, SCr level, urinary protein excretion, total cholesterol level, and uric acid level) and therapeutic interventions within 1 year of kidney biopsy (renin-angiotensin-aldosterone system blockers and immunosuppressants) and stratified on facilities.

Abbreviations: ESRD, end-stage renal disease; SCr, serum creatinine.

[a]Non-/past smokers were set as the reference group.

[b]$P < 0.01$.

[c]$P < 0.001$.

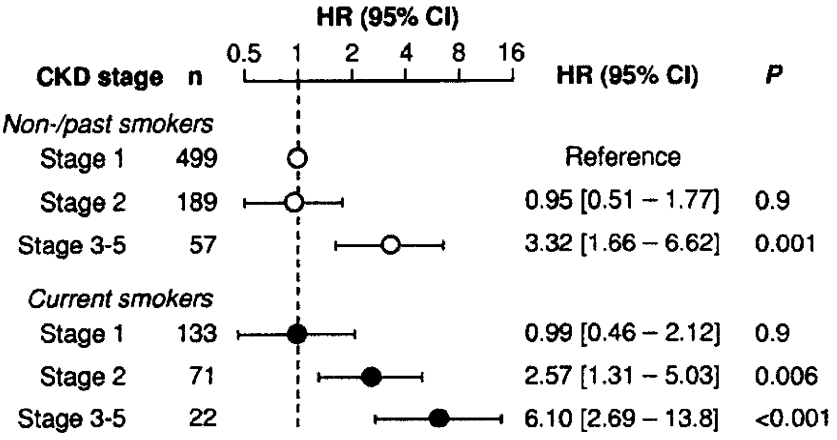

Figure 2. Effect modification between smoking status and chronic kidney disease (CKD) stages at kidney biopsy. Hazard ratio (HR) for each category for primary outcome was calculated in a facility-stratified multivariate Cox proportional hazards model adjusted for baseline clinical characteristics (age, sex, body mass index, hypertension, urinary protein excretion, total cholesterol level, and uric acid level) and therapeutic interventions (renin-angiotensin-aldosterone system blockers and immunosuppressants). Abbreviation: CI, confidence interval.

2) did. On the contrary, current smokers even with CKD stage 2 were significantly vulnerable to progression (HR, 2.57 [95% CI, 1.31-5.03]; $P = 0.006$), along with those with CKD stages 3-5 (HR, 6.10 [95% CI, 2.69-13.8]; $P < 0.001$).

DISCUSSION

We found that cigarette smoking was a dose-dependent predictor of progression of IgA nephropathy, even after adjusting for conventional risk factors (impaired kidney function, proteinuria, and hypertension) and metabolic atherosclerotic factors (hypercholesterolemia and hyperuricemia) using different propensity score–based methods. Significant effect modification between serum creatinine level and smoking status at kidney biopsy interestingly showed that patients with decreased kidney function at kidney biopsy were more vulnerable to cigarette smoking. Advantages of the present study are an etiologically homogenous cohort with substantially younger age and higher proportion of patients with impaired kidney function in contrast to previous community-based studies,[24-33] larger sample size than those in previous cohort studies of IgA nephropathy,[4-19] and robust results based on multiple kidney outcomes (50% increase in serum creatinine level, a composite outcome of 100% increase in serum creatinine level or ESRD, and ESRD) in different propensity score–based models controlling for significant differences in clinical characteristics between non-/past smokers and current smokers (Table 4).

Along with smoking status at kidney biopsy, the present study clarified that number of cigarettes smoked at the time of diagnosis using kidney biopsy was a significant predictor of progression of IgA nephropathy. Few studies of primary kidney diseases have found a dose-dependent association between progression and cigarette smoking in a multivariate model. Even in community-based large-scale cohort studies, their dose-dependent association was identified in only 2 studies based on the cohorts of the Cardiovascular Health Study, which enrolled elderly participants aged at least 65 years,[24] and the Second National Health and Nutrition Examination Survey (NHANES II), including entirely middle-aged participants (aged 49.3 ± 13.3 years).[27] Results of the present study were compatible with those of NHANES II, which showed that current smokers reporting more than 20 cigarettes per day were at significantly higher risk of ESRD or CKD-associated death compared with nonsmokers. Our findings extend the dose-dependent nephrotoxic effect of cigarette smoking, especially more than 20 cigarettes per day, to younger patients with IgA nephropathy. Smoking cessation should be recognized as one of

the potential treatment modalities of IgA nephropathy.

The present study also showed an interesting interaction between baseline serum creatinine level and current smokers, suggesting that the nephrotoxic effect of cigarette smoking was enhanced in patients with decreased kidney function. Although the precise mechanism of a nephrotoxic effect of cigarette smoking is unsolved, one of the biologically plausible hypotheses is oxidative stress, which may be the reason that patients with IgA nephropathy with impaired kidney function were substantially vulnerable to cigarette smoking. Oxidative stress is already increased at early stages of CKD because of enhanced production of oxidants and a compromise in the antioxidant mechanism.[44] and oxidative stress may have an important role in the progression of CKD. A French cohort study of 120 patients with IgA nephropathy showed that increased serum levels of advanced oxidation protein products, a relevant marker of oxidative stress, proved a potential renal prognostic factor.[45] Long-term smoking can result in depletion of antioxidants, leading to a systemic imbalance between oxidants and antioxidants.[46] Consequently, current smokers with impaired kidney function might easily expose themselves to endogenous and exogenous (smoke-derived) oxidants and induce a remarkably increased risk of progression of IgA nephropathy in a dose-dependent manner.

Our study has several limitations. First, smoking status only at diagnosis was assessed. It was uncertain whether current smokers at diagnosis kept smoking during the entire follow-up period. Second, smoking status was based on a questionnaire filled in at admission for kidney biopsy. Smoking status was not validated using biochemical tests, such as measurements of cotinine and carbon monoxide. Self-reported smoking status might be biased. Third, lack of calibration of serum creatinine levels between facilities might lead to biased results. Fourth, although all patients were given a diagnosis of IgA nephropathy using kidney biopsy, histologic findings were not included as covariates of interest in the present study, partly because each facility used a different histologic grading system and changed its grading system during 14 years of the entry period between 1992 and 2005. Another critical reason was that a large number of specimens stained with periodic acid–Schiff or other methods became too pale for histopathologic reevaluation. Fifth, eGFR was relatively inaccurate in the present study because most patients had CKD stages 1 and 2, based on eGFR. Because a recent study of 255 kidney donors with mainly CKD stages 1 and 2 showed a moderately positive correlation between iohexol-measured GFR and eGFR ($R^2 = 0.41$),[47] distribution of "real" GFR of patients with eGFR-based CKD stage decreased as eGFR-based CKD stage advanced, even CKD stages 1 and 2.

In conclusion, our long-term retrospective cohort study of approximately 1,000 patients with IgA nephropathy showed that cigarette smoking was one of the key predictors of progression of IgA nephropathy in a dose-dependent manner. The deleterious impact of cigarette smoking was likely to be enhanced as IgA nephropathy progressed. Thus, smoking cessation should be considered as one of the potential treatment modalities to suppress further progression at an advanced stage of IgA nephropathy and also prevent future progression at an earlier stage.

ACKNOWLEDGEMENTS

Aspects of this report were contained in a poster presentation at the 40th Annual Meeting of the American Society of Nephrology, San Francisco, CA, on November 4, 2007.

We are grateful for the time and efforts of nephrologists who managed STOP-IgAN: Dr Yoshiyuki Furumatsu, Dr Kenichiro Iio, Dr Takahito Ito, Dr Harumi Kitamura, Dr Isao Matsui, Dr Satoshi Mikami, Dr Chigure Suzuki, and Dr Yoshitsugu Takabatake (Osaka University Graduate School of Medcine); Dr Daisuke Hayashi and Dr Akihiro Shimomura (Osaka General Medical Center); Dr Tomoko Namba, Dr Kanaki Sakai, Dr Ken Takahara, Dr Atsushi Takahashi, and Dr Masanori Takeji (Osaka Rosai Hopital); and many members of the Osaka Collaborative Research Group of Kidney Disease (OCKD).

Support: This study was supported by Young Scientist B grants-in-aid (18790563 and 21790809) and a grant from the Osaka Kidney Foundation (OKF 09-0004).

Financial Disclosure: The authors declare that they have no relevant financial interests.

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Qual Life Res
DOI 10.1007/s11136-010-9763-9

Presenteeism in college students: reliability and validity of the Presenteeism Scale for Students

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Accepted: 27 September 2010

Abstract
Objective Presenteeism is the impaired work performance due to health problems. We aimed to develop a Presenteeism Scale for Students (PSS), and to reveal the existence of presenteeism among students.
Methods Students ($n = 5{,}701$) in 4 national universities in Japan were recruited via the school-based health examination. Moreover, 122 students participated in a 2-week interval test–retest to examine the reliability and criterion-related validity of the PSS.
Results Of the students, 59.2% indicated some health problems. Allergy was most prevalent health problems, affecting 35.7% of the whole students. Students with emotional problems had higher degree of presenteeism than those with the other problems. The Cronbach's α of the work impairment score of the PSS was 0.90. The Spearman's coefficient for the test–retest score was 0.80 ($P < 0.001$). Regarding criterion-related validity, Spearman's coefficient between the work impairment score of the PSS and summary score of the SF-36 was -0.60 ($P < 0.001$).
Conclusions These findings suggest that the PSS can be expected to be useful for assessment of students with presenteeism. Furthermore, we found that the majority of students have some health problems, and proposed that the issue of presenteeism on campus should be addressed.

Keywords Presenteeism Scale for Students (PSS) · Presenteeism · Absenteeism · Campus health · Health problems

Abbreviations

PSS	Presenteeism Scale for Students
SF-36	Medical Outcomes Study 36-Item Health Survey
PHC	Primary health condition
WIS	Work impairment score
WOS	Work output score
HA	Hours of absenteeism

Introduction

Presenteeism, defined as a self-rated measurable loss of work performance due to health problems in the workplace,

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Published online: 14 October 2010

contributes to economic costs through loss in productivity [1, 2]. Presenteeism is coinage contrary to absenteeism, and the impact of presenteeism in the field of occupational health has been discussed. Presenteeism among workers has been associated not only with the economic cost of lost productivity in an enterprise but also with an individual's health, deterioration of quality of life (attention-concentration problems, mood disturbances, or fatigue), and increased medical costs [3–5].

The number of college students who visit academic healthcare centers because of both physical and psychiatric illness has increased recently. It can be considered that many of these students have been frustrated with academic life. This behavior can be interpreted as presenteeism in school. Although the negative impact of absenteeism from the classroom on academic achievement can be easily understood, no study has been done to reveal the effect of presenteeism on academic performance. If students' mental and physical illnesses are left untreated in the early stage, these conditions will become aggravated, leading to the need for long-term medical treatment [6]. Recognition of a student's health condition in the early stage might be crucial to decrease the risk of further morbidity. Hence, more attention should be given to the issue of presenteeism in school and a credible measurement of presenteeism for students should be developed.

Assessment of presenteeism has been made by means of self-reported scales, the most often used being the Work Limitations Questionnaire developed by Lerner et al. [7], Work Productivity and Activity Impairment questionnaire, general health version, constructed by Reilly et al. [8], and the Stanford Presenteeism Scale (SPS) established by Koopman et al. in the United States [9, 10]. In Japan, only one document has examined the applicability of the SPS translated into Japanese, reporting good reliability and validity in workers [11]. However, a questionnaire on presenteeism for students has not been developed even though the generalizability of the issue of presenteeism among non-workers is important.

In this study, we aimed to develop a Presenteeism Scale for Students (PSS) and to examine its reliability and criterion-related validity. In addition to assessing the PSS, we examined the extent of presenteeism among students.

Methods

Procedure

This study was carried out at 4 universities that cooperated within the framework of the National University Council of Health Administration Facilities. These universities had different characteristics. Geographically, Akita University is located in the northeast area of Japan and is hit by heavy snowfall during the winter. Osaka University is located in the metropolitan area of Japan, and has the largest number of students among Japanese national universities. Fukuoka University of Education had been founded as a teacher-training institution, which is located in Kyushu Island. Finally, Nara Woman's University is located in Nara Prefecture, and had taken on a historic role of fostering women teachers.

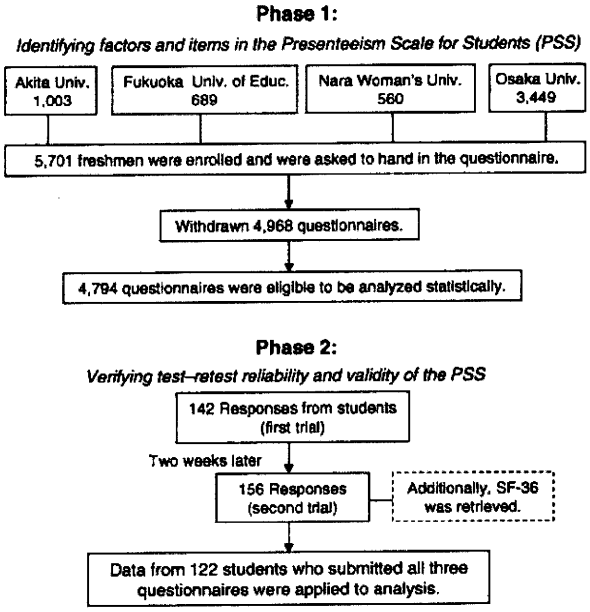

Fig. 1 Flowchart of the two phases in the present study

This study consisted of two phases (Fig. 1). For the first phase, in April 2008, staff of 4 health administration centers distributed the packaged questionnaire to all first-year students in each of the 4 universities. This package, which was collected at the school-based health examination, not only included a survey on presenteeism, but also a questionnaire on mental health and eating behavior. Findings on the latter issues will be reported separately. The rate of data collection was 87.1%.

In phase 2, test–retest reliability of the PSS was determined in students of Osaka University in 2008 November at a 2-week interval. The questionnaire in the second survey (retest) also included the Medical Outcomes Study 36-Item Health Survey (SF-36) to test criterion-related validity of the PSS.

Informed consent was obtained from participants after we provided them with a written explanation of the aims of this study. This study protocol was approved by the Ethics Committee of the Osaka University Health Care Center.

Participants

We recovered 4,968 questionnaires from the 4 universities. Eligible for data analysis were 4,794 college students (valid response rate: 96.5%). The average age of responders was 18.56 years (SD = 1.82), and 2,774 students (58.2%) were male (female, 1,990; unknown, 30). The participants in phase 2 were those who attended a class that was part of a university course and were recruited through an announcement. Participating in the test of reliability and validity of the PSS were 122 students.

Measures

Presenteeism

The 13-item Stanford Presenteeism Scale (SPS) was designed as a measure of lost productivity derived from being at work with a specific health condition over the previous 4 weeks [10]. Based on the established SPS, Yamashita and Arakida developed a Japanese version of the SPS [11]. In the present study, amending the instrument for the intended subjects was taken into consideration. Therefore, we modified two points in the Japanese version of the SPS to adapt this questionnaire to our purpose. Firstly, the word "work" in the Japanese version of the SPS was changed to "academic" to apply to the health of students. Secondly, we added three health problems that had been observed characteristically in the Osaka University Health Care Center to the list of health conditions in the Japanese version of the SPS to make this list more specific to students. These problems were "menstrual pain or irregular menstruation", "injury of limb" and "eating disorder". With respect to modifying the SPS, we obtained permission from Merck & Co., Inc., which holds the copyright of the original SPS.

The PSS is composed of the following 4 modules: (1) list of health conditions with yes/no responses as to whether the student has or has had a particular condition within the past month and the request to select a single primary health condition (PHC) from that list that most influenced the student's functioning; (2) degree of presenteeism due to the PHC [work impairment score (WIS)]; (3) effect of the PHC on work output [work output score (WOS)]; and (4) hours of absenteeism (HA) due to the PHC.

(1) The list of health conditions includes 16 conditions that might have affected the student's health/disability status in the past 1 month (allergies, arthritis or joint pain/stiffness, injury of limb, asthma, back or neck pain, breathing disorder (bronchitis, emphysema), depression/anxiety or emotional disorder, insomnia, diabetes, menstrual pain or irregular menstruation, disturbance of liver function, heart or circulatory problem (artery disease, high blood pressure, angina), migraines/chronic headaches, stomach or bowel disorder, eating disorder, and other). The respondent indicates whether these conditions occurred by "yes" or "no." Then, the respondent is asked to choose from the list the one condition (PHC) that most affected him or her. Respondents who did not indicate the presence of any of these health conditions did not have to complete the other 3 modules comprising the PSS.

(2) The WIS is assessed with the question: "In the past 4 weeks, how often has your primary health condition (PHC) affected your academic work?" and 10 items that determine the degree of presenteeism due to the PHC. Responses are on a 5-point Likert scale (from 'always' to 'never'), which are shown in Table 2. The raw score of the WIS is converted to a 100-point scale; the higher the score, the more serious is the degree of presenteeism. Factor analysis of the original [10] and Japanese versions of the SPS [11] found two underlying factors, which were designated as 'completing work' and 'avoiding distraction.'

(3) The WOS, which is a single visual analog scale, is an index of the magnitude of the effect of the PHC on performance. We asked the following question: "Given your primary health condition, what percentage of your usual productivity level were you able to achieve academically over the last 4 weeks?" The respondents were required to indicate what point on the scale best described their feelings. This item is scored ranging from 0% (incapable) to 100% (capable) scale.

(4) To determine the HA, respondents were asked "Because of your primary condition, how many academic hours (and/or work hours) did you miss in the past 4 weeks?" Subjects selected the number of hours from 0 to 40 on a straight line with reference anchors of '0 h' on the left side and 'over 40 h' on the right. Each unit on the scale represents 1 h.

Quality of life

The Japanese language version of the Medical Outcomes Study 36-Item Health Survey (SF-36) [12, 13] was used to address the relationships between presenteeism and the quality of life. The SF-36 is a self-report scale about the quality of life and is composed of the following 8 subscales: Physical Functioning, Role Physical, Bodily Pain, General Health Perception, Vitality, Social Functioning, Role Emotional, and Mental Health. The Japanese language version asks additional questions for comparisons of

the quality of life with that of the previous year. The summary score for the SF-36 ranges from 0 to 100, with a higher score reflecting a more favorable quality of life. The internal consistency of this scale in the present study was excellent (Cronbach's $\alpha = 0.89$).

Statistical analysis

Demographic data on the health conditions were expressed as frequency. The χ^2 test was used to test gender differences in health status. In factorial analysis, the Principal factor method and Promax rotation with Kaiser Normalization were performed to confirm the underlying factorial structure. A greater than 0.35 factor loading was considered as sufficient. Internal consistency of the PSS was determined by computing Cronbach's α. Regarding test–retest methods, the stability of the PSS between the first and second assessments was appraised using Spearman's ranked sign correlation (ρ) and the intra-class correlation coefficient ($ICC_{(1,x)}$). To examine the criterion-related validity of the PSS, we used Spearman's ranked sign correlation analysis. When we conducted between-group comparisons, non-parametric Mann–Whitney tests were conducted to evaluate the relationship between presenteeism and the type of health problem.

All statistical tests were performed using SPSS ver.15.0 for Windows and we considered $P < 0.05$ as significant (two-tailed).

Results

Prevalence of health conditions

Table 1 shows data on health conditions listed on the first module of the PSS according to gender. Health conditions selected in order of prevalence were allergy (35.7%), back or neck pain (21.0%), menstrual pain or irregular menstruation (19.9%), migraines or chronic headaches (9.7%), stomach or bowel disorder (9.5%), and depression, anxiety or emotional disorder (8.7%). As to gender difference, 'back or neck pain', 'depression, anxiety or emotional disorder', 'migraines or chronic headaches', and 'stomach or bowel disorder' were more frequent in female students than in male students at the 1% significance level. Only 1,943 students (40.8%) were symptom free for the period analyzed.

WIS was significantly correlated with WOS ($\rho = -0.71$, $P < 0.001$) and HA ($\rho = 0.54$, $P < 0.001$).

Factorial validity

Results of our factor analysis to confirm the factorial structure of the PSS are shown in Table 2. Two factors were extracted, and they explained 54.3% of the total variance. The value for the Kaiser–Meyer–Olkin measurement of sampling adequacy was 0.85. There was no item with a factor loading value of 0.35 or above across the two factors. The internal consistency (Cronbach's α) of each factor was 0.88 (factor I, $P < 0.001$) and 0.81 (factor II, $P < 0.001$), respectively, which were satisfactory values. According to previous studies [10, 11], we labeled the first factor as 'Completing work' and the second factor as 'Avoiding distraction.' All of the items correlated with the score of WIS, ranging from 0.57 to 0.80 ($P < 0.01$ in all cases).

Test–retest reliability and concurrent validity

Regarding test–retest reliability, we estimated Spearman's correlation coefficients and the intra-class correlation coefficient (ICC). Spearman's correlation coefficient for WIS was 0.80 ($P < 0.001$), suggesting a substantial level of reliability. The value of $ICC_{(1, 2)}$ of WIS between the first and second assessment was 0.88 (95% CI, $P < 0.001$), indicating excellent stability. For WOS, the ρ and $ICC_{(1, 2)}$ values were 0.77 ($P < 0.001$) and 0.83 (95% CI, $P < 0.001$), respectively. For HA, ρ and $ICC_{(1, 2)}$ values were 0.78 ($P < 0.001$) and 0.88 (95% CI, $P < 0.001$), respectively.

Correlation coefficients between the variables in the PSS and each score on the SF-36 are shown in Table 3. The results revealed that students who experience presenteeism have a low quality of life.

Gender differences in the work impairment score, work output score, and hours of absenteeism

The mean scores of the WIS, WOS and HA of PSS are shown in Table 4. There were significant gender differences in results for the WIS, WOS and HA. Female students had higher values for the WIS and HA compared to male students. Also, concerning the WOS, female students had a weaker work performance than males.

Comparison of the work impairment score by health status

To more closely examine the distribution of the score of the WIS, we drafted box and whisker plots of WIS (Fig. 2). Each box has a horizontal line, placed either at the median value, in the lower quartile (25th percentile) or in the upper quartile (75th percentile). The ends of the whiskers represent the minimum and maximum values. Categories for which there were too few samples for statistical comparisons were removed ($n < 20$). The highest value of WIS was given to 'Depression, anxiety or emotional disorder'.

Table 1 Prevalent health condition according to gender

	Akita Univ.		Fukuoka Univ. of Educ.		Nara Woman's Univ.	Osaka Univ.		Total			
	Male (%)	Female (%)	Male (%)	Female (%)	Female (%)	Male (%)	Female (%)	Male (%)	Female (%)	*P*	
Number of valid responses	548	292	65	175	457	2,150	1,065	2,763	1,989		4,752
Allergies	163 (29.7)	67 (22.9)	20 (30.8)	53 (30.3)	158 (34.6)	817 (38.0)	417 (39.2)	1,000 (36.2)	695 (34.9)	0.375	1,695 (35.7)
Arthritis or joint pain/stiffness	22 (4.0)	6 (2.1)	3 (4.6)	5 (2.9)	13 (2.8)	66 (3.1)	21 (2.0)	91 (3.3)	45 (2.3)	0.035*	136 (2.9)
Injury of limb	17 (3.1)	4 (1.4)	2 (3.1)	6 (3.4)	8 (1.8)	47 (2.2)	13 (1.2)	66 (2.4)	31 (1.6)	0.046*	97 (2.0)
Asthma	11 (2.0)	4 (1.4)	1 (1.5)	7 (4.0)	1 (2.4)1	52 (2.4)	2 (2.0)1	64 (2.3)	43 (2.2)	0.723	107 (2.3)
Back or neck pain	59 (10.8)	70 (24.0)	7 (10.8)	60 (34.3)	122 (26.7)	341 (15.9)	337 (31.6)	407 (14.7)	589 (29.6)	<0.001**	996 (21.0)
Breathing disorder (bronchitis or emphysema)	1 (0.2)	3 (1.0)	0 (0.0)	5 (2.9)	1 (0.2)	27 (1.3)	12 (1.1)	28 (1.0)	21 (1.1)	0.886	49 (1.0)
Depression, anxiety or emotional disorder	51 (9.3)	34 (11.6)	3 (4.6)	13 (7.4)	38 (8.3)	153 (7.1)	122 (11.5)	207 (7.5)	207 (10.4)	<0.001**	414 (8.7)
Insomnia	20 (3.6)	6 (2.1)	0 (0.0)	11 (6.3)	8 (1.8)	85 (4.0)	38 (3.6)	105 (3.8)	63 (3.2)	0.244	168 (3.5)
Diabetes	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	1 (0.2)	18 (0.8)	5 (0.5)	18 (0.7)	9 (0.5)	0.368	27 (0.6)
Menstrual pain or irregular menstruation		50 (17.1)		44 (25.1)	76 (16.6)		226 (21.2)		396 (19.9)		396 (19.9)
Disturbance of liver function	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.7)	0 (0.0)	16 (0.7)	3 (0.3)	16 (0.6)	6 (0.3)	0.165	22 (0.5)
Heart or circulatory problem (artery disease, high blood pressure, angina)	2 (0.4)	1 (0.3)	0 (0.0)	3 (1.7)	1 (0.2)	35 (1.6)	8 (0.8)	37 (1.3)	13 (0.7)	0.022*	50 (1.1)
Migraines or chronic headaches	31 (5.7)	38 (13.0)	4 (6.2)	18 (10.3)	48 (10.5)	156 (7.3)	166 (15.6)	191 (6.9)	270 (13.6)	<0.001**	461 (9.7)
Stomach or bowel disorder	32 (5.8)	36 (12.3)	5 (7.7)	18 (10.3)	54 (11.8)	134 (6.2)	173 (16.2)	171 (6.2)	281 (14.1)	<0.001**	452 (9.5)
Eating disorder	3 (0.5)	7 (2.4)	2 (3.1)	5 (2.9)	6 (1.3)	32 (1.5)	27 (2.5)	37 (1.3)	45 (2.3)	0.016*	82 (1.7)
Other	9 (1.6)	8 (2.7)	1 (1.5)	8 (4.6)	7 (1.5)	56 (2.6)	19 (1.8)	66 (2.4)	42 (2.1)	0.527	108 (2.3)

Responses with missing values were excluded. The answer from allowed multiple answers

* $P < 0.05$

** $P < 0.01$

Table 2 Factor analysis on work impairment score items of Presenteeism Scale for Students

Work impairment score item		I. Completing work	II. Avoiding distraction
3	Were you able to focus on achieving academic (work) goals?	0.836	0.006
1	Were you able to finish hard academics (work)?	0.747	−0.023
7	Were you able to focus on finding a solution when unexpected problems arose in your academics (work)?	0.730	0.065
4	Did you feel energetic enough to complete your academics (work)?	0.728	0.122
9	Were you able to complete academic work with other people on shared tasks?	0.631	0.043
5	Were the stresses of your academics (job) hard to handle?	−0.054	0.882
8	Did you need to take breaks from your academics (work)?	0.105	0.543
10	Were you tired because you lost sleep?	−0.012	0.523
6	Did you feel hopeless about finishing your academics (work)?	0.317	0.508
2	Did you find your attention wandering?	0.277	0.452
Cronbach's alpha		0.88	0.81
Cumulative contribution		50.3	54.3

Values show factor loading

Table 3 Spearman's correlation coefficients between WIS, WOS, HA and SF-36

	SF-36 subscores								
	Physical functioning	Role physical	Bodily pain	General health perception	Vitality	Social functioning	Role emotion	Mental health	Summary score
WIS									
ρ	−0.32*	−0.48**	−0.41**	−0.51**	−0.37**	−0.43**	−0.40**	−0.36**	−0.60**
P	0.012	<0.001	<0.001	<0.001	0.004	<0.001	0.001	0.005	<0.001
WOS									
ρ	0.31*	0.51**	0.37**	0.49**	0.50**	0.41**	0.34**	0.35**	0.60**
P	0.015	<0.001	0.003	<0.001	<0.001	<0.001	0.006	0.005	<0.001
HA									
ρ	−0.18	−0.33**	−0.20	−0.45**	−0.32*	−0.16	−0.16	−0.25*	−0.39**
P	0.177	0.008	0.120	<0.001	0.012	0.222	0.210	0.049	0.002

WIS work impairment score, *WOS* work output score, *HA* hours of absenteeism, *SF-36* Medical Outcomes Study 36-Item Health Survey, $n = 61$

* $P < 0.05$; ** $P < 0.01$

Table 4 Gender differences in WIS, WOS, and HA

	Median		P
	Male	Female	
WIS	18.4	20.0	<0.001***
WOS	85.9	83.6	0.001**
HA	1.1	2.2	<0.001***

WIS work impairment score, *WOS* work output score, *HA* hours of absenteeism

** $P < 0.01$; *** $P < 0.001$

Results of the Mann–Whitney test showed that the score for 'Depression, anxiety or emotional disorder' was significantly higher than for all other categories (*P with Bonferroni correction* <0.001 in all cases).

Discussion

In this study, we investigated the factor structure and psychometric properties of the PSS using data from the 4 school-based surveys performed through cooperation within the framework of the National University Council of Health Administration Facilities to reveal the utility of the PSS. In our research, the Kaiser–Meyer–Olkin value was adequate, and the factor structure matrix was similar to that found previously in Japanese workers [11]. The value of internal consistency of the WIS in students was $\alpha = 0.90$, which was somewhat higher than in the original report showing an α of 0.82 [10]. With respect to test–retest reliability, both the ICC and Spearman's ρ for the PSS were almost equivalent to the Japanese version of the SPS;

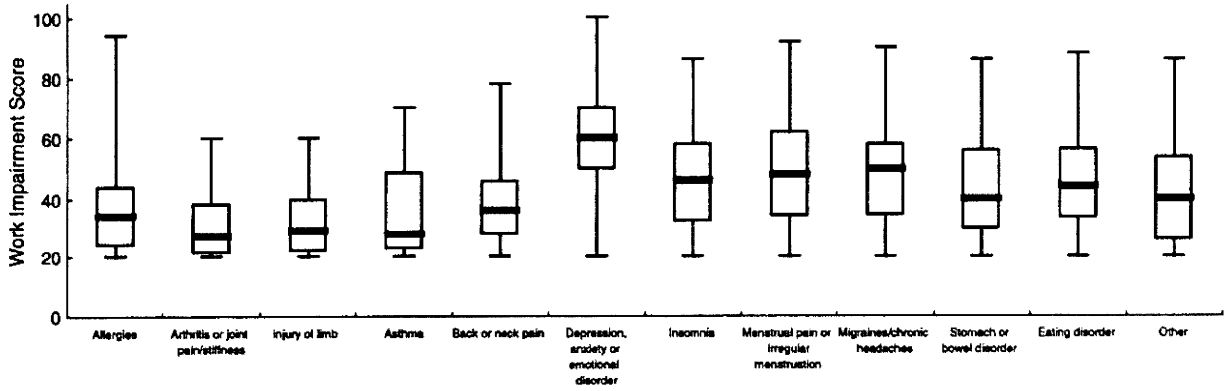

Fig. 2 The box and whisker plots of work impairment score

this clearly proves that both values reflected a good level of reliability. Regarding external validity, this study was conducted in four universities that varied in geographical location and other characteristics and results showed no between-school differences on presenteeism. That presenteeism among students was seen in all of these schools regardless of differences among them would indicate a high degree of generalizability of this survey. Also, confirming results of a previous report, the concurrent validity of the PSS in the present study is further supported by the acceptable correlation with the SF-36 [10, 11]. Thus, these results indicated that the PSS had sufficient test–retest reliability and concurrent validity and suggested that the PSS could estimate presenteeism among students.

While much research on presenteeism has been reported in the field of occupational health, no attention, antithetically, has been given to presenteeism among students. The present research, however, found that only 40.8% of the overall sample did not experience problems concerning health in the 1 month prior to the survey. This indicates that presenteeism is prevalent among students. Bergström et al. additionally reported that presenteeism will have an adverse effect on general health 3 years later [14]. Thus, encouraging the early attention to presenteeism due to sickness may be crucial in improving the quality of campus life and has been considered to prevent absenteeism in the future.

Among students, the most frequently reported problem was allergy. This result is coincident with that in a previous report [15]; however, our results may have been influenced by a seasonal effect. Hay fever is an allergic response to the microscopical particles of pollen of certain plants such as Japanese cypress and Japanese cedar, which are known as common causes of allergy in Japan [16]. Allergic rhinitis is more likely to occur in spring, which coincides with the time of the investigation. This result, therefore, may reflect the seasonal effect of pollen. Despite the relatively low prevalence of psychiatric sickness in comparison with allergy, students who reported mental problems were prone to higher levels of presenteeism. In other words, the fact that students with mental illness had the highest value of WIS suggests that psychiatric problems have a profound effect on academic performance. Recently, Sanderson et al. revealed a significant difference in presenteeism between employees with and without depressive/anxiety symptoms, varying in parallel with presenteeism and the extent of depressive symptoms [17]. Future research should verify the usefulness of the PSS in evaluating treatment outcome for illnesses that contribute to presenteeism and should provide long-term follow-up of the effects of presenteeism.

On the other hand, with regard to gender differences, female students had higher scores than males on the WIS. Also, the prevalence of menstrual problems was from 16.6 to 25.1% in this study. We found that students who reported menstrual pain had relatively high presenteeism. Teperi and Rimpelä showed that 79% of 18-year-old women experience menstrual pain and that 21% of 16-year-old women stayed at home due to menstrual pain [18]. Furthermore, when compared to males, an approximately two-fold frequency of back or neck pain, migraines/chronic headaches and bowel disorders in females was found. Consequently, it has been suggested that these symptoms may play an important disincentive role in the quality of campus life for female students.

As to future directions, we have the following suggestions. First, we should establish benchmark scores on the PSS according to health problems. The availability of benchmark scores for health problems might indicate when early healthcare interventions are needed. Second, not only specific health problems but also individual-specific lifestyle factors such as alcohol drinking, dietary habits, sleep time or hours commuting to school might affect presenteeism directly or indirectly. In addition to these factors, difficulties in psychosocial adjustment or low self-esteem have been found to be related to the severity of some chronic illnesses such as affective disorders, arthritis and asthma [19–22]. Because presenteeism impairs the quality of life, it may also bring about low self-esteem secondarily.

The determinants or confounding factors on presenteeism are still not well understood; thus, further studies of students will provide interesting results. Third, the list of health conditions (first module of PSS) consisting of 16 sicknesses observed empirically through health care activity in a university setting was used to elicit information on the presence of a health problem, but the response to this question would not reflect progressive aspects of a condition such as chronic or temporal sickness. To clarify this issue, additional study in a clinical setting should be carried out to characterize the effect of such illnesses on presenteeism. Fourth, students do their academic work under different conditions and work in different ways compared to employees. Since the concepts of "completing work" and "avoiding distraction" may be experienced differently in students than in workers, qualitative research, for example, conducting interviews, might be warranted to test the hypothesis that there are differences in experiences between workers and students with regard to presenteeism.

In conclusion, this study is the first to reveal the impact of presenteeism on academic performance. Up to now, no validated Japanese language questionnaire was available to estimate presenteeism among students. In the present study, we found excellent reliability and concurrent validity for the PSS. In addition, we disclosed that the majority of college students have some health problems and proposed that the issue of presenteeism on campus should be addressed.

Acknowledgments The authors would like to thank all of the staff of Akita University Health Administration Center, Nara Women's University Health Administration Center, Fukuoka University of Education Health Center and Osaka University Health Care Center for conducting this survey. The authors are also grateful to Yasunobu Kabeshita, M.D. for helpful comments on an earlier draft of this paper.

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1. CKD診療ガイドラインに基づく蛋白尿症例の診療

Guideline - based management of proteinuria

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Key words 蛋白尿 CKD 慢性腎臓病 ACEI ARB

1. 参考ガイドライン

1) エビデンスに基づくCKD診療ガイドライン2009(2009年. 日本腎臓学会編, 東京医学社)
2) 日本腎臓学会編CKD診療ガイド2009(2009年, 日本腎臓学会編, 東京医学社)

2. 蛋白尿症例診療のポイント

1) 尿蛋白は腎機能障害進行と心血管疾患発症の危険因子であり積極的な治療介入が必要である.
2) 外来診療では, 尿蛋白/尿クレアチニン比を算出し, 一日蛋白尿の指標とする.
3) 腎臓専門医への紹介基準は, ①血尿(1+)未満の場合：尿蛋白(2+)以上もしくは0.5g/日または0.5g/gクレアチニン以上, ②血尿(1+)以上の場合：尿蛋白(1+)以上である.
4) 尿蛋白症例はその原疾患にかかわらず, 禁煙指導・高血圧治療・血糖管理・脂質管理・肥満治療を行い, これらの危険因子を長期間にわたり目標内に管理することが非常に重要である.
5) 降圧薬の第一選択はアンギオテンシン変換酵素阻害薬(ACEI)またはアンギオテンシン受容体拮抗薬(ARB)である.

3. 蛋白尿の重要性

CKD診療ガイドラインステートメントより

①蛋白尿およびアルブミン尿は末期腎不全の危険因子である. 蛋白尿, アルブミン尿の程度が増すごとにリスクが高くなる. グレードA・レベル1
②治療介入による, 蛋白尿, アルブミン尿の減少の程度は, 腎機能悪化抑制と相関がある. グレードA・レベル2
③蛋白尿およびアルブミン尿は心血管病の危険因子である. 蛋白尿, アルブミン尿の程度が増すごとに心血管病のリスクが高くなる. グレードA・レベル1
④蛋白尿は微量アルブミン尿の段階から心血管病の危険因子であり, 積極的に減少を目指す. グレードA・レベル2
⑤治療介入による, 蛋白尿, アルブミン尿の減少の程度は, 心血管病発症の抑制と相関がある. グレードA・レベル1

慢性腎臓病(CKD)診療ガイドラインでは, 尿蛋白陽性症例への積極的な治療介入により, 尿蛋白を減少させ, 腎機能障害進行および心血管病発症を抑制する必要性が強調されている. そのエビデンスとして, ①新規尿蛋白陽性例の5～10%前後が最終的に透析に移行すること, ②蛋白尿が多いほど透析に移行しやすいこと, ③ACEI/ARBの腎障害進行抑制効果は尿蛋白減少効果に依存すること, さらに, ④ACEI/ARBの心血管病発症抑制効果は尿アルブミン減少効果と相関することなどが記載されている.

0371-1900/10/¥50/頁/JCLS

4. 蛋白尿の評価法

CKD 診療ガイドラインステートメントより

①随時尿を用いた試験紙法による定性検査，あるいは随時尿や蓄尿(1日あるいは時間)を用いた定量検査を行う．随時尿を用いた定量検査では，尿 Crtn を同時測定してアルブミン/Crtn 比または蛋白/Crtn 比を求めて，排泄量を評価する(1g の Crtn 当たりの量)．アルブミン/Crtn 比が30～299mg/gCrtn であれば微量アルブミン尿と診断する．起立性蛋白尿を除外するため，随時尿を用いる場合，一度は早朝第一尿を用いて検査する．グレードA・コンセンサス

尿試験紙法は，簡便性に優れ，尿蛋白(1＋)は30mg/dL，(2＋)は100mg/dL の蛋白濃度に相当する．尿定量検査法は，定量性に優れる．24時間蓄尿により一日尿量と蛋白濃度を測定し，結果を積算することで一日蛋白尿が計算できる．随時尿の尿蛋白/尿クレアチニン比による評価は，尿中にクレアチニンが1g排泄されたと仮定したときに想定される尿蛋白排泄量を一日尿蛋白量とする方法で，普通の体格の人の尿クレアチニン排泄量が約1g/日であることを利用している．一日尿アルブミン量を，24時間蓄尿，またはクレアチニン比から算出して腎障害の指標とすることも多い．ただし，アルブミン尿についてのエビデンスは糖尿病性腎症が中心で，他の腎疾患については今後のエビデンスの蓄積が必要である．

CKD 診療ガイドラインでは，0.15g/日以上の蛋白が尿中に排泄される場合を，蛋白尿と定義している．一方，臨床の場で蛋白(1＋：30mg/dL)以上を蛋白尿陽性とすると，一日の尿量を1,000ml と仮定して，0.3g/日以上の蛋白尿症例をスクリーニングすることになる．蛋白尿には，腎臓の障害に由来する病的蛋白尿と，激しい運動などのストレスや起立により生じる生理的蛋白尿があり，病的蛋白尿のみが精査・加療の対象となる．そこで，健診で尿蛋白を認めた症例は，起立性蛋白尿の鑑別のため，非生理時の早朝尿中の蛋白を尿試験紙法と尿定量検査で再検査する．以下に，蛋白尿症例の腎臓専門医への紹介基準を示す．

蛋白尿症例の腎臓専門医への紹介基準(CKD 診療ガイドラインより)

①血尿(1＋)未満の場合：尿蛋白(2＋)以上もしくは0.5g/日または0.5g/g クレアチニン以上

②血尿(1＋)以上の場合：尿蛋白(1＋)以上

①の基準である尿蛋白(2＋：100mg/dL)以上は，一日の尿量を1,000ml と仮定すると1.0g/日以上の蛋白尿に相当する．つまり，尿定量検査の基準(0.5g/日または0.5g/g クレアチニン)の方が厳しいので，尿定量検査で評価した方がよい．また，糖尿病性腎症第2期(早期腎症期：糖尿病の項参照)の診断に用いられる微量アルブミン尿30mg/gCrtn のレベルでは，尿試験紙法(±)であり，微量アルブミン尿のスクリーニングにも，尿試験紙法は不適切である．②の血尿と蛋白尿合併例では尿蛋白(1＋)以上が紹介基準であり，0.3g/日以上の蛋白尿症例をスクリーニングすることになる．ただし，CKD 診療ガイドラインに血尿単独例の約10％は蛋白尿陽性に移行すると記載されている事実が示すように，血尿単独例と，血尿と蛋白尿合併例の境界は明確なものではない．筆者らは，長期にわたる腎保護が必要な若年血尿症例では，蛋白尿の基準である0.15g/日(または早朝尿0.15g/gCrtn)以上の蛋白尿を認めれば腎生検を行っている．その多くは，IgA 腎症の比較的予後良好群～不良群と診断され，治療の対象となっている．

5. 蛋白尿の治療総論

CKD 診療ガイドラインステートメントより

①喫　煙：喫煙は慢性腎臓病の発症および進行に関連する独立した危険因子であり，心血管病の発症リスクを増加させることから，慢性腎臓病患者は禁煙すべきである．グレードA・レベル4

②飲　酒：中等度の飲酒(エタノール20～40g/日)は慢性腎臓病のリスクとはならず，むしろ進行を抑制し，心血管病の発症も抑制する．一方，大量飲酒(エタノール60g/日以上)は慢性腎臓病のリスクとなり，心血管病の発症も増加させるため，避けるべきである．グレードB・レベル4

③身体活動性の維持：慢性腎臓病患者に安静・運動制限を一律に行うべきでなく，肥満の是正，糖尿病新規発症の予防，高血圧の治療，心血管病予防のために身体活動度を維持すべきである．グレードA・コンセンサス

④運動強度：運動疲労を起こさない程度の運動(5METS 前後：速歩や自転車・水中運動やゴルフ)が安定した慢性腎臓病を悪化させるという根拠はなく，合併症などの身体的状況が許す限り，定期的施行が推奨される．グレードB・レベル3

⑤ワクチン接種：慢性腎臓病患者には，インフルエンザワクチンの接種が推奨される．グレードB・レベル4

6 食塩制限：慢性腎臓病患者では，6g/日未満の食塩制限が推奨される．グレードA・レベル2

蛋白尿の原疾患を確定し，原疾患に対する治療を行

うことは最も重要である．また，尿蛋白症例ではその原疾患にかかわらず，禁煙指導・高血圧治療・血糖管理・脂質管理・肥満治療を行う必要がある．CKD診療ガイドラインでは，過去に腎疾患の既往のある症例も，これらの危険因子の管理を行うこと，そしてCKDの家族歴があれば，症例の家族も危険因子の管理を行うことを推奨している．蛋白尿症例を対象とした摂取総カロリー量についての規定はないが，肥満症や糖尿病を合併していればその治療ガイドラインに従う．また，腎機能が正常な蛋白尿症例にも，6g/日未満の食塩制限が推奨されている．蛋白制限についてのエビデンスは限られているが，米国の推奨栄養所要量に相当する0.8g/kg標準体重/日の蛋白制限がひとつの目安となる．

6．蛋白尿の治療：高血圧

CKD診療ガイドラインステートメントより

①慢性腎臓病における高血圧：慢性腎臓病では高血圧を合併する頻度が高く，高血圧は慢性腎臓病の進行や心血管病の発症リスクとなる．慢性腎臓病における降圧療法は慢性腎臓病の進行を抑制し，心血管病の発症や死亡のリスクを軽減する．グレードA・レベル1

②慢性腎臓病患者の血圧測定：外来血圧のみならず，起床時と就寝前の家庭血圧を測定し評価することが望ましい．グレードA・レベル4

③慢性腎臓病の降圧目標：降圧目標として，尿蛋白1g/日未満の場合には130/80mmHg未満が，1g/日以上の場合には125/75mmHg未満が推奨される．グレードA・レベル1

④降圧薬の選択1：降圧薬は，原則としてRA系阻害薬(ACEIもしくはARB)を第一選択薬とする．グレードA・レベル1

⑤降圧薬の選択2：降圧目標の達成には，第二選択薬(利尿薬やCa拮抗薬)との併用療法を考慮する．グレードA・レベル2

CKD診療ガイドラインでは，①降圧が微量アルブミン尿や蛋白尿の減少に有効であること，②蛋白尿の減少自体が心血管疾患発症および腎障害進展の軽減をもたらす可能性をもつことが示されている．さらに，家庭血圧を重視すること，そして，収縮期血圧と拡張期血圧の降圧目標を双方とも達成することを推奨している．治療では，生活指導，とくに前項で示した食塩制限や運動療法を薬物治療と組み合わせることが重要で，降圧薬の第一選択はアンギオテンシン変換酵素阻害薬(ACEI)またはアンギオテンシン受容体拮抗薬(ARB)である．ACEI/ARBの特徴として，①ACEI/ARBは高血圧の有無にかかわらず腎保護効果が期待できる，②ただし，非高血圧蛋白尿症例への保険適用はない，③ACEI/ARBは糖尿病自体の発症抑制効果をもつ，④ACEI/ARBの効果発現には食塩制限が重要であることが示されている．

ACEI/ARBによる降圧が不十分な場合，ACEIとARBの併用療法，または利尿薬かCa拮抗薬を追加する．ACEIとARBの併用療法は，腎障害が進展したとの報告もあり評価は定まっていない．利尿薬では，とくに腎機能の保たれた蛋白尿症例へのサイアザイド系利尿薬低用量投与または抗アルドステロン薬の投与が支持されている．低用量のサイアザイド系利尿薬(フルイトラン®で0.5mg程度)は降圧および心血管疾患の発症抑制効果，抗アルドステロン薬は蛋白尿低下作用を示す．Ca拮抗薬では，反射性交感神経刺激作用のない，長時間作用型ジヒドロピリジン系Ca拮抗薬または非ジヒドロピリジン系Ca拮抗薬(ワソラン®・ヘルベッサー®)に心血管や腎保護作用を示すエビデンスがあるが，長時間作用型ジヒドロピリジン系Ca拮抗薬を選択する場合が多い．いずれの第二選択薬を使用する場合も，目標血圧を達成することが最も重要であり，必要に応じて，薬の増量や他の降圧剤(利尿薬・Ca拮抗薬・$\alpha\beta$遮断薬)への変更・追加を行う．どの薬剤の組み合わせでも，目標血圧を達成し，降圧療法開始6ヵ月以内に30%以上の蛋白尿減少効果を認めれば，腎障害進展抑制効果が得られている可能性は高い．

7．蛋白尿の治療(脂質代謝異常)

CKD診療ガイドラインステートメントより

①脂質異常症は，慢性腎臓病の発症・進行だけではなく，心血管病発症の危険因子である．グレードA・レベル4

②管理目標として，LDLコレステロール≦120mg/dLが推奨される(可能なら≦100mg/dL)．生活習慣の改善により管理目標値に達しない場合，薬物療法を考慮する．グレードA・コンセンサス

③スタチンを用いた脂質管理により，慢性腎臓病の進行抑制と心血管病発症予防が期待される．グレードA・レベル4

脂質異常症の治療では，生活指導(食事療法と運動療法)を優先する．食事療法は，脂肪摂取制限・コレステロール摂取制限・アルコール制限からなり，これに前記の運動療法・食塩制限と蛋白制限を組み合わせ，脂質データの反応を検討しながら調整する．動脈硬化のハイリスク群や6ヵ月の生活指導にても改善を認めない症例は，薬物治療の適応となる．スタチンの

尿蛋白減少効果と腎障害抑制効果を示した報告は多いが，否定的な報告も存在する．一方，スタチンの心血管疾患予防効果は確立しており，CKD 診療ガイドラインでは，心血管病発症のハイリスク群である蛋白尿症例へのスタチン投与による積極的な LDL 低下を推奨している．その他の脂質代謝異常症治療薬については，蛋白尿症例での心血管病発症予防効果は明確でなく，今後のエビデンスの蓄積が期待される．

8．蛋白尿の治療(糖尿病)

CKD 診療ガイドラインステートメントより

①診　断：すべての糖尿病患者では，定期的に検尿(微量アルブミン尿，蛋白尿)と eGFR の測定をし，糖尿病性腎症の早期発見に努めるべきである．グレードA・コンセンサス

②治療 1：厳格な血糖コントロール(目標 HbA1c 6.5％未満)は，糖尿病性腎症の発症および進行を抑制する．グレードA・レベル 2

③治療 2：高血圧を合併した糖尿病患者では，ACEI や ARB を中心とした降圧療法により，130/80mmHg 未満に管理する．グレードA・レベル 1

④治療 3：尿蛋白が 1 g/日(または g/gCrtn)以上の糖尿病患者では，平均血圧92mmHg 未満(125/75mmHg に相当)を目標とする．グレードB・レベル 2

⑤治療 4：ACEI や ARB は腎症の進行を抑制するため，正常血圧の患者でも血圧低下に注意しつつ投与することが望ましい．グレードB・レベル 2

⑥治療 5：糖尿病性腎症のステージにかかわらず，高血圧を合併している症例には減塩食の指導をおこなう．グレードB・コンセンサス

⑦治療 6：2 型糖尿病では厳格な血糖・血圧管理，ACEI や ARB の投与，スタチンによる脂質低下，低用量アスピリン，抗酸化薬，運動・禁煙指導のチーム医療による多角的強化療法により早期の腎障害の進行が抑制される．グレードB・レベル 2

糖尿病性腎症は，微量アルブミン尿で発症し，持続性蛋白尿に進展すると考えられてきた．しかし，微量アルブミン尿は陰性であるが腎機能が低下している糖尿病症例も多いことが報告され，微量アルブミン尿の早期腎症マーカとしての意義には再検討の必要が生じている．一方，微量アルブミン尿を積極的治療の対象とすることに疑問の余地はない．午前中に採取した尿で尿中アルブミン(mg)/尿中 Crtn (g)比の測定を行い，3 回の検査のうち 2 回以上で30～299mg/gCrtn であれば，微量アルブミン尿と判定し，糖尿病性腎症第 2 期(早期腎症期)と診断する．300mg/gCrtn 以上であれば顕性蛋白尿と判定し，糖尿病性腎症第 3 期以降となる．

治療には，運動療法・食事療法(糖尿病食＋高血圧があれば食塩制限・顕性蛋白尿があれば食塩制限＋蛋白制限)・禁煙指導・脂質管理・血圧管理，さらに血糖管理と低用量アスピリン投与を多角的に組み合わせる．降圧剤の第一選択は ACEI/ARB で，糖尿病症例でも血圧に依存しない腎保護・抗蛋白尿効果が報告されている．血糖管理目標に関しては，HbA1c 6.5％未満・空腹時血糖110mg/dL 未満・食後 2 時間血糖値180未満への管理により腎症の発症および進展が抑制される可能性が報告されている．ただし，症例の年齢や糖尿病発症後年数により適切な血糖管理目標値が異なる可能性もあり，今後もエビデンスの蓄積が必要である．

9．蛋白尿症例のフォローアップ

蛋白尿症例のフォローアップの目的は，腎機能障害進展と心血管疾患発症の防止にある．そのためには，生活指導および薬物治療の効果を定期的に評価し，これまでに述べてきた危険因子を長期間にわたり目標内に管理することが非常に重要である．主治医には，管理が不良な症例を速やかに腎臓専門医へ紹介する義務がある．

フォローアップ検査(CKD 診療ガイド2009より)

毎診察時：血圧測定と家庭血圧測定結果の評価
(糖尿病症例では 1～3 ヵ月ごと：HbA1c)

3～6 ヵ月ごと：尿蛋白/尿 Crtn 比・血清 Crtn (eGFR 算出)・一般血液検査・血清脂質・血清電解質・血清総蛋白・血清アルブミンの評価

1 年に 1 回から必要に応じて：蓄尿による尿蛋白，塩分摂取，蛋白摂取の評価・腎臓超音波検査・心電図・胸腹部 X 線検査

診療の実際

コレステロール塞栓症

Cholesterol crystal embolism : CCE

特集

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腎不全を診る

Key words コレステロール塞栓症 腎不全 blue toe syndrome

コレステロール結晶がさまざまな小動脈を閉塞して組織障害を起こすことをドイツの病理学者 Panum[1]が初めて報告したのは，100年以上前のことである．その後1945年に Flory[2]は，コレステロール塞栓症(cholesterol crystal embolism：CCE)の原因が大動脈の粥状硬化であるとの仮説をたて，267人の剖検例で詳細に報告した．その後本症が注目されることは少なかったが，近年心臓カテーテル検査や血管手術の増加に伴い，特発性以外に，医原性の CCE が注目されるようになった．

コレステロール塞栓症(CCE)とは

CCE とは，大動脈またはその近傍の動脈(腸骨動脈，大腿膝窩動脈など)にある粥状硬化のプラークが何らかの原因によって破綻し，それらが，シャワーのように下流に降り注ぐことによって生じる末梢血管塞栓症である．この末梢血管の閉塞による虚血のため，種々の臓器および組織が障害され，“blue toe syndrome”などのさまざまな症状を呈する．

本症の発症は男性に多く(男：女＝91％：9％)，60歳以上の高齢者に多い[3]．CCE のリスクファクターは動脈硬化と同じであり，加齢，喫煙，脂質代謝異常，高血圧，肥満，糖尿病や冠動脈疾患，心血管系疾患の既往があげられる[4]．発症の誘因としては，76～79％[3][4]は医原性であり，血管内のカテーテル操作(大動脈造影，冠動脈撮影，心カテーテルなど)が50％，心血管手術(大動脈瘤手術，大動脈冠動脈バイパス)が15％を占める．腹部外傷による頻度は少ないが，ヘパリン，ワーファリンなどによる長期の抗凝固療法や血栓溶解療法などでも CCE が起こることが報告されている．

急性心筋梗塞に対して CABG が施行された60症例(半数の症例で血栓溶解療法を併用)を対象とした前方視的観察研究[5]では，CABG 施行後1ヵ月と2ヵ月目に筋生検および皮膚生検を施行したところ，筋生検において7人12％に CCE を病理学的に認めたが，臨床的な症状を認めたのは1人であったと報告されている．

特発性の CCE もしばしば認められることもあるが，剖検症例の検討においては動脈硬化性疾患などの有無に限らない場合，CCE を認めるのは

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0371-1900/10/¥50/頁/JCOPY