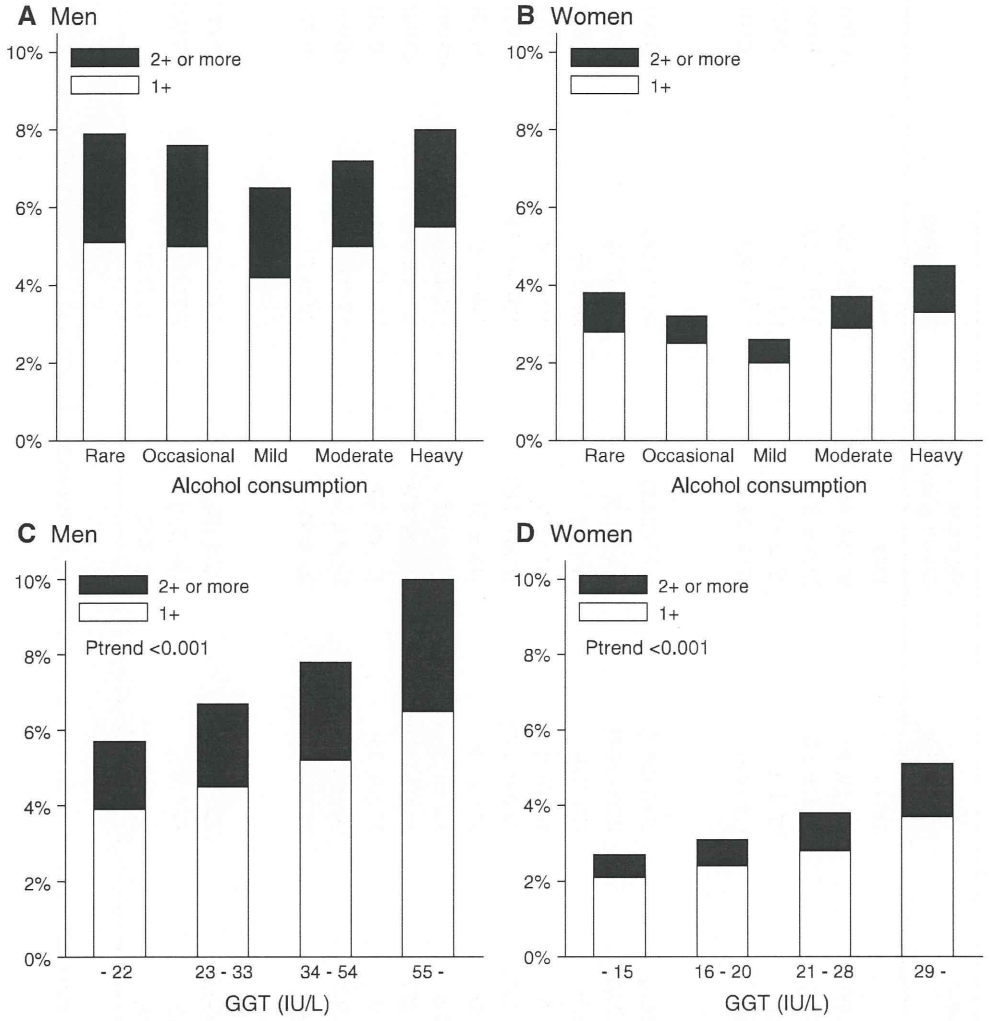

Fig. 1 Prevalence of proteinuria stratified by alcohol consumption (**a** and **b**) and serum γ-glutamyltransferase (*GGT*) quartiles (**c** and **d**) in men (**a** and **c**) and women (**b** and **d**). Alcohol consumption was categorized into rare, occasional, mild (ethanol intake ≤19 g/day), moderate (20–39 g/day), and heavy drinking (≥40 g/day)

calculated in multivariate-adjusted models. Rare drinkers with the lowest GGT quartile were set as a reference (Fig. 3). Interestingly, among men in the lowest GGT quartile (≤22 IU/L), mild to heavy drinkers had lower PRRs of proteinuria defined as ≥1+ of urinary protein, compared with rare and occasional drinkers [rare, occasional, mild, moderate and heavy drinkers in the lowest GGT quartile (≤22 IU/L): 1.00 (reference); 0.91 (0.82–1.00), 0.74 (0.63–0.86), 0.76 (0.65–0.89), 0.78 (0.57–1.06)] (Fig. 3a). Another, more interesting finding was that men in the highest GGT quartile (≥55 IU/L) had a higher PRRs, irrespective of alcohol consumption [rare, occasional, mild, moderate and heavy drinkers with highest GGT quartile (≥55 IU/L): 1.27 (1.15–1.41), 1.33 (1.21–1.46), 1.21 (1.08–1.35), 1.29 (1.18–1.40), 1.39 (1.27–1.52)]. Similar to men, women in the highest quartiles of GGT had higher PRRs (Fig. 3c). However, a stepwise association between GGT and proteinuria in each category of alcohol consumption was not as evident among the female participants as among the male participants. As a sensitivity analysis, we redefined proteinuria as ≥2+ of urinary protein and compared the impact of serum GGT level and alcohol consumption on proteinuria. Similar superiority of serum GGT level over alcohol consumption was observed (Fig. 3b, d). After excluding 20,547 (15.3 %) men and 30,991 (15.7 %) women without serum uric acid data, we also assessed the associations of serum GGT and alcohol consumption with proteinuria. The results of multivariate-adjusted models adjusting additionally for uric acid were comparable to Fig. 3, ascertaining that their associations were independent of serum uric acid (data not shown).

To identify the optimal cutoff point of GGT, we calculated the Youden index of serum GGT level. Area under the curve of receiver–operator characteristics curve was 0.571 and 0.574 in men and women, respectively. The optimal cutoff points in men and women were 43.6 IU/L

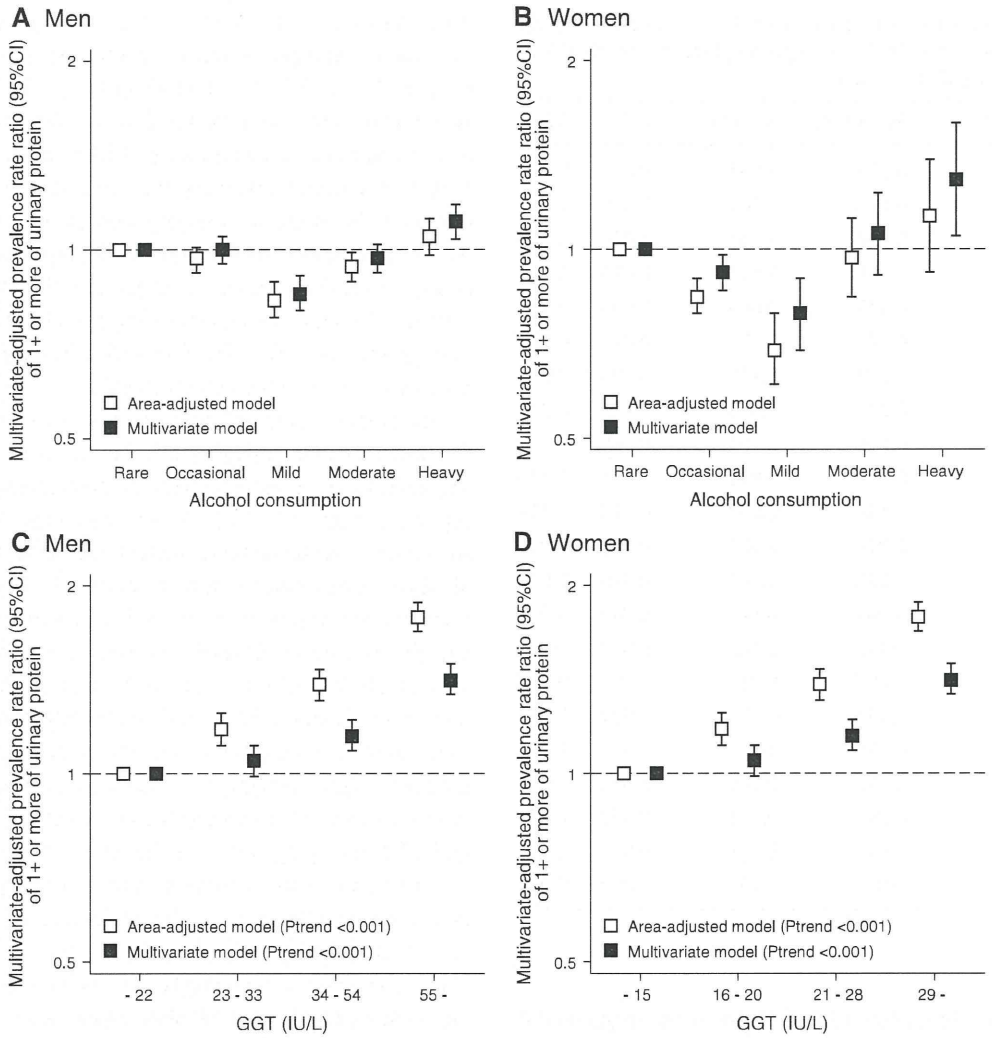

Fig. 2 Association of alcohol consumption (**a** and **b**) and serum γ-glutamyltransferase (*GGT*) level (**c** and **d**) with proteinuria defined as ≥1+ of urinary protein in men (**a** and **c**) and women (**b** and **d**). Prevalence rate ratios with 95 % confidence interval were calculated after adjusting for area in area-adjusted models and clinically relevant factors in multivariate-adjusted models, including area, age, body mass index, mean arterial pressure, current smokers, current treatment for hypertension, dyslipidemia and diabetes, past history of cardiovascular disease, log triglyceride, low-density lipoprotein cholesterol, hemoglobin A1c, and estimated glomerular filtration rate. Alcohol consumption was categorized into rare, occasional, mild (ethanol intake ≤19 g/day), moderate (20–39 g/day), and heavy drinking (≥40 g/day)

(sensitivity 0.442, specificity 0.663, positive predictive value 0.096, and negative predictive value 0.936) and 23.2 IU/L (sensitivity 0.467, specificity 0.649, positive predictive value 0.048, negative predictive value 0.970), respectively (Table 3).

Discussion

The present cross-sectional study showed that serum GGT level was associated with proteinuria independently of alcohol consumption and, more interestingly, revealed that both drinkers and non-drinkers with the higher serum GGT level had higher probability of proteinuria (Fig. 3). Based on these results, drinkers with higher serum GGT level may potentially reap the benefit of abstinence from drinking. In other words, serum GGT level possibly gives an answer to a personal question for each drinker, "to drink or not to drink?" This novel finding indicates that serum GGT level is clinically more useful to identify subjects at a higher risk of proteinuria, a predictor of ESRD [43, 44] and CVD [18], than self-reported alcohol consumption.

Although some early epidemiological studies failed to show a beneficial effect of alcohol consumption on renal prognosis [45, 46], more recent and well-designed cohort studies have showed that mild drinkers were likely to be at lower risk of a progressive GFR decline [25, 26, 29, 47–50]. However, renal prognosis of heavier drinkers is

Table 3 Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of γ-glutamyltransferase (GGT) in 134,600 men and 197,696 women

	GGT (IU/L)	Sensitivity	Specificity	PPV	NPV
Men	10	0.997	0.004	0.075	0.945
	20	0.853	0.201	0.080	0.944
	30	0.636	0.461	0.087	0.940
	40	0.475	0.627	0.094	0.936
	43.6[a]	0.442	0.663	0.096	0.936
	50	0.367	0.729	0.099	0.934
	60	0.292	0.793	0.103	0.933
	70	0.237	0.838	0.106	0.931
	80	0.196	0.869	0.108	0.930
	90	0.168	0.891	0.111	0.930
	100	0.144	0.909	0.113	0.929
Women	10	0.976	0.029	0.037	0.970
	20	0.566	0.544	0.045	0.971
	23.2[a]	0.467	0.649	0.048	0.970
	30	0.305	0.789	0.052	0.968
	40	0.185	0.880	0.055	0.966
	50	0.127	0.923	0.059	0.965
	60	0.096	0.947	0.064	0.965
	70	0.072	0.962	0.066	0.965
	80	0.059	0.971	0.072	0.965
	90	0.047	0.978	0.075	0.964
	100	0.037	0.983	0.077	0.964

[a] Youden index

controversial. Some studies reported that renal prognosis of heavier drinkers was comparable with, or ever better than, that of mild drinkers [25, 26, 29, 47, 48], whereas others suggested that heavier alcohol consumption might predict a larger GFR decline [28, 47, 49]. Regarding proteinuria, only a limited number of cohort studies assessed an association between alcohol consumption and incidence of proteinuria. An Australian cohort study reported that heavier drinkers were at a higher risk of incident albuminuria in a stepwise fashion [26]. On the contrary, a Japanese cohort study revealed a U-shaped association between alcohol consumption and incidence of proteinuria [29]. Compared with the non-drinkers, the mild drinkers with <20 g/day of ethanol were at lower risk of incidence of proteinuria, whereas the heavier drinkers with ≥20 g/day of ethanol were at similar risk. Their study and ours, two Japanese large studies, led to the similar results of lowest probability of proteinuria in mild drinkers. As a previous study indicates that the renoprotective effect is different among alcohol beverages [25], different consumption patterns of alcohol beverages in different countries may affect these internationally conflicting results. Another potential reason may be the different categories of alcohol consumption. The lower limits of highest category of alcohol consumption were various; 10 [49], 15 [48], 20 [29], 30 [26], 37.5 [25], and 48 g/day [47] of ethanol intake and 1 [50] and 4 drinks/day [28] of alcohol beverages. A lower limit and, consequently, wider range of highest category of alcohol consumption may dilute an association between the highest category and proteinuria, leading to the results biased to the null. Although the present study design is cross-sectional, a larger sample size enables us to reveal a J-shape association between alcohol consumption and proteinuria after the fine and clinically relevant categorization of alcohol consumption.

Predictive value of self-reported alcohol consumption for proteinuria is easily biased due to several reasons. Self-reported alcohol consumption is notoriously vulnerable to reporting bias [51, 52]. Biased measure of alcohol consumption, consequently, blunts an association between alcohol consumption and proteinuria. Even if drinkers honestly answered their alcohol consumption, the biological differences in alcohol metabolism between individuals modify clinical effect of alcohol consumption. The alcohol metabolite acetaldehyde and acetaldehyde-induced oxidative stress are thought to be the main cause of alcohol-induced organ damage [53]. Genetic factors, such as variations in alcohol dehydrogenase, aldehyde dehydrogenase and CYP2E1, play pivotal roles in alcohol metabolism [54, 55]. Previous studies reported that polymorphisms of these genes potentially predict the incidence of CVD [56, 57] and even modify the effect of alcohol consumption on CVD [58, 59]. Accordingly, we need clinically relevant biomarkers to indicate alcohol insult more accurately than self-reported alcohol consumption. The present study suggested that GGT, a conventional marker of excessive alcohol consumption, is a potential candidate for a biomarker of a detrimental effect of alcohol consumption.

Oxidative stress, one of the key players of pathogenesis of proteinuria [60], may contribute to an association between serum GGT level and proteinuria. GGT is expressed in many kinds of cells, especially in hepatocyte and renal proximal tubular cells [61], and plays a vital role in cellular antioxidant system dependent on glutathione (GSH) [62]. Because oxidative stress induces GGT expression [63] and serum GGT level is well associated with serum marker of oxidative stress [64–66], serum GGT is now regarded as an adaptive marker of systemic oxidative stress [11]. In the present study, the drinkers with higher serum GGT level were probably exposed to higher oxidative insults and were at higher risk of proteinuria, even though their self-reported alcohol consumption was at the same level. Compatible with our hypothesis, a previous cross-sectional study reported that serum GGT is well associated with the serum makers of oxidative stress in all subgroups stratified by alcohol consumption [66].

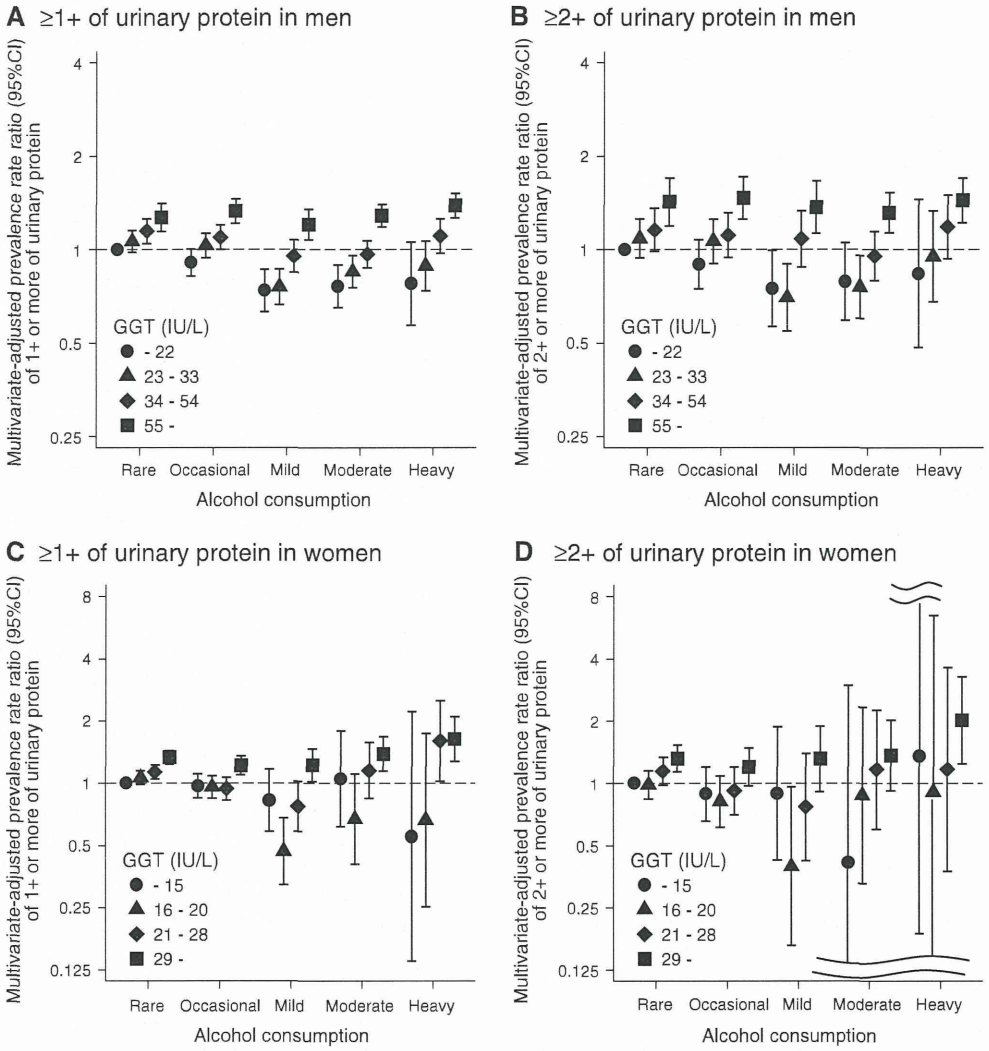

Fig. 3 Associations of GGT and alcohol consumption with proteinuria defined as ≥1+ of urinary protein by dipstick test (**a** and **c**) or ≥2+ (**b** and **d**) in men (**a** and **b**) and women (**c** and **d**) Prevalence rate ratios with 95 % confidence interval were calculated after area, age, body mass index, mean arterial pressure, current smokers, current treatment for hypertension, dyslipidemia and diabetes, past history of cardiovascular disease, log triglyceride, low-density lipoprotein cholesterol, hemoglobin A1c, and estimated glomerular filtration rate. Alcohol consumption was categorized into rare, occasional, mild (ethanol intake ≤19 g/day), moderate (20–39 g/day), and heavy drinking (≥40 g/day)

Alternatively, GGT may directly induce oxidative stress [67]. In the presence of iron or other transitional metals, cysteinylglycine, a GGT-induced GSH metabolite, potentially produces free radical species, promoting oxidative stress [68, 69]. Precise mechanisms of a link between serum GGT and proteinuria remain to be investigated.

Our study has several limitations. First, the results of the present cross-sectional study should be confirmed in a longitudinal study. Second, the impact of alcohol consumption on proteinuria in this study might be underestimated. Previous studies demonstrated that excessive alcohol consumption is a risk factor of dyslipidemia, diabetes, and cardiovascular disease. However, in this study, current treatments for dyslipidemia and diabetes and past history of cardiovascular disease were more common in the participants with lower alcohol consumption, as compared with those with higher consumption (Tables 1, 2). This paradoxical association suggests that the past health problems had affected current alcohol consumption (sick-quitter effect) [70]. Unfortunately information on the past alcohol consumption was not available in the present study, which is essential to assess a precise impact of alcohol consumption on proteinuria [71]. Third, proteinuria was determined with a single dipstick test measurement, which might lead to misclassifications. However, the majority of such misclassifications would bias our findings towards the null hypothesis and thus weaken the associations. In addition, prior studies have shown that even a single

measurement of dipstick proteinuria is a significant risk factor for all-cause mortality, cardiovascular mortality [72], and ESRD [43, 73].

In conclusion, higher serum GGT level was associated with a higher probability of proteinuria in both drinkers and non-drinkers, indicating that serum GGT level is a more useful marker to identify the subjects at higher risk of proteinuria, compared with self-reported alcohol consumption. Serum GGT level may provide a practical clue to the personalized answer to the question "to drink or not to drink?"

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Conflict of interest The authors have declared that no conflict of interest exists.

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ORIGINAL ARTICLE

Health-related quality of life and prognosis in patients with chronic kidney disease: a 3-year follow-up study

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Abstract
Background Chronic kidney disease (CKD) is a major global problem and is also associated with a decreased health-related quality of life (HRQOL). The aim of this study was to evaluate measured HRQOL based on the new CKD classification including proteinuria stage, and the effect of measured HRQOL on CKD progression and clinical outcomes over a 3-year period.
Methods EuroQol (EQ-5D), a generic preference-based questionnaire, was administered to 537 CKD outpatients at the University of Tsukuba Hospital between November and December 2008. We evaluated disease progression in CKD patients including the incidence of end-stage kidney disease (ESKD), cardiovascular disease (CVD) and all-cause mortality over a 3-year follow-up period.
Results The proportions progressing to the higher stages were 32.6, 20.0, 36.6, 39.5, and 45.8 % from glomerular filtration rate (GFR) stages (G) 1–4, respectively. The proportion progressing to ESKD (G5D) was 0.7 % from G2, 3.9 % from G3b, 20.8 % from G4 and 63.4 % from G5. The incidence of CVD and/or death was 1.2, 4.6, 4.9, 5.3, 8.3 and 21.1 % from G1−G5, respectively. The quality-adjustment weights at G4–5 were significantly lower than at G1–2 and the weights at proteinuria stage (A) 3 were significantly lower than at A1–2. The quality-adjustment weights of patients with events such as 50 % estimated GFR decline, dialysis, CVD, and/or death were significantly lower than those without events.
Conclusion We showed CKD progression and clinical outcomes over a 3-year period. Quality-adjustment weights in CKD patients were associated with not only disease progression such as initiation of dialysis treatment and incidence of CVD events and all-cause death, but also the level of proteinuria at baseline.

Keywords Chronic kidney disease (CKD) · Health-related quality of life (HRQOL) · Quality-adjustment weight · EuroQol (EQ-5D) · Prognosis · Proteinuria

Introduction

Chronic kidney disease (CKD) is a major independent risk factor for cardiovascular disease (CVD), including progression to end-stage kidney disease (ESKD), stroke and premature death [1, 2]. CKD is thus a worldwide public health problem and socioeconomic concern. In fact, there are >300,000 ESKD patients in Japan. The annual medical cost of dialysis treatment was >130 billion yen in 2011 [3]. Moreover, the total number of cases estimated for CKD stages G1, G2, G3, G4 + 5 in the Japanese adult population were 0.61, 1.71, 10.74, and 0.23 million, respectively [4]. Therefore, early detection and initiation of treatment for CKD are important in order to prevent progression to kidney failure as well as cardiovascular complications and death, and also to decrease medical cost. However, patient characteristics and clinical course in predialysis stages under the care of nephrologists are not well described. Therefore, the first objective of this study was to evaluate disease progression in patients with CKD including

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incidence of ESKD, CVD and all-cause death over a study period of 3 years.

The high morbidity of CKD and high cost of dialysis have promoted interest in developing cost-effective interventions for CKD and in understanding the health-related quality of life (HRQOL) of patients with CKD. It is now widely accepted that HRQOL is significantly compromised in patients with ESKD and is associated with increased mortality and morbidity [5, 6]. It is also well known that CKD including dialysis patients is associated with a decreased HRQOL [7–9]. We first measured the HRQOL in terms of quality-adjustment weight using EuroQol (EQ-5D), a generic preference-based questionnaire [10, 11], in patients with CKD to conduct a cost-effective analysis. HRQOL decreases with progression of CKD stages and measured weights were 0.940 for stage 1, 0.918 for stage 2, 0.883 for stage 3, 0.839 for stage 4, 0.798 for stage 5, and 0.885 for all stages. We also showed decreases of HRQOL with presence of anemia, undernutrition, hypertension, diabetes, or history of CVD [12]. In this study, we aimed to evaluate the effect of the measured HRQOL on CKD progression and clinical outcomes including development to ESKD, CVD events and all-cause death over a 3-year study period, because few studies have investigated longitudinal effects of HRQOL on disease progression in CKD patients.

Recently, the Kidney Disease: Improving Global Outcomes (KDIGO) group recommended that patients with CKD should be assigned to stages and composite relative risk groups according to criteria of glomerular filtration rate (GFR) (G) and proteinuria (A) [13]. In Japan, the CKD Clinical Practice Guide was revised by the Japanese Society of Nephrology, and the stages and composite relative risk groups were described according to GFR (G) and proteinuria (A) criteria. Proteinuria, an independent risk factor for death, myocardial infarction and progression to kidney failure at a given level of eGFR [14], are also related to HRQOL in patients with advanced type 2 diabetic nephropathy [15]. However, whether proteinuria is also related to HRQOL in patients with CKD has not been examined. Therefore, we evaluated the relationship between HRQOL and proteinuria according to the new CKD classification. Thus, the association of HRQOL in CKD patients, disease progression such as initiation of dialysis treatment and incidence of CVD events and all-cause death, and the level of proteinuria of baseline can all be studied.

Materials and methods

Instrument for measuring quality-adjustment weights

We used EQ-5D, a generic preference-based measure of quality-adjustment weights, which is standardized and validated for use in Japan [10, 11]. It is administered to patients who are asked to grade five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) of their health state as one of three levels ('no problem', 'some problems', and 'extreme problem'). The quality-adjustment weight ranges from 1 for perfect health (no problem in any dimension) to 0 for death and −0.111 for severe problems in all dimensions. A positive weight means that the health status is better than death and a negative weight is worse than death in EQ-5D.

Study design and patients

A 3-year follow-up study was conducted with outpatients previously diagnosed with CKD at the Department of Nephrology, University of Tsukuba Hospital. A total of 537 patients were recruited between November 2008 and December 2008 and followed prospectively until January 2012. At baseline, EQ-5D was given after written informed consent was obtained. This study complied with the Helsinki Declaration and was approved by the Ethics Committee of the Graduate School of Comprehensive Human Science, University of Tsukuba (approval number H20-295).

Study variables

From patient records, sex and age were included in our analysis as demographic baseline characteristics. Assays were performed for creatinine, hemoglobin, serum albumin, urinary protein, and urinary creatinine on the day of the questionnaire survey. GFR was estimated (eGFR) from serum creatinine, age, and sex using the new Japanese equation as follows: eGFR (ml/min/1.73 m^2) = 194 × serum creatinine$^{-1.094}$ × age$^{-0.287}$ × 0.739 (if female) [16]. CKD stage was determined at baseline according to the modified classification for the Japanese people based on the KDIGO Consensus Conference [13]; GFR stages G1–5 were defined as G1, GFR ≥90 ml/min/1.73 m^2; G2, 60–89; G3a, 45–59; G3b, 30–44; G4, 15–29; and G5, <15. Proteinuria stages A1–3 were defined as A1, <0.15 g/g creatinine; A2, 0.15–0.49; and A3, ≥0.50. Annual eGFR decline was calculated as last available eGFR minus baseline eGFR divided by 3 years. Annual eGFR decline of patients who started dialysis treatment at the University of Tsukuba Hospital during the 3-year study period was corrected by the duration from baseline to initiating dialysis. A 50 % eGFR decline was defined when the eGFR declined to 50 % from baseline. The primary disease was defined by clinical course, diagnostic imaging or biopsy findings. According to progression of CKD stages, patients were stratified into 'non-progressive group' if their stages were stable or improved, 'progressive group' if their stages progressed, 'dialysis group' if they

started dialysis therapy among progress group, and 'death group' if they died during the follow-up period. The presence of complications and clinical outcomes was also assessed using the records. Hypertension and diabetes were classified based on clinical records. A history of CVD was regarded as present if stroke, congestive heart disease, or ischemic heart disease was recorded. Primary outcomes included CVD such as angina pectoris, acute myocardial infarction, congestive heart failure, stroke and all-cause death were surveyed using hospital medical records and interviews with attending physicians.

Statistical analysis

All statistical analyses were performed using SAS. Quality-adjustment weights were calculated as the mean weight values of a group of patients according to the Japanese value set for EQ-5D, and 95 % confidence intervals were computed. The weight differences among CKD stages were tested by ANOVA. The level of significance was set at $P < 0.05$.

Results

The patients included 282 males (52.5 %) and 255 females (47.5 %) with an overall mean age of 55.2 years. Mean creatinine was 1.7 mg/dl; mean eGFR was 56.1 ml/min/1.73 m^2; mean hemoglobin 12.7 g/dl; and mean serum albumin was 4.1 g/dl. Regarding complications, 388 (72.3 %) patients had hypertension; 146 (27.2 %) patients had diabetes, with a mean HbA1c (NGSP) of 6.4 %; and 38 (7.1 %) patients had a history of CVD [12]. Proportions of patients in new CKD stages were 16.0, 27.9, 15.3, 14.2, 13.4 and 13.2 % for GFR stages G1–5 and 40.5, 19.7 and 39.9 % for proteinuria stages A1–3, respectively. During the 3-years observation period, 460 patients (85.7 %) completed follow-up visits, 64 (11.9 %) progressed to ESKD, 21 CVD events (3.9 %) occurred, and 19 patients (3.5 %) died (Fig. 1).

Figure 2 shows the CKD stage progression and incidence of CVD and/or death during 1 year of observation. The proportions progressing to higher stages were 18.6, 6.0, 14.6, 17.1 and 25.0 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 1.3 % from stage G3b, 1.4 % from stage G4 and 42.3 % from stage G5. The incidence of CVD and/or death was 1.2, 1.3, 1.2, 2.6, 4.2, and 9.9 % for stages G1–5, respectively. The proportion of unchanged CKD stage was 66.3, 77.3, 64.6, 63.2, 63.9, and 49.3 % for stages G1–5, respectively (data not shown). Figure 3 shows the progression of CKD stages and incidence of CVD and/or death during 3-year observation period. The proportions

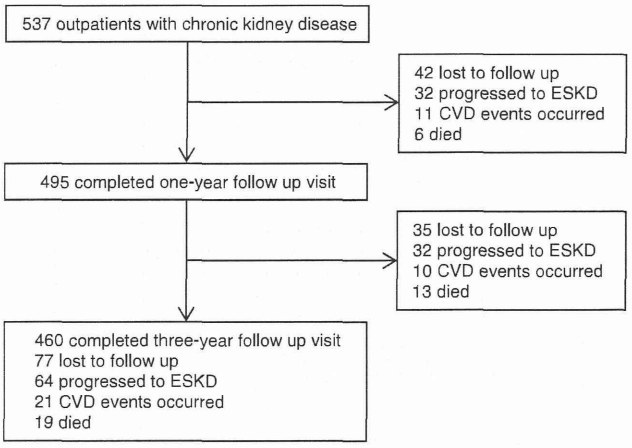

Fig. 1 Patient flow during the 3-year study period—460 patients (85.7 %) completed follow-up visits, 77 (14.3 %) moved away or were lost-to-follow-up, 64 (11.9 %) progressed to ESKD, 21 CVD events (3.9 %) occurred, and 19 patients (3.5 %) died

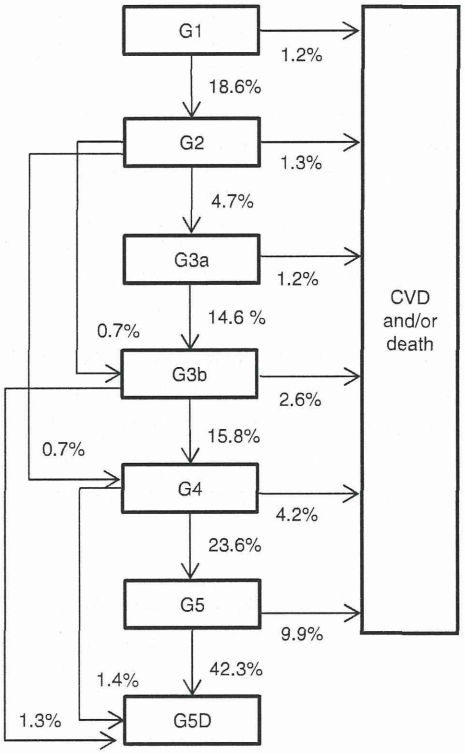

Fig. 2 CKD stage progression and incidence of CVD and/or death (after 1 year). The proportion progressing to the higher stages was 18.6, 6.0, 14.6, 17.1, and 25.0 % from stages G1–4, respectively. The proportion progressing to ESKD (stage G5D) was 1.3 % from stage G3b, 1.4 % from stage G4 and 42.3 % from stage G5. The incidence of CVD and/or death was 1.2, 1.3, 1.2, 2.6, 4.2, and 9.9 % for stages G1–5, respectively

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