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Decreases in urine specific gravity and urinary creatinine in elderly women

Abstract *Objective*: To examine the effects of aging on urinary levels of creatinine (CR) and urine specific gravity (SG) among women in a large-scale epidemiology survey. *Methods*: Data on CR and SG in urine, together with smoking habits and menopausal status, were selected from previously established databases and combined with the results of supplemental sample collection. In total, CR and SG data were available for 11,090 never-smoking women (total group; 29–80 years of age); a subgroup of 1,851 women who lived in Kyoto was also selected from the total group. Data from the two groups were subjected to statistical analyses. In statistical evaluation, SG was converted to factor G, which was defined as $(SG-1.000)\times1,000$. *Results*: Classification by decade of years of age showed that both CR and SG decreased steadily as a function of advancement in age over 30 years, both in the total group and in the Kyoto subgroup, showing high reproducibility of the observation on a whole-country basis and on a local basis. When the levels at 80 years of age were compared with those at 30 years, there was an approximately 60% and 30% decrease in CR and factor G, respectively. Thus, the effects of aging were more marked on CR than on factor G (and therefore on SG). Menopause appeared to be an influential factor in the reduction of CR and SG, separately from aging itself. *Conclusions*:
Urinary levels of creatinine and, to a lesser extent, urine specific gravity, steadily decreased as a function of ages of over 30 years in women.

Keywords Aging · Creatinine in urine · Menopause · Urine specific gravity · Women

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Introduction

Urinary levels of chemicals, including elements, have been widely used as useful markers of exposure to various organic chemicals as well as metals (World Health Organization 1996a, b). In reflection of concerns about apparent differences in urine density among samples, urinary levels of creatinine (CR) (Jackson 1966) and specific gravity (SG) (Buchwald 1964; Rainsford and Lloyd Davies 1965; Elkins et al. 1974) have been employed as common denominators of analyte levels in urine to "adjust" or "correct" for urine density.

One of the problems associated with urine density correction in terms of CR or SG is that CR concentration tends to be lower among aged people. In an early report, for example, Alessio et al. (1985) observed an age-dependent decrease in urinary CR in a group of men between the ages of < 30 years to > 50 years. Literature survey appears to suggest that less discussion has been made on age-dependent changes in SG. Nevertheless, because SG correlates significantly with CR, to be discussed later, the criticism on CR correction (Greenberg and Levine 1989) may also be applicable to correction in terms of SG. In practice, both CR and SG correction do not always improve the correlation on a group basis between chemical exposure and levels of analytes in urine (Berlin et al. 1985; Boeniger et al. 1993; Inoue et al. 1998; Ikeda 1999; Kawai et al. 2001), although the correction for CR and SG may reduce intra-individual variation (Mason et al. 1998).

The present study was initiated to examine, in a large-scale epidemiology of women, whether CR and SG

would decrease as a function of advancement in age, and, if so, to what extent. Correlation between CR and SG, and possible effects of menopause on CR and SG were also examined.

Materials and methods

Databases, and addition of survey results on aged populations

Two databases on women (who gave written informed consents for participation) in non-polluted areas in Japan were re-examined for urine dilution parameters of creatinine (CR) and specific gravity (SG), and smoking habits as well as age, menopausal status and place of residence (in terms of prefecture; Japan consists of 47 prefectures). One database (Ezaki et al. 2003), established in 2000–2001, was on 10,883 women (aged mostly from 40 years to 60 years) in ten prefectures all over Japan, and the other (Tsukahara et al. 2003), established in 2002, was on 1,482 women (mostly aged 35 years–60 years) in six prefectures out of the ten. In both surveys the second morning urine samples were collected. The two databases were combined after adjustment for those who were registered in both databases (with priority given to the first database for data adoption). Selection for never-smoking women gave 8,972 and 995 cases from the first and second databases, respectively.

Because the number of women over 60 years of age was rather limited in the two databases, a supplemental survey was conducted in 2003 on an additional 1,274 women volunteers (mostly ≥60 years of age). The subjects also provided written informed consent to join the survey, offered peripheral blood and second morning urine samples, and filled questionnaires; the procedures were exactly the same as those in previous surveys (Ezaki et al. 2003; Tsukahara et al. 2003). Selection for never-smokers (excluding those with no clear answer with regard to smoking habits) gave 1,123 women in total. The selection rate for never-smoking women was 88.1% [=(1,123/1,274)×100].

Thus, 11,090 never-smoking women were available in total (the total group). In addition to the total group, a subgroup of 1,851 women was selected from Kyoto city only, so that it could be determined whether the observation in the total group was reproducible, even after the potential effects of location had been excluded. The distribution of the women by age was such that approximately 35%–40% each were 40–49 years and 50–59 years and about 15% were ≥60 years, in the total group, whereas, in the Kyoto subgroup, those aged 40–49 years and 50–59 years accounted for approximately 30%–35%, and those ≥60 years accounted for nearly 20% (Table 1).

The subjects were classified into pre-menopausal, menopausal, and post-menopausal, according to the information self-reported in the questionnaires. The information was available from 10,135 women in the total group including 1,729 women in the Kyoto subgroup, of whom 315 (the total group) and 20 women (the Kyoto subgroup) became amenorrheic after having undergone gynecological operations and were not taken into account in menopause-related analyses.

Urinalysis for creatinine and specific gravity

The urine samples in the Ezaki et al. collection (Ezaki et al. 2003), the Tsukahara et al. collection (Tsukahara et al. 2003) and the supplemental collection were analyzed for CR by alkali–picric acid colorimetry taking advantage of an Hitachi autoanalyzer (Model 700; Hitachi, Hitachinaka, Japan), and for specific gravity with a refractometer (Atago, Tokyo, Japan). The quality of CR measurement was certified by an external quality control program (run annually by the Japan Medical Association).

Statistical analysis

Normality of analyte distribution was examined by Kolmogorov–Smirnov test and Wilcoxon signed rank test, taking $P < 0.05$ for both as the significant level. Arithmetic means (AMs) and arithmetic standard deviations (ASDs) were taken as the parameters of distribution for normal distribution. In the analysis, SG was expressed in terms of factor G, which was defined by the equation factor $G = (SG - 1.000) \times 1,000$ (Levine and Fahy 1945; Sherwood 1999) for practical convenience.

Both linear and quadratic regression analyses were conducted between the age and urine density indicators of CR and SG. With quadratic assumption, the age for a local maximum or minimum ($age_{max/min}$) was calculated by the equation $age_{max/min} = -\beta/2\gamma$ (as the point where $dY/dX = 0$), in which β and γ are the parameters in a quadratic equation $Y = \alpha + \beta X + \gamma X^2$, where X is the age in years and Y is an analyte concentration. When $-\beta/2\gamma$ was out of the age range of 0–80 years, the $age_{max/min}$ was considered not meaningful because the life expectancy for the year 2000 among people in Japan was 77.72 and 84.60 years for men and women, respectively (Health and Welfare Statistics Association 2003).

Multiple regression analysis was conducted, taking ten prefectures together with age, CR and SG (excluding either CR or SG when it was a dependent variable) as independent variables (1 and 0 were allocated for the prefecture concerned, e.g., prefecture A, and other prefectures, i.e., prefectures non-A) and CR or SG as a dependent variable.

Results

Age and urinary parameters

Multiple comparison test (Scheffe) showed that age, CR, and SG were not uniform among the ten prefectures.

Table 1 Number of women and age distribution by group

Group		Age range in years							
		≤29	30–39	40–49	50–59	60–69	70–79	≥80	Total
The total group	Number	131	1,503	3,652	4,154	1,256	346	48	11,090
	Percentage	1.2	13.6	32.9	37.5	11.3	3.1	0.4	100.0
The Kyoto subgroup	Number	45	209	544	660	360	32	1	1,851
	Percentage	2.4	11.3	29.4	35.7	19.4	1.7	0.1	100.0

Multiple regression analysis, with CR or SG as a dependent variable, and the ten prefectures, age, CR, and SG (excluding CR or SG when it was a dependent variable) as independent variables, however, showed that none of the standardized regression coefficients for the prefectures was statistically significant ($P > 0.10$). The coefficients for SG and age were significant ($P < 0.01$) when CR was the dependent variable, and similarly, the coefficients for CR and age were significant ($P < 0.01$) when SG was the dependent variable. It was also observed that the coefficients for CR and SG were significant ($P < 0.01$) when age was the dependent variable.

Means of the age distribution were approximately 50 years both in the total group and in the Kyoto subgroup (Table 2), and the ages of the oldest subjects were in excess of 80 years. Age distributed normally with ASDs of about 10 years or about 10% of corresponding AM values. ASD values were in excess of 50% AM values for CR and approximately 37% for factor G. Bias from normal distribution was, however, not significant ($P > 0.05$). It should be noted that the AM of CR was approximately 1 g/l and the AM of factor G was 17 or very close to 16 (or 1.016 as SG, the standard SG value proposed by Buchwald 1964 and Rainsford and Lloyd Davies 1965).

Age-dependent changes in CR and SG

In order to examine if CR and SG values vary age-dependently, the subjects were classified by decades of age, and AM values (together with ASD) for the age classes were calculated. The results, summarized in Table 3, showed that both CR and factor G (and, therefore, SG) decreased as a function of advancement in age, although the difference in the values for ages between the 20s and 30s appeared to be not very substantial, especially in the case of the total group. Whereas AM values decreased at higher ages, both for CR and factor G, coefficients of variation (CVs, which is ASD/AM in percent) stayed essentially unchanged.

Linear regression of CR and SG with age

Age-dependent changes in CR and factor G were examined with two assumptions of linear and quadratic relations; the latter was examined to determine if the regression of higher degree might give a larger correlation coefficient (Table 4). Comparison of R^2 values as a marker of closeness in the regression showed that the R^2 after quadraticity assumption was either no or only slightly larger than that after linearity assumption, indicating that that the decrease continued, essentially, throughout life. For visual understanding, the relationships for the total group are depicted in Fig. 1 after quadraticity assumption.

Based on the linear regression equations of CR and factor G with age, the values were estimated for the two ages, 30 years and 80 years (Table 5). It was clear that the values for 80 years of age (i.e., II) were substantially smaller than the values for 30 years (i.e., I) both for CR and factor G in the total group and the Kyoto subgroup. The ratio of the values for 80 years over that for 30 years (or II/I ratio in Table 5) was approximately 0.4

Table 2 Basic parameters of the two groups (*AM* arithmetic mean, *ASD* arithmetic standard deviation, *GM* geometric mean, *GSD* geometric standard deviation)

Parameter	Unit	The total group[a]				The Kyoto subgroup[b]			
		AM	ASD	GM	GSD	AM	ASD	GM	GSD
Number of women		11,090				1,851			
Age	Years	50.0 (minimum 20, maximum 86)	9.8			50.8 (minimum 21, maximum 82)	10.0		
Urine									
Creatinine	g/l	0.99	0.57	0.83	1.91	0.96	0.57	0.79	1.93
Factor G[c]		17.4	6.52	15.9	1.60	17.3	6.44	15.8	1.59

[a]Non-smoking women all over Japan
[b]Those from Kyoto city only, extracted from the total group
[c]Factor G = (specific gravity−1.000)×1,000

Table 3 Age-dependent decrease in CR and specific gravity

Group Age range (years)	Number	Age (years)			CR (g/l)			Factor G[a]		
		AM	ASD	CV[b]	AM	ASD	CV[b]	AM	ASD	CV[b]
The total group[c]										
20–29	131	26.2	2.3	8.9	1.25	0.70	55.9	19.7	7.6	38.3
30–39	1,503	36.3	2.2	6.2	1.24	0.66	53.1	19.2	7.0	36.6
40–49	3,652	44.8	2.9	6.5	1.10	0.60	54.2	18.3	6.7	36.4
50–59	4,157	54.0	2.9	5.3	0.90	0.50	55.2	16.8	6.2	36.7
60–69	1,257	63.2	2.8	4.4	0.78	0.41	52.5	15.6	5.6	35.7
70 and over	394	74.5	3.7	5.0	0.69	0.41	59.1	14.2	5.7	40.2
Kyoto subgroup[d]										
20–29	45	25.5	2.4	9.3	1.44	0.79	54.5	21.4	7.5	34.9
30–39	209	36.6	2.0	5.6	1.25	0.72	58.1	19.1	7.2	37.7
40–49	544	44.6	2.8	6.4	1.07	0.58	54.7	18.3	6.6	36.0
50–59	660	54.4	2.9	5.3	0.84	0.49	58.4	16.5	6.2	37.6
60–69	360	63.1	2.8	4.4	0.80	0.44	54.7	15.8	5.3	33.6
70 & over	33	72.6	3.0	4.1	0.76	0.36	46.9	15.5	5.4	34.7

[a]Specific gravity is expressed in terms of factor G, which is defined as (specific gravity−1.000)×1,000
[b]Coefficient of variation (ASD/AM in percent)
[c]11,090 women from all over Japan
[d]1,851 women from Kyoto city only

for CR (i.e., a decrease by 60%) and it was approximately 0.7 (a 30% decrease) for factor G, indicating that the decrease appeared to be more substantial for CR than for factor G. The extent of the decrease was essentially the same for the total group and the Kyoto subgroup.

Correlation between CR and SG

When correlation between CR and factor G was examined in the total group (Fig. 2) with a linear regression assumption, the regression line obtained was $Y = -0.29 + 0.074 \, X$, where X and Y were factor G and CR (grams per liter), respectively. The correlation coefficient (r) was as high as 0.846 ($P < 0.01$). Similar calculation with the Kyoto subgroup data gave an equation of $Y = -0.35 + 0.076 \, X$ ($r = 0.848$, $P < 0.01$). Quadraticity assumption did not induce a substantial

increase in the coefficient, partly because the coefficient was already close to 1.

Effects of menopause on the decrease in CR and factor G

Because the decrease in CR and factor G was observed at advanced ages (Tables 3 and 4), effects of menopause were suspected. For the analysis, those in the age ranges of 40–49 years and 50–59 years were selected because substantial numbers of women were available for different menopausal status; information on menopause status was available on 3,486 (95.5%) and 3,708 women (89.3%) among 3,465 and 3,532 women at the ages of 40–49 years and 50–59 years, respectively, excluding those who had undergone gynecological operations and had not menstruated since then. The women were classified as pre-menopausal, menopausal, and

Table 4 Age-dependent changes in creatinine concentration and specific gravity, with an assumption of linear or quadratic relation. The values are parameters of a regression line in which $Y = \alpha + \beta X$ (in the case of linear regression) or $Y = \alpha + \beta X + \gamma X^2$ (in the case of quadratic regression), where X is the age in years

Y in the equation	Unit	Equation type	The total group[a]					The Kyoto subgroup[b]				
			α	β	γ	R²	Maximum/ minimum[c] at the age of	α	β	γ	R²	Maximum/ minimum[c] at the age of
Creatinine	g/l	Linear	1.786	−0.016		0.075		1.792	−0.016		0.081	
	g/l	Quadratic	2.059	−0.027	11×10^{-5}	0.075	(Minimum > 80)	2.547	−0.048	32×10^{-5}	0.087	Minimum 76
Factor G[d]		Linear	23.957	−0.130		0.038		23.980	−0.131		0.042	
		Quadratic	23.325	−0.105	-25×10^{-5}	0.038	(Maximum < 0)	27.634	−0.284	15×10^{-4}	0.043	(Minimum > 80).

[a]11,090 women from all over Japan
[b]1,851 women from Kyoto city only
[c]The age (in years) of local minimum or local maximum
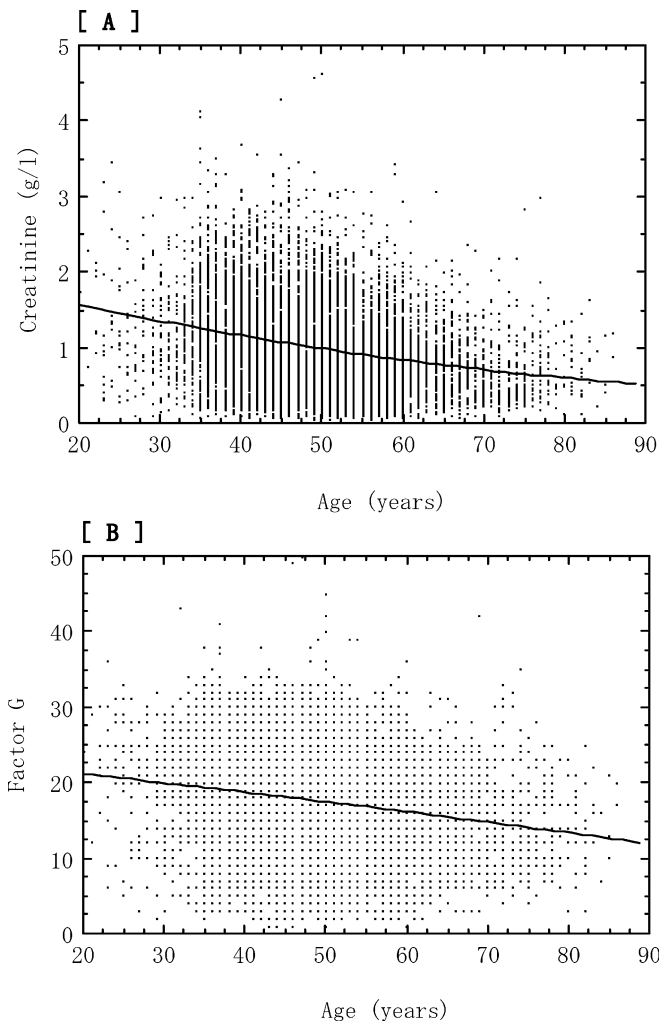[d]Factor G = (specific gravity−1.000)×1,000

Fig. 1 Age-dependent reduction in (A) creatinine and (B) specific gravity in urine. *Each dot* represents one woman (11,090 in the total group), and *the curve* is drawn with an assumption of quadratic relation. The equation for the curve in **A** is $Y = 2.059 - 0.027X + 0.00011X^2$ ($r = 0.27$, $P < 0.01$), where X is age (in years) and Y is creatinine (g/l urine), and that in **B** is $Y = 23.325 - 0.105X - 0.00025X^2$ ($r = 0.19$, $P < 0.01$), where X is age (in years) and Y is factor G [defined as (specific gravity − 1.000)×1,000]

post-menopausal, and mean age, CR and factor G were calculated (Table 6). Analysis of variance, followed by multiple comparison, in the 40 to 49-year-old group

showed that the AM for CR (although not for factor G) of the post-menopausal group was significantly ($P < 0.05$) lower than that for the other two groups (Table 6).

The age was also different among the three groups. Nevertheless, regression analysis (Table 4) suggested that the difference between the pre-menopausal and post-menopausal groups, by 3.7 years ($= 47.9 - 44.2$ years) in the 40–49-year-old group, would result in a decrease in CR by 0.059 g/l ($= 0.016 \times 3.7$), or less than one-third of the decrease observed in reality (0.19 g/l; Table 6). For factor G the estimate was 0.481, whereas the real decrease was 1.3.

In the 50 to 59-year-old group, the AM for both CR and factor G of the pre-menopausal subjects were significantly ($P < 0.05$) higher than for the menopausal and post-menopausal subjects; the difference from the post-menopausal women was 0.17 g/l (AM) for CR and 1.4 (AM) for factor G. The decreases were approximately three-times larger than the estimated decreases, 0.06 g/l ($= 0.016 \times 3.6$) for CR and 0.48 ($= 0.13 \times 3.6$) for factor G, attributable to the advancement in age by 3.6 years (Table 6).

Multiple regression analysis, taking either CR or factor G as a dependent variable and menopausal status and age as two independent variables (Table 7), showed that, although the standardized regression coefficients (SRCs) were not large, menopausal status was a statistically significant determinant both in the 40 to 49-year-old group and the 50 to 59-year-old group (and, to a lesser extent, age also), especially as determinants of CR, although less influential in factor G, in general. It should be noted that menopausal status was more influential than age in all cases studied.

Discussion

The present analyses on adult women clearly demonstrated that both CR and SG decrease as a function of age, especially in the age ranges above 30 years (Table 3). The effects of aging on renal function has been considered such that the function will be generally decreased in elderly populations (Hosoya et al. 1995; Lubran 1995; Worsfold et al. 1999), although Filser et al. (1999) found no decrease in glomerular filtration

Table 5 Ratio of estimates at the ages of 80 years over that at 30 years. The values are estimated with an assumption of linear regression

Y in the equation	Unit	The total group[a]			The Kyoto subgroup[b]		
		I[c] (at 30 years)	II[d] (at 80 years)	II/I[e]	I[c] (at 30 years)	II[d] (at 80 years)	II/I[e]
Creatinine	g/l	1.31	0.51	0.39	1.31	0.51	0.39
Factor G		20.1	14.2	0.70	20.1	13.5	0.67

[a] 11,090 women from all over Japan
[b] 1,851 women from Kyoto city only
[c] The estimate for the age of 30 years
[d] The estimate for the age of 80 years
[e] The ratio of the estimate for the age of 80 years over that for the age of 30 years
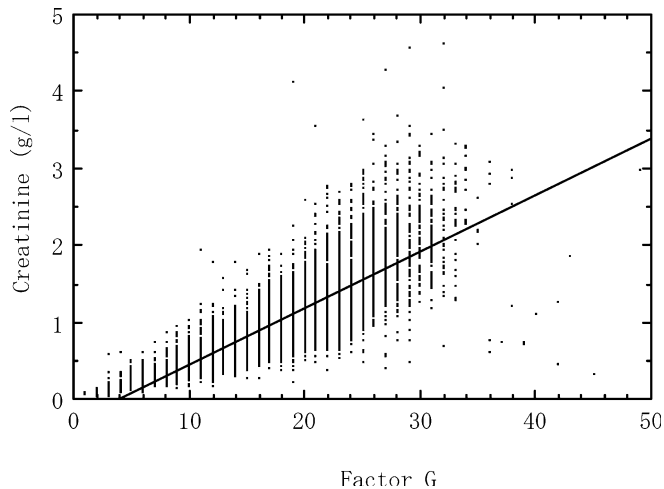
Fig. 2 Correlation between specific gravity in urine and concentration of creatinine; 11,090 women aged < 29 to > 80 years (the total group) were subjected to the analysis. *Each dot* represents one woman, and *the line in the middle* is a calculated regression line, represented by the equation $Y = -0.29 + 0.074\ X$, ($r = 0.85$, $P < 0.01$), where X is factor G [defined as (specific gravity-1.000)×1,000], and Y is creatinine (g/l urine). The curves to show the upper and lower 95% limits of confidence ranges are very close to the regression line, so that they cannot be drawn separately from the line

rate (GFR) in healthy elderly subjects (aged 68 years on average) as compared with young people (25 years of age).

On urinary excretion of creatinine, Alessio et al. (1985) examined CR levels in the second morning spot urine samples of 202 men (aged < 30 to > 50 years) in the general population and found that the mean CR levels gradually decreased, from 1.63 g/l in the < 30-year-old group to 1.18 g/l in the > 50-year-old group, with a decrease by 28%. Hosoya et al. (1995) studied 329 in-patients (191 men and 138 women) who had no renal diseases and found that the average urinary excretion of creatinine in 24-h urine samples decreased from 1.25 g/day in < 50-year-old men to 0.76 g/day in ≥80-year olds,

with a decrease by 39%. The counterpart change in women was from 0.78 g/day to 0.53 g/day with a decrease by 32%. Similarly, Nordin et al. (1998) observed an age-dependent decrease in CR in 24-h urine samples from < 51 to > 75-year-old post-menopausal women, and Worsfold et al. (1999) obtained essentially the same results in a study in which 24-h urine samples from 201 apparently healthy women at the ages of 40–90 years were analyzed. The present observation, with much larger survey populations, is in agreement with observations on healthy women (Nordin et al. 1998; Worsfold et al. 1999) or hospitalized women (Hosoya et al. 1995). In addition, the observation on men (Alessio et al. 1985; Hosoya et al. 1995) suggests that the age-dependent decrease in urinary creatinine levels should be common to both men and women, possibly more substantial in men than in women. Creatinine clearance also decreased as a function of age in both genders (Hosoya et al. 1995). Interestingly, serum creatinine levels changed little at old age, that is, from 1.07 mg to 1.10 mg per 100 ml serum (2.8% increase) at 35–39 years of age to 55–59 years in men, respectively, and 0.86–0.90 mg per 100 ml (4.6% increase) in women of the same age ranges (Bulpitt et al. 1994).

Other factors (Boeniger et al. 1993) may also need attention in considering the observed age-dependent decrease in CR. As creatinine is a metabolite of creatine (Wyss and Kaddurah-Daouk 2000), physiological loss of muscle at advanced ages (Piers et al. 1998) is among the most possible cause of the decrease. No data for lean body mass were available for the women in the present study, unfortunately.

Increase (Mayersohn et al. 1983; Hultman et al. 1996) as well as reduction (Levey et al. 1996) in dietary intake of meat is known to affect urinary CR levels. Dietary intake of meat (combination of animal meat, poultry and fish) of the ≥70-year-old women (133 g/day) was, however, only insignificantly ($P > 0.10$) lower than that of younger people (e.g., 175 g/day for 15–19-year-old women, at which the intake was highest among women of a whole age range) due to wide inter-individual variation (the ASD being nearly equal to the AM) (Ministry

Table 6 CR and factor G by menopausal status. The 40 to 49-year-old and 50 to 59-year-old women in the total group were subjected to analysis

Age group Menopausal status	Number	Age (years)			CR (g/l)			Factor G[a]		
		AM	ASD	CV[b]	AM	ASD	CV[b]	AM	ASD	CV[b]
40 years to 49 years of age										
Pre-menopausal	2,696	44.2	2.8	6.3	1.12	0.61	54.5	18.4	6.8	37.0
Menopausal	594	46.5	2.5	5.4	1.06	0.55	51.9	18.0	6.3	35.0
Post-menopausal	195	47.9	1.6	3.3	0.92	0.48	52.2	17.1	6.1	35.7
50 years to 59 years of age										
Pre-menopausal	340	51.3	1.6	3.1	1.05	0.57	54.3	18.1	6.2	34.3
Menopausal	595	51.6	1.5	2.9	0.91	0.49	53.8	17.0	6.4	37.6
Post-menopausal	2,597	54.9	2.7	4.9	0.88	0.49	55.7	16.7	6.1	36.5

[a]Specific gravity is expressed in terms of factor G, which is defined as (specific gravity-1.000)×1,000
[b]Coefficient of variation (ASD/AM in percent)

Table 7 CR and factor G by menopausal status

Age group	Dependent variable	Number	Independent variables				|R|	R²
			First variable (SRC[a])		Second variable (SRC[a])			
40 to 49 years of age	CR	3,465	Menopausal status	(−0.062**)	Age	(−0.043*)	0.088	0.008
	Factor G	3,465	Menopausal status	(−0.037*)	Age	(−0.017)	0.046	0.002
50 to 59 years of age	CR	3,532	Menopausal status	(−0.078**)	Age	(−0.040*)	0.104	0.011
	Factor G	3,532	Menopausal status	(−0.050**)	Age	(−0.029)	0.068	0.005

** and * for $P < 0.01$ and < 0.05, respectively
[a]standardized regression coefficient

of Health, Labor and Welfare 2003). Thus, the effects of changes in dietary habits should be minimum.

The present analysis made it clear that menopause is an influential factor of CR, the power being comparable to that of age (Table 7). The finding that urinary CR was lower among post-menopausal women than among pre-menopausal women was as previously reported; for example, Nordin et al. (1991) observed that average CR in spot urine samples from post-menopausal women was significantly ($P < 0.01$) lower than that from pre-menopausal subjects, and the same was also the case when CR levels were compared in 24-h urine samples, although statistical power for the difference varied depending on the studies (Nordin et al. 1993, 1999).

Post-menopausal women naturally tend to be older than pre-menopausal ones, and it is difficult to evaluate the effects of menopause separately from that of aging. The observation by Alessio et al. (1985) on the age-dependent reduction in CR in men and that by Hosoya et al. (1995) reporting more marked decrease in CR in elderly men than in elderly women suggest that aging itself is a factor in the reduction of urinary CR. Nevertheless, quantitative estimation (Table 6) in the present study showed that the difference in urinary CR between pre-menopausal and post-menopausal women was larger than what could be explained by the advancement in age. It appears likely, therefore, that menopause is an influential factor in the reduction of urinary CR level, independent of the effect of aging. It is apparent that this possibility deserves further studies.

There is a paucity of studies with regard to the effect of aging on urine specific gravity. It should be noted, however, that a close and statistically significant correlation ($r > 0.8$, $P < 0.01$) was detected, in the present analysis, between CR and factor G (and, therefore, SG), in agreement with the observation by Carrieri et al. (2001). Whereas they observed normality in the distribution of both CR and SG, the present analysis showed that ASD values were close to 60% of the AM in the case of CR and 37% in the case of factor G, although the GSD values were less than 2, irrespective of correction for CR or SG (Table 2). Larger ASD/AM ratios may be due to the fact that the age range of the subjects in the present study was wide; some subjects were ≤ 29 years and others were

≥ 80 years (Table 2). The close correlation between two parameters of urine dilution may suggest that the same care should be practiced when urinary analyte levels are corrected for urine density not only in terms of CR but SG as well, although more care may be necessary when correction for CR rather than for factor G (or SG) is employed.

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