$F_{2\alpha}$) in the culture supernatants and mouse plasma were measured using a commercially available EIA kit (Cayman Chemical). Culture supernatants were directly applied to EIA, while plasma was applied to EIA after solid phase extraction purification according to the manufacturer's instructions.

2.5. Western blotting

Western blotting was performed as previously described [30], to detect the expression of VCAM-1 and 4-HNE in cultured ECs and mouse aortas. Descending aortas were prepared as described in ROS measurements. The antibodies used in this study were anti-4-HNE monoclonal antibody (JaICA, Shizuoka, Japan), anti-VCAM-1 polyclonal antibody (Santa Cruz Biotechnology) and anti-3-nitrotyrosine monoclonal antibody (Upstate). Densitometric analysis was performed using an image scanner and the NIH software.

2.6. Data analysis

All values are express as mean ± S.E.M. Data were analyzed using one-factor ANOVA. If a statistically significant effect was found, Newman–Keuls' test was performed to isolate the difference between the groups. Differences with a value of $P < 0.05$ were considered statistically significant.

3. Results

3.1. Effects of edaravone on H_2O_2-induced EC apoptosis and ROS

As shown in Fig. 1A, edaravone dose-dependently inhibited EC apoptosis in culture, which was induced 24 h after H_2O_2 treatment. Edaravone was then employed in a rat model of H_2O_2-induced EC apoptosis. Consistent with the *in vitro* experiment, edaravone of 10 mg/kg/day decreased EC apoptosis of the rat carotid artery by approximately 40% (Fig. 1B).

We next examined whether edaravone decreased ROS production in the process of H_2O_2-induced EC apoptosis. For this purpose, DHE fluorescent, a marker of intracellular production of superoxide anions, release of 8-isoprostane into the culture supernatants and accumulation of 4-HNE, a pivotal end-product of lipid peroxidation [31], were measured using cultured ECs. We also examined the expression of VCAM-1 as a marker of endothelial injury or activation [32]. Edaravone decreased DHE fluorescent, 8-isoprostane formation and VCAM-1 expression at 3 h after H_2O_2 treatment in a dose-dependent manner (Fig. 2A–C). As shown in Fig. 2D, multiple bands showing 4-HNE-Michael protein adducts [33,34] were accumulated after H_2O_2 treatment in a time-dependent manner. Consequently, the effect of edaravone on 4-HNE expression was examined at 3 h after H_2O_2 treatment (4.5 h after H_2O_2 was initially added). Edaravone decreased 4-HNE expression in a dose dependent manner.

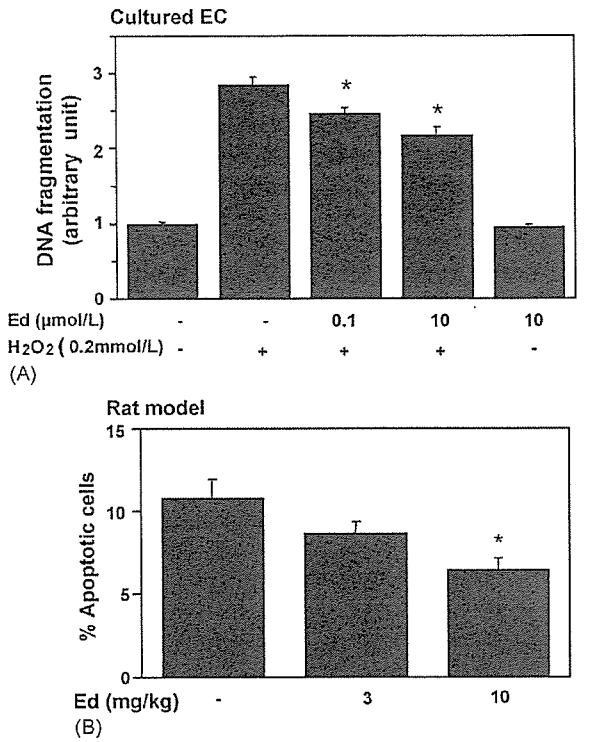

Fig. 1. Effects of edaravone (Ed) on H_2O_2-induced EC apoptosis in culture (A) and in a rat model (B). (A) Ed or its vehicle was added to the culture medium 24 h before H_2O_2 treatment until assay. EC apoptosis was evaluated 24 h after H_2O_2 treatment (0.2 mmol/L) by means of DNA fragmentation. Values are expressed as mean ± S.E.M. ($n = 3$). $^*P < 0.05$ vs. H_2O_2 (+) + Ed (−). (B) Ed or its vehicle was intraperitoneally injected once a day for 3 days before H_2O_2 treatment. At 24 h after H_2O_2 treatment, apoptotic ECs were counted per high power field and the ratio of the apoptotic cell number to the intact cells was calculated using *en face* specimens of the carotid artery stained with Hoechst 33342. Values are expressed as mean ± S.E.M. ($n = 7$). $^*P < 0.05$ vs. vehicle.

3.2. Effects of edaravone on atherosclerotic lesions and ROS in ApoE-KO mice

In the next set of experiments, we examined whether edaravone could suppress the atherosclerotic lesions in ApoE-KO mice fed a high cholesterol diet for 4 weeks. As shown in Fig. 3A and B, atheromatous lesions both in the aortic sinus and the descending aorta were smaller in mice treated with 10 mg/kg/day edaravone than in those with vehicle. This dose of edaravone did not influence body weight, blood pressure or plasma LDL and HDL cholesterol levels (Table 1).

Then, we examined whether the anti-atherogenic effects of edaravone were associated with the decrease in ROS production. Peroxynitrite formation was assessed as 3-nitrotyrosine accumulation in the aorta [28]. Both immunohistochemistry and Western blotting showed that edaravone inhibited nitrotyrosine accumulation in the aorta of ApoE-KO mice (Fig. 4A(a) and A(b)). Superoxide production *in situ* was examined using DHE staining of the descend-

Table 1
Body weight, blood pressure and plasma lipid levels in ApoE-KO mice treated with edaravone or vehicle

	Vehicle	Edaravone
Body weight (g)	21.4 ± 0.5	21.0 ± 0.5
Systolic blood pressure (mmHg)	106 ± 2	103 ± 3
Total cholesterol (mg/dL)	1967 ± 38	1872 ± 66
HDL cholesterol (mg/dL)	66 ± 6	82 ± 9
LDL cholesterol (mg/dL)	602 ± 24	602 ± 12

The values are shown as mean ± S.E. ($n = 14$). There were no significant differences in the values between the two groups.

ing aorta. As shown in Fig. 4B, ethidium fluorescence, which was amplified in ApoE-KO mice, was decreased by edaravone treatment. A quantitative analysis by the superoxide dismutase-inhibitable cytochrome *c* reduction assay revealed that $O_2^{\bullet -}$ levels in aortic rings of ApoE-KO mice were decreased by 43% in edaravone-treated ApoE-KO mice compared to those in vehicle-treated mice (Fig. 4C). Consistent with these results, plasma 8-isoprostane levels and 4-HNE expression in the descending aorta, both of which were elevated in ApoE-KO mice compared to

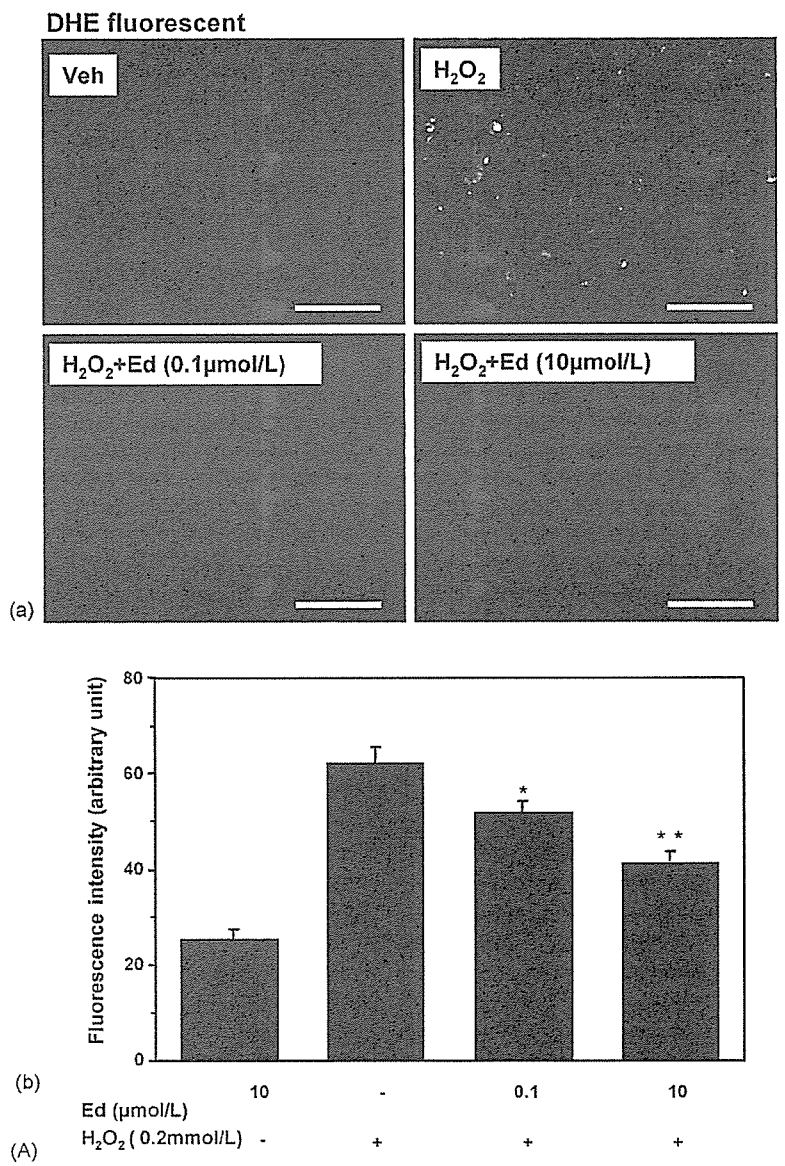

Fig. 2. Effects of edaravone (Ed) on DHE fluorescent (A) and 8-isoprostane formation (B), VCAM-1 expression (C) and 4-HNE expression (D) in cultured EC. Ed or its vehicle was added to the culture medium 24 h before H_2O_2 treatment until assay. DHE fluorescent ($n = 6$), 8-isoprostane concentration ($n = 3$) and VCAM-1 expression ($n = 3$) in the cell lysate were measured 3 h after H_2O_2 treatment. Values are expressed as mean ± S.E.M. Time dependent changes of 4-HNE expression after H_2O_2 treatment was detected by Western blotting. Representative image showed that 4-HNE-Michael protein adducts were accumulated after treatment (D(a)). The major 97 kDa band was measured 4.5 h after H_2O_2 treatment in the presence or absence of edaravone (D(b)). Values are expressed as mean ± S.E.M. ($n = 3$). $^{*}P < 0.05$, $^{**}P < 0.01$ vs. H_2O_2 (+) + Ed (−).

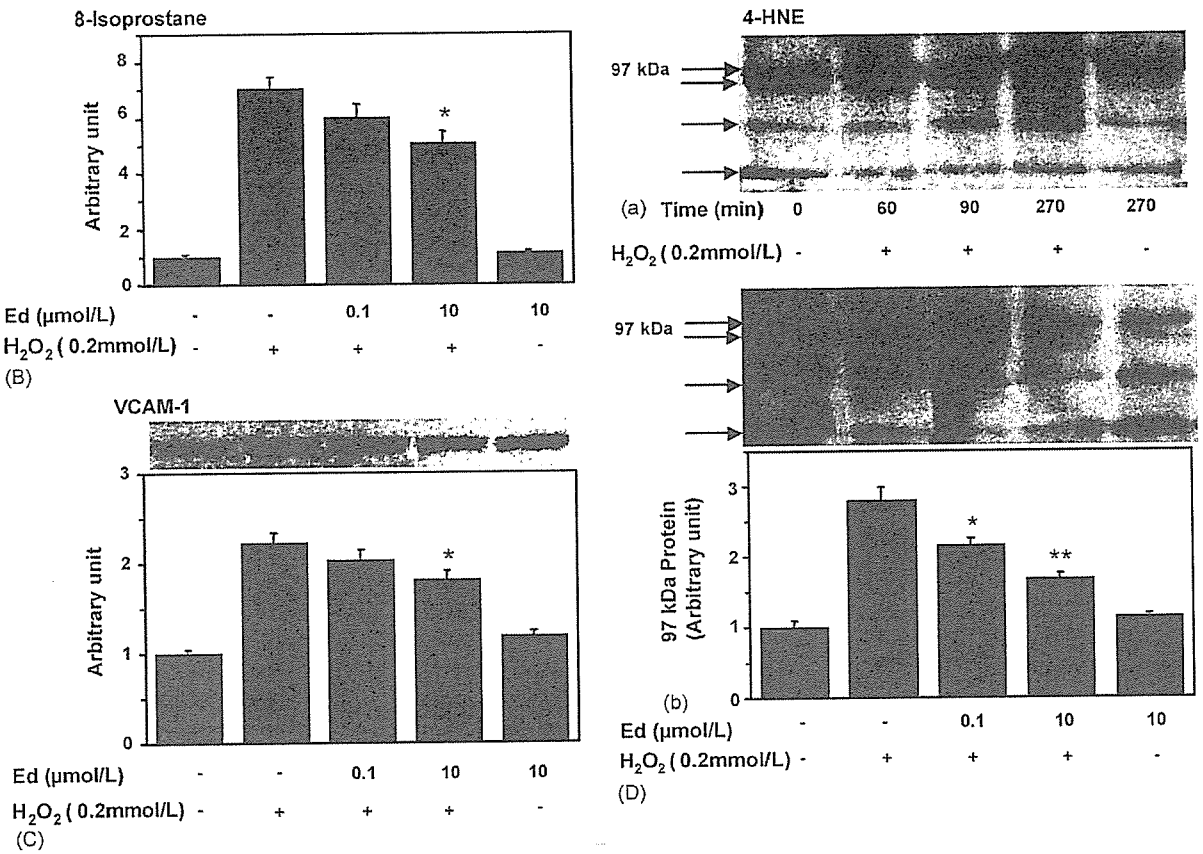

Fig. 2. (*Continued*).

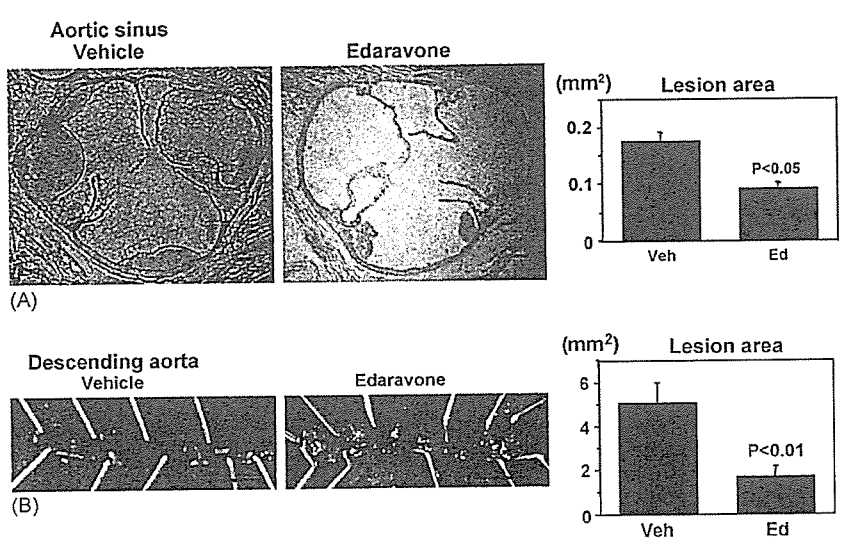

Fig. 3. Effects of edaravone on atherosclerotic lesion in ApoE-KO mice. ApoE-KO mice were fed a high-cholesterol diet for 4 weeks with the administration of edaravone (10 mg/kg daily) or its vehicle by i.p. injection. (A) Oil red O-stained cross-sections of the aortic sinus (bar = 100 μm) and morphometric analysis of the lesions are shown. (B) Oil red O-stained *en face* specimens of the descending aorta (bar = 5 mm) and morphometric analysis of the lesions are shown. Values are expressed as mean ± S.E.M. ($n = 14$).

those in wild-type C57BL/6 mice fed a normal chow, were decreased by edaravone treatment (Fig. 4D and E). Finally, the increase in VCAM-1 expression in the aorta of ApoE-KO mice was attenuated by edaravone as well (Fig. 4F).

4. Discussion

A number of studies have shown that ROS contribute to the pathogenesis of endothelial dysfunction and atherosclerosis formation. In addition to $O_2^{\bullet -}$ that is predominantly pro-

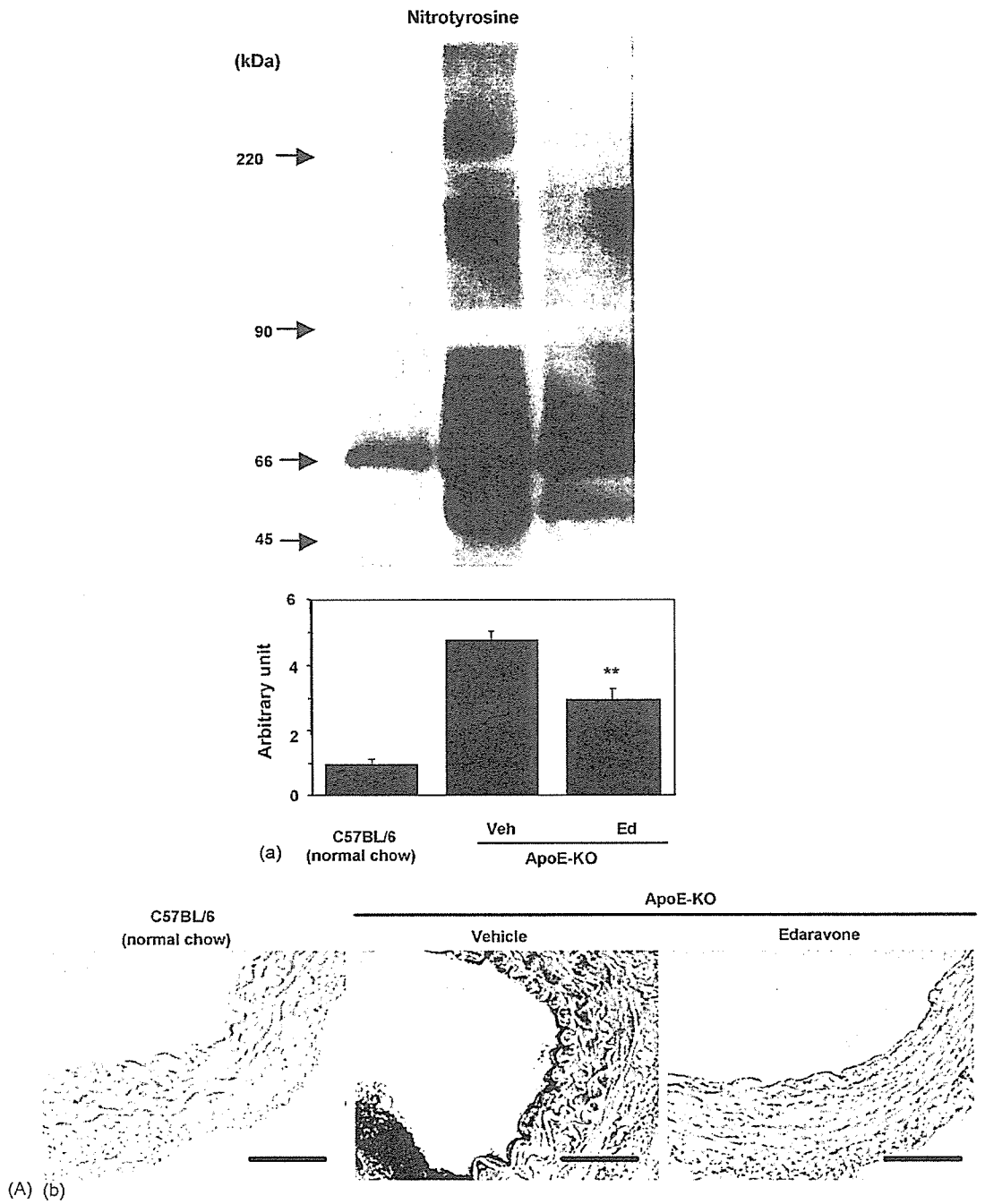

Fig. 4. Effects of edaravone (Ed) on ROS production (A–E) and VCAM-1 expression (F) in ApoE-KO mice. (A) Nitrotyrosine contents in the aorta was examined by Western blot analysis (A(a), $n=6$) and immunohistochemistry (A(b)). Bar = 50 μm. (B) Fresh-frozen cross-sections of the aorta were stained with DHE, and representative fluorescent micrographs are shown (bar = 100 μm). (C) Superoxide anion in aortic rings was determined using SOD inhibitable-cytochrome *c* reduction assay ($n=6$). (D) 8-Isoprostane level in mouse plasma was measured with EIA ($n=6$). (E and F) Representative Western blotting for 4-HNE (97 kDa band) and VCAM-1 expression in the aorta and densitometric analysis are shown ($n=3$). Values are expressed as mean ± S.E.M. $^{*}P<0.05$, $^{**}P<0.01$ vs. vehicle (Veh). C57/BL6 mice fed a normal chow serve as the control.

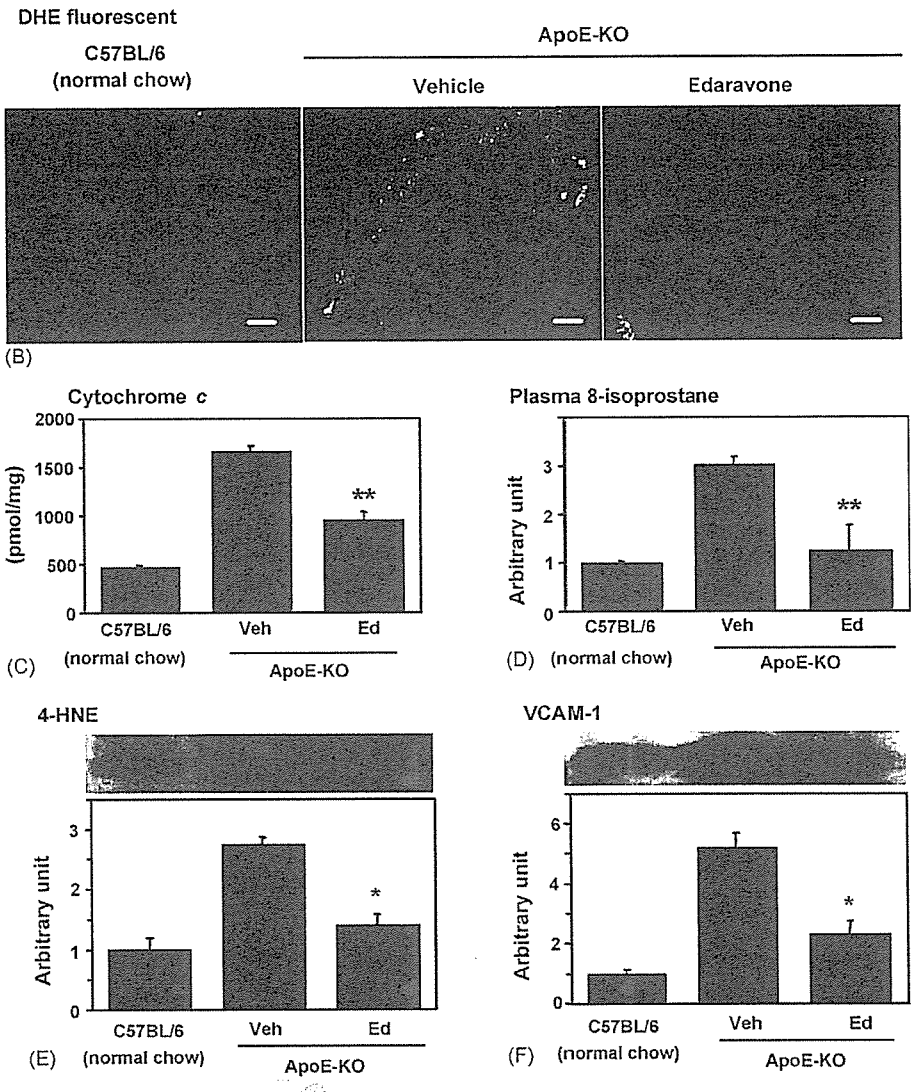

Fig. 4. (*Continued*).

duced via NAD(P)H oxidase [35], •OH as well as LOO• [36] and $ONOO^-$ [37] play a role in atherogenesis. In particular, •OH is extremely strong in terms of oxidative activity and cellular damage [38]. Therefore, it might be essential to scavenge the wide range of ROS for the prevention of atherosclerosis. As a matter of fact, recent clinical trials have denied the protective effects of Vitamin E, which predominantly reacts with LOO• [39], on cardiovascular events [18,19].

Edaravone, a potent free radical scavenger with unique properties, works by donating an electron from edaravone anion to free radicals [22]. Edaravone quenches •OH and inhibits both •OH-dependent and •OH-independent lipid peroxidation [22]. Edaravone shows inhibitory effects on both water-soluble and lipid-soluble LOO-induced peroxidation systems [22]. Edaravone also inhibits $ONOO^-$-induced tyrosine nitration [22]. These properties are different from those of water-soluble Vitamin C and lipid-soluble Vitamin E.

In the present study, we demonstrated that edaravone suppressed endothelial apoptosis and fatty streak formation. Reduced expression of VCAM-1, a marker of vascular injury and activation [32], were corroborated with these results. In cultured ECs, protein expression of VCAM-1 was induced as early as 3 h after H_2O_2 treatment (actually 4.5 h after addition of H_2O_2, Fig. 2C). This is reasonable based on our time course experiments (data not shown), and is consistent with the previous reports that VCAM-1 protein has been induced 4–6 h after cytokine stimulation through an antioxidant-sensitive mechanism [40,41]. Although the experimental conditions were different between the cell culture and animal studies, edaravone inhibited both the rapid induction of VCAM-1 in cultured ECs and the chronic upregulation of VCAM-1 in the aorta of ApoE-KO mice, further supporting the vasoprotective effects of edaravone.

Edaravone has been clinically used as a neuroprotectant in the treatment of ischemic stroke in Japan from 2001. The dose of edaravone used in this study (intraperitoneal injection of 10 mg/kg) has been reported to be comparable to that of intravenous injection in clinical use in terms of plasma concentration [42]. This compound has been reported to preserve endothelial function in ischemic brain [43] and ameliorate ischemia-reperfusion injury in various organs such as kidney [44] and heart [45]. Also, edaravone has been shown to inhibit pressure overload-induced cardiac hypertrophy [42]. To our knowledge, however, the effect of edaravone on atherosclerosis has never been reported till now.

The effects of edaravone on endothelial injury and atherosclerosis were associated with the decrease in ROS production including peroxynitrite, superoxide anion and 8-isoprostane, suggesting the mechanistic role of antioxidation in vascular protection. Edaravone also inhibited the expression of 4-HNE in vascular tissues, further indicating the antioxidant activity and suggesting the signaling cascade leading to endothelial injury, because 4-HNE triggers cellular damages through the MAP kinase pathway as an end-product of ROS [34]. Antioxidant effects of edaravone on lipoproteins were not determined in the present study because of the methodological limitation in mice. It has been reported, however, that edaravone can inhibit oxidative modification of low-density lipoprotein *in vitro* and in rats [46]. Consequently, it is likely that reduced lipoprotein oxidation would have played a role in the anti-atherosclerotic effects of edaravone in ApoE-KO mice. Furthermore, edaravone has been reported to stimulate the expression of endothelial nitric oxide synthase in cultured ECs [46] and the artery [47], leading to the increased production of nitric oxide. Taken together with the effects on peroxynitrite formation, edaravone might synergistically increase the availability of nitric oxide, which exerts vasoprotective and anti-atherosclerotic action.

The effects of edaravone on advanced and complicated lesions of atherosclerosis were not investigated in this study. Neither, the effects on plaque ruptures nor consequent cardiovascular events are known. This study demonstrated that edaravone might be a potential new therapeutic agent for the prevention and treatment of early atherosclerosis. For the purpose of chronic use, however, the innovation of drug preparation for oral administration is necessary. Another application of edaravone might be the prevention of restenosis after percutaneous coronary interventions, since ROS plays an important role in neointimal formation after angioplasty [48]. Intravenous injection of edaravone for several days might inhibit neointimal formation in addition to ischemia reperfusion injury of cardiomyocytes [45]. Taken together, edaravone is expected to show protective effect on ROS-related vascular diseases beyond cerebral infarction.

In summary, edaravone, a free radical scavenger with unique properties, attenuated oxidative stress-induced endothelial damage in rats and early atherosclerosis in ApoE-KO mice in association with the inhibition of ROS formation. These findings provide new information on the role of ROS in atherogenesis and the therapeutic strategy for atherosclerosis.

Acknowledgements

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ORIGINAL ARTICLE

Simple screening test for risk of falls in the elderly

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Background: The aim of this study is to construct a simple screening test for the risk of falls in community-dwelling elder persons.

Methods: A total of 1378 community-dwelling people aged 65 years and older in five different communities in Japan were asked to answer a self rated questionnaire including 22 items covering physical, cognitive, emotional and social aspects of functioning and environmental factors. At a six-month follow-up, the outcome of fall occurrence and the number of falls was ascertained by social workers, health visitors or nurses.

Results: Five out of 22 items were selected using a logistic regression model. Using this five-item version, a screening test was constructed, and at the best cut-off point, the sensitivity and specificity were 68% and 70%, respectively. The validity of this scale was tested on persons with cognitive dysfunction.

Conclusion: The simplicity and the predictive validity of the screening test support the use of this test in health check ups or general outpatient facilities.

Keywords: accidental fall, aged, mass screening, reliability and validity, risk factor.

Introduction

Falls are rated as the third leading cause of a bed-ridden state and are among the principal causes of morbidity in the elderly in Japan.[1] Previous studies evaluating the risk factors for falls have used history of falls, results of physical performance tests,[2] activity of daily living (ADL)[2,3] and balance and gait[4] as predictors.

Early identification of falls risk is likely to result in earlier implementation of interventions and to minimize development of unwanted sequels such as reduced confidence and activity levels.[5]

In Japan, the Ministry of Health, Labour and Welfare has put roughly 6000 local home care support centers around Japan. The task of these centers, according to Long-Term Care Insurance for the elderly, includes screening of the elders at risk of developing disabilities, including risk for falls. In this context, it is critical to develop a simple screening test to adequately evaluate the risk of falls for each elderly person.

The aim of this study is to evaluate predictive validity of a simple questionnaire composed of 22 items, with the intention of constructing a shortened version that would be simple, but effective to assess the future risk of falls during periodic health check-up or outpatient visits.

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All elderly persons who participated in this research gave written informed consent.

Methods

The initial 22-item questionnaire was constructed by the Working Group of Fall Prevention commissioned by the Japanese Ministry of Health, Labour and Welfare. Known risk factors are transformed into comprehensible text for the elderly, as shown in Table 1. These items were selected by studying both international and Japanese research articles on fall risk factors.[6]

The interclass coefficient (ICC) of the one month test-retest reproducibility study of the 22-item questionnaire score was satisfactory (ICC 0.74, 95% CI 0.46–0.89, $n = 21$).[6]

Individuals chosen for this study lived in five different urban and rural communities and they were over 65 years old.

In cases where subjects had cognitive impairment or difficulty answering, a family member acted as a proxy to help answer the questionnaire.

The outcome of fall occurrence and the number of falls were confirmed by social workers, health visitors or nurses six months after baseline measurement. A fall was defined as an unintentional change in position resulting in coming to rest on the ground or other lower positions.[3]

Statistical analysis was performed on subjects who completed the questionnaire both at baseline and at six month follow-up. One half of the subjects were randomly selected, and the relationship between falls and potential predictors was examined by χ^2 test for each predictor separately (developing samples). Items that achieved statistical significance of $P < 0.05$ were incorporated in the logistic regression analysis to identify predictors. Then, the questionnaire items considered to be associated with falls were selected using any falls as an outcome variable, by forward stepwise selection by the logistic regression model ($P < 0.05$).

The predictive power of the set of selected items, adjusted by the odds ratio, was determined using the area under the Receiver-Operating Characteristic (ROC) curve (AUC) on the other half of the subjects as the validating sample. Finally, the sensitivity and specificity of the model were calculated to obtain the cut-off point.

To test the validity of the scale on persons with cognitive dysfunction, different item functioning (DIF) analysis was performed on subgroups with and without cognitive dysfunction using the Rasch measurement

Table 1 The initial 22-item questionnaire constructed by the Working Group of Fall Prevention and commissioned by the Japanese Ministry of Health, Labour and Welfare

Questionnaire items	Answer (%)†	Incidence of fall (%)‡	*P*
Q1. History of fall within one year = yes	107 (16%)	54 (50%)	$P < 0.0001$
Q2. History of stumbling within one year = yes	288 (42%)	75 (42%)	$P < 0.0001$
Q3. Can you climb stairs without help? = no	261 (38%)	65 (25%)	$P = 0.0001$
Q4. Do you feel your walking speed declined recently? = yes	353 (51%)	76 (22%)	$P = 0.0025$
Q5. Can you cross the road within the green signal interval? = no	74 (11%)	25 (11%)	$P = 0.0019$
Q6. Can you walk 1 km continuously? = no	172 (25%)	46 (27%)	$P = 0.0011$
Q7. Can you stand on one foot for about five seconds? = no	180 (26%)	55 (31%)	$P < 0.0001$
Q8. Do you use cane when you walk? = yes	123 (18%)	43 (35%)	$P < 0.0001$
Q9. Can you squeeze the towel tightly? = no	80 (12%)	26 (33%)	$P = 0.0026$
Q10. Do you feel dizzy? = yes	151 (22%)	39 (26%)	$P = 0.0076$
Q11. Is your back bended? = yes	213 (31%)	62 (29%)	$P < 0.0001$
Q12. Do you have knee pain? = yes	264 (38%)	64 (24%)	$P = 0.0005$
Q13. Do you have a vision problem? = yes	292 (42%)	56 (19%)	$P = 0.2794$
Q14. Do you have a hearing problem? = yes	227 (33%)	48 (21%)	$P = 0.0781$
Q15. Do you think you are forgetful? = yes	332 (48%)	73 (22%)	$P = 0.0020$
Q16. Do you feel anxious to fall when you walk? = yes	226 (33%)	60 (27%)	$P = 0.0001$
Q17. Do you take more than five kinds of prescribed medicines? = yes	161 (23%)	39 (24%)	$P = 0.0231$
Q18. Do you feel dark walking within your home? = yes	54 (8%)	18 (33%)	$P = 0.0124$
Q19. Are there any obstacles within the house? = yes	87 (13%)	25 (29%)	$P = 0.0181$
Q20. Is there any level difference within your home? = yes	426 (62%)	79 (19%)	$P = 0.1799$
Q21. Do you have to use stairs in daily living? = yes	129 (19%)	23 (18%)	$P = 0.7951$
Q22. Do you walk steep slope around the house? = yes	202 (29%)	28 (14%)	$P = 0.2517$

†The answers as indicated in the question raw. ‡The incidence of fall among the relevant answer.

technique.[7–9] Three hundred persons were randomly selected to obtain adequate sample size for this analysis.[10]

In addition, results of the ROC curve were stratified by the presence and absence of memory problem using Q15 of the questionnaire to test the validity of the short version on those with cognitive function problems.

Results

Of 1734 elderly, 1378 (79%) completed the questionnaire both at the baseline study and its six month follow-up. The mean age of the subjects was 75.8 (SD 6.8) years. The number of elders by five research centers was, 1050, 104, 82, 81 and 61, respectively. At least one fall had occurred in 208 elderly (15.1%) during the six month follow-up period. Of these, 103 (50%) suffered from multiple falls, ranging in number from 2 to 20.

Of eligible samples, 1026 elders provided information regarding mobility, cognitive status and ADL regarding eating and toileting. In mobility, no disability was seen in 69.8% of them, while mild difficulty in climbing stairs was present in 18.1%, and moderate or severe difficulty required cane or wheel chair for moving around outside in 12.1%.

In cognitive status, no memory disturbance was seen in 62.8%, while mild and severe memory dysfunctions were in 26.0% and 8.0%, respectively.

Regarding eating ADL, 93.4% showed no problem, while 4.6% complained they had a mild problem, and 2.0% required assistance. Toileting related ADL was intact in 89.0% of the elders while mild difficulty and dependent status on toileting were seen in 6.0% and 5.0%, respectively. Although 8.3% of them were living alone, 23.0% were with their spouse, and the rest were with their children.

The samples were then divided into the developing samples ($n = 689$) and validating samples ($n = 689$). There was no statistical significance between these two samples, in distribution of living areas, gender and response pattern to the questionnaire items examined by χ^2 test (data not shown). The average age of the validating samples (75.8) was not significantly different from developing samples (75.7) by t-test.

Table 1 shows the predictors in relation to falls in developing samples. The incidence of at least a single fall and multiple falls were 108 (15.7%) and 55 (8.0%), respectively. Gender did not achieve the statistical significance to single fall ($P = 0.05$) and multiple falls ($P = 0.15$), respectively. Fallers were elder than non-fallers ($P < 0.01$) with average age of 79.1 versus 75.8, respectively.

Questionnaire items, except for Q13, Q14, Q20, Q21 and Q22, achieved statistical significance and were entered into the regression model. Table 2 shows the item selected by the stepwise logistic regression model.

Using the odds ratio at integer level as the weight of these five items, we constructed a screening test whose score ranged from 0 to 14, and the AUC was 74% (95% CI 69–79%) in the validating samples, as shown in Figure 1. This was at the same level as the AUC of initial 22 items score (72%:95% CI 67–79%)

The maximum sum of sensitivity and specificity reached <6 (sensitivity 0.68, specificity 0.70) and <7 (sensitivity 0.67, specificity 0.71). If a cut-off score of <6 was applied, subjects identified as positive had a 27.9% rate of falls (positive predictive value) compared with a

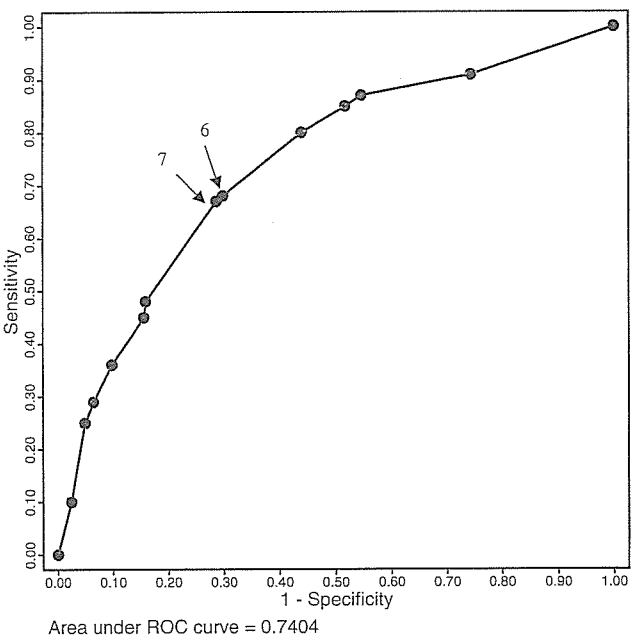

Figure 1 The Receiver-Operating Characteristic (ROC) of the five-item screening test to detect elderly persons at risk of falling.

Table 2 Questionnaire items selected by the stepwise logistic regression model

Questionnaire item selected by step wise logistic regression model	Odds ratio	95%CI	P
Q1. History of fall within one year = yes	4.5	(2.8–7.2)	0.00
Q4. Do you feel your walking speed declined recently? = yes	1.9	(1.0–3.6)	0.04
Q8. Do you use cane when you walk? = yes	1.8	(1.1–2.8)	0.02
Q11. Is your back bended? = yes	1.8	(1.1–2.8)	0.02
Q17. Do you take more than five kinds of prescribed medicines? = yes	1.7	(1.0–2.7)	0.03

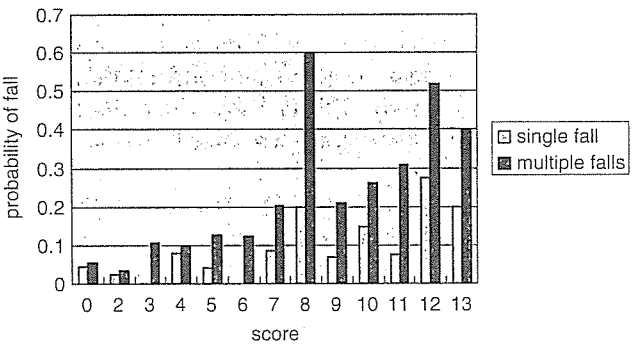

Figure 2 The probability of single and multiple falls by score.

7.2% rate in negative individuals (negative predictive power: 93%), with an odds ratio of 3.88 (95% CI 3.16–4.75).

The sensitivity and specificity was 0.63 and 0.67, respectively, for multiple falls. The positive and negative predictive value at this cut off score for multiple falls was 0.12 and 0.96, respectively, with the odds ratio of 3.04. Figure 2 illustrates the probability of fall by score levels.

On Rasch analysis of each item, some items did not fit the Rasch Model (Q16, Q20, Q21 and Q22) and these items were deleted for subsequent DIF analysis. Then no item showed DIF on cognitive functioning after Bonferroni adjustment (data not shown). After stratifying the sample with Q15, the area under ROC curve was 0.74 (95% CI 0.66–0.82) and 0.74 (0.69–0.78) for with and without cognitive dysfunction, respectively.

Discussion

Falls are considered as having multiple risk factors.[11] Previous epidemiological studies have identified the risk for falls, for example, history of falls,[2,3,12–15] activity of daily living (ADL),[2,3,15] cognitive and sensory function,[2,3,12,15] chronic conditions,[12,16,17] and medication use.[3,16–19]

Many studies tried to convert these risk factors for fall risk screening.[3,4,20] These screening tools for elders have been developed for various care settings, including residential,[14,21] intermediate[22] and inpatient care[23–25] as well as for community.[26–28]

Initially, the authors selected a comprehensive questionnaire composed of 22 items that can be answered by yes or no, and then selected several items that can be applied for mass screening or in general practice settings[6] because of the requirement of Japanese long-term care insurance (LTCI) law.

The items selected by the logistic model in this study were history of falls, walking speed, cane use, back deformation and medication use. All of these items were in concordance with the previous reports.

We also included environmental factors as part of the questionnaire. On comparison between fallers and non-fallers, environmental barriers such as level difference, stair and slope were not identified as risk factors, indicating the barrier recognized by the elders may not be associated with falls. All other items, except for vision problems were associated with incidence of falls.

The use of large prospective validating samples adds strength to this study. In most similar studies, the predictive validity is tested only on the developmental sample of the tools, and thus the predictive performance in a new sample is expected to be optimistic.[29] Although the predictive power on the development sample is usually high, the predictive power is usually lower in the validating samples.[30] In addition, the sensitivity of the scale is lower in the validating sample[31] and only a few studies use a large scale validating sample as was used in this study.[26]

Finally, the AUC of the initial 22 items were at the same level of the shortened five-item version. Therefore, the shortened version is preferred for its simplicity. In addition, the five-item scale was validated on the elderly with and without problems of cognitive function.

In the process of item selection using the logistic regression, inclusion criteria were $P < 0.05$, and exclusion criteria were $P > 0.10$. This procedure resulted in inclusion of items with weak association, such as Q4 and Q17. However, the adequacy of including these two items was proved on the validating sample.

In validating samples, the negative predictive value was 0.92 for single falls and 0.96 for multiple falls indicating that those with negative result have very low risk of falling in the next six months. This property of the high negative predictive validity makes the use of the screening test useful in mass screening.

History of fall was one of the most frequently reported risk factor of falls.[32,33] Decline of walking speed was captured with other questionnaire studies, as well as by physiological measurement.[6,18,34] Cane users and kolioskiphosis might have relation to bone abnormalities such as osteoporosis or arthritis.[13] These Q4, Q8 and Q11 compose a spectrum of physiologic decline referred to as frailty.[35,36] The relationship between medication use and falls can be explained by the effects of a drug itself that might cause sensory and balance disturbance, and also decreased metabolism, which relates to the loss of physiologic and metabolic function. Medication review is a possible intervention to prevent falls.[37]

In conclusion, a simple screening tool for falls is constructed using a large scale developing and validating sample. The scale constructed in this study is simple and valid. Therefore, it can be used as a screening tool of falls for community-dwelling elders.

Acknowledgment

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CASE REPORT

Elderly patient presenting with severe thyrotoxic hypercalcemia

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An 81-year-old woman with Graves' disease and osteoporosis was referred to the hospital because of anorexia over one month and impaired consciousness. She also presented with low-grade fever and emaciation. Laboratory tests revealed marked hypercalcemia (corrected serum calcium level of 12.4 mg/dL), which was initially suspected to result from vitamin D toxicity, because she had been taking vitamin D3 (alphacalcidol of 0.5 μg/day) for the treatment of osteoporosis. However, discontinuation of vitamin D3 and fluid infusion did not ameliorate hypercalcemia one week later. After excluding hyperparathyroidism and malignancy-related hypercalcemia, hypercalcemia was considered to be attributable to the exacerbation of hyperthyroidism (free T4 of 6.69 ng/dL, free T3 of 13.27 pg/mL and thyroid stimulating hormone (TSH) <0.015 μIU/mL) with increased bone resorption. Finally, the increased dose of thiamazole (30 mg/day) normalized serum calcium level and thyroid function three months later. Laboratory tests suggested that normal bone formation in spite of increased bone resorption contributed to hypercalcemia in hyperthyroid state.

Keywords: deoxypyridinoline, hypercalcemia, hyperthyroidism, osteoporosis, p-N-telopeptides of collagen cross-links.

Introduction

Hypercalcemia has been associated in approximately 20% of the patients with hyperthyroidism, but is mild in most cases, ranging from the upper normal limit to the slightly elevated level.[1–3] Consequently, we rarely see hyperthyroidism with symptomatic hypercalcemia. Many genotypes have been associated with Graves' disease.[4] Also, a small number of studies have shown that polymorphisms in calcium-regulating genes such as calcium-sensing receptor[5] and vitamin D receptor[6] may influence calcium metabolism in adults. However, no study has reported the association of those polymorphisms with thyrotoxic hypercalcemia. More studies as well as more polymorphisms including haplotype analysis should be performed to clarify the underlying mechanism.

Here, we report an elderly patient presenting with severe symptomatic hypercalcemia resulting from hyperthyroidism.

Case report

An 81-year-old woman was admitted to the Department of Geriatric Medicine, Kyorin University Hospital because of hypercalcemia on February 14 2004. She had Basedow's disease and osteoporosis, and had been taking thiamazole 5 mg/day and alphacalcidol 0.5 μg/day. In January 2004, anorexia had gradually developed followed by gait disturbance. When she was referred to the hospital on February 14, she also presented with confusion and low-grade fever of 37.2°C. Her blood pressure was 122/62 mmHg with a pulse rate of 98 bpm. Physical examination showed a soft diffuse goiter and a systolic ejection murmur of Levine II/VI at the apex, while abdominal and neurological findings were normal.

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Table 1 Laboratory tests on admission

Test	Result
Hb	10.5 g/dL
Ht	32.6%
RBC	$367 \times 10^4/\mu L$
PLT	$22.2 \times 10^4/\mu L$
WBC	3200/μL
Na	144 mEq/L
K	3.1 mEq/L
Cl	100 mEq/L
Ca	11.7 mg/dL
IP	3.4 mg/dL
BUN	19.3 mg/dL
Cr	0.7 mg/dL
TP	6.4 g/dL
Alb	3.3 g/dL
ALP	226 IU/L
AST	37 IU/L
ALT	35 IU/L
LDH	333 U/L
CK	25 IU/L
Glu	126 mg/dL
CRP	0.2 mg/dL

1 Alb, ...; ALP, ...; ALT, ...; AST, ...; BUN, ...; CK, ...; CRP, ...; LDH, ...; PLT, ...; RBC, ...; TP, ...; WBC, ...

Table 2 Results of thyroid function test

Test	Result (normal range)
FreeT4	6.69 ng/dL (0.73–1.53)
FreeT3	13.27 pg/mL (1.63–3.20)
Thyroid stimulating hormone (THS)	0.015 IU/mL (0.41–5.27)
TSH receptor antibody	51.2% (15<)
TSAb (thyroid stimulatory antibody)	540% (180<)
Antithyroid peroxydase antibody	43.8 U/mL (0.3<)
Serum thyroglobulin autoantibodies	0.3 < U/mL (0.3<)

On laboratory tests (Table 1), she showed blood hemoglobin of 10.5 g/dL, white blood cell counts of 3200/μL and serum calcium of 11.7 mg/dL (corrected calcium of 12.4 mg/dL). Other electrolytes as well as liver and kidney function were normal. Thyroid function tests (Table 2) revealed marked hyperthyroidism; free T4 of 6.69 (reference, 0.90–1.70) ng/dL, free T3 of 13.27 (2.3–4.3) pg/mL and thyroid stimulating hormone (TSH) of <0.015 (0.5–5.0) μIU/mL. Plasma levels of TSH receptor antibody, thyroid stimulating antibody and anti-TPO antibody were elevated, compatible with the findings in Graves' disease. Plasma intact PTH was 13 (10–65) pg/mL and PTH-related protein was not detected.

Table 3 Results of markers of bone metabolism

Marker	Result (normal range)
Osteocalcin	9.5 ng/mL (2.5–13)
Bone-specific alkaline phosphatase	24.2 U/L (9.6–35.4)
p-N-telopeptides	43.3 nMBCE/L (10.7–24.0)
Deoxypyridinoline/Cr	43.8 nmol/L/nMCr (2.8–7.6)
calcitonin	33 pg/mL
1–25(OH)VitD_3	6 pg/mL (20–60)

Figure 1 X-ray of lumbar vertebrae.

As shown in Table 3, markers of bone resorption such as deoxypyridinoline (DPD) and N-telopeptides of collagen cross-links (NTx) were elevated, whereas those of bone formation such as osteocalcin and bone-type alkaline phosphatase were not. Bone mineral density of lumbar vertebrae was −3.29 (T score), and that of femur was −3.72 (T score). Multiple compression fractures and remarkable reduction in bone mineral density were found on spinal lateral X-rays and dual energy X-ray absorptiometry, respectively (Fig. 1).

Initially, vitamin D toxicity was suspected as a cause of hypercalcemia; thus, alphacalcidol was ceased with fluid infusion to wash out calcium. However, the

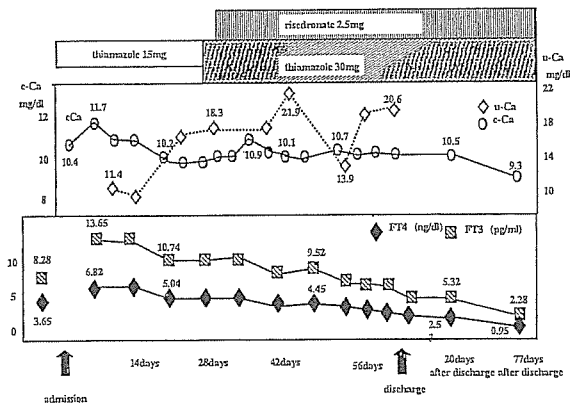

Figure 2 Clinical course of the patient. Thyroid stimulating hormone (TSH) was below the detection limit throughout the clinical course. c-Ca, collected serum calcium; u-Ca, urinary calcium; FT4, free thyroxine; FT3, free triiodothyronine.

hypercalcemia had not improved one week later. Laboratory and imaging tests were carried out to exclude hyperparathyroidism, humoral hypercalcemia of malignancy, osteolytic bone metastases and multiple myeloma. Finally, hypercalcemia was considered to be attributable to the exacerbation of hyperthyroidism with high bone turnover. Consequently, the dose of thiamazole was increased to 30 mg/day to normalize thyroid function. As shown in Figure 2, free T4 and free T3, as well as serum calcium were gradually decreased, and the patient was discharged on May 14 2004. In August 2004, her thyroid function returned to normal (free T4 of 0.95 ng/dL and free T3 of 2.28 pg/mL) with corrected serum calcium concentration of 9.2 mg/dL.

Discussion

Hypercalcemia associated with hyperthyroidism has been reported to occur more frequently in elderly patients than in younger patients; the incidence of hypercalcemia was 2.3% in hyperthyroid patients under 60 years of age and was 18.8% in those over 60 years of age.[2] The severity of hypercalcemia, however, is generally mild, ranging from the upper normal limit to the slightly elevated level,[3] and other complications should be suspected when serum calcium concentration is over 12 mg/dL[7] Actually, case reports have shown that hyperparathyroidism is uncommonly associated with hypercalcemia in thyrotoxicosis.[8] Only several cases have been reported that hyperthyroidism was considered the only cause of hypercalcemia over 12.0 mg/dL[9–11] In our case, laboratory tests and diagnostic imaging excluded hyperparathyroidism as well as malignant neoplasms. Furthermore, hypercalcemia was ameliorated in parallel with the improvement of hyperthyroidism, indicating that hypercalcemia resulted from hyperthyroidism.

Thyroid hormones play a critical role in bone development because hypothyroidism in childhood results in the impaired skeletal development.[12] In adults, thyroid hormones are important in the maintenance of bone mass. Thyroid hormone receptors are expressed in bone cells such as osteoblasts and osteoclasts.[12] In adult hyperthyroidism, there is increased bone remodelling, characterized by an increase in both bone resorption and formation, and an imbalance between bone resorption and formation, which results in bone loss and an increased risk for osteoporotic fracture.[12] In our case, however, the markers of bone resorption were elevated but those of bone formation were not. This pattern is consistent with the changes of bone metabolism in older osteoporotic patients,[13] but is different from that in hyperthyroidism as mentioned above. This might be due to the age-related decline in thyroid hormone signaling that leads to bone formation. However, no reports including animal experiments to support this hypothesis can be found so far. This should be investigated in the future.

Anti-thyroid drugs restore not only serum calcium levels[14] but also bone mineral density[15] in patients with thyrotoxic hypercalcemia. It has been also reported that a β blocker, propranolol,[16,17] and radioiodine therapy[10] may ameliorate thyrotoxic hypercalcemia. In our case, an increased dose of thiamazole normalized both thyroid function and serum calcium levels several months later, but bone mineral density was not increased. Longer time periods would be necessary to see the recovery of bone mass if possible.

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〈原　著〉

超高齢者におけるクレアチニンクリアランス推定式の比較検討

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小林　義雄[2)]　杉山　陽一[2)]　長谷川　浩[2)]　神崎　恒一[2)]　井上　剛輔[3)]
鳥羽　研二[2)]

要　約　**目的**：高齢患者は外来では24時間クレアチニンクリアランスの測定が困難であり，服用薬物数も多いため，クレアチニンクリアランス実測値をできるだけ正確に反映する推定式を利用することは臨床上重要である．**対象**：各種基礎疾患を有する85歳以上の超高齢者67名を含む入院高齢者143名（男性73名　女性70名　平均年齢82.9±8.6歳）．**方法**：4種のクレアチニンクリアランス推定式から得られた推定値と24時間クレアチニンクリアランスの実測値との相関を比較検討した．**結果と結論**：全体として今回の検討では超高齢者においてもCockcroft and Gaultの式による推定値が最もよい相関を示した．85歳以上の女性超高齢者において実測値と推定式の相関が低く，推定式の改定についても今後の検討課題と思われる．

Key words：超高齢者，クレアチニンクリアランス，推定式，Cockcroft and Gaultの式，安田の式

（日老医誌　2007；44：90-94）

緒　言

高齢社会の到来により，外来入院を問わず，高齢患者が増加の一途をたどっている．厚生労働省の推計によると，2004年度において85歳以上の超高齢者は273.4万人と報告されている[1)]．高齢者に腎排泄型薬剤を投与する際，適正な用量を設定するため腎機能を正確に評価する必要がある．腎機能を表す指標として，糸球体濾過量には一般的に内因性クレアチニンクリアランス（以下Ccrと略す）が使われている．クリアランス試験には24時間蓄尿が必要であるが，時間を要することや被験者に排尿，蓄尿という負担があり繁雑であることから外来で測定することは容易ではない．このため血清クレアチニン値（以下Scrと略す）からCcrを推定するいくつかの数式が提案されている．しかしこれらの数式は実際に投薬の必要な諸疾患を有する高齢者に当てはめる際，筋肉量の減少などのためScrによるCcr推定値と実測したCcrがかけ離れた値を取ることがある．外来の超高齢患者においても適切な薬物療法を行うためには腎機能を正確に評価する必要がある．このため種々の推定式による相関を調べどの推定式が最もよく超高齢者に適合するか検討を行った．

対象及び方法

杏林大学病院高齢医学科に2004年9月から2006年1月の間に入院した60歳以上の症例のうち，短期入院や，蓄尿不可能症例を除外し，尿道留置カテーテルを使用している患者や蓄尿が可能と判断された症例全例を対象にした．疾患や治療による除外は設けず，脳血管障害，感染症，経口摂取不良，利尿剤，補液などの様々な基礎疾患，治療を有する高齢者（平均年齢82.9±8.6歳（男性82.0±8.8歳　女性83.8±8.3歳））例を対象に行った．男女比及び84歳以下と85歳以上の症例数に偏りはなかった（表1）．対象高齢者全体の平均Scrは1.31±0.87mg/dlであった．身体測定，血液検査，尿検査などを測定し24時間蓄尿によるCcrを計算した．なお，Ccrは未補正のものを使用した．安田の式[2)]，Cockcroft and Gaultの式[3)]（以下C&G式と略す），折田の式[4)]，Walserの式[5)]の推定値を算出し，それぞれ推定値と実測値の相関を回帰分析，相関係数の差の検定により解析し比較検討した．さらに，層別解析として，84歳までの前期及び後期高齢者群76名と，85歳以上の超高齢者67名について男女別に層別解析を行った．

また実測値と推定式からの値との一致を箱ヒゲ図で求

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2）R. Kikuchi, S. Inoue, D. Tsukahara, Y. Suemitsu, Y. Kobayashi, Y. Sugiyama, H. Hasegawa, K. Kouzaki, K. Toba：杏林大学病院高齢医学科
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受付日：2006.4.18，採用日：2006.7.12

表1　対象年齢分布

Age（歳）	n		
	男性	女性	全体
～84	42	34	76
85～	31	36	67
全体	73	70	143

め，値が外れ値となった症例については，患者の疾患や治療の背景，測定時の問題点について調査した．

本研究は，杏林大学高齢医学の入院に際して，CCr測定値を臨床研究に使用することを口頭で説明し同意を得て試行した．

(1) 安田の式

男性：Ccr（ml/min）＝（176－年齢）×体重（kg）÷（100×Scr（mg/100 ml））

女性：Ccr（ml/min）＝（158－年齢）×体重（kg）÷（100×Scr（mg/100 ml））

(2) Cockcroft and Gault の式

男性：Ccr（ml/min）＝（140－年齢）×体重（kg）÷（72×Scr（mg/100 ml））

女性：Ccr（ml/min）＝｛(140－年齢）×体重（kg）÷（72×Scr（mg/100 ml））｝×0.85

(3) 折田の式

男性：Ccr（ml/min）＝（－0.065×年齢－0.493×BMI＋33）÷（体重（kg）×Scr（mg/100 ml））×14.4

女性：Ccr（ml/min）＝（－0.052×年齢－0.202×BMI＋21）÷（体重（kg）×Scr（mg/100 ml））×14.4

(4) Walser の式

男性：Ccr（ml/min）＝7.57÷Scr（mM）－0.103×年齢＋0.096×体重（kg）－6.66

女性：Ccr（ml/min）＝6.06÷Scr（mM）－0.08×年齢＋0.08×体重（kg）－4.81

成　績

85歳未満の前期及び後期高齢者群において，安田，C&G，折田，Walser の推定値と24時間蓄尿による実測値の相関係数（r）は安田 r＝0.761，C&G　r＝0.761，折田 r＝0.693，Walser　r＝0.553 と安田の式，C&G 式で強い傾向があった．超高齢者群において，各々の推定式による推定値と実測値の相関係数は安田 r＝0.718，C&G r＝0.739，折田 r＝0.697，Walser r＝0.645 と，安田の式，C&G 式で相関が強い傾向があった（図1，図2）．超高齢者を男女に分け両群で各々の推定値と実測値の相関係数 r を比較したところ，男性で安田 r＝0.840，C&G r＝0.841，折田 r＝0.791，Walser　r＝0.736，女性で安田 r＝0.678，C&G　r＝0.690，折田 r＝0.667，Walser　r＝0.582 となり，男性に強い相関傾向があり，女性の相関係数は低かった（図3，図4）．また，超高齢者群において回帰係数を比較したところ，男性で安田＝0.796，C&G＝0.988，折田＝0.577，Walser＝0.375　女性で安田＝1.088，C&G＝1.262，折田＝0.776，Walser＝0.395 となった．

図5は超高齢者を男女で比較したものである．縦軸は実測値と推定値のずれの割合を示したもの（(実測値－推定値）×100/実測値）である．折田，Walser の式では，男女共に推定値が高く評価される傾向がある．

85歳以上の超高齢者での箱ひげ図における外れ値を検討し，実測値が高値となる6例の患者背景を調べた．輸液4例，利尿剤や Ca 拮抗薬など腎血流量を増加させる薬剤4例，腎不全2例，Scr 高値2例，心不全2例，CRP 高値2例であった．また，推定値が高値となる7例の患者背景を調べた．輸液5例，蓄尿不全または蓄尿少量4例，腎不全4例，癌3例，コントロール不良の糖尿病1例，胸水貯留，腹水貯留1例，肥満1例であった．

考　察

服用薬物数が多いほど薬剤有害作用の発現率は増加する傾向にある．また，加齢によってもその傾向は増加する[6]．その原因には加齢に伴う薬物動態学的・薬力学的な変化，多剤併用による相互作用，日常生活活動度（ADL）・認知機能の低下などが考えられるが，特に重大な原因として，腎機能の低下による相対的過量投与が挙げられる．Scr による腎機能の推定にはいくつか方法があるが高齢者，特に超高齢者になると筋肉量の低下により Scr が腎機能の低下と不相応な低値を示すことがしばしば見られる．Ccr 測定上の更なる問題点として正確な蓄尿の可否がある．加齢に伴う残尿，失禁の増加や患者自身による蓄尿もれなどにより，正確な24時間蓄尿が困難なことがある．1日尿量が少ないとき，Ccr 実測値と推定値のばらつきが大きいとの報告もある．今回は尿道留置カテーテルを使用している患者や蓄尿が可能と判断された患者の症例を対象とし，努めて正確な採尿を試みた．しかしながら，本来行うべきクリアランス法の実施には正確な蓄尿と安静を要し，判定に時間がかかるため実際の外来診療では実施困難なことが多い．従って Scr より Ccr を推定する種々の方法が提案されてきた．今回検討した安田の式，Cockcroft and Gault の式，折田の式，Walser の式は代表的な推定式であり Scr 値，性別，年齢，体重より Ccr を推定できる．C&G 式は欧米で最も広く用いられており欧米人によい相関を示して

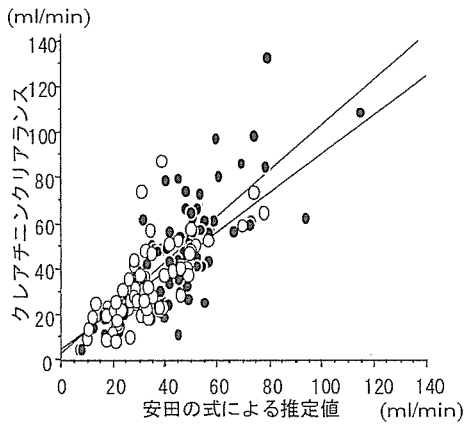

図1　安田の式　84歳以下と85歳以上の比較
○85歳以上；Y = 4.57 + 0.860X（r = 0.718）
●84歳以下；Y = 1.85 + 1.007X（r = 0.761）

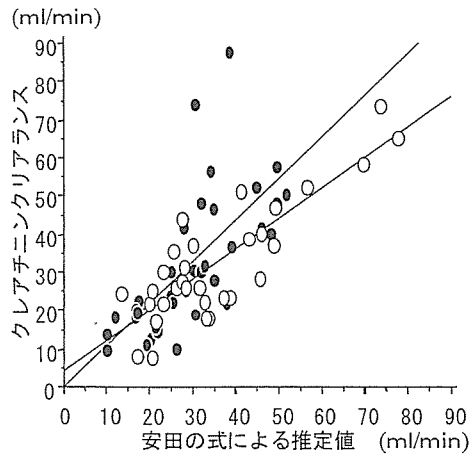

図3　安田の式　85歳以上の性差
○男性；回帰式 Y = 4.09 + 0.796X（r = 0.840）
●女性；回帰式 Y = 0.21 + 1.088X（r = 0.678）

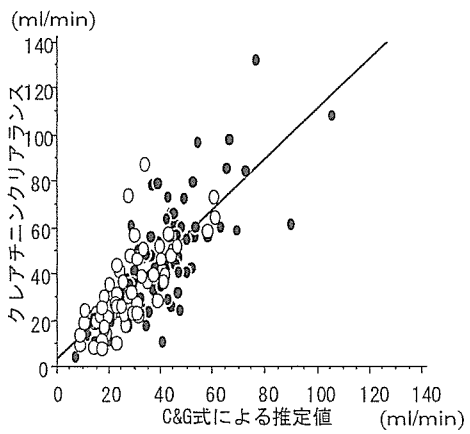

図2　C&G式　84歳以下と85歳以上の比較
○85歳以上；Y = 3.20 + 1.078X（r = 0.739）
●84歳以下；Y = 3.33 + 1.082X（r = 0.761）

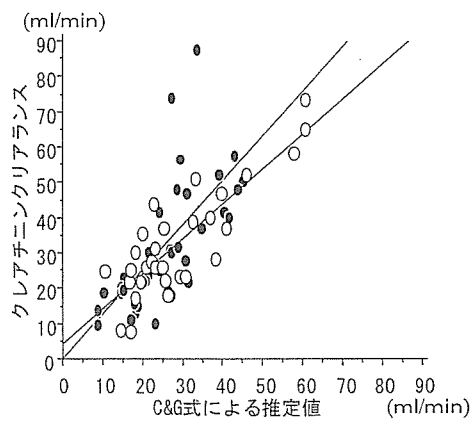

図4　C&G式　85歳以上の性差
○男性；回帰式 Y = 4.07 + 0.988X（r = 0.841）
●女性；回帰式 Y = − 0.09 + 1.262X（r = 0.690）

いる．今回の検討でも超高齢者における相関が0.739と最もよい相関を示した．この原因として日本人の体格が欧米化してきたことやC&G式作成時の対象年齢が18～92歳と超高齢者も含まれていること，作成時の対象症例数が多いことが考えられる．C&Gの式に対して他の3式はいずれもその後に発表されたもので，安田の式は1.4mg/d*l*以下の血清クレアチニン値を示す高齢者に限定して式を求めたもので，腎不全患者は含めずに高齢者の腎機能を推定しようとしたものである[2]．一方，Walserの式は血清クレアチニン値を2.0mg/d*l*以上におき，腎不全患者のみを対象としている[5]．堀尾らの式は腎疾患患者を対象として，推定式にBMIの項を加えて肥満の特徴加味して作成された[4]．したがって，今回の対象のように腎機能が広範囲に亘る場合，C-Gの式以外では，いずれもずれが出てしまう結果となったのは，式の作成経緯による要素も大きいと考えられる．

今回，臨床の現場では安定した時期より外来や急性期での腎機能評価を必要とするため，疾患による除外は設けず，脳血管障害，感染症，経口摂取不良，利尿剤，補液などの様々な基礎疾患，治療を有する高齢者を対象に行った．推定式と実測値の乖離に関して，実測値が大きい場合は，輸液や降圧剤など腎血流量を増加させる治療が関与していた場合が多かった．この場合は臨床的には大きな実害は考えられない．一方，実測値が推定式より小さい場合は，相対的な薬物の過量投与など安全管理上

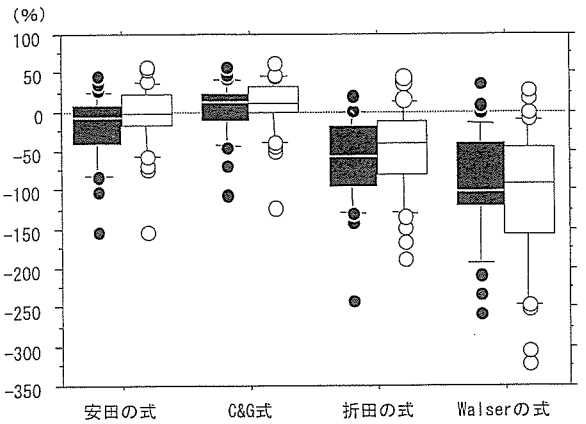

図5　超高齢者男女別において各推定式による推定値と実測値とのずれを箱ひげ図で％表示したもの
縦軸（実測値－推定値）×100/実測値
●男性
○女性

も問題となる．今回の検討では，腎不全，癌，乏尿，コントロール不良の糖尿病，胸水，腹水など複数の病態が重なる重症例で，有効循環血液量も日々変動しうる症例であった．このような症例に救急外来で遭遇した場合，血清クレアチニンから推定されるCcrの精度が低い可能性があることを銘記すべきであろう．Scrについては6.9までの高値も含まれているが，高値を除いた検討を行っても相関に大きな変化は見られなかった．全式において84歳までの前期及び後期高齢者群と85歳以上の超高齢者群に分け，相関を比較したところ，超高齢者群での相関が低い傾向にあり，超高齢者群での合併疾患の増加の影響が示唆される．これらを考慮しても，4種の推定式を比べると相関係数が最も高いC&G式が本邦超高齢者におけるCcr推定式として最適と考えられた．

超高齢者群を男女にわけC&Gの相関係数を比較したところ，男性0.841女性0.690と男性の相関が高い傾向にあった．また，回帰係数を比較したところ男性ではC&G式，女性では安田の式が1に近い値を示した．85歳以上の男性に安田の式を用いると過大評価する可能性があり，85歳以上の女性にC&G式を用いると過小評価する可能性がある．

一方，前期及び後期高齢者群の回帰係数を比較したところ男女ともに安田の式が1に近い値を示した．超高齢者の筋肉量について本邦での正確なデータは少ないが，中島らによれば70歳以降男性では上腕筋周囲，上腕筋面積が急速に減少するが女性ではほとんど変わらない[7]ことから女性の筋肉減少が時代とともに変化し，推定式の再構築が迫られている可能性があり，今後の検討課題と思われた．

本研究の限界として，膀胱留置カテーテルの適応がない蓄尿不可能症例を除外していることがあげられる．具体的には尿失禁症例や，認知症などが含まれるが，これらの症例に対してカテーテル留置を行ってクレアチニンクリアランスを測定し，高齢者全体に対するの推定式の良否を判断する研究は今後の課題であろう．

結　語

超高齢者において，正常値から腎不全を含む範囲の腎機能の判定に，24時間クレアチニンクリアランスの実測値と，すでに発表されている4つの式から求めた推定値とを比較して，超高齢者での推定式の有用性を検討した．4つの推定式のうち，C-Gの式はこの研究の目的にもっとも合致していた．一方，安田の式（高齢者，Scr: 1.4mg/dl以下），Wの式（Scr　2.0mg/dl以上）はいずれもその適用の目的の範囲で，また堀尾の式は腎疾患群内で有用と思われた．

全体として，臨床的に使用するうえでC&G式が最も優れているが，超高齢者への適用に当たっては，10%程度，推定値が低く求まるので，補正が望ましい．

今後超高齢者については，体格，サルコペニアの時代的変遷を考慮して改訂していく必要がある．

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