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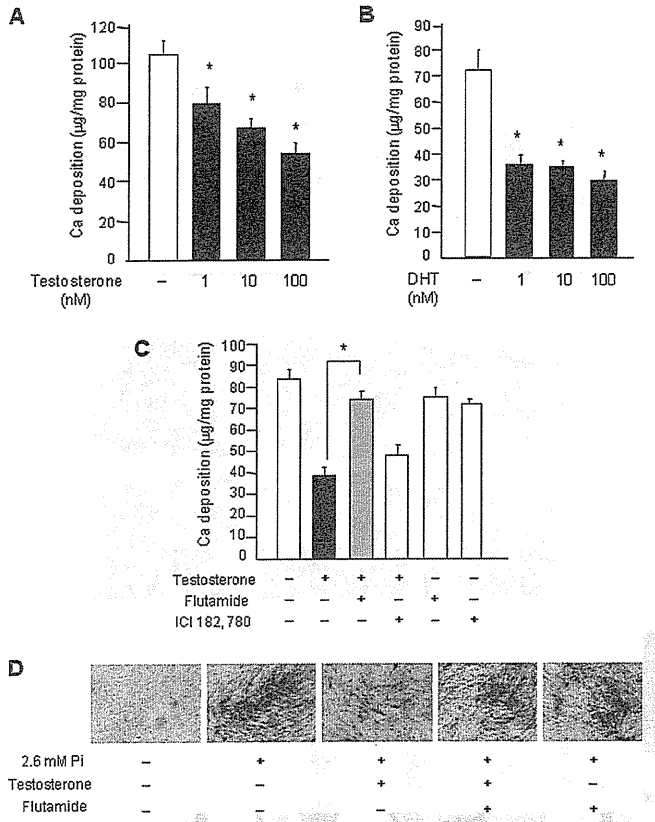

FIGURE 2. **Androgens prevent P_i-induced calcification via the AR.** HASMC were cultured with the indicated concentrations of androgens (testosterone (*A*) and DHT (*B*)) in the presence of 2.6 mM P_i for 6 days. Calcium deposition was measured by the *o*-cresolphthalein complexone method and normalized by cell protein content. *, $p < 0.05$ *versus* androgens (−) by Fisher's test. HASMC were cultured with flutamide (10 μM) or ICI 182,780 (10 μM) in the presence or absence of testosterone (100 nM) with 2.6 mM P_i treatment. On day 6 calcium deposition was measured (*C*) and was evaluated at the light microscopic level with von Kossa staining (*D*). All values of calcium deposition are presented as the mean ± S.E. of quintuplicate samples. Similar results were obtained from three independent experiments. *, $p < 0.05$ by Fisher's test.

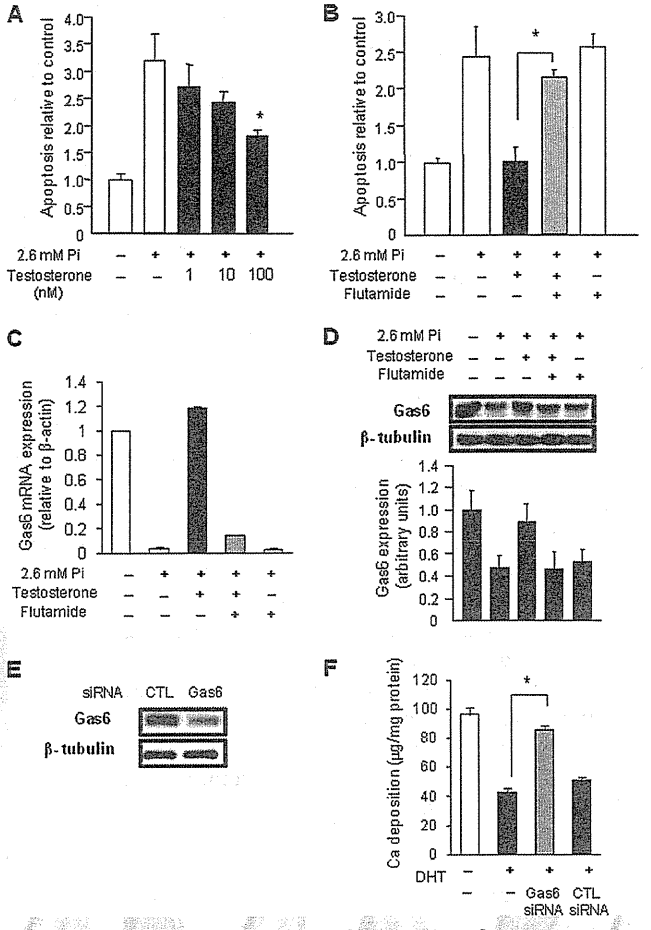

FIGURE 3. **Androgens inhibit P_i-induced apoptosis and restore Gas6-mediated survival pathway.** *A*, HASMC were cultured with the indicated concentrations of testosterone in the presence of 2.6 mM P_i for 6 days. A quantitative index of apoptosis, determined by DNA fragmentation enzyme-linked immunosorbent assay, is presented as the value relative to that without P_i treatment. *, $p < 0.05$ *versus* 2.6 mM P_i, testosterone (−) by Fisher's test. *B*, HASMC were treated with testosterone (100 nM), or flutamide (10 μM) in the presence of 2.6 mM P_i for 6 days. *C* and *D*, on day 6, RNA and cell lysates were harvested and analyzed for Gas6 mRNA and protein levels by real-time PCR (*C*) and immunoblotting (*D*), respectively. β-Actin mRNA and β-tubulin protein levels were also measured as loading control. The average results of three separate measurements of mRNA are shown. The *panel* shows a representative blot, and *bar graphs* show quantitative analyses of three independent immunoblotting experiments. *E*, HASMC were transfected with two Gas6 or control siRNA (100 nM). Gas6 protein was efficiently decreased by two siRNAs targeting Gas6 at 48 h after transfection. *CTL*, control. *F*, for measurement of calcium deposition, HASMC were transfected with 100 nM Gas6 siRNA and nonspecific (*CTL*) siRNA and incubated with DHT (100 nM) and 2.6 mM P_i for 6 days. All values of apoptosis and calcium deposition are presented as the mean ± S.E. of triplicate samples. Similar results were obtained from three independent experiments. *, $p < 0.05$ by Fisher's test.

Because apoptosis is a crucial and initiating event in P_i-induced VSMC calcification (16, 17), we examined whether androgens inhibit P_i-induced apoptosis. Furthermore, in our recent study apoptosis induced by P_i has been shown to be associated with inhibition of Gas6 expression and secretion (16, 17). Androgens, at concentrations exerting an inhibitory effect on calcification, significantly reduced P_i-induced apoptosis, as quantified by analysis of cytoplasmic histone-associated DNA fragments (Fig. 3*A*). Flutamide significantly abrogated the inhibitory effect of androgens on apoptosis in HASMC (Fig. 3*B*). We further examined the effect of androgens on Gas6 expression. Both Gas6 mRNA and protein expression down-regulated by P_i were restored by the addition of testosterone. Moreover, flutamide abrogated the increase in Gas6 expression by testosterone in HASMC (Fig. 3, *C* and *D*).

The preventive effect of Gas6 on P_i-induced apoptosis and calcification is mediated by the phosphatidylinositol 3-OH kinase/Akt pathway, a well known anti-apoptotic signaling pathway, through Bcl2 family proteins (17). We found that testosterone restored the Akt phosphorylation down-regulated by P_i, and this increase in phosphorylation was blocked by flutamide (supplemental Fig. 1*A*). Furthermore, SH-5, an Akt inhibitor, abolished the effect of androgens on HASMC calcification (supplemental Fig. 1*B*).

To determine whether Gas6 is required for androgen-mediated effects, we blocked the action of Gas6 using siRNA (Fig. 3*E*) and examined the effect of androgens on P_i-induced calcification. As shown in Fig. 3*F*, knockdown of the Gas6 gene significantly reversed the inhibitory effect of androgens on P_i-induced calcification.

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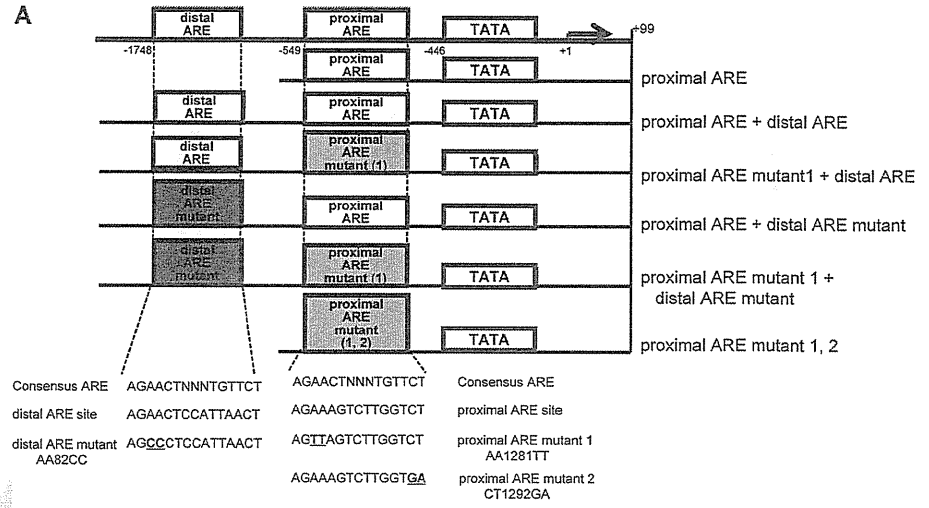
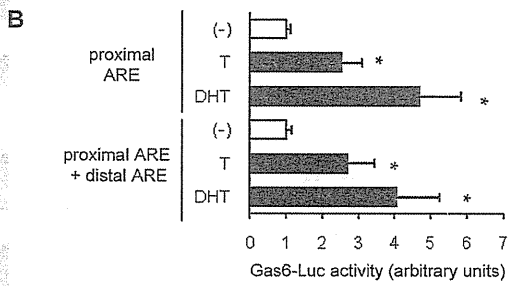
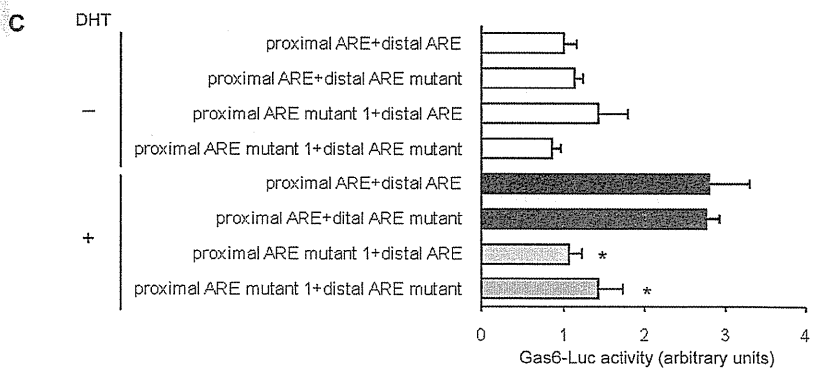
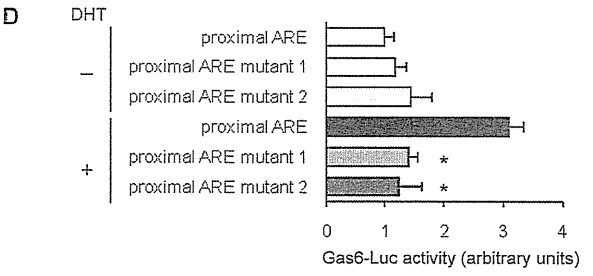
The Proximal ARE in Gas6 Promoter Is Essential for Androgen-stimulated Gas6 Transcriptional Activation—To investigate the molecular mechanism involved in up-regulation of Gas6 expression by androgens, we explored the existence of ARE sites in the promoter region of the Gas6 gene (−1827 to +99 bp). We found that the Gas6 promoter contained two consensus ARE sites. One ARE (−535 to −549 bp) was located close to the transcription start site, whereas the other was located at −1733 to −1748 bp (Fig. 4*A*). To examine whether AREs in Gas6 were functional, we made two constructs; one contained only the proximal ARE site of the Gas6 promoter, and the other contained both the proximal and distal ARE sites. With transient transfection, androgens significantly stimulated Gas6 promoter activity of the proximal ARE, whereas an additional increase in Gas6 promoter activity was not observed by transfection of the construct containing both the proximal ARE and the distal ARE (Fig. 4*B*). Then we performed site-directed mutagenesis to confirm whether the proximal ARE is critical. The distal and proximal ARE sites were mutated, as shown in Fig. 4*A*. Mutation of the proximal ARE completely abrogated DHT-stimulated Gas6 transcription activity. However, we did not observe a reduction in Gas6 transcription activity with the distal ARE mutation (Fig. 4*C*). To further verify the importance of the proximal ARE sequence in androgen-dependent activation of Gas6, we examined two mutants of the proximal ARE. As expected, both of the mutants abrogated DHT-stimulated Gas6 promoter activity, whereas they had no effect in the absence of DHT (Fig. 4*D*). Taking these results together, we identified two ARE sites in the Gas6 promoter and found that the proximal ARE is essential for androgen-induced activation of the Gas6 promoter.

Androgen-dependent Gas6 Promoter Activity Is Mediated by Binding of the AR to the ARE—To examine the role of the AR in androgen-dependent Gas6 promoter activation, we used flutamide and AR siRNA to block the function of the AR. First, we found that flutamide completely eliminated DHT-induced activation of the Gas6 promoter (Fig. 5*A*). However, P_i did not affect Gas6 promoter activity. Next, AR siRNA clearly down-regulated AR protein expression, as shown in Fig. 5*B*. By transient transfection of AR siRNA, Gas6 promoter activity was significantly inhibited in the









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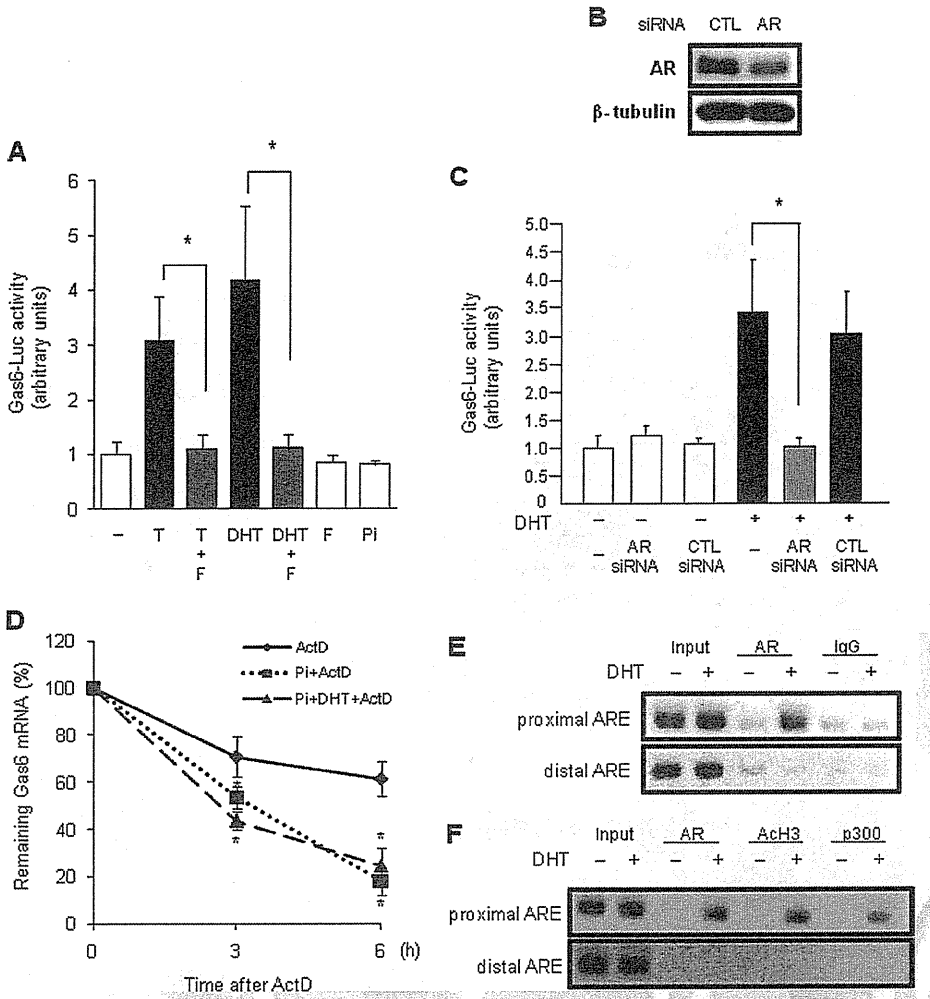

FIGURE 5. **Interaction of the AR with the proximal ARE is essential for transactivation of Gas6 gene by androgen.** *A*, HASMC were transfected with the Gas6-luc construct containing the proximal ARE. Twenty-four hours after transfection, testosterone (*T*, 100 nM), DHT (100 nM), P_i (*Pi*, 2.6 mM), or flutamide (*F*, 10 μM) was added, and the cells were incubated for an additional 24 h. *, $p < 0.05$ by Fisher's test. *B*, HASMC were transfected with AR or control (*CTL*) siRNA (100 nM). The AR protein was efficiently decreased by AR siRNA at 48 h after transfection. *C*, HASMC were transfected with 0.8 μg of Gas6 proximal ARE together with AR siRNA or nonspecific (*CTL*) siRNA (100 nM). Twenty-four hours later, DHT (100 nM) or vehicle was added. After a further 24 h, luciferase activity was assayed. *D*, serum-starved HASMC were incubated with Act D (5 μg/ml) in the presence of 2.6 mM P_i after 12 h of DHT (100 nM) treatment. The remaining Gas6 mRNA was determined at 0, 3, and 6 h after Act D treatment by real-time PCR analysis. Values of Gas6 mRNA with P_i (*dotted line with squares*), with P_i and DHT (*dashed line with triangles*), or without P_i (*solid line*) in the presence of Act D were normalized to that of β-actin mRNA at each time point. Gas6 mRNA level at time 0 was expressed as a percentage of the maximum value. The results are the average of three separate experiments. *, $p < 0.05$ *versus* Act D by Fisher's test. *E*, chromatin extracts were obtained from HASMC after treatment with or without 100 nM DHT for 12 h, and the ChIP assay was performed using an antibody against AR or control IgG. DNA fragments were extracted from immunoprecipitates. The Gas6 promoter region containing proximal ARE was amplified, but distal ARE was not. *F*, a ChIP assay was performed using an antibody against AR, acetylhistone H3 (*AcH3*), or p300 with chromatin extracts with or without treatment with 100 nM DHT for 24 h. Relative promoter activities are expressed as the mean ± S.E. of quadruplicate samples. Similar results were obtained from four independent experiments. *, $p < 0.05$ by Fisher's test.

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presence of DHT (Fig. 5*C*). These findings suggest that Gas6 transactivation by androgens was dependent on the AR.

Because P_i did not affect Gas6 transcriptional activity, we further explored the effect of P_i on Gas6 regulation at the post-transcriptional level. The stability of Gas6 mRNA was examined in the presence or absence of Act D. We found that Gas6 mRNA was significantly more degraded in the presence of P_i than in its absence after Act D treatment (Fig. 5*D*). DHT did not have an effect on mRNA degradation (Fig. 5*D*). These findings suggest that P_i down-regulated Gas6 expression by increasing the mRNA degradation rate and not by decreasing transcriptional activity.

To confirm a direct association of the AR with the proximal ARE in the Gas6 gene, we performed a ChIP assay in HASMC. After 12 h of DHT treatment, a polyclonal antibody against the AR could efficiently precipitate the androgen-responsive region of Gas6, showing that the AR directly binds to the Gas6 gene promoter region containing the proximal ARE site in HASMC (Fig. 5*E*). We did not observe binding of the AR to the distal ARE site in the Gas6 gene (Fig. 5*E*). Furthermore, we attempted a characterization of the promoter interactions with an AR-containing transcriptional complex. Histone acetyltransferase, such as p300, is a well established coactivator of the AR, and acetylation of histone H3 is an important determinant of AR action, possibly mediated by p300 (19). We performed a ChIP assay with antibodies against acetylhistone H3 and p300. When the AR binds to the proximal ARE site of the Gas6 gene, acetylhistone H3 and p300 also bind to this site as coactivators (Fig. 5*E*). We did not

FIGURE 4. **Androgens stimulate Gas6 promoter activity in HASMC.** *A*, shown is a schematic representation of the sequence for ARE sites in wild-type human Gas6 promoter and mutant construct. Site-directed mutagenesis was used to alter the ARE sites within the Gas6 construct. The sequences of the consensus ARE site, Gas6 ARE sites, and the mutated ARE sites with altered bases *underlined* are shown. *B*, 24 h after transfection of 0.8 μg of Gas6-luc construct containing only the proximal ARE or the construct containing both the proximal and distal AREs, androgens (testosterone (*T*) and DHT, 100 nM) were added, and the cells were incubated for an additional 24 h. *, $p < 0.05$ *versus* androgens (−) by Fisher's test. *C*, HASMC were treated with DHT (100 nM) or vehicle for 24 h after transfection of the Gas6-luc constructs containing both proximal and distal AREs or mutants. *, $p < 0.05$ *versus* DHT (+) wild-type Gas6 by Fisher's test. *D*, HASMC were transfected with wild-type or two proximal ARE mutants. Twenty-four hours after transfection, DHT (100 nM) was added for an additional 24 h. Luciferase activity was normalized to that of the DHT-free wild-type Gas6 construct. *, $p < 0.05$ *versus* DHT(+) wild-type Gas6 by Fisher's test. Relative promoter activities are expressed as the mean ± S.E. of quadruplicate samples. Similar results were obtained from five independent experiments.

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observe any binding of the AR, acetylhistone H3, or p300 to the distal ARE site in the Gas6 gene (Fig. 5*F*).

DISCUSSION

The effect of testosterone replacement therapy on atherosclerosis is controversial (21–25), although testosterone deficiency is known to be associated with cardiovascular disease in men (26–30). We and others have shown that a low testosterone level is associated with markers of atherosclerosis such as impaired endothelial vasomotor function (27), increased carotid intima-media thickness (28), and aortic calcification (9). Recently, testosterone has also been reported to inhibit VSMC proliferation and neointima formation (7), suggesting a direct action of testosterone on the vasculature. In this *in vitro* study we examined the effect of androgens on P_i-induced VSMC calcification and found that androgens at physiological concentrations exhibited inhibitory effects on VSMC calcification. In contrast to the present study, it has been reported that androgens induced vascular calcification in apolipoprotein E knockout mice (31). This discrepancy may derive from the complex *in vivo* effects of testosterone. Further work is required to define the role of androgens in vascular calcification.

Androgens act mainly through transcriptional control of target genes mediated by the nuclear AR (11, 32). In the present study we found that the AR was expressed predominantly in the nucleus of VSMC and had transcriptional activity. Recently, it was demonstrated that the AR-dependent action of androgens protects against angiotensin II-induced vascular remodeling (33). Consistent with this, our results showed that the inhibitory effect of androgens on VSMC calcification was mediated by the AR and not by estrogen receptor.

Recently, we demonstrated that apoptosis plays a central role in the process of P_i-induced VSMC calcification through down-regulation of the Gas6-mediated survival pathway (16, 17). In the present study we found that androgens prevented VSMC apoptosis and restored Gas6 expression and Akt survival signaling. These inhibitory effects of androgens on apoptosis and calcification were eliminated by flutamide and Gas6 siRNA. Our findings indicate that AR-dependent restoration of Gas6 by androgens contributes to the inhibition of apoptosis and VSMC calcification.

Although the involvement of other molecules such as protein kinase Cδ (7) and endothelial nitric-oxide synthase (33) in the vasoprotective actions of androgens is unclear, our data showed that Gas6 plays a pivotal role in the inhibitory effect of androgen on P_i-induced calcification. Several genes containing AREs and having AR-mediated actions have been identified (34, 35). However, little is known about transcriptional regulation and the target genes of the actions of the AR in the vascular system. In this study we identified two AREs in the promoter region of the Gas6 gene and characterized specific direct binding of the AR to the proximal ARE, in contrast to the nonfunctional distal ARE. Interestingly, Mo *et al.* (36) identified that an estrogen response (ER) element spanning −72 to −89 bp from the translation start site in Gas6 and ERα is recruited by estrogen-mediated stimulation of Gas6 gene expression in mouse mammary epithelial cells. In the human Gas6 promoter domain, we also found the existence of an estrogen response element at −243 to −251 bp. In clinical studies, a low serum estradiol level in women was correlated with increased arterial calcification (37), and estrogen replacement could reduce coronary calcification (38, 39). However, in experimental studies, estradiol treatment showed variable effects on vascular calcification with either inhibition (40, 41) or stimulation of calcification (42). Further studies are needed to elucidate the actions of estrogens in vascular calcification.

In summary, this study showed that Gas6 is a novel target that is directly and transcriptionally regulated by the AR, and direct interaction of the AR and Gas6 mediates the inhibitory effects of androgens on vascular calcification. This study provides a new mechanistic insight into the vascular protective action of androgens.

Acknowledgments—We thank Yuki Ito for technical assistance and Prof. Satoshi Inoue, Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, for providing the LNCaP and PC3 cells.

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Geriatr Gerontol Int 2011; **11:** *328–332*

ORIGINAL ARTICLE: EPIDEMIOLOGY, CLINICAL PRACTICE AND HEALTH

Relationship between interleukin-6 and cerebral deep white matter and periventricular hyperintensity in elderly women

Kumiko Nagai,[1] Koichi Kozaki,[1] Kazuki Sonohara,[1] Masahiro Akishita[2] and Kenji Toba[1]

[1]*Department of Geriatric Medicine, Kyorin University School of Medicine, and* [2]*Department of Geriatric Medicine, Graduate School of Medicine, University of Tokyo, Tokyo, Japan*

Aim: We evaluated the relationships between serum levels of high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 with the severity of leukoaraiosis.

Methods: One hundred and thirty-seven elderly women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were enrolled in this study. Leukoaraiosis was assessed by periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score.

Results: Serum log IL-6 level correlated with PVH and DWMH scores, but hsCRP did not. By multinomial logistic analysis, IL-6 was significantly related to DWMH score, independent of age and systolic blood pressure.

Conclusion: IL-6 is presumably an important marker of leukoaraiosis, as is the case with silent cerebral infarction. **Geriatr Gerontol Int 2011; 11: 328–332.**

Keywords: interleukin-6, leukoaraiosis, white matter hyperintensity.

Introduction

Leukoaraiosis, an isointense lesion on T_1-weighted images and hyperintense lesion on T_2-weighted images of magnetic resonance imaging (MRI), is considered to be a type of ischemic change in the brain on the basis of decreased blood flow in the area of leukoaraiosis.[1] In addition, leukoaraiosis is likely to have a relationship with vascular risk factors such as hypertension and diabetes.[2] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of the geriatric syndromes such as dementia, gait disturbance and functional disability.[3–5] Hence, leukoaraiosis is regarded as a significant brain lesion linking vascular risk factors and the occurrence of geriatric syndromes. Previous research on leukoaraiosis showed that women tended to have more white matter lesions than men,[6] and progression of deep white matter hyperintensity (DWMH) lesion was grater in women than men.[7] Furthermore, Gouw *et al.* showed that leukoaraiosis tended to develop greater in women than men and lacunes were vice versa.[8] Recently, many studies have focused on the relationships between brain ischemia and inflammation. Above all, Hoshi *et al.* demonstrated that serum high-sensitivity C-reactive protein (hsCRP) and interleukin (IL)-6 levels correlated with silent brain infarction.[9] They suggested an involvement of inflammation in cerebral infarction. However, few studies have examined the relationships between inflammatory markers and other cerebral ischemic changes such as leukoaraiosis.Therefore, we investigated whether serum levels of hsCRP and IL-6 have a relationship with leukoaraiosis in elderly women.

Accepted for publication 14 December 2010.

Correspondence: Dr Koichi Kozaki MD PhD, Department of Geriatric Medicine, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan. Email: kozaki-tky@umin.ac.jp

 doi: 10.1111/j.1447-0594.2010.00686.x

Methods

Patients

One hundred and thirty-seven women who attended the Center for Comprehensive Care on Memory Disorders at Kyorin University Hospital were included in this study. This study was approved by the Ethics Committee of Kyorin University School of Medicine. Accordingly, written informed consent was obtained from all patients.

MRI

Magnetic resonance imaging (MRI) was performed on 1.5-T scanners (Toshiba Medical Systems, Tochigi, Japan). T_1-weighted images (repetition time [TR] = 496 msec, echo time [TE] = 12 msec), T_2-weighted images (TR = 4280 msec, TE = 105 msec) and fluid attenuated inversion recovery-weighted images (TR = 8000 msec, TE = 105 msec, 5 mm slice thickness) were obtained in the axial planes.

Periventricular hyperintensity and DWMH Score

Leukoaraiosis was classified as periventricular hyperintensity (PVH) adjacent to the lateral ventricle, and DWMH located in the deep white matter apart from the lateral ventricles. PVH was evaluated in six regions in three slices. Each region was rated as five grades (0–4) according to the systematic quantification method developed by Junque *et al.*[3] The sum of all grades in the six regions was defined as the PVH score (range 0–40).[4] DWMH was evaluated in the frontal, temporal, parietal and occipital lobes and in the basal ganglia in both hemispheres. Each lesion was rated as three grades according to the diameter, as described by de Groot *et al.*[5] The sum of all grades in five regions in both hemispheres was defined as the DWMH score.[4]

Laboratory tests

Blood samples were obtained in the morning after an overnight fast. Serum levels of hsCRP and IL-6 were measured using nephelometry and enzyme-linked immunosorbent assay, respectively. The intra-assay coefficients of variation for the measurements of hsCRP and IL-6 were 1.3% and 2.9%, respectively.

Statistical analysis

Because the distribution of hsCRP and IL-6 levels appeared to be left-skewed, they were normalized by logarithmic transformation. We used Spearman's ρ to investigate correlations between parameters and PVH score or DWMH score. Also, to test independently the effect of the inflammatory markers associated with the severity of leukoaraiosis, multinomial logistic regression analysis was performed with the grade of PVH (tertiles of PVH score) or DWMH (tertiles of DWMH score) as the dependent variable; and hsCRP or IL-6, together with age and systolic blood pressure (SBP) as independent variables. $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS ver. 17.0.

Results

The characteristics of the study subjects are shown in Table 1. They were non-obese normolipidemic elderly persons, however, SBP was elevated. The distribution of PVH score and DWMH score of these subjects were 1–24 and 0–209, respectively. In Spearman's correlation coefficient, IL-6 correlated with PVH score ($\rho = 0.340$, $P \leq 0.05$) and DWMH score ($\rho = 0.299$, $P \leq 0.05$) (Fig. 1), whereas hsCRP showed no relation to PVH score or DWMH score (Table 2). PVH score and DWMH score also correlated with age and SBP. When log IL-6 and log hsCRP were grouped by tertile (see legend to Fig. 2), it was found that the average PVH score and DWMH score were higher in the highest tertile of IL-6 level than in the lowest tertile according to the Kruskal–Wallis test (Fig. 2a,b). On the other hand, this increment was not found in hsCRP (Fig. 2c,d).

Because leukoaraiosis can be observed on MRI even in normal elderly persons,[10] and hypertension is known to be a risk factor for leukoaraiosis,[11] we performed multinomial logistic regression analysis using PVH or DWMH severity (tertiles of PVH and DWMH score) as the dependent variable, and age, SBP and inflammatory

Table 1 Clinical characteristics of study subjects (women, $n = 137$)

Age (years)	76 ± 7
BMI (kg/m^2)	20.8 ± 3.3
SBP (mmHg)	142 ± 26
DBP (mmHg)	80 ± 14
PVH score (points)	8.2 ± 4.0
DWMH score (points)	61.4 ± 51.0
Total cholesterol (mmol/L)	5.38 ± 0.91
HDL cholesterol (mmol/L)	1.50 ± 0.36
LDL cholesterol (mmol/L)	3.23 ± 0.65
Triglyceride (mmol/L)	1.08 ± 0.46
Log IL-6 (ng/L)	0.35 ± 0.46
Log hsCRP (μg/L)	2.58 ± 0.58

All parameters are expressed as mean ± standard deviation. IL-6 and CRP are shown as log transformed. BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

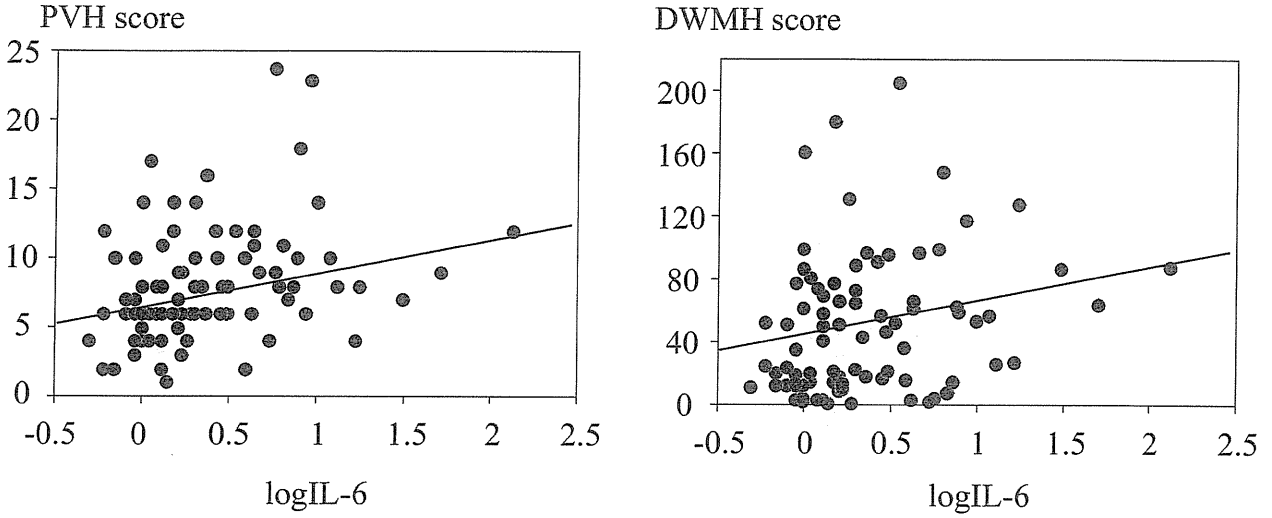

Figure 1 Relations between periventricular hyperintensity (PVH) score and log interleukin (IL)-6 (left panel; $\rho = 0.340$, $P \leq 0.05$, $n = 137$), and deep white matter hyperintensity (DWMH) score and log IL-6 (right panel; $\rho = 0.299$, $P \leq 0.05$, $n = 137$).

Table 2 Spearman's correlation coefficient between leukoaraiosis and parameters

	PVH score		DWMH score	
	ρ	*P*	ρ	*P*
Age	0.411	<0.001	0.271	0.002
BMI	−0.156	0.085	−0.124	0.179
SBP	0.215	0.014	0.232	0.009
Total cholesterol	−0.128	0.192	−0.149	0.134
HDL cholesterol	−0.053	0.595	−0.205	0.041
LDL cholesterol	−0.093	0.349	−0.025	0.802
Triglyceride	−0.014	0.885	0.080	0.421
Smoke	0.337	0.005	0.443	0.000
Log IL-6	0.340	0.002	0.299	0.006
Log hsCRP	−0.018	0.867	0.019	0.855

BMI, body mass index; DBP, diastolic blood pressure; DWMH, deep white matter hyperintensity; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; IL-6, interleukin-6; LDL, low-density lipoprotein; PVH, periventricular hyperintensity; SBP, systolic blood pressure.

markers as independent variables. As shown in Table 3, it was confirmed that the level of IL-6 was significantly associated with the progression of PVH grade (from lowest to middle and middle to highest) and DWMH score (from middle to highest). However, this trend was not found in hsCRP.

Discussion

In this study, we showed relationships between IL-6 and PVH score and IL-6 and DWMH score. It is assumed that IL-6 has an association with cerebral ischemic changes such as leukoaraiosis as well as silent brain infarction.[9] Additionally, PVH and DWMH were correlated with IL-6, but not with hsCRP. With respect to this point, Schmidt *et al.* suggested that CRP is a marker of active carotid atherosclerosis, but not of a small vessel disease-related brain lesion.[12] On the other hand, it is envisaged that elevated hsCRP levels generally reflect large vessel atherosclerosis. Because leukoaraiosis is regarded as one of the brain changes caused by small vessel disease, our results support the idea of Schmidt *et al.*

Interleukin-6 is one of the principal acute-phase reactants, playing a significant role in the activation of the coagulation–fibrinolysis system. On the other hand, leukoaraiosis has been associated with a hypercoagulable condition. Endothelium-derived adhesion molecules have been reported to be elevated in patients with great leukoaraiosis or lacunar infarcts. Leukocyte-mediated injury of the small vessels and ensuing upregulation of endothelial adhesion molecules are implicated in the pathogenesis of leukoaraiosis.[13]

The Rotterdam Scan Study showed that higher hsCRP levels were associated with presence and progression of leukoaraiosis after adjustment for cardiovascular risk factors and carotid atherosclerosis.[14] The subjects in the Rotterdam Scan Study were a population-based cohort ($n = 1033$), while the subjects in the present study were outpatients in the memory clinic ($n = 137$). In this respect, the difference in characteristics and numbers of the subjects may have given rise to the different results in terms of hsCRP in the present study and the Rotterdam Scan Study.

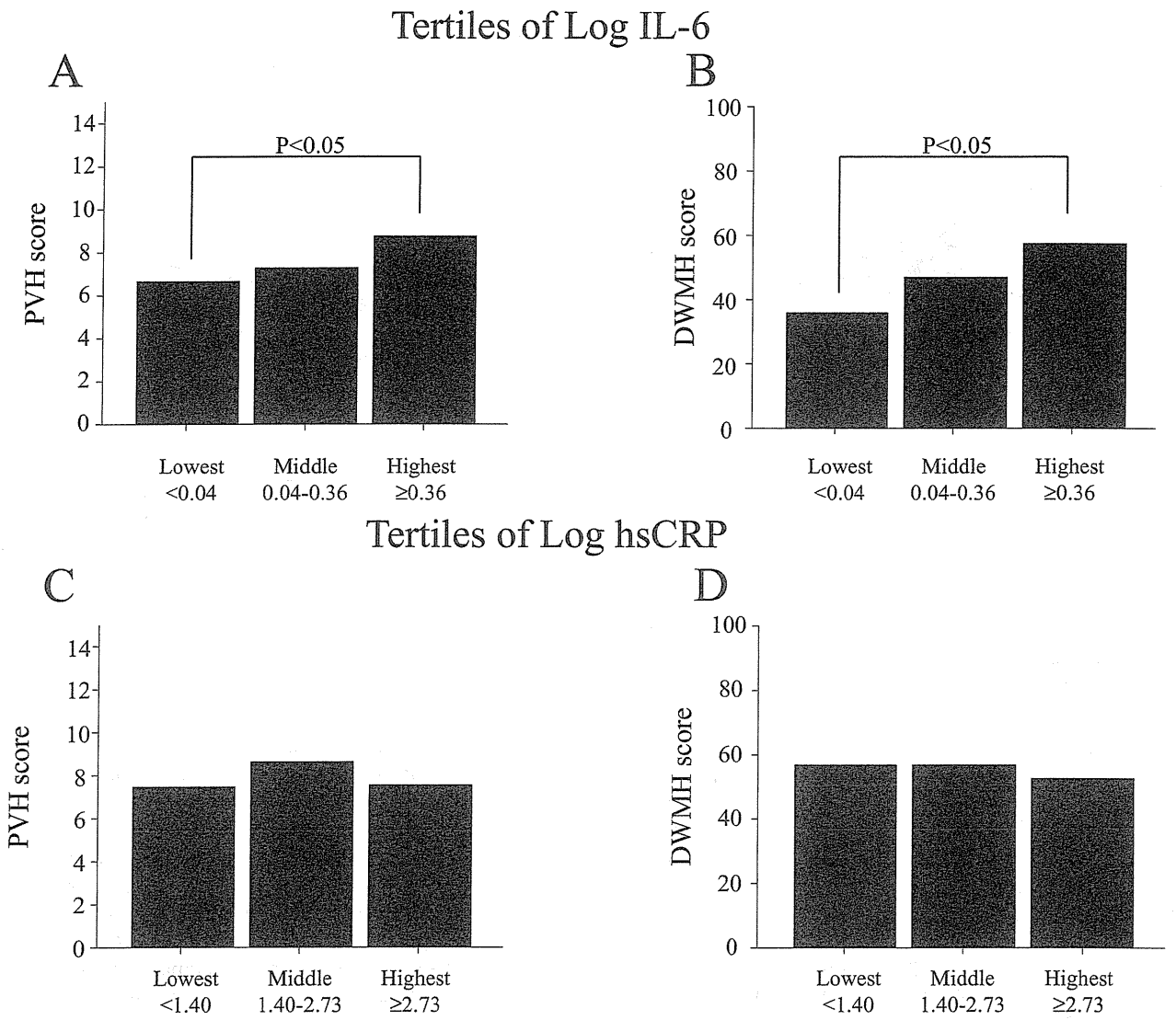

Figure 2 Average of periventricular hyperintensity (PVH) score and deep white matter hyperintensity (DWMH) score by tertile of interleukin (IL)-6 (a,b) and tertile of high-sensitivity C-reactive protein (hsCRP) (c,d). Log IL-6 tertile; lowest, <0.04 pg/mL, $n = 55$, 73.4 ± 7 1 years old (y/o); middle, 0.04–0.36 pg/mL, $n = 38$, 76.9 ± 6.8 y/o; highest, ≥0.36 pg/mL, $n = 44$, 79.5 ± 5.3 y/o. Log hsCRP; lowest, <1.40 ng/mL, $n = 44$, 73.9 ± 7.0 y/o; middle, 1.40–2.73 ng/mL, $n = 46$, 77.6 ± 7.1 y/o; highest, ≥2 73 ng/mL, $n = 41$, 77.8 ± 6.3 y/o.

In the Framingham Heart Study, no association was found between hsCRP and leukoaraiosis on MRI.[15] In the Cardiovascular Health Study, hsCRP level was modestly associated with semi-quantified leukoaraiosis volume, but the effect attenuated after excluding prevalent cerebrovascular and coronary disease cases.[13] In addition, Wright *et al.* was not able to find an association between hsCRP and leukoaraiosis volume.[16] Together, the relationships between leukoaraiosis and hsCRP varied depending upon different reports. This may come from the difference in study subjects and analytical methods. Further investigation is necessary to hold more definite opinion about which inflammatory biomarker represents the presence and development of leukoaraiosis.

Several lines of evidence suggest a relationship between IL-6 and symptoms of the geriatric syndromes, unique features of common health problems associated with poor morbidity in elderly people, such as dementia,[17] functional disability[18] and frailty.[19] On the other hand, the severity of leukoaraiosis also has a relationship with symptoms of geriatric syndromes such as dementia, falls, gait disturbance and functional disability.[3–5] Therefore, IL-6 may be an important biomarker linking the severity of leukoaraiosis to the geriatric syndromes. Because the present study is

Table 3 Associations between inflammation markers and the severity of leukoaraiosis according to tertiles (PVH score or DWMH score) adjusting for age and systolic blood pressure (logistic regression analysis)

	Log hsCRP, μg/L Odds ratio (95% CI)	Log IL-6, ng/L Odds ratio (95% CI)
PVH grade (tertiles)		
Lowest to middle	1.84 (0.78–4.31)	5.80 (1.43–23.60)
Middle to highest	0.39 (0.12–1.32)	4.39 (1.02–18.85)
DWMH grade (tertiles)		
Lowest to middle	0.81 (0.333–1.99)	3.18 (0.78–12.95)
Middle to highest	1.25 (0.48–3.29)	7.85 (1.69–36.38)

Grade of leukoaraiosis according to tertiles of PVH score or DWMH score. CI, confidence interval; DWMH, deep white matter hyperintensity; IL-6, interleukin-6; hsCRP, high-sensitivity C-reactive protein; PVH, periventricular hyperintensity.

cross-sectional, a longitudinal study would corroborate the associations of IL-6 with leukoaraiosis, and IL-6 with the geriatric syndromes.

In conclusion, we demonstrated that IL-6 level is significantly associated with the severity of PVH and DWMH lesions. The results of the present study, together with the previous studies, suggest that IL-6 is an important marker of the progression of cerebral ischemic disease, linking to the presence of geriatric syndromes.

Acknowledgments

This study was supported by a Health and Labor Sciences Research Grant (H18-Choju-031) from the Ministry of Health, Labor and Welfare of Japan, by the Mitsui Sumitomo Insurance Welfare Foundation (2006), and by the Japan Health Foundation (2007). We thank Yukiko Yamada and Ayako Machida for their technical assistance.

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Geriat. Med. 49(9) : 971～975, 2011

Geriatric Medicine（老年医学）9月号　　Vol.49 No.9 2011

特集：骨粗鬆症診療の最近の進歩

総説

3．骨粗鬆症と高齢者の虚弱

神崎　恒一

株式会社　ライフ・サイエンス

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KEY WORD

- 骨折
- ADL
- サルコペニア
- 転倒スコア
- 虚弱

SUMMARY

骨粗鬆症は虚弱の重要な一因であり，椎体骨折，関節の変形とあいまって姿勢変化を生み，歩行障害を来す．さらに転倒を起こしやすく，これによって高齢者のQOL，ADLは低下する．骨粗鬆症以外にもサルコペニアなど虚弱には多くの要因が関わるため，原因を求め，介入することは難しい．しかしながら，そういった中で骨粗鬆症は数少ない介入可能な因子であり，したがってエビデンスに基づく評価・介入を実践することが重要である．

骨粗鬆症に伴うADLの低下

骨粗鬆症とは骨量の減少と骨質の低下(海綿骨，皮質骨の減少よる骨微細構造の劣化)を特徴とし，その結果，骨の脆弱性が増し骨折しやすくなった全身性骨疾患である．ここに転倒などの外力が加わると，軽微な力であっても骨折が生ずる．骨粗鬆症に伴って起こりやすい骨折部位は大腿骨頸部，橈骨遠位端，上腕骨，脊椎(圧迫骨折)である．骨折すると痛みのため，生活の質(QOL)や日常生活活動度(ADL)が低下する(図1)．また，転倒は再発率が高いこともあり，再転倒することへの不安から，外出や生活そのものに対する意欲が損なわれ，これによってもQOLやADLが低下する．この状態が長く続くと，やがて要介護状態に至る危険が高い．

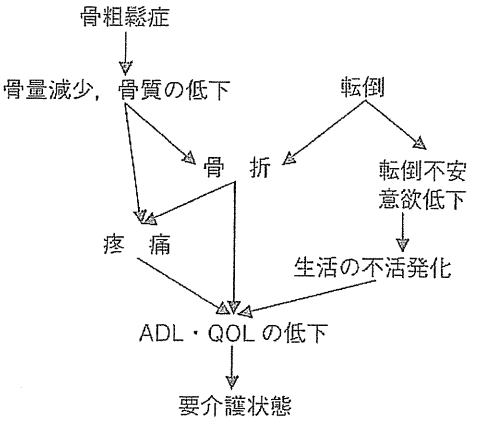
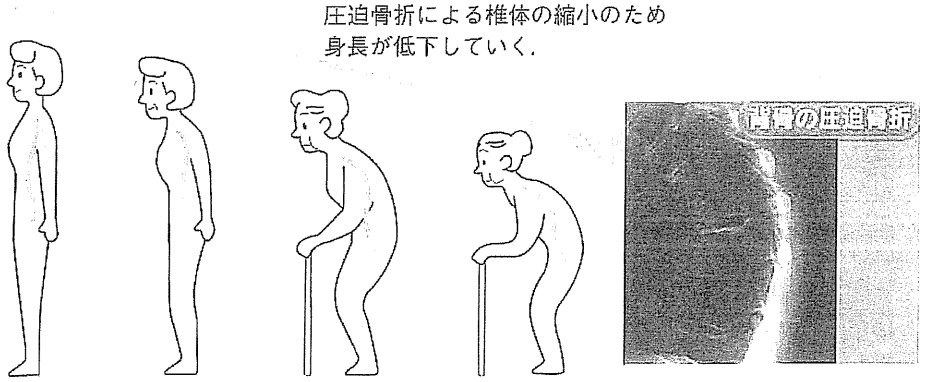


図1　骨粗鬆症と転倒によるADL，QOLの低下

骨粗鬆症，椎体骨折に伴う姿勢の変化

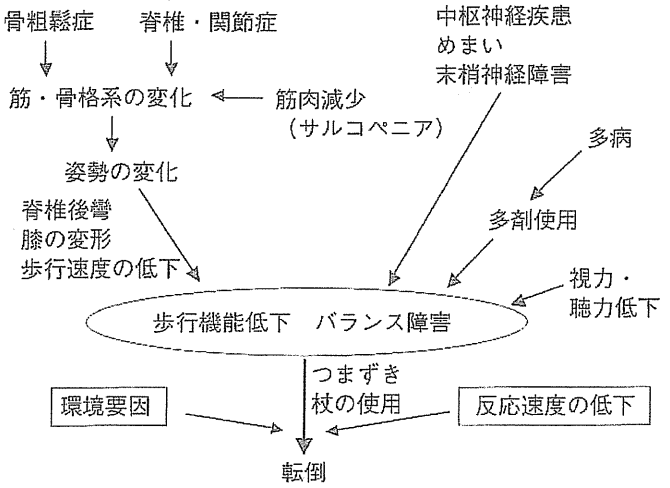
骨粗鬆症による椎体の変形に圧迫骨折を伴うと後彎が進み，身長が短縮する(図2)．脊椎が後彎すると，立位で重心が後方に移動するため，これを補正しようとして膝が前方に偏位する．このような姿勢の変化は歩行に支障を来し，これがもとで運動量が低下し，骨の粗鬆症化が進行する．このような悪循環が進むことで，高齢者の機能障害が進むと考えられる(図3)．われわれは，杏林大学医学部付属病院に通院する高齢患者を対象に，脊椎の後彎角度と転倒の既往との関係について解析した結果，後彎角度が大きいほど，また独自の計測機器を用いて，つま先が上がらない人ほど転倒率が高いことを見出

こうざき　こういち(杏林大学医学部高齢医学)



森井浩世：やさしい骨粗鬆症の自己管理，p6，医療ジャーナル社，大阪，2000より一部改変引用

図2　椎体圧迫骨折による姿勢の変化



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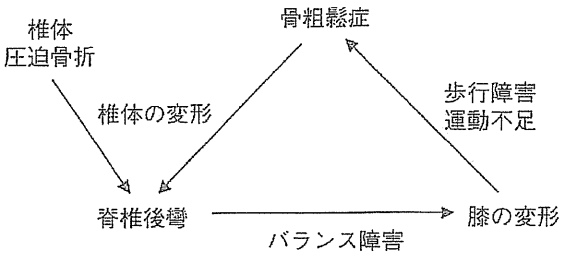

図3　骨粗鬆症に伴う姿勢変化の悪循環

している（未発表データ）．

多要因による歩行障害と転倒

高齢者のQOL，ADLを障害する歩行障害や転倒には，骨粗鬆症以外に多くの要因が関わる．姿勢の変化をもたらす骨・関節系の変化以外に，①高齢期に多くみられる筋肉減少症（サルコペニア），バランス保持能や深部感覚の低下，視力，聴力障害，運動速度や姿勢反射の低下などいわゆる加齢に伴う身体の虚弱化，②循環器系要因（起立性低血圧など），神経系要因（パーキンソン病，認知症などの中枢神経疾患，末梢神経障害，眩暈症など），脳血管障害後遺症などの身体疾患，③薬物（ベンゾジアゼピン系および非ベンゾジアゼピン系の鎮静睡眠薬，抗うつ薬，抗パーキンソン病薬，降圧薬，定型・非定型抗精神病薬など），④屋内の段差や障害物，手すりの有無，履物など環境要因など，要因は多岐に

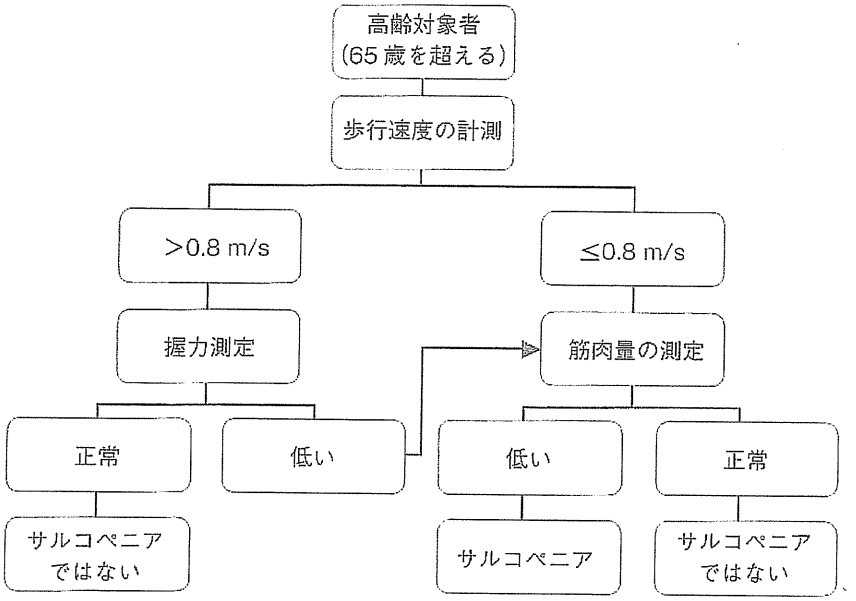

図5　高齢者におけるサルコペニアの発見のためのアルゴリズム

わたる(図4)．しかも，これらは複合して関わるため，1つひとつを区別して要因を分析することが難しい．

加齢性筋肉減少症(サルコペニア)

サルコペニアとは高齢者が虚弱(心身の機能低下)過程で全身，特に四肢の筋肉が量的，質的に低下することを指し，その結果，歩行機能をはじめとする身体機能が低下する．サルコペニアの原因や対策は世界的に注目されており，2010年にBritish Geriatrics Societyからサルコペニアの定義に関するコンセンサスレポート[1]が発表された．この中で，筋肉量の低下のみの場合“前サルコペニア(サルコペニアの前段階)”，筋肉量の低下に加えて筋力の低下もしくは身体機能の低下が認められる場合“サルコペニア”，筋肉量の低下，筋力の低下，身体機能の低下が3つとも認められる場合“重度のサルコペニア”と定義している．さらに，同コンセンサスレポートでは筋肉量をDXA法もしくは生体インピーダンス法で，筋力を握力で，身体機能を歩行速度，バランス，Up & Goテストの組み合わせで評価し，これを組み合わせて図5のような流れで判断するよう勧めている．また，サルコペニアの結果生じる事象として，日常生活自立度(基本的ADL，手段的ADL)，生活の質(QOL)，代謝・生化学・炎症マーカー，転倒，介護施設や病院への入所・入院，社会的支援，死亡率などに注目するよう勧めている．

転倒の評価方法

上記のコンセンサスレポートを加味して，われわれの施設では表1に示すような検査を行い，高齢者の易転倒性を評価している．もちろん，これらの検査は転倒リスクの評価に有用であるが，機器や人手，時間を要するなどマススクリーニングに向かない面もある．そこで，転倒のハイリスク者をより簡易な方法でスクリーニングするために考案したのが転倒スコアである．転倒スコアは自己記入式の調査票であり，身体機能に関する8項目，疾患もしくは老年症候群に関する8項目，環境要因に関する5項目の計21項目と，過去1年間での転倒歴を問う全22項目から成っている(表2)．“はい”，“いいえ”で答える二者択一形式になっており，転倒しやすい方の答えが多いほど転倒リスクが高い．地域在住高齢者を対象とした横断調査の結果，「つまずくことがある」，「信号が青の間に横断

表1　転倒評価のための検査

問診(転倒歴，ADL，環境要因，基礎疾患，服用薬剤)
診察(身長，体重，体脂肪率，血圧，下腿最大周囲径)
視力
下肢筋力
体組成測定
握力
片足立ち時間(開眼，閉眼)
継ぎ足歩行
手伸ばし試験
Up & Go テスト
重心動揺検査
脊椎X線
骨量測定
起立性血圧
頭部MRI
聴力・内耳機能

表2　転倒スコア

過去1年に転んだことがありますか？	(はい　いいえ)	
「はい」の場合，転倒回数(　回/年)		
1．つまずくことがありますか	(はい　いいえ)	身体機能
2．手すりを使わないと階段昇降ができませんか	(はい　いいえ)	
3．歩く速度が遅くなってきましたか	(はい　いいえ)	
4．横断歩道を青のうちに渡りきれますか	(はい　いいえ)	
5．1kmくらい続けて歩けますか	(はい　いいえ)	
6．片足で5秒くらい立つことができますか	(はい　いいえ)	
7．杖を使ってますか	(はい　いいえ)	
8．タオルは固く絞れますか	(はい　いいえ)	
9．めまい・ふらつきがありますか	(はい　いいえ)	疾患 老年症候群
10．背中が丸くなってきましたか	(はい　いいえ)	
11．膝が痛みますか	(はい　いいえ)	
12．目が見えにくいですか	(はい　いいえ)	
13．耳が聞こえにくいですか	(はい　いいえ)	
14．もの忘れが気になりますか	(はい　いいえ)	
15．転ばないかと不安になりますか	(はい　いいえ)	
16．毎日，お薬を5種類以上飲んでいますか	(はい　いいえ)	
17．家の中が暗く感じますか	(はい　いいえ)	環境要因
18．家の中によけて通るものがありますか	(はい　いいえ)	
19．家の中に段差がありますか	(はい　いいえ)	
20．階段を使わなくてはなりませんか	(はい　いいえ)	
21．生活上，急な坂道を歩きますか	(はい　いいえ)	

歩道を渡れない」，「杖の使用」，「タオルを固く絞れない」，「めまい・ふらつきがある」，「膝が痛む」，「屋内の障害物」の7項目が，調査以前の転倒歴と関連すること[2]，「過去(調査以前)の転倒歴」，「歩行速度が遅くなった」，「杖の使用」，「背中が丸くなった」，「5種類以上の服薬」の5項目が，調査後の転倒発生と関連すること[3]が報告されている．転倒スコアは，簡便かつ包括的な転倒評価方法ということができる．

骨粗鬆症と虚弱

“虚弱”は高齢者が抱える普遍的な問題であり，要介護状態を生む大きな原因である．虚弱

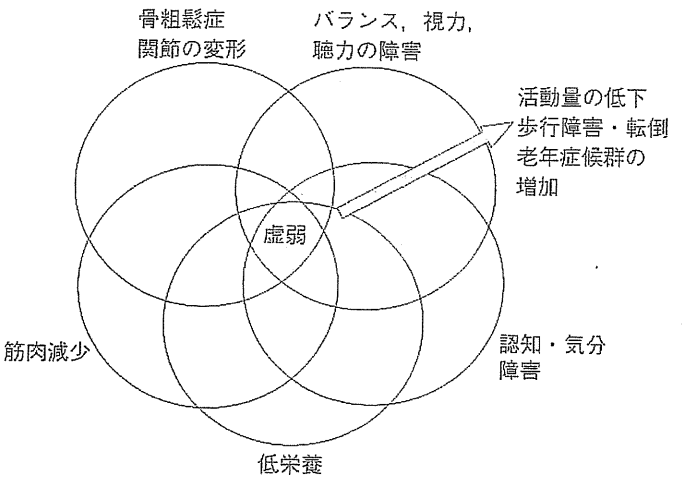

図6

とは加齢に伴って生ずる心身の脆弱な状態であり，複数の臓器・器官の機能低下に起因する．骨粗鬆症やサルコペニアはその主な要因であり，ほかに摂食・嚥下障害と関連する低栄養状態や認知・気分障害(意欲低下，うつなど)など様々な要因が関わる(図6)．虚弱は，活動量の低下，歩行障害・転倒，痩せ，そのほか老年症候群の集積をもたらす．虚弱はその多因子性ゆえ，原因を求め介入することが容易ではないが，骨粗鬆症はその中で数少ない介入可能な要因である．後述されるSeminarを基に，エビデンスに基づく評価・介入を行うことが大切である．

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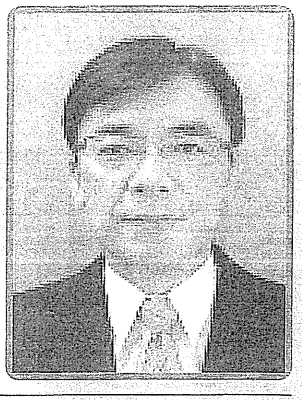
(執筆者連絡先)　神崎恒一　〒181-8611　東京都三鷹市新川6-20-2　杏林大学医学部高齢医学

CGAと包括的ケア



こうざきこういち
神崎恒一
杏林大学医学部高齢医学教授

【略歴】1960年生まれ。86年：東京大学医学部卒業、88年：東京大学医学部附属病院老年病学教室入局、95年：同助手、97年：ワシントン大学医学部病理学教室フェロー、2002年、東京大学医学部附属病院老年病科講師、05年：杏林大学医学部高齢医学助教授、07年：同准教授、10年より現職
【専門分野】老年医学・循環器・動脈硬化・認知症。医学博士

高齢者の特徴とCGA

高齢になると種々の臓器、器官の機能が低下し、種々の疾患の発生、ストレス応答の低下、日常生活を阻害するさまざまな症候（老年症候群）が増加する（図1）。したがって、高齢者をみるうえでは病気を診るだけでなく、心身の機能を多面的に評価し、日常生活の様子を知る必要がある。たとえば、糖尿病のある独居高齢者で認知機能とADLに問題があり、食事や服薬に問題がある場合、いくら熱心に食事指導を行い、効果の高い糖尿病薬を使用しても血糖管理はうまくいかない。このように患者の生活環境、ADL、認知機能などを把握したうえで疾患の管理を行うことが必要である。

そのために役に立つのが高齢者総合的機能評価（CGA）である。CGAでは手段的ADL（独居生活の自立度）、基本的ADL（屋内生活の自立度）、生活環境、うつ（GDS15）、生活意欲（vitality index）、認知機能（MMSE、HDS-R）、その他を評価する（表1）。詳細は杏林大学医学部高齢医学教室のホームページ< http://www.kyorin-u.ac.jp/univ/user/medicine/geriatrics/medicine04.html >を参照されたい。なお、ADLとvitality indexは観察型評価なので、患者からの情報に問題があると考えられる場合、生活を共にする家族から情報を得る必要がある。一方、MMSE、HDS-R、GDS15は検者を必要とする質問式評価である。

CGA 7によるスクリーニング

上記の機能評価をすべて行うには時間がかかるので、これらの検査のうち代表的な7項目についてチェックする高齢者総合的機能簡易評価法（CGA7；表2）がある。5分以内で実施可能であり、スクリーニングに適している。表3に示すように、各項目はそれぞれ意欲、認知機能、手段的ADL、認知機能、基本的ADL、基本的ADL、うつについての質問項目であり、問題ありと判断したら、"次へのステップ"に示されるCGAを実施する。

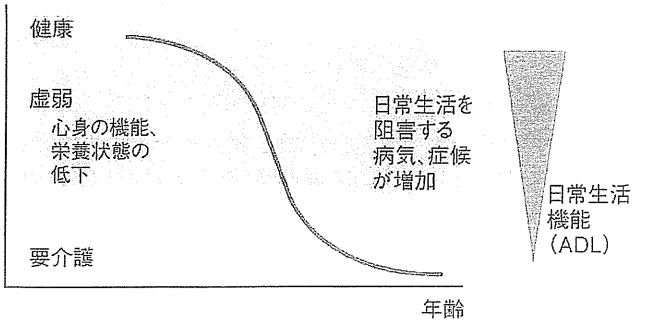


図1　身心の虚弱化

表1　認知症高齢者を診る上で知っておきたいこと
（高齢者総合的機能評価）

- 手段的ADL、基本的ADL
- 生活環境：住居、同居者とその人間関係、日中の過ごし方、外出状況、介護状況など
- うつの状態 → GDS15
- 生活意欲 → vitality index（リハビリ、活動への積極性）
- 認知機能 → MMSE, HDS-R
- 合併疾患は？ 服用薬は？
- 老年症候群

表2　高齢者総合的機能簡易評価法(CGA7)

(1)外来患者の場合：診察時に被験者の挨拶を待つ
入院患者もしくは施設入所者の場合：　自ら定時に起床するか、もしくはリハビリへの積極性で判断

(2)「これから言う言葉を繰り返してください
(桜、猫、電車)」
「あとでまた訊きますから覚えておいてください」

(3)「普段バスや電車、自家用車を使ってデパートやスーパーマーケットに出かけますか？」

(4)「先ほど覚えていただいた言葉を言ってください」

(5)「お風呂は自分ひとりで入って、洗うのに手助けは要りませんか？」

(6)「失礼ですが、トイレで失敗してしまうことはありませんか？」

(7)「自分が無力だと思いますか？」

高齢者総合的機能評価簡易版CGA7の開発.
日本老年医学会雑誌41, 124, 2004より一部改変

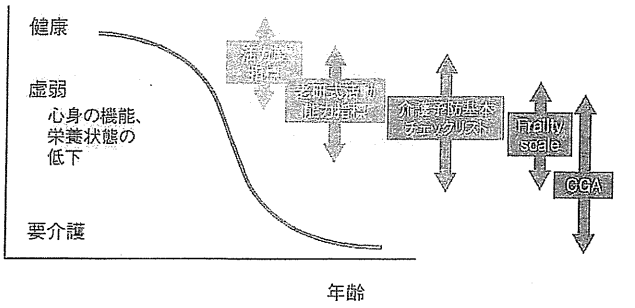


図2　虚弱とその評価方法

虚弱の評価としてのCGA

虚弱とは、複数の臓器・器官の機能低下基づく心身の脆弱な状態をさし、したがって複数の機能を多面的に評価する必要がある。その際、病気を抱えていても普通に生活している地域在住高齢者から、要支援に陥る可能性があるハイリスク高齢者、すでに介護保険を使用している高齢者、ADLが低下した施設利用者など、それぞれの生活機能に適した評価を行う必要がある。図2は健康→虚弱→要介護状態の各段階での評価方法である。

1．活力度指標（表4）

活力度指標は地域在住高齢者の日常生活の活力度を評価するための尺度であり、20項目の質問項目よりなる。1～6は「気分・意欲」に関する項目（12点）、7～11は「認知」に関する項目（10点）、12～17は「心身の健康」に関する項目（12点）、18～20は「社会参加」に関する項目（6点）であり40点満点である。習慣的に運動している高齢者は、運動していない高齢者に比べて加齢に伴う活力度

表3　CGA7：評価内容・正否と解釈・次へのステップ

番号	CGA7の質問	評価内容	正否と解釈	次へのステップ
①	<外来患者>　診察時に被験者の挨拶を待つ	意欲	正：自分から進んで挨拶する 否：意欲の低下	Vitality index
	<入院患者・施設入所者>　自ら定時に起床するか、もしくはリハビリへの積極性で判断		正：自ら定時に起床する、またはリハビリその他の活動に積極的に参加する 否：意欲の低下	
②	「これから言う言葉を繰り返して下さい(桜、猫、電車)」、「あとでまた聞きますから覚えておいて下さい」	認知機能	正：可能(できなければ④は省略) 否：復唱ができない　⇒　難聴、失語などがなければ中等度の認知症が疑われる	MMSE・HDS-R
③	<外来患者>　「ここまでどうやって来ましたか？」 <入院患者・施設入所者> 「普段バスや電車、自家用車を使ってデパートやスーパーマーケットに出かけますか？」	手段的ADL	正：自分でバス、電車、自家用車を使って移動できる 否：付き添いが必要　⇒　虚弱か中等度の認知症が疑われる	IADL
④	「先程覚えていただいた言葉を言って下さい」	認知機能	正：ヒントなしで全部正解。認知症の可能性は低い 否：遅延再生(近時記憶)の障害　⇒　軽度の認知症が疑われる	MMSE・HDS-R
⑤	「お風呂は自分ひとりで入って、洗うのに手助けは要りませんか？」	基本的ADL	正：⑥は、失禁なし、もしくは集尿器で自立。入浴と排泄が自立していれば他の基本的ADLも自立していることが多い 否：入浴、排泄の両者が×　⇒　要介護状態の可能性が高い	Barthel index
⑥	「失礼ですが、トイレで失敗してしまうことはありませんか？」			
⑦	「自分が無力だと思いますか？」	情緒・気分	正：無力と思わない 否：無力だと思う　⇒　うつの傾向がある	GDS-15

健康長寿診療ハンドブック(日本老年医学会編)より引用

表4　活力度指標(activity scale for the elderly: ASE)その1

1. 夢や希望があると思いますか？
(そう思う、どちらともいえない、そう思わない)
2. 物事を明るく考えるほうだと思いますか？
(そう思う、どちらともいえない、そう思わない)
3. 新しいことに挑戦したいと思いますか？
(はい、少しおっくう、大分おっくう)
4. 困難な課題に以前と同様取り組めますか？
(はい、少しおっくう、大分おっくう)
5. 楽しいことがないと思いますか？
(そう思う、どちらともいえない、そう思わない)
6. 自分からすすんで挨拶をしますか？
(いつも、ときどき、していない)
7. 知りあいの名前がとっさに出ないことがありますか？
(いつもある、時々ある、まれにorない)
8. 物忘れが気になりますか？
(気にならない、少し気になる、大分気になる)
9. 用語が乏しくなった気がしますか？
(しない、少しする、とてもする)
10. 昨日の夕食の内容が思い出せないことがありますか？
(いつもある、時々ある、まれにorない)

活力度指標(activity scale for the elderly: ASE)その2

11. 同じ話をしたことを指摘されることがありますか？
(いつもある、時々ある、まれにorない)
12. 他人より病弱だと思いますか？
(そう思う、どちらともいえない、そう思わない)
13. 全く健康であると思いますか？
(そう思う、どちらともいえない、そう思わない)
14. 疲労感がありますか？
(いつもある、時々ある、まれにorない)
15. 腰痛・関節痛がありますか？
(いつもある、時々ある、まれにorない)
16. 気分の落ち込みがありますか？
(いつもある、時々ある、まれにorない)
17. 不眠がありますか？
(いつもある、時々ある、まれにorない)
18. 自治体行事に参加していますか？
(定期的に、時に、していない)
19. 近所づきあいをしていますか？
(定期的に、時に、していない)
20. ボランティア活動をしていますか？
(定期的に、時に、していない)

1～4, 6, 8, 9, 13, 18～20は括弧内の選択肢について左から2, 1, 0を各配点。5, 7, 10～12, 14～17は括弧内の選択肢について左から0, 1, 2を各配点。

表5　老研式活動能力指標

	質問	1	0	1か0を記入
1	バスや電車を使って1人で外出できますか	はい	いいえ	
2	日用品の買い物ができますか	はい	いいえ	
3	自分で食事の用意ができますか	はい	いいえ	
4	請求書の支払いができますか	はい	いいえ	
5	銀行預金・郵便貯金の出し入れが自分でできますか	はい	いいえ	
6	年金などの書類が書けますか	はい	いいえ	
7	新聞を読んでいますか	はい	いいえ	
8	本や雑誌を読んでいますか	はい	いいえ	
9	健康についての記事や番組に関心がありますか	はい	いいえ	
10	友だちの家を訪ねることがありますか	はい	いいえ	
11	家族や友だちの相談にのることがありますか	はい	いいえ	
12	病人を見舞うことができますか	はい	いいえ	
13	若い人に自分から話しかけることがありますか	はい	いいえ	
点数が高いほど自立していることを表す。		合計得点		点

表6　The Edmonton Frailty scale

1. 認知機能　時計描画テスト：「この円を時計の文字盤だと思ってください。ここに時計の数字を正しく記入してください。そして、時計の針を11時10分となるように記入してください。

2. 一般的な健康状態
a) 昨年、何回病院に入院しましたか？
□0回　□1-2回　□2回以上
b) 概してご自分の健康状態をどう思いますか？
□良い　□普通　□不良

3. 機能的自立（手段的ADL）
以下の生活動作のうち、介助が必要なのものはいくつありますか？
・食事の準備　・買い物・乗り物の利用・電話の使用
・清掃等家事　・洗濯　・家計管理　・服薬管理
□0-1個　□2-4個　□5-8個

4. 生活支援への期待
あなたが生活支援を必要とする時、誰かを頼りにできますか？
□常に頼りにできる人がいる　□時々ならいる
□誰もいない

5. 薬の服用
a）5種類以上の定期薬を服用していますか？
□いいえ　□はい
b）ときどき内服を忘れてしまうことがありますか？
□いいえ　□はい

6. 栄養：最近、洋服がゆるくなるくらい体重が減少しましたか？
□いいえ　□はい

7. 抑うつ状態：悲しくなったり気分がふさぐことがしばしばありますか？　□いいえ　□はい

8. 失禁：尿が漏れることがありますか？
□いいえ　□はい

9. 機能的動作：Up&Go テスト
所要時間：　秒　□ 0-10秒、□ 11-20秒、□ >20秒

の低下が低いことが報告されている[1]。運動の有用性を活力度指標で検証した内容である。

2．老研式活力度指標（表5）

老研式活力度指標も地域在住高齢者の生活機能の自立性を測定する尺度である。1～5は手段的自立、6～9は知的能動性、12～17は社会的役割（他者との関わり）を表している[2]。加齢に伴って低下し、低下者は生活満足度、ソーシャルネットワークとサポート、趣味の活動が低下し、うつ傾向が高まることが知られている。

3．介護予防のための基本チェックリスト

介護予防のための基本チェックリストは、文字どおり要介護状態になるのを防ぐための日常生活上におけるチェックリストであり、手段的ADL、交流活動、運動器、栄養状態、口腔機能、閉じこもり、認知症、うつに関する25の質問項目からなっている。一定の基準以上に該当すると要支援に近いハイリスク高齢者とみなされ、介護予防プログラムを受けるよう求められる。

4．Edmonton frailty scale（表6）

Edmonton frailty scaleは、2006年にカナダのアルバータ大学のRolfsonらが提唱した虚弱の指標であり、複数の領域として認知、健康状態、手段的ADL、介護者の有無、服用薬剤数、栄養状態、うつ、失禁、歩行機能に関する項目が設定されている[3]。17点満点で点数が高いほど虚弱度が高い。

以上の1～4の指標はそれぞれ多面的に高齢者の機能を評価する尺度であり、広い意味でCGA（総合的機能評価）と考えることができる。活力度指標は虚弱に至る前の段階（prefrail）、老研式活力度指標と介護予防のための基本チェックリストは虚弱の前段階～虚弱の段階、Edmonton frailty scaleは虚弱～要支援または要介護の段階を評価するのに適している。また、施設入所者に対しては表3のCGAもしくはさらに機能の低い高齢者用のチェックリストが必要（実際には各施設で使われている）である。

おわりに

高齢者は活動性（社会活動、人的交流、知的活動）、家族との関わり、ADL、認知機能、気分（うつ）、意欲、栄養状態、病気の状況（服薬状況）など知っておかなければならないことが多い。しかしながら、これらの情報を一人で収集することはむずかしいので、医療、介護、福祉、その他複数の業務に当たる職種が協働してこれに当たり、得られた情報を共通のフォーマットで管理するような仕組みづくりが今後必要と思われる。

[文献]
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