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Table 2 Correlations Between ROCK Activity Before and After L-NMMA and Variables

Variable	ROCK Activity Before L-NMMA		ROCK Activity After L-NMMA	
	Coefficient	p Value	Coefficient	p Value
Age (yrs)	0.636	<0.001	0.635	<0.001
Body mass index (kg/m^2)	−0.019	0.892	−0.007	0.961
Systolic blood pressure (mm Hg)	0.437	0.002	0.396	0.007
Diastolic blood pressure (mm Hg)	−0.093	0.516	−0.134	0.358
Heart rate (beats/min)	−0.089	0.533	−0.131	0.368
Total cholesterol (mmol/l)	0.414	0.004	0.471	0.001
HDL cholesterol (mmol/l)	−0.157	0.277	−0.156	0.290
Triglyceride (mmol/l)	0.167	0.248	0.089	0.547
Mean fasting glucose (mmol/l)	0.097	0.555	−0.048	0.778
Serum insulin (pmol/l)	0.066	0.677	0.087	0.590
Insulin resistance (HOMA index)	0.033	0.852	0.026	0.888
Number of pack-yrs smoked	0.515	<0.001	0.487	<0.001

L-NMMA = N^G-monomethyl-L-arginine; ROCK = Rho-associated kinase; other abbreviations as in Table 1.

$p < 0.01$). The ratio of SNP-stimulated maximal FBF to basal FBF was not significantly correlated with cf-PWV. The cf-PWV was not correlated with other parameters. The correlations between cf-PWV and variables are summarized in Table 5. For multiple regression analysis, variables showing a p value of <0.1 in Spearman correlation analysis were selected; age, systolic blood pressure, serum concentration of total cholesterol, number of pack-years smoked, endothelial function, and ROCK activity before or after L-NMMA, were entered as candidates for independent variables. Stepwise multiple regression analysis revealed that age (standardized $r = 0.71$) and ROCK activity (standardized $r = 0.27$) were independent predictors of cf-PWV (multiple $R^2 = 0.79$; $p < 0.01$) and that age (standardized $r = 0.51$) and ROCK activity after co-infusion of L-NMMA (standardized $r = 0.54$) were independent predictors of cf-PWV (multiple $R^2 = 0.91$; $p < 0.01$). In addition, the serum concentration of MDA-LDL was significantly correlated with cf-PWV ($r = 0.57$; $p < 0.01$).

Discussion

In the present study, there were significant relationships between ROCK activity and age, systolic blood pressure, serum concentration of total cholesterol, and number of pack-years smoked in healthy male subjects. In multivariate analysis, age and number of pack-years smoked were independent predictors of ROCK activity among the candidates that were correlated with ROCK activity. In addition, the concentration of serum MDA-LDL, one of the established markers of oxidative stress, was correlated with ROCK activity. To the best of our knowledge, this is the first study to provide clinical evidence revealing significant involvement of ROCK activity with age, accumulating current smoking habit, and oxidative stress in humans.

Recently, increasing evidence has indicated that ROCK is significantly associated with the regulation of not only endothelial nitric oxide synthase (eNOS) expression but also eNOS phosphorylation, both of which are important mechanisms for regulating endothelial function and subsequent cardiovascular injury (2–4,16). We have also demonstrated a significant relationship between endothelial dysfunction

Table 3 Correlations Between the Ratio of SNP-Stimulated Maximal FBF to Basal FBF and Variables

Variables	Coefficient	p Value
Age (yrs)	−0.127	0.372
Body mass index (kg/m^2)	−0.049	0.730
Systolic blood pressure (mm Hg)	0.107	0.453
Diastolic blood pressure (mm Hg)	0.040	0.780
Heart rate (beats/min)	−0.086	0.546
Total cholesterol (mmol/l)	−0.120	0.407
HDL cholesterol (mmol/l)	0.005	0.972
Triglyceride (mmol/l)	0.147	0.308
Mean fasting glucose (mmol/l)	0.049	0.768
Serum insulin (pmol/l)	−0.045	0.776
Insulin resistance (HOMA index)	−0.044	0.801
Number of pack-yrs smoked	0.021	0.886

SNP = sodium nitroprusside; other abbreviations as in Table 1.

Table 4 Correlations Between Endothelial Function and Variables

Variables	Coefficient	p Value
Age (yrs)	−0.548	0.003
Body mass index (kg/m^2)	−0.020	0.915
Systolic blood pressure (mm Hg)	−0.313	0.092
Diastolic blood pressure (mm Hg)	0.140	0.451
Heart rate (beats/min)	0.218	0.241
Total cholesterol (mmol/l)	−0.671	<0.001
HDL cholesterol (mmol/l)	0.071	0.709
Triglyceride (mmol/l)	−0.074	0.694
Mean fasting glucose (mmol/l)	0.281	0.187
Serum insulin (pmol/l)	0.179	0.353
Insulin resistance (HOMA index)	0.346	0.113
Number of pack-yrs smoked	−0.588	0.002

Abbreviations as in Table 1.

Table 5 Correlations Between Pulse Wave Velocity and Variables

Variables	Coefficient	p Value
Age (yrs)	0.882	<0.001
Body mass index (kg/m^2)	0.025	0.884
Systolic blood pressure (mm Hg)	0.418	0.015
Diastolic blood pressure (mm Hg)	0.211	0.218
Heart rate (beats/min)	−0.141	0.411
Total cholesterol (mmol/l)	0.472	0.006
HDL cholesterol (mmol/l)	−0.085	0.620
Triglyceride (mmol/l)	0.133	0.437
Mean fasting glucose (mmol/l)	−0.069	0.695
Serum insulin (pmol/l)	−0.060	0.729
Insulin resistance (HOMA index)	−0.145	0.421
Number of pack-yrs smoked	0.377	0.028
The ratio of SNP-stimulated maximal FBF to basal FBF (%)	−0.155	0.373
Endothelial function (%)	−0.543	0.009
ROCK activity (%)	0.670	<0.001
ROCK activity after coinfusion of L-NMMA (%)	0.746	<0.001

Abbreviations as in Tables 1, 2, and 3.

and increased ROCK activity in current smokers (11). The results of the present study show that aging and cigarette smoking are involved in an increase in ROCK activity, which might be partly explained by the significant correlation between ROCK and endothelial function. Our results are supported by several recent studies showing that aging is significantly related to activation of the Rho/ROCK pathway (26,27). Those findings suggest that activation of ROCK is involved in several aspects of the atherosclerotic process, including endothelial dysfunction.

Fasudil, which competes with adenosine 5'-triphosphate (ATP) for binding to ATP-dependent kinase domains, has recently been shown to be a potent and specific inhibitor of ROCK (5,6,28). ROCK activity in humans has been investigated in several previous studies using fasudil (8,29). Masumoto et al. (7). demonstrated that ROCK activity, evaluated by the vasodilative response to fasudil, is increased at the segment of coronary vasospasm in patients with vasospastic angina. In addition, we evaluated ROCK activity after co-infusion of L-NMMA to assess ROCK activity in the forearm vasculature. Although it is not clear whether ROCK activity before or after co-infusion of L-NMMA is appropriate for assessing ROCK activity, ROCK activity after co-infusion of L-NMMA may be appropriate for precise assessment of ROCK activity because it may avoid the contribution of endogenous nitric oxide to ROCK in VSMC. Interestingly, we could not find a significant correlation of forearm vasodilatory response to SNP with the variables in this study, which is in accordance with previous evidence (8,18). This discrepancy between the vasodilative effects of fasudil and SNP may be due to the different pharmacologic mechanisms of the drugs, dependency on Ca^{2+} sensitivity, or Ca^{2+} concentration in VSMC.

One of the novel findings in the present study is that ROCK activity, but not endothelial function, is one of the independent predictors of increased PWV, indicating that ROCK is significantly involved in the pathogenesis of aortic stiffness. Aortic stiffness has been shown to be closely associated with cardiovascular risks (22,24,30) and to be a significant predictor of cardiovascular morbidity and mortality in subjects with a smoking habit, hypertension, end-stage renal disease, and aging (21,31,32). Of great interest are the results of a recent study by Willum-Hansen et al. (33) showing that PWV predicted a composite of cardiovascular outcomes over a median follow-up period of 9.4 years beyond 24-h mean arterial pressure and other traditional risk factors such as gender, age, BMI, current smoking habit, and alcohol intake in middle-aged and elderly individuals, results that are significant from the point of view of clinical benefit. According to previous studies, ROCK plays an important role in atherosclerotic processes, especially in VSMC (5,6,12,13,28), indicating that ROCK modulates VSMC function via several kinds of mechanisms, including regulation of Ca^{2+} sensitivity, which may explain the discrepancy in the results of the present study showing that ROCK activity but not endothelial function is an independent predictor of PWV.

Oxidative stress is known to be crucial for the development of cardiovascular disease and subsequent mortality (15,34). In the present study, we measured the concentration of serum MDA-LDL to evaluate the contribution of oxidative stress to ROCK activity and aortic stiffness. Thus, the significant correlations of ROCK activity with age and number of pack-years smoked may be evoked partly through excess oxidative stress. Indeed, several investigators have demonstrated a possible correlation of ROCK with oxidative stress in in vitro and in vivo studies (20). Consequently, it is feasible that oxidative stress is significantly correlated with ROCK activity and further aortic stiffness in the present study. Collectively, these findings support our hypothesis that activation of ROCK in VSMC leads to impaired aortic stiffness, although we could not determine from the results of the present study whether increased ROCK activity causes oxidative stress or whether oxidative stress caused by various variables such as aging and accumulating smoking habit leads to increased ROCK activity. Furthermore, endothelial dysfunction, which is significantly related not only to excess oxidative stress but also to activated ROCK, may also be an important mechanism of impairment of aortic stiffness. Although the precise mechanism remains to be determined, ROCK plays a critical role in the modulation of aortic stiffness through a pathway in which oxidative stress is involved.

Study limitations. Although, we obtained the striking finding that aortic stiffness significantly correlates with ROCK and oxidative stress, several limitations remain in the present study. It has been shown that creatinine clearance is negatively associated with PWV in subjects with moderate reduction of creatinine clearance (35). Although serum concentrations of creatinine in all subjects in this study were normal (<106 μmol/l), additional data on the correlation of creatinine clearance with ROCK or PWV might make the results more plausible. In addition, recent studies have revealed significant relationships between aortic stiffness and several candidates such as serum high-sensitivity C-reactive protein (hs-CRP) and criteria for the diagnosis of the metabolic syndrome (36–38). Indeed, it has been shown that CRP activates ROCK, leading to plasminogen activator inhibitor-1 expression and atherothrombogenesis in vitro. Those findings suggest that serum level of hs-CRP may correlate with ROCK activity and may cause the elevation of PWV in humans (39). In the present study, waist circumference was not measured. The BMI was measured in all subjects instead of waist circumference, and BMI was <30 kg/m^2 in all subjects. Accordingly, our results might not have been greatly influenced by the lack of measurement of waist circumference. It is thought that many disorders of biologic and physiologic factors are related to impaired aortic stiffness. Therefore, further investigations are required to clarify the precise mechanism underlying impairment of aortic stiffness.

Conclusions. We have demonstrated that ROCK activity in the forearm vasculature is significantly associated with age and number of pack-years smoked and that increased cf-PWV is significantly related to age and ROCK activity. In addition, excess oxidative stress is significantly correlated with increased ROCK activity and PWV. These findings suggest that excessive oxidative stress might be involved in increased ROCK activity in the vasculature, leading to impaired aortic stiffness, and that not only oxidative stress but also ROCK might be vital therapeutic targets for cardiovascular protection.

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ORIGINAL ARTICLE

Strategy for treating elderly Japanese with hypercholesterolemia*

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Background: It has been widely accepted that control of serum cholesterol levels is effective for prevention of cardiovascular events. Recent data have suggested that this is also the case in the elderly.

Methods: A research group (chaired by T. Kita) was organized as part of the Comprehensive Research on Aging and Health conducted by the Japanese Ministry for Health, Labour, and Welfare in 1999–2002 to determine the best strategy for control of cholesterol levels in elderly Japanese with hypercholesterolemia. In order to do this a review of the literature was conducted.

Conclusion: The research group concluded: (i) Japanese patients aged 65–74 years with hypercholesterolemia should be treated by following the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases by the Japan Atherosclerosis Society (2002), as cholesterol-lowering therapy would bring a similar, or even larger, preventive effect to the elderly, whose absolute risk of cardiovascular events is higher than that in the younger population; (ii) target cholesterol levels in elderly Japanese aged ≥ 75 years with

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hypercholesterolemia should be determined individually according to their physical activities. It is noted that the elderly are more susceptible to drug-related adverse effects than the younger since renal and liver functions, required for metabolizing drugs, in the elderly are relatively weaker.

Keywords: cardiovascular event, elderly, hypercholesterolemia, Japanese, statin.

Introduction

It is well known that cardiovascular events occur in elderly people more frequently than in the younger population. It is also known that the incidence of these events increases as serum cholesterol levels are elevated. In Japan, populations of elderly people are rapidly increasing and serum cholesterol levels have been clearly rising in all ranges of ages probably due to westernization of our dietary habits.[1] Therefore, a rapid increase in atherosclerotic diseases is anticipated in Japan, especially in the elderly, without appropriate prevention.

Data obtained in many clinical studies performed in Western countries have demonstrated that cholesterol-lowering therapy with HMG-CoA reductase inhibitors, statins, reduces cardiovascular events by 26–37%.[2–4] Therefore, therapeutic intervention to control serum cholesterol levels is widely accepted. So far, guidelines for controlling cholesterol levels have been established in several countries, such as ATPIII (http://www.nhlbi.nih.gov/guidelines/cholesterol/atp_iii.htm) in the USA. Since the incidence of cardiovascular events in the Japanese population is clearly lower than that in Western countries, establishment of the Japanese guideline has been considered necessary. The first Japanese guideline was established by the Japanese Atherosclerosis Society in 1997 and it has been revised in 2002 (http://jas.umin.ac.jp). Since the subjects for the guideline are those aged ≤ 65 years, the guideline for elderly Japanese has been expected to be established.

In 1996–99, the research group for 'Establishing Japanese guidelines for treating atherosclerotic diseases in the elderly' was organized as part of the Comprehensive Research on Aging and Health conducted by the Japanese Ministry for Health, Labour and Welfare and the first guideline was proposed in 1999 (Kita & Hata *et al.* unpublished report to the Japanese Ministry of Health and Welfare 1999). In this guideline, the target cholesterol levels for the elderly were recommended to be 20 mg/dL higher than those for the younger population, based on the comparison of relative risk increase in relation to serum cholesterol levels between younger people and the elderly (Kita & Hata *et al.* unpublished report to the Japanese Ministry of Health and Welfare 1999). Since then, several important clinical datasets in Western countries and results of studies conducted in Japan,[2–4] such as the KLIS,[5,6] the J-LIT and PATE have been produced.[7–9] Therefore, the research group was again organized in 1999–2002 in order to conduct a research project entitled 'Long-term prognosis of the elderly with hyperlipidemia' (chaired by T. Kita) as a part of the Comprehensive Research on Aging and Health with a view to re-evaluating the proposed guideline (Kita & Hata *et al.* unpublished report to the Japanese Ministry of Health and Welfare 1999). The research group has concluded that serum cholesterol levels in Japanese aged 65–74 years are recommended to be controlled in the same way as for patients aged ≤ 65 years by following the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases (2002) by the Japan Atherosclerosis Society (http://jas.umin.ac.jp/), and that for those aged ≥ 75 years the control levels should be determined individually based on their physical activities (Kita & Matsuzawa *et al.* unpublished report to the Japanese Ministry of Health and Welfare 2002).

Clinical data in Western countries

Secondary prevention studies such as 4S and CARE have been analyzed with a focus on the elderly.[10,11] In both studies, treatment with simvastatin and pravastatin in the elderly patients was as safe and effective for reducing serum cholesterol levels as it was in younger patients.[10,11] In the 4S study, 4444 patients with established coronary heart diseases were divided into simvastatin and placebo groups, and followed for 5.4 years.[10] In this study, simvastatin treatment reduced total cholesterol levels by 26% in the elderly aged 65–70 years and by 25% in younger patients,[10] indicating that the cholesterol lowering effect of simvastatin in the elderly is similar to that in the younger. The relative risk reduction of major coronary events, including coronary artery death and non-fatal myocardial infarction, by simvastatin in the elderly patients was 34%, similar to that in younger patients aged < 65 years.[10] In the CARE study, 4159 patients were divided into pravastatin and placebo groups and followed for 5 years.[11] In this study, pravastatin treatment reduced total cholesterol levels by 19% in the elderly aged 65–75 years and by 20% in patients aged < 65 years,[11] indicating that the cholesterol lowering effect of simvastatin in the elderly is similar to that in younger patients. The relative risk reduction in the elderly group was 39% while that in the younger was 13%.[11] Because of the higher absolute risk and greater effect on risk reduction in the elderly group, the number needed to treat (NNT) in the 5-year follow-up period in the elderly group was 15 while that in the younger group was 67.[11]

Recently, the results of the PROSPER study have been published.[12] In this study, approximately 5800 high-risk patients aged 70–82 (mean 75 years) with normal total cholesterol levels (mean 217 mg/dL) were divided into pravastatin and placebo groups, and followed for 3 years. In this elderly population, the statin reduced coronary events by 19%. Since the preventive effects by statins become obvious in 1–2 years after starting the medication in many studies,[2–4] the risk reduction ratio in the PROSPER study could be relatively smaller during the 3-year follow-up period.[12] In the ASCOT study, approximately 19 000 hypertensive high-risk patients with total cholesterol levels of ≤ 250 mg/dL (213 mg/dL average), aged 40–79 years (mean 63 years), were assigned into placebo and 10 mg/day atorvastatin groups, and followed for 3 years.[13] The results showed that treatment with atorvastatin reduced coronary events by 36%. The risk reduction in the subgroup aged ≥ 60 years was also 36%, which was similar to that in younger patients aged < 60 years. Thus, it has been demonstrated in studies conducted in Western countries that cholesterol-lowering therapy in the elderly brings similar, or even better, effects in the prevention of coronary events, compared with its effects on younger patients.

It has been demonstrated that cholesterol lowering therapy by statins slowed the narrowing of coronary arteries and reduced intima-media thickness in carotid arteries.[14,15] Thus, cholesterol lowering by statins could stabilize atheromatous plaque, thereby inhibiting the event occurrence.

Clinical data in Japan

The Hisayama study was an epidemiological study conducted in the Hisayama community in Japan.[16] In this study, where 2673 people aged ≥ 40 years were followed from 1988 to 1996, the absolute risk for ischemic heart diseases (myocardial infarction and sudden death) was reported to be 2.3/1000/year and that for cerebral infarction to be 3.1/1000/year.[17]

The J-LIT study was a cohort observational study in Japan. In this study, approximately 50 000 hypercholesterolemic patients aged ≤ 70 years undergoing 5–10 mg/day simvastatin treatment were followed for 6 years. A subanalysis focusing on elderly patients without prior coronary events was performed.[18] In both the elderly group, aged 65–70 years (mean 67 years) and consisting of 9860 patients, and the younger group, aged ≤ 64 years (mean 55 years) and consisting of 32 500 patients, total cholesterol levels were approximately 270 mg/dL at enrollment and 210–220 mg/dL during follow-up periods under simvastatin treatment. Changes in low-density lipoprotein (LDL)-cholesterol levels were also similar: levels of approximately 180 mg/dL at the baseline were reduced to approximately 130 mg/dL in the follow-up periods in both groups. No severe drug-related adverse effects occurred in either group. Thus, statin treatment in the elderly is as safe and effective for reducing serum cholesterol levels as it is in younger patients. The doses of the statin were lower than those used in Western countries, where 20–40 mg/day simvastatin was used.[2]

In the J-LIT study, the incidence of coronary events (sudden cardiac death and acute myocardial infarction) in the elderly was 1.30/1000/year and that in the younger 0.8/1000/year. When occurrence of angina was included in coronary events, the incidence in the elderly was 2.25/1000/year and that in the younger 1.35/1000/year. Cox-biohazard analysis revealed that the relative risks of coronary events increased by 1.7% as serum LDL-cholesterol levels increased by 1 mg/dL, which were similar in both groups.[18] Importantly, in any LDL-cholesterol levels, the absolute risk in the elderly was higher than that in the younger. Generally, coronary events occur twice as often in men as in women, which was also observed in the J-LIT study.[7,8] In the J-LIT study, 35% of the study subjects were male in the younger group and 21% were male in the elderly group.[18] Therefore, upon interpretation of this J-LIT data, the male : female ratio should be considered. Indeed, in male patients, the coronary events (sudden cardiac death and acute myocardial infarction) occurred at a rate of 2.45/1000 patients/year in the elderly and 1.41/1000 patients/year in younger patients.

The KLIS study was planned as a primary prevention study for male patients aged 45–74 years with serum cholesterol levels ≥ 220 mg/dL.[5,6] Enrolled patients were assigned into a conventional therapy group and a pravastatin group, and followed for 5 years. However, since the results of several studies revealed superior effects of statin therapy for the event prevention during the study period, the assignment could not be kept completely. As a result, 2219 cases in the pravastatin group and 1634 cases in the conventional therapy group were analyzed. Coronary events (sudden death, myocardial infarction, coronary intervention and bypass surgery) occurred in 5.95/1000 per year in the conventional therapy group and 5.77/1000 per year in the pravastatin group. Cerebral infarction occurred in 5.15/1000 per year in the conventional therapy group and 4.19/1000 per year in the pravastatin group. In the pravastatin group, 1105 cases were of good compliance for the drug-intake. The relative risk of coronary events plus cerebral infarction of the good-compliance group was 0.57 (0.54–0.98) compared with that of the conventional therapy group. A subanalysis examining those aged ≥ 65 years in this study revealed a tendency similar to that observed in the J-LIT study.[18] Namely, coronary events increased as serum LDL-cholesterol levels increased in both elderly and younger groups, and the absolute risks in the elderly were higher than those in the younger in any given LDL-levels (Sasaki *et al.* in preparation).

In the PATE study, 665 patients (male ratio 21%) aged ≥ 60 years (mean 73 years) with serum total cholesterol levels of 220–280 mg/dL were followed for 3–5 years (mean 3.9 years) under treatment with low-dose (5 mg) or high-dose (10–20 mg) pravastatin.[9] In this study, events were defined as cerebral bleeding, cerebral infarction, transient ischemic attack, subarachnoid hemorrhage, myocardial infarction, angina pectoris, cardiac failure, arrhythmia, arteriosclerosis obliterance, dissecting aortic aneurysm, and peripheral artery thrombosis. During the follow-up period, acute myocardial infarction occurred in 11 cases (4.2/1000/year). In the patient group without diabetes and with serum cholesterol levels of < 253 mg/dL and triglyceride levels of ≥ 133 mg/dL, the event-free ratio in the high-dose group was significantly higher than that in the low-dose group.

Thus, we could expect similar, or even more beneficial, effects of cholesterol-lowering therapy to reduce cardiovascular events in elderly Japanese compared with those in the younger population, although the studies described above appear to be somewhat indirect. Urgently and absolutely required are complete epidemiological and/or interventional large-scale studies, from which we can definitely estimate the absolute risks and the risk reduction rates in the current Japanese population.

Cerebral infarction and hypercholesterolemia

Cerebral infarction is also a disease that occurs more frequently in the elderly. Cerebral infarction is classified into following three: (i) lacunar infarction caused by small artery occlusion which is correlated with hypertension; (ii) cardiogenic cerebral embolism, which is usually associated with atrial fibrillation; and (iii) cerebral infarction caused by atherothrombotic arterial occlusion. Hypercholesterolemia is considered to be linked to atherothrombotic occlusion.

In the 4S secondary prevention study, simvastatin reduced total strokes by 35%.[2] The data obtained in secondary prevention studies with pravastatin, including the LIPID and CARE studies, have been combined and analyzed.[19] The results demonstrated that pravastatin treatment reduced total strokes by 22% and non-hemorrhagic strokes by 23%.[19] In the ASCOT study, atorvastatin reduced fatal and non-fatal strokes by 27%.[13] In the MRC/BHF Heart Protection Study, where approximately 20 000 high-risk patients aged 40–80 years had been randomly assigned into placebo and simvastatin-treated groups and followed for 5 years, simvastatin reduced ischemic strokes by 29%.[20] In the KLIS study conducted in Japan, the incidence of cerebral infarction was 5.15/1000 per year in the conventional therapy group and 4.19/1000 per year in the pravastatin group.[5,6] In the KLIS study, the incidence of cerebral infarction increased as LDL-cholesterol levels increased in elderly aged ≥ 65 years (Sasaki *et al.* in preparation). In the J-LIT study, the incidence of ischemic cerebrovascular events was 1.41/1000 per year in the subgroup without prior coronary or cerebral infarction (Nakaya *et al.* unpublished data). In both studies, the incidence of ischemic cerebral events was clearly higher in the elderly than that in the younger. Thus, evidence is accumulating to support the preventive effects of serum cholesterol-lowering on the occurrence of cerebral infarction. We may expect risk reduction for not only coronary events but also cerebral infarction in cholesterol-lowering therapy. Although the incidence of coronary events in Japan is much lower compared with that in Western countries, the incidence of cerebrovascular events are similar. Since incidence of cerebrovascular events in Japan is similar to that of coronary events, impact of the prevention of cerebrovascular events is as large as that of coronary events in Japan.

Conclusions: Strategy for treating elderly Japanese with hypercholesterolemia

As reviewed above, the control of serum cholesterol levels appears effective in risk reduction of cardiovascular events in elderly Japanese as well as in the younger population. The incidence of such events in the elderly is generally higher than that in younger people. Therefore, the elderly would be even more suitable subjects for preventative intervention. Although it may take long periods to develop atherosclerosis, the preventive effects for cardiovascular events become apparent in 1–2 years after cholesterol-lowering therapy has started, as demonstrated in many studies.[2,3,11,12,20] Therefore, it is not too late for us to start cholesterol-lowering therapy in the elderly. We have concluded after discussion in the research group 'Long-term prognosis of elderly Japanese with hypercholesterolemia' that we could expand the subjects of the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases by the Japan Atherosclerosis Society (2002) to include elderly Japanese aged ≤ 74 years (Kita & Matsuzawa *et al.* unpublished report to the Japanese Ministry of Health and Welfare 2002). In the guideline, patients are divided into several categories based on risk factors and the target cholesterol levels for each category is indicated (http://jas.umin.ac.jp/). Aging, ≥ 45 years for men and ≥ 55 years for women, is defined as a risk factor. Therefore, the target total cholesterol level for the elderly aged 65–74 years without additional risk factors is to be less than 220 mg/dL and the target LDL-cholesterol level, less than 140 mg/dL. The target levels become lower when elderly patients possess additional risk factors. As described in the guideline (http://jas.umin.ac.jp/), the control of cholesterol levels should be started by changing life styles, followed by drug therapy when appropriate cholesterol levels are not obtained.

For the elderly aged ≥ 75 years, few data for Japanese are available at the moment. Furthermore, it was reported that all causes of mortality increased in the group with lower total cholesterol levels due to an increase in death from infections and malignant tumors in an investigation in Holland, where people aged ≥ 85 years were enrolled.[21] Furthermore, in the Honolulu Heart Program, Japanese–Americans aged 75–93 years (mean 78 years) with a mean total cholesterol level of 149 mg/dL have been reported to have higher mortality than the other groups with the levels at 178, 199 and 232 mg/dL.[22] The physical and nutritional conditions of the highly-aged elderly are various and low cholesterol levels may reflect their worsened health conditions. Therefore, we concluded that, for the highly-aged elderly ≥ 75 years, the target cholesterol levels should be determined individually according to physical and nutritional factors, although a higher absolute risk of cardiovascular events would be expected in the elderly aged ≥ 75 years.

Finally, we again emphasize that physicians should be more careful in their use of drugs in elderly patients since physiological functions of the elderly, such as renal and liver functions required for metabolizing drugs, are not as good as those of the younger patients.

The recommended strategy for treatment for elderly Japanese with hypercholesterolemia

Patients aged 65–74 years

Follow the Guideline for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases by the Japan Atherosclerosis Society (2002) (http://jas.umin.ac.jp/).

Patients aged ≥ 75 years

The target values of total and LDL-cholesterol levels should be determined individually.

Points of consideration for treatment of elderly with hypercholesterolemia

1 Cholesterol-lowering therapy reduces relative risk of coronary events in not only the younger but also in the elderly to a similar extent.
2 The elderly would be even more suitable subjects of lipid-lowering therapy, since the absolute risk in the elderly is higher than that in the younger.
3 The elderly might be more susceptive to drug-related adverse effects than the younger since renal and liver functions, required for metabolizing drugs, in the elderly are weaker.

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Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy

Takashi Ohrui,* Kazunori Tanaka,[3*] Kazue Chiba,[3] Toshifumi Matsui, Satoru Ebihara, Mei He, Ichiro Tsuji,[1] Hiroyuki Arai[2] and Hidetada Sasaki

Department of Geriatric and Respiratory Medicine, [1]Division of Epidemiology, Department of Public Health, [2]Department of Geriatric and Complementary Medicine, Tohoku University Graduate School of Medicine, Sendai, and [3]Teijin Home Healthcare East Japan Limited, Saitama, Japan

Ohrui, T., Tanaka, K., Chiba, K., Matsui, T., Ebihara, S., He, M., Tsuji, I., Arai, H. and Sasaki, H. *Cognitive Decline in Patients with Long-Term Domiciliary Oxygen Therapy.* Tohoku J. Exp. Med., 2005, **206** (4), 347-352 —— Cognitive and psycho-physiological condition in patients with long-term domiciliary oxygen therapy (DOT) remains uncertain. A cross sectional analysis was performed to investigate the age-related changes in cognitive and psycho-physiologic functions in patients with chronic respiratory failure receiving long-term DOT. Two expert practitioners visited the patient's home and examined them for analysis of cognitive function, emotional status, physical activity and degree of dyspneic sensation. One hundred and thirty-five patients completed the study. Control data from a cohort of 718 community dwellers were also included in this study. Male patients had significantly higher rates of chronic obstructive pulmonary disease (71% vs 47%, $p = 0.001$), lower values of forced expiratory volume in one second (FEV1.0) % (49.7 ± 10.3 [standard deviation, s.d.] vs 66.0 ± 7.5% predicted, $p = 0.002$) and higher Borg score, an indicator of dyspneic sensation, during daily exercise (3.2 ± 0.8 [s.d.] vs 1.4 ± 0.6, $p = 0.01$) compared with female patients. Linear regression analysis based on mean Mini-Mental State Examination scores, an indicator of cognitive function, showed that age-related cognitive decline was more pronounced in female patients than in female controls (–0.524/year, $R^2 = 0.426$ vs –0.120/year, $R^2 = 0.027$, $p < 0.0001$), while there was no significant difference between male patients and male controls (–0.156/year, $R^2 = 0.054$, vs –0.077/year, $R^2 = 0.016$, $p = 0.231$). These results demonstrate that age-related cognitive decline is more exaggerated in female patients receiving long-term DOT which should be taken into consideration in caring for patients with chronic respiratory failure. ——— chronic respiratory failure; domiciliary oxygen therapy; long-term survivor; cognitive function; Borg scale

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Previous studies have reported that patients with chronic respiratory failure frequently suffer from neuropsychologic deficit and experience a disturbed mood, personality and life quality (Grant et al. 1982; Heaton et al. 1983; Incalzi et al. 1993). In a study assessing the neuropsychologic profile of patients with chronic obstructive pulmonary disease (COPD), diffuse mental deterioration characterized the study population with particular impairment of higher cognitive functions, and this was thought to be due to accelerated aging of the brain (Grant et al. 1982). To date, although long-term domiciliary oxygen therapy (DOT) has been proved to prolong survival of patients with chronic respiratory failure (The Medical Research Council Working Party 1981), its impact on cognitive function in long-term survivors remains uncertain.

In the present study, we, therefore, examined the cognitive and psycho- physiologic functions in patients receiving long-term DOT and compared them with those in age-matched community dwellers. We focused especially on the issue of the sex-related difference in cognitive function in patients with long-term DOT, because it remains unclear whether there is a gender difference in age-related cognitive decline in these subjects (Heaton et al. 1983; Scherr et al. 1988; Incalzi et al. 1993; Mortensen and Hogh 2001). We also aimed to identify possible contributing factors for the alteration in cognitive function in patients with long-term DOT.

Patients and Methods

A total of 264 patients with COPD, sequelae of tuberculosis or chronic interstitial pneumonia, who were ex-smokers and had been followed as outpatients in the Pneumology Department for 9 to 16 years, were recruited from 34 medical institutions in Sendai, Japan. They were receiving continuous oxygen therapy (24 h/day) at home via nasal prongs sufficient to maintain a PaO_2 between 60 and 80 mmHg from the start of oxyhemoglobin desaturation. One hundred and sixty- seven of the 264 patients agreed to participate in this study in the period from March 2001 to July 2002.

Two expert nurses unaware of the findings at clinical examination visited the patient's home and examined them for analysis of cognitive function, emotional status, degree of dyspneic sensation and physical activity, by Mini-Mental State Examination (MMSE) score (Folstein et al. 1975), geriatric depression scale (GDS) (Sheikh and Yesavage 2000), Borg scale (Borg 1982) and functional/performance status (Katz index) (Katz et al. 1970), respectively. Cognitive impairment was present if total MMSE score was 23 or below. At the time of the study, patients were receiving a regular dose of oxygen. Patients were excluded from this study if they used sedative drugs or they had cardio- and cerebro-vascular diseases, major psychiatric disorders, and acute infectious diseases.

Control data from a cohort of community dwellers were also included in this study. These data were obtained from the Tsurugaya Aging Study comprised of several studies of the biomedical and psychological determinants of cognitive ageing conducted in July 2002 in Sendai, Japan. The control group included 718 subjects (male 301) of comparable age, sex, duration of education and socio- economic status to patients receiving long-term DOT. This study was approved by the Tohoku University Ethical Committee and informed consent was obtained from each subject.

Student's t-test or chi-square test for independent samples was performed to determine whether clinical variables and cognitive and psycho-physiological functions of patients with long-term DOT differed from those of control subjects and whether there was a gender difference among these parameters. Linear regression analysis was used to evaluate the relation between age and cognitive function in male and female patients with long-term DOT vs control subjects. The strength of the relations was quantified by partial correlation coefficients. SPSS version 10.0 (SPSS, Chicago, IL, USA) statistical packages were used. A p value of < 0.05 was regarded as significant.

Results

Of the 167 participating patients, 8 subjects refused to complete all subsets of examinations because of fatigue, 10 subjects were admitted to other hospitals and 14 died during the study period. Finally, 135 subjects (male 101) completed the study. Clinical characteristics of control subjects and patients with long-term DOT are described in Table 1. The mean duration of DOT was 4.2 yr (4.3 yr and 3.6 yr for male and female patients, respectively) and the mean oxygen flow was 1.2 l/min (1.1 l/min and 1.4 l/min for male and female patients, respectively). There were no significant differences between male and female patients among these values. However, male patients had a significantly higher rate of COPD (71% vs 47%, $p = 0.001$) and lower values of forced expiratory volume in one second (FEV_1) (49.7 ± 10.3 [standard deviation, S.D.] vs 66.0 ± 7.5% predicted, $p = 0.002$) compared with female patients (Table 1).

The proportion of patients with cognitive impairment (MMSE, lower than 23 points) was significantly higher in female patients than in male patients with long-term DOT (14[41%] vs 15[15%], respectively; $p = 0.01$, after correction for differences in age, education, and disease duration). In contrast, there were no significant differences between male and female controls in these data (Table 2). The relation between MMSE score and age is illustrated in Fig. 1. There were significant negative correlations between MMSE

TABLE 1. *Clinical characteristics*

Variable	Controls		Patients		*p* value*
	Male ($n = 301$)	Female ($n = 417$)	Male ($n = 101$)	Female ($n = 34$)	
Age (yr)	77.4 ± 8.2	78.3 ± 9.2	77.4 ± 8.3	79.0 ± 7.3	0.96
Education (yr)	11.4 ± 2.7	10.8 ± 2.1	11.3 ± 1.9	10.9 ± 2.2	0.08
COPD diagnosed - No. (%)	36(12)	25(6)	72(71)	16(47)	0.001
FEV1.0 (% predicted)	82.7 ± 19.6	87.5 ± 24.6	49.7 ± 10.3	66.0 ± 7.5	0.002
Blood gas analysis					
PaO_2 (mmHg)	85.2 ± 3.6	84.4 ± 5.3	71.0 ± 6.8	69.0 ± 7.3	0.23
$PaCO_2$ (mmHg)	42.8 ± 2.7	41.2 ± 3.4	48.9 ± 2.2	47.6 ± 3.1	0.44
PH	7.41 ± 0.2	7.42 ± 0.1	7.37 ± 0.1	7.36 ± 0.1	0.88

Plus-minus values are means ± S.D. *Comparisons were made between male patients and female patients with long-term DOT.

Blood gas data refer to the patient breathing oxygen at the usual therapeutic concentration via nasal prongs. COPD and FEV1.0 denote chronic obstructive pulmonary disease and forced expiratory volume in one second.

TABLE 2. *Clinical outcomes*

Variable	Controls		Patients		*p* value*
	Male ($n = 301$)	Female ($n = 417$)	Male ($n = 101$)	Female ($n = 34$)	
MMSE score	27.0 ± 3.0	26.4 ± 3.4	26.0 ± 2.4	23.4 ± 2.1	0.02
≦ 23 No. (%)	18(6)	29(7)	15(15)	14(41)	0.01
> 24 No. (%)	283(94)	388(93)	86(85)	20(59)	
GDS score	4.4 ± 2.8	4.2 ± 2.9	6.2 ± 3.4	5.9 ± 2.6	0.16
Functional/performance status (Katz index)	6.2 ± 1.8	6.2 ± 2.1	7.7 ± 3.3	7.0 ± 2.4	0.17
Borg score	1.1 ± 1.0	1.2 ± 1.1	3.2 ± 0.8	1.4 ± 0.6	0.01

Plus-minus values are means ± S.D. *Comparisons were made between male patients and female patients with long-term DOT.

MMSE and GDS denote Mini-Mental State Examination and Geriatric depression scale.

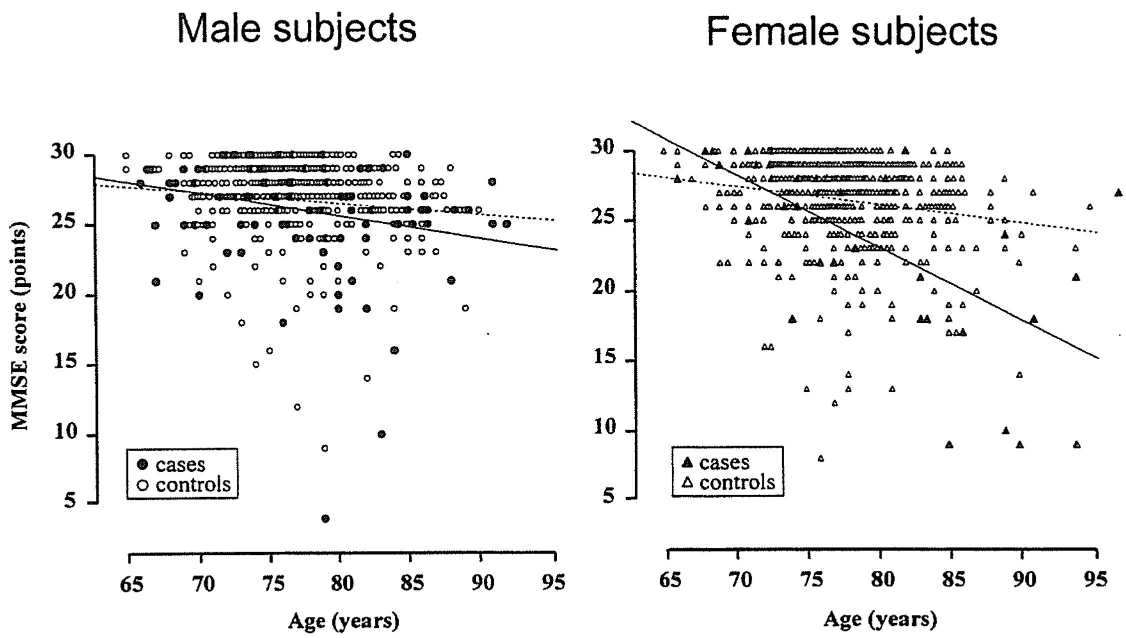

Fig. 1. Correlation between MMSE score and age in male and female subjects.
Open circles indicate male controls and closed circles indicate male patients receiving long-term DOT. Open triangles indicate female controls and closed triangles indicate female patients receiving long-term DOT. The straight lines are fitted to patients with long-term DOT and dashed lines to controls. MMSE denotes Mini-Mental State Examination and DOT denotes domiciliary oxygen therapy.

score and age in both controls and patients receiving long-term DOT. There was no significant difference in declining rate of MMSE score between male controls and patients (–0.077/year, R^2 = 0.016 vs –0.156/year, R^2 = 0.054, respectively, p = 0.231) (Fig. 1). By contrast, a significant difference in declining rate of MMSE score was observed between female controls and patients (–0.120/year, R^2 = 0.027 vs –0.524/year, R^2 = 0.426, respectively, $p < 0.0001$). Furthermore, although there was no significant difference in declining rate of MMSE score between male and female controls, a significant difference was observed between male and female patients (–0.156/year, R^2 = 0.054 vs –0.524/year, R^2 = 0.426, respectively, p = 0.021), which demonstrated age-related cognitive decline was more pronounced in female patients receiving long-term DOT (Fig. 1). Male patients had a significantly higher Borg score during daily exercise compared with female patients (3.2 ± 0.8 [S.D.] vs 1.4 ± 0.6, p = 0.01, respectively) (Table 2). There seemed to be a positive correlation between the MMSE score and the Borg score in both male and female patients, whereas it was not statistically significant (data not shown). There were no correlations between the MMSE score and the $FEV_1\%$, GDS score, Katz index, PaO_2, $PaCO_2$ or the duration of DOT by multi-regression analysis in male and female patients with long-term DOT (Table 2).

Discussion

Oxyhemoglobin desaturation is reported to be an important determination of mental deterioration (Heaton et al. 1983; Incalzi et al. 1993). A previous study has shown that 6 months oxygen treatment is associated with small but definite improvement in brain functioning among patients with hypoxemic COPD (Heaton et al. 1983). However, cognitive function in patients receiving long-term oxygen treatment and its gender difference has not been studied. The present study demonstrated that age-related cognitive decline was more pronounced in female patients receiving long-term DOT, while cognitive function in male patients was fairly preserved compared with control subjects of the same age. To the best of our knowledge, there are no published data concerning interactions between sex and cognitive outcome after long-term DOT. There were no significant differences among several clinical parameters except the Borg score, probably due to the difference in the lung function, between male and female patients. Despite the lack of clear knowledge of the mechanism for the interaction of sex and cognitive outcome after long-term DOT, a possible explanation for this finding might be a contribution of substance P (SP) in the CNS. Several findings indicate involvement of tachykinins in stress-related anxiety and depressive states (Megens et al. 2002). Especially, SP plays a role in dyspnea perception and in some autonomic reflexes and behaviors (Megens et al. 2002). SP release is suggested in stressful situations in the CNS (Culman and Unger 1995) and the NK_1 receptor antagonist has been shown to improve anxiety and depression rating scales in depressed patients (Rupniak and Kramer 1999). SP might be released significantly in the CNS in male patients with long-term DOT and an increased release of SP might up-regulate neprilysin (Stefano et al. 1992), a major amyloid-β peptide degrading enzyme in the brain, leading to protection against cognitive decline in male patients (Iwata et al. 2000).

That continuous oxygen therapy did not provide a complete protection against the deteriorating cognition in both male and female patients is not surprising, since several factors related chronic respiratory failure other than hypoxemia are known to affect cognition. Among these factors, hypercapnia, acidosis, and hypocapnia resulting from hypoxemia-induced hyperventilation should be taken into consideration (Heaton et al. 1983; Incalzi et al. 1993).

The limitation of the present study should be discussed. First, we did not conduct a longitudinal but a cross-sectional analysis of the cognitive and psychologic functions in patients receiving long-term DOT. A longitudinal study for a long-term period may provide more detail information about the age-related cognitive decline in each subject. Second, the absolute number of the female patients with long-term DOT is limited, which is pointed out in other previous reports (Heaton et al. 1983; Incalzi et al. 1993). This is probably due to a gender difference in the prevalence of pulmonary diseases such as COPD, which require DOT in the case of disease progression. Third, although a significant negative correlation between MMSE scores and age in both controls and patients with long-term DOT was found, the correlation coefficient values were low in individual groups. A further study with a large number of patients is needed to translate the present findings to patients with DOT in general. However, we believe that our data provide sufficient grounds for a reexamination of the effect of long-term DOT on cognitive function in those patients.

In conclusion, the current study demonstrates that the effect of long-term DOT on cognitive outcome differs between men and women. The increased life expectancy of patients with chronic respiratory failure after the introduction of the oxygen therapy implies that a growing fraction of physically disabled and to a various extent mentally impaired patients can be alive until old age especially in female patients (Sasaki et al. 1998; Kubo et al. 2005). Thus, end-stage pulmonary diseases will become a growing geriatric problem, and health care systems should be prepared to deal with it.

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ORIGINAL ARTICLE

Dental status and mortality in institutionalized elderly people

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Background: Inadequate dentition for mastication is one of the major issues associated with systemic health for institutionalized elderly people, but its prognostic value and related deaths have not been fully examined.

Methods: Four hundred and three patients aged 65 and older were recruited from nine nursing homes and were prospectively followed up for morbidity and mortality for 5 years in Japan. These patients were classified into three groups according to dental status: patients who had adequate dentition with natural teeth only or natural teeth with partial dentures (Group A); those who were edentulous but wearing full dentures (Group B); and those who had inadequate dentition without dentures (Group C).

Results: Dental status was strongly related to age, cognitive function and activities of daily living. After allowing for confounding effects, the 2-year risk of mortality among those in Group C was 1.84 times that of Group A (95% confidence interval 1.01–3.36, $P = 0.047$). Furthermore, the 5-year mortality rate in Group C was higher than that in Group A, whereas that was not significant with a hazard ratio of 1.30 (0.90–1.88, $P = 0.168$). The main causes of death were respiratory infections, which explained 14.1% of all causes of death in Group A, 14.3% in Group B and 18.3% in Group C. Any associations between a specific cause of death and the different dental status did not reach a significant level.

Conclusion: Inadequate dental status is associated with high overall mortality. Our findings suggest that systemic attention to dental status should be recommended in institutionalized elderly people.

Keywords: activities of daily living, dental status, mortality, respiratory infections.

Introduction

The loss of teeth is an irreversible process that peaks in old age and seriously influences oral function including mastication, deglutition and phonation.[1] A common cause of teeth loss in elderly people is alveolar pyorrhea, which can be prevented by intensive oral care.[2] Although elderly populations are retaining their teeth due to recent heightened concern about oral hygiene,[3] institutionalized elderly people still have poor oral health.[4,5] Simons reported that elderly people in residential homes had a high proportion of edentulousness of 57.4%, and high plaque and gingival indices of 2.3 and 1.7, respectively.[6] Moreover, in Japan, even though many institutionalized elderly people have lost many teeth, they do not use dentures to keep their masticatory capacity.[7] Such poor oral status of the institutionalized elderly may contribute to eating problems, low nutrition and an increase in intraoral bacteria.[8–12] Because many institutionalized elderly people are chronically infirm, these results may cause weight loss, disability and respiratory infections.[13,14]

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Little is known about the effect of inadequate dental status for mastication on mortality in the institutionalized elderly. Shimazaki *et al.* demonstrated that institutionalized elderly people being edentulous without dentures were 1.8 times more prone to death during the 6-year follow up as compared with those with 20 or more teeth.[15] However, they did not determine the underlying and immediate cause of death. Therefore, we conducted a study of elderly Japanese people to analyze recent dental status in nursing homes, poor dental status as a risk factor for mortality, and a relationship between dental status and specific causes of death. During the entire 5-year follow-up period, these patients were examined. We also analyzed cognitive function and activities of daily living (ADL), which might be potentially related to mortality.

Methods

Study population

Subjects were members of the Oral Care Study cohort.[16] A total of 403 patients consisting of 86 men and 317 women, aged 65 years or older (82.8 ± 7.7 [mean ± SD] years) were recruited at nine nursing homes in Japan in September 1999. Each nursing home had 50–100 beds and served as long-term care facilities for older patients who were physically handicapped and/or suffering from mental deterioration.

The criterion for patient selection was that physical symptoms were stable for the preceding month. All patients had no acute disorders, for example, pulmonary diseases with dyspnea, infection, heart failure, or stroke requiring special treatment and intensive care. In addition, patients with immunocompromised disorders such as active malignant disease, renal dialysis, hypogammaglobulinemia or HIV-1 infection, were excluded from the study. Our study protocol was approved by the ethical review committee at Tohoku University School of Medicine, and all patients or their families provided written informed consent.

Dental and clinical examination

At baseline, we evaluated the patients' dental status for mastication. Patients were grouped into one of the following three categories according to different levels of dental status: Group A consisted of patients whose dental status was functionally adequate for mastication by natural teeth only or natural teeth with partial denture(s); Group B consisted of patients who were edentulous but kept their masticatory capacity by dentures in both jaws; and Group C consisted of patients with a functionally inadequate dental status without dentures. There was no significant difference in the percentage of the basic clinical conditions among the groups, of which information was given on admission by patients' family member and/or other reliable collateral source such as cardiac diseases, cerebrovascular diseases, hypercholesterolemia, diabetes mellitus and cardiac arrhythmias, and the use of medications for these diseases (Table 1). During follow up, tooth brushing was performed by the patients themselves or by caregivers at least once a day. If patients were using dentures, nurses cleaned the dentures with a denture brush every day and with denture cleanser once a week.

Because of the potential effects on mortality, cognitive function and ADL were evaluated in all the patients. Cognitive function was examined using the Mini-Mental State Examination (MMSE).[17] ADL was evaluated using the modified Barthel Index.[18] Both MMSE and the modified Barthel Index have a 30-point scale for healthy older people, with a score of 0 indicating complete loss of cognition and dependence. If the MMSE score was 22 points or less, patients were considered as cognitively demented. If the modified Barthel Index was 20 points or less, patients were considered as physically disabled.

Following up the patients

These patients were followed up for mortality until September 2004. If the patients were discharged from the nursing home, mortality was ascertained by contact with their families. When the patients died, the underlying and immediate causes of death were determined by medical doctors. Their death certificates and medical records were reviewed (by M.Y., T.M. and T.O.) and the only medical events leading directly to death were coded according to the ninth version of the International Classification of Diseases (ICD-9).[19] Any other records about other significant conditions contributing to death but not related to cause were not considered here.

Statistical analysis

Statistical analyses were carried out with statistical software package SPSS version 10.0 (SPSS, Chicago, IL, USA). Baseline characteristics among age groups and different levels of dental status were compared by one-way ANOVA for continuous variables and by χ^2 tests for categorical variables. When significant differences between groups were found, a post hoc analysis was performed to test by Fisher's test on the groups significantly differing from each other.

A Cox proportional-hazards model was used to estimate mortality risk by levels of dental status, with adjustments for other potential covariates: age, gender, basic clinical conditions, cognitive function and ADL.[20] Because mortality, cognitive function and dental status are all strongly linked with age, all models were validated using graphical and analytical techniques to

Table 1 Distribution of clinical characteristics and 2-year and 5-year mortality according to dental status

Variables	Total	Oral status Group A	Group B	Group C	*P*-value*
Number of patients	403	99	98	206	
Age, year	82.8 ± 7.7	79.5 ± 6.9**	84.3 ± 6.8	83.7 ± 8.0	< 0.001
Gender (male/female)	86/317	25/74	13/85	48/158	0.075
Dentition					
Natural teeth	5.1 ± 7.4	12.7 ± 8.9	0	3.9 ± 5.3	< 0.001
Edentulousness, n/N (%)	192/403 (47.6%)	0/99 (0%)	98/98 (100%)	112/206 (54.4%)	< 0.001
Clinical basic conditions					
Cardiac disease, n/N (%)	68/403 (16.9%)	17/99 (17.2%)	18/98 (18.4%)	33/206 (16.0%)	0.874
Cerebrovascular disease, n/N (%)	117/403 (29.0%)	21/99 (21.2%)	26/98 (26.5%)	70/206 (34.0%)	0.061
Diabetes mellitus, n/N (%)	31/403 (7.7%)	11/99 (11.1%)	5/98 (5.1%)	15/206 (8.3%)	0.275
Arrythmia, n/N (%)	39/403 (9.7%)	8/99 (8.1%)	12/98 (12.2%)	19/206 (9.2%)	0.581
Medications, n/N (%)	166/403 (41.2%)	36/99 (36.4%)	42/98 (42.9%)	88/206 (42.7%)	0.533
Cognitive function					
MMSE (points)	10.6 ± 9.5	15.4 ± 9.4**	13.4 ± 8.9**	7.6 ± 8.3	< 0.001
Dementia, n/N (%)	346/403 (85.9%)	72/99 (72.7%)	81/98 (82.7%)	193/206 (93.7%)	< 0.001
ADL					
Barthel Index (points)	15.8 ± 7.1	19.2 ± 6.3**	18.8 ± 6.0**	12.8 ± 6.7	< 0.001
Disability, n/N (%)	283/403 (70.2%)	51/99 (51.5%)	57/98 (58.2%)	175/206 (85%)	< 0.001
Mortality					
2 years, n/N (%)	112/403 (27.8%)	14/99 (14.1%)	21/98 (21.4%)	77/206 (37.4%)	< 0.001
5 years, n/N (%)	235/403 (58.3%)	45/99 (45.5%)	54/98 (55.1%)	136/206 (66.0%)	0.002

*One-way ANOVA for different dental status. **The post hoc significant differences from corresponding values in Group C are indicated by $P < 0.0001$. Group A, adequate dentition with natural teeth only or natural teeth and partial dentures; Group B, edentulous and denture wearers; Group C, inadequate dentition without dentures. Mean ± SD for continuous variables and number (%) for categorical variables. ADL, activities of daily living; MMSE, Mini-Mental State Examination.

check for possible non-linearity and interactions. Kaplan–Meier curves were used to display the results. All tests were two-sided and statistical significance was set at $P < 0.05$.

Results

Dental status and other variables

Of the 403 patients who were evaluated at baseline, 192 (47.7%) were edentulous. The prevalence of edentulousness and number of natural teeth strongly correlated with age (Table 2). The prevalence of edentulousness for patients 65–74 years of age was 24.6%; this significantly increased to 40.4% for those 75–84 and to 63.4% for those 85 and older ($P < 0.001$). The number of natural teeth for patients 65–74 years of age was 9.4 ± 8.9; this significantly decreased to 5.6 ± 7.4 for those 75–84 and to 3.0 ± 5.8 for those 85 and older ($P < 0.001$). Ninety-eight of the 192 edentulous patients (51.0%) were denture wearers and the prevalence significantly decreased in patients 85 and older ($P = 0.008$).

When each patient was categorized into one of the groups according to levels of dental status, 99 patients met the criteria for Group A, which consisted of patients who had adequate dentition with natural teeth only or natural teeth with partial dentures; 98 patients were in Group B, which consisted of patients who were edentulous but wearing full dentures; and 296 patients were in Group C, which consisted of patients who had inadequate dentition without dentures. In univariate analysis, these different levels of dental status were significantly associated with age ($P < 0.001$), MMSE score ($P < 0.001$) and Barthel Index ($P < 0.001$) (Table 1).

Dental status and overall mortality

During the first 2-year follow up, 112 patients died. There were 14 (12.5%) deaths in Group A, 21 (18.8%) in Group B and 77 (68.8%) in Group C ($P < 0.001$) (Table 1). By the end of the 5-year follow up there were another 123 deaths (total 235): 45 (19.1%) of the death were in Group A, 54 (23.0%) were in Group B, and 136 (57.9%) were in Group C ($P = 0.002$) (Table 1) (Fig. 1).

Table 2 Demographic variables among different age groups

Variables	65–74 years	75–84 years	85 ≤ years	*P*-value*
Number of patients	65	166	172	
Gender (male/female)	27/38	32/134	27/145	< 0.001
Dentition				
Natural teeth*, N	9.4 ± 8.9**	5.6 ± 7.4**	3.0 ± 5.8	< 0.001
Edentulousness, n/N (%)	16/65 (24.6%)	67/166 (40.4%)	109/172 (63.4%)	< 0.001
Denture wearers in edentulous, n/N	11/16 (68.8%)	42/67 (62.7%)	45/109 (41.3%)	0.008
Cognitive function				
MMSE (points)	13.7 ± 9.5**	11.5 ± 9.9**	8.7 ± 8.7	< 0.001
Dementia, n/N (%)	51/65 (78.5%)	139/166 (83.7%)	156/172 (90.7%)	0.032
ADL				
Barthel Index (points)	16.7 ± 6.8	16.5 ± 6.9	14.9 ± 7.4	0.059
Dependence, n/N (%)	44/65 (67.7%)	114/166 (68.7%)	125/172 (72.7%)	0.643

*One-way ANOVA for different dental status. **The posthoc significant differences from corresponding values in Group C are indicated by $P < 0.0001$. Mean ± SD for continuous variables and number (%) for categorical variables.

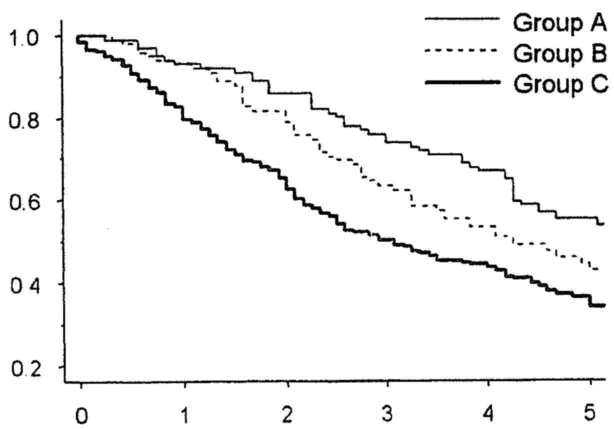

Figure 1 Cumulative event plots according to different dental status were estimated by the Kaplan–Meier method and compared using the log–rank test: survival curves for all causes of death by different levels of dental status. Group A indicates subjects with adequate dentition with natural teeth only or natural teeth and partial dentures. Group B indicates subjects with edentulous and denture wearers. Group C indicates subjects with inadequate dentition without dentures.

In an unadjusted analysis, we examined the effect of dental status on 2-year and 5-year mortality. As compared with Group A, Group C had a relative risk of mortality of 3.09 (2-year: 95% confidence interval [CI] 1.75–5.46, $P < 0.001$) and 1.93 (5-year: 1.38–2.71, $P < 0.001$); Group B did not significantly increase the risk of mortality (Table 3). After allowing for confounding effects of age, gender, basic clinical conditions including cardiac disease, cerebrovascular disease and diabetes mellitus, cognitive function and ADL, the 2-year risk of death among those in Group C was 1.84 times that of Group A (95% CI 1.01–3.36, $P = 0.047$) (Table 3). However, the 5-year mortality among those of Group C was no longer significantly different from that of Group A (hazard ratio: 1.30, 95% CI 0.90–1.88, $P = 0.168$). However, if age or ADL were excluded from the potential confounders, the dental status of Group C independently increased the 5-year mortality (data not shown).

Dental status and specific causes of death

The underlying and immediate causes of deaths are shown in Table 4. Respiratory infections (66 deaths) and senility (52 deaths) were common causes of 5-year mortality. The mortality rate by respiratory infections for patients in Group C was 18.4% (38 deaths/206 patients). This mortality rate was not significantly different as compared with that for patients in Group A (14.1%, 14 deaths/99 patients, $P = 0.079$) and Group B (14.3%, 14 deaths/98 patients, $P = 0.165$). Any other associations between a specific cause of death and the different dental status also failed to reach a significant level (data not shown).

Discussion

Our study had three major findings. First, inadequate dentition for mastication was common in institutionalized elderly patients over the age of 65, and its prevalence is clearly increasing with age and is strongly associated with impaired cognitive function and lower ADL. Second, this poor dental status was associated with approximately a twofold increase in the 2-year risk of death independent of age, gender, basic clinical conditions, cognitive function and ADL. Third, this poor dental status was involved in overall mortality rather than mortality due to specific diseases such as respiratory infections because the number of events may have been too small to permit a detailed, cause-specific analysis.