Table 4. Relationships between the Serum Levels of VEGF and Other Variables in All subjects

	p	r
AHI (/hour)	0.05	r= 0.401
Baseline SaO_2 (%)	0.27	r=–0.223
Nadir SaO_2 (%)	0.01	r=–0.457
N of 4% desaturation	0.01	r= 0.581
Mean SaO_2 (%)	0.05	r=–0.389
Systolic BP	0.34	r= 0.027
Diastolic BP	0.41	r= 0.123

BP: blood pressure.

VEGF level (Table 3).

In examining the relationship between VEGF levels and numerous of parameters (AHI, nadir SaO_2, systolic blood pressure, diastolic blood pressure, arterial oxygen desaturation), we found that there were significant relationships between VEGF levels and AHI, nadir SaO_2, mean SpO_2, and the number of 4% oxygen desaturation (Table 4).

Discussion

The present study demonstrates that the administration of 2 *l*/min oxygen during the night to OSAS patients improves nocturnal hypoxemia in parallel with a decrease in VEGF levels. Serum VEGF levels were greater in obese patients with OSAS than in obese control subjects. Therefore, we conclude that circulating VEGF levels are elevated in OSAS patients, primarily due to nocturnal hypoxemia. Nevertheless, numerous factors might influence VEGF serum levels and must be taken into consideration when discussing these observations. The most common conditions known to be associated with elevated VEGF serum levels, such as disseminated cancer and chronic inflammatory and autoimmune disease, were not present in either the patients or the control subjects in the current study (17).

It has been reported that serum VEGF levels are significantly higher in patients with polysomnographically confirmed OSAS (AHI>15 and AI>5 in adults and children, respectively) than in patients with mild disease or no disease (18, 19). Furthermore, significant correlations have been found between VEGF concentrations and respiratory disturbance index and sleep time spent at SpO_2 <90% (18). Schulz et al reported that serum levels of VEGF are elevated in severely hypoxic patients with OSAS and are related to the degree of nocturnal oxyhemoglobin desaturation (20). They speculated that the most likely trigger of VEGF release in OSAS is hypoxia, since a close linear relationship between the degree of nocturnal oxyhemoglobin desaturation and VEGF concentrations was observed (20). If this is true, the administration of oxygen to patients with OSAS could reduce their VEGF levels to the normal levels found in subjects without OSAS. In the present study, we found that nighttime administration of oxygen, but not compressed air, decreased the VEGF level and improved nocturnal oxyhemoglobin desaturation, but did not affect the occurrence of nocturnal apneas. It is reasonable to assume that repeated episodes of nocturnal hypoxemia are the primary mechanism of the increased production of VEGF in patients with OSAS.

However, previous studies have suggested that AHI is correlated with VEGF levels in OSAS patients (20). Because the administration of oxygen to OSAS patients improves both VEGF levels and nocturnal hypoxemia but not AHI, the relationship between AHI and VEGF levels may be associated with AHI-related nocturnal hypoxemia, but not directly with the number of apneas/hypopneas.

Other mediator systems related to hypoxia may also be involved in the mechanism of VEGF increase in patients with OSAS. Because reactive oxygen species and endothelin are elevated in OSAS patients (21, 22), these mediators may enhance gene expression of VEGF (23, 24). Because nitric oxide synthesis is downregulated in OSAS patients (25, 26), the inhibitory effect of nitric oxide on VEGF gene induction could be weakened in these patients.

The clinical significance of elevated VEGF concentrations in patients with sleep apnea remains a matter of speculation at this stage. VEGF is a mitogen specific for endothelial cells, which appears to play a pivotal role in physiological and pathological angiogenesis (13). VEGF has been shown to be an important factor in the pathogenesis of vascular-related diseases, including the growth of tumors, vascular dysfunction in diabetes mellitus, and atherosclerosis of the coronary arteries (13, 27, 28). The increased VEGF production found in OSAS patients might contribute to new vessel formation in ischemic and atherosclerotic vascular regions. Thus, enhanced VEGF production may constitute an adaptive mechanism to counterbalance the emergence of cardiovascular disease in patients with OSAS. The augmented VEGF concentration in sleep apnea patients having comorbidities may reflect a contributory mechanism for the development of cardiovascular disease. Recent data have suggested that amelioration of nocturnal hypoxia by nasal continuous positive airway pressure (nCPAP) is associated with a significant decrease in morning VEGF concentrations (29). The alterations of the VEGF system in patients with OSAS may have an impact on the development of cardiovascular abnormalities in these patients. Therefore, a reduction of VEGF concentration following treatment of sleep apnea and potentially reduced angiogenesis may be a clinically significant goal of treatment.

In conclusion, serum levels of VEGF are elevated in patients with OSAS and are closely correlated with the degree of nocturnal oxyhemoglobin desaturation. This increased VEGF was decreased by nighttime oxygen administration in OSAS patients, suggesting that nighttime hypoxia is a primary mechanism of VEGF increase in these patients. However, further studies are necessary to explore the clinical significance of VEGF increase on outcome in terms of cardiovascular diseases and mortality in OSAS patients.

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LETTERS TO THE EDITOR

THE AMERICAN GERIATRICS SOCIETY/AMERICAN ASSOCIATION FOR GERIATRIC PSYCHIATRY MENTAL HEALTH IN NURSING HOMES CONSENSUS STATEMENT

To the Editor: The National Citizens' Coalition for Nursing Home Reform (NCCNHR) had the privilege of serving on the expert panel involved in the development of two articles found elsewhere in this issue of the *Journal of the American Geriatrics Society:* the American Geriatrics Society/American Association for Geriatric Psychiatry *Recommendations for Policies in Support of Quality Mental Health Care in U.S. Nursing Homes* and the *Consensus Statement on Improving the Quality of Mental Health Care in U.S. Nursing Homes: Management of Depression and Behavioral Symptoms Associated with Dementia.* We are pleased to endorse the consensus statement but regret that the policy recommendations do not call for prompt implementation of nurse staffing ratios that experts consistently identify as necessary to provide for the basic care of nursing home residents. Although additional research might find an ideal ratio for caring for those with dementia and mental illnesses, we know from existing research that minimum needs cannot be met without at least 4.1 hours of direct care a day. Fewer than 10% of nursing homes meet this standard, and more than half fall so far below it that residents are in jeopardy. NCCNHR advocates a minimum standard of 4.13 hours—a level validated by a consensus panel of the Hartford Center for Geriatric Nursing, a congressional study of nurse staffing ratios released by the Department of Health and Human Services last year, and other research. As the policy statement says so well, "High-quality mental health care in nursing homes is possible only when the level of nurse staffing is adequate to provide the necessary amount of direct care."

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RESPONSE TO DONNA LENHOFF'S LETTER ON MENTAL HEALTH CARE IN NURSING HOMES, NURSE STAFFING STUDIES

The above letter was referred to the authors of the original paper, and their reply follows.

To the Editor: The participation of the National Citizens' Coalition for Nursing Home Reform (NCCNHR), in addition to that of a broad group of organizations that reflect the multidisciplinary nature of nursing home care for frail elderly people, greatly enhanced the American Geriatrics Society/American Association for Geriatric Psychiatry Expert Panel on Quality Mental Health Care in Nursing Homes. Through its representative on the panel and considerable input from other leadership NCCNHR made major contributions to the consensus and policy documents published in this issue of the *Journal.* We believe that their participation added a unique perspective, and we thank them for their hard work and endorsement of the consensus statement.

It was the panel's concern over the adequacy of current nursing home staffing, along with several other concerns, that prompted the panel to develop a policy document along with the consensus statements. The panel felt strongly that the consensus statements themselves, without changes in health policy, would not result in meaningful improvements in mental health care in nursing homes. Although we cannot speak for the entire panel or all of the organizations represented on it, we would certainly not argue with NCCNHR's recommendation for immediate implementation of the staffing standards outlined in Ms. Lenhoff's letter in the 90% of facilities that currently do not meet these standards. Nevertheless, we believe that further research into optimal staffing, in terms of numbers and training, is necessary and will be a worthwhile investment in improving the care of the large and growing numbers of nursing home residents with depression and behavioral symptoms associated with dementia, as well as with other mental health conditions.

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TESTOSTERONE AND COMPREHENSIVE GERIATRIC ASSESSMENT IN FRAIL ELDERLY MEN

To The Editor: A low plasma testosterone level in elderly men has been implicated in various diseases, including atherosclerosis, osteoporosis, and dementia,[1] but the relationship between plasma testosterone and functional measures in frail elderly men has not been addressed. Here, we report a small-scale study in which a low plasma testosterone

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level was associated with a functional decline based on comprehensive geriatric assessment in frail elderly men without malnutrition.

Fifty-four consecutive men (aged 70–95, mean age ± standard deviation = 82 ± 6 years) attending the health service facilities for the elderly (Mahoroba-no-Sato) located in Nagano Prefecture for admission or day-care service were enrolled. Of the subjects, five were diagnosed as having dementia of the Alzheimer type, six had history of stroke, five had a history of heart failure, eight had hypertension, and five had hyperlipidemia. Subjects with malnutrition, malignancy, or endocrine disease were excluded because these diseases may affect plasma androgen level. A commercial laboratory determined plasma total testosterone (total-T) and free testosterone (free-T) in addition to blood cell counts and blood chemical parameters. Total-T and free-T were assayed using a sensitive radioimmunoassay, and the intra-assay coefficients of variation were 5% to 6% and 2% to 5%, respectively. Basic activities of daily living (ADLs) were assessed using Barthel Index, instrumental activities of daily living (IADLs) by Lawton and Brody, cognitive function using Hasegawa Dementia Scale—Revised (HDS-R), mood using the Geriatric Depression Scale (GDS; 15 items), and ADL-related vitality using Vitality Index.[2]

On average, the subjects showed mild to moderate functional decline (Table 1). Also, mean plasma levels of total-T (365 ± 172 ng/dL) and free-T (5.7 ± 2.8 pg/mL) were lower than those reported in healthy elderly men[3] but comparable with those in frail elderly men.[4] As shown in Table 1, total-T and free-T were significantly correlated with functional measures except for GDS. There was no significant correlation between total-T or free-T and age, body mass index, blood hemoglobin, lymphocyte count, serum albumin, or serum total cholesterol, probably because the subjects had good nutritional status; serum albumin was 4.1 ± 0.3 g/dL, and serum total cholesterol was 179 ± 28 mg/dL. Furthermore, multivariate analysis with age, serum albumin, and serum total cholesterol as independent variables revealed that free-T was an independent determinant for the HDS-R ($R = 0.403$, $P = .03$) and Vitality Index ($R = 0.407$, $P = .02$). In similar multivariate analyses, free-T was not an independent determinant for the Barthel Index or IADLs, and total-T was not an independent determinant for each of the functional measures (data not shown).

The present study demonstrated that a higher plasma testosterone level was associated with higher scores of comprehensive geriatric assessment except for the GDS. Free-T, the active form of testosterone, showed a stronger correlation than did total-T. It has been reported that a higher total-T was associated with better ADL performance such as transferring and eating in frail elderly men.[4] The result is consistent with ours, but free-T and nutritional assessment were not included in that report. It is known that malnutrition is associated with low ADL and low plasma testosterone. In our preliminary study in elderly male patients in sanatorium-type wards, serum albumin was correlated with the Barthel Index and plasma total-T and free-T (data not shown). Consequently, nutritional markers such as serum albumin should be included as confounding factors in a study that examines the relationship between plasma testosterone and ADLs in frail elderly men. In fact, no significant relationship was found between plasma testosterone (total-T and free-T) and ADLs (Barthel Index and IADLs) in multivariate analyses including nutritional markers, although the subjects were well nourished. Alternatively, the correlation of free-T with cognitive function and ADL-related vitality remained significant in multivariate analyses. Contrary to a previous report,[5] depressed mood did not relate to plasma testosterone in this study. The reason is unknown, but it might be due simply to the cohort difference between community-dwelling healthy men[5] and frail elderly men or to the low reliability of GDS in demented people.[2]

The detailed and causal relationships need to be examined in large-scale and longitudinal studies. Nevertheless, our results suggest that testosterone treatment might improve global function in frail elderly men with low testosterone levels.

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Table 1. Distribution of Functional Measures and Correlation Coefficients Between Plasma Testosterone Level and Functional Measures

Measure	Barthel Index	IADL	HDS-R	GDS	Vitality Index
Mean ± standard deviation (range)	73 ± 27 (5–100)	2.1 ± 2.0 (0–5)	18 ± 7 (2–29)	6.3 ± 3.1 (1–13)	8.8 ± 1.8 (3–10)
Total testosterone	.422†	.279*	.344*	.077	.370†
Free testosterone	.369†	.390†	.512‡	.164	.464‡

Note: The Barthel Index was used to assess Activities of daily living, Lawton and Brody's instrumental activities of daily living (IADL) index to assess IADLs, the Hasegawa Dementia Scale—Revised (HDS-R) to assess cognitive function, the Geriatric Depression Scale (GDS—15 items) to assess mood, and the Vitality Index to assess ADL-related vitality.
*$P < .05$;
†$P < .01$;
‡$P < .001$.

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ROLE OF CHOLINESTERASE INHIBITOR IN THE MANAGEMENT OF SEXUAL AGGRESSION IN AN ELDERLY DEMENTED WOMAN

To the Editor: Aggressive behavior, seen in elderly demented patients, includes hitting, grabbing, pushing, biting, kicking, scratching, and throwing objects. Sexual aggression is seen in some of these patients. Sexual activity can increase in association with progression of dementia. This can result in unreasonable and exhausting demands on sexual partners at unacceptable times and inappropriate places. Occasionally, aggression may result if these needs are not met. This challenging behavior is seen in elderly patients living in nursing homes and at home. These patients are among the most difficult to manage and present a tremendous challenge to physicians. Except for hormonal therapy in male patients, pharmacotherapy has shown minimal efficacy. We present a case report of sexual aggressiveness seen in an elderly demented woman and discuss the options for management.

CASE

The patient was a 72-year-old white female who came to the outpatient senior's clinic for cognitive and behavioral evaluation. Her behavioral problems included a 6-month history of agitation and sexual aggressiveness. According to her husband, she had been sexually passive throughout her life. During the previous 6 months, she had wanted intercourse or oral sex multiple times a day, which had caused considerable stress for the husband. Her medical history included osteoporosis and she was being treated for this with etidronate. No past psychiatric history was reported. No alcohol or recreational drug abuse was reported. There was no history of aggressiveness or sexually deviant behavior in the past.

She scored 16 of 30 on Mini-Mental State Examination and 3 of 15 on the Geriatric Depression Scale. A diagnosis of mixed dementia (Alzheimer's and vascular) of moderate severity was made after cognitive evaluation, laboratory evaluation, and neuroimaging investigations. She was started on rivastigmine 1.5 mg orally two times a day. After 4 weeks, her husband reported some improvement in the patient behavior. The dose of rivastigmine was increased to 3 mg two times a day. After an additional 4 weeks, her husband reported that her agitation had decreased and her sexual aggressiveness had subsided significantly. She continued 3 mg twice a day with no apparent adverse effects.

DISCUSSION

Most of the treatments suggested for aggressiveness in dementia have only marginal benefit for controlling sexual aggressiveness. These include drugs such as antipsychitric including the newer neuroleptics like risperidone, olanzapine, clozapine, and quetiapine and the selective serotonin reuptake inhibitors, trazodone, buspirone, lithium, and valproate.[1,2]

Sexually aggressive behavior in men has been treated with antiandrogens, estrogen, and medroxyprogesterone acetate.[3,4] One study points out that cimetidine, which has antiandrogen properties, decreases libido and hypersexual behavior without serious side effects.[5]

To the best of our knowledge, this is the first case report discussing sexual aggressiveness in a female and the use of cholinesterase inhibitor in the treatment of sexual aggressiveness. Our experience with this patient indicates that cholinesterase inhibitors may be helpful in controlling sexual aggressiveness in demented patients. There have been reports that neurotransmitters, such as dopamine, and low serotonin levels played a role in aggressive behavior. The resolution of this patient's sexual aggressiveness when treated with rivastigmine raises the possibility that neurotransmitter deficits including acetylcholine play a role in the causation of sexual aggression in demented patients.

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PROLONGED SURVIVAL OF AN ELDERLY WOMAN WITH SALMONELLA DUBLIN AORTITIS AND CONSERVATIVE TREATMENT

To the Editor: The incidence and the mortality of bacteremia increases with age.[1] Of all organisms causing bacteremia in patients aged 65 and older, gram-negative bacilli account for approximately 60% of cases.[2] The following is a case of a female patient who presents an infrequent complication of a gram-negative bacteremia.

CASE REPORT

An 81-year-old female patient was admitted to our geriatric department with a fever persisting for 1 month. Ischemic and hypertensive heart failure associated with type 2 diabetes mellitus characterized her medical history. One

Table 1. Frequency and Prognosis of Visual Ischemic Symptoms in Patients Younger than 80 and 80 and Older with Temporal Arteritis (TA)

Symptom	≥80 (n = 56) n (%)	<80 (n = 151) n (%)	*P*-value‡
Transient visual ischemic symptoms (TVIS)	9 (16.1)	33 (21.9)	.66
Permanent visual loss	10 (17.9)	17 (11.3)	.31
Preceded by TVIS	2 (20)	9 (52.9)	.1
Bilateral visual loss	3 (30)	1 (5.9)	.13
Recovery with treatment*	0	5 (29.4)	.8
Irreversible complete blindness	4 (40)†	0	.01
Death after permanent visual loss	5 (55.6)	6 (35.3)	.28

Note: Mean time from onset of TA to visual loss in patients aged 80 and older was 49.5 days and in patients younger than 80 was 37.0 days ($P = .17$).
* Complete recovery in two patients with bilateral retrobulbar ischemic optic neuropathy and partial recovery in three patients with anterior ischemic optic neuropathy.
† Due to anterior ischemic optic neuropathy, bilateral in three cases and unilateral on the only functional eye in one case.
‡ Comparisons of continuous variables were performed using Student *t* test. Proportions were analyzed using Fisher exact test.

could have been avoided had TA been recognized and treated earlier. Patients with permanent visual loss not only had a poor visual prognosis but also were at higher risk of early death than patients without this problem. Such an adverse outcome in patients with TA and permanent reduction of vision has been observed previously.[7,13] The negative outcome of patients with visual loss may be related to the high doses of corticosteroids used or to more-severe disease. The present study also shows that the older patients are more prone than younger group to developing irreversible complete blindness but less often complain of warning transient visual ischemic symptoms before visual loss. Moreover, sudden total blindness in the older patients with TA was associated with a high short-term fatality rate. In the opinion of the investigators of this study, the high risk of unexpected blindness related to TA in old-old patients makes it difficult to use smaller initial doses of corticosteroids in these patients, despite the risk of side effects.

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RECURRENT COLITIS WITH DIFFERENT CAUSES

To the Editor: A 66-year-old woman was admitted to a geriatric department in Tokyo on August 1, 2000, with lower abdominal pain and hemorrhagic diarrhea. She had hyperlipidemia on monthly follow-up for 16 years but did not have any history of bowel disease. For 4 days at the end of June, she had taken cefpodoxime proxetil for the treatment of acute pharyngitis. Two weeks later, hematochezia and repeated diarrhea developed, which progressed to severe hemorrhagic diarrhea. This prompted her to come to our emergency unit. Her white blood cell count was 11,500/μL, and erythrocyte sedimentation rate was 47 mm/h. Toxin-producing *Clostridium difficile* was isolated from stool cultures. Colonoscopy revealed that the whole surface of the rectum and sigmoid colon was covered with small, yellow-white, discrete raised plaques (Figure 1A). Pathologically, a band-like pseudomembrane

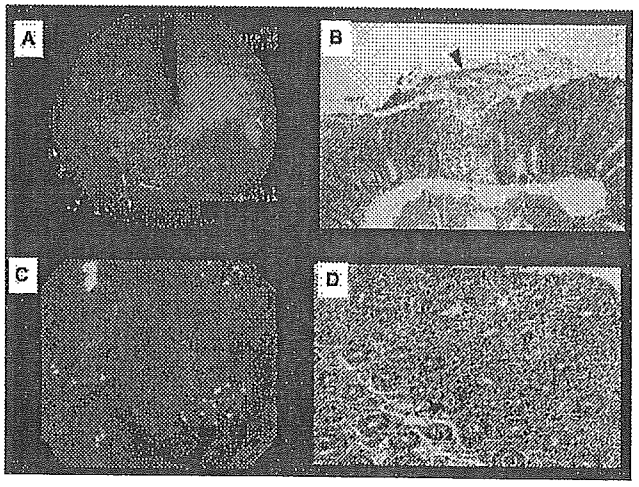

Figure 1. Colonoscopic (A,C) and histopathological (B,D) findings showing the characteristics of pseudomembranous colitis (A,B) and ulcerative colitis (C,D); (B) arrowhead, pseudomembrane; (D) arrow, crypt abscess.

overlying the mucosal epithelium was seen (Figure 1B). After the diagnosis of pseudomembranous colitis (PMC) was made, vancomycin was given orally. The symptoms soon resolved with the improvement of inflammatory markers. On August 15, colonoscopy showed the disappearance of yellow-white plaques and the recovery of mucosal sheen and vascularity. On August 28, a week after discharge, lower abdominal pain and hematochezia recurred, and the patient was readmitted to the hospital. Surprisingly, colonoscopy showed typical findings of ulcerative colitis (UC): continuous mucosal disease, extending into the sigmoid colon, manifested by mucosal granularity, friability, a subtle loss of mucosal sheen and vascularity, purulent exudate and ulcerations (Figure 1C). Histopathological findings confirmed the diagnosis of UC: prominent inflammatory infiltrate, crypt abscesses, and a reduction of glands and goblet cells (Figure 1D). *C. difficile* was not isolated from stool cultures. Salazopyrin was administered for 3 weeks, and the symptoms resolved, with recovery confirmed by endoscopic findings.

PMC or *C. difficile* colitis, a common complication in therapeutic courses of antibiotics, has been known to occur during relapse of UC,[1] suggesting the interaction of inflammatory and microbial factors in these bowel diseases. However, to the investigators of this study, this is the first report showing that UC can occur after PMC. On the first endoscopic examination when PMC was diagnosed, neither macroscopic nor microscopic findings of UC existed, even on retrospective observation. Also, this case is unique in that normal endoscopic findings were obtained 2 weeks before the onset of UC. Thus, the mucosal damage induced by PMC did not directly lead to UC, even if there is some causal link between PMC and UC.

Environmental factors seem to play more-important roles than genetic factors in the pathogenesis of UC.[2,3] Microbial factors have been shown to be associated with UC.[3] Of them, strong evidence was provided by transgenic rats that developed UC-like colitis when exposed to nonpathogenic microflora, but not when they were in a germ-free environment.[4] Taken together, several hypotheses can be raised with regard to the pathogenesis of UC in this case: (1) commensal organisms reconstituted after the cure of PMC might be pathogenic in susceptible mucosa or in a susceptible person, (2) *C. difficile* might have stimulated immune factors that are related to the pathogenesis of UC, or (3) UC was a totally incidental occurrence. In this case, psychological stress[3] due to PMC could trigger UC, but nonsteroidal antiinflammatory drugs, which can induce UC,[3] were not used.

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THE USE OF ORAL NUTRITIONAL SUPPLEMENTS AND ANOREXIGENIC MEDICATIONS IN HOMEBOUND OLDER ADULTS

To the Editor: It is estimated that malnutrition affects up to 83% of homebound older adults, a population two to three times larger than the nursing home population.[1,2] Despite the lack of agreement regarding their benefits, primary care physicians commonly recommend nutritional supplements to frail elderly patients who have experienced weight loss or are at a high clinical risk for weight loss.

Several primary care–focused articles have listed various medications that may be associated with weight loss.[3–6] These often-extensive lists are derived by individual expert opinion rather than a consensus or evidence-based design. For many medications, evidence-based data about the side effects of involuntary weight loss are often lacking. Much of the knowledge about anorexigenic medications is based upon the results of clinical trials of younger patients or upon anecdotal experience and case reports. This study reports on the prevalence of nutritional supplements and the concomitant use of medications associated with unintentional weight loss in a nursing home–eligible homebound managed care population.

A retrospective review was conducted on a cohort of 3,688 nursing home–eligible homebound persons enrolled in a managed care plan. Patients receiving new prescriptions for oral nutritional supplements between January and December 1999 were identified. Data collected in-

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Adiponectin Replacement Therapy Attenuates Myocardial Damage in Leptin-deficient Mice with Viral Myocarditis

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The effects of adiponectin replacement therapy on myocardial damage were studied in leptin-deficient (OB) mice with acute viral myocarditis. Encephalomyocarditis virus was injected intraperitoneally into OB and wild-type (WT) mice. One subgroup of OB mice received no intervention and another subgroup received daily adiponectin replacement, simultaneously with viral inoculation. Differences in heart weight, cardiac histological score, numbers of infiltrating or apoptotic cells in the myocardium and the immunoreactivity of adiponectin receptors in myocytes were determined. The reactivity of adiponectin receptor 1 in myocytes from OB mice on day 4 and day 8 after viral inoculation was significantly decreased compared with that in myocytes from WT mice; the OB mice also had elevated cardiac weights and severe inflammatory myocardial damage. Adiponectin replacement in OB mice inhibited the development of severe myocarditis by augmenting myocyte adiponectin receptor 1 reactivity. Exogenously administered adiponectin may inhibit the progression of viral myocarditis through binding to the adiponectin receptor 1 in leptin-deficient conditions.

KEY WORDS: ADIPONECTIN; VIRAL MYOCARDITIS; LEPTIN DEFICIENCY; MYOCARDIAL DAMAGE

Introduction

Several studies have reported an association between leptin and cardiovascular conditions such as hypertension and chronic heart failure with cachexia. Reduced leptin concentrations may diminish the degree of cardiac adaptation in heart failure,[1] and plasma leptin levels were inappropriately low in patients with cachectic chronic heart failure.[2] We have recently found that leptin deficiency enhanced myocardial necrosis and lethality in a mouse model of viral myocarditis. However, leptin replacement inhibited the development of severe myocarditis, suggesting a protective role for leptin against myocyte damage,[3] although the mechanisms involved are unclear.

Adiponectin, also known as adipocyte complement-related protein of 30 kDa,[4] is a cytokine secreted by adipocytes that has anti-diabetic and anti-atherogenic effects.[5] Concentrations of adiponectin in blood are diminished in obesity, insulin resistance and type 2 diabetes.[4] The adiponectin gene and the obese gene, which encodes leptin, show several striking similarities in humans.[6] Both genes are composed of three exons and have a long first intron, and are expressed specifically in adipose tissues.[6] Adiponectin and leptin control fuel homeostasis, body weight and insulin sensitivity. Amelioration of insulin resistance, pancreatic β-cell degranulation and diabetes after crossing leptin-deficient mice with globular domain adiponectin transgenic mice has been described, indicating that globular adiponectin and leptin may have overlapping functions.[5] Thus, adiponectin may also possess functions similar to those of leptin in the development of heart failure.

In this study, we hypothesized that adiponectin could play a protective role against the progression of severe viral myocarditis in leptin deficiency. We examined the effects of adiponectin replacement therapy on myocardial damage in leptin-deficient mice with acute viral myocarditis.

Materials and methods

INFECTION PROTOCOL

Six-week-old female leptin-deficient *ob/ob* mice and C57BL wild-type mice were obtained from the Jackson Laboratory (Bar Harbor, ME, USA). A myocarditic variant of the encephalomyocarditis (EMC) virus was obtained from Dr Y Seto (Keio University, Tokyo, Japan). The viral preparations were stored at –80 °C in Eagle's minimum essential medium supplemented with 0.1% fetal bovine serum. Ethical approval for this study was obtained from the animal experimental committee in Kanazawa Medical University. All animals were treated in accordance with the Kanazawa Medical University guidelines for the care and use of laboratory animals. All animals were inoculated intraperitoneally with 500 plaque-forming units of EMC virus suspended in 0.1 ml of saline.

TREATMENT PROTOCOL

The leptin-deficient mice were randomly assigned to one of two groups. The first group did not receive interventional therapy (OB group). The second group received daily subcutaneous injections of recombinant mouse full-length adiponectin (30 μg/g per day, starting simultaneously with the EMC virus injection) (OB + Adipo group).[7]

HISTOLOGICAL EXAMINATION OF THE HEART

The mice were weighed and then killed by cervical dislocation on either day 4 or day 8 after viral inoculation. Cardiac tissues were immediately extracted, weighed, fixed in 10% buffered formalin and stained with haematoxylin and eosin (H&E). Two transverse sections of the ventricular myocardium were assessed for the severity of necrosis and mononuclear cell infiltration by an experienced pathologist who had no knowledge of the study design. Sections were scored according to the following scale: 1, lesions involving < 25% of the ventricular myocardium; 2, lesions involving 25 – 50% of the myocardium; 3, lesions involving 50 – 75% of the myocardium; and 4, lesions involving > 75% of the myocardium. The sections were also stained for myosin in order to confirm the presence of myocyte necrosis.

Five high-power fields (HPFs) (magnification × 400) were randomly selected from each transverse section of the myocardium, and the number of infiltrating cells counted. The number of apoptotic cells per section in these HPFs was also determined using *in situ*

terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick-end labelling, as described previously.[8]

IMMUNOREACTIVITY OF ADIPONECTIN RECEPTORS IN MYOCYTES

To examine the immunoreactivity of adiponectin receptors 1 and 2 (AdipoR1 and AdipoR2), immunohistochemical staining using a streptavidin biotin complex method (K0675 and E0353, DAKO Cytomation Co. Ltd, Kyoto, Japan) was performed on serial sections of transverse ventricular myocardium from different mice on day 4 or day 8 after viral inoculation. The immunoreactivity of AdipoR1 and AdipoR2 in vessels and macrophages from a normal wild-type mouse that had not received viral inoculation or adiponectin administration was used as a positive control.

Rabbit polyclonal anti-mouse AdipoR1 and AdipoR2 antibodies (ADIPOR11-A and ADIPOR21-A, Alpha Diagnostic International Inc., San Antonio, TX, USA) were applied at a dilution of 1:50. Control slides were treated with normal diluted rabbit serum.

The slides were blindly reviewed by the same pathologist. The degree of adiponectin receptor reactivity was assessed in 30 randomly selected myocytes corresponding to surviving cells found on the respective H&E and myosin-stained slides, and was semi-quantitatively graded according to the degree of immunoreactivity: 0, absence of staining; 1+, weak staining; 2+, moderate staining; and 3+, strong staining.[9] The slides were also compared with the respective control slides to exclude non-specific staining.

STATISTICAL ANALYSIS

Data were expressed as the mean ± SD. Analysis of variance was used to evaluate differences in body and cardiac weights, cardiac histological scores, numbers of infiltrating or apoptotic cells in the myocardium and immunoreactivity of adiponectin receptors in myocytes between the groups. A P-value < 0.05 was considered to be statistically significant.

Results

Eight wild-type and 28 leptin-deficient mice were inoculated with EMC virus. Eighteen of the leptin-deficient mice did not receive interventional therapy (OB group); the remaining 10 leptin-deficient mice received daily injections of adiponectin (OB + Adipo group).

Eight of the mice in the OB group died from viral myocarditis during the study protocol; there were no deaths in the wild-type (WT) or OB + Adipo groups over the same period. The numbers of mice killed on day 4 and day 8 after viral inoculation were four and four, respectively, in the WT group, six and four, respectively, in the OB group, and five and five, respectively, in the OB + Adipo group.

BODY AND CARDIAC WEIGHTS

Body weights on days 0, 4 and 8 after viral inoculation were significantly higher ($P < 0.05$) in the OB and OB + Adipo groups than in the WT group (Table 1). Cardiac weights in the OB mice on day 8 after viral inoculation were significantly increased ($P < 0.05$) compared with those in the WT mice (Table 1). There was no significant difference in cardiac weight between the OB + Adipo group and the WT group.

HISTOLOGICAL FINDINGS

The histological scores of myocardial necrosis, and the numbers of infiltrating and apoptotic cells per HPF, in hearts from the different types of mice on day 4 and day 8 after viral inoculation are shown in Fig. 1. Hearts from the OB group showed severe myocardial necrosis and mononuclear cell

TABLE 1:
Body weight and cardiac weight after viral inoculation in various types of mice

	Body weight (g)			Cardiac weight (mg)	
Type	Day 0	Day 4	Day 8	Day 4	Day 8
WT	18.3 ± 1.5	18.7 ± 1.8	19.1 ± 1.5	96 ± 8	102 ± 10
OB	37.5 ± 2.4*	37.8 ± 2.9*	38.4 ± 3.1*	103 ± 7	121 ± 9*
OB + Adipo	37.8 ± 2.2*	37.3 ± 2.8*	35.6 ± 3.9*	94 ± 6	98 ± 12

WT, wild-type mice; OB, leptin-deficient ob/ob mice; OB + Adipo, OB mice receiving adiponectin.
Data are the mean ± SD.
*$P < 0.05$ compared with WT mice.

infiltration. The histological scores, numbers of infiltrating cells and numbers of apoptotic cells were significantly higher ($P < 0.05$ for all) in the OB group than in the WT group on day 8 (Fig. 1). There were no significant differences in the histological scores or the number of infiltrating or apoptotic cells between the OB + Adipo group and the WT group.

IMMUNOREACTIVITY OF ADIPONECTIN RECEPTORS

In the normal WT group, immunoreactivity for AdipoR1 was found in the arterial walls and immunoreactivity for AdipoR2 was found in macrophages. The degrees of immunoreactivity for AdipoR1 and AdipoR2 in myocytes from different mice on day 4 and day 8 are shown in Fig. 2. In the OB group, the AdipoR1 reactivity in myocytes was significantly reduced ($P < 0.05$) compared with reactivity observed in the WT group on day 4 and day 8 (Fig. 2A), but the AdipoR1 reactivity was similar in the OB + Adipo group and the WT group. There were no significant differences in the immunoreactivity for AdipoR2 among the groups (Fig. 2B).

Discussion

Circulating levels of leptin and adiponectin are either undetectable or decreased in OB mice.[10] The protective role of adiponectin against fatty liver diseases has recently been demonstrated in non-alcoholic OB mice with insulin resistance and dyslipidaemia.[11] Replacement therapy with adiponectin could in part compensate for the absence of leptin in terms of ameliorating hepatomegaly and steatosis and decreasing serum alanine aminotransferase levels,[11] although such therapy would not alter the primary aetiology. Injection of adiponectin has also been reported to elevate insulin sensitivity and alleviate hyperlipidaemia.[11] Consistent with these findings, adiponectin administration to OB mice receiving EMC viral inoculation in the present study was found to protect the OB mice from inflammatory myocardial damage.

Complementary DNA encoding the two adiponectin receptors AdipoR1 and AdipoR2, which are distantly related to the family of seven-transmembrane spanning G protein-coupled receptors, has been cloned.[12] AdipoR1 and AdipoR2 are expressed ubiquitously in most organs, with AdipoR1 being especially expressed in skeletal muscle and AdipoR2 in liver.[12] Pancreatic β-cells have also been shown to express adiponectin receptors in a cell culture system.[13] These receptors have seven transmembrane domains and activate signalling molecules

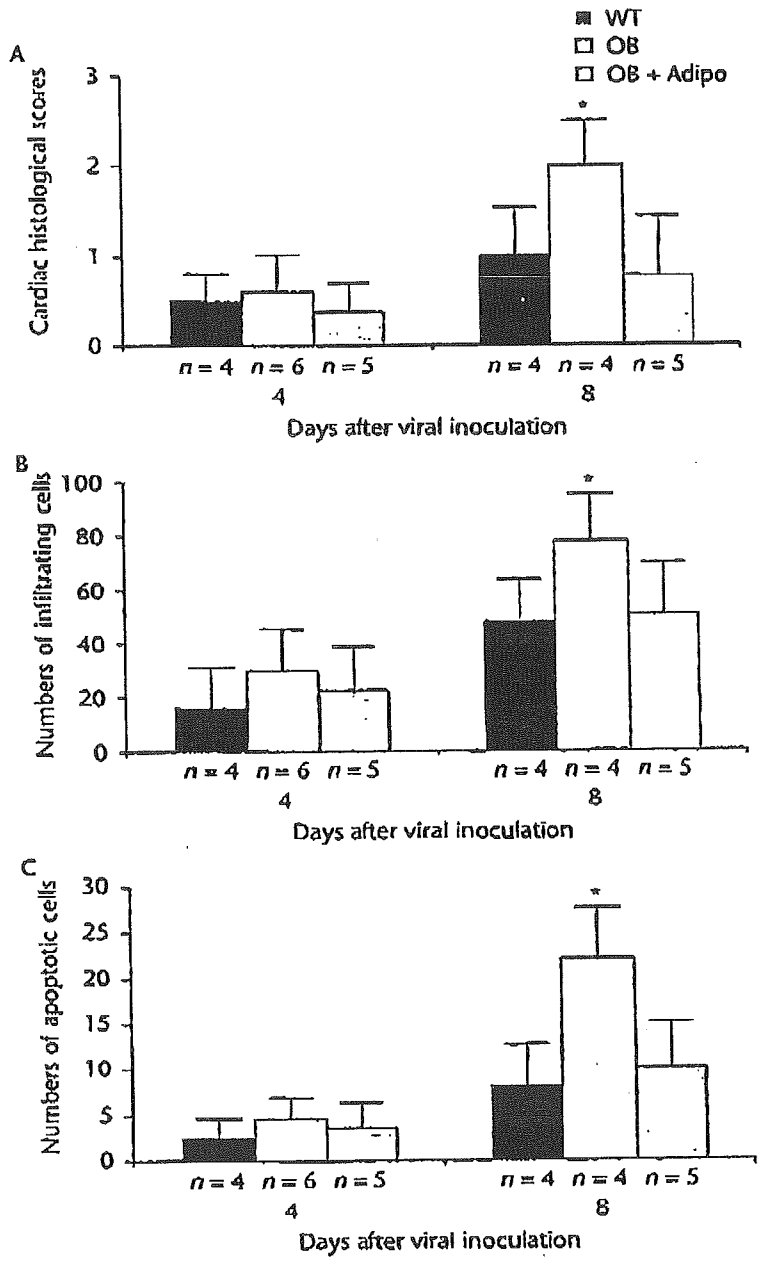

FIGURE 1: Results of histological examination of myocardial sections. (A) Histological scores, (B) numbers of infiltrating cells and (C) numbers of apoptotic cells in different types of mice on day 4 and day 8 after viral inoculation. Data are expressed as the mean ± SD. WT, wild-type mice; OB, leptin-deficient ob/ob mice; OB + Adipo, OB mice receiving subcutaneous administration of mouse adiponectin (30 µg/g daily, starting simultaneously with viral inoculation). $^{*}P < 0.05$ compared with WT group

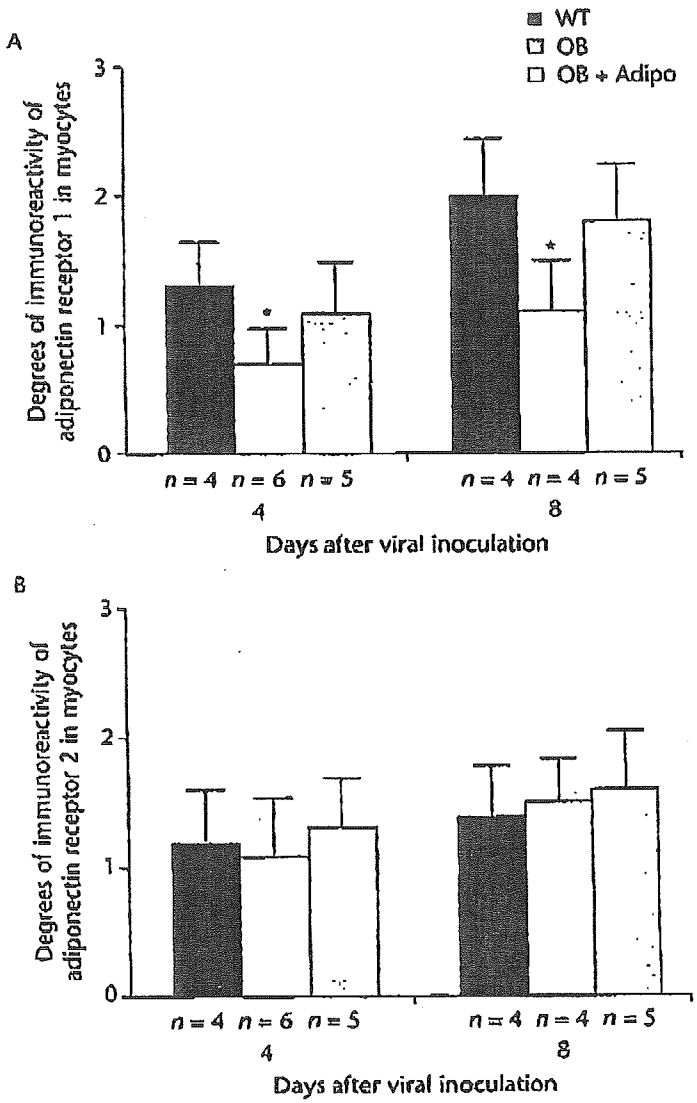

FIGURE 2: Degrees of immunoreactivity of adiponectin receptor 1 (A) or adiponectin receptor 2 (B) in myocytes from different types of mice on day 4 and day 8 after viral inoculation. Data are expressed as the mean ± SD. WT, wild-type mice; OB, leptin-deficient *ob/ob* mice; OB + Adipo, OB mice receiving subcutaneous administration of mouse adiponectin (30 μg/g daily, starting simultaneously with viral inoculation). $^{*}P < 0.05$ compared with WT group

such as peroxisome proliferator-activated receptor-α, adenosine monophosphate-activated protein kinase, and mitogen-activated protein kinase.[12] Possible alterations to adiponectin utilization in the coronary artery and/or heart have been described in type 2 diabetic patients compared with non-diabetic patients based on the transcardiac gradient of adiponectin levels from aortic root to coronary sinus.[14]

One mechanism of impaired transcardiac utilization of adiponectin in subjects with diabetes seems to be a decreased receptor-binding ability of adiponectin in the cardiac myocytes.[14] Interestingly, in the present study we found decreased AdipoR1 immunoreactivity in damaged myocytes from OB mice with viral myocarditis, and adiponectin replacement therapy in OB mice led to recovery of the suppressed AdipoR1 reactivity. These results indicate that adiponectin may act through binding to the AdipoR1, leading to protection against the progression of myocardial inflammation.

In summary, we determined the effects of adiponectin replacement therapy on myocardial damage in OB mice with viral myocarditis. There was significantly decreased reactivity of AdipoR1 in damaged myocytes from OB mice on day 4 and day 8 after viral inoculation compared with that in myocytes from WT mice, together with elevated cardiac weights and severe inflammatory myocardial damage. Replacement of adiponectin in the OB mice inhibited the development of severe myocarditis through augmentation of the AdipoR1 reactivity in the injured myocytes. Our data suggest that exogenously administered adiponectin may inhibit the progression of viral myocarditis through binding to the AdipoR1 in leptin-deficient conditions.

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Conflicts of interest

No conflicts of interest were declared in relation to this article.

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Spontaneous Fractures of Long Bones Associated with Joint Contractures in Bedridden Elderly Inpatients: Clinical Features and Outcome

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Running head: ***Spontaneous Fractures Associated with Joint Contractures in Bedridden Elderly***

2504 words from Introduction through Discussion

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ABSTRACT

PURPOSE: To describe clinical features and outcome of long-bone fractures associated with joint contractures in bedridden elderly inpatients.

METHODS: We conducted an observational study in a 1993-bed hospital, serving as a hospital and long-term care facility for elderly subjects, from 1998 to 2004 in Japan.

RESULTS: We identified 18 permanently bed-ridden inpatients [one male and 17 female, mean (± SD) age 88 ± 9 years] with spontaneous fractures over a 7-year period. Their mean period of being bedridden was 7 ± 6 years. Nutritional state of the patients just before they sustained fractures was poor, as evaluated by serum albumin level. Spontaneous fractures affected femur in 12 cases (8 supracondylar fractures, 2 intertrochanteric fractures, one shaft fracture, and one surgical neck fracture), humerus in 5 cases (2 surgical neck fractures, 2 shaft fractures and one supracondylar fracture), and proximal phalanx in one case. All spontaneous fractures occurred near joint contractures at proximal and/or distal sites of extremity bones. Ten patients had previously suffered from long-bone fractures during non-bedridden periods, and in 6 of these 10 cases, spontaneous fractures reoccurred in the same bone. Four of 5 fractures in hemiplegic patients occurred on paralytic side. Although one patient died due to worsening of pneumonia one month after fracture, 17 of 18 subjects were successfully treated with bandage procedures and showed recovery within approximately two months after fractures.

CONCLUSION: These results show that long-term bedridden patients, especially those

with joint contractures, a history of long-bone fractures and/or hemiplegia, have a high risk of spontaneous fractures.

Key words: spontaneous fracture, joint contracture, bedridden, hemiplegia, long bone.

INTRODUCTION

Although advancement of aging of society is observed in almost all industrialized nations, one of the greatest differences between Japan and western countries is the number of bedridden patients. The current number of bedridden elderly subjects in Japan is about one million (1), which is estimated to increase to about 2.3 million in 2025. On the other hand, evolutional osteoporosis is one of the most common complications in the elderly. Osteoporotic elderly persons are well known to be vulnerable to bone fractures at the time of falling or trauma, such as hip fractures, compression fractures of the vertebrae, and distal radioulnar fractures. Severe osteoporosis may develop when the elderly become immobilized or non-weight-bearing (2). However, reports on the occurrence of fractures without any apparent external force in completely bedridden elderly patients under care, are limited.

Thus far, three studies have been conducted on such bone fractures in bedridden elderly subjects. Kane and Goodwin (3) firstly described 6 individuals with "spontaneous fractures of long bones" in nursing home patients. Sherman (4) also reported another elderly non-weight-bearing woman with "transfer" and "turning" fracture. Kane and colleagues (5) identified 16 subjects with such fractures by a survey in 11 nursing homes, and named them "minimal trauma fractures". More recently, Martin-Hunyadi and colleagues (6) have summarized 55 "spontaneous long-bone insufficiency fractures" in 53 extremely elderly residents including 38 completely bedridden subjects in long-term nursing homes.

In the present study, we identified 19 long-bone fractures without any apparent external force or abuse that occurred during daily care procedures in 18 completely bedridden elderly subjects in a hospital for the elderly, during the past 7 years. As particular characteristics, proximal and/or distal joint contracture(s) were observed adjacent to the fractured bone in all these 18 cases. In addition, we herein describe other clinical features and the outcome of the fractures.