Table 1. Association Between Polycythemia and Glucose Intolerance in Elderly High-Altitude Dwellers in Asia

Characteristic	Yushu in Qinghai, China		Domkhar in Ladakh, India	
	Without Polycythemia, n = 114 (55%)	With Polycythemia, n = 95 (45%)	Without Polycythemia, n = 81 (69%)	With Polycythemia, n = 36 (31%)
Male, %	48	34*	44	33
Age, mean ± SD	65.7 ± 5.8	66.6 ± 6.1	69.0 ± 6.5	70.1 ± 7.3
Hemoglobin, g/dL, mean ± SD	15.3 ± 1.6	17.6 ± 1.7***	14.1 ± 1.9	17.6 ± 1.7***
saturation of peripheral oxygen, %				
Mean ± SD	89.5 ± 3.1	88.8 ± 3.6	89.6 ± 4.8	87.1 ± 6.5*
<90, %	42.5	51.1	45.7	66.7*
BMI, kg/m^2, mean ± SD	26.2 ± 4.3	28.8 ± 4.4***	22.0 ± 3.2	22.4 ± 2.7
Obese (BMI > 25.0) %	54	82***	15	14
Hypertension, %	49	73***	51	58
Diabetes mellitus, %	10	18	3	19**
Diabetes mellitus or impaired glucose tolerance, %	41	56*	36	58*
Odds ratio (95% confidence interval) for diabetes mellitus or impaired glucose tolerance†	1.0	2.3 (1.2–4.3)*	1.0	3.0 (1.2–7.1)*

*P<.05, **.01, ***.001; normocythemia versus polycythemia; chi-square test, Student t-test, logistic regression.
†After adjusting for age, sex, obesity, and saturation of peripheral oxygen (SpO_2) <90% using multiple logistic regression.
SD = standard deviation; BMI = body mass index.

lower in elderly subjects with polycythemia than those without in Domkhar (P = .02) but not in Yushu. Mean body mass index (BMI), prevalence of obesity (BMI > 25 kg/m^2), and prevalence of hypertension (blood pressure ≥ 140/90 mmHg or taking hypertensive medicine) in elderly subjects were much higher in Yushu than in Domkhar.

The prevalence of DM or IGT in elderly people with polycythemia was higher than in those without polycythemia in Yushu (56% vs 41%) and in Domkhar (58% vs 36%). The odds ratio for DM or IGT in elderly people with polycythemia compared with those without polycythemia was 3.0 (95% confidential interval (CI) = 1.2–7.1; P = .01) in Domkhar and 2.3 (95% CI = 1.2–4.3; P = .01) in Yushu, after adjustment for age, sex, obesity, and hypoxia (SpO2 < 90%) according to multiple logistic regression (Table 1).

A strong association was found between excessive polycythemia and glucose intolerance in elderly highlanders living in two distinct regions of Asia, despite differences in the prevalence of obesity and hypertension with the different influence of socioeconomic globalization.

There appear to be two reasons for the association between polycythemia and glucose intolerance. First, glucose intolerance may cause deterioration of blood vessels, metabolic dysfunction, and subsequent insufficient supply of oxygen to the human body; polycythemia might develop as a compensatory response. Second, people with polycythemia seem to be particularly vulnerable to glucose intolerance, suggesting poorer adaptation to hypoxia than in those without.

It is important to further examine this association between excessive polycythemia and DM in longitudinal follow-up of highlanders to prevent not only DM but also chronic mountain sickness.

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Author Contributions: Kiyohito Okumiya, Ryota Sakamoto, and Kozo Matsubayashi conceived and designed the project. All authors participated in the medical surveys in China or India. Kiyohito Okumiya, Ryota Sakamoto, and Kozo Matsubayashi analyzed and interpreted the data and prepared the manuscript.

Sponsor's Role: None.

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THE AGE- AND SEX-SPECIFIC INCIDENCE AND MEDICAL EXPENSES OF HEART FAILURE HOSPITALIZATION IN 2005 IN TAIWAN: A STUDY USING DATA FROM THE NATIONAL HEALTH INSURANCE

To the Editor: Heart failure increases sharply with aging.[1–6] Vital statistics in Taiwan show that life expectancy has been increasing—from 70.8 in 1985 to 71.9 in 1995 and 74.5 in 2005 for men and from 75.8 in 1985 to 77.8 in 1995 and 80.8 in 2005 for women.[7] Although the clinical burden of heart failure is expected to increase in Taiwan, its epidemiology remains unclear. This study analyzed the incidence of and medical expenses for hospitalization for heart failure in Taiwan during 2005 using the reimbursement data of the National Health Insurance (NHI), which is a compulsory and universal health insurance implemented since March 1, 1995.[8]

METHODS

The NHI covered 98.0% of the total population, and more than 90% of the medical institutes were contracted to the Bureau of NHI for providing healthcare services (those not contracted provided fewer services) in 2005.[9] For each admission, computerized data of medical expenses, dates of admission and discharge, identification number, sex, birth date, and diagnostic codes based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) were available. The National Health Research Institute of Taiwan extracted the data of a random sample of 1,000,000 subjects covered by the NHI during 2005 for the purpose of academic research. The sample was representative of the general population of Taiwan.[10] A total of 79,299 of the 1,000,000 subjects had records of one or more hospitalizations during 2005. Of them, 2,712 (3.4%) had a diagnosis of heart failure (ICD-9-CM codes 398.91, 402.11, 402.91, 404.11, 404.13, 404.91, 404.93, and 428) as a primary or secondary diagnosis. Patients with a first hospitalization with a diagnosis of heart failure were recruited.

The incidence of and total medical expenses for hospitalization for heart failure for 2005 were calculated according to age (each 5-year increment) and sex. The numerators of the incidences were the total number of patients with a diagnosis of heart failure in the specific subgroups of age and sex, and the denominators were the number of insured in the subgroups in the randomly selected 1,000,000 subjects from the NHI data set.

RESULTS AND DISCUSSION

The incidence of hospitalization for heart failure and percentage of total medical expenses according to age and sex are shown in Table 1. The total medical expenses for men, women, and all patients were 151,752,015, 123,736,224, and 275,488,239 New Taiwan dollars, respectively (33 New Taiwan dollars equals approximately 1 U.S. dollar). Incidence was highly dependent on age in either sex and was especially high in subjects aged 65 and older. Men had a higher incidence than women in all age groups except those aged 75 and older. The population aged 65 and older represented less than 10% of the total population in either sex but used 81.1% (77.5% in men and 85.6% in women) of the total medical expenses for first hospitalization for heart failure.

Consistent with other studies,[1–6] these data showed that heart failure was age dependent and that men had a higher incidence than women (Table 1). In the Framingham follow-up study, the incidence of heart failure was 2, 5, and 10 per 1,000 person-years for subjects aged 45 to 54, 55 to 64, and 65 to 74, respectively, in men and 1, 3, and 8 per 1,000 person-years, respectively, in women.[2] These were comparable to the data in Table 1.

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Author Contributions: Sophie Pautex, Vito Curiale, Lourdes Rexach, and Nele Van Den Noortgate: study concept and design, acquisition of subjects and data, analysis and interpretation of data, and preparation of manuscript. Mathias Pfisterer and Miel Ribbe: study concept and design, acquisition of subjects and data, analysis and interpretation of data.

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COMMUNITY-BASED GERIATRIC ASSESSMENT AND PREVENTIVE INTERVENTION LOWERED MEDICAL EXPENSES FOR THE ELDERLY

To the Editor: Before the introduction of the national long-term care insurance system, it was reported that community-based geriatric assessment might lower the increasing rate of medical expenses in a rural town in Kochi Prefecture, Japan.[1] Even after the introduction of the national long-term care insurance system in 2000, total medical expenses for older adults has increased with the growth of the older population in Japan. Since 2004, community-based comprehensive geriatric assessments and interventions have been performed for older adults living in Tosa Town, Kochi Prefecture, Japan. Geriatric assessments included a comprehensive annual health-related questionnaire of all eligible people aged 65 and older (75–95% response rate) and annual geriatric examinations for people aged 75 and older (30–40% participant rate).[2] This longitudinal community-based project in cooperation with local government and resident organizing committees has attained several medical achievements: early detection of latent diabetes mellitus or impaired glucose tolerance in older adults because of community-based oral glucose tolerance tests,[3] improvement of impaired glucose tolerance by lifestyle change interventions,[4] increasing public awareness of hypertension in older adults,[5] public education of dietary diversity,[6] and early detection of fallers[7] by introducing a fall risk index that can be completed in a brief amount of time.[8]

In parallel with medical and geriatric achievements of the community-based project, an additional achievement regarding changes in medical expenses for the elderly in this town was found. Changes in medical expenses from 2004 to 2007 in Tosa Town, where we have intervened, compared with medical expenses for older adults in two other communities (Motoyama Town and Kochi City) in Kochi prefecture and the average medical expenses of 35 communities in Kochi Prefecture[9] are reported here. Kochi prefecture is located in Shikoku province in southwestern Japan and has 11 cities and 24 towns with a total population of 796,292 people, of whom 25.9% were aged 65 and older in 2006. Tosa Town is one of the 24 small towns in Kochi Prefecture and had a population of 4,632 people, of whom 40.6% were aged 65 and older in 2006. This comparative study on changes in medical expenses for older adults included two control communities: Motoyama Town, which neighbors Tosa Town and has a sociodemographic profile similar to that of Tosa Town, and Kochi City, which is the seat of Kochi prefecture. Total populations (and % of the population aged $\geq$ 65) in Motoyama Town and Kochi City in 2006 were 4,374 (37.9%) and 333,484 (20.5%), respectively.

Figure 1 compares annual changes in medical expenses in the national medical insurance system for one person aged 65 and older in Tosa Town from 2004 to 2007 with expenses in Motoyama Town, in Kochi City, and the average from 35 communities in Kochi Prefecture. Although medical expenses for older adults increased over the 4 years in Motoyama Town and Kochi City and in Kochi prefecture in general, expenses in Tosa Town decreased yearly from 2004 to 2007. The decrease in medical expenses for older adults in Tosa Town is probably due to community-based geriatric assessments and preventive interventions introduced since 2004. In 2007, differences in medical expenses between Tosa Town and neighboring Motoyama Town reached 140,000 Japanese yen (approximately $1,075) for each elderly person each year, which totals approxi-

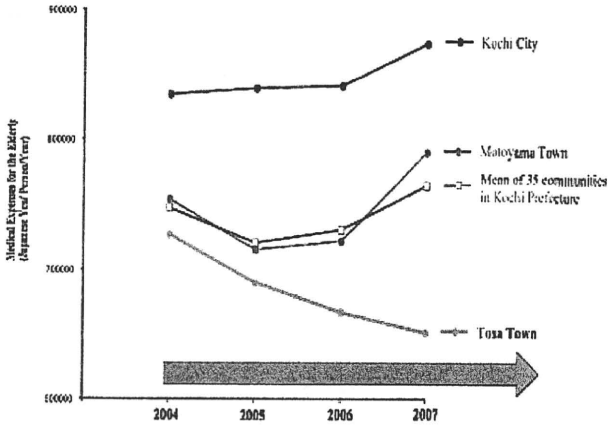

Figure 1. Annual changes in medical expenses for one person aged 65 and older in Tosa Town from 2004 to 2007, compared with expenses in Motoyama Town, in Kochi City, and the average expenses of 35 communities in Kochi Prefecture.

mately 200,000,000 Japanese yen (~ $2 million) for 1,500 elderly persons in each town. The total annual budget of community-based geriatric assessments and preventive interventions in our project is 10 million Japanese yen (~ $100,000). The decrease in medical expenses in Tosa Town suggests that it might be worthwhile to consider the community-based project not only from the perspective of geriatric achievements, but also from the financial dimension.

The elderly population is rapidly growing in Japan, especially in Kochi Prefecture. The percentage of the population aged 65 and older was greater than 30% in three of 11 cities and in 21 of 24 towns in Kochi prefecture.[9] Considering public health results and financial conditions, community-based strategies to prevent disease and promote health of older adults are urgently needed in each community. In conclusion, community-based and field-setting geriatric assessment and preventive intervention may be extremely beneficial for health promotion of older adults and financial efficiency.

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Author Contributions: Kozo Matsubayashi and Masayuki Ishine: study design and preparation of letter. Taizo Wada, Ryota Sakamoto, Kiyohito Okumiya, Motonao Ishikawa, Gaku Yamanaka, Naomune Yamamoto, Kuniaki Otsuka, Masanori Nishinaga, Yoshinori Doi, Shogo Murakammi, and Mihiko Fujisawa: field studies and analysis, interpretation, and discussion of data. Shoki Yano: arrangement of field settings in Tosa Town.

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GERO-ECONOMICS

To the Editor: Dear Congressional Representative and Program Administrator:

Not being an economist I hesitated to venture into the fray, but a geriatrician who could provide a different perspective might clarify, at least a bit, the debate about how to fund our healthcare system and the retirement years. The purpose of a national healthcare plan and a national retirement package is to maximize each individual's function and quality of life throughout the full span of life. We must recognize that healthcare and retirement needs are intertwined.

As most readers of this *Journal* know, the age of 65 as a starting point for the beginning of "old age" has no basis in physiology. Politicians, rather than scientists or physicians, were responsible for making that decision in the 19th and early 20th centuries. In those times, life expectancy was far shorter than it is today, assuring planners that relatively few would achieve the distinction of being elderly. Therefore, the costs of a national healthcare system and a national retirement system would have been modest. It was only after life expectancy at birth in the developed nations increased from approximately 47 years to almost 80 years that funding these programs became a significant issue.

To be successful and cost efficient, it is necessary for the designers of healthcare and retirement programs to have an appreciation of the aging process and the advent of chronic illness. Aging may be viewed as a process characterized by a diminution in reserve capacity in most organ systems, albeit to a different degree in each and with considerable variation from person to person. In addition, over the course of a lifetime, most of us accumulate a number of chronic diseases. Diabetes mellitus, arthritis, hypertension, coronary heart disease, cerebrovascular disease, and even many cancers are appropriately viewed as chronic conditions, rather than acute illnesses, under most circumstances. Such illnesses diminish the reserve capacity further.

The changes associated with aging and chronic illness cause the elderly population to be far from homogeneous. Therefore, perhaps the retirement system could be designed to mesh more closely with the health status of those it is supporting. For example, perhaps there might be an option for a perfectly well 65-year-old to receive a considerably smaller retirement benefit between the ages of 65 and 75 and a considerably larger benefit during the years that follow. This would allow that person to have some money early on but far more money when that individual might need the funds to remain independent or to reside at home. This might also decrease the costs to Medicaid, the funding source for the majority of nursing home beds.

Furthermore, as a long-time practicing geriatrician, I can assure you that there are innumerable opportunities to save money in the healthcare system and improve the outcomes for older adults at the same time. Many incentives in the healthcare system foster unnecessary costs, not to mention poor clinical outcomes. Payment for many procedures is outrageously excessive compared with payment for the comprehensive evaluation of an older adult with multiple chronic illnesses.[1] Payment for preventive health measures is often inadequate. Unnecessary testing and hospitalization are associated with huge costs. How often does a physician order multiple studies and admit an older adult to a hospital for fear of charges of malpractice? Are not huge numbers of admissions for congestive heart failure, pneumonia, and many of the other most common conditions unnecessary?[2,3] If we were able to eliminate some of the waste in the healthcare system, we could add those savings to more-effective healthcare programs and the associated retirement programs.

Geriatric medicine is coming to have an influence on other medical specialties from general surgery to emergency medicine. Perhaps it should influence some of our associates in economics as well as those concerned with healthcare and retirement planning.

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SOUND-ALIKE SYNDROMES REVISITED

To the Editor: A year ago I wrote of a newly described concern, "Sound-Alike Syndromes" when one of our facility's new admissions suffered from Morvan's syndrome when Marfans was expected.[1] Much to my surprise, another example appeared, this time to my amusement.

A 95-year-old resident of our facility was admitted to a local medical center after a syncopal episode of unclear

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特集：高齢者在宅医療の新しい展開

序文：きょうから学ぶ高齢者在宅医療

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Geriat. Med. 48(11)：1461～1462, 2010

特集 高齢者在宅医療の新しい展開

序文：きょうから学ぶ高齢者在宅医療

西永 正典

わが国は，人類史上経験したことがない高齢化の「津波」に襲われる．それもここ30年以内に確実に，である．地震に対する備えはなされているのに，一方，著しい高齢化の「津波」に対する備えは十分といってよいのであろうか．

私ごとで恐縮だが，筆者がまだ駆け出しのころ，年に数回心不全で入退院を繰り返していた80歳代半ばの女性に出会った．公営住宅に独居で，心機能は低下し，ADLも低下して歩くこともままならなかった．当時は，転院やむなしとする状況であったが，御本人は在宅療養を強く望み転院を拒まれた．退院支援室を介して，あるいは個人的なつながりで在宅療養を引き受けてくれる先生を探し回ったが，高齢の慢性心不全患者を引き受けてくれる地元の先生は，当時はいなかった．総合機能評価とともに多職種協同で病院内外のスタッフや本人，家族と話し合いが重ねられ，リハビリテーションも施行された．訪問看護やヘルパーなど様々な手段を導入し，ようやく自宅退院にこぎ着けた．当時としては例外中の例外であった．退院してもすぐに緊急入院するのではないかと筆者だけでなく，スタッフの多くが心配していたと思う．しかし，多職種の方々から様々な生活情報が入ることで，利尿薬の量を調節し，半年に1回ほど数日間の検査入院で薬や社会的資源の再調整がなされ，結局，独居のまま90歳半ばに達するまで，生き生きと在宅療養を続けられた．入院回数，日数は定期的な検査・調整入院のみに減少し，心不全悪化による入院はなかった．また，医療費や介護費用をすべて含めても，入退院を繰り返していた1年前のそれらに比べて2/3程度に抑えられた(図)．が，何よりも最期まで「自宅に居られて幸せ」といっておられたことが，

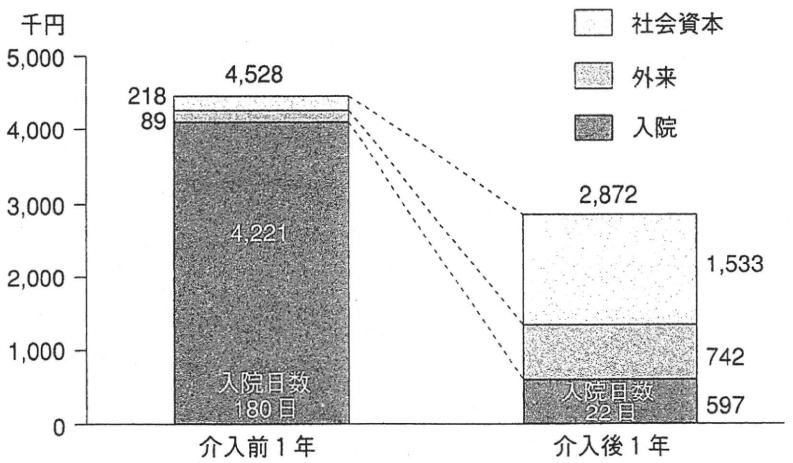

図 年間コストの比較

にしなが まさのり(東京大学高齢社会総合研究機構特任准教授)

病院における医療とともに，在宅における医療がいかに重要であるかを筆者に再認識させてくれた．

今や在宅医療は多くの方々の努力で，発展を続けている．老年医学においても，その意義は大きくなっているように思う．

本特集では，わが国の在宅医療の第一人者の方々に執筆をお願いし，快く引き受けていただいた．老年医学を学んでいるわれわれが，在宅医療をきょうからでも，さらに学べるようにと願って序文としたい．

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高齢者の安全な薬物療法　第23回

監修：秋下　雅弘，葛谷　雅文

降圧薬合剤使用には注意が必要

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2006年2種類の降圧薬，アンジオテンシンⅡ受容体拮抗薬(ARB)のロサルタンカリウムとサイアザイド系利尿薬のヒドロクロロチアジドが配合された降圧薬の合剤が販売された．世界的には1995年以降，フランス，米国をはじめとして82カ国で承認され，広く臨床で使用されている．その後，ここ2～3年の間に，少量の利尿薬とARBの降圧薬合剤が次々と販売され(表1)，その市場は確実に増大している．それらの合剤の特徴は，ARB単独で用いられる効果に比し，比較的強い降圧効果を発揮するが，利尿薬配合量が少量のため，その副作用を十分認識されずに使用されることも少なくない．また，高齢者では，合併症や非典型的な症状のため，副作用と認識されにくく，その発見が遅れる場合もある．本稿では，われわれが経験した苦い症例を中心に概説する．

症例呈示

84歳/女性

主訴：食欲低下，ふらついて歩けない．

既往歴：うつ病で精神科通院中．

生活歴：長年小学校の教員を勤め，定年後はご主人と2人だけの生活．近くに住む娘が1人いるが，時々旅行に行ったりして楽しんでいる．

総合的機能評価：基本的ADLは保たれている(Barthel index：95/100点)，手段的ADLは，服薬能力，家事(炊事，掃除，洗濯)，買物，金銭管理，電話，交通機関の利用(車の運転はご主人)も可能であった．ミニメンタルテストは28/30点，Geriatric depression scale 15では6/15点．

現病歴：近医に十数年前から高血圧の診断で降圧薬(カルシウム拮抗薬)をもらって服用していたが，顔が火照るなどの症状があり，服薬を止めていた．体重が3カ月で7kg以上減少するため，近くの総合病院で採血，内視鏡やエコー，CTなどの検査を受けるも異常が認められず，食欲低下や昼夜逆転なども出現したため，当科を受診．総合的機能評価などから認知機能低下よりもうつ症状が目立ったため，精神科紹介入院となる．抗うつ薬が著効し，食欲も改善，その後，体重ももとのレベルに戻った．精神科入院中から，高血圧に対してロサルタン50 mgが処方され，入院中は138/78前後でコントロールされていたが，退院後より体重がもとのレベルに戻るに伴って，抗うつ薬(トリプタノール)は漸減，しかし，次第に家庭血圧値が上昇，特に起床時の血圧値が180/95を超えることが多くなったため，当科外来を受診し，腎機能が正常範囲(eGFR：65)，カルシウム拮抗薬で副作用が出たことがあること，抗うつ薬が漸減中で服用薬剤数の増加を望まなかったため，これまで服用してきたロサルタンに加えて，少量のサイアザイド系利尿薬のヒドロクロロチアジド配合の合剤を服用することにした．

表1　アンジオテンシンⅡ受容体拮抗薬(ARB)と降圧利尿薬の配合薬

ARB		降圧利尿薬	
ロサルタンカリウム	50 mg/	ヒドロクロロチアジド	12.5 mg
バルサルタン	80 mg/	ヒドロクロロチアジド	6.25 mg
バルサルタン	80 mg/	ヒドロクロロチアジド	12.5 mg
カンデサルタンシレキセチル	4 mg/	ヒドロクロロチアジド	6.25 mg
カンデサルタンシレキセチル	8 mg/	ヒドロクロロチアジド	6.25 mg
テルミサルタン	40 mg/	ヒドロクロロチアジド	12.5 mg
テルミサルタン	80 mg/	ヒドロクロロチアジド	12.5 mg

初診時		1回目入院(うつ)	外来時	14日後	2回目入院(低Na血症)	
家庭血圧(朝) 164/88		入院中(朝) 138/78	家庭血圧(朝) 176/92	家庭血圧(朝) 142/78	退院前(朝) 136/74	
カルシウム拮抗薬内服していなかった		ロサルタン50 mg	ロサルタン50 mg ⇩ ロサルタン50 mg/HCTZ 12.5 mg		ロサルタン50 mg	
体重(kg)	52	46	48	47	46	47
Na(mEq)	142	144	139	136	124	134
K(mEq)	3.9	4.2	3.8	3.7	3.6	3.9
Cl(mEq)	102	108	104	101	92	100
BUN(mg/dL)	14	18	16	12	22	16
CRE(mg/dL)	0.66	0.70	0.64	0.70	0.92	0.72

家庭血圧は受診前7日間の平均値　HCTZ：ヒドロクロロチアジド　BUN：尿素窒素　CRE：クレアチニン

図1　本症例の経過(84歳，女性)

経過

2週間後の外来再来では，朝の血圧値も140/75程度に落ち着き(就寝前は130/70くらい)，娘さんと1泊2日の旅行に行ってくるとのことで調子はよかった．合剤に変更後1カ月，娘さんからうつが再発し，食事がほとんど食べられない．歩行にも不安定さが増し，精神科で抗うつ薬が増量されたがあまり効果がないとの電話があったため，早めに受診してもらった．血清ナトリウム値が124 mEqと低下し，入院の上，降圧薬をロサルタンのみに戻し，電解質をゆっくり補正すると活気が少しずつ戻り，食欲も改善，歩行も安定し(MRIなどでほかの合併症もなく)，低ナトリウム血症も改善して入院7日目に退院した(図1)．

解説

高齢者では多剤併用や服薬管理能力の低下が原因で服薬アドヒアランスに問題を生ずることが知られている．具体的には，用法や薬効の理解度，認知機能，薬剤包装の開封能力，処方薬剤数，最近の処方変更が高齢者の服薬アドヒア

高齢者における降圧薬合剤使用のポイント

- 近年，降圧薬を中心に多くの合剤が市場に出回るようになった．
- 高齢者では服薬アドヒアランスを考えると，なるべく服薬数を少なくするため，合剤を用いることが臨床の現場では増えている．
- 合剤を用いても薬物相互作用のリスクは変わらず，薬剤数が少なくなるため，むしろ有害作用に対する警戒が薄まる可能性は否定できない．
- 高齢者では，合併症や非典型的な症状のため，副作用と認識されにくい．

ランスと深く関連する[1]．

2008年のHYVET試験の結果により，80歳代の高齢者であっても，脳卒中や心不全の発症を減少するなど降圧薬による治療の効果が確認された．特に高齢者では服薬アドヒアランスを考えると，なるべく1剤，あるいは合剤にまとめることが合理的であると考えられ，『高血圧治療ガイドライン2009』においても，「合剤の使用により服薬錠剤数を少なく，処方を単純化することは，アドヒアランス改善に有用である」としており[2]，降圧薬合剤の使用頻度は今後さらに高まるであろう．

しかし，秋下が指摘するように，合剤を用いても薬物相互作用のリスクは変わらず，薬剤数が少なくなるため，かえって有害作用に対する警戒が薄くなる可能性は否定できない[3]．

また，2成分を含んでいることから，過度の降圧が起こる可能性もあり，本薬を安易に高血圧治療の第1選択薬としては用いるべきではない．このことは，添付文書の「用法・用量」にも明記されているが，さらに，「高齢者への投与について，高齢者では低ナトリウム血症，低カリウム血症があらわれやすい．75歳以上の高齢者に対する安全性は確立していない(使用経験がない)」と記載されており，われわれの苦い経験を含めて十分に留意したい．

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Visceral Fat Accumulation and Metabolic Risk Factor Clustering in Older Adults

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OBJECTIVES: To examine the relationship between visceral fat area (VFA) evaluated using computed tomography (CT) scans and the number of metabolic risk factors in older adults.

DESIGN: Cross-sectional study

SETTING: A community clinic in Tokyo, Japan.

PARTICIPANTS: Two hundred eighteen individuals aged 65 and older without impairments in activities of daily living who underwent geriatric health examination (63 men, mean age 74.5 ± 7.1; 155 women, mean age 75.3 ± 6.7).

MEASUREMENTS: VFA was obtained from a cross-sectional image at umbilical level in the supine position using CT scanning. Metabolic syndrome components except waist circumference were measured using the criteria of the International Diabetes Federation.

RESULTS: There was a positive correlation between VFA and number of metabolic risk factors in men and women. Multiple regression analysis demonstrated that only VFA was significantly correlated with number of risk factors in men, whereas age and VFA were significantly correlated in women; body mass index was not correlated with number of metabolic risk factors in men or women. Dyslipidemia and high blood glucose were associated with higher VFA, but high blood pressure was not. There was a negative correlation between VFA and serum adiponectin level and a positive correlation between VFA and homeostasis model assessment of insulin resistance.

CONCLUSION: Visceral fat accumulation is associated with metabolic risk factor clustering even in the elderly population. These results have clinical implications for the management of obesity in older adults. **J Am Geriatr Soc 58:1658–1663, 2010.**

Key words: visceral fat; metabolic syndrome; elderly; BMI

Several lines of evidence have suggested that visceral fat accumulation is associated with metabolic abnormalities such as high blood pressure (BP), high serum triglycerides, low serum high-density lipoprotein cholesterol (HDL-C), and high blood glucose through insulin resistance and abnormal secretion of adipocytokines.[1–4] Thus, visceral fat obesity has been established as a cause of cardiovascular disease,[5,6] although most of the subjects of studies delineating the relationship between visceral fat accumulation and metabolic abnormalities have consisted of middle-aged adults.[7–9] Therefore, the clinical significance of visceral fat accumulation in older adults is unclear in relation to metabolic abnormalities.

Aging is generally associated with a relative increase in visceral fat mass.[10,11] This is considered to be mainly due to decreased basal metabolism caused by loss of muscle mass, low physical activity, and an increase in carbohydrate intake.

Nevertheless, the prevalence of each metabolic syndrome component increases with age, and accordingly, elderly patients tend to have a higher number of metabolic abnormalities than other adults,[12–14] although it remains to be determined whether metabolic risk factor clustering, which is often observed in older adults, is attributable to visceral fat accumulation. It was assumed that visceral fat might affect this increase in the number of metabolic abnormalities with aging, through insulin resistance and abnormal secretion of adipocytokines. Thus, this study was conducted to clarify the relationship between visceral fat area (VFA) precisely evaluated using abdominal computed tomography (CT) scanning and the number of metabolic risk factors in an elderly sample.

METHODS

Subjects

Subjects who voluntarily participated in geriatric health examination were recruited at a community clinic from September 1 to November 30, 2005. Two hundred seventy-two subjects aged 65 and older who had no impairments in

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activities of daily living and consented to this study were selected.

Medical history and information on medications and smoking status were obtained from all subjects. Body weight, height, and waist circumference were measured, and BP was measured in the sitting position. Body mass index (BMI) was calculated (weight/height^2, kg/m^2). Venous blood samples were collected in the early morning after a 12-hour fast.

People with a history of cancer or gastrointestinal tract surgery; under treatment for endocrine disease or heart failure; taking pioglitazone, metformin, insulin, alpha-blockers, beta-blockers, beta-stimulators, or hormone therapy (including glucocorticoids); and with serum albumin of 3.0 g/dL or lower, serum creatinine greater than 1.5 mg/dL, or blood hemoglobin of 10.0 g/dL or lower were excluded because such factors as abnormal fat metabolism and insulin resistance might have affected them, leaving 218 subjects to be enrolled in this study.

The ethics committee of Abe Clinic approved this study, and written informed consent was obtained from all subjects.

VFA Measurement

VFA was obtained from a cross-sectional image at the umbilical level in the supine position using CT scanning (X Vision Scanner, Toshiba Medical Systems, Tokyo, Japan) and calculated using commercially available software (Fat Scan, N2 System, Osaka, Japan).

Definition of Metabolic Risk Factors

Components of the metabolic syndrome except waist circumference were defined using the criteria of the International Diabetes Federation (IDF): systolic BP (SBP) of 130 mmHg, greater or diastolic BP (DBP) of 85 mmHg or greater, or treatment with antihypertensive drug; fasting serum triglyceride level of 150 mg/dL or greater or treatment with fibrate; serum HDL-C level less than 40 mg/dL in men and less than 50 mg/dL in women; fasting plasma glucose of 100 mg/dL or greater or treatment with an antidiabetic drug.[15]

Homeostasis Model Assessment of Insulin Resistance and Serum Adiponectin Level

Homeostasis model assessment of insulin resistance (HOMA-IR), calculated as fasting insulin level (μIU/mL) × early morning fasting blood glucose level (mg/dL)/405, was evaluated to determine degree of insulin resistance.[16,17] Subjects with diabetes mellitus were excluded from HOMA-IR calculation because of a lack of reliability of their data.

Serum level of adiponectin was measured using an enzyme-linked immunosorbent assay (Human Adiponectin ELISA Kit, Otsuka, Tokyo, Japan).

Statistical Analysis

The subjects were divided into four groups according to individual calculated VFA values in men and women. High BP, high triglycerides, low HDL-C, and high blood glucose were used as metabolic risk factors. The number of metabolic risk factors was calculated as their sum (0–4). Data were expressed as means ± standard deviations or standard errors. The statistical significance of differences was assessed using unpaired *t*-tests for two groups and analysis of variance for three or more groups, followed by the Fisher protected least significant difference test to compare each group. Multiple regression analysis was performed to determine independent factors for the number of metabolic risk factors. The correlation of VFA with HOMA-IR or serum adiponectin level was analyzed using the Pearson correlation coefficient.

$P < .05$ was considered significant. Statistical analysis was performed using Stat View software (version 5.0, SAS Institute, Inc., Cary, NC).

RESULTS

Clinical characteristics of the subjects are depicted in Table 1. Mean VFA in men was significantly higher than in women, although BMI (kg/m^2) was comparable. The prevalence of subjects with high BP was 79.4% in men and 78.7% in women, including 46.8% in men and 43.2% in

Table 1. Clinical Characteristics of Study Population

Characteristic	Men (n = 63)	Women (n = 155)
Age, mean ± SD (range)	74.5 ± 7.1 (65–93)	75.3 ± 6.7 (65–92)
Body mass index, kg/m^2, mean ± SD (range)	22.9 ± 2.8 (15.4–29.4)	22.5 ± 3.3 (15.9–33.4)
Waist circumference, cm, mean ± SD (range)	86.6 ± 8.3 (63.0–104.3)	83.7 ± 11.0 (54.0–111.0)
Visceral fat area, cm^2, mean ± SD (range)	134.8 ± 53.0 (33.2–258.3)	91.2 ± 44.8* (17.5–240.5)
Components of metabolic syndrome, n (%)†		
High blood pressure	50 (79.4)	122 (78.7)
High serum triglycerides	8 (12.7)	15 (9.7)
Low HDL-C	9 (14.3)	33 (21.3)
High blood glucose	21 (33.3)	42 (27.1)
Smoking status, n (%)		
Current	14 (22.6)	8 (5.2)
Former	24 (38.7)	4 (2.6)
Never	24 (38.7)	143 (92.6)
Past history, n (%)		
Cerebral infarction	5 (8.1)	5 (3.2)
Ischemic heart disease	1 (1.6)	6 (3.9)
Medications, n (%)		
Antihypertensive drugs	29 (46.8)	67 (43.2)
Fibrates	0 (0.0)	3 (1.9)
Statins	7 (11.3)	38 (24.5)
Antidiabetic drugs	4 (6.5)	2 (1.3)

* $P < .001$ vs men.

† Components of the metabolic syndrome were diagnosed according to the definition of the International Diabetes Federation: high blood pressure = systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or treatment with antihypertensive drug; high serum triglycerides = fasting serum triglyceride level ≥150 mg/dL or treatment with fibrates; low high-density lipoprotein cholesterol (HDL-C) = serum HDL-C level <40 mg/dL in men and <50 mg/dL in women; high blood glucose = fasting plasma glucose ≥100 mg/dL or treatment with antidiabetic drugs.

SD = standard deviation.

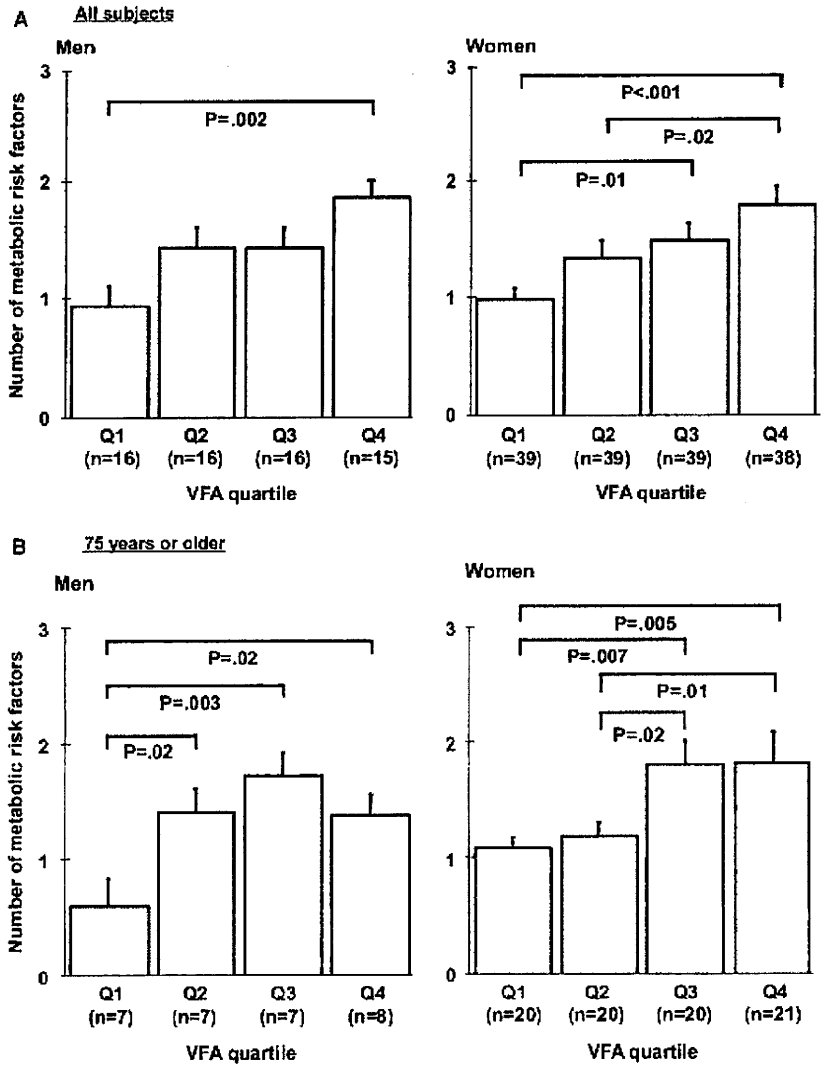

Figure 1. Number of metabolic risk factors according to quartile (Q) of visceral fat area (VFA) in all subjects (A) and subjects aged 75 and older (B). Metabolic risk factors include high blood pressure, high serum triglycerides, low serum high-density lipoprotein cholesterol, and high blood glucose. Data are expressed as means ± standard errors.

women receiving antihypertensive treatment. The prevalence of subjects who had never smoked was markedly higher in women (92.6%) than in men (38.7%).

Figure 1A shows the relationship between VFA and number of metabolic risk factors. The number of risk factors was greater with larger VFA values in men and women. This positive relationship was also observed in subjects aged 75 and older, especially in women (Figure 1B).

Next, multiple regression analysis was performed to detect independent factors for number of metabolic risk factors, using age, VFA, and BMI as independent variables. In men, VFA and in women, VFA and age were positively correlated with number of risk factors (Table 2). BMI was not correlated with number of metabolic risk factors in men or women. Moreover, when waist circumference was added in this multiple regression analysis, VFA was significantly correlated with number of metabolic risk factors in men and women ($P = .02$; data not shown). Waist circumference was not correlated with number of metabolic risk factors in men or women ($P = .85$ in men, $P = .08$ in women; data not shown).

Table 2. Multiple Regression Analysis with Number of Metabolic Risk Factors

Independent Variable	Coefficient (Standard Error)	Standardized Coefficient	P-Value
Men*			
Age	0.012 (0.014)	0.10	.39
VFA	0.006 (0.002)	0.39	.01
BMI	0.055 (0.047)	0.18	.25
Women†			
Age	0.027 (0.011)	0.19	.01
VFA	0.007 (0.002)	0.33	.001
BMI	0.010 (0.028)	0.04	.72

*Correlation coefficient (R) = 0.515, coefficient of determination (R^2) = 0.265, $P < .001$.

†$R = 0.393$, $R^2 = 0.154$, $P < .001$.

VFA = visceral fat area; BMI = body mass index.

Metabolic risk factors indicate components of the metabolic syndrome except abdominal obesity according to the definition of the International Diabetes Federation.

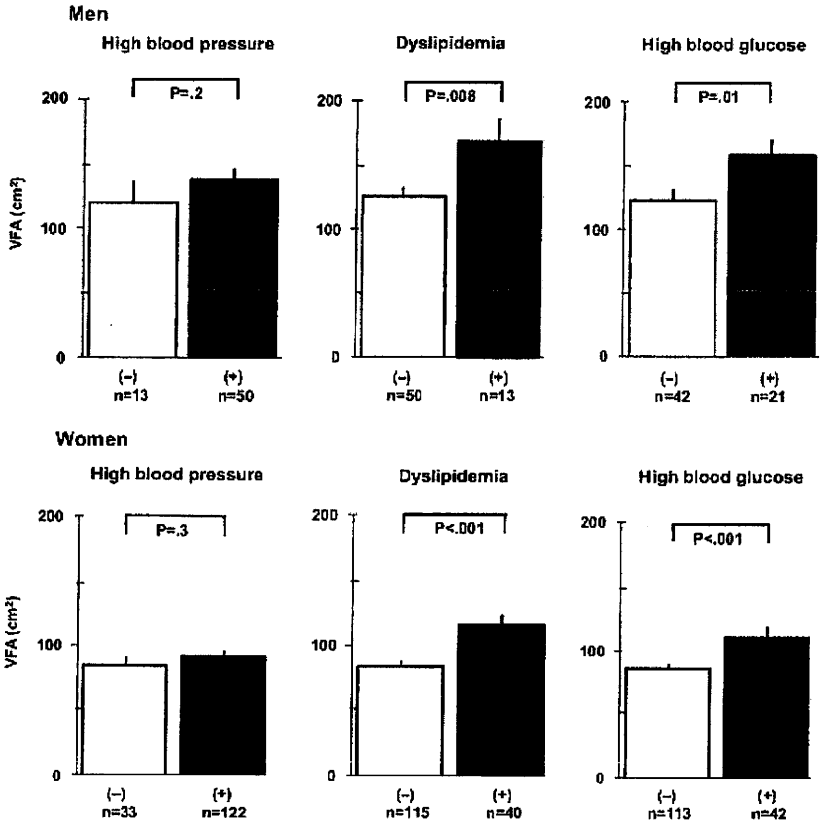

Figure 2. Visceral fat area (VFA) in the absence (–) and presence (+) of each metabolic risk factor. Dyslipidemia includes high triglycerides, low high-density lipoprotein cholesterol, or both. Data are expressed as means ± standard errors.

The relationship between each metabolic risk factor and VFA in elderly subjects was examined. As shown in Figure 2, men and women with dyslipidemia (high triglycerides, low HDL-C, or both) had a significantly greater mean VFA than those without dyslipidemia. Similar results were observed in subjects with and without high blood glucose, although there was no significant difference in VFA between subjects with and without high BP. Changing the cutoff values to 140/90 mmHg from 130/85 mmHg in this analysis made no difference in the results ($P = .25$ in men, $P = .41$ in women; data not shown). A simple regression analysis between VFA and SBP or DBP in subjects not receiving antihypertensive treatment showed no correlation (SBP: $P = .51$ in men, $P = .72$ in women; DBP: $P = .81$ in men, $P = .11$ in women; data not shown).

Finally, a significant negative correlation was observed between VFA and serum adiponectin and a positive correlation between VFA and HOMA-IR in men and women (Figure 3).

DISCUSSION

VFA is associated with metabolic abnormalities, as previously shown in studies of middle-aged populations.[7–9] This association was still observed after adjustment for age and BMI, suggesting that visceral fat accumulation might be a strong risk factor for the metabolic syndrome even in older adults. This association was observed even in subjects aged 75 and older, and VFA was correlated with components of the metabolic syndrome even in subjects who on average had a normal BMI.

Nevertheless, in multiple regression analysis, BMI was not correlated with number of metabolic risk factors in men or women. These results suggest that, for the evaluation of metabolic abnormalities in older adults, VFA is more useful than BMI because BMI in older adults might reflect not only visceral fat mass, but also lower muscle mass and intercellular fluid associated with aging. Thus, because of a reduction of muscle mass with aging, studies that use only BMI would underestimate the health effect of body fatness. Moreover, even if waist circumference was added in this multiple regression analysis, VFA was significantly correlated with number of metabolic risk factors in men and women, but waist circumference was not, suggesting that VFA rather than waist circumference may strongly predict metabolic abnormalities. Data from the Diabetes Prevention Program Research Group showed that visceral adipose tissue predicted the development of type 2 diabetes mellitus better than BMI or waist circumference, but analyses were not limited to older adults (only 20% were ≥60).[18] Thus, it would be important to assess the value of VFA prospectively in predicting the worsening of metabolic risk factors and age-related diseases (e.g., diabetes mellitus and cardiovascular disease).

A strength of this study is the precise assessment of visceral fat according to CT scanning instead of the generally used waist circumference for assessment of abdominal obesity. In many clinical studies, large waist circumference, representing visceral fat accumulation, has been reported to

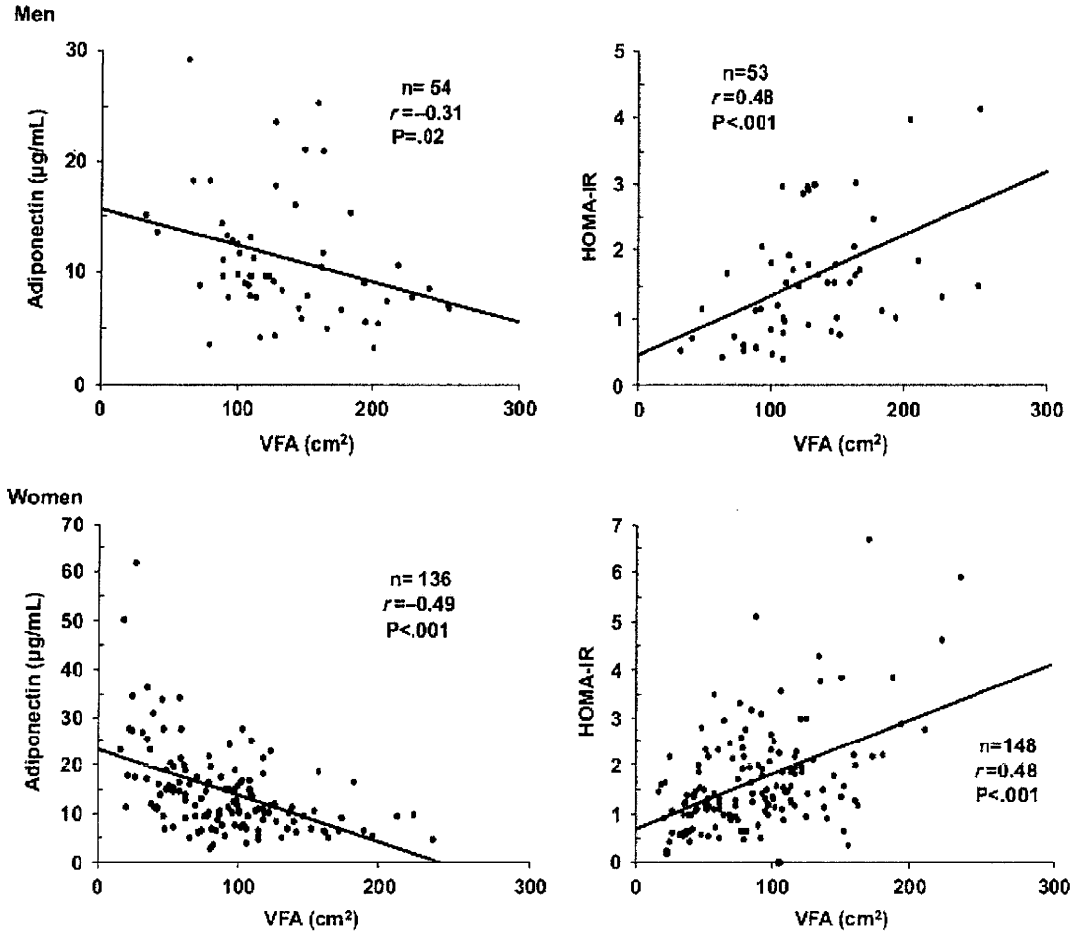

Figure 3. Correlation between visceral fat area (VFA) and serum adiponectin in all subjects and homeostasis model assessment of insulin resistance (HOMA-IR) in older men and women without diabetes mellitus. There was a significant negative correlation between VFA and serum adiponectin and a positive correlation between VFA and HOMA-IR in men and women. r = correlation coefficient.

be associated with greater cardiovascular disease and mortality.[19–21] As the mechanism of this association, it has been proposed that visceral fat accumulation is associated with metabolic abnormalities through insulin resistance and abnormal secretion of adipocytokines.[22,23] This study confirmed that visceral fat accumulation was negatively correlated with serum adiponectin level and positively correlated with insulin resistance as estimated by HOMA-IR in older adults. These findings suggest that older adults with visceral fat accumulation might tend to show metabolic abnormalities through decreased secretion of adiponectin and exacerbation of insulin resistance, similar to middle-aged adults with abdominal obesity.

No association was observed between high BP and VFA. Although the high rate (nearly 80%) of high BP may have affected this result, an additional analysis of this study showed no association between VFA and high BP using a modified cutoff value (140/90 mmHg). Moreover, the simple regression analysis showed no correlation between VFA and SBP or DBP in subjects not receiving antihypertensive treatment. These results suggest that factors other than visceral fat accumulation, such as sclerosis of blood vessels and enhancement of salt sensitivity, both of which are associated with aging, might affect BP in older adults. To the contrary, impaired energy metabolism (e.g., high blood glucose and dyslipidemia) was closely associated with visceral fat accumulation.

It has been reported that weight-reduction therapy using diet, exercise, or both is efficacious in terms of improvement of insulin resistance and dyslipidemia even in older adults.[24,25] Thus, taking together the results of this study and these reports, it appears that the beneficial effects of weight-reduction therapy for older adults even with normal BMI might result from a reduction of visceral fat mass and subsequent improvement in energy metabolism. However, severe dietary therapy for weight reduction is difficult to achieve in elderly patients and has potential risks of causing micronutrient deficiencies,[26–28] generalized weakness, and loss of lean body mass.

There are some limitations of this study. First, because of exclusion criteria, the results of this study might not be generalizable to the general elderly population,. Second, this study did not determine the effects of other body parameters such as subcutaneous fat and nonfat mass on metabolic abnormalities. Third, with the cross-sectional design, causal relationships cannot be established between VFA and metabolic risk factors. Finally, it remains to be determined whether metabolic syndrome in older adults

contributes to cardiovascular events or mortality.[29,30] Confirmation by a large prospective study with precise assessment, such as CT scanning, will be needed to determine whether visceral fat accumulation in older adults directly contributes to cardiovascular events or mortality.

In conclusion, this study suggests that visceral fat accumulation is associated with metabolic risk factor clustering even in older adults with normal BMI. These results provide important insight into the management of metabolic abnormalities in older adults.

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Induction of Endothelial Nitric Oxide Synthase, SIRT1, and Catalase by Statins Inhibits Endothelial Senescence Through the Akt Pathway

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Induction of Endothelial Nitric Oxide Synthase, SIRT1, and Catalase by Statins Inhibits Endothelial Senescence Through the Akt Pathway

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Objective—Statins (3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitors) have pleiotropic vascular protective effects besides cholesterol lowering. Recently, experimental and clinical studies have indicated that senescence of endothelial cells is involved in endothelial dysfunction and atherogenesis. Therefore, the present study was performed to determine whether statins would reduce endothelial senescence and to clarify the molecular mechanisms underlying the antisenescent property of statins.

Methods and Results—Senescent human umbilical vein endothelial cells were induced by hydrogen peroxide (H_2O_2), as judged by senescence-associated β-galactosidase assay and cell morphological appearance. Atorvastatin, pravastatin, and pitavastatin inhibited the oxidative stress induced-endothelial senescence. These statins phosphorylated Akt at Ser473 and subsequently led to increased expression of endothelial nitric oxide synthase (eNOS), SIRT1, and catalase. Treatment with LY294002 or Akt short interfering RNA decreased the eNOS activation, SIRT1 expression, and antisenescent property of atorvastatin. Moreover, in streptozotocin-diabetic mice, administration of pitavastatin increased eNOS, SIRT1, and catalase expression and decreased endothelial senescence, but levels remained unaltered in *Sirt1* knockout mice.

Conclusion—Our results indicate that treatment with statins inhibits endothelial senescence and that enhancement of SIRT1 plays a critical role in prevention of endothelial senescence through the Akt pathway, a direct target of statins. **(*Arterioscler Thromb Vasc Biol.* 2010;30:2205-2211.)**

Key Words: endothelium ■ nitric oxide synthase ■ SIRT1 ■ senescence ■ statin

The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, statins, are effective in lowering the plasma concentration of low-density lipoprotein cholesterol and are widely used in patients with hypercholesterolemia. Recently, experimental and clinical evidence has indicated that the pleiotropic effects of statins involve improvement or restoration of endothelial function, enhanced activity of endothelial nitric oxide synthase (eNOS), and decreased oxidative stress.[1]

Oxidative stress is implicated in the pathogenesis of cardiovascular diseases, such as atherosclerosis.[2] Excessive production of reactive oxygen species inflicts damage on endothelial cells and leads to the onset of endothelial senescence. Senescence of endothelial cells is involved in endothelial dysfunction and atherogenesis.[3] Histological study of human atherosclerotic lesions has demonstrated the existence of endothelial cells that exhibit the morphological features of senescence.[4] Assmus et al have shown that statins reduce senescence and increase proliferation of endothelial progenitor cells.[5]

In *Saccharomyces cerevisiae*, the silent information regulator 2 (*Sir2*) family of genes governs budding exhaustion and replicative life span.[6,7] *Sir2* has been identified as an NAD^+-dependent histone deacetylase and is responsible for maintenance of chromatin silencing and genome stability.[8] *Sir2* genes are conserved during evolution, and 7 homologs of sirtuins (*Sirt1* to *Sirt7*) have been cloned in mammals. Mammalian sirtuin 1 (*Sirt1*), the closest homolog of *Sir2*, regulates the cell cycle, senescence, apoptosis, and metabolism by interacting with a number of molecules, including p53, promyelocytic leukemia (PML), and peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α).[9–11] A recent study has shown that production of NO, stimulated by caloric restriction, increases SIRT1 expression; this study suggests that eNOS may be involved in regulation of the expression of SIRT1 in murine white adipocytes.[12] Importantly, SIRT1 has been recognized as a key regulator of vascular endothelial homeostasis, controlling angiogenesis, endothelial senescence, and dysfunction.[13–15]

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The present study indicated that statins reduced oxidative stress-induced endothelial senescence, and SIRT1 played a critical role in prevention of endothelial senescence through the Akt pathway.

Methods

Materials

Pravastatin, atorvastatin, and pitavastatin were provided by Sankyo Co Ltd, Pfizer Inc (New York, NY), and Kowa Co (Nagoya, Japan), respectively. Mevalonate, geranylgeranylpyrophosphate (GGPP), farnesylpyrophosphate (FPP), Y27632, and LY294002 were purchased from Sigma (St. Louis, Mo). (*Z*)-1-[2-(2-aminoethyl)-*N*-(2-ammonioethyl)amino] diazen-1-IM1,2 diolate (DETA-NO) was from Cayman Chemical (Ann Arbor, Mich).

Cell Culture

Human umbilical vein endothelial cells (HUVEC) were purchased from Cambrex (Walkersville, Md). Population doubling levels were calculated as described previously,[16] and all experiments were performed at a population doubling level of 10 to 11.

Inhibition and Overexpression of SIRT1 and eNOS

Proliferating cells were washed 3 times with growth medium and exposed for 24 hours to the indicated concentrations of sirtinol (Calbiochem) or N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME, Sigma) diluted in medium. Proliferating cells were transfected with 200 pmol/L short interfering RNA (siRNA) for SIRT1 (GAT GAA GTT GAC CTC CTC A[17] and TGA AGT GCC TCA GAT ATT A) using silMPORTER (Upstate Cell Signaling Solutions). siRNAs for Akt, eNOS, PGC-1α, and catalase were purchased from Santa Cruz Biotechnology Inc. The pIRES-SIRT1 plasmid was provided by Dr M. Takata and Dr R.A. Weinberg,[18] and pcDNA3-eNOS plasmid was provided by Dr T Hayashi.[19] SIRT1 and eNOS were overexpressed by transfection using Lipofectamine LTX and PLUS reagents (Invitrogen) for HEK293 cells and jetPEI-HUVEC (Polyplustransfection, Illkirch, France) for HUVEC according to the manufacturer's instructions.

Senescence-Associated β-Galactosidase Staining

HUVEC were pretreated with vehicle (0.05% dimethyl sulfoxide), atorvastatin (50 and 100 nmol/L), pravastatin (50 and 100 nmol/L), or pitavastatin (50 and 100 nmol/L) diluted in EGM-2 medium for 1 day. HUVEC were washed 3 times with EGM-2 and then treated for 1 hour with 100 μmol/L H_2O_2 diluted in EGM-2. After treatment, HUVEC were trypsinized, reseeded at a density of 1×10^5 cells per 60-mm dish, and cultured with EGM-2 containing the above compounds for 10 days. The proportion of SA-βgal-positive cells was determined as described by Dimri et al.[20]

Nitric Oxide Synthase Activation Assay

Nitric oxide synthase (NOS) activity was determined using an NOS assay kit (Calbiochem) according to the manufacturer's instructions.

Antibodies, Immunoprecipitation, and Immunoblotting

Immunoprecipitation of eNOS and SIRT1 was carried out by incubating 2.5 μg of antibody with 1 mg of cell lysate overnight, followed by 40 μL of Sepharose slurry (Amersham, Piscataway, NJ) for 6 hours. After washing, immunoprecipitates were boiled in SDS-PAGE sample buffer. After blocking, the filters were incubated with the following antibodies; anti-phospho-Akt (Ser473), anti-Akt (Cell Signaling Technology), anti-eNOS, anti-SIRT1, anti-mangenese superoxide dismutase (MnSOD), anti-PGC-1α (H-300), anti-catalase (N-17) (Santa Cruz Biotechnology), and anti-β-actin (Sigma).

Real-Time Quantitative Reverse Transcription

Total RNA in HUVEC was isolated with Isogen (Nippon Gene Inc, Toyama, Japan). After treatment with RNase-free DNase for 30 minutes, total RNA (50 ng/μL) was reverse transcribed with random hexamers and oligo(dT) primers. The expression levels of nuclear respiratory factor 1 (NRF-1) and mitochondrial transcription factor A (TFAM) relative to GAPDH were determined by means of staining with SYBR green dye and a LineGene fluorescent quantitative detection system (Bioflux Co, Tokyo, Japan). The following primers were used: NRF-1, forward, 5′-GATGGCACTGTCTCACTTATCC-3′, reverse, 5′-CTGATGCTTGCGTCGTCT-3′; TFAM, forward, 5′-CATCTGTCTTGGCAAGTTGTCC-3′, reverse, 5′-CCACTCCG-CCCTATAAGCATC-3′; GAPDH, forward, 5′-ACCACAGTCCAT-GCCATCAC-3′, reverse, 5′-TCCACCACCCTGTTGCTGTA-3′.

Animal Experiments

The animal experiments were approved by our institutional review board. Twelve-week-old specific pathogen free (SPF) male wild-type B57/BL6 mice (n=40, weighing approximately 29 g) were supplied by Charles River Laboratories Inc. Twelve-week-old *Sirt1*-heterozygous knockout (KO) mice (provided by Dr F.W. Alt, n=14, weighing approximately 25 g), designated *Sirt1* +/−, were generated in a previous study.[21] These mice were randomly assigned to 2 treatment groups (control group, n=20/7; pitavastatin group, n=20/7). Each group received, by oral administration, vehicle alone or pitavastatin 3 mg/kg per day for their lifetimes. We made mice diabetic by a single intraperitoneal injection of streptozotocin (STZ) (60 mg/kg, Sigma). Tail blood glucose level and plasma insulin levels were assayed 3 days after injection using glucose test strips (Roche) and CLEIA. Blood pressure and pulse rate were measured by BP-98A (Softron Co, Tokyo, Japan). The primary antibody was purified rat anti-mouse CD31 (platelet endothelial cell adhesion molecule) monoclonal antibody from Pharmingen (San Jose, CA , USA). TOTO-3 for nuclear staining, secondary antibodies (Alexa Fluor 488 donkey anti-rat IgG and Alexa Fluor 594 donkey anti-rat IgG), and antifade reagent were from Molecular Probes (Invitrogen). Fluorescent images were analyzed using a confocal laser microscope (LSM510, Carl Zeiss MicroImaging Co Ltd).

Data Analysis

Values are shown as mean±SEM in the text and figures. Differences between the groups were analyzed using 1-way analysis of variance followed by the Bonferroni test. Probability values less than 0.05 were considered significant.

Results

Treatment With Atorvastatin, Pravastatin, and Pitavastatin Inhibits Oxidative Stress-Induced Endothelial Senescence

Endothelial senescence was induced by addition of 100 μmol/L H_2O_2 for 1 hour. Treatment with atorvastatin, pravastatin, or pitavastatin inhibited the senescent phenotype at 10 days (Figure 1A and 1B). Mitosis-related growth arrest and reduction of telomerase activity is a critical event for cellular senescence. In parallel with this, an increased rate of 5-bromodeoxyuridine (BrdU) (index of proliferation) incorporation and telomerase activity were restored by treatment with atorvastatin, pravastatin, and pitavastatin (Supplemental Figure IA and IB, available online at http://atvb.ahajournals.org). These results indicate that these statins inhibit oxidative stress-induced endothelial senescence.

Statins prevent mevalonate formation and the downstream products FPP and GGPP, which finally inactivate Rho kinase. To clarify the involvement of these intermediates, we examined the influence of statins on mevalonate, FPP, and GGPP.