Geriatr Gerontol Int 2005; 5: 293–297

Incidence of adverse drug reactions in geriatric units of university hospitals

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Background: Adverse drug reactions (ADR) in elderly people are often attributed to functional decline and polypharmacy.

Methods: In this study, a multi-institutional retrospective survey was undertaken to investigate the current status of ADR in geriatric units of university hospitals. The inpatient databases from 2000 to 2002 for five university hospitals were studied, and a total of 1289 patients were analyzed.

Results: The incidence of ADR, as determined by attending physicians, was 9.2% on average, but varied from 6.3 to 15.8% among the institutions. Factors significantly related to ADR were the number of diagnoses, the number of geriatric syndromes, the number of prescribed drugs, an increase of two or more drugs during hospitalization, longer hospital stay, emergency admission, depression and apathy.

Conclusion: These results are mostly consistent with previous reports and provide important information on drug treatment in elderly people.

Keywords: adverse drug reaction, elderly, medication error.

Introduction

Adverse drug reactions (ADR) in elderly people are common causes of admission to hospitals and are important causes of morbidity and mortality.[1,2] The risk of ADR has been shown to be related to the number of prescribed drugs and elderly people tend to receive more medications than younger people,[3] which are sometimes inappropriately prescribed.[4] Indeed, the risk of ADR is exponentially rather than linearly related to the number of medications taken.[5] Factors that predispose to pharmacological ADR include the dose, drug formulation, pharmacokinetic or pharmacodynamic abnormalities and drug interactions. Frail elderly patients may be more vulnerable because of impaired homeostatic reserve, multiple medication use, cognitive decline and impaired functional status. Drug therapy taking account of safety as well as effectiveness is still needed in the elderly, although there is accumulating evidence on drug therapy in the elderly with hypertension and hyperlipemia.[6]

Although the incidence of ADR for specific drugs can be obtained by large-scale examination and post-marketing surveillance studies by pharmaceutical companies, little data are available on ADR in the elderly as a whole. Previously, we reported the incidence of ADR in inpatients of the geriatric unit of the University of

Accepted for publication 4 July 2005.

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Tokyo Hospital, and showed that drug overdose and polypharmacy are important factors in ADR.[8,9] However, it is necessary to confirm whether similar results are obtained in geriatric units of other hospitals. Therefore, in this study, we analyzed the inpatient databases of five university hospitals with geriatric units, and examined the incidence of ADR and factors related to ADR.

Methods

Subjects

We performed a retrospective investigation of the hospital records of five university hospitals with geriatric units: Kyorin University Hospital, University of Tokyo Hospital, Kyoto University Hospital, Kanazawa Medical University Hospital and Tohoku University Hospital. We surveyed the records of inpatients from January 2000 to December 2002 in these hospitals, and a total of 1289 cases were used for analysis.

Investigation and analysis

We studied the incidence of ADR as judged by attending physicians during hospitalization, along with the number of medications taken on admission and on discharge. We also examined the number of final diagnoses on discharge, the length of hospital stay, age, sex and body weight of each patient, and whether or not the admission was emergent. We investigated the number of geriatric syndromes in the cases at Kyorin University Hospital and the University of Tokyo Hospital and performed comprehensive geriatric assessments (CGA). The 30 most significant of 51 geriatric syndromes are listed in Table 1. The CGA included Barthel Index on admission and discharge to evaluate activities of daily living (ADL), Hasegawa's Dementia Scale-Revised (HDS-R) to assess cognitive function, Geriatric Depression Scale 30-items (GDS-30) to assess depressive mood, and Vitality Index to assess energy.[10]

The data were expressed as means ± SD. The unpaired *t*-test was used to compare the data between two groups, and comparison among multiple groups was performed by ANOVA followed by Newman-Keuls' test. The incidences were compared using the χ^2 test. Correlation was analyzed according to Pearson's correlation coefficient. A value of $P < 0.05$ was considered statistically significant.

Results

Frequency of adverse drug reaction

In the analysis of a total of 1289 cases, the incidence of ADR was 9.2%. We analyzed the incidence at each hospital and found that the lowest incidence was 6.6%, while the highest was 15.8% among the five hospitals studied (Fig. 1).

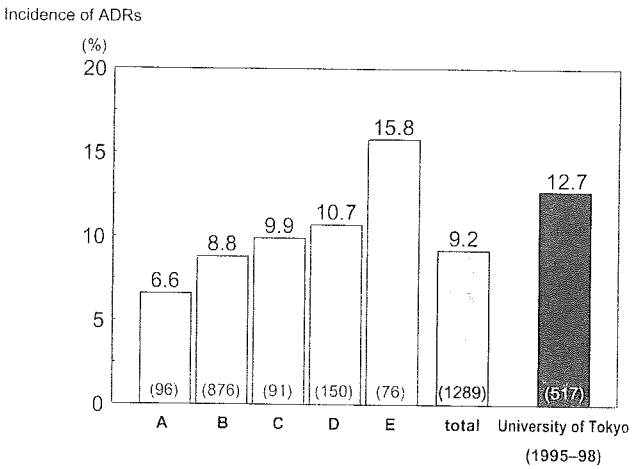

Figure 1 Incidence of ADR in inpatients of geriatric units of five university hospitals. The incidence of ADR in the geriatric unit of University of Tokyo Hospital in 1995–98 is shown as a reference.[9] The numbers of patients surveyed are shown in parentheses.

Table 1 List of major geriatric syndromes

Consciousness disturbance	Chest pain/chest oppression	Edema
Delirium	Palpitation/shortness of breath	Dehydration
Dementia	Arrhythmia	Hearing impairment
Insomnia	Abdominal pain	Motor disturbance
Depression	Constipation	Visual impairment
Dizziness/vertigo	Diarrhea	Back pain
Headache	Body weight loss	Fever
Anemia	Appetite loss	Arthralgia
Pressure ulcers	Nausea/vomiting	Osteoporosis
Falls	Malnutrition	Bleeding tendency
Hemoptysis	Dyspnea	Dysphasia
Urinary incontinence	Pollakisuria	Cough/sputum

Factors related to adverse drug reactions

Background factors related to ADR in cases with or without ADR are summarized in Table 2. There was no significant difference in sex, age or body weight between the two groups. However, patients with ADR had more diagnoses, were taking more drugs on discharge, and stayed longer in hospital than those without ADR ($P < 0.05$). They also showed a tendency to be taking more drugs on admission ($P = 0.08$). When we analyzed the relationship between ADR and the increase in medication during hospitalization, the incidence of ADR in patients with an increase of two or more drugs was 14.4%, which was significantly higher than in those with an increase of one drug (7.9%) and those without an increase (7.8%). Moreover, the incidence of ADR was higher in patients who received emergency admission than in those with scheduled admissions (12.5% vs 7.8%, $P < 0.05$).

The relationship between the factors related to ADR and the variation in ADR among the hospitals was analyzed. In hospital A, where the incidence of ADR was lowest, the number of diagnoses at discharge (2.8 ± 1.1 diseases), number of medications (4.3 ± 1.9 drugs), and the length of hospital stay (28.5 ± 6.8 days) were lowest among the five hospitals. Intriguingly, the mean age of the patients in hospital A was 82 years, while it was 67 years in hospital E, where the incidence of ADR was highest. The mean age of the patients was 71–72 years at other hospitals.

Age was positively correlated with the number of diagnoses ($r = 0.219$, $P < 0.001$) and the number of drugs at discharge ($r = 0.213$, $P < 0.001$), as previously reported.[8,9]

Geriatric syndrome and CGA were analyzed in relation to ADR in the cases at University of Tokyo Hospital and Kyorin University Hospital. The number of geriatric syndromes was significantly higher in patients with ADR than in those without ADR (Table 3). Patients with ADR showed depressed moods and apathy, as assessed by GDS and the Vitality Index, compared to those without ADR, while cognitive function and basic ADL, as assessed by HDS-R and Barthel index, did not differ between the two groups (Table 3).

Table 2 Characteristics of patients with or without adverse drug reactions (ADR)

	ADR (–)	ADR (+)
Number of patients	1170	119
Sex (female, %)	46%	50%
Age (years)	72 ± 14	73 ± 14
Body weight (kg)	56 ± 14	54 ± 14
Number of diagnoses	4.1 ± 2.0	4.9 ± 2.3*
Number of drugs on admission	5.0 ± 3.6	5.7 ± 4.1**
Number of drugs on discharge	5.3 ± 3.3	6.2 ± 3.7*
Length of hospital stay (days)	28 ± 27	38 ± 27*

*$P < 0.01$; **$P = 0.08$ by unpaired t-test.
Data are means ± SD.

Discussion

In this study, we surveyed ADR in the geriatric units of five university hospitals and found that the number of diagnoses, number of geriatric syndromes, number of prescribed drugs, an increase of two or more drugs during hospitalization, longer hospital stay, emergency admission, depression, and apathy were related to the incidence of ADR in elderly inpatients. Our study indicates that the number of diagnoses and drugs would be a better predictor for ADR in the elderly than age.

According to reports on ADR from the USA and Europe, the incidence of ADR in elderly inpatients is 6–15%.[11] The incidence was 1.5–2 fold higher in patients older than 70 years than in patients younger than 60 years. In nursing home residents, the incidence of ADR per year has been reported to be 15–20%.[11] In the outpatient setting, ADR were found in more than 10%

Table 3 Geriatric syndrome and comprehensive geriatric assessment in patients with or without adverse drug reactions (ADR)

	ADR (–)	ADR (+)
Number of geriatric syndromes	4.6 ± 3.8 (866)	6.4 ± 4.7** (85)
Barthel Index on admission	84 ± 28 (854)	80 ± 31 (82)
Barthel Index on discharge	86 ± 27 (840)	85 ± 28 (79)
HDS-R	23.0 ± 8.2 (358)	24.4 ± 6.3 (35)
GDS-30	10.2 ± 6.0 (325)	12.5 ± 6.8* (33)
Vitality index	9.0 ± 2.1 (535)	8.4 ± 2.6* (52)

*$P < 0.05$; **$P < 0.01$ by unpaired t-test. Data are mean ± SD. Numbers in parentheses indicate number of patients studied.
HDS-R, Hasegawa dementia scale-revised; GDS-30, Geriatric depression scale-30 items.

of elderly patients, although the study relied on self-reporting and review of medical records.[11] Only a few studies have been reported in Japan; the incidence was 12.7% in elderly inpatients of the geriatric unit of University of Tokyo Hospital.[9] In the present survey, the average incidence was 9.2%, ranging from 6.6 to 15.8% among facilities, but was similar to that reported previously.[9] Although the incidence varied among hospitals, it is important to note that the incidence of ADR was more than 5% in all hospitals.

Adverse drug reactions were judged by attending physicians in this study, whereas they were determined by objective review of the medical records in addition to judgment by attending physicians in the previous report from the geriatric unit of University of Tokyo Hospital. In the present study, the incidence of ADR in this facility was 8.8%, which was 30% lower than that in our last survey. This difference may be attributable to underestimation by the attending physicians rather than a decrease in ADR over this short period of 3 years. Therefore, if another authorized person judged the ADR strictly, the overall incidence rate might have been slightly higher.

Our results on the incidence of ADR in elderly patients may add important information. However, all the facilities in this survey were geriatric units of university hospitals, where most of the inpatients were older than 65 years and the doctors in those units are careful in prescribing medication to elderly patients. Therefore, our data might not be directly applicable to elderly patients in other hospitals or units. In fact, ADR were found in nearly half of elderly inpatients of the neuropsychiatry unit of University of Tsukuba Hospital (unpubl. obs, Mizukami *et al.*). In addition, our data in university hospitals, which are acute care hospitals, might not be applicable to chronic care facilities such as long-term care facilities. Since the introduction of the fixed payment system, Diagnosis Procedure Combination system, to university hospitals in Japan in 2003, drug treatment in university hospitals might be changing in the future. Therefore, the incidence of ADR in various types of hospitals in Japan needs to be studied.

In this study, depression and apathy were found to be associated with ADR in addition to the accumulation of diseases and geriatric syndromes, polypharmacy, an increase of prescribed drugs during hospitalization, longer hospital stay and emergency admission. This result is consistent with other reports.[9] However, the causal relationship remains unknown. A higher number of diseases or geriatric syndromes can lead to an increase in ADR through polypharmacy[8,9] while ADR themselves may increase diseases or geriatric syndromes. Similarly, longer hospital stays can increase the risk of ADR, while ADR prolong the duration of hospitalization. The latter point is critical to medical economics as well. Age was not associated with ADR in this study, inconsistent with other studies. This might be due to effects of education on pharmacotherapy in elderly patients for several years at university hospitals. Although we did not analyze the types or classes of ADR in this survey, it has been reported that severe ADR such as neuropsychiatric disorders or cardiovascular injury occur in elderly patients.[9]

Recently, evidence has been accumulating on drug therapy in the elderly. However, there are very few data available in people aged 75 years and older or in frail elderly people. Therefore, it is necessary to establish the safety and effectiveness of drug therapy in these patients in the future. Evidence-based medicine in the elderly aims to discontinue unnecessary drugs and to avoid polypharmacy. On the other hand, a fixed payment system such as the long-term care insurance system in Japan forces doctors to reduce prescribed drugs from a business viewpoint. Indeed, it has been reported that 0.6 drugs were on average discontinued within a month after admission to long-term care facilities, although adverse drug withdrawal events were very few.[12] Because minimally prescribed drugs have not increased ADR in patients with dementia and a low capacity for medication management,[13] it is necessary to cut down unnecessary drugs in frail elderly patients based on evidence-based medicine. In the USA, Beers' criteria are available to identify potentially inappropriate medication use, in order to reduce drug-related problems.[14] In Japan, however, we do not have such guidelines for drug treatment in the elderly. Because the drugs and medical situation in Japan are different from those in the USA, we need to establish our own guidelines, which will be published this year. In addition, we need to accumulate clinical evidence to support the guidelines. We also need to utilize pharmacists more efficiently, because they are an underused resource in avoiding medication errors and can provide important safeguards for elderly patients in hospitals and nursing homes.

Elderly patients are exposed to more medications and have an increased risk of ADR, many of which are avoidable. Knowledge of pharmacological principles and age-related effects on pharmacokinetics/pharmacodynamics is essential to promote safe prescribing. Other factors related to ADR such as polypharmacy, long admission and depression should also be evaluated during hospitalization.

Acknowledgments

This study was supported by a Research Grant for Longevity Sciences from the Ministry of Health, Labor, and Welfare, Japan.

References

1 Cunningham G, Dodd TR, Grant DJ, McMurdo ME, Richards RM. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention

and subsequent reassessment. *Age Ageing* 1997; **26**: 375–382.
2 Mannesse CK, Derkx FH, de Ridder MA, Man in't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. *Age Ageing* 2000; **29**: 35–39.
3 Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. *Age Ageing* 1980; **9**: 73–80.
4 Straand J, Rokstad KS. Elderly patients in general practice: diagnoses, drugs and inappropriate prescriptions. A report from the More & Romsdal Prescription Study. *Fam Pract* 1999; **16**: 380–388.
5 Carbonin P, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? *J Am Geriatr Soc* 1991; **39**: 1093–1099.
6 Horiuchi H, Kita T, Mabuchi H *et al.* Primary cardiovascular events and serum lipid levels in elderly Japanese with hypercholesterolemia undergoing 6-year simvastatin treatment: a subanalysis of the Japan lipid intervention trial. *J Am Geriatr Soc* 2004; **52**: 1981–1987.
7 Hiwada K, Ogihara T, Morimoto S *et al.* [Guidelines on treatment of hypertension in the elderly – 1999 revised version. A comprehensive study on geriatric science by the Ministry of Health and Welfare. A Section for the 'Study on Long-Term Prognosis of Hypertension among the Aged'.] *Jpn J Geriat* 1999; **36**: 576–603. (In Japanese.)
8 Akishita M, Ouchi Y, Toba K *et al.* [Compliance with prescriptions and adverse drug reactions in the elderly.] *Jpn J Geriat* 1995; **32**: 178–182. (In Japanese.)
9 Toba K, Akishita M, Mizuno Y *et al.* [Adverse drug reaction in the elderly.] *Jpn J Geriat* 1999; **36**: 181–185. (In Japanese.)
10 Toba K. [Who watch and how to improve quality of long-term residential care in Japan? – it is a role of geriatrician.] *Jpn J Geriat* 1997; **34**: 981–986. (In Japanese.)
11 Rothschild JM, Bates DW, Leape LL. Preventable medical injuries in older patients. *Arch Intern Med* 2000; **160**: 2717–2728.
12 Mita Y, Akishita M, Tanaka K *et al.* Improvement of inappropriate prescribing and adverse drug withdrawal events after admission to long-term care facilities. *Geriatr Gerontol Int* 2004; **4**: 146–150.
13 Akishita M, Toba K, Nagano K, Ouchi Y. Adverse drug reactions in older people with dementia. *J Am Geriatr Soc* 2002; **50**: 400–401.
14 Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly. An update. *Arch Intern Med* 1997; **157**: 1531–1536.

0021-972X/05/$15.00/0
Printed in U.S.A.

The Journal of Clinical Endocrinology & Metabolism 90(7):4035–4040

doi: 10.1210/jc.2004-2092

A Single Bout of Exercise at Higher Intensity Enhances Glucose Effectiveness in Sedentary Men

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Objective: Previous studies have shown that glucose effectiveness and insulin sensitivity are acutely enhanced by exercise at various intensities. The aim of this study was to determine the effects of a single bout of exercise at intensities recommended by the American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) on glucose uptake-specific glucose effectiveness (S_G^{2*}) and insulin sensitivity (S_I^{2*}). S_G^{2*} and S_I^{2*} were estimated by a two-compartment minimal model.

Design: Six healthy men (age, 28.5 ± 2.0 yr) performed a stable-labeled frequently sampled iv glucose tolerance test (FSIGT) under three separate conditions: without any prior exercise, and immediately after single 20-min bouts of cycle ergometer exercise at an intensity of 50% and 70% of maximal oxygen uptake ($\dot{V}O_{2max}$). The exercise intensities were close to the lower and upper boundaries recommended by the ADA and ACSM.

Results: Glucose disappearance constant (K_G), S_G^{2*}, and S_I^{2*} increased after exercise in an intensity-dependent manner. Increases in S_G^{2*} (+237.1 ± 50.5%), S_I^{2*} (+225.6 ± 51.9%), and K_G (+151.7 ± 16.5%) following exercise at 70% $\dot{V}O_{2max}$ were statistically significant ($P < 0.05$), whereas those at 50% $\dot{V}O_{2max}$ were not.

Conclusions: In conclusion, a single bout of exercise acutely improves S_I^{2*} and S_G^{2*} in individuals with normal glucose tolerance in an intensity-dependent manner. (***J Clin Endocrinol Metab* 90: 4035–4040, 2005**)

EXERCISE IS WELL known to improve glucose tolerance through its acute and chronic effects (1). Effectiveness of exercise prescription has been proposed not only for obesity, hypertension, and hypertriglyceridemia, but also for diabetes mellitus. For individuals with type 2 diabetes mellitus, exercise intensities between 50 and 70% of maximal oxygen uptake ($\dot{V}O_{2max}$) have been recommended by the American Diabetes Association (ADA) (2). The American College of Sports Medicine (ACSM) also recommends a range of exercise intensities corresponding to 50–85% of $\dot{V}O_{2max}$ as a standard guideline for adequate glycemic control (3).

Insulin sensitivity was found to increase after a single bout of exercise at 85% of maximal theoretic heart rate (HR) (70–80% $\dot{V}O_{2max}$, as predicted by age) at 70% $\dot{V}O_{2max}$ and at 150 W (64 ± 1% $\dot{V}O_{2max}$) (4–6). However, relatively mild exercise at lactate threshold (LT) (45.4 ± 3.1% $\dot{V}O_{2max}$) did not improve insulin sensitivity (7). In addition to insulin sensitivity, overall glucose tolerance is influenced by glucose effectiveness, which is the combined ability of glucose *per se* to stimulate its own uptake and suppress its own production (8–10). Applying minimal model analysis of an iv glucose tolerance test, it has been demonstrated that glucose effectiveness is enhanced after a single bout of exercise at 45% and 70–80% $\dot{V}O_{2max}$ levels (4, 7). Thus, exercise at recommended intensity levels is hypothesized to acutely enhance both insulin sensitivity and glucose effectiveness.

Minimal model analysis has been widely used to assess both insulin sensitivity and glucose effectiveness. However, this classical method could not single out the estimates of glucose uptake alone from the combined ability of insulin or glucose *per se* to stimulate glucose uptake and suppress glucose production (11–15). A recently proposed stable-labeled two-compartment minimal model enabled us to single out the estimates of the glucose uptake-specific insulin sensitivity (S_I^{2*}) and glucose effectiveness (S_G^{2*}) (16, 17). The purpose of the present study was to investigate the effects of a single bout of exercise on S_G^{2*} and S_I^{2*} at two different levels of exercise intensity within the recommended ranges suggested by the ADA and ACSM.

Subjects and Methods

Subjects

Six healthy men (23–35 yr old) participated in this study. Physical characteristics of these participants are listed in Table 1. All participants were healthy and relatively active only during their leisure time. Before the onset of the study, the nature, purpose, and risk of the study were

First Published Online April 19, 2005

Abbreviations: AMPK, AMP-activated protein kinase; EGP, endogenous glucose production; FSIGT, frequently sampled iv glucose tolerance test; GLUT-4, glucose transporter-4; HR, heart rate; LT, lactate threshold; RPE, rating of perceived exertion; S_G^{2*}, glucose uptake-specific glucose effectiveness; S_I^{2*}, glucose uptake-specific insulin sensitivity; $\dot{V}_E$, ventilation; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_{2max}$, maximal oxygen uptake; VT, ventilatory threshold.

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TABLE 1. Characteristics of the participants at baseline

Characteristic	Value
Age (yr)	28.5 ± 2.0
Height (cm)	173.7 ± 2.5
Weight (kg)	69.1 ± 2.4
Body mass index (kg/m^2)	22.9 ± 0.5
Body fat (%)	21.2 ± 1.9
$\dot{V}O_{2max}$ (ml/kg/min)	45.2 ± 2.7
O_2 uptake at VT (ml/kg/min)	22.9 ± 1.3 (50.7 ± 3.0% $\dot{V}O_{2max}$)
50% $\dot{V}O_{2max}$ (ml/kg/min)	22.6 ± 1.3
70% $\dot{V}O_{2max}$ (ml/kg/min)	31.6 ± 1.9
Workload at maximal work load (W)	245.0 ± 16.7
Workload at VT (W)	115.0 ± 11.4
Workload at 50% $\dot{V}O_{2max}$ (W)	107.5 ± 9.8
Workload at 70% $\dot{V}O_{2max}$ (W)	155.0 ± 12.0

Values are means ± SE; n = 6 participants.

fully explained to all participants, and informed written consent was obtained. All individuals were free from diabetes, and none were taking any medications. All participants were asked not to change their normal dietary habits, and not to change their levels of spontaneous physical activity. The protocol was approved by the local ethical committee of the Jichi Medical School and was conducted in accordance with the Helsinki Declaration.

Preliminary testing

Before starting the experimental program, the participants underwent a symptom-limited graded exercise test. After a 2-min warm-up exercise on a Monark cycle ergometer (818E, Monark, Stockholm, Sweden) at 0 W, the power output was set at 15 W and then increased 15 W every minute until the participant demonstrated symptoms for termination of the exercise test (3). For detection of $\dot{V}O_{2max}$ and ventilatory threshold (VT), oxygen consumption ($\dot{V}O_2$), carbon dioxide production, and ventilation ($\dot{V}E$) were measured by standard techniques of open-circuit spirometry using Mijnhardt Oxycon System (Oxycon-alpha, Bunnik, The Netherlands) during the exercise test. $\dot{V}O_{2max}$ was chosen as the highest $\dot{V}O_2$ value in the series of minute-by-minute $\dot{V}O_2$ values. VT was determined as a nonlinear increase in $\dot{V}E$ when plotted against $\dot{V}O_2$ or a simultaneous breakpoint in $\dot{V}E/\dot{V}O_2$ and the partial pressure of oxygen in end-tidal expired air (18). Calculation of carbohydrate oxidation rates was assessed from gas exchange measurements according to the nonprotein respiratory quotient technique (19). The values were then converted into kilocalories.

Experimental design

Participants consumed a diet containing 58.5 ± 0.8% carbohydrate, 14.5 ± 0.3% protein, and 27.2 ± 0.6% fat calories on 3 consecutive days previous to each frequently sampled iv glucose tolerance tests (FSIGT). A 12- to 13-h fast was imposed on the participants. They were admitted to the hospital one night before each FSIGT and woke up at 0700 h.

At 0800 h, the participants rested in a sitting position for 30 min. The participants then exercised on a cycle ergometer for 30 min (from 0830–0900 h) at a workload of either 107.5 ± 24.0 W or 155.0 ± 29.5 W on separate days that elicited 53.9 ± 6.1% and 74.6 ± 8.2% of $\dot{V}O_{2max}$, respectively. These intensities correspond to the "moderate" and "hard" intensities according to the most recent position statement by the ADA (20), and both are within the ACSM-recommended range of exercise intensities for diabetes mellitus (3). In this study, we adopted 30 min as the exercise time based on recommendations of the ADA (2) and ACSM (3). Throughout each exercise of 50% $\dot{V}O_{2max}$ and 70% $\dot{V}O_{2max}$, expiratory gases of the participants were sampled breath-by-breath and averaged over 30 sec. All metabolic measurements of expiratory gases were determined by the same respirometry system. HR was recorded at every 1-min interval during exercise. The participants were asked to provide their ratings of perceived exertion (RPE) every 2 min during exercise using the 15-point Borg scale (21).

The FSIGT was performed three times with an interval of at least 1 wk between tests: 1) 30 min after the exercise at 50% $\dot{V}O_{2max}$, 2) 70% $\dot{V}O_{2max}$, and 3) without any prior exercise (nonexercise trial). These three trials were randomly assigned to each participant.

FSIGT

Each FSIGT started at 0930 h (min 0) regardless of exercise, as previously described (22). In brief, four baseline samples were taken at min −20, −10, −3, and immediately before the glucose injection from an antecubital vein in one arm, which was kept in a radiant warmer at 70 C to provide an arterialized blood source. In our experience, the procedure to warm the sampling arm guarantees taking blood samples from well-mixed circulation as assumed in minimal model analysis. Glucose isotopically labeled with [6,6-$^2H_2$]glucose (Aldrich, Milwaukee, WI) was then administered in the contralateral antecubital vein (300 mg/kg body weight) within 1 min, and subsequent blood samples for glucose and insulin were taken until min 180. Regular insulin (Humulin; Shionogi, Osaka, Japan) was administered from min 20–25 at doses of 20 mU/kg (nonexercise trial), 16.5 ± 1.6 mU/kg (50% $\dot{V}O_{2max}$ trial), and 13.8 ± 2.0 mU/kg (70% $\dot{V}O_{2max}$ trial), respectively. Because insulin sensitivity is known to increase after a bout of exercise, the doses of insulin injection after the exercise trials were individually reduced to minimize hypoglycemia, considering the results of previous FSIGTs in the present study.

Analytic methods of glucose

Plasma glucose concentrations were measured in triplicate using the glucose oxidase method. The immunoreactive insulin levels were measured in duplicate using a Phadeseph insulin RIA kit (Shionogi). Deuterated glucose was analyzed as a pentaacetate derivative by use of the method of Wolfe, as previously described (23, 24). The measurement error associated with the labeled glucose measurement was assumed to be independent, and Gaussian, with a zero mean and a coefficient of variation of 3.0%.

Calculations of S_G^{2*} and S_I^{2*}

The indices of S_G^{2*} and S_I^{2*} specific for glucose uptake were estimated by a two-compartment minimal model (16, 17). Endogenous glucose production (EGP) was estimated by nonparametric deconvolution (16). The insulin area above the basal during 10 and 20 min immediately after the administration of glucose was calculated according to a previously described method (25). The glucose disappearance constant (K_G) was calculated as the slope of the least squares regression line related to the natural logarithm of the glucose concentration to the time when samples were drawn between min 10–19 after glucose load.

Statistics

All values are shown as the means ± SE. Data were analyzed using the SPSS for Macintosh package (SPSS, Inc., Chicago, IL). Statistical comparisons of percent $\dot{V}O_{2max}$, HR, glucose, insulin, exogenous glucose, endogenous glucose, and EGP among nonexercise, 50% $\dot{V}O_{2max}$, and 70% $\dot{V}O_{2max}$ trials over time were performed by a mixed design two-way ANOVA with repeated measures. After significant interactions, one-way ANOVA were employed each time (28 points) to compare and contrast the effect of trials. If a significant difference was detected, these were further evaluated by *post hoc* Tukey's test and a Bonferroni-corrected 95% confidence interval. The comparison of energy expenditure from carbohydrate oxidation and average of RPE during 30 min exercise between the 50 and 70% $\dot{V}O_{2max}$ trials was performed using Student's *t* test. A one-way ANOVA was used to test for statistically significant differences in S_G^{2*}, S_I^{2*}, insulin area, K_G, and basal EGP among the three trials. When appropriate, Tukey's test and a Bonferroni-corrected 95% confidence interval were used *post hoc*. Statistical significance was set at $P < 0.05$.

Results

Measurements during a single bout of exercise

Mixed design two-way ANOVA with repeated measures for percent $\dot{V}O_{2max}$ and HR showed significant trial-by-time

interactions as well as three trials and time effects. The average values of absolute work rate performed during the 50% and 70% $\dot{V}o_{2max}$ trials were 107.5 ± 9.8 and 155.0 ± 12.0 W, which corresponded to 53.9 ± 6.1% and 74.6 ± 8.2% $\dot{V}o_{2max}$, respectively. HR increased progressively to 133.0 ± 17.3 and 165.0 ± 17.6 beats per minute at the end of the 50% and 70% $\dot{V}o_{2max}$ trials, respectively. Average RPE during the 70% $\dot{V}o_{2max}$ exercise (14.7 ± 0.9) was significantly higher ($P < 0.05$) than during 50% $\dot{V}o_{2max}$ (12.8 ± 0.8). An energy expenditure by carbohydrate oxidation during the 70% $\dot{V}o_{2max}$ trial (397.6 ± 66.6 kcal) was 68% greater ($P < 0.05$) than the 50% $\dot{V}o_{2max}$ trial (236.8 ± 36.7 kcal). During and after the exercise, nobody reported chest pain and extreme fatigue.

FSIGT

The plasma glucose, insulin, exogenous glucose, and endogenous glucose during FSIGT in three trials are illustrated in Fig. 1. According to mixed design two-way ANOVA with repeated measures for the plasma concentrations of glucose, insulin, exogenous glucose, and endogenous glucose, trial-by-time interactions as well as a trial effect were significant in the 70% $\dot{V}o_{2max}$ trial but not significant in the 50% $\dot{V}o_{2max}$ trial. The plasma glucose concentration was significantly lower in the 70% $\dot{V}o_{2max}$ trial than the nonexercise trial from min 10–33, respectively. As can be seen in Fig. 1A, plasma glucose in the 70% $\dot{V}o_{2max}$ trial returned to the basal level at min 36 in the experiment. Plasma glucose in the 50% $\dot{V}o_{2max}$ trial returned to the basal level at min 40, and in the nonexercise trial it came back to the basal level at min 50. The plasma insulin at min 24 during FSIGT was significantly lower in the 70% $\dot{V}o_{2max}$ trial than the nonexercise and 50% $\dot{V}o_{2max}$ trials (Fig. 1B). The exogenous and endogenous glucose concentrations were significantly lower in the 70% $\dot{V}o_{2max}$ trial than the nonexercise trial from 14–33 min and from 3–33 min, respectively (Fig. 1, C and D). Endogenous glucose concentration during the last 120 min of FSIGT was higher in the 50% and 70% $\dot{V}o_{2max}$ trials than the nonexercise trial, but the differences were not statistically significant.

Minimal model analysis

Among the nonexercise, 50% $\dot{V}o_{2max}$ and 70% $\dot{V}o_{2max}$ trials, a significant main effect was demonstrated by an intensity-dependent increase in S_I^{2*}, S_G^{2*}, and K_G, respectively (Table 2). The S_I^{2*} was significantly higher in the 70% $\dot{V}o_{2max}$ trial than the nonexercise trial, whereas S_G^{2*} in the 70% $\dot{V}o_{2max}$ trial was significantly higher than the other two trials.

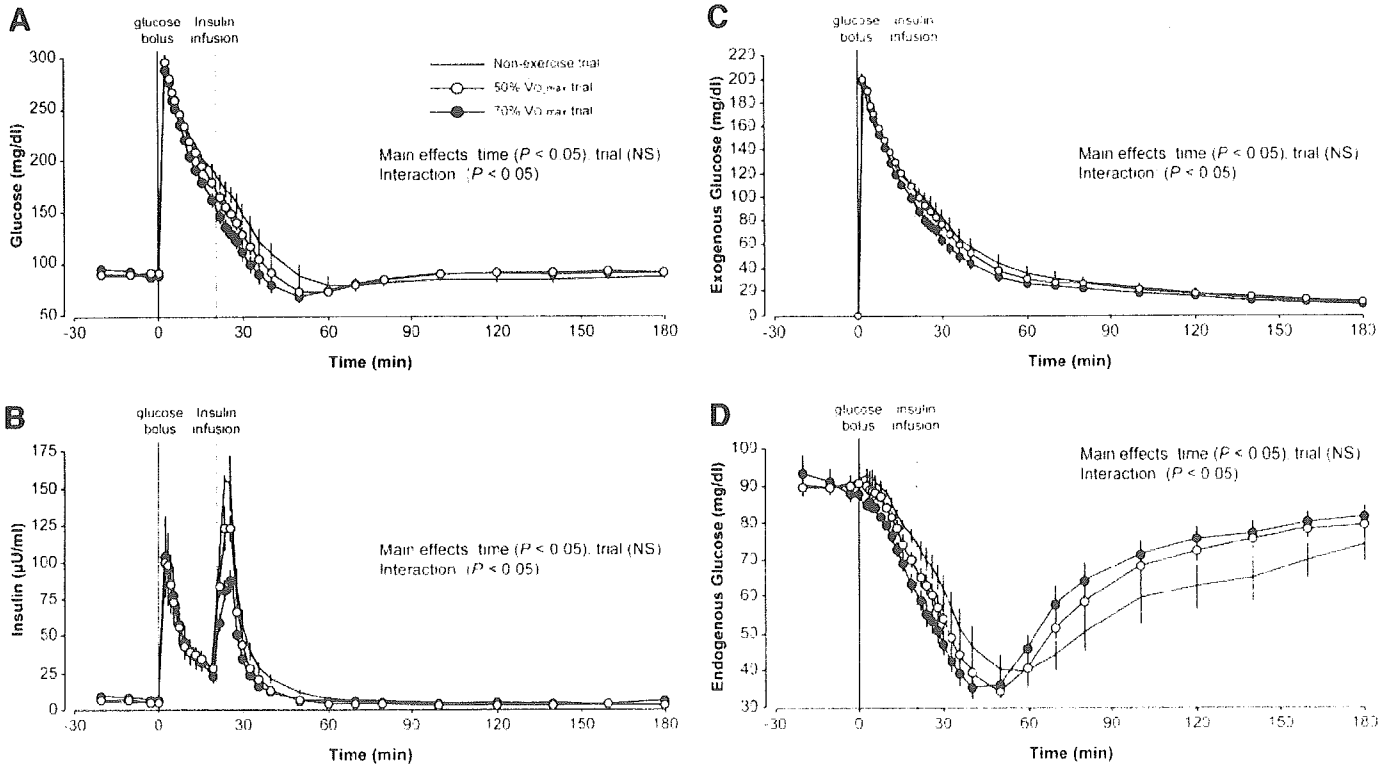

FIG. 1. Time courses of plasma glucose (A), insulin (B), exogenous glucose (C), and endogenous glucose (D) concentration during the iv glucose tolerance test under control (nonexercise trial) and after 50% (50% $\dot{V}o_{2max}$ trial) and 70% $\dot{V}o_{2max}$ (70% $\dot{V}o_{2max}$ trial) exercise. *Vertical dotted line* indicates the initiation of insulin infusion. Main effects for time, trials, as well as time by trial interaction are indicated in each subpanel. Values are means ± SE. A, Plasma glucose concentration in 70% $\dot{V}o_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 10, 12, 14, 16, 19, 22, 24, 26, 28, 30, and 33. B, Plasma insulin concentration in 70% $\dot{V}o_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 10, 22, 24, 26, 28, 30, 33, 36, 40, and 50 and with 50% $\dot{V}o_{2max}$ trial at 24 min. Also, the plasma insulin concentration in 50% $\dot{V}o_{2max}$ trial was significantly lower as compared with nonexercise trial at min 24. C, Exogenous glucose concentration in 70% $\dot{V}o_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 14, 16, 19, 22, 24, 26, 28, 30, and 33. D, Endogenous glucose concentration in 70% $\dot{V}o_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 26, 28, 30, and 33.

TABLE 2. Metabolic parameters of participants

	Nonexercise trial	50% $\dot{V}O_{2max}$ trial	70% $\dot{V}O_{2max}$ trial
S_G^{2*} [$\times 10^2$ dl/kg/min]	0.53 ± 0.12	0.72 ± 0.08	1.02 ± 0.11[a,b]
S_I^{2*} [$\times 10^4$ dl/kg/min/(μU/ml)]	9.36 ± 1.24	13.61 ± 1.37	18.34 ± 3.20[a]
Insulin area (μU/ml/min)			
0–10 min	600.2 ± 92.5	604.0 ± 68.0	610.2 ± 151.4
0–20 min	887.4 ± 131.9	903.5 ± 100.3	887.8 ± 196.1
K_G (%/min)	2.40 ± 0.28	2.98 ± 0.20	3.48 ± 0.30[a]
Basal EGP (mg/kg/min)	1.49 ± 0.10	1.65 ± 0.06	1.90 ± 0.11[a]

Values are means ± SE; n = 6 participants.
[a] Significantly different from nonexercise trial, $P < 0.05$.
[b] Significantly different from 50% $\dot{V}O_{2max}$ trial, $P < 0.05$.

K_G was also significantly greater in the 70% $\dot{V}O_{2max}$ trial than the nonexercise trial. The integrated area of plasma insulin during the first 10 and 20 min remained unchanged among the three trials.

EGP

Basal EGP in the 70% $\dot{V}O_{2max}$ trial (1.90 ± 0.11 mg/kg/min) was significantly higher than that in the nonexercise trial (1.49 ± 0.10 mg/kg/min), but did not differ from that in the 50% $\dot{V}O_{2max}$ trial (1.65 ± 0.06 mg/kg/min) (Table 2). After the glucose bolus, EGP was similarly suppressed, followed by its overshoot (Fig. 2). EGP at around 70 min in the experiment tended to be higher in the 50% and 70% $\dot{V}O_{2max}$ trials than the nonexercise trial ($P = 0.056$).

Discussion

In this study, workloads corresponding to 50% and 70% $\dot{V}O_{2max}$ in a symptom-limited graded exercise test were adopted as a target exercise intensity. Oxygen uptake throughout the 30-min constant-load exercise averaged 53.9 ± 2.5% and 74.6 ± 3.3% $\dot{V}O_{2max}$ at 50% and 70% $\dot{V}O_{2max}$ intensities, respectively. This indicates that the participants exercised approximately at our intended target intensities. The major finding of the present study was that both S_G^{2*} and S_I^{2*}, glucose uptake-specific indices analyzed by a two-compartment minimal model, were enhanced immediately after a single bout of exercise in an exercise intensity-dependent manner. Nearly 2-fold increases in S_G^{2*} and S_I^{2*} after the exercise at the 70% $\dot{V}O_{2max}$ were statistically significant, whereas the changes at 50% $\dot{V}O_{2max}$ were modest.

Applying an original minimal model approach, several previous studies evaluated an acute effect of exercise on glucose effectiveness. Brun *et al.* (4) reported that glucose effectiveness and insulin sensitivity markedly increased at min 25 after 15-min hard exercise at 85% of estimated maximum HR that corresponded to about 70–80% $\dot{V}O_{2max}$, as predicted by age. Sakamoto *et al.* (7) observed a significant increase in glucose effectiveness without improvement of insulin sensitivity 25 min after 60 min of mild exercise at LT intensity (45.4 ± 3.1% $\dot{V}O_{2max}$). Using the stable-labeled two-compartment minimal model, the present study demonstrated that the exercise at 70% $\dot{V}O_{2max}$ level improved S_I^{2*} and S_G^{2*}.

It is worth mentioning that the effects of acute exercise analyzed by minimal model approach require cautious interpretation. First, additional insulin infusion is imposed on endogenous insulin secretion to estimate the minimal model parameters accurately, and the dose of insulin was empirically reduced to avoid hypoglycemia after a bout of exercise. The effect of insulin dose on insulin sensitivity and glucose effectiveness estimated by the minimal model technique has been evaluated (26, 27). According to studies on a "single"-compartment minimal model, lower dose of insulin resulted in higher insulin sensitivity and lower glucose effectiveness. The effect of insulin dynamics on the glucose effectiveness is most likely a consequence of single-compartment undermodeling. Monte Carlo simulation on a "two"-compartment model of glucose kinetics with various insulin response patterns revealed that glucose effectiveness is influenced by the early insulin response (0–20 min) but not by the late one (20–180 min) (28). The early insulin response remained unchanged irrespective of exercise in the present study. Col-

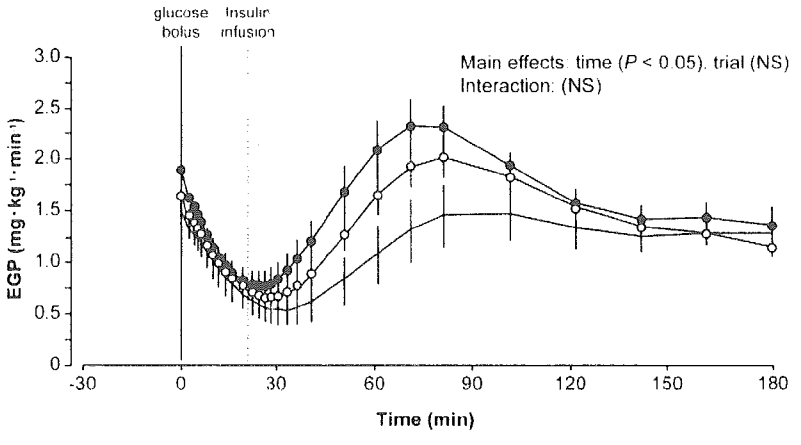

FIG. 2. Time course of EGP during the iv glucose tolerance test under control (nonexercise trial) and after 50% (50% $\dot{V}O_{2max}$ trial) and 70% $\dot{V}O_{2max}$ (70% $\dot{V}O_{2max}$ trial) exercise. *Vertical dotted line* indicates the initiation of insulin infusion. Values are means ± SE.

lectively, the present finding of the increased S_G^{2*} after a single bout of exercise seems robust against the use of variable dose of exogenous insulin, whereas the increased S_I^{2*} after exercise may, at least partly, reflect the reduced dose of exogenous insulin.

Secondly, an inherent assumption of parameter estimation of the model is that its parameters are constant during the FSIGT, although it is uncertain whether this assumption holds during the 3-h period after a bout of exercise. In fact, muscle glucose transport (29) and AMP-activated protein kinase (AMPK) activity (30, 31) can be changed during the FSIGT, depending on insulin dose and/or exercise intensity. In the present study, a 30-min interval was set between the end of exercise and FSIGT. As a result, plasma concentrations of glucose and insulin immediately before the glucose bolus were comparable among the three trials ($P > 0.1$), suggesting that the changes in glucose and insulin kinetics induced by a bout of exercise were restored in part to resting levels. In addition, minimal model analysis of exogenous glucose, which was simulated by increases in S_G^{2*} and S_I^{2*} through changing parameters (k_{21}, k_{12}, k_{02}, k_b, k_s, and v_1 in Ref. 17) in linear or stepwise manner *in silico*, resulted in enhanced S_G^{2*} and S_I^{2*}. Therefore the results of the present study suggest that S_G^{2*} and S_I^{2*} were increased after a bout of exercise.

Glucose effectiveness and insulin sensitivity seem to be separately regulated and functionally distinct (10). Insulin-stimulated recruitment of glucose transporter (GLUT-4) to the plasma membrane and activation of glycogen synthase in muscle are the major mechanisms responsible for the enhanced insulin-stimulated glucose transport and metabolism (32). In contrast, the physiological basis for the effect of exercise on glucose effectiveness remains vague, although several factors have been proposed. First, muscle contraction stimulates AMPK, particularly its α2 isoform, which induces translocation of GLUT-4 to the plasma membrane and enhances cellular glucose uptake (33–35). Recent studies have provided evidence that the activation of α2-AMPK by muscle contraction depends on exercise intensities. Activity of skeletal muscle α2-AMPK was 3- to 4-fold higher immediately after high-intensity exercise (75% $\dot{V}o_{2max}$ for 60 min), whereas no activation was observed after low-intensity exercise (50% $\dot{V}o_{2max}$ for 90 min) (30). Similarly, the effect of exercise intensity on α2-AMPK activity was examined by 20-min cycle ergometer exercise at low (40 ± 2% $\dot{V}o_2$ peak), medium (59 ± 1% $\dot{V}o_2$ peak), and high (79 ± 1% $\dot{V}o_2$ peak) intensities. α2-AMPK activity increased 5-fold from low to medium intensity, and it increased further from medium to high intensity (36). Cycling for 30 min at a workload requiring 62.8 ± 1.3% of peak O_2 uptake significantly enhanced α2-AMPK activity after 5 min (2-fold), and the activity further elevated after 30 min (3-fold) of exercise (37). Collectively, at least 60% of $\dot{V}o_{2max}$ as a threshold intensity of exercise may be required to stimulate α2-AMPK activity in human skeletal muscle. It seems possible that the activation of α2-AMPK contributes to the increased S_G^{2*} in the 70% $\dot{V}o_{2max}$ trial of the present study.

Secondly, increased blood flow that enhances glucose delivery to peripheral tissue might contribute to the increased glucose effectiveness after exercise. Glucose uptake in muscle is stimulated by increased blood flow in the absence of insulin (38). Leg blood flow and glucose effectiveness increased immediately even after mild exercise at LT intensity (45.4 ± 3.1% $\dot{V}o_{2max}$) for 60 min (7). Thirdly, decreasing muscle glycogen content after exercise may play a role, because the activation of AMPK and its associated increases in muscle glucose uptake are affected by glycogen content (32). In the present study, the amount of carbohydrate oxidized during the 70% $\dot{V}o_{2max}$ exercise was significantly greater than the 50% $\dot{V}o_{2max}$ exercise (236.8 ± 36.7 kcal and 397.6 ± 66.6 kcal), and it might be related to the intensity-dependent increase in S_G^{2*} after the exercise. Finally, in addition to changes in intracellular location of GLUT-4, its content may also increase after exercise. Studies performed in rodent skeletal muscle have indicated that GLUT-4 mRNA and protein are rapidly increased after intensive exercise (39). Consistently, exercise for 60 min on a cycle ergometer at a power output requiring 73 ± 4% peak oxygen uptake acutely increased GLUT-4 gene expression in human skeletal muscle (29).

In previous studies, an increase in glucose effectiveness after an acute bout of moderate exercise disappeared after several hours (40, 41). No effects in insulin sensitivity and glucose effectiveness were observed 11 h after a single bout of exercise at the LT level (60 min) or the 4 mM lactate level (36 ± 1 min) (40). In contrast, 11 h after the exhaustive exercise bout (96 ± 7 min), insulin sensitivity and glucose effectiveness were still higher than these indices without any prior exercise. Therefore, the effects of an acute exercise at higher intensity on insulin sensitivity and glucose effectiveness may persist at least 11 h after the exercise (40). It remains to be determined how long the acute effect of higher intensity exercise on S_I^{2*} and S_G^{2*} lasts. In addition, although the effects of a single bout of the 50% $\dot{V}o_{2max}$ exercise on S_I^{2*} and S_G^{2*} were not statistically significant in the present study, habitual exercise at lower intensities seems to be beneficial to improve these indices. In fact, cycle ergometer exercise at LT (49.1 ± 2.8% $\dot{V}o_{2max}$) for 60 min/d, 5 d/wk for 12 wk enhanced S_I^{2*} and S_G^{2*} (42).

Combination of two-compartment minimal model analysis and deconvolution technique provides a reliable profile of EGP (16). During exercise, EGP is shown to be increased by an exercise intensity-dependent manner, and the increase in EGP is restored to basal levels at around 30 min (43). In the present study, basal EGP at the time of glucose bolus was the highest after exercise at the 70% $\dot{V}o_{2max}$ among the three experimental trials. During the first 30 min after glucose load, when plasma glucose concentration was elevated above the basal level (Fig. 1A), EGP in the three experimental conditions was similarly suppressed (Fig. 2). During this period, plasma glucose and insulin, both of which are capable of suppressing EGP, were lower after the 70% $\dot{V}o_{2max}$ exercise (Fig. 1, A and B). Therefore, these results suggest that a single bout of high-intensity exercise may also increase hepatic insulin sensitivity and/or glucose effectiveness to suppress EGP as well as S_I^{2*} and S_G^{2*}. The suppression of EGP was followed by its overshoot, which was earlier and greater after the exercise, presumably reflecting differences in plasma glucose level and/or the reduced exogenous insulin dose in the FSIGTs after the exercise trials.

In conclusion, a single bout of exercise acutely improved

S_I^{2*} and S_G^{2*} for ordinary men with normal glucose tolerance in an intensity-dependent manner, and an exercise intensity toward the higher ends of the ranges recommended by the ADA 1993 and ACSM 2000 has a greater potential. The beneficial effect of such exercise for glucose-intolerant participants remains to be studied.

Acknowledgments

Received October 22, 2004. Accepted April 11, 2005.

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This work was supported by grants and fellowships from The 21st Century Center of Excellence program (2002–2003 project: Promotion of health and sport scientific research) and the Ministry of Education, Culture, Sports, Science and Technology.

References

1. **Henriksen EJ** 2002 Effects of acute exercise and exercise training on insulin resistance. J Appl Physiol 93:788–796
2. **American Diabetes Association** 1993 Exercise and NIDDM. Diabetes Care 16(Suppl 2):54–58
3. **American College of Sports Medicine** 2000 General principles of exercise prescription: cardiorespiratory endurance. In: ACSM's guidelines for exercise testing and prescription. 6th ed. Philadelphia: Williams & Wilkins; 212–214
4. **Brun JF, Guintrand-Hugret R, Bouix O, Orsetti A** 1995 Influence of short-term submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. Metabolism 44:833–840
5. **Rheaume C, Waib PH, Kouame N, Nadeau A, Lacourciere Y, Joanisse DR, Simoneau JA, Cleroux J** 2003 Effects of intense and prolonged exercise on insulin sensitivity and glycogen metabolism in hypertensive participants. Circulation 108:2653–2659
6. **Mikines KJ, Sonne B, Farrell PA, Tronier B, Galbo H** 1988 Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol 254:E248–E259
7. **Sakamoto M, Higaki Y, Nishida Y, Kiyonaga A, Shindo M, Tokuyama K, Tanaka H** 1999 Influence of mild exercise at the lactate threshold on glucose effectiveness. J Appl Physiol 87:2305–2310
8. **Soskin S, Allweiss MD, Cohn DJ** 1934 Influence of the pancreas and the liver upon the dextrose tolerance test. Am J Physiol 109:155–165
9. **Ader M, Pacini G, Yang YJ, Bergman RN** 1985 Importance of glucose per se to intravenous glucose tolerance. Comparison of the minimal-model prediction with direct measurements. Diabetes 34:1092–1103
10. **Best JD, Kahn SE, Ader M, Watanabe RM, Ni TC, Bergman RN** 1996 Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 19:1018–1030
11. **Bergman RN, Ider YZ, Bowden CR, Cobelli C** 1979 Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667–E677
12. **Bergman RN, Finegood DT, Ader M** 1985 Assessment of insulin sensitivity *in vivo*. Endocr Rev 6:45–86
13. **Bergman RN** 1989 Toward physiological understanding of glucose tolerance. Minimal-model approach. Diabetes 38:1512–1527
14. **Bergman RN, Hope ID, Yang YJ, Watanabe RM, Meador MA, Youn JH, Ader M** 1989 Assessment of insulin sensitivity in vivo: a critical review. Diabetes Metab Rev 5:411–429
15. **Bergman RN, Lovejoy JC** 1997 The minimal model approach and determination of glucose tolerance. Pennington Center nutrition series. Vol 7. Baton Rouge, LA: Louisiana State University Press
16. **Caumo A, Cobelli C** 1993 Hepatic glucose production during the labeled FSIGT: estimation by deconvolution with a new minimal model. Am J Physiol 264:E829–E841
17. **Vicini P, Caumo A, Cobelli C** 1997 The hot IVGTT two-compartment minimal model: indexes of glucose effectiveness and insulin sensitivity. Am J Physiol 273:E1024–E1032
18. **Beaver WL, Wasserman K, Whipp BJ** 1986 A new method for detecting anaerobic threshold by gas exchange. J Appl Physiol 60:2020–2027
19. **Peronnet F, Massicotte D** 1991 Table of nonprotein respiratory quotient: an update. Can J Sport Sci 16:23–29
20. **American Diabetes Association** 2004 Physical activity/exercise and diabetes. Diabetes Care 27(Suppl 2):S58–S62
21. **Borg G** 1973 Perceived exertion: a note on "history" and methods. Med Sci Sports Exercise 5:90–93
22. **Nishida Y, Tokuyama K, Nagasaka S, Higaki Y, Fujimi K, Kiyonaga A, Shindo M, Kusaka I, Nakamura T, Ishikawa S, Saito T, Nakamura O, Sato Y, Tanaka H** 2002 SG, SI, and EGP of exercise-trained middle-aged men estimated by a 2-compartment labeled minimal model. Am J Physiol 283: E809–E816
23. **Wolfe RR** 1992 Radioactive and stable-isotope tracers in biomedicine: principles and practice of kinetic analysis. New York: Wiley-Liss
24. **Nagasaka S, Tokuyama K, Kusaka I, Hayashi H, Rokkaku K, Nakamaura T, Kawakami A, Higashiyama M, Ishikawa S, Saito T** 1999 Endogenous glucose production and glucose effectiveness in type 2 diabetic participants derived from stable-labeled minimal model approach. Diabetes 48:1054–1060
25. **Tokuyama K, Higaki Y, Fujitani J, Kiyonaga A, Tanaka H, Shindo M, Fukushima M, Nakai Y, Imura H, Nagata I, Taniguchi A** 1993 Intravenous glucose tolerance test-derived glucose effectiveness in physically trained humans. Am J Physiol 265:E298–E303
26. **Prigeon RL, Roder ME, Porte Jr D, Kahn SE** 1996 The effect of insulin dose on the measurement of insulin sensitivity by the minimal model technique. Evidence for saturable insulin transport in humans. J Clin Invest 97:501–507
27. **Finegood DT, Tzur D** 1996 Reduced glucose effectiveness associated with reduced insulin release: an artifact of the minimal-model method. Am J Physiol 271:E485–E495
28. **Cobelli C, Bettini F, Caumo A, Quon MJ** 1998 Overestimation of minimal model glucose effectiveness in presence of insulin response is due to undermodeling. Am J Physiol 275:E1031–E1036
29. **Kraniou Y, Cameron-Smith D, Misso M, Collier G, Hargreaves M** 2000 Effects of exercise on GLUT-4 and glycogenin gene expression in human skeletal muscle. J Appl Physiol 88:794–796
30. **Wojtaszewski JF, Nielsen P, Hansen BF, Richter EA, Kiens B** 2000 Isoform-specific and exercise intensity-dependent activation of 5′-AMP-activated protein kinase in human skeletal muscle. J Physiol 528:221–226
31. **Wojtaszewski JF, MacDonald C, Nielsen JN, Hellsten Y, Hardie DG, Kemp BE, Kiens B, Richter EA** 2003 Regulation of 5′AMP-activated protein kinase activity and substrate utilization in exercising human skeletal muscle. Am J Physiol Endocrinol Metab 284:E813–E822
32. **Wojtaszewski JFP, Nielsen JN, Richter EA** 2002 Invited review: effect of acute exercise on insulin signaling and action in humans. J Appl Physiol 93:384–392
33. **Sakamoto K, Goodyear LJ** 2002 Intracellular signaling in contracting skeletal muscle. J Appl Physiol 93:369–383
34. **Kurth-Kraczek EJ, Hirshman MF, Goodyear LJ, Winder WW** 1999 5′ AMP-activated protein kinase activation causes GLUT4 translocation in skeletal muscle. Diabetes 48:1667–1671
35. **Winder WW, Hardie DG** 1996 Inactivation of acetyl-CoA carboxylase and activation of AMP-activated protein kinase in muscle during exercise. Am J Physiol 270:E299–E304
36. **Chen Z-P, Stephens JT, Murthy S, Canny BJ, Hargreaves M, Witters LA, Kemp BE, McConell GK** 2003 Effect of exercise intensity on skeletal muscle AMPK signaling in humans. Diabetes 52:2205–2212
37. **Stephens TJ, Chen ZP, Canny BJ, Michell BJ, Kemp BE, McConell GK** 2002 Progressive increase in human skeletal muscle AMPKα2 activity and ACC phosphorylation during exercise. Am J Physiol Endocrinol Metab 282:E688–E694
38. **Hespel P, Vergauwen L, Vandenberghe K, Richter EA** 1995 Important role of insulin and flow in stimulating glucose uptake in contracting skeletal muscle. Diabetes 44:210–215
39. **Kuo CH, Browning KS, Ivy J** 1999 Regulation of GLUT4 protein expression and glycogen storage after prolonged exercise. Acta Physiol Scand 165:193–201
40. **Higaki Y, Kagawa T, Fujitani J, Kiyonaga A, Shindo M, Taniguchi A, Nakai Y, Tokuyama K, Suzuki M, Tanaka H** 1996 Effects of a single bout of exercise on glucose effectiveness. J Appl Physiol 80:754–759
41. **Pestell RG, Ward GM, Galvin P, Best JD, Alford FP** 1993 Impaired glucose tolerance after endurance exercise is associated with reduced insulin secretion rather than altered insulin sensitivity. Metabolism 42:277–282
42. **Nishida Y, Tokuyama K, Nagasaka S, Higaki Y, Shirai Y, Kiyonaga A, Shindo M, Kusaka I, Nakamura T, Ishibashi S, Tanaka H** 2004 Effect of moderate exercise training on peripheral glucose effectiveness, insulin sensitivity, and endogenous glucose production in healthy humans estimated by a two-compartment-labeled minimal model. Diabetes 53:315–320
43. **Marliss EB, Vranic M** 2002 Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. Diabetes 51(Suppl 1):S271–S283

Attitudes of medical students and residents toward multidisciplinary team approach

Makoto Tanaka & Masayuki Yokode

Editor – Interdisciplinary teams are essential in providing quality patient care.[1,2] In the May 2005 issue of *Medical Education*, Rudland and Mires reported negative perceptions of medical students about the nursing profession and discussed the propriety of the early introduction of shared learning aimed at defining the role and responsibility of each profession.[3] In the same issue, McNair discussed professionalism and interprofessional education and presented a suggested model for learning professionalism and interprofessional practice.[4] These papers indicated that health care professionals are poorly prepared for interdisciplinary teamwork and that the introduction of interprofessional learning is critical, particularly for medical school students.[3,4] This is also the case in Japan, and education on a multidisciplinary team approach is rarely focused upon at medical schools. At Kyoto University Hospital, we recently conducted a questionnaire survey of fourth-grade medical school students who had completed a clinical training programme and residents who had completed a 1-year residency about their attitude towards teamwork, using the Attitudes Toward Health Care Teams Scale.[5] We also asked about their experience of collaboration on patient care with other health-care professionals. All (100%) the students and 92% of the residents completed the questionnaire (Table 1). The medical students moderately agreed that team care improves patient outcomes, but were not inclined to the concept of shared team decision-making. Although the residents had a great deal more experience in collaboration with other professions, they were still negatively inclined to shared team leadership. Moreover, the residents expressed significantly less positive attitudes toward the quality of care provided by interdisciplinary teams than the medical students (Table 1).

The results of the survey suggested that experience in collaboration with other health care professionals in real practice may not necessarily promote the recognition and understanding of team value in physicians. Rather, clinical experience may strengthen their belief in physician centrality, leading to misunderstanding that a team's primary purpose is to provide support for physicians. Therefore, clinical practice without interdisciplinary education may not correct, or rather may promote physicians' misconceptions about multidisciplinary teamwork. Based on these results, we agree strongly that interprofessional education should be included in core undergraduate medical curricula.[4] Shared teaching and team practice at undergraduate level should be considered and medical students should learn the role and responsibility of each health care professional. Moreover, continuous exposure to real-world teamwork is also required for medical students and residents to learn appropriate interprofessional collaboration.

ACKNOWLEDGEMENTS

This study was supported by the Research Grant for Longevity Sciences (15C-3) from the Ministry of Health, Labour and Welfare of Japan.

REFERENCES

1 Sommers LS, Marton KI, Barbaccia JC, Randolph J. Physician, nurse, and social worker collaboration in primary care for chronically ill seniors. *Arch Intern Med* 2000;**160**:1825–33.
2 Tanaka M. Multidisciplinary team approach for elderly patients. *Geriatr Gerontol Int* 2003;**3**:69–72.
3 Rudland JR, Mires GJ. Characteristics of doctors and nurses as perceived by students entering medical school: implications for shared teaching. *Med Educ* 2005;**39**:448–55.
4 McNair RP. The case for educating health care students in professionalism as the core content of interprofessional education. *Med Educ* 2005;**39**:456–64.
5 Heinemann GD, Schmitt MH, Farrell MP, Brallier SA. Development of an Attitudes Toward Health Care Teams Scale. *Eval Health Prof* 1999;**22**:123–42.

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doi: 10.1111/j.1365-2929.2005.39_12.x

Table 1 Results of the survey

	Students	Residents
n	101	102
Experience in collaboration with		
Nurses	67.3%	95.1%*
Social workers	15.8%	57.4%*
Physical therapists	12.9%	65.6%*
Pharmacists	45.5%	62.3%**
Dietitians	41.6%	42.6%
The Attitudes Toward Health Care Teams Scale[1]		
Team value (11 items)	50.1 ± 0.37	46.9 ± 0.48*
Team efficiency (5 items)	19.7 ± 0.29	19.3 ± 0.44
Physician's shared role on team (4 items)	14.8 ± 0.26	14.2 ± 0.43

*$P < 0.01$, **$P < 0.05$.
[1]The response for each item ranges from 1, strongly disagree, to 6, strongly agree.[5]

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BRIEF REPORT

A New Simple Method for the Measurement of Visceral Fat Accumulation by Bioelectrical Impedance

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We and others (1–9) have shown that the accumulation of visceral fat is associated with multiple risk factor syndrome more closely than with the BMI itself or the amount of subcutaneous fat. In these studies, computed tomography (CT) scan at the umbilical level (10) was used for the assessment of visceral fat area (VFA). However, the method is not cost-effective and/or radiation exposure is problematic; thus, it is often unsuitable for screening large groups of individuals. There is a need for a simple and noninvasive method to assess visceral fat accumulation. The bioelectrical impedance analysis (BIA) method, which is based on the electric resistance difference between the fat and components of other organs (11–14), should meet this need. Conventional BIA approaches have estimated total fat content but not regional fat distribution (11–13). Recently, attempts to assess the amount of abdominal subcutaneous fat by the local BIA method were reported (14). Here, we developed a new technique to specifically evaluate VFA by using the abdominal BIA method.

RESEARCH DESIGN AND METHODS — The study subjects were 59 healthy volunteers and 32 inpatients with suspected cardiovascular disease at Osaka University Hospital. Waist circumference (Wc) at the umbilical level was measured in the late exhalation phase while standing. All subjects underwent the abdominal BIA method to estimate VFA. The voltage occurring at the flank to the flow of current between the umbilicus and the back correlates significantly with VFA and is unaffected by subcutaneous fat area. The voltage becomes larger as visceral fat accumulates even in the subjects with the same Wc because the electric resistance of intra-abdominal fat is greater than that of fat-free mass, and the density of the equipotential lines between two electrodes becomes denser (15) (Fig. 1*A*). The voltage correlates with the ratio of VFA to the total cross-sectional area of the abdomen, which can be approximated by using Wc^2 (Fig. 1*B*). Thus, the VFA can be expressed as

$$VFA = a_0 + a_1 Vo' Wc^2 \quad (1)$$

where a_0 and a_1 are constants and Vo′ is the voltage measured at the flank. Equation 1 means that the distance between two measuring electrodes on the flank must change in proportion to Wc. The voltage Vo′ used in equation 1 can be approximately related to the voltage Vo measured with the electrodes with a fixed distance in the form of

$$Vo' = bWcVo \quad (2)$$

where b is a constant. Hence, substituting equation 2 into equation 1, we obtain

$$VFA = a_0 + a_1' VoWc^3 \quad (3)$$

where a_1' is a constant. Then, we calculate presumed VFA by using linear regression equation for volunteers and patients. The correlation between presumed VFA and VFA determined by CT and the effects of posture and respiration on abdominal BIA were investigated. The usefulness of abdominal BIA on evaluating metabolic syndrome was also investigated. Factors characteristic for the metabolic syndrome were defined as follows. Hypertriglyceridemia: serum triglyceride concentration ≥150 mg/dl and/or on medication; low HDL cholesterol: serum HDL cholesterol concentration <40 mg/dl; hypertension: systolic blood pressure ≥130 mmHg and/or diastolic blood pressure ≥85 mmHg and/or having received antihypertensive medication; and high fasting glucose: serum glucose concentration ≥110 mg/dl and/or having received antidiabetic medication. In the Japanese subjects, the best combination of sensitivity and specificity for detecting subjects with multiple risk factors was VFA level ≥100 cm^2 (3). All statistical analysis was performed with Stat View J 5.0 (SAS). The χ^2 test and Mann-Whitney's *U* test were used to compare the risk factors between two groups: the high and normal VFA groups.

RESULTS — The VFA presumed by abdominal BIA correlated significantly with VFA determined by CT ($r = 0.88$, $P < 0.0001$) (Fig. 1*C*). This correlation

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Received for publication 9 November 2004 and accepted 10 November 2004.

Abbreviations: BIA, bioelectrical impedance analysis; CT, computed tomography; VFA, visceral fat area; Wc, waist circumference.

A table elsewhere in thise issue shows conventional and Système International (SI) units and conversion factors for many substances.

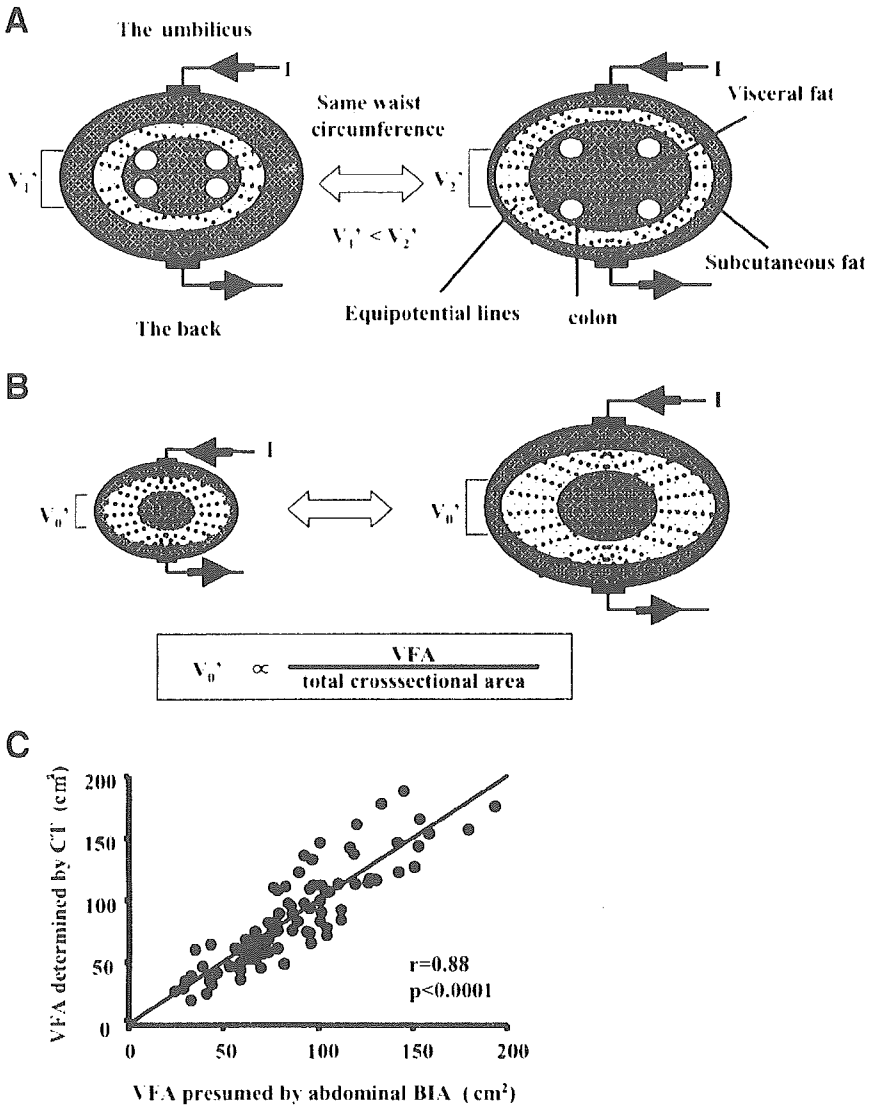

Figure 1—*Abdominal bioelectrical impedance analysis (BIA) method. (A) The electric current (I) flows across the abdomen between the umbilicus and the back. Equipotential lines, form inside the peritoneal cavity, penetrate the visceral fat and emerge on the body surface at the flank. The voltage (V_1', V_2') measured at the flank becomes large with accumulation of visceral fat. (B) The voltage (V_0') measured at the flank correlates with the ratio of visceral fat area (VFA) to the total cross-sectional area of the abdomen. (C) Correlation between VFA presumed by abdominal BIA and VFA determined by computed tomography (CT) (n = 91). Voltage measurement condition was the standing-late exhalation.*

was significantly stronger than those between VFA determined by CT and Wc (r = 0.77). BMI (r = 0.62), and percent body fat × weight (r = 0.73–0.76) measured by the conventional BIA method based on induction between both hands (HBF-302; Omron, Kyoto, Japan) and both feet (TF-701; Tanita, Tokyo, Japan). In considering the reproducibility and correlation, the best measurement condition was the standing posture and late exhalation in both sexes (data not shown). The high VFA group (presumed VFA ≥100 cm^2) showed a higher prevalence of hypertriglyceridemia (48.3 vs. 12.9%, $P < 0.001$), low HDL cholesterol (17.2 vs. 11.3%), high fasting glucose (13.8 vs. 9.7%), and hypertension (24.1 vs. 22.6%) than the normal VFA group (<100 cm^2). The number of risk factors was also significantly higher in the high VFA group than the normal VFA group (no risk factor: 37.9 vs. 61.3%, single risk factor: 24.1 vs. 22.6%, two risk factors: 24.1 vs. 12.9%, and three risk factors: 13.8 vs. 3.2%, $P < 0.05$).

CONCLUSIONS — Conventionally, Wc is a well-used anthropometric measure for the assessment of visceral fat. Furthermore, the criteria for the metabolic syndrome according to National Cholesterol Education Program (16) include Wc. In fact, Wc correlates with VFA determined by CT (3,9,17). However, these parameters are considerably variable among individuals. It has been reported (3), for example, that men with Wc between 85.0 and 86.0 cm had VFA in the range of 67 and 137 cm^2 in a Japanese population. Furthermore, in premenopausal women, Wc underestimates visceral fat amount because of the accumulation of abdominal subcutaneous fat (18). For the above reason, we decided to develop a new method that is simple and accurately measures VFA.

Our new method using BIA is quite simple and noninvasive for evaluation of visceral fat amount. The time required for measurement is only a few minutes, and the instrument is inexpensive and portable. This method requires no advanced skills on the part of the operator, and, on the other hand, subject cooperation is minimal. Excellent correlation was observed in the estimation of visceral fat accumulation between abdominal BIA method and CT. Indeed, the prevalence of multiple risk factors was significantly higher in the high VFA group than in the normal VFA group.

Collectively, the abdominal BIA method should become a useful instrument in routine clinical practice for the evaluation of visceral fat accumulation associated with the metabolic syndrome.

Acknowledgments— We are grateful to Dr. Kazuo Maki and Masaki Fukuhara of Kao Corporation for their assistance in developing the visceral fat–measuring apparatus and Dr. Masahiko Takahashi and Dr. Kikuko Hotta for their great help in measuring VFA by the abdominal BIA method at Osaka University Hospital.

References

1. Nakamura T, Tokunaga K, Shimomura I, Nishida M, Yoshida S, Kotani K, Islam AHMW, Keno Y, Kobatake T, Nagai Y,

Fujioka S, Tarui S, Matsuzawa Y: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 107:239–246, 1994
2. Matsuzawa Y, Nakamura T, Shimomura I, Kotani K: Visceral fat accumulation and cardiovascular disease. *Obes Res* 3 (Suppl. 5):645S–647S, 1995
3. The Examination Committee of Criteria for "Obesity Disease" in Japan, Japan Society for the Study of Obesity: New criteria for "obesity disease" in Japan. *Circ J* 66:987–992, 2002
4. Pascot A, Despres JP, Lemieux I, Bergeron J, Nadeau A, Prud'homme D, Tremblay A, Lemieux S: Contribution visceral obesity to the deterioration of the metabolic risk profile in men with impaired glucose tolerance. *Diabetologia* 43:1126–1135, 2000
5. Pascot A, Despres JP, Lemieux I, Almeras N, Bergeron J, Nadeau A, Prud'homme D, Tremblay A, Lemieux S: Deterioration of the metabolic risk profile in women. *Diabetes Care* 24:902–908, 2001
6. Fujimoto WY, Bergstrom RW, Boyko EJ, Chen KW, Leonetti DL, Newell-Morris L, Shofer JB, Wahl PW: Visceral adiposity and incident heart disease in Japanese-American men: the 10-year follow-up results of the Seattle Japanese-American Community Diabetes Study. *Diabetes Care* 22:1808–1812, 1999
7. Boyko EJ, Fujimoto WY, Leonetti DL, Newell-Morris L: Visceral adiposity and risk of type 2 diabetes: a prospective study among Japanese Americans. *Diabetes Care* 23:465–471, 2000
8. Hatashi T, Boyko EJ, Leonetti DL, McNeely MJ, Newell-Morris L, Kahr SE, Fujimoto WY: Visceral adiposity and the prevalence of hypertension in Japanese Americans. *Circulation* 108:1718–1723, 2003
9. Ryo M, Nakamura T, Kihara S, Kumada M, Shibazaki S, Takahashi M, Nagai M, Matsuzawa Y, Funahashi T: Adiponectin as a biomarker of the metabolic syndrome. *Circ J* 68:975–981, 2004
10. Yoshizumi T, Nakamura T, Yamane M, Islam AHMW, Menju M, Yamasaki K, Arai T, Kotani K, Funahashi T, Yamashita S, Matsuzawa Y: Abdominal fat: standardized technique for measurement at CT. *Radiology* 211:283–286, 1999
11. Lukaski HC, Johnson PE, Bolonchuk WW, Lykken GI: Assessment of fat-free mass using bioeletrical impedance measurements of the human body. *Am J Clin Nutr* 41:810–817, 1985
12. Lukaski HC, Bolonchuk WW, Hall CB, Siders A: Validation of tetrapolar bioelectrical impedance method to assess human body composition. *J Appl Physiol* 60: 1327–1332, 1986
13. Nakadomo F, Tanaka K, Hazama T, Maeda K: Validation of body composition assessed by bioelectrical impedance analysis. *Jpn J Appl Physiol* 20:321–330, 1990
14. Scharfetter H, Schlager T, Stollberger R, Felsberger R, Hutten H, Hinghofer-Szalkay H: Assessing abdominal fatness with local bioimpedance analysis: basics and experimental findings. *Int J Obes* 25:502–511, 2001
15. Geddes LA, Baker LE: The specific resistance of biological material: a compendium of data for the biomedical engineer and physiologist. *Med Biol Eng* 5:271–293, 1967
16. Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults: Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA* 285: 2486–2497, 2001
17. Rankinen T, Kim SY, Perusse L, Despres JP, Bouchard C: The prediction of abdominal visceral fat level from body composition and anthropometry: ROC analysis. *Inter J Obes* 23:801–809, 1999
18. Kotani K, Tokunaga K, Fujioka S, Kobatake T, Keno Y, Yoshida S, Shimomura I, Tarui S, Matsuzawa Y: Sexual dimorphism of age-related changes in whole-body fat distribution in the obese. *Int J Obes* 18:207–212, 1994

Thrombosis Research (2005) 115, 483–490

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Regular Article

Levels of the adipocyte-derived plasma protein, adiponectin, have a close relationship with atheroma

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Received 23 June 2004; received in revised form 10 September 2004; accepted 13 September 2004
Available online 28 October 2004

KEYWORDS
Adiponectin;
Coronary artery disease (CAD);
C-reactive protein (CRP);
High-density lipoprotein cholesterol (HDL-C);

Abstract

Introduction: Inflammation is a key process in atherosclerotic formation. Structural changes in the carotid arterial wall including detection of focal plaques are measured as the intima-media thickness (IMT) providing an index of atheroma. Coronary arterial plaques may be considered as vascular structural changes. Distensibility of the arteries can be assessed by functional changes in pulse wave velocity (PWV) providing an index of sclerosis. Adiponectin has potential antiatherosclerotic properties. We hypothesized that adiponectin was associated with atherosclerotic vascular changes involved in inflammation.
Materials and methods: We enrolled 142 patients with coronary artery disease (CAD) and 108 control patients, matched for age, sex, and body mass index (BMI) with CAD

Abbreviations: ABPI, ankle/brachial pressure index; apo, apolipoprotein; baPWV, brachial and ankle pulse wave velocity; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; ELISA, enzyme-linked immunosorbent assay; HDL-C, high-density lipoprotein cholesterol; IGT, impaired glucose tolerance; IMT, intima-media thickness; PAI-1, plasminogen activator inhibitor type 1; TC, total cholesterol; TG, triglyceride.

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0049-3848/$ - see front matter
doi:10.1016/j.thromres.2004.09.012

Intima-media thickness (IMT); Atherosclerosis

patients. We investigated the relationship between adiponectin, C-reactive protein (CRP), and atherosclerotic vascular changes.
Results: CRP (p=0.0009), high-density lipoprotein cholesterol (HDL-C; p=0.02), and IMTmax (p=0.02) were determinants of adiponectin independent of glucose intolerance (p=0.0001), BMI (p=0.002), and CAD (p=0.03), all of which have been significantly associated with adiponectin (r=0.38). Adiponectin was not correlated with PWV. CRP, glucose intolerance, and HDL-C that correlated with adiponectin were inversely correlated with IMTmax and CAD. CRP was negatively correlated with HDL-C (r=−0.24, p=0.0002) and positively correlated with glucose intolerance (r=0.15, p=0.01).
Conclusions: Adiponectin has a close relationship with CRP, IMTmax, CAD, HDL-C, and other established risk factors. CRP, glucose intolerance, and HDL-C are common mediators between adiponectin and atheromatous vascular changes, which are contrary to each other. The exacerbation of atherogenesis may be involved in a decrease of adiponectin through abnormal glyco- and lipid-metabolism by promoting inflammation.

Introduction

Atherosclerosis involves a combination of fatty degeneration (atheroma) and vessel stiffening (sclerosis) of the arterial wall [1]. Atheroma is closely associated with high levels of cholesterol with lipid-rich atheromatous plaques contributing to vascular obstruction and end-organ damage [2,3], and it is well established that lipid lowering therapy reduces the progression of the vascular lesions [4]. In contrast, the role of sclerosis in coronary artery diseases (CAD) is less clear and has attracted considerably less attention mainly as a result of there being little evidence of end-organ damage due to sclerosis alone. In addition, it is relatively difficult to obtain an assessment of sclerosis [2], as it is influenced by a diverse number of factors including age, blood pressure, diabetes, and renal function [5–8].

Adiponectin is an adipocyte-specific protein abundantly present in human plasma, which has been proposed to play an important role in the development of atherosclerosis [9–12]. There is evidence that physiological concentrations of adiponectin dose-dependently inhibit tumor necrosis factor-α-mediated expression of adhesion molecules produced during the early stage of atherosclerosis that include vascular cell adhesion molecule-1, endothelial–leukocyte adhesion molecule-1, and intracellular adhesion molecule-1 [13]. Adiponectin therefore has potential antiatherosclerotic effects in addition to having a protective role against neointimal formation in humans [14,15].

The development of high-resolution ultrasonography has facilitated the noninvasive evaluation of structural changes in the carotid arterial wall including detection of focal plaques. These changes are measured as the intima-media thickness (IMT) that is considered as an index of atheroma [7]. Recent developments have also enabled simple measurement of brachial and ankle pulse wave velocity (baPWV) by simultaneous monitoring using a phonocardiogram, electrocardiogram, and both sides of brachial and ankle pressure waveforms [16]. Distensibility of the arteries can be assessed by functional changes in PWV, providing an index of sclerosis [17]. Low-grade chronic inflammation is also an important factor in atherosclerosis and is indicated by elevated levels of plasma C-reactive protein (CRP) [18]. In the present study, we hypothesized that plasma adiponectin levels were closely associated with atherosclerotic vascular changes involved in inflammation.

Patients and methods

Study population

We studied 250 patients who underwent diagnostic catheterization (164 men and 86 women, mean age 68±9, range 40–89 years). The group with CAD consisted of 142 patients whose coronary angiography showed 50% or greater narrowing of the major coronary arteries. The control group consisted of 108 patients matched for age, sex, and body mass index (BMI) with the CAD group, who had atypical chest pain at rest, or following minimal exercise associated with coronary spasm or 25% or less narrowing of the major coronary arteries. Patients

who were taking antihypertensive drugs or whose baseline blood pressure was ≥140/90 mm Hg were classified as hypertensive. Impaired glucose tolerance (IGT) and diabetes were diagnosed according to World Health Organization criteria [19], with all these patients being classified as glucose intolerant for the purposes of this study. None of the patients were taking any type of thiazolidinedione or had symptoms of atrial fibrillation, peripheral artery diseases such as arteriosclerosis obliterans [bilateral ankle/brachial pressure index (ABPI) ≤0.90], or inflammatory diseases such as collagen disease, advanced liver disease, malignant disease, septicemia, or arthritis.

Blood sampling and measurement of plasma adiponectin and high-sensitivity CRP levels

Blood samples were obtained from all subjects after a 12-h fast from a sheath inserted into the femoral vein, prior to the administration of heparin for coronary angiography. The first 3 mL of blood was obtained for assessment of plasma lipid profile [total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and apolipoproteins levels], with the subsequent 3 mL of venous blood being collected into an evacuated tube for measurement of plasma adiponectin and CRP levels. Plasma samples were stored at −80 C for subsequent assay with adiponectin levels being determined by enzyme-linked immunosorbent assay (ELISA), as described previously [9]. Plasma CRP levels were measured using a clinically validated high-sensitivity assay (Dade-Behring, Marburg, Germany) [20].

Carotid ultrasound evaluation

Carotid ultrasound examination using an 11.0-MHz linear array transducer (SONOS 5500, Philips, Amsterdam, The Netherlands) was performed in all patients. All these procedures were performed by the same operator who had no knowledge of the clinical characteristics of the individual patients. Images of the common, internal, and external carotid artery were obtained in the anterior oblique, lateral, and posterior oblique planes in order to identify atherosclerotic lesions. Longitudinal images of each carotid artery were used to determine IMT, measured as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface. Atheromatous plaques were defined as a lesion with a focal IMT associated with localized protrusion of the vessel wall into the lumen (Fig. 1A). The IMTmax was defined as

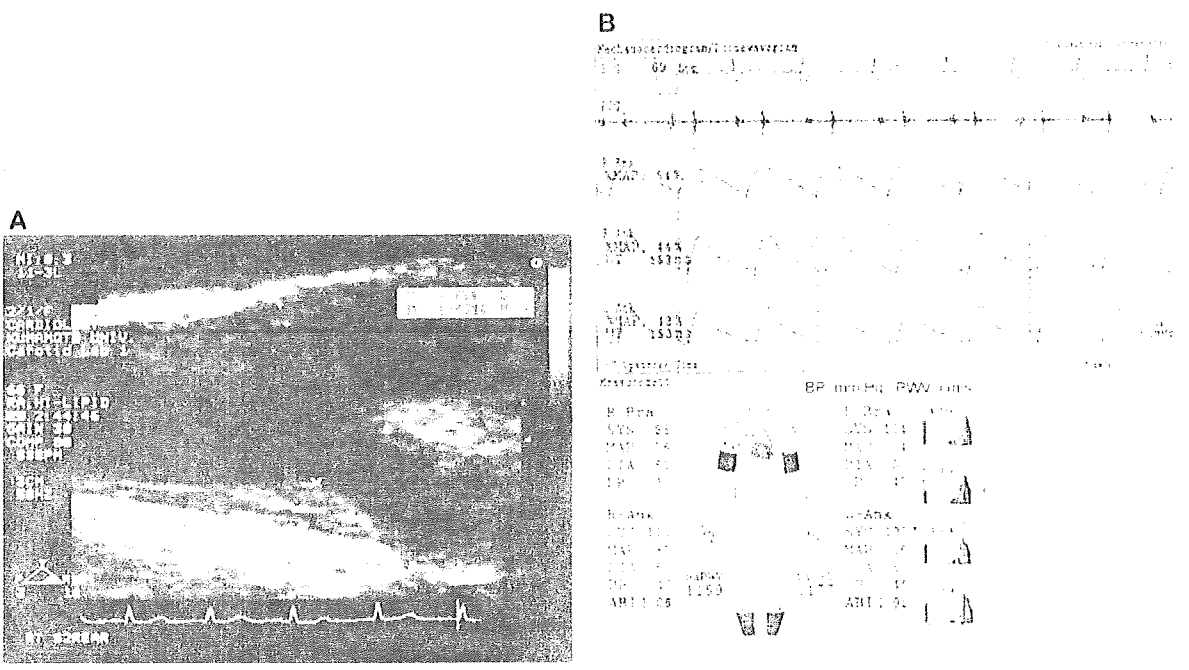

Figure 1 (A) Measurement of atheromatous plaques as a lesion with a focal intima-media thickness (IMT) in the common carotid artery. (B) Report of ankle/brachial pressure index (ABPI) and brachial and ankle pulse wave velocity (baPWV). BP—blood pressure; DIA—diastolic blood pressure; L-Ank.—left ankle blood pressure; L-Bra.—left brachial blood pressure; MAP—mean arterial blood pressure; PP—pulse pressure; PWV—pulse wave velocity; R-Ank.—right ankle blood pressure; R-Bra.—right brachial blood pressure; SYS—systolic blood pressure.

the greatest axial thickness in IMT in the carotid artery.

Measurement of ABPI, baPWV, and assessment of structural and functional vascular changes

An automatic waveform analyzer (form PWV/ABI; Colin, Komaki, Japan) that recorded bilateral baPWV and ABPI, electrocardiography, and heart sounds simultaneously [16,17] was used (Fig. 1B). The patient was examined in the supine position, with the electrocardiogram electrodes placed on both wrists, a microphone for detecting heart sounds placed on the left edge of the sternum, and pressure cuffs applied around both the brachia and ankles. Volume waveforms for the brachium and ankle were stored over a sampling time of 10 s with automatic gain analysis and quality adjustment. The time interval between the wave fronts of the brachial and ankle waveform was defined as the time interval between the brachium and ankle (ΔTba). The distance between sampling points of baPWV was calculated automatically according to the height of the patient. The path length from the suprasternal notch to the brachium (Lb) was determined from superficial measurements and was calculated using the equation Lb=0.2195×height of the patient (cm)−2.0734. The path length from the suprasternal notch to the ankle (La) was obtained in a similar manner calculated as La=0.8129×height of the patient (cm)+12.328. The equation (La−Lb)/ΔTba was used to calculate baPWV. In all patients, baPWV was measured after at least 5 min of rest, with the validity and reproducibility of these measurements being comparable to carotid–femoral PWV obtained by using a catheter tip with a pressure manometer [16].

Our study included the presence of the affected coronary vessel and IMTmax as an index of vascular structural (atheromatous) change and bilateral baPWV as an index of vascular functional (sclerotic) change. A mean value of bilateral baPWV was used to investigate the degree of correlation with plasma levels of adiponectin.

Statistical analysis

All data are expressed as mean±S.D. Differences in frequencies were analyzed through the chi-square method. Comparison of the continuous data between the two groups was performed by one-way analysis of variance (ANOVA). Linear relationships between key variables were determined using Pearson's correlation coefficient, while a multiple linear regression analysis was performed to evaluate independent relationships of the variables. A value of $p<0.05$ was considered as statistically significant.

Results

Patient characteristics

The clinical characteristics of the study patients are summarized in Table 1 that shows that there were significant differences in pulse pressure, the

Table 1 Clinical characteristics of the two study groups

	CAD (n=142)	Control (n=108)	p
Age, y	69±8	68±10	0.25
Men/women, n	97/45	67/41	0.30
Hypertension, n (%)	92 (65)	60 (56)	0.14
Systolic blood pressure, mm Hg	133±20	131±20	0.32
Diastolic blood pressure, mm Hg	74±11	75±12	0.24
Mean blood pressure, mm Hg	94±13	94±13	0.85
Pulse pressure, mm Hg	59±16	55±17	0.04
Heart rate, bpm	67±11	66±12	0.25
Glucose intolerance, n (%)	85 (60)	40 (37)	0.0004
Fasting blood glucose, mg/dL	106±34	93±18	0.0003
Hemoglobin A_{1c}, %	6.1±1.2	5.5±0.8	<0.0001
Total cholesterol, mg/dL	191±35	194±38	0.48
Triglyceride, mg/dL	140±73	125±71	0.10
LDL cholesterol, mg/dL	122±31	120±32	0.65
HDL cholesterol, mg/dL	47±15	56±19	<0.0001
Apo A-I, mg/dL	121±23	129±28	0.01
Apo A-II, mg/dL	26±14	28±14	0.29
Apo B, mg/dL	100±20	94±24	0.02
Apo C-II, mg/dL	4±3	4±2	0.32
Apo C-III, mg/dL	9±3	9±3	0.99
Apo E, mg/dL	4±1	4±1	0.88
Smoking, n (%)	42 (30)	26 (24)	0.33
Body mass index, kg/m^2	24±3	24±3	0.42
Creatinine, mg/dL	1.0±1.2	0.8±0.2	0.05
Adiponectin, μg/dL	5.8±3.2	9.1±5.2	<0.0001
C-reactive protein, mg/dL	0.13±0.10	0.07±0.08	<0.0001

Apo—apolipoprotein; CAD—coronary artery disease; HDL—high-density lipoprotein; LDL—low-density lipoprotein.