表1　患者背景因子

因　子	再喫煙群（n＝7）	禁煙継続群（n＝33）	p 値
年齢（歳）	58.0 ± 29.0	61.0 ± 11.0	n.s
性別（男性）	7 名	31 名	n.s
BMI	25.4 ± 4.3	23.8 ± 5.6	n.s
左室駆出率（%）	49.2 ± 19.5	56.5 ± 15.3	n.s
HbA1c（%）	5.7 ± 2.7	5.5 ± 1.5	n.s
診断名　例（%）			
急性心筋梗塞	1（14.2%）	18（54.5%）	n.s
心筋症	3（42.9%）	4（12.1%）	n.s
大血管疾患	2（28.6%）	4（12.1%）	n.s
合併症　例（%）			
高血圧	7（100%）	27（81.8%）	n.s
脂質異常症	2（28.6%）	15（45.5%）	n.s
糖尿病	3（42.9%）	24（72.7%）	n.s
肥満	2（28.6%）	13（39.4%）	n.s
入院時胸痛症状有り　例（%）	5（71.4%）	25（75.8%）	n.s
入院時心肺停止　例（%）	0（0%）	2（6.0%）	n.s
IABP/PCPS の挿入　例（%）	0（0%）	3（9.0%）	n.s
集中治療室入室　例（%）	1（14.3%）	19（57.6%）	＜ 0.05
職業　例（%）			
デスクワーク	2（28.6%）	11（33.3%）	n.s
非デスクワーク	2（28.6%）	1（3.0%）	＜ 0.05
在院日数（日）	26.8 ± 6.6	26.2 ± 13.3	n.s
退院後3ヵ月間の外来心リハ参加回数（回）*	5.0（7.5）	3.0（2.0）	＜ 0.05
過去の禁煙経験例（%）	2（28.6%）	22（66.7%）	n.s
退院時呼気 CO 濃度（ppm）	2.0 ± 2.8	1.1 ± 2.1	n.s
退院1ヵ月後呼気 CO 濃度（ppm）	6.0 ± 4.2	0.8 ± 1.1	＜ 0.05

平均値±標準偏差，*中央値（四分位範囲）
BMI：body mass index, IABP：intraaortic balloon pumping, PCPS：percutaneous cardiopulmonary support
TDS：the tabacco dependence screener, FTND：The Fagerstrom Test for Nicotine Dependence, CO；一酸化炭素，n.s：not significant

ためのもので，禁煙治療のための標準手順書第3版の帳票5を採用した[8]．

統計解析は，対応のないt検定，χ^2検定ならびにMann-WhitneyのU検定を用いて禁煙継続群と再喫煙群を比較した．

結　果

患者背景因子を**表1**に示す．再喫煙群は7名（17.5%），禁煙継続群は33名（82.5%）であった．再喫煙群は，禁煙継続群と比較して集中治療室への入室を経験した割合が低く（$p < 0.05$），非デスクワーク就労者の割合が高く，退院後3ヵ月間の外来心臓リハビリテーション参加回数が多いことが示された（$p < 0.05$）．

入院前の喫煙開始年齢，1日あたりの喫煙本数，喫煙年数，およびブリンクマン指数を**図2**に示す．喫煙開始年齢の比較では，禁煙継続群では16〜36歳，中央値は20歳であったのに対し，再喫煙群では13〜21歳，中央値が16歳と，喫煙開始年齢は禁煙継続群に比較して再喫煙群で有意に低いことが示された（$p < 0.05$）．

入院中に調査したTDS，FTND，禁煙セルフエフィカシー，および禁煙宣言受容の割合を**図3**に示す．再喫煙群では，禁煙セルフエフィカシーと禁煙宣言受容の割合が低いことが示された（それぞれ$p < 0.05$）．

考　察

健常成人において，喫煙開始年齢が低い，1日喫煙本数が多い，起床から喫煙までの時間が短い，同居人が喫煙している，たばこ依存度が高い，ブリンクマン指数が高いなどの場合には再喫煙の可能性が高いと報告されている[9〜12]．また，心疾患患者では，安定狭心症の場合や

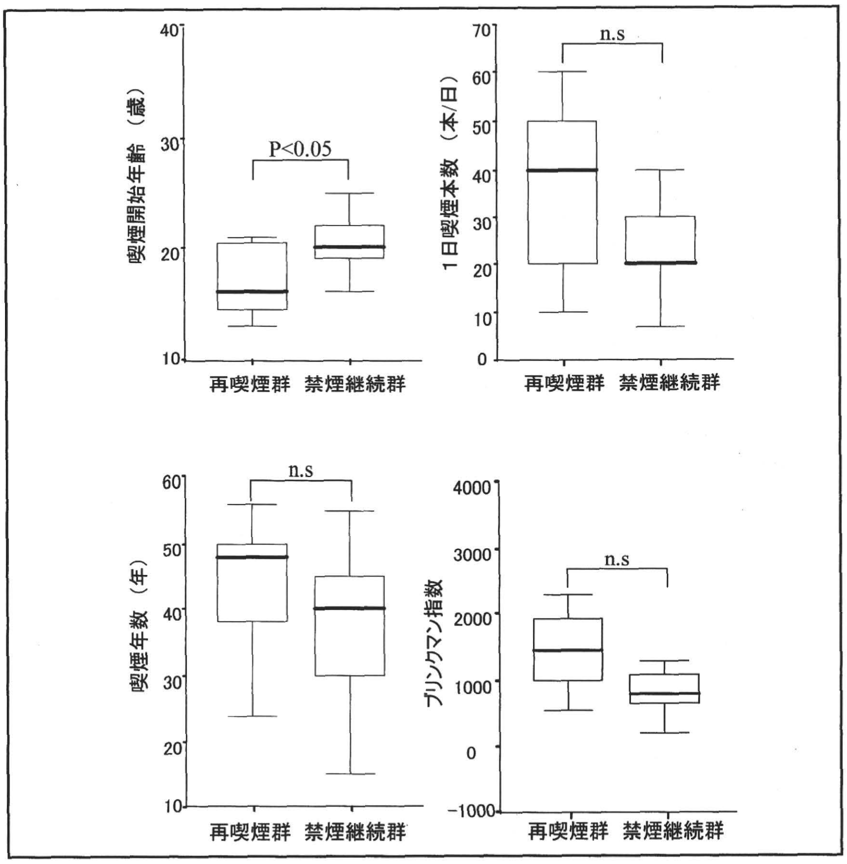

図２　喫煙開始年齢，１日喫煙本数，喫煙年数，ブリンクマン指数の比較
n.s：not significant

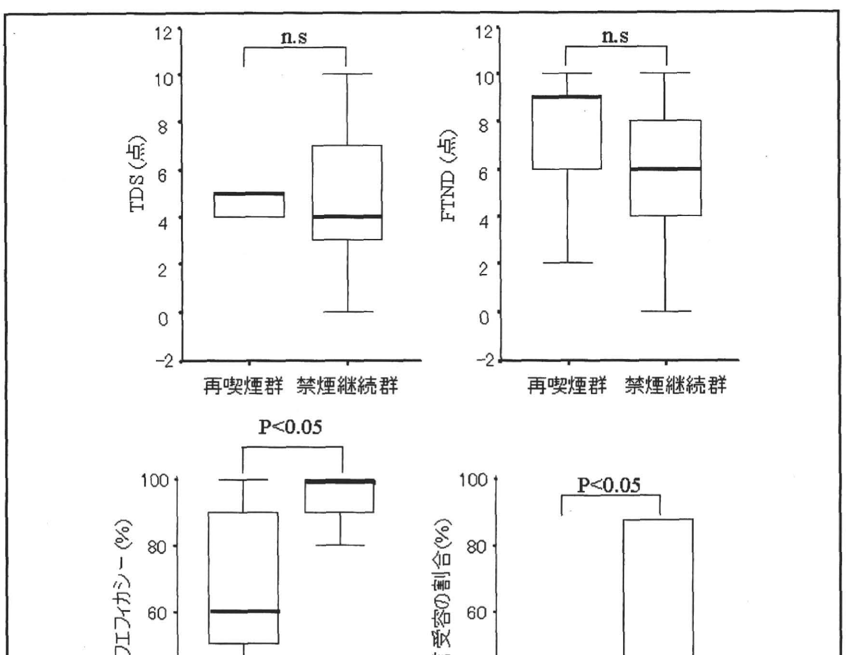

図３　TDS，FTND，禁煙セルフエフィカシー，禁煙宣言受容割合の比較
TDS：the tabacco dependence screener, FTND：the fagestrom test for nicotine dependence, n.s：not significant

低収入，うつの既往などが再喫煙の可能性を高めると報告されている[13,14].

本研究では，再喫煙者の特徴として，喫煙開始年齢が低い，非デスクワーク就労者である，集中治療室に入室歴がない，外来心臓リハビリテーションの参加回数が多い，禁煙セルフエフィカシーが低い，禁煙宣言をしないことが抽出された．集中治療室への入室歴と再喫煙との関係では，集中治療室に入室して急性期治療を受けたことが，患者自身に生命の危機感を自覚させ再喫煙の防止につながったと考えられた．また，職業と再喫煙との関係では，非デスクワーク就労者の再喫煙率が高い値にあったことから，喫煙する同僚との関係や職場の分煙環境などが影響していると思われた．再喫煙群において外来心臓リハビリテーション参加回数が多かった理由として，再喫煙患者に対する積極的禁煙支援の必要性から，心臓リハビリテーション専門職員が外来心臓リハビリテーションへの参加を強く勧めたことなどが影響したと考えられた．また，呼気一酸化炭素濃度が再喫煙群と禁煙継続群との間で有意差を認めなかった理由として，症例数が少数であることに加えて，外来心臓リハビリテーションを受ける24時間前から禁煙をしていた患者がいたため，そのことが再喫煙群における平均呼気一酸化炭素濃度を低下させた一因であると考えられた.

本研究で抽出された再喫煙の予測因子の中で，禁煙宣言の受容は入院後に決定される因子であり，禁煙指導の効果が期待できる介入点と考えられる．そこで，禁煙を受容しない患者に対しては，医師による頻回の禁煙勧告，患者の理解度に合わせた禁煙教育，家庭や職場における環境整備や支援の依頼，禁煙外来との連携，臨床心理士によるカウンセリングなどの支援の強化を行い，再喫煙の防止に努めることが重要であると考えられた．そして，患者自身が循環器疾患に対する喫煙の悪影響を正しく理解し，禁煙治療は他の治療と同様な効果が得られる治療法であることを納得する必要があると思われた.

結　論

禁煙支援において，入院中に行う禁煙宣言は患者の禁煙継続に直接関与するため，その受容の有無は退院後の再喫煙予防に際して有用な因子になると考えられた.

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Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 15(2):185–194
doi: 10.1111/j.1744-9987.2010.00905.x

Development of a Novel Questionnaire Evaluating Disability in Activities of Daily Living in the Upper Extremities of Patients Undergoing Maintenance Hemodialysis

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Abstract: The aim of the present study was to develop a novel questionnaire evaluating disability in the activities of daily living in the upper extremities of hemodialysis (HD) patients (QDUE-HD). We recruited 83 patients (40 males and 43 females) aged 66 ± 8 years, and measured their muscle strength and range of motion in the upper extremities. Moreover, 14 patients performed a six-week exercise training regimen (the exercise group) and were compared with 15 patients not performing such training (the control group). In an initial questionnaire consisting of 37 items, 30 were taken from the Disabilities of the Arm, Shoulder and Hand questionnaire and the Activities of Daily Living Test, and the remaining seven were selected from activities that HD patients perceived as impossible or extremely difficult to perform. The principal factor analysis focused on 11 items, as 26 showing floor and ceiling effects were excluded. These 11 items were divided into two categories consisting of six items termed "light work" and five termed "holding activities". The scores for light work and holding activities correlated significantly and positively with both muscle strength and range of motion in the upper extremities. These scores increased significantly after the six-week exercise training as compared with those before training in the exercise group. We conclude that the QDUE-HD is clinically useful for evaluating disability in activities of daily living in the upper extremities of HD patients because of its high reliability, validity and responsiveness. **Key Words:** Activities of daily living, Disability, Hemodialysis patient, Questionnaire, Upper extremity.

Because the number of elderly patients with end-stage renal disease (ESRD) on maintenance hemodialysis (HD) is increasing annually in Japan (1), improvement in their quality of life (QOL) is considered to be one of the main goals of maintenance HD treatment (2). Maintaining the ability to perform activities of daily living (ADL), such as eating, dressing, bathing, walking and housekeeping, is essential for HD patients to prevent QOL deterioration, because ADL disability is known to be one of the causes of worsening QOL (3). It is generally accepted that HD patients have greater decreases in physical function and more severe ADL disability than age-matched, non-HD patients (4,5). It has also been reported that the initiation of HD not only markedly elevated mortality, but also reduced the ability to perform ADLs in elderly patients with ESRD (6). In addition, it is well known that the proportion of HD patients who suffer from dialysis-associated musculoskeletal disorders increases gradually with prolongation of the duration of HD (7). Recent studies have shown that the function in the upper extremities of HD patients is lower than that of healthy adults and decreases with the prolongation of HD duration (8,9). It has been also demonstrated

Received May 2010; revised November 2010.
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that dialysis-associated musculoskeletal disorders, in particular carpal tunnel syndrome and destructive spondyloarthropathy, often cause the impairment of upper extremities resulting in the deterioration of physical function in HD patients (8,9). Although many studies have described disability in basic self-care activities and locomotion in HD patients, few have documented ADL disability focusing on the upper extremities (10).

Recently, the Functional Independence Measure (FIM) has come into widespread use for evaluating the effects of rehabilitation on ADL disability in patients suffering from cerebral vascular disease or musculoskeletal disorders (11). However, it appears to be difficult to precisely evaluate ADL disability using the FIM in community-dwelling individuals who rarely need ADL assistance, because the FIM evaluation is based on how much assistance is needed to perform the ADL. On the other hand, scales that measure perceived difficulty are more useful for evaluating the severity of ADL disability in patients who do not need assistance in performing the ADL, because such scales can rate their ability to perform these activities from no difficulty to severe difficulty.

The aim of the present study was to develop a novel questionnaire evaluating ADL disability in the upper extremities of HD patients (QDUE-HD) indicating perceived difficulty, and to examine its reliability, validity and responsiveness. In addition, we examined whether or not the FIM was suitable for accurate evaluation of ADL disability in outpatients receiving maintenance HD treatment.

PATIENTS AND METHODS

Study protocol

The study protocol was approved by the Ethics Committee of Kitasato University, and informed consent was obtained from each patient after a detailed explanation of the protocol. This was designed as a prospective study, consisting of three parts: Studies 1 and 2 were cross-sectional and Study 3 was longitudinal. Study 1 was performed to develop the QDUE-HD, and then to examine its reliability. The test-retest reliability of the QDUE-HD was examined with a one week interval between the first and second surveys. Study 2 was performed to confirm the validity of the QDUE-HD by evaluating the relationship between the QDUE-HD and physical function. Study 3 was designed as a non-randomized controlled trial to examine the responsiveness of the QDUE-HD by comparing scores in the QDUE-HD measured before and after the six-week exercise training regimen.

Patients

Outpatients who went to the HD center by themselves three times a week to receive maintenance HD were recruited. Patients were excluded if they had been hospitalized within three months prior to the study, suffered from a recent myocardial infarction or angina pectoris, had uncontrolled cardiac arrhythmias, hemodynamic instability, uncontrolled hypertension, severe arthralgia or myalgia, severe motor paralysis or dementia, or had been performing regular exercise training for more than three months prior to the study. We also excluded patients with missing data for one or more of the analytical variables. As a result, 65 and 83 patients were found to be eligible for the analysis in Studies 1 and 2, respectively (Table 1). Moreover, 29 patients who agreed to participate in Study 3 were divided into two groups: the exercise group consisting of 14 patients performing exercise training, and the control group consisting of 15 who did not exercise (Table 1). The exercise group patients performed exercise training for six weeks, while the control group lived as usual during the six-week study period.

Measurements

Clinical characteristics

Age, sex, height, dry weight, body mass index, HD duration and primary cause of ESRD were investigated using clinical records. The body mass index was calculated from dry weight in kilograms divided by the square of height in meters. Blood hemoglobin and hematocrit, and serum albumin and creatinine concentrations were measured just before each HD session.

ADL disability in the upper extremities

The questionnaire evaluating ADL disability in the upper extremities measures the perceived difficulty of HD patients when they perform certain activities using their arms (Table 2). The questionnaire consists of 37 items, of which 19 were taken from the Disabilities of the Arm, Shoulder and Hand questionnaire Japanese version (12) and 11 from the Activities of Daily Living Test (13). The remaining 7 items were taken from among the 14 obtained from the answers given by 10 outpatients, who did not participate in the present study, asked which activities that they felt were impossible or extremely difficult to perform when using their upper extremities for ADLs. Because 7 of the 14 items were included among the initial 30 items, the remaining 7 were added to the questionnaire. Each item was rated from 1 to 5 points,

TABLE 1. *Patient characteristics in studies 1, 2 and 3*

	Study 1	Study 2	Study 3	
			Exercise group	Control group
Age (years)	66 ± 10	66 ± 8	63 ± 8	64 ± 7
Number of patients (male/female)	65 (24/41)	83 (40/43)	14 (4/10)	15 (4/11)
Height (cm)	156.6 ± 8.2	157.8 ± 8.8	156.3 ± 7.8	155.2 ± 7.1
Dry weight (kg)	52.5 ± 10.1	53.6 ± 10.3	50.7 ± 8.2	52.4 ± 9.5
Body mass index (kg/m^2)	21.3 ± 3.0	21.6 ± 3.3	20.6 ± 1.7	21.7 ± 3.0
Duration of hemodialysis (years)	9.2 ± 7.5	8.6 ± 6.5	12.7 ± 7.2	8.4 ± 7.1
Primary cause of end-stage renal disease (%)				
Glomerulonephritis	35.4	34.9	42.9	40.0
Diabetic nephropathy	23.1	39.8	35.7	26.7
IgA nephropathy	7.7	4.8	7.1	6.7
Polycystic kidney	3.1	2.4	0.0	0.0
Nephrosclerosis	1.5	1.2	0.0	0.0
Unknown	20.0	7.2	7.1	13.3
Other	9.2	9.6	7.1	13.3
Hemoglobin (g/dL)	10.5 ± 0.7	10.3 ± 0.6	10.7 ± 1.0	10.5 ± 1.0
Hematocrit (%)	33.0 ± 2.4	32.3 ± 2.2	32.4 ± 3.1	31.9 ± 2.8
Serum albumin (g/dL)	3.9 ± 0.3	4.0 ± 0.3	3.9 ± 0.2	4.0 ± 0.3
Serum creatinine (mg/dL)	10.6 ± 2.4	10.7 ± 2.6	11.7 ± 1.4	11.3 ± 2.3

Data are expressed as mean ± standard deviation. IgA: immunoglobulin A.

indicating not possible, severe difficulty, moderate difficulty, mild difficulty and ease, respectively.

The FIM score was also measured to evaluate whether, in comparison to the QDUE-HD, the FIM was useful for assessing ADL disability in HD patients. Six items in the FIM were used to assess eating, grooming, bathing, upper and lower body dressing, and toileting activities performed with their upper extremities by HD patients (11). Each item was rated from 1 to 7 points, indicating total, maximal, moderate and minimal assistance, supervision, modified independence and complete independence, respectively. The FIM score was defined as the sum of points for these six items, and ranged from 6 to 42 points.

Physical function

The physical function tests were performed an hour before the HD session to measure muscle strength and range of motion (ROM) in joints with an interval of 1 min or more between the measurements.

Handgrip strength, biceps strength, palmar pinch strength and key pinch strength were measured as

TABLE 2. *Questionnaire evaluating disabilities concerning the activities of daily living in the upper extremities*

1. Opening a jar that has a tight lid
2. Writing
3. Turning a key
4. Preparing a meal
5. Pushing and opening a heavy door
6. Placing an object on a shelf above your head
7. Doing heavy household chores (e.g. washing walls, washing floors)
8. Gardening or doing yard work
9. Making a bed
10. Carrying a shopping bag or briefcase
11. Carrying a heavy object (over 5 kg)
12. Changing a lightbulb overhead
13. Washing or blow-drying your hair
14. Washing your back
15. Putting on a pullover sweater
16. Using a knife to cut food
17. Recreational activities which require little effort (e.g. playing cards, knitting, playing go, playing shogi)
18. Recreational activities in which there is some force or impact on your arm, shoulder or hand (e.g. golf, tennis, catch, hammering)
19. Recreational activities in which you move your arm freely (e.g. playing frisbee, badminton)
20. Drinking water from a glass
21. Turning faucets on and off
22. Pouring water from a kettle into a glass
23. Putting on and taking off your trousers or pants
24. Fastening a belt around your waist
25. Buttoning a long-sleeved shirt
26. Putting on shoes
27. Brushing your teeth
28. Washing and drying your face
29. Combing your hair
30. Wringing out a towel
31. Opening a new milk carton
32. Fastening shoelaces tightly
33. Unscrewing a PET bottle cap
34. Holding a PET bottle
35. Using a frying pan with one hand
36. Using chopsticks
37. Opening a pull-tab can

indicators of the muscle strength of the upper extremities. The handgrip strength measurement required patients to grip a hand-held dynamometer (Grip-D; Takei Scientific Instruments, Niigata, Japan) as tightly as possible (14). The biceps strength measurement was performed using a hand-held dynamometer (μ Tas F-1; Anima, Tokyo, Japan). The patients were asked to flex their elbow joint as tightly as possible, while the sensor of the hand-held dynamometer was placed between the radial and ulnar styloid processes of the upper extremity without the shunt for blood access, in order to avoid compression of the shunt (15). The palmar pinch strength and key pinch strength measurements required patients to pinch the sensor of the hand-held dynamometer (μ Tas F-1) as tightly as possible (14). Each muscle strength measurement was performed twice, and the average of the maximum strength obtained from the right and left upper extremities was calculated for each muscle, except for the biceps.

Active ROM was measured in joints of the shoulder, wrist and fingers as the ROM of the upper extremities, according to the method established by the Japanese Orthopaedic Association and the Japanese Association of Rehabilitation Medicine (16). While sitting on a chair, the patients were asked to move their joints without pain or numbness. Each ROM measurement was performed twice, and the average of the maximum ROM obtained from the right and left upper extremities was calculated for each joint. Shoulder ROM was defined as the sum of the flexion, abduction and external rotation angles for the shoulder joint. Hand ROM was defined as the sum of the palmar flexion and dorsiflexion angles for the wrist joint, the flexion angle for the metacarpophalangeal joint of the thumb, and the flexion angle for the metacarpophalangeal and proximal interphalangeal joints of the second finger.

Exercise training

In the exercise group of Study 3, the exercise training was carried out before HD sessions three times a week for six weeks. The exercise training program consisted of four resistance training exercises with elastic tubing (Thera-Band Tubing; Hygenic Corporation, Akron, OH, USA), shoulder external rotation, seated row, chest press and biceps curl, in which the patients performed two sets of 15 repetitions in each resistance training session (Fig. 1). The physical therapist prescribed the exercise intensity for this training after the patient had been instructed how to perform the exercise training. If the patient had a rating of 14 or greater for the perceived exertion (17) or experienced arthralgia during the training, the exercise intensity and repetitions were reduced until the symptoms showed amelioration. However, all patients in the exercise group were able to complete the six-week exercise training without suffering arthralgia in the present study.

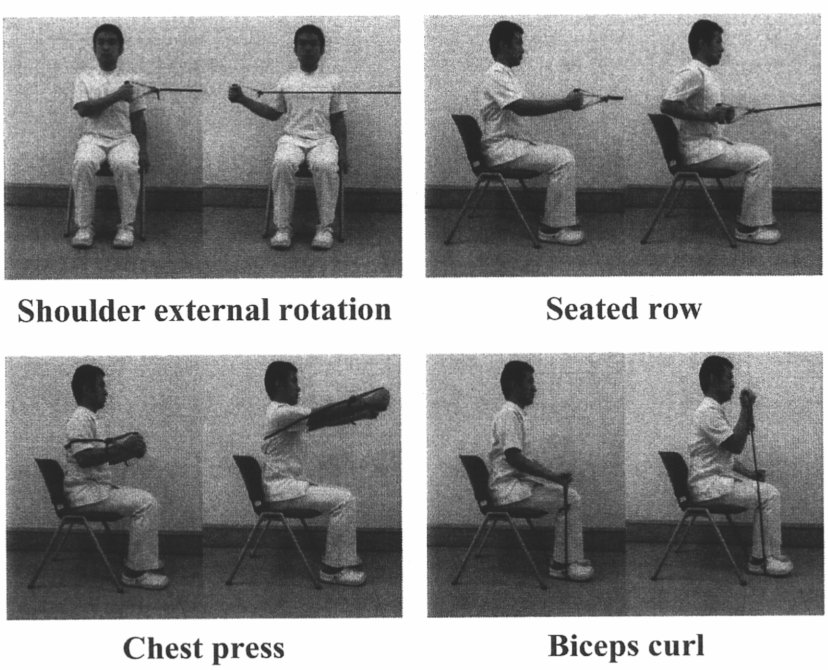

FIG. 1. Exercise training for the upper extremities. Exercise training for the upper extremities consisted of shoulder external rotation, seated row, chest press and biceps curl.

Statistical analysis

Study 1

The score distributions for the 37 items of the questionnaire were expressed as a percentage of the number of patients rating each item as 1, 2, 3, 4 or 5 to the total number of HD cases, using stacked bar charts. Of the 37 items in the questionnaire, they were used for the principal factor analysis with promax rotation unless more than 40% of the HD patients rated the item as 1 or 5 points, indicating floor and ceiling effects, respectively. The principal factor analysis with promax rotation identified intrinsic factors in the items used as the QDUE-HD. The intrinsic factors were considered significant, in terms of forming the categories of the QDUE-HD, if their eigenvalues obtained from the principal factor analysis with promax rotation were >1.00 (18). Correlations between each item and the intrinsic factors were evaluated using factor loadings obtained from the principal factor analysis with promax rotation. The items were grouped into a category if their factor loadings were >0.40 for each intrinsic factor (18).

Moreover, the internal consistency and test-retest reliability of the QDUE-HD were examined by calculating the Cronbach α coefficient and the intraclass correlation coefficient, respectively, to evaluate the reliability of the QDUE-HD (18).

Study 2

The correlations between ADL disability in the upper extremities and physical function were examined by calculating Spearman's rank correlation coefficients to evaluate the validity of the QDUE-HD.

Study 3

A two-way analysis of variance for repeated measures (groups vs. time courses) was used to analyze changes in clinical characteristics, ADL disability in the upper extremities and physical function measured before and after the six-week study period.

In all analyses, statistical significance was established if the *P*-value was <0.05. All analyses were performed using the Statistical Package for the Social Sciences (SPSS version 12.0; SPSS, Chicago, IL, USA).

RESULTS

Items and categories of the QDUE-HD

The score distributions for the 37 items of the questionnaire evaluating ADL disability in the upper extremities are shown in Figure 2. Because floor and ceiling effects were observed in items 2 and 24 of the 37 items, respectively, the principal factor analysis with promax rotation was performed on the remaining 11 items. The factor analysis identified two intrinsic factors among the 11 items for the QDUE-HD, because their eigenvalues were 6.13 and 1.51, respectively.

The factor loadings for the 11 items of the QDUE-HD are shown in Table 3. The 11 items were divided into groups of six and five items based on the factor loadings and formed the two categories termed "light work" and "holding activities", respectively. The score for light work was defined as the sum of points obtained from the six items, which ranged between 6 and 30 points. The score for holding activities was defined as the sum of points obtained from the five items, which ranged between 5 and 25 points.

Reliability of the QDUE-HD

The Cronbach α coefficients and intraclass correlation coefficients of the QDUE-HD are shown in Table 4. The Cronbach α coefficients of the scores for light work and holding activities were 0.92 and 0.87, respectively. The intraclass correlation coefficients of the scores for light work and holding activities were 0.95 and 0.92, respectively.

Validity of the QDUE-HD

Spearman's rank correlation coefficients between ADL disability in the upper extremities and physical functions are shown in Table 5. The score for light work correlated significantly and positively with handgrip strength, biceps strength, palmar pinch strength and shoulder ROM ($P < 0.001$, $P < 0.001$, $P = 0.007$ and $P = 0.02$, respectively). The score for holding activities correlated significantly and positively with handgrip strength, biceps strength, palmar pinch strength, key pinch strength and hand ROM ($P = 0.005$, $P = 0.002$, $P < 0.001$, $P < 0.001$ and $P = 0.03$, respectively). On the other hand, the FIM score did not correlate significantly with handgrip strength, biceps strength, palmar pinch strength, key pinch strength, shoulder ROM or hand ROM.

Responsiveness of the QDUE-HD

There were no significant differences in clinical characteristics at the beginning of the study between the exercise and control groups. Furthermore, the clinical characteristics of dry weight, body mass index, blood hemoglobin and hematocrit, and serum albumin and creatinine concentrations did not change significantly during the six-week study period in either the exercise or the control groups.

Changes in ADL disability in the upper extremities are shown in Figure 3a–c. The scores for light work

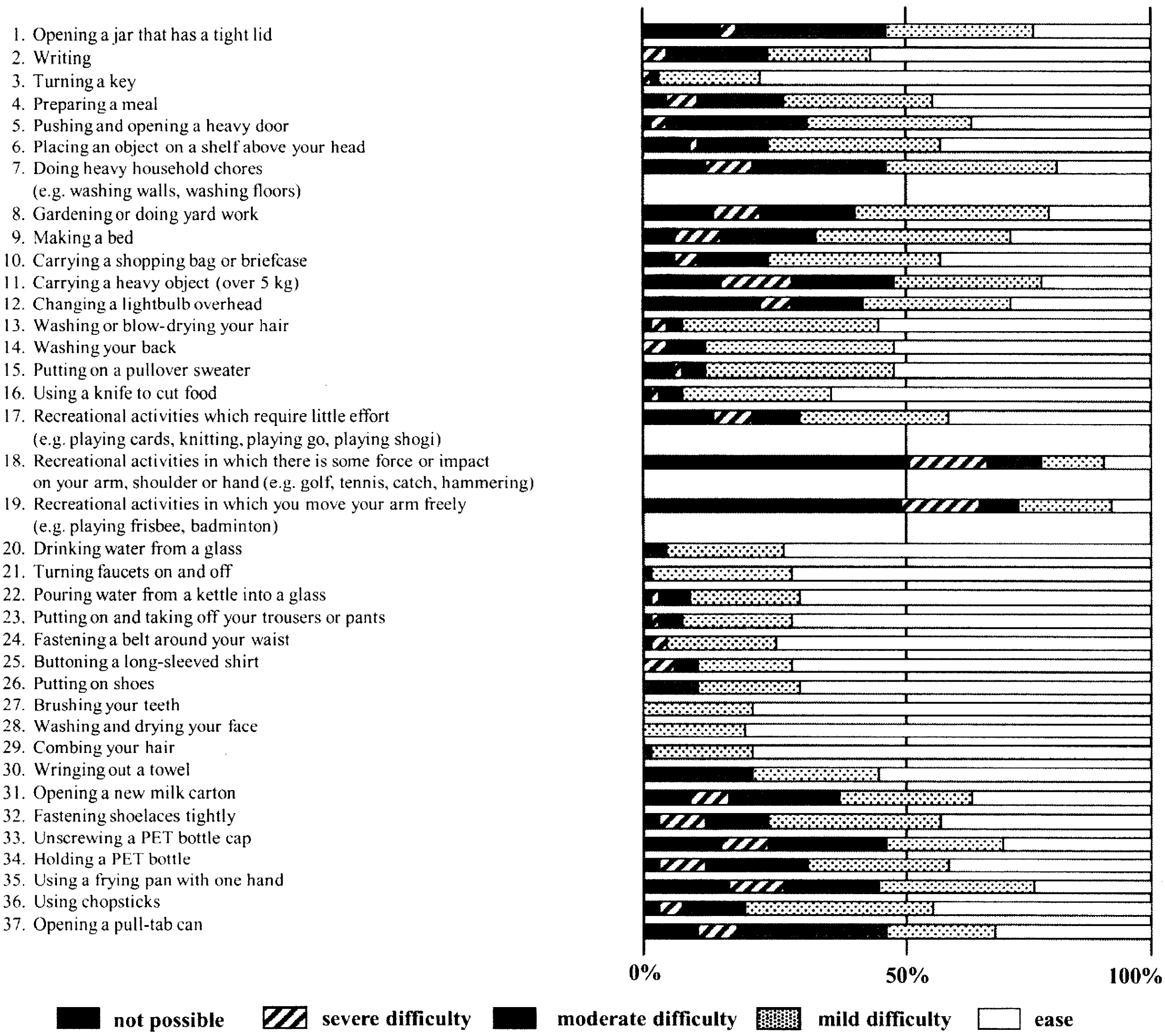

FIG. 2. Score distributions for the 37 items of the questionnaire evaluating disability in activities of daily living in the upper extremities.

and holding activities were significantly increased at the end of the six-week study period as compared with those at the beginning of the study in the exercise group ($P = 0.005$ and $P = 0.01$, respectively), while no significant changes were seen at any time during the six-week study period in the control group. The FIM score remained unchanged throughout six-week study period in the exercise and control groups.

Changes in physical function are shown in Figure 4a–f. Handgrip and biceps strengths were significantly increased at the end of the six-week study period as compared with those at the beginning of the study in the exercise group ($P < 0.001$ and $P = 0.01$, respectively), while no significant changes were seen at any time during the six-week study period in the control group. Palmar pinch strength, key pinch strength, shoulder ROM and hand ROM showed no significant changes during the six-week study period in either the exercise or the control group.

DISCUSSION

Dialysis-associated musculoskeletal disorders frequently cause impairment of the upper extremities, and thereby deterioration of physical function, resulting in decreased ability by HD patients to perform

TABLE 3. *Factor loadings for the 11 items of the QDUE-HD*

QDUE-HD items	Intrinsic factor	
	Light work	Holding activities
Gardening or doing yard work	**0.88**	−0.08
Carrying a heavy object (over 5 kg)	**0.82**	0.03
Making a bed	**0.76**	−0.01
Doing heavy household chores (e.g. washing walls, washing floors)	**0.74**	0.01
Changing a lightbulb overhead	**0.73**	0.16
Pushing and opening a heavy door	**0.70**	0.02
Unscrewing a PET bottle cap	−0.15	**1.06**
Opening a pull-tab can	−0.06	**0.87**
Opening a new milk carton	0.24	**0.74**
Using a frying pan with one hand	0.07	**0.60**
Opening a jar that has a tight lid	0.19	**0.51**

QDUE-HD, questionnaire evaluating disability in activities of daily living in the upper extremities of hemodialysis patients.

ADL using the upper extremities (8–10). ADL disability is well known to be one of the predictors of hospitalization and survival in elderly persons and patients with rheumatoid arthritis (19,20); therefore, preventing ADL disability is essential for HD patients to continue stable maintenance HD treatment. However, to our knowledge, few reports have documented ADL disability in the upper extremities in these patients, nor are there any specific scales for evaluating such disability.

In the present study, our goal was to develop a novel QDUE-HD allowing precise identification of ADL disability in the upper extremities of HD patients with high reliability, validity and responsiveness. A questionnaire developed to be specific for HD patients should adequately reflect individual differences in ADL disability among HD patients. Duruöz et al. reported that HD patients had mild ADL disability when their perceived difficulty was assessed using Duruöz's Hand Index, a scale developed for the evaluation of hands with rheumatoid arthritis (10). However, their study apparently could not precisely show the ADL disability in HD patients, because Duruöz's Hand Index assesses only light and basic activities. When developing the QDUE-HD in the present study, we excluded items indicating very light or very difficult activities for HD patients from the 37 items we initially chose. Therefore, we elected to use 11 items for the QDUE-HD, not only to assess the severity of ADL disability, but also for comparing ADL disability among HD patients.

These 11 items of the QDUE-HD were grouped into two categories that showed sufficient reliability. We designated the first category "light work", because the six items in this category indicated mainly common features concerning movements of the shoulder and elbow joints. Furthermore, the

TABLE 4. *Cronbach α coefficients and intraclass correlation coefficients of the QDUE-HD*

Scores	Cronbach α coefficient	Intraclass correlation coefficient
Light work	0.92	0.95
Holding activities	0.87	0.92

QDUE-HD, questionnaire evaluating disability in activities of daily living in the upper extremities of hemodialysis patients.

TABLE 5. *Spearman's rank correlation coefficients between disability in activities of daily living in the upper extremities and physical functions*

Scores	Handgrip strength	Biceps strength	Palmar pinch strength	Key pinch strength	Shoulder ROM	Hand ROM
Light work	0.42***	0.41***	0.29**	0.16	0.26*	0.09
Holding activities	0.31**	0.33**	0.44***	0.37***	0.09	0.23*
FIM	0.19	0.18	0.16	0.16	0.08	0.17

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$. FIM, Functional Independence Measure; ROM, range of motion.

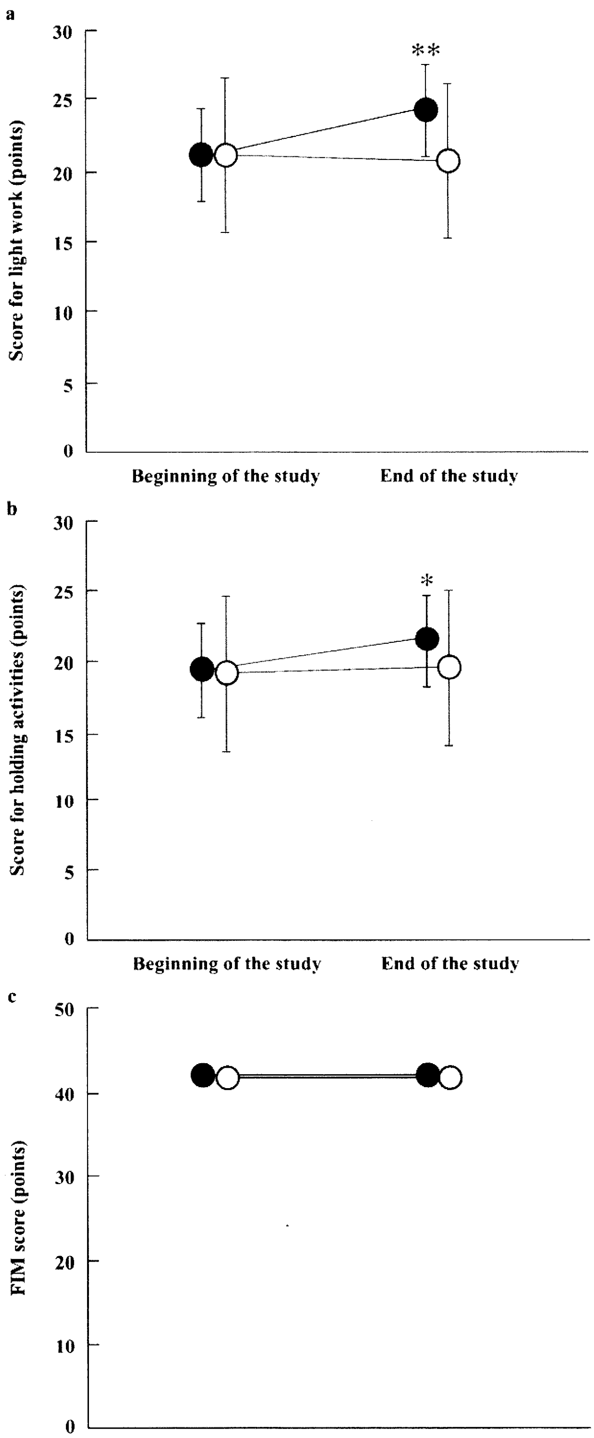

FIG. 3. Changes in scores in the (●) exercise group and the (○) control group for (a) light work, (b) holding activities, and (c) FIM. Data are expressed as mean ± standard deviation. $*P < 0.05$ and $**P < 0.01$ vs. the beginning of the study. FIM, Functional Independence Measure.

second category was termed "holding activities", because the five items in this category indicated mainly common features concerning movements of the hand and finger joints. HD patients reportedly often have musculoskeletal disorders, such as shoulder impingement syndrome and carpal tunnel syndrome, resulting in ADL disability for large and fine movements in the upper extremities, respectively (8,9). Therefore, it was necessary to separately evaluate large and fine activities performed using the upper extremities in HD patients.

We investigated the correlations between ADL disability in the upper extremities and physical functions in HD patients. The scores for light work and holding activities correlated significantly and positively with muscle strength of the upper extremities. Previous studies demonstrated skeletal muscle mass to be reduced in HD patients as compared with age-matched, non-HD cases, and that skeletal muscle atrophy remarkably decreased muscle strength in HD patients (21,22). Therefore, the significant correlation of QDUE-HD with muscle strength of the upper extremities reflected ADL disability due to decreased physical function in HD patients with high validity.

The present study revealed that exercise training improved both handgrip and biceps strengths, resulting in improved scores for light work and holding activities. Recent studies have shown that exercise training increases muscle strength of the upper extremities and the ability to perform ADL in elderly patients with arthritis (23,24). On the other hand, although many studies have shown that exercise training improves physical functions, such as exercise capacity and leg strength, few reports have documented the effects of exercise training on ADL disability in HD patients (25). One of the reasons for this is considered to be the lack of scales that can precisely assess the effects of exercise training on ADL disability in HD patients. Based on our present results, we believe that the QDUE-HD is suitable for evaluating the effects of exercise training on ADL disability in the upper extremities of HD patients, because the QDUE-HD sufficiently reflected improvement in muscle strength in response to exercise training.

The FIM score showed no significant correlations with physical function parameters. Furthermore, no significant changes were seen throughout the six-week study period in either the exercise or the control groups. Most HD patients participating in the present study had maximal scores for the FIM measurements before and after the study period, because they required no assistance in ADLs, even if they felt

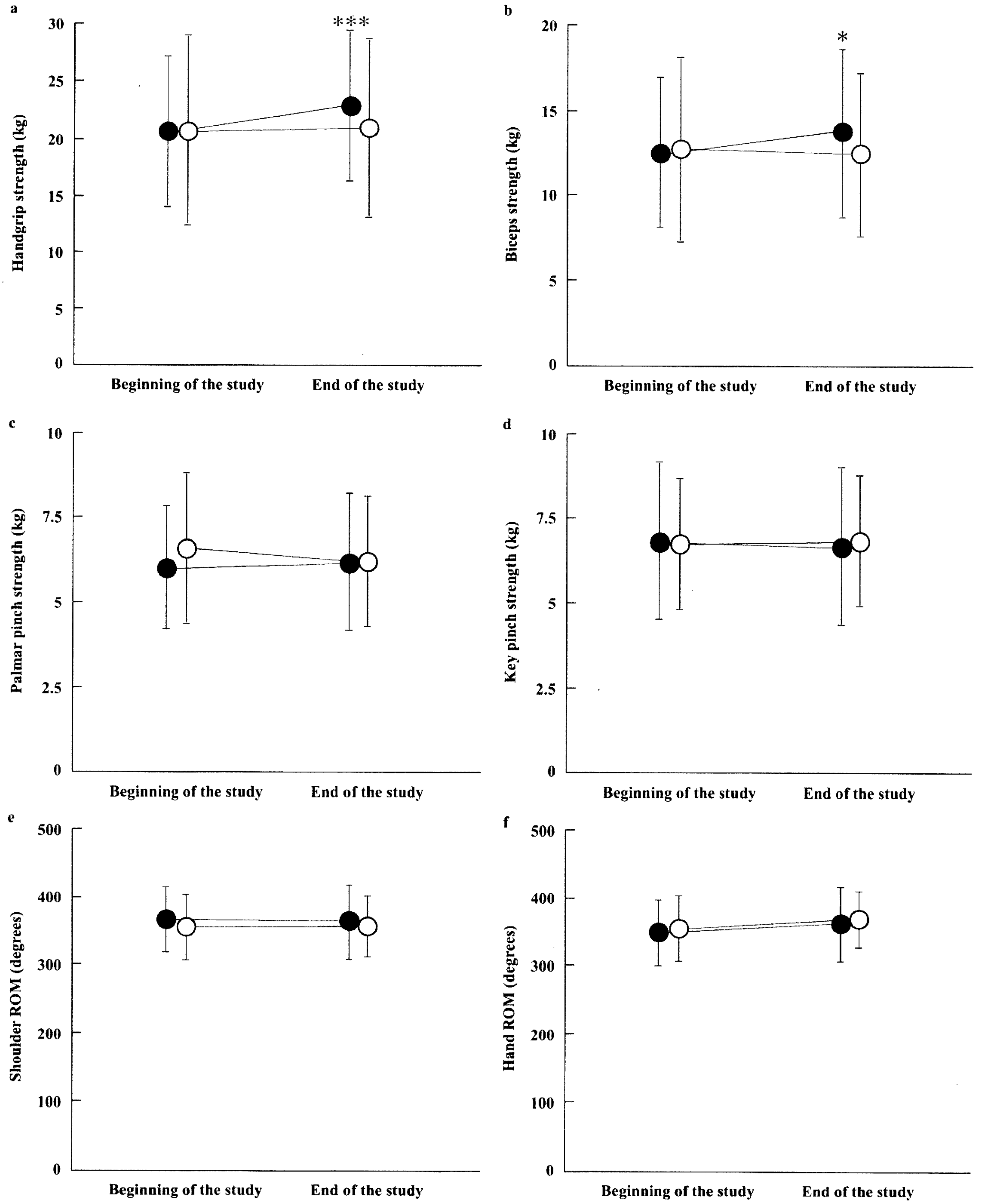

FIG. 4. Changes in the (●) exercise group and the (○) control group for (a) handgrip strength, (b) biceps strength, (c) palmar pinch strength, (d) key pinch strength, (e) shoulder range of motion (ROM), and (f) hand ROM. Data are expressed as mean ± standard deviation. $*P < 0.05$ and $***P < 0.001$ vs. the beginning of the study.

a perceived difficulty. Therefore, the FIM, a questionnaire measuring the amount of ADL assistance needed, was considered not to be suitable for evaluating ADL disability in HD patients. In fact, the QDUE-HD appeared to be more suitable than the FIM for evaluating ADL disability in HD patients because the QDUE-HD allows classification of the severity of ADL disability by measuring the perceived difficulty of patients in performing ADLs.

Study limitations

The QDUE-HD was developed using items indicative of ADL disability in HD outpatients who had neither arthralgia nor myalgia due to severe carpal tunnel syndrome or arthritis. Therefore, it is difficult to assess ADL disability using the QDUE-HD in patients with obvious ankylosis or palsy affecting the upper extremities.

CONCLUSION

The QDUE-HD, which is composed of 11 items, is clinically useful for evaluating activities of daily living disability in the upper extremities of hemodialysis patients because it has high reliability, validity and responsiveness.

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Yamaoka-Tojo et al. Nutrition & Metabolism 2011, 8:3
http://www.nutritionandmetabolism.com/content/8/1/3

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Circulating interleukin-18: A specific biomarker for atherosclerosis-prone patients with metabolic syndrome

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Abstract

Background: Metabolic syndrome (MetS) is associated with an increased risk of the development of atherosclerotic cardiovascular disease (CVD). Interleukin-18 (IL-18), which is a pleiotropic proinflammatory cytokine with important regulatory functions in the innate immune response system, plays a crucial role in vascular pathologies. IL-18 is also a predictor of cardiovascular death in patients with CVD and is involved in atherosclerotic plaque destabilization.

Results: In order to determine if circulating levels of IL-18 can serve as a specific biomarker for distinguishing MetS patients from pre-MetS subjects, we studied 78 patients with visceral fat deposition and 14 age-matched control subjects. Increased levels of IL-18 were observed more frequently in patients with MetS than in pre-MetS subjects and were positively associated with waist circumference. Serum levels of IL-18 were significantly reduced by a change in weight caused by lifestyle modifications. There was a significant interaction between waist circumference and serum IL-18 concentration. Weight loss of at least 5% of the body weight caused by lifestyle modification decreased IL-18 circulating levels relative to the reduction in waist circumference and blood pressure, suggesting that this degree of weight loss benefits the cardiovascular system.

Conclusion: IL-18 may be a useful biomarker of the clinical manifestations of MetS and for the management of the risk factors of CVD.

Background

Obesity and the related metabolic syndrome (MetS) are major public health problems [1] that are associated with an increased risk of the development of atherosclerotic cardiovascular disease (CVD). The mechanism of which may be mediated, at least in part, by increased secretion of proinflammatory cytokines by the adipose tissue [2]. MetS consists of atherogenic dyslipidemia (elevated triglycerides and low high-density lipoproteins [HDLs]), elevated blood pressure and glucose levels, and abdominal obesity with prothrombotic and proinflammatory states [1]. MetS is associated with a 5-fold higher risk of the development of type 2 diabetes and a 2.6- to 3-fold higher risk of the development of CVD [3,4]. The pathophysiology underlying MetS is not well defined, and several investigators have sought to identify a single factor that could explain all of the components of the syndrome. In addition to insulin resistance and/or hyperinsulinemia, investigators have found several biomarkers that are associated with MetS, including leptin [3], catecholamines [5], brain natriuretic peptide (BNP) [6], oxidized low-density lipoprotein (LDL) cholesterol [7], uric acid [8], C-reactive protein (CRP) [3], plasminogen activator inhibitor-1 [3], aldosterone [3], cystatin C [9], and carboxy-terminal prevasopressin (copeptin) [10]. This wide variety of biomarkers highlights the diverse pathophysiological perturbations that occur in MetS [10].

Interleukin-18 (IL-18), which is a pleiotropic proinflammatory cytokine with important regulatory functions in the innate immune response system, plays a crucial role in vascular pathologies. IL-18 is also known as a predictor of cardiovascular death in CVD patients and is

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involved in atherosclerotic plaque destabilization. A growing body of evidence suggests that IL-18 levels may be closely related to MetS and its consequences [11-13]. Increasing levels of circulating IL-18 have been reported to be closely associated with the components of MetS and to predict type 2 diabetes, cardiovascular events, and mortality [14,15]. IL-18 is secreted constitutively in many different cell types in the adipose tissue, including macrophages, vascular endothelial cells, vascular smooth muscle cells, and adipocytes [16,17]. On the other hand, aerobic exercise has been reported to reduce levels of CRP and IL-18 in subjects with type 2 diabetes [18,19].

We hypothesized that circulating levels of IL-18 may enhance atherosclerosis-prone conditions in patients with MetS. In order to examine this hypothesis, we studied the circulating levels of IL-18 in MetS patients and in subjects with pre-MetS conditions. Furthermore, the circulating levels of IL-18 were examined in MetS patients before and after lifestyle modifications that resulted in weight loss.

Results and Discussion

Results

Circulating IL-18 levels as a specific biomarker to distinguish MetS patients from subjects with pre-MetS conditions

In order to determine whether the circulating levels of IL-18 could be a specific biomarker to distinguish MetS patients from subjects with pre-MetS conditions, we studied 42 patients with MetS or pre-MetS and 14 control subjects (average body mass index [BMI], 23.3). There were 28 patients diagnosed as having MetS (BMI, 30.9), and the remaining 14 patients were designated as pre-MetS (BMI, 29.6), which was defined as the subjects having only 1 component of the MetS criteria proposed by the Japanese Society of Internal Medicine. The baseline characteristics of the subjects are shown in Tables 1 and 2. Patients with MetS had a higher BMI and waist circumference.

As shown in Table 2, fasting plasma glucose levels, plasma insulin levels, a homeostasis model assessment (HOMA-IR), and triglyceride levels increased in both MetS and pre-MetS subjects. Among them, only plasma

Table 1 Characteristics of the study participants

Characteristics	MetS (n = 28)	Pre-MetS (n = 14)	Control (n = 14)
Age (year)	54.8 ± 12.9	58.9 ± 13.0	56.4 ± 10.1
Sex, female (%)	9 (32.1%)	6 (42.9%)	8 (57.1%)
BMI (kg/m^2)	30.9 ± 7.7*	27.6 ± 3.2	23.3 ± 2.9
Waist circumference (cm)	102.7 ± 13.2*#	95.0 ± 7.5*	78.7 ± 7.2

Data are means ± SD. *P < 0.01 for MetS (or pre-MetS) vs. Control. #P < 0.01 for MetS vs. pre-MetS. BMI, body mass index; MetS, metabolic syndrome.

Table 2 Components of the metabolic syndrome

Components	MetS	Pre-MetS	Control
Plasma glucose (mg/dL)	136 ± 50*	110 ± 12	99 ± 7
Plasma insulin (IU/mL)	8.7 ± 5.6*#	6.3 ± 2.7	5.2 ± 1.5
HOMA-IR	2.0 ± 1.1*	1.7 ± 0.7*	1.3 ± 0.4
HDL cholesterol (mg/dL)	48 ± 12*	59 ± 16*	71 ± 16
Triglyceride (mg/dL)	187 ± 25*	160 ± 24*	69 ± 21
Hypertension, n (%)	21 (75.0%)*	5 (35.7%)#	3 (21.4%)

Data are means ± SD. *P < 0.01 for MetS (or pre-MetS) vs. Control. #P < 0.05 for MetS vs. pre-MetS. HOMA-IR, homeostatis model assessment; HDL, high density lipoprotein; MetS, metabolic syndrome.

insulin levels were significantly higher in patients with MetS compared to those who were pre-MetS. These data suggest that more severe hyperinsulinemia may exist in MetS patients compared to subjects with pre-MetS conditions.

Increased levels of glycated hemoglobin (HbA1c), CRP, and IL-18 were observed in MetS patients (Table 3). Decreased serum adiponectin levels were observed in patients with both MetS and pre-MetS compared with those in control subjects (Figure 1a). There was no difference in adiponectin levels between MetS and pre-MetS patients (Table 3). Increased levels of CRP and IL-18 likely reflect a low-grade systemic inflammation and the development of atherosclerosis.

As shown in Figure 1b, increased levels of IL-18 were observed more frequently in patients with MetS than in those who were pre-MetS (P < 0.01), and these levels were positively associated with fasting insulinemia (P < 0.05). Interestingly, serum levels of IL-18 were slightly, but significantly, correlated with the waist circumference in patients with MetS and pre-MetS conditions (Figure 1c). These data suggest that IL-18 may reflect visceral fat deposition and insulin resistance. In conclusion, IL-18 may be a useful biomarker of the clinical manifestations of MetS and for the management of the risk factors of CVD.

Circulating IL-18 as a useful biomarker for lifestyle modification

We hypothesized that body weight loss from lifestyle modification would improve systemic inflammation in patients with MetS. Serum IL-18 levels were measured in 57 patients with MetS (average BMI, 32.0) before and after they lost at least 5% of their initial weight by lifestyle modification. As shown in Table 4, subjects in the study were typically abdominally obese patients, 74% of the subjects were diagnosed with hypertension, and 61% had diabetes mellitus (DM) and/or impaired fasting glucose (IFG). There was a significant interaction between serum CRP levels and IL-18 levels in patients with MetS (P < 0.01).

Among all of the subjects undergoing lifestyle modifications, 89% achieved significant reductions in weight,

Table 3 Interleukin-18 and related biomarkers

	MetS	Pre-MetS	Control
HbA1c (%)	6.3 ± 1.3*	5.4 ± 0.4	5.0 ± 0.3
CRP (μg/dL)	365 ± 272*	114 ± 98	82 ± 55
adiponectin (μg/mL)	5.0 ± 0.7*	5.5 ± 0.8*	6.3 ± 0.9
IL-18 (pg/mL)	301 ± 220*#	121 ± 31	112 ± 29

Data are means ± SD. *$P < 0.05$ for MetS (or pre-MetS) vs. Control. #$P < 0.01$ for MetS vs. pre-MetS. HbA1c, haemoglobinA1c; CRP, C-reactive protein; IL-18, interleukin-18; MetS, metabolic syndrome.

waist circumference, HOMA-IR, and blood pressure after the lifestyle modification was maintained for an average of 22.6 (5.6) weeks. As shown in Table 5, 22-23 weeks of lifestyle modification could significantly reduce obese conditions, including body weight and waist circumference. Systolic blood pressure was also markedly reduced in these subjects ($P < 0.01$).

Serum levels of IL-18 were significantly reduced with weight loss ($P < 0.01$), and the levels significantly correlated with the change in weight ($P = 0.046$). Lifestyle modification-induced weight loss of 5% body weight significantly improved the levels of circulating biomarkers that are related to metabolic and vascular inflammation (Table 6). Most importantly, 5% body weight loss reduced serum levels of IL-18 and synergistically increased serum adiponectin levels in these obese patients (Figure 2).

The reduction in IL-18 concentration correlated with increases in adiponectin ($P = 0.015$). A 5% weight loss

Table 4 Baseline characteristics of the study participants for lifestyle modification

Characteristics	Values	(range)
Age (year)	55.4 ± 13.2	28-76
Sex, female (%)	27 (54.0%)	
Body mass index (kg/m^2)	31.9 ± 6.2	24-61
Body weight (kg)	84.5 ± 18.6	54.5-138
Waist circumference (cm)	104.5 ± 12.0	85.5-144
Systolic blood pressure (mmHg)	138.7 ± 17.7	
Diastolic blood pressure (mmHg)	78.3 ± 11.8	
Triglyceride (mg/dL)	189.5 ± 121.3	
HDL-cholesterol (mg/dL)	50.1 ± 11.5	
Plasma glucose (mg/dL)	123.4 ± 37.0	
Hypertension (%)	74	
High triglyceride (%)	49	
Low HDL-cholesterol (%)	11	
DM/IFG (%)	61	

Values are means ± SD or presence of comorbidities (%). HDL, high-density lipoprotein; DM, diabetes mellitus; IFG, impaired fasting glucose.

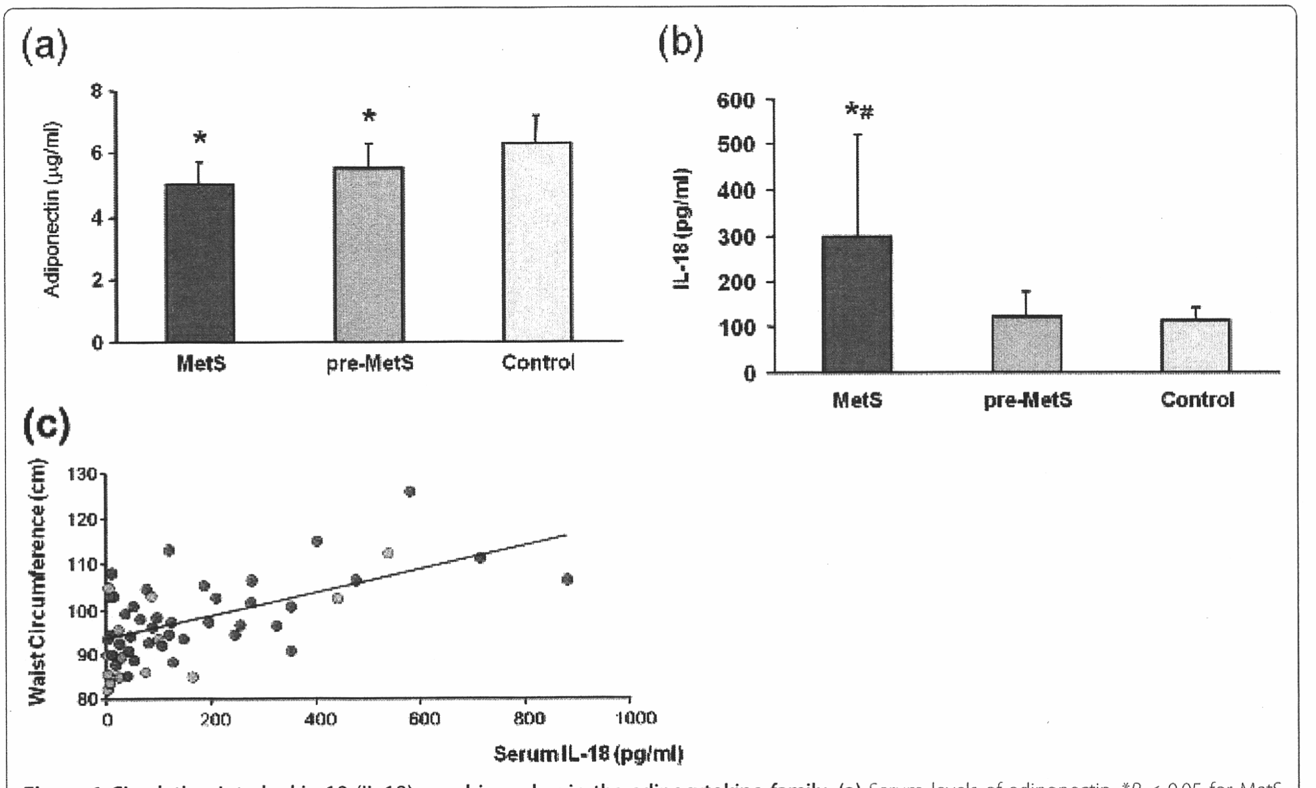

Figure 1 Circulating Interleukin-18 (IL-18) as a biomarker in the adipocytokine family. **(a)** Serum levels of adiponectin. *$P < 0.05$ for MetS (or pre-MetS) vs. Control. **(b)** Circulating levels of IL-18. *$P < 0.01$ for MetS (or pre-MetS) vs. Control. #$P < 0.01$ for MetS vs. pre-MetS. **(c)** Serum levels of IL-18 and waist circumference. Correlations: $P < 0.01$.

Table 5 Lifestyle modification-induced changes in anthropometric variables

Characteristics	Values	(range)
Δ Body mass index (kg/m²)	1.6 ± 1.1#	(0.4-5.0)
Δ Body weight (kg)	5.4 ± 4.4#	(2.8-33.0)
Δ Waist circumference (cm)	9.6 ± 5.5*	(1.5-24.5)
Δ Systolic blood pressure (mmHg)	15.3 ± 17.5*	
Δ Diastolic blood pressure (mmHg)	12.1 ± 19.1#	

Values are means ± SD (range).*$P < 0.01$ and #$P < 0.05$ for baseline vs. after lifestyle modification in patients with metabolic syndrome.

from lifestyle modification decreased the circulating levels of IL-18 in relation to the reduction in waist circumference, serum CRP levels, and blood pressure, suggesting that this degree of weight loss resulted in cardiovascular benefits.

Discussion

To the best of our knowledge, this is the first study showing that circulating IL-18 levels can be a useful biomarker for distinguishing patients with MetS from subjects with pre-MetS conditions. Furthermore, a 5% weight loss from lifestyle modification decreased circulating IL-18 levels, a prognostic biomarker for coronary artery disease, in patients with MetS.

IL-18 and vascular inflammation

In the last decade, accumulating evidence has suggested the importance of a low but chronic inflammatory state in obesity and in MetS. Recent research has revealed a role of adipose tissue beyond energy storage that involves the harboring of inflammatory cells that are believed to sustain inflammation and impair adipocyte function [20,21]. IL-18 was originally found as an interferon-gamma (IFN-γ)-inducing factor (IGIF) [22] and belongs to the IL-1 family of cytokines [23]. The expression of IL-18 has been reported to be higher in atherosclerotic plaques than in normal control arteries. In addition, IL-18 was found to localize mainly in plaque macrophages and express strongly in unstable plaques [24]. These data suggested that IL-18 plays a major role in atherosclerotic plaque destabilization, which leads to

Table 6 Changes in circulating interleukin-18 and related biomarkers by lifestyle modification

	before	after	*P* values
Triglyceride (mg/dL)	190 ± 121	139 ± 67	0.049
HDL-cholesterol (mg/dL)	50 ± 12	56 ± 11	< 0.001
Glucose (mg/dL)	123 ± 37	105 ± 19	0.041
Adiponectin (μg/mL)	5.4 ± 1.5	6.5 ± 2.1	0.034
IL-18 (pg/mL)	158 ± 97	119 ± 75	0.021
CRP (μg/dL)	311 ± 315	204 ± 219	0.012

Data are means ± SD. HDL, high density lipoprotein; IL-18, interleukin-18; CRP, C-reactive protein.

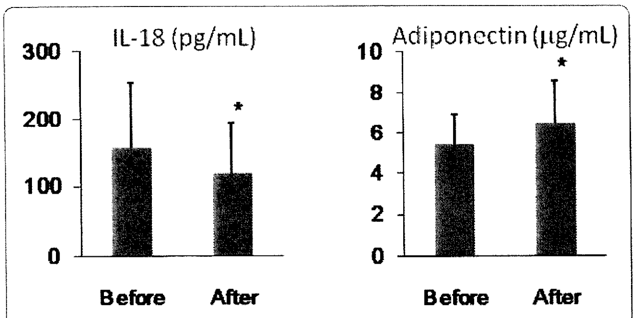

Figure 2 Circulating levels of interleukin-18 (IL-18) and adiponectin in patients with metabolic syndrome before and after lifestyle modification. *$P < 0.05$ for baseline vs. after lifestyle modification in patients with metabolic syndrome.

acute ischemic syndromes. In an atherosclerotic animal model, murine IL-18 binding protein (the endogenous inhibitor of IL-18) prevents fatty streak development in the thoracic aorta of apoE knockout mice and slows the progression of advanced atherosclerotic plaques in the aortic sinus [25]. Moreover, IL-18 has been recently shown to contribute to cardiac dysfunction following ischemic reperfusion in vitro [26]. These findings, taken together, identify the inhibition of IL-18 signaling as an important therapeutic target for preventing atherosclerotic plaque development and for inhibiting plaque complications [25].

IL-18 and metabolic syndrome

IL-18 concentrations are increased in patients with type 2 diabetes, obesity, and polycystic ovary syndrome [27-29]. In addition, circulating IL-18 has been reported to be closely associated with MetS and its components [30]. Paradoxically, IL-18-deficient mice had markedly increased body weight compared with wild type littermates at 3 months of age, and these mice exhibited obesity, insulin resistance, hyperglycemia, lipid abnormalities, and atherosclerosis. The weight gain was associated with significantly increased body fat; food intake; and glucose, insulin, glucagon, cholesterol, and leptin levels. A histological analysis of various organs of the mutant mice showed only an increased size of the pancreatic islets. Leptin administration or the intracerebral, but not intravenous, administration of recombinant IL-18 reduced food intake. Intraperitoneal administration of recombinant IL-18 restored insulin sensitivity and corrected the hyperglycemia through the activation of signal activation of transcription 3 (STAT3) phosphorylation in IL-18 double-knockout mice. These data suggest that IL-18 has an important role in the homeostasis of energy intake and insulin sensitivity.

In the present study, circulating levels of IL-18 were significantly reduced after lifestyle modification, which resulted in a synergistic reduction in serum CRP levels, plasma glucose levels, and triglyceride levels in patients with MetS. On the other hand, obese patients with type 2 diabetes have been reported to produce significantly less IFN-γ in the peripheral blood mononuclear cells in response to IL-18 stimulation compared to lean controls, which was most likely due to the reduced expression of the IL-18 receptor β chain [31]. This has led to a new concept of IL-18 resistance, which is similar to insulin resistance, in MetS patients. This new concept of IL-18 resistance may shed further light upon the mechanisms involved in the IL-18-related effect on systemic metabolic disorder. At this point, IL-18-mimetic agents or interventions, including lifestyle modifications, may be novel therapeutic strategies for patients with not only pre-MetS conditions but also MetS and atherosclerosis-prone conditions.

IL-18 gene polymorphisms have been shown to be associated with increased levels of circulating IL-18 [32] and one such polymorphism was associated with impaired insulin sensitivity and an increased risk of having MetS [33,34]. These findings suggest that IL-18 may be involved in the pathogenesis of MetS [11]. Therefore, genetic variations of IL-18 influence circulating levels of IL-18 and the clinical outcome in patients with coronary artery disease.

IL-18 as a predictive biomarker for cardiovascular events

In previous studies in patients with documented coronary artery disease, serum IL-18 levels were elevated in patients with acute coronary syndrome [35] and were a strong independent predictor of cardiovascular death [14,36]. In a previous cohort study, circulating IL-18 was the only independent predictor of cardiovascular mortality in a subgroup with MetS [37]. Moreover, circulating IL-18 levels were a strong and independent predictor of cardiovascular events in elderly men with MetS [38]. Increased levels of IL-18 were associated with the presence of subclinical atherosclerosis, which was evaluated by an examination of the intima media thickness of the carotid artery [39], and by measurement of arterial stiffness, which was determined on the basis of brachial pulse wave propagation [40], after adjustment for traditional risk factors. However, others have reported that circulating IL-18 levels were associated with carotid media thickness in univariate analyses, but not after adjustment for traditional risk factors [13,41] or in multiple analyses [42].

IL-18 as a therapeutic biomarker to enhance coronary risk factor management in MetS patients

A growing body of evidence supports an important role of IL-18 in the pathogenesis of MetS and atherosclerosis. In this study, a 5% weight loss from lifestyle modification decreased circulating levels of IL-18 and CRP. According to the results of previous clinical studies, weight loss mediated by calorie-restricted diet interventions [43], Mediterranean-like diets, and omega-3 fatty acid supplementation [44], or combined interventions with diet and exercise [45,46], were reported to decrease IL-18 levels [40]. Aerobic exercise has been reported to reduce circulating levels of IL-18 in patients with type 2 diabetes [18,19] and IL-18 expression in adipose tissue in obese subjects [47].

Study limitations

A limitation of the current study is that the study cohort was small. Since the circulating levels of IL-18 correlated well with the waist circumference in patients with MetS and subjects with pre-MetS conditions, it is reasonable to speculate that there may have also been a difference detected between the MetS and pre-MetS groups, if the group sizes were bigger. However, the group sizes for the examination of the effects of lifestyle modification were adequate to reveal significant differences in the changes in the circulating levels of IL-18 and other inflammatory biomarkers.

Conclusions

In summary, higher circulating levels of IL-18 were associated with increased MetS scores and systemic inflammation, which was independent of the presence of diabetes or dyslipidemia. Circulating IL-18 may be a novel biomarker for high-risk patients with MetS, and further studies are warranted in order to assess its utility as a predictor of the presence of MetS and atherogenic conditions. These findings suggest that IL-18 dysfunction or resistance is a novel pathophysiological mechanism underlying insulin resistance and MetS. Moreover, a 5% weight loss from lifestyle modification decreased the circulating levels of IL-18 relative to the reduction in waist circumference, vascular inflammation, and blood pressure, suggesting that this degree of circulating IL-18-guided weight management may be effective for cardiovascular benefits and the prevention of cardiovascular events.

Materials and methods

Subjects

The study included 78 Japanese outpatients with abdominal obesity (waist circumference, >85 cm for men and >90 cm for women) who consulted for medical care in the Metabolic Syndrome Clinic, Department of Cardioangiology, Kitasato University Hospital. All subjects provided informed consent before participating in this study, and anonymity was maintained by tracing the patients through their clinical history number.

The project was approved by the Scientific and Ethical Committee of the Kitasato University School of Medicine, Japan. BMI was calculated as weight divided by height squared. Systolic and diastolic blood pressures were measured after a rest of at least 15 min with a sphygmomanometer while subjects were in a sitting position. HOMA-IR, which was used as a measure of insulin resistance, was calculated as fasting plasma insulin (μU/mL) × glucose (mg/dL)/405 [48]. All subjects were free from chronic inflammation, immune disease, acute coronary syndrome, renal and/or liver dysfunction, malignancy, or immune diseases.

Definitions of MetS and pre-MetS

Metabolic scores were calculated using MetS components according to the MetS criteria proposed by the Japanese Society of Internal Medicine [49]. The score consisted of 4 independent components, including abdominal obesity, which was defined as a waist circumference of ≥85 cm in men or ≥90 cm in women; high triglyceride and/or low HDL-cholesterol levels; hypertension; and elevated fasting glucose levels. The diagnosis of hypertension was made on the basis of blood pressure levels measured at the study visit (≥130/85 mmHg) or a prior diagnosis of hypertension and current treatment with antihypertensive medications. DM and/or IFG was considered present if the subject had a history of diabetes or had a fasting glucose level of 110 mg/dL or greater. Participants who had low metabolic scores (1 or 2) were designated as the pre-MetS subjects, whereas the patients who had high metabolic scores (3 or 4) were defined as MetS subjects. There were 64 patients diagnosed as having MetS and the remaining 14 patients were designated as pre-MetS, which was defined as having only 1 component of the MetS criteria.

Serum Sample Collection

After an overnight fast, blood serum samples were collected by venipuncture from 78 patients with abdominal obesity and from 14 healthy donors. The age range of the healthy donors matched that of the patients. For the IL-18 biomarker study examining the differences in IL-18 levels between MetS patients and subjects with pre-MetS conditions, 36 patients out of the 64 patients with MetS were excluded because they were taking metabolic-mimetic agents (statins, anti-diabetic drugs, and/or colestimide).

Measurement of Clinical Biomarkers

Biochemical markers such as triglycerides, LDL cholesterol, HDL cholesterol, insulin, plasma glucose, HbA1c, uric acid, gamma-glutamyl transpeptidase (γ-GTP), CRP, and BNP were measured.

Lifestyle Modification

In order to examine the effects of lifestyle modification in the IL-18 biomarker study, 64 patients with MetS were recruited to lose weight in order to improve their cardiovascular risk factors. We studied 57 patients with MetS (average BMI, 31.9) who successfully lost at least 5% of their initial weight through lifestyle modification. All subjects were instructed to maintain a standard mild energy-restricted diet and to engage in walking for at least 30 min a day, 5 days a week. Serum IL-18 and adiponectin levels were measured in these subjects before and after lifestyle modification, which was maintained for 8-34 weeks.

Measurement of Adipocytokines

Circulating levels of human IL-18 and adiponectin were determined by an enzyme-linked immunosorbent assay (ELISA) using the human IL-18 ELISA Kit (MBL, Co., Ltd., Nagoya, Japan) and the CircuLex™ human adiponectin ELISA Kit (CycLex Co., Ltd., Nagano, Japan), respectively. Samples were processed according to the manufacturer's instructions [35,50].

Statistical Analysis

Continuous data are summarized as either mean (SD) or median and quartiles, and categorical data are expressed as percentages. The data were compared by an unpaired *t*-test or Mann-Whitney *U*-tests, where appropriate. Differences in the proportions of variables were determined by a chi-squared analysis. In order to evaluate the relationship between IL-18 and selected variables, we calculated Spearman correlation coefficients between the circulating levels of fasting IL-18 and the following variables: (1) conventional risk factors for CVD (i.e., LDL cholesterol, HDL cholesterol, triglycerides, HbA1c, the presence of hypertension, and current smoking status), and history of coronary artery disease; (2) measures of adiposity and insulin resistance (i.e., BMI, waist circumference, fasting blood glucose levels, insulin levels, and HOMA-IR); and (3) metabolic risk scores (i.e., abdominal obesity, hypertension, high triglycerides and/or low HDL cholesterol, and glucose intolerance or diabetes) and MetS-related co-morbid conditions (i.e., hyper-uric acidemia, fatty liver disease, chronic kidney disease, and sleep apnea syndrome).

In order to evaluate the association of IL-18 with MetS, we constructed multivariable logistic regression models in order to assess whether the circulating IL-18 levels were independently associated with MetS. We calculated the odds ratio for the presence of MetS in each IL-18 level quartile, and the participants with IL-18 levels in the lowest IL-18 quartile were considered as the reference group. Adjustments were performed for age and sex and for age, sex, and β-blocker use. Two-sided *P*-values of < 0.05 were considered significant.

Acknowledgements

This work was partly supported by KAKENHI: Health Labour Science Research Grant 10103153 (TI) and Grants-in-Aid for Young Scientists 21790743 (MY-T) and 21790744 (TT) from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

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Authors' contributions
MY-T participated in the design of the study and performed the statistical analysis. TT conceived of the study, and participated in its design and coordination and helped to draft the manuscript. Other authors participated in enrolling patients in the study and discussion. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

Received: 14 November 2010 Accepted: 20 January 2011
Published: 20 January 2011

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