資料１：
日本予防医学リスクマネジメント学会発表資料

オフィスワーカーにおける腰痛発生要因の横断的検討

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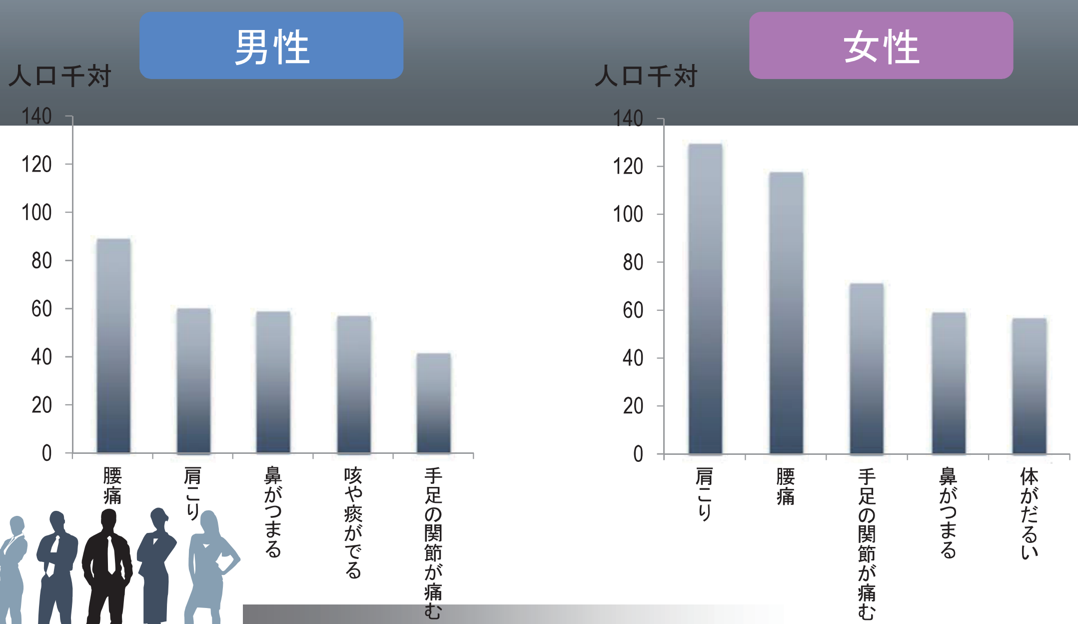
Introduction

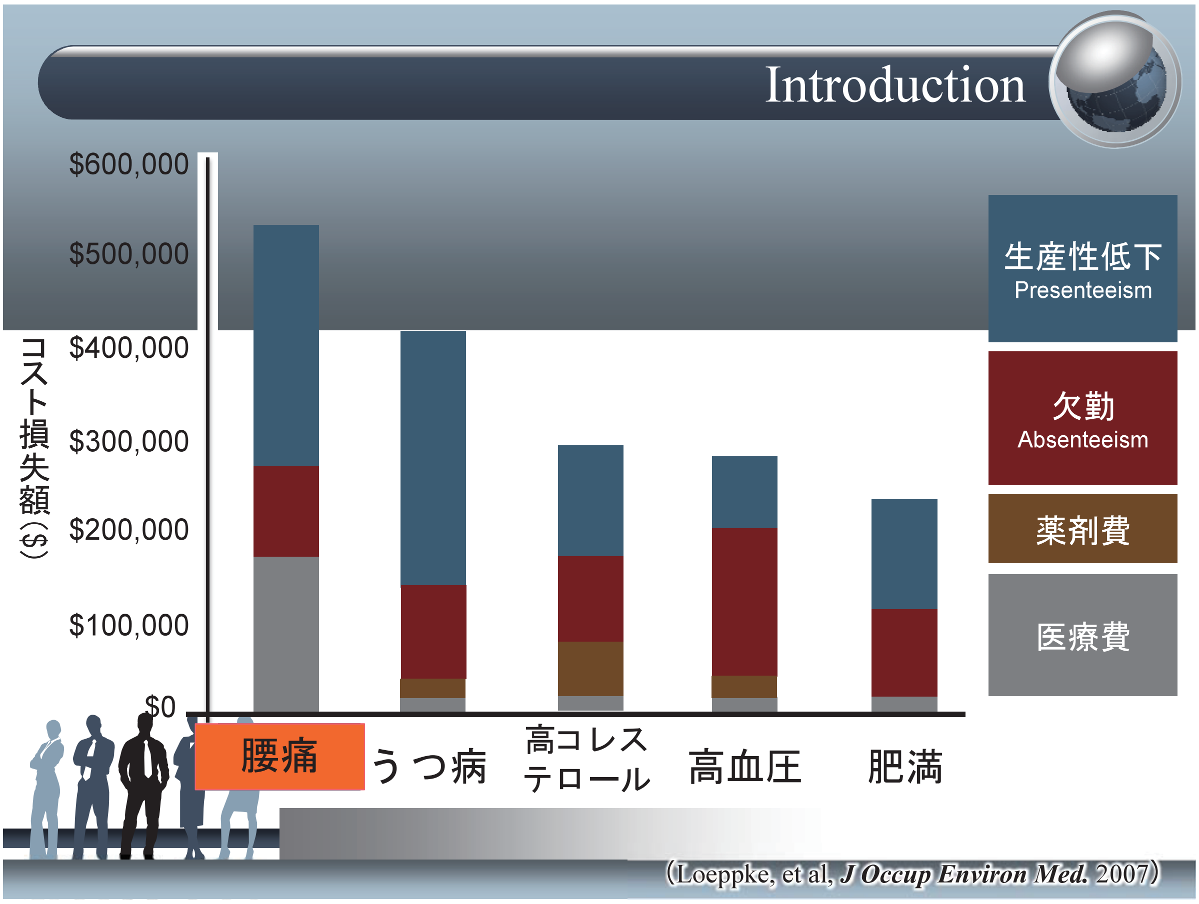
有訴率の上位5症状

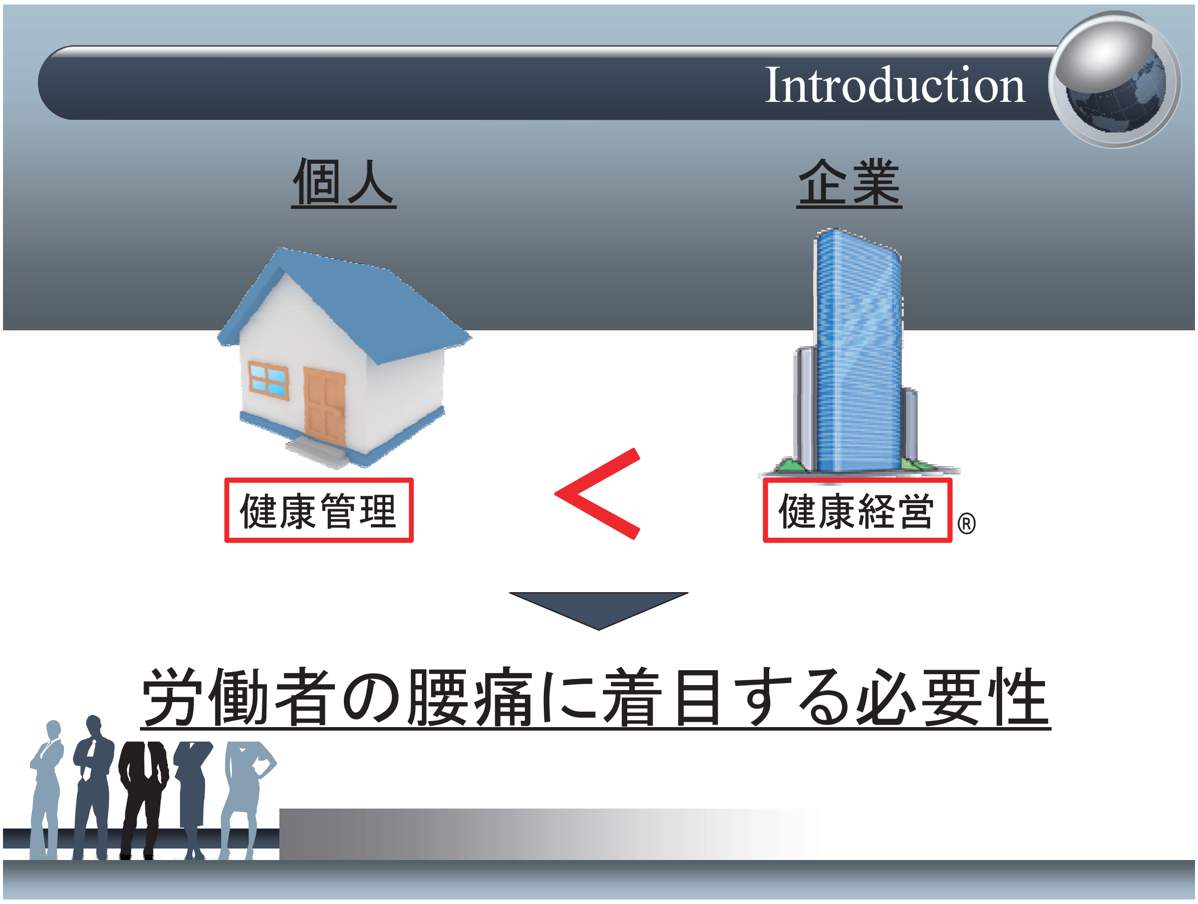


出典：厚生労働省「平成22年国民生活基礎調査」より作成


Introduction
有訴率の上位5症状
男性
女性
人口千対
140
120
100
80
60
40
20
0
腰痛
肩こり
鼻がつまる
咳や痰がでる
手足の関節が痛む
人口千対
140
20
0
肩こり
腰痛
手足の関節が痛む
鼻がつまる
体がだるい
推計：2,800万人
厚生労働省 研究班
出典：厚生労働省「平成22年国民生活基礎調査」より作成


職業性疾病の6割が腰痛


Introduction
$600,000
$500,000
$400,000
$300,000
$200,000
$100,000
$0
コスト損失額（$）
腰痛
うつ病
高コレステロール
高血圧
肥満
生産性低下
Presenteeism
欠勤
Absenteeism
薬剤費
医療費
（Loeppke, et al, J Occup Environ Med. 2007）


Introduction
個人
企業
健康管理
<
健康経営®
労働者の腰痛に着目する必要性

Introduction

➢腰痛の有訴率は、職業別で異なる

(Kaneda K, et al. *J Nippon Med Sch*. 2001)

39%

技能職

46-65%

保健衛生業

71-74%

運輸業

IT社会の進展に伴い増加している
オフィスワーカーに着目した研究は数少ない

オフィスワーカーにおける腰痛の
リスク要因は明らかにされていない

Purpose

オフィスワーカーの腰痛に関連する
要因を明らかにすること

Materials & Methods

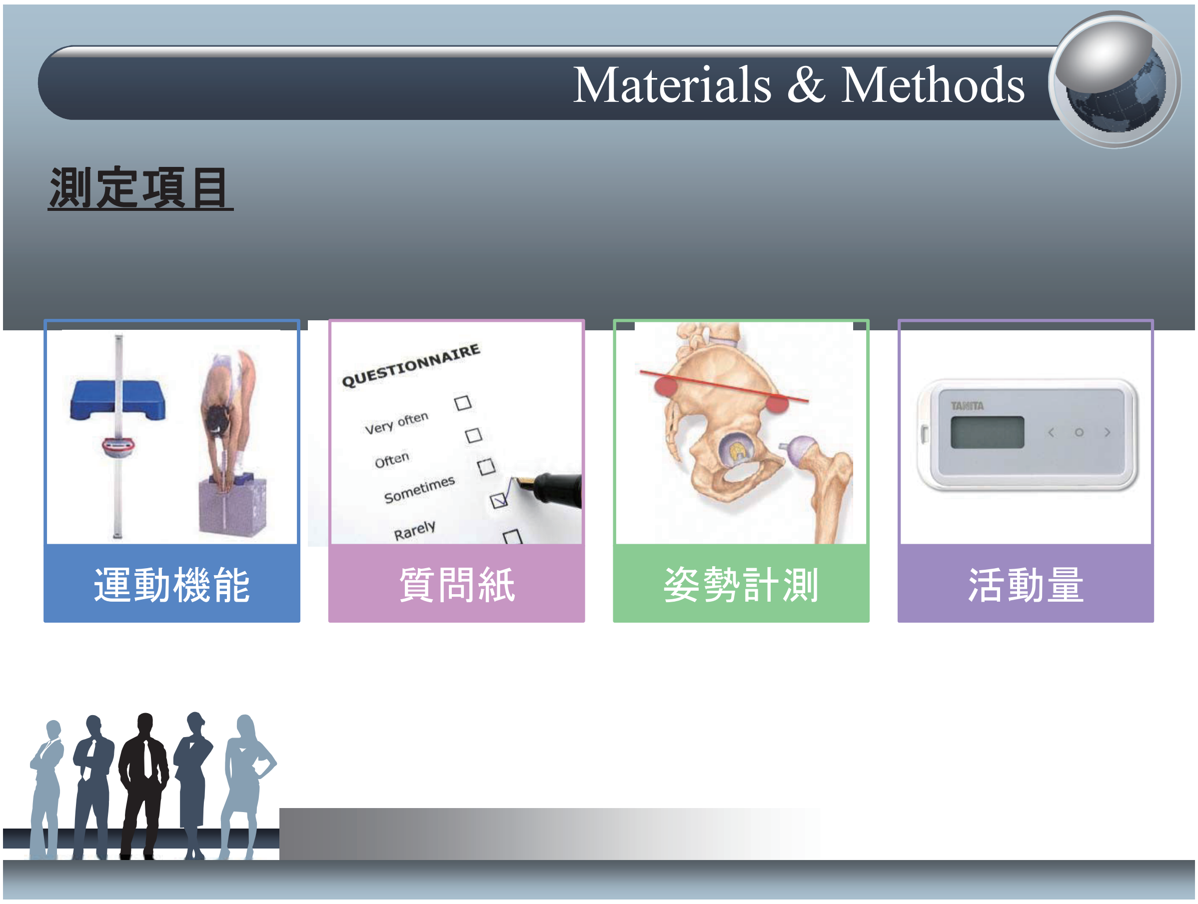
研究デザイン

- 横断的研究

対象者

- 株式会社フジクラの本社社員（オフィスワーカー）
- 腰痛検診に参加した601名（M：433名、F：168名）
- 包含基準は、腰痛検診に耐える能力を有する者とした

本研究は、当該施設の倫理委員会の承認を得て行った.

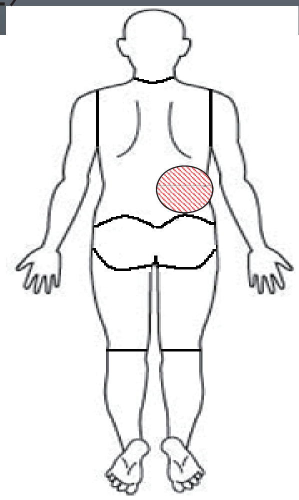

Materials & Methods
測定項目
QUESTIONNAIRE
Very often
Often
Sometimes
Rarely
TANITA
運動機能
質問紙
姿勢計測
活動量


Materials & Methods
運動機能
筋力
柔軟性
平衡感覚
イス
握力
30秒立ち上がりテスト
立位体前屈
閉眼片脚立位
（労働安全衛生法に準ずる項目）

Materials & Methods

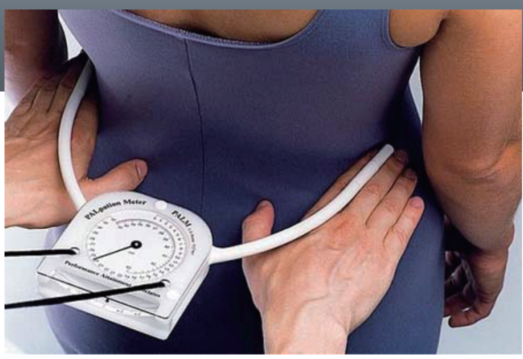
質問紙

- 基本情報（年齢・性別・身長・勤続年数・喫煙歴）
- 腰痛の有無
  - ✓ 期間：過去2週間（はい/いいえ）
  - ✓ 部位：肋骨最下端～臀溝の間の領域
- Self-reporting Depression Scale（以下、SDS）
  - ✓ 40点以上でうつ傾向あり



Materials & Methods

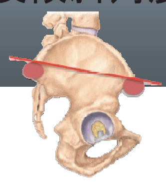
姿勢計測



検者内信頼性：0.78　（Palpation meterを使用）
検者間信頼性：0.76

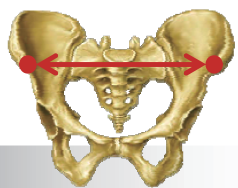
（Bruno RC, et al. ***Physiotherapy***. 2010）

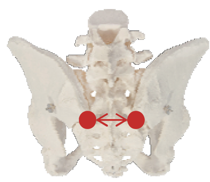
- 前後傾斜角度（°）



- 左右傾斜角度（°）

- 骨盤の開き（cm）_前後





※体格の影響を除外するため、身長^2で補正

Materials & Methods

活動量(歩数)

- 入浴・睡眠・水に関わる活動以外のときは、基本的に常時着用
- 2週間の歩数データを平均し、代表値とした.

タニタ社製活動量計(FB-730)

2週間前 → 計測日

平均値を算出

Statistical Analysis

単変量解析(2群間の比較)

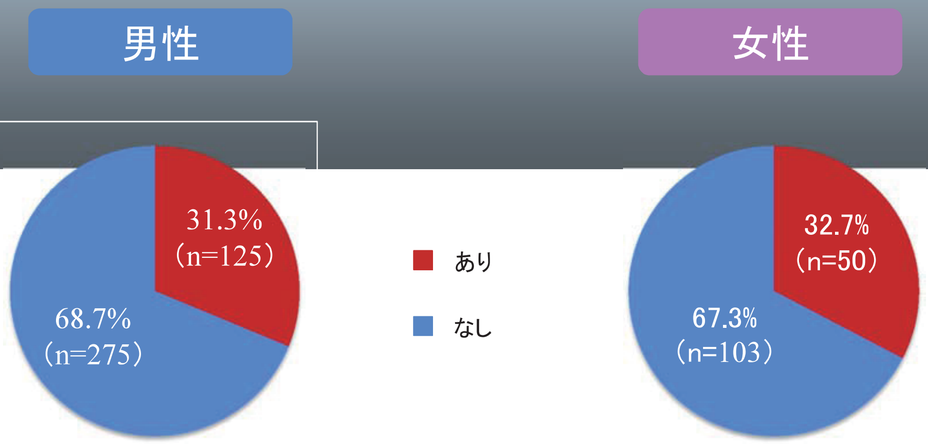
腰痛の有無 ― ✓ 対応のないt検定 ✓ カイ二乗検定

多変量解析(ロジスティック回帰分析)

- 従属変数:腰痛の有無
- 独立変数:単変量解析で有意差が認められた項目
- 調整変数:年齢

全ての解析は、男女別に行った.
統計学的有意水準は5%未満とした.

Results



罹患率:31.3%

罹患率:32.7%

Results

単変量解析

	男性			女性		
	なし群(n=275)	あり群(n=125)	P-value	なし群(n=103)	あり群(n=50)	P-value
基本情報						
年齢(歳)	45.9 ± 10.4	46.2 ± 9.9	0.760	39.9 ± 9.0	41.5 ± 8.4	0.291
BMI(kg/m²)	23.9 ± 3.2	25.2 ± 4.1	0.004*	21.6 ± 3.7	21.4 ± 3.1	0.730
勤続年数(year)	18.4 ± 10.8	18.2 ± 10.6	0.857	15.8 ± 10.2	14.7 ± 10.5	0.541
喫煙歴(有/無)	57.1%	62.9%	0.320	8.1%	14.0%	0.263
運動機能						
握力(kg)	45.2 ± 6.8	48.9 ± 39.8	0.310	27.6 ± 4.9	28.5 ± 4.9	0.492
30秒立ち上がり(回)	27.6 ± 5.8	27.2 ± 5.1	0.464	25.8 ± 5.9	25.3 ± 5.7	0.650
立位体前屈(cm)	-1.9 ± 9.9	-4.0 ± 9.5	0.050	4.6 ± 9.8	2.8 ± 6.8	0.244
片脚立位(sec)	35.9 ± 48.6	27.7 ± 37.9	0.096	29.3 ± 42.6	27.3 ± 41.3	0.780
姿勢計測						
骨盤傾斜__前後(°)	5.8 ± 3.2	6.0 ± 3.6	0.490	7.9 ± 4.3	8.6 ± 4.5	0.340
骨盤傾斜__左右(°)	-0.1 ± 1.5	-0.03 ± 1.1	0.586	0.3 ± 1.2	0.06 ± 1.3	0.322
骨盤の開き__前(cm)※	8.9 ± 0.9	9.0 ± 0.9	0.425	24.7 ± 2.0	24.8 ± 2.2	0.775
骨盤の開き__後(cm)※	2.8 ± 0.9	2.9 ± 0.9	0.256	9.0 ± 2.7	8.4 ± 3.2	0.227
精神機能						
うつ傾向の有無(≧40点)	39.1%	45.1%	0.269	42.4%	71.1%	0.002*
活動量						
歩数(steps/day)	8331.9 ± 2622.7	7861.9 ± 2840.9	0.186	7569.5 ± 2493.9	8042.8 ± 2750.9	0.401

※身長^2で補正　(*P< 0.01)

Results

多変量解析（ロジスティック回帰分析）

		Odds Ratio (95% CI)	P-value
男性	BMI	1.11 (1.03, 1.19)	0.007*
	年齢	1.00 (0.98, 1.03)	0.784
女性	うつ傾向	3.42 (1.59, 7.34)	0.002*
	年齢	1.02 (0.97, 1.06)	0.446

（*P< 0.01）

Discussion

男性

BMI

Odds ratio : 1.11

女性

うつ傾向

Odds ratio : 3.42

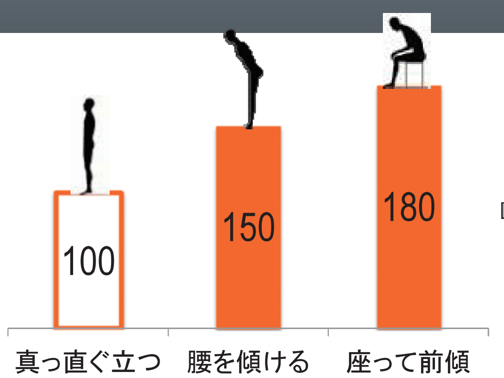
Discussion

腰痛 ー BMI

- 腰痛と体格に関する十分なエビデンスに基づく文献は存在しない.
  （Wai EK,et al. ***Spine J***. 2012）
- <u>男性</u>の若年時の高BMIは、将来の腰椎椎間板障害に関連する.
  （Takatalo J, et al. ***BMC Musculoskelet Disod***. 2013）
- 高BMIは、腰痛発生、腰椎椎間板障害ともに関連する.
  （Dario AB, et al. ***Spine J***. **systematic review of twin studies**. 2015）

Discussion

腰痛 ー BMI

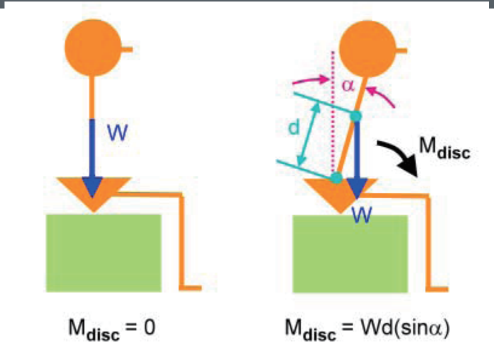


（Nachemson AL. ***Spine***. 1981）

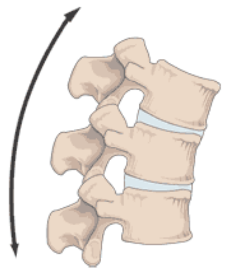
＋ BMI

Discussion

腰痛 ー BMI



（Chaffin D.B, et al. ***Occupational Biomechanics***. 1999）



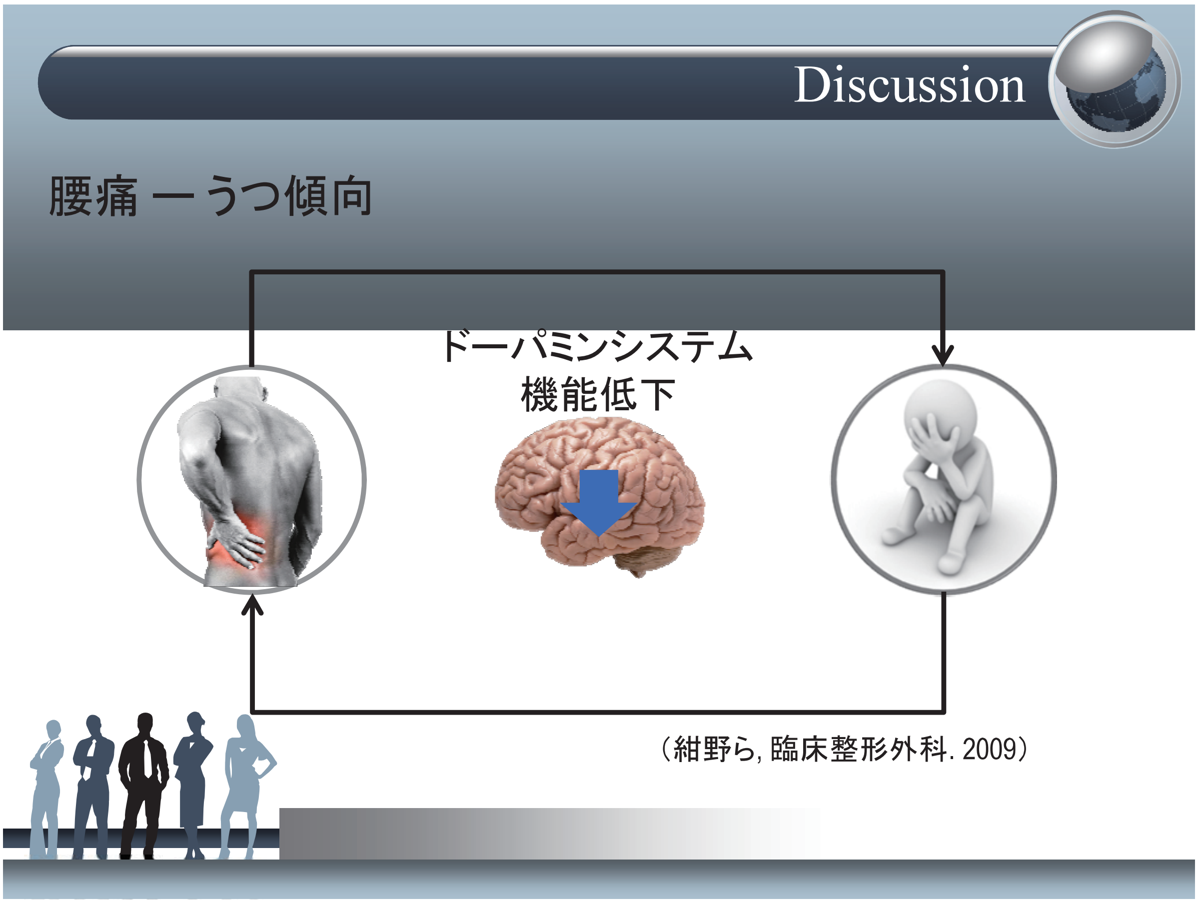
椎間板の負荷↑
筋・筋膜の緊張↑

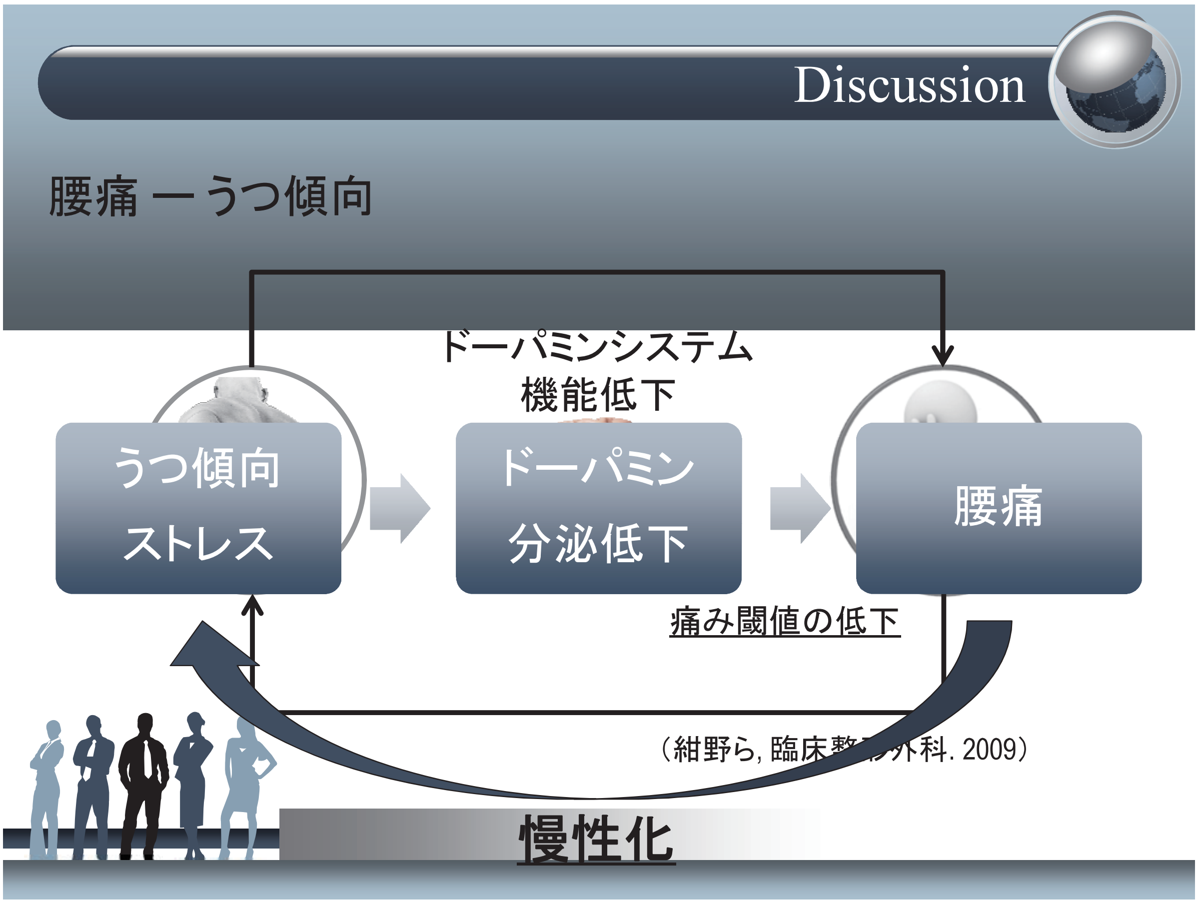
⇒ **腰痛**

Discussion

腰痛 ー うつ傾向

- 心理社会的要因は腰痛発生に関連する.
  （Waddell G, et al. ***Occup Med***. 2001）
- 腰痛発生を予測する因子として、うつ病が最も影響度が強い.
  （Currie SR,et al. ***Phychol Med***. 2005）
- 腰痛発生におけるうつ病のオッズ比は2.88である.
  （Currie SR, et al. ***Phychol Med***. 2005）


Discussion
腰痛 ー うつ傾向
ドーパミンシステム
機能低下
（紺野ら, 臨床整形外科. 2009）


Discussion
腰痛 ー うつ傾向
ドーパミンシステム
機能低下
うつ傾向
ストレス
ドーパミン
分泌低下
腰痛
痛み閾値の低下
（紺野ら, 臨床整形外科. 2009）
慢性化

Conclusions

- オフィスワーカーにおける腰痛の罹患率は、男性で31.3%、女性で32.7%であった.
- 男性では、BMIが有意に腰痛の有無に関連していた.
- 女性では、うつ傾向が有意に腰痛の有無に関連していた.

資料２：

J Woman's Health Care 誌発表論文

Women's Health Care

Morino, et al, J Women's Health Care 2015, 4:1
http://dx.doi.org/10.4172/2167-0420.1000222

Research Article Open Access

The Association between Pregnancy-Related Discomforts and Pre-Pregnancy Body Mass Index in Japanese Women

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Abstract

Objective: To determine the association between pregnancy-related discomforts and pre-pregnancy body mass index in a longitudinal study.

Methods: The study included 355 pregnant women (age, 31.1 ± 4.1 years). Participants were divided into three groups according to their pre-pregnancy body mass index: the low body mass index group, normal body mass index group, and high body mass index group. The occurrence of pregnancy-related discomforts during the second and third trimesters was investigated. Binomial logistic regression analysis was used to examine the association between pre-pregnancy body mass index and pregnancy-related discomforts experienced during the last two trimesters.

Results: The occurrence of most pregnancy-related discomforts increased in the third trimester, while that of constipation and shoulder stiffness or headache decreased. Based on logistic regression analysis, pre-pregnancy body mass index was significantly associated with various discomforts. The occurrence of hip joint or pubis pain (odds ratio/95% confidence interval = 2.38/1.14–4.95) during the second trimester, and sleeping difficulty (2.00/1.09–3.67), hand or finger stiffness (3.00/1.36–6.45), leg cramps (2.29/1.32–3.98), low back pain (2.20/1.29–3.75), hip joint or pubis pain (2.14/1.23–3.73), and shoulder stiffness or headache (2.01/1.06–3.82) during the third trimester was significantly higher in the high body mass index group than in the normal body mass index group. The low body mass index group exhibited a significantly a higher occurrence of shoulder stiffness or headache (2.84/1.35–5.96) during the second trimester and constipation (2.28/1.08–4.82) during the third trimester than the normal body mass index group.

Conclusion: The occurrence of discomforts decreased or increased during pregnancy. Furthermore, both pre-pregnancy high and low body mass index represent important risk factors for many pregnancy-related discomforts, compared with a pre-pregnancy normal body mass index.

Keywords: Health promotion; Pregnancy; Pregnancy-related discomforts; Pre-Pregnancy BMI; Prevention

Introduction

Methods

Anatomical, physiological, hormonal, and psychological changes occur in woman during pregnancy [1,2], causing a variety of discomforts such as low back pain, ligament pain, fatigue, and headache [3]. These pregnancy-related discomforts negatively impact mother and child health and affect the quality of life and limit the daily activities of mothers [4,5]. Despite a number of researchers investigating the management of pregnancy-related discomforts [6,7], there are several limitations to the treatments available during pregnancy. For example, non-prescribed medicines are usually unsuitable because of their adverse effects on pregnant women themselves and on the developing fetus [8,9]. Therefore, a longitudinal study is necessary to collect information on the prevalence of discomforts through the stages of pregnancy. Such information will increase the knowledge of the measures that can be taken to protect women from pregnancy-related discomfort and will be essential to prevent their onset.

Before pregnancy, it is important for women to maintain an appropriate body mass index (BMI) to avoid hormone imbalance and its negative impact on fertility [10]. Furthermore, some research indicates that the pre-pregnancy BMI is a predicting factor for conditions such as gestational diabetes, and thus for adverse pregnancy outcomes [11,12]. Pre-pregnancy obesity may also be a modifiable risk factor for intellectual disability in children [13]. On the other hand, women with pre-pregnancy low weight are at an increased risk of intrauterine growth restriction, perineal tears, preterm birth (spontaneous and induced), and low birth weight [14,15]. These results suggest that both pre-pregnancy high and low BMI negatively affect the progress of the pregnancy. Information about the occurrence of discomforts at each gestational period is necessary for their prevention. Moreover, a normal BMI before pregnancy promotes an uneventful progress through pregnancy. However, to date, very few studies have been conducted on the association between pre-pregnancy BMI and pregnancy-related discomforts. Accordingly, we conducted a longitudinal study aimed to identify pregnancy-related discomforts throughout pregnancy and to identify possible associations between these discomforts and the pre-pregnancy BMI.

Settings

We collected information from 355 women (age, 31.1 ± 4.1 years) at the obstetrics and gynecology clinics in the Aichi Prefecture, Japan, between 2009 and 2013. When the pregnant women visited the clinic for their periodic health examination, the information was collected by the hospital staff such as nurses. The inclusion criteria for the survey were the lack of serious orthopedic disorders, neurological diseases, and high-risk pregnancy. At the first medical examination, we recorded the personal information (age and BMI before pregnancy) of each participant by using a questionnaire.

Questionnaire about Pregnancy-Related Discomforts

The subjects of this study were asked to complete a questionnaire during the second trimester (22.4 ± 2.1 weeks of gestation) and third trimester (33.7 ± 2.1 weeks of gestation). We used the Medical Check Sheet to track pregnancy-related discomforts during gestation. The sheet, developed by the Japan Maternity Fitness Association, is a self-entry questionnaire for the management of physical conditions, to be completed before exercise. Questions were related to the expected date of birth, weeks of gestation, blood pressure, and 10 different pregnancy-related discomforts (i.e., sleeping difficulty, constipation, hand or finger stiffness, swelling, leg cramps, low back pain, hip joint or pubis pain, shoulder stiffness or headache, rib pain, and anorexia or heartburn), reported to commonly occur and to have an adverse effect on pregnancy. If the participants had felt discomfort due to any of the items on the list, those items were checked.

Ethical Considerations

After the purpose of the study had been explained, written informed consent was obtained from each participant in accordance with the guidelines approved by the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1975. The protocol was approved by the Ethics Committee of Kyoto University Graduate School of Medicine (protocol approval E-2110).

Statistical Analyses

Participants were divided into three groups (low BMI group, normal BMI group, and high BMI group) according to their pre-pregnancy BMI (<18 kg/m^2, ≥18 kg/m^2, and <22 kg/m^2 or ≥22 kg/m^2, respectively). We statistically calculated the differences in age between these three groups using analysis of variance. Based on the Medical Check Sheet completed during the second and third trimester, we determined the occurrence of each symptom during the second and third trimesters and analyzed this using descriptive statistics. Binomial logistic regression analysis was used to examine the association between each discomfort and the pre-pregnancy BMI for each trimester. We referred to discomforts as the dependent variables, to low and high BMI groups as the independent variables (with the normal BMI group as reference), and to age as the adjustment variable. Data were entered and analyzed using the Statistical Package for the Social Sciences (Windows version 20.0; SPSS Inc., Chicago, IL, USA). For all analyses, $p<0.05$ was considered statistically significant.

Result

Information on 355 women (pre-pregnancy BMI= 20.3±2.1 kg/m^2) who met the inclusion criteria was collected. We assigned 37 women to the low BMI group (BMI= 17.4±0.6 kg/m2), 246 women to the normal BMI group (BMI= 19.8 ± 1.0 kg/m2), and 72 women to the high BMI group (BMI= 23.5±1.8 kg/m^2). There were no significant differences between the three groups (low, normal, and high BMI groups) in age (30.4 ± 4.2 years, 31.2 ± 4.0 years, and 31.2 ± 4.2 years, respectively).

The occurrence of most of the pregnancy-related discomforts analyzed increased from the second to third trimester, in contrast to that of constipation and shoulder stiffness or headache that showed a decrease (Figure 1).

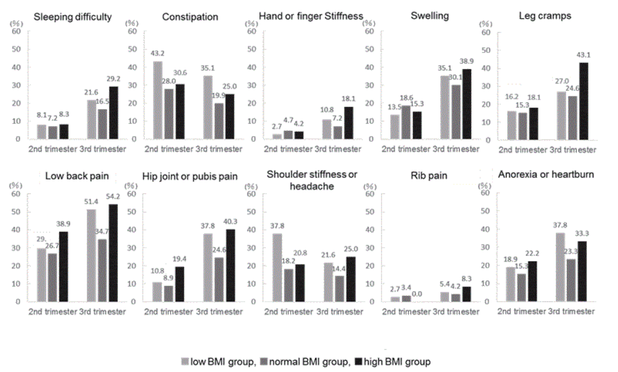

Figure 1: The prevalence of pregnancy-related discomforts during second and third trimester.

Multivariate analysis revealed that pre-pregnancy BMI was significantly associated with some of the discomforts during pregnancy (Table 1). The occurrence of hip joint or pubis pain (odds ratio/95% confidence interval=2.38/1.14–4.95) during the second trimester, and sleeping difficulty (2.00/1.09–3.67), hand or finger stiffness (3.00/1.36–6.45), leg cramps (2.29/1.32–3.98), low back pain (2.20/1.29–3.75), hip joint or pubis pain (2.14/1.23–3.73), and shoulder stiffness or headache (2.01/1.06–3.82) during the third trimester was significantly higher in the high BMI group than in the normal BMI group ($p<0.05$). The occurrence of shoulder stiffness or headache (2.84/1.35–5.96) during the second trimester, and constipation (2.28/1.08–4.82) during the third trimester was significantly higher in the low BMI group than in the normal BMI group ($p < 0.05$). No significant differences were observed in swelling, rib pain, and anorexia or heartburn.

Discussion

We analyzed the changes in the occurrence of pregnancy-related discomforts throughout pregnancy and whether their occurrence was significantly associated with pre-pregnancy BMI. We observed a different trend in the occurrence of the pregnancy-related discomforts analyzed; in fact, while some of them tended to decrease, others appeared to increase during pregnancy progression. Furthermore, we found that both low and high BMI before pregnancy represent important risk factors for many pregnancy-related discomforts, compared with normal BMI.

		second trimester		second trimester	
Discomforts	**BMI group**	**Odds ratio**	**95%CI**	**Odds ratio**	**95% CI**
sleeping difficulty	**low BMI**	1.13	0.32-4.01	1.32	0.57-3.11
	normal BMI	1[reference]		1[reference]	
	high BMI	1.15	0.44-3.02	2.00*	1.09-3.67
constipation	**low BMI**	1.92	0.95-3.91	2.28*	1.80-4.82
	normal BMI	1[reference]		1[reference]	
	high BMI	1.13	0.64-2.00	1.38	0.74-2.56
hand or finger stiffness	**low BMI**	0.6	0.08-4.81	1.61	0.74-2.09
	normal BMI	1[reference]		1[reference]	
	high BMI	0.93	0.25-3.43	2.97*	1.36-6.45
swelling	**low BMI**	0.68	0.25-1084	1.25	0.60-2.58
	normal BMI	1[reference]		1[reference]	
	high BMI	0.51	0.38-1061	1.45	0.84-2.51
leg cramps	**low BMI**	1	0..39-2.55	1.1	0.50-2.40
	normal BMI	1[reference]		1[reference]	
	high BMI	1.14	0.57-2.26	2.29*	1.32-3.98
low back pain	**low BMI**	1.15	0.54-2.45	1.98	0.99-3.98
	normal BMI	1[reference]		1[reference]	
	high BMI	1.74	1.00-3.01	2.20*	1.29-3.75
hip joint or pubis pain	**low BMI**	1.27	0.41-3.94	1.95	0.94-4.03
	normal BMI	1[reference]		1[reference]	
	high BMI	2.38*	1.14-4.95	2.14	1.23-3.73
shoulder stiffness or headache	**low BMI**	2.84*	1.35-5.96	1.63	0.69-3.86
	normal BMI	1[reference]		1[reference]	
	high BMI	1.21	0.63-2.33	2.14	1.06-3.82
rib pain	**low BMI**	0.83	0.10-6.86	1.32	0.28-6.31
	normal BMI	1[reference]		1[reference]	1.06-3.82
	high BMI	0	0	2.14	0.75-6.11
anorexia or heartburn	**low BMI**	1.24	0.51-3.03	1.97	0.95-4.08
	normal BMI	1[reference]		1[reference]	1.06-3.82
	high BMI	1.56	0.81-3.01	1.62	0.92-2.87

Table1: The influence of pre-pregnancy BMI on pregnancy related discomforts (logistic regression analysis). **Note:** The analysis for discomforts was adjusted for age. *: $p < 0.05$

The occurrence of most pregnancy-related discomforts increased from the second to third trimester, while the occurrence of constipation and shoulder stiffness or headache decreased. The tendency for the occurrence of the two discomforts of current study was almost equivalent to previous reports. A previous study in the United States showed that the occurrence of constipation decreased (26.3% to 15.7%) from the second to the third trimester [16], and in another cross-sectional study, the occurrence of headache decreased (44.9% to 37.6%) and that of constipation increased (38.6 to 45.2%) from the second to the third trimester [3]. Here, we observed a difference when compared with the previous study of Nazik and Eryilmaz, where the prevalence of constipation decreased in our study but increased in that study. However, it is worth noting that ours is a longitudinal study, and thus, we collected information during each trimester from the same participants, and that found that some discomforts might improve during the course of pregnancy. Therefore, pregnant women should pay attention to constipation and shoulder stiffness or headache during the early stages of pregnancy, especially during the second trimester, and of other discomforts thereafter.

We found significant differences in the occurrence of analyzed discomforts according to pre-pregnancy BMI. The occurrence of hip joint or pubis pain was higher during the second trimester, and the occurrence of sleeping difficulty, hand or finger stiffness, leg cramps, low back pain, hip joint or pubis pain, and shoulder stiffness or headache during the third trimester was higher in the high BMI group than in the normal BMI group. These discomforts are related to changes in the musculoskeletal and cardiovascular systems, common during pregnancy [17-21]. Overweight exposes the musculoskeletal system to excessive loads, resulting in conditions such as low back pain and hand pain (22,23). Overweight might also affect the cardiovascular system [24,25], leading to leg cramps and hand or finger stiffness.

Accordingly, discomforts, especially those related to the musculoskeletal and cardiovascular systems, might occur in the high BMI group. The occurrence of shoulder stiffness or headache during the second trimester, and constipation during the third trimester, was higher in the low BMI group than in the normal BMI group. These discomforts are related to fluctuations in hormones such as estrogen, occurring during pregnancy [26,27], and low weight might determine hormone imbalance, in particular by decreasing the effects of female hormones [28]. Therefore, pre-pregnancy low BMI might hamper the hormonal balance and lead to the observed pregnancy-related discomforts.

In recent years, the occurrence of obesity has increased worldwide [29],while women, especially young adults, attempt to lose weight despite being of normal weight or underweight [30,31]. In this respect, our study showed that both women with high or low pre-pregnancy BMI have a high risk of pregnancy-related discomforts that not only affect their quality of life and limit their daily activities, but might also have a negative impact on their children's health [4,5]. Hence, our findings suggest that young women should maintain an appropriate BMI before getting pregnant, in order to have a good pregnancy progression.

This study has several limitations. First, we could not obtain information on some factors that could affect pregnancy-related discomforts (e.g. living environment, parity, and hormonal fluctuations during pregnancy). These factors may have affected our results. Second, we could not investigate the occurrence of additional discomforts that occur during pregnancy: it is known that more than 30 discomforts might be experienced by pregnant women [3]. In the future, a similar study investigating various pregnancy-related discomforts should be conducted, taking into account the different factors related to the discomforts.

Conclusion

The current study showed that pregnancy-related discomforts have different trends in occurrence from the second to the third trimester. Therefore, pregnant women should pay attention to different discomforts depending on the pregnancy period. Moreover, pre-pregnancy low or high BMI might be a risk factor for pregnancy-related discomforts, regardless of age. These findings indicate that women should maintain an appropriate BMI before pregnancy to prevent potential discomforts during pregnancy.

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資料3：
The Orthop J Sports Med 誌発表論文

A Preseason Checklist for Predicting Elbow Injury in Little League Baseball Players

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Background: Despite pitch count limits, the incidence of Little League elbow is increasing. A risk-evaluation tool capable of predicting which players are predisposed to throwing injury could potentially prevent injuries.

Purpose: To investigate the effectiveness of a risk factor checklist for predicting elbow injury in Little League baseball players during 1 season. The hypothesis was that a preseason risk-evaluation checklist could predict which players were predisposed to elbow injury.

Study Design: Case-control study; Level of evidence, 3.

Methods: A preseason risk-evaluation checklist was distributed to Little League baseball teams in Japan. Six months later, a follow-up questionnaire was mailed to determine injuries sustained during the season. Logistic regression analysis was performed, assigning presence or absence of elbow injury during the season as the dependent variable, and an injury risk score (IRS) was developed based on the statistically significant variables. Receiver operating characteristic (ROC) curve analysis was conducted to determine the predictive validity of the checklist and the optimal cutoff IRS.

Results: Data from 389 Little League players were analyzed. Among them, 53 players experienced an elbow injury requiring medical treatment during the season. Six checklist items associated with a medical history of throwing injury, pitch volume, and arm fatigue were found to be significant. Responses to the items could predict the players who were susceptible to injury during the season, with a two-thirds cutoff value for a 6-item checklist (area under the curve, 0.810; sensitivity, 0.717; specificity, 0.771).

Conclusion: Results from a 6-item preseason checklist can predict which Little League players are to sustain an elbow injury by the end of the season.

Clinical Relevance: The ability to predict which Little League baseball players are predisposed to elbow injury allows parents and coaches to initiate preventive measures in those players prior to and during the baseball season, which could lead to fewer elbow injuries.

Keywords: Little League elbow; prevention; checklist

Throwing injuries in young baseball players are a serious problem. Little League elbow, including epicondylitis and osteochondrosis dissecans, is one of the most severe throwing injuries, occurring in 20% to 40% of school-aged pitchers.[11,13-15] Such an injury can prematurely end a baseball career[4]; therefore, adults should do everything possible to protect children from these injuries.

Many studies have reported the risk factors for throwing injury. Ways to prevent such injuries, including limiting the number of pitches, have been suggested to protect players.[3,14,15,18] As a result, USA Baseball Medical and Safety Advisory Committee guidelines were developed in 2006 to provide recommendations for limiting pitch counts similar to recommendations made in Japan in 1995.[9,20,22] However, there are several problems with these recommendations. For one, these recommendations are meaningless without strict compliance, and a small proportion of coaches have complied with these recommendations. According to 2 recent studies, coaches in the United States answered 43% of questions regarding pitch count and rest periods correctly, whereas 28% of coaches complied with the recommendations in Japan.[1,22] Because few coaches follow these limits regularly, despite evidence that the number of pitches strongly influences development of Little League

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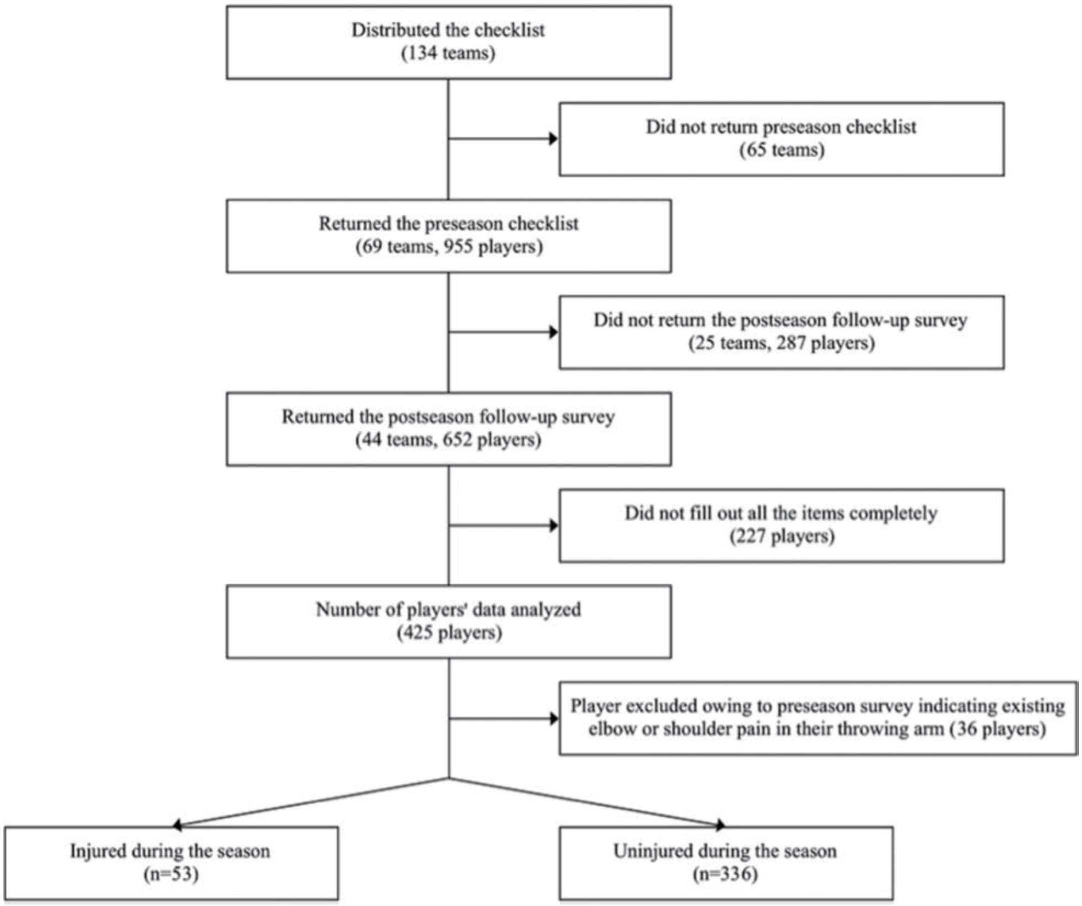

Figure 1. Flowchart showing the process of this research.

elbow, especially in Japan, another approach for prevention of elbow injury must be considered in addition to these limits.

When developing another strategy for primary prevention of youth baseball elbow injury, several things must be taken into account. First, it must be easy for coaches and parents to understand. Medical evaluation by experts, including medical doctors and physical therapists, has been reported to be an effective prevention strategy for throwing injury.[7] However, a large number of children play baseball worldwide: 5.7 million children in eighth grade or lower in the United States, and there are nearly 15,000 elementary school baseball teams in Japan.[2,8] With such large numbers, it is almost impossible for medical specialists to assess all of them. Therefore, coaches and parents, most of whom have no medical knowledge, inevitably have to be responsible for protecting children from injury. Second, the various factors must be evaluated comprehensively. Research has shown that the amount of force placed on a player's elbow is the principal risk factor for injury. Such force is influenced by pitching mechanics, pitch type, and pitch volume.[10] Other risk factors, including arm fatigue, playing baseball outside the league, and range of motion of the shoulder joint, also have been reported.[6,15,18] Thus, prevention cannot focus only on 1 factor, but various factors must be considered comprehensively to successfully prevent throwing injury.

Considering this, we created a checklist for predicting which Little League baseball players are predisposed to elbow injury. To our knowledge, studies using a checklist for injury prevention have not been performed for baseball or any other sport. The aim of the current study was to investigate the effectiveness of a risk factor checklist for predicting elbow injury in Little League baseball players during 1 season.

METHODS

This prospective cohort study investigated the effectiveness of a checklist for predicting elbow injury in young baseball players. Initially, we created an original checklist for predicting Little League elbow based on previous research that explored the risk factors for this injury. This checklist was distributed to each team's representative who participated in the annual tournament in Kyoto and Fukuoka in March 2013 (preseason). A total of 134 teams in 4 cities in Japan received the checklist (Figure 1). To increase response reliability, the players' parents were instructed to work with the players to help complete the

TABLE 1
Preseason Checklist for Little League Players

	Yes	No
Condition of the elbow of the pitching arm		
1. Is the angle of the elbow in full extension different between your arms?	1	0
2. Do you have pain in the elbow of the pitching arm when it is extended?	1	0
3. Is the angle of the elbow in full flexion different between your arms?	1	0
4. Do you have pain in the elbow of the pitching arm when it is flexed?	1	0
Information about baseball playing		
5. Are you a regular player?	1	0
6. Do you often throw more than 100 pitches per week?	1	0
7. Do you have an off-season (a period when you do not throw anything for at least 1 month)?	0	1
8. Does your pitching arm often feel fatigued while playing baseball?	1	0
9. Do you practice throwing breaking pitches often?	1	0
10. Are you more often satisfied than dissatisfied with your performance?	0	1
11. Do you often play catch or throw a ball in noncompetition settings?	1	0
12. Do you often participate in resistance training?	1	0
Pitching form		
13. Is your elbow in a straight line with your shoulders (horizontal shoulder abduction) when in the cocking stage of a pitch?	0	1
14. Is your elbow at or above shoulder level (abducted $\geq 90°$) in the acceleration phase of a pitch?	0	1
15. Is your front foot pointed straight on an extension of the pitcher-catcher line or angled slightly toward third base (for a right-handed pitcher)?	0	1
16. Is your front foot angled straight toward or slightly inward from the catcher?	0	1
Flexibility		
17. When prone with knees flexed at 90°, is there a difference in the internal rotation angle of your hips?	1	0
18. Is there a difference in the height of your thumbs when the dorsum of your hand is placed at maximum height against your back on the line of the spine? (Reflecting range of motion of the shoulders when internally rotated.)	1	0
19. With your knee fully flexed, is the distance between your heel and buttock 0 cm for both legs? (Reflecting flexibility of the quadriceps.)	0	1
20. When you are fully flexed at the waist, is the distance between your fingers and the floor 0 cm? (Reflecting flexibility of the hamstrings.)	0	1

checklist. After the parents had verified the responses, the players/parents mailed back the completed checklist. The purpose and methods of this study were explained to the players' parents in detail in a verbal statement, and written informed consent was obtained from the coaches and parents. This study was approved by the Institutional Review Board of Kyoto University (Approval No. E1669).

Checklist

We designed a 20-item checklist (Table 1). These items were chosen according to 2 criteria: (1) whether the factors were already reported as risk factors for throwing-related elbow injury in previous studies and (2) whether the coaches and parents could easily evaluate the factors with reliability. This checklist consisted of 4 areas of risk: condition of the elbow of the throwing arm, information about the individual player's baseball playing and practice, pitching form, and flexibility. All questions had to be easily answered by parents without medical knowledge. Therefore, pitching form and flexibility were illustrated using photos, and alternative flexibility tests rather than direct range of motion or muscle flexibility tests were used because of the large size of the participants. In addition, each question was designed with a yes/no answer. Intrarater reliability of pitching form and flexibility evaluation was tested by 10 subjects who were not medical specialists, who assessed each variable twice on separate occasions. Pitching form was quoted from the pitching model developed by the American Sports Medicine Institute and American Baseball Foundation.[5,14] These intrarater tests revealed kappa coefficient consistency >0.60 (range, 0.73-1.00) for all 4 pitching form and flexibility variables. These data ranges suggested that coaches and parents with no medical knowledge could answer with substantial reliability.[12] In addition to the checklist questions, basic player information was investigated, including age, height, weight, number of months playing baseball, field position (fielder, pitcher, catcher, or pitcher who concomitantly plays catcher), number of team-training days per week (<4 or ≥4), number of self-training days per week (≤6 or 7), presence or absence of pain with throwing in the shoulder or elbow in the preseason, pain in the shoulder or elbow of the throwing arm over the preceding 12 months, and elbow or shoulder injury that ever required medical treatment.

Follow-up Survey

Six months after distributing the preseason checklist, a follow-up questionnaire to determine injuries sustained during the season was distributed to players who had returned the preseason questionnaire. For this study, injury was defined as an elbow injury in the dominant arm sustained during the baseball season that required any medical treatment at least once. After the players' parents had verified the responses, the completed follow-up survey was returned.

Statistical Analysis

We excluded players who had ongoing throwing pain in the elbow or shoulder at the start of the season documented on the preseason questionnaire. We divided the players into 2 groups: those with occurrence of elbow injury during the season and those without injury. We statistically analyzed the differences between these 2 groups using the unpaired *t* test for interval items (age, height, weight, and number of months playing baseball) and the chi-square test for ordinal items.

Next, logistic regression analysis, performed in a stepwise manner, was carried out to examine whether the potential determinants were independently associated with occurrence of elbow injury during the season. In this analysis, presence or absence of elbow injury during the season was used as the dependent variable, and all items with a *P* value <.1 in univariate analyses were employed as independent variables.

Finally, we developed an "injury risk score" (IRS) based on the logistic regression analysis, distributing 1 point for significant variables to each individual. We then used receiver operating characteristic (ROC) curve analysis to examine the predictive validity of the checklist and the optimal cutoff IRS based on the Youden index,[21] assigning occurrence of elbow injury as a state variable. Area under the curve (AUC), sensitivity, and specificity of the IRS were calculated based on the ROC curve. The cutoff value for the IRS was determined based on optimal sensitivity and specificity. A *P* value <.05 was considered to be statistically significant for all analyses.

RESULTS

The 20-item preseason checklist was completed and returned by 69 teams representing 955 players (mean age, 10.0 ± 1.0 years). Of those, 25 teams failed to return the postseason follow-up survey, leaving us with pre- and postseason data from 44 teams, representing 652 players (mean age, 10.0 ± 1.0 years). After eliminating all players with incomplete surveys, data from 425 players remained. After eliminating 36 more players whose preseason surveys indicated existing elbow or shoulder pain in their throwing arm, data from 389 players remained (mean age, 10.1 ± 0.9 years) (Figure 1).

By the end of the season, 53 of 389 players had experienced an elbow injury, resulting in an injury rate of 13.6%. Basic information of these players is shown in Table 2. Results of the unpaired *t* test showed that age, height, weight, and length of time playing baseball were significantly different between the 2 groups, whereas results of the chi-square test showed that pain in the elbow or shoulder while throwing within the past 12 months (n = 37, 69.8%), throwing-related elbow or shoulder injury ever requiring medical treatment (n = 22, 41.5%), status of pitcher (n = 31, 58.5%), team training ≥4 days per week (n = 23, 43.4%), self-training 7 days per week (n = 10, 18.9%), and checklist items 5 (starting lineup member; n = 52, 98.1%), 6 (frequently throwing >100 pitches per week; n = 13, 24.5%), and 8 (frequently feeling fatigue in the throwing arm during the season; n = 23, 43.4%) were significantly different between players with and without elbow injury (Table 2).

TABLE 2
Comparison of Players With and Without Elbow Injury Sustained During the Season[a]

	With Injury (n = 53)	Without Injury (n = 336)	*P* Value
Age, y, mean ± SD	10.4 ± 0.7	10.0 ± 1.0	<.01[b]
Height, cm, mean ± SD	141.5 ± 7.1	138.5 ± 7.6	<.01[b]
Weight, kg, mean ± SD	35.2 ± 7.6	32.6 ± 6.2	<.01[b]
Previous baseball experience, mo, mean ± SD	33.9 ± 16.0	28.0 ± 15.4	.01[c]
Has experienced shoulder or elbow pain while throwing in the preceding 12 months	37 (69.8)	108 (32.1)	<.01[b]
Has ever experienced an elbow or shoulder injury requiring medical attention	22 (41.5)	38 (11.3)	<.01[b]
Fielding position			
Pitcher	31 (58.5)	111 (33.0)	<.01[b]
Catcher	12 (22.6)	86 (25.6)	.74
Fielder	49 (92.5)	316 (94.0)	.55
Pitcher who concomitantly plays catcher	6 (11.3)	42 (12.5)	>.99
Team training ≥4 days per week	23 (43.4)	78 (23.2)	<.01[b]
Self-training 7 days per week	10 (18.9)	23 (6.8)	.01[c]
Checklist item			
No. 1	4 (7.5)	16 (4.8)	.33
No. 2	1 (1.9)	4 (1.2)	.52
No. 3	2 (3.8)	6 (1.8)	.30
No. 4	0 (0.0)	3 (0.9)	>.99
No. 5	52 (98.1)	266 (79.2)	<.01[b]
No. 6	13 (24.5)	37 (11.0)	.01[c]
No. 7	51 (96.2)	322 (95.8)	>.99
No. 8	23 (43.4)	52 (15.5)	<.01[b]
No. 9	1 (1.9)	8 (2.4)	>.99
No. 10	26 (49.1)	158 (47.0)	.88
No. 11	26 (49.1)	167 (49.7)	>.99
No. 12	7 (13.2)	52 (15.5)	.84
No. 13	17 (32.1)	133 (39.6)	.36
No. 14	11 (20.8)	47 (14.0)	.21
No. 15	10 (18.9)	66 (19.6)	>.99
No. 16	8 (15.1)	43 (12.8)	.66
No. 17	7 (13.2)	43 (12.8)	>.99
No. 18	19 (35.8)	100 (29.8)	.42
No. 19	5 (9.4)	32 (9.5)	>.99
No. 20	18 (34.0)	129 (38.4)	.65

[a]Values are reported as n (%) unless otherwise indicated.
[b]$P < .01$.
[c]$P < .05$.

Logistic regression analysis revealed that pain in the elbow or shoulder while throwing within the past 12 months

TABLE 3
Factors Associated With Occurrence of Elbow Injury During the Season According to Stepwise Logistic Regression Analysis

	Odds Ratio	95% CI	*P* Value
Has experienced shoulder or elbow pain while throwing in the preceding 12 months	2.64	1.31-5.34	.007
Has ever experienced an elbow or shoulder injury requiring medical attention	4.10	1.96-8.54	<.001
Team training ≥4 days per week	2.58	1.30-5.12	.007
Self-training 7 days per week	3.15	1.23-8.09	.017
Checklist item No. 5	10.29	1.26-84.0	.030
Checklist item No. 8	3.01	1.48-6.11	.002

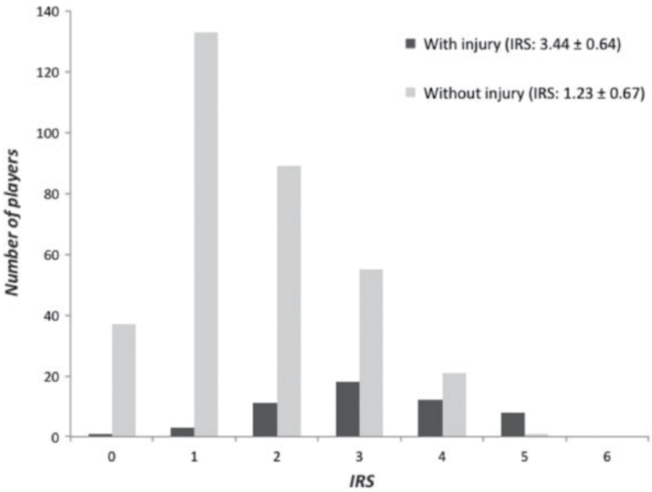

Figure 2. Injury risk score for players with and without elbow injury during the season. IRS, injury risk score.

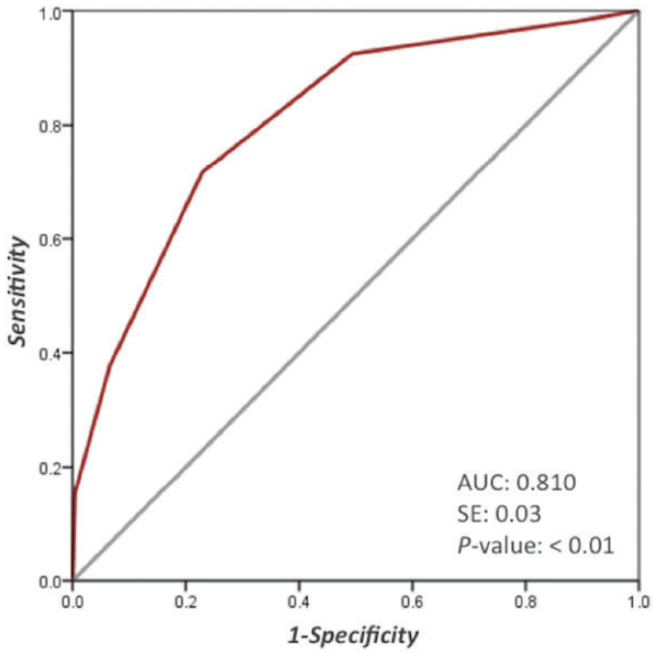

Figure 3. Receiver operating characteristic (ROC) curve analysis for injury risk score (IRS). ROC analysis was conducted to determine the predictive validity of the checklist and the optimal cutoff IRS, assigning occurrence of elbow injury as a state variable. We were able to predict the players who were injured during the season with a two-thirds cutoff value for a 6-item checklist (area under the curve [AUC], 0.810; sensitivity, 0.717; specificity, 0.771).

(odds ratio [OR], 2.64; 95% CI, 1.31-5.34; *P* = .007), throwing-related elbow or shoulder injury ever requiring medical treatment (OR, 4.10; 95% CI, 1.96-8.54; *P* < .001), team training ≥4 days per week (OR, 2.58; 95% CI, 1.30-5.12; *P* = .007), self-training 7 days per week (OR, 3.15; 95% CI, 1.23-8.09; *P* = .017), checklist item 5 (OR, 10.29; 95% CI, 1.26-84.0; *P* = .030), and checklist item 8 (OR, 3.01; 95% CI, 1.48-6.11; *P* = .002) were independently associated with occurrence of elbow injury during the season (Table 3).

Using the 6 variables that were significant in the logistic regression analysis, we calculated the IRS going up to 6 points. In the injured player group, the mean IRS was 3.44 ± 0.64, whereas that in the noninjured player group was 1.27 ± 0.67 (*P* < .01) (Figure 2). The ROC curve had a relatively high AUC for the IRS (0.810), and we determined that a two-thirds cutoff point had a sensitivity of 0.717 and a specificity of 0.771 (Figure 3). Among players with an IRS of 3 to 6 (n = 115), 38 players had been injured during the season (injury rate, 33.0%). Among players with an IRS of 0 to 2 (n = 274), 15 players (injury rate, 5.5%) had been injured (Figure 2).

DISCUSSION

We developed a preseason checklist to predict predisposition to elbow injury in Little League baseball players. As a result, we could predict the players who would be injured during the season with a two-thirds cutoff value for a 6-item checklist. The final version of the checklist (Table 4) has some desirable features, such as being easy to answer for coaches and parents, and comprehensively considering the risk factors. Therefore, we believe this checklist will be helpful for primary prevention of Little League elbow in the future. To our knowledge, this is the first longitudinal study aimed to develop an injury-predicting checklist for Little League baseball players.

The IRS of this checklist is composed of 6 items. As demonstrated in many previous studies,[3,14,15,18] volume of playing baseball was a significant risk factor in our study. Playing baseball outside of league competition also has been reported to be a risk factor,[15,18] which might be close

TABLE 4
Final Version of Checklist

	Yes	No
1. Have you experienced shoulder or elbow pain while throwing in the preceding 12 months?	1	0
2. Have you ever experienced a shoulder or elbow injury requiring medical treatment?	1	0
3. Do you participate in team training ≥4 days per week?	1	0
4. Do you participate in self-training 7 days per week?	1	0
5. Are you in the starting lineup?	1	0
6. Does your pitching arm often feel fatigued while playing baseball?	1	0

to our finding: A similar measure, number of self-training days per week = 7, was found to be significant in our study. The more frequently baseball is played, the larger the amount of force a player's elbow receives. Players who spend a significant amount of time training outside the league competition should be monitored closely for signs of injury. Arm fatigue in the preseason also was found to be a significant risk factor. We cannot confirm whether this fatigue would continue during the season, but fatigue on a daily basis could affect the onset of injury. As shown in several studies,[15,18] coaches and parents may be able to use such fatigue as an easily observed predictor of elbow injury. In addition, a medical history of throwing injury was shown to be a significant factor. Some studies excluded players who had preexisting throwing injury or did not consider the history of injury[6,18]; therefore, the causal relationship between past medical history and new onset of injury remains unknown. Medical history may be misleading in players who continue to use their throwing arm despite known abnormalities on imaging studies or ongoing clinical symptoms.[7,16] These players often have worse outcomes[19] for several reasons: An injury that is not completely treated may become more severe with activity; an injury may have changed the player's pitching mechanics, making the player more susceptible to injury; and players who have experienced an injury in the past are more likely to sustain a new injury. Consequently, players with signs or symptoms of a previous or ongoing injury should be followed more closely for evidence of a new or worsening injury than players without a preexisting injury. In this study, one of the most important risk factors, pitching mechanics, was not shown to be significant. However, this may be because the checklist was designed to be easily answered by parents, and proper pitching motion analysis is quite complicated[17]; thus, only 4 of 24 items in the pitching model developed by the American Sports Medicine Institute and American Baseball Foundation were selected for evaluation. Incorporating pitching mechanics into our checklist will be considered in a future study.

Researchers have identified risk factors for Little League elbow, including age, height, weight, range of motion of the shoulder joint, pitch count, fatigue, pitching biomechanics, and pitch type.[3,6,14,15,18] Based on this information, several primary prevention strategies have been considered. Limiting pitch count is regarded as the most effective way to prevent throwing injury.[2,11] While we agree that this is true, these limits are meaningless without strict compliance.[1,22] One cause of poor compliance is that pitch count limits are monitored by coaches rather than parents, and coaches may have less interest in protecting players from injury than parents. We believe that parents have the potential to prevent children from being injured, and our checklist, which we have shown can predict predisposition to injury, was designed to be easy for parents to use. The most important clinical implication of this study is that parents can evaluate and follow their child's condition and determine whether the child is at risk of developing Little League elbow. When parents are aware that their child is at risk for elbow injury, they can monitor pitch count limits themselves and encourage coaches to apply the limits more strictly. Closer monitoring by parents may lead to earlier detection and prevention of Little League elbow. Players with an IRS of ≥3 on this checklist had only a 33% chance of injury; therefore, it might be exaggerated to suggest that use of this checklist only is effective for prevention of injury. However, this is a step in the right direction, and the checklist would be more valuable in combination with other preventive measures. We expect that use of our checklist in combination with pitch count limits or other preventive measures in collaboration between coaches and parents will be helpful for primary prevention of Little League elbow.

Our study has several limitations. First, selection bias might have influenced the results. Participants were lost to dropout, preexisting injury, and omissions on the follow-up survey. Second, pitching mechanics were not fully investigated in the study. Until the checklist is more comprehensive in its coverage of pitching mechanics, its usefulness for predicting risk of elbow injury may be limited. Finally, because the study was confined to Japanese children, the generalizability of this study to other populations or geographic areas is unknown. Further research is required to ensure the external validation of our checklist.

CONCLUSION

Our study showed that responses on a 6-item checklist of risk factors for elbow injury can predict which Little League baseball players are predisposed to elbow injury. The ability to predict which Little League baseball players are predisposed to elbow injury allows parents and coaches to initiate preventive measures in those players prior to and during the season, which could lead to fewer elbow injuries.

The 6-item checklist should be applied to all Little League baseball players in the preseason to determine their predisposition to elbow injury.

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資料 4：
Age Clin Exp Rese 誌発表論文

Factors associating with shuttle walking test results in community-dwelling elderly people

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ORIGINAL ARTICLE

Factors associating with shuttle walking test results in community-dwelling elderly people

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Abstract
Background The shuttle walking test (SWT) is a simple, widely used method for assessing endurance performance in the elderly. Despite widespread community use, its associated factors are unclear.
Aims We aim to identify previously undefined SWT association factors in community-dwelling elderly people.
Methods Herein, 149 healthy elderly Japanese subjects performed the SWT, and were assessed for height, weight, smoking history, 10-m walk time, Timed Up and Go (TUG) scores, handgrip strength, skeletal mass index (SMI), forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), cardio-ankle vascular index, and ankle brachial index. We divided men and women into higher and lower SWT score groups, compared between-group parameters, and performed stepwise multivariate logistic regression analysis to identify factors independently associated with SWT scores.
Results Age, BMI, 10-m walk time, TUG score, SMI, FVC (L; %-predicted), and FEV_1 (L; %-predicted) were significantly different between SWT score groups for men, while in women, significant differences were observed in age, TUG score, handgrip strength, FVC (L; %-predicted), and FEV_1 (L; %-predicted) ($p < 0.05$). In the multivariate logistic regression model, 10-m walk time, and FEV_1 showed significant associations with SWT results in men; among women, age was the only significantly associated factor ($p < 0.05$).
Conclusions Results indicate that better lung function and shorter walk time independently associate with SWT results in community-dwelling men; in women, age is the only association. Our findings may offer insight when considering the focus of community exercise programs among the elderly.

Keywords Shuttle walking test · Endurance function · Community-dwelling elderly people · Lung function

Introduction

In our currently aging society, it has been shown that preserving higher endurance in elderly populations increases their level of physical activity [1] and prevents frailty [2], cardiovascular disease [3], and even mortality [4]. The accepted standard for endurance evaluation is the measuring of maximum oxygen consumption (VO_2 max) via treadmill. However, this requires technical equipment and the expertise of a tester, and is instituted only in laboratory or hospital settings. Thus, to preserve endurance among the community-dwelling elderly, a more straightforward and acceptable endurance assessment is required.

The incremental shuttle walking test (SWT) was developed by Singh [5] to assess the endurance of patients with chronic obstructive pulmonary disease (COPD) [5] or chronic heart failure [6, 7]. The SWT required subjects to walk back and forth along a 10-m flat course, with progressive increases in pace imposed by audio signals, until the subject was no longer able to maintain the pace [5]. The SWT can yield a physiological response similar to a treadmill test [8]. Therefore, use of the SWT is pervasive as

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a reliable endurance assessment test. The SWT can be administered in the local community; some previous studies have demonstrated its usefulness for evaluating endurance in community-dwelling people [9–11]. Moreover, to evaluate large numbers of people in varied non-laboratory settings, the SWT is a simpler and low-cost method than the treadmill test, which is regarded as the most precise endurance test for community-dwelling elderly.

In recent years, SWT results have been shown to associate with various factors such as age [10, 11], sex [11], body composition [10], gait parameter [7, 10, 12], lung function [13] and cardiovascular function [14]. However, the enrolled study subjects were of varied age, and presented with an array of health conditions ranging from healthy subjects to patients suffering from COPD or heart failure. For the community-dwelling elderly, investigating the determinants of SWT data may reveal what function physicians should focus on to increase endurance performance of this demographic. However, relatively few studies exist that aim to investigate SWT results in such an age group. Therefore, the aim of the present study was to determine the factors associated with SWT results in community-dwelling elderly people.

Materials and methods

Subjects

Elderly community-dwelling subjects were recruited through local press advertising from November 11–12, 2012. A total of 149 subjects (73 men and 76 women aged 74 $\pm$ 4 years) were enrolled upon having met the inclusion criteria (age $\geq$65 years, able to walk independently). Exclusion criteria were using walking aids such as a cane or walker, having a medical history (or post-operative history) of severe cardiac, musculoskeletal, or pulmonary disease, and having significant hearing impairment. Demographic data including age, body mass index (BMI), and smoking history were obtained. To assess smoking history, the pack-years index [15] was calculated for each subject by multiplying the number of cigarette packs smoked per day by the number of smoking years.

Written informed consent was obtained from each subject in accordance with the guidelines of the Kyoto University Graduate School of Medicine and the 1995 Declaration of Helsinki. This study protocol was approved by the ethics committee of the Kyoto University Graduate School of Medicine.

SWT

The SWT required subjects to walk back and forth along a 10-m flat course, with progressive increases in pace imposed by audio signals, until the subject was no longer able to maintain the pace. Up to 50 successions of the SWT were performed (500 m total walking). We divided subjects into two groups based on SWT scores: $\leq$40 or >41 [16].

Motor function tests

All subjects were assessed using the 10-m walk test, Timed Up and Go (TUG) test, and handgrip strength test. In the 10-m walk test, subjects walk along 10-m flat pathways at a comfortable speed [17]. In the TUG test, participants were instructed to stand up from a standard chair with a seat height of 40 cm, walk a distance of 3 m at their fastest pace, turn, walk back to the chair, and sit down. The time elapsing from the verbal command to begin the task until completion was recorded with a stopwatch [18]. The 10-m walk time and TUG scores were defined as the mean time in seconds recorded at the subjects' second trials. In the handgrip strength test, participants used a hand-held dynamometer with the arm kept to the side of the body. Participants squeezed the dynamometer with maximum isometric effort. No other body movement was allowed [19]. The handgrip test score was defined as the better performance of two trials.

Skeletal muscle mass index (SMI)

A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co., Ltd., Seoul, Korea) was used to determine body composition [20]. Participants were asked to stand on two metallic electrodes and hold metallic grip electrodes while the system applied a constant current of 800 mA at 50 kHz through the body. The data acquisition system calculated the resistance value and muscle mass of the respective body parts (right arm, left arm, right leg, left leg, and trunk). Appendicular skeletal muscle mass was determined using segmental body composition and muscle mass excluding the trunk; a value for the appendicular skeletal muscle mass was determined and used for the current analysis. SMI was obtained by dividing the appendicular skeletal muscle mass by the square of height (kg/m^2). This index has been used and well documented in several epidemiological studies [21].

Lung function

All subjects underwent spirometric evaluation. Forced vital capacity (FVC), and forced expiratory volume in 1 s (FEV_1) were measured by a spirometer (Spiro Sift SP-370; Fukuda Denshi Co., Ltd., Tokyo, Japan). Next, we calculated percent predicted FVC and FEV_1, corrected for height and age. Pulmonary function tests were carried out according to the guidelines of the Japanese Respiratory Society [22]. The formulae for calculating percent predicted FVC and FEV_1 were derived from Japanese criteria [23]. The FEV_1/FVC ratio was also calculated.

Cardiovascular function

All subjects underwent cardio-ankle vascular index (CAVI) evaluation and ankle brachial index (ABI) evaluation, which were determined using the VaSera-1500 (Fukuda Denshi Co., Ltd., Tokyo, Japan) as previously reported [24, 25].

CAVI is a novel method for measuring arterial stiffness. Until recently, pulse wave velocity (PWV) was the most popular measure; however, PWV was dependent on blood pressure at the time of measurement. CAVI was calculated based on parameter β, independent of blood pressure [26]. Scores $\leq$9.00 were considered normal while scores $>$9.00 were considered indicative of suspected arteriosclerosis [27]. The ABI described the arterial occlusion with a ratio of the ankle to brachial systolic blood pressure [28]. Normal values $0.91 \leq \text{ABI} \leq 1.30$ and values $\leq$0.90 indicated suspected peripheral artery disease (PAD) [29].

When measuring CAVI and ABI, subjects were supine and had blood pressure cuffs on both of the brachia and ankles. Measurements were taken once per subject, and mean values of the right and left CAVI and ABI scores were calculated. Using these index values, we calculated the population (%) with suspected arteriosclerosis and PAD.

Statistical analyses

We analyzed the difference in each variable between men and women, and between subjects with higher and lower SWT results. We performed a Chi-squared (χ^2) test to analyze the population with suspected arteriosclerosis and PAD. Moreover, statistical tests such as *t* tests were also conducted to assess the influence of other variables.

Next, we examined factors associated with the SWT results using a stepwise multivariate logistic regression model. We assigned the high SWT results group as a dependent variable and age, BMI, SMI, 10-m walk time, handgrip strength, FVC (L), FEV_1 (L), FEV_1/FVC ratio, and suspected arteriosclerosis population as explanatory variables.

All statistical analyses were performed with SPSS 20.0 software (SPSS Inc., Chicago, IL, USA). A $p < 0.05$ was considered statistically significant for all analyses.

Results

Measurements of the 149 subjects are summarized in Table 1. There were significant differences between men and women in the pack-years index, TUG score, handgrip strength, SMI, FVC (L), FEV_1 (L), FEV_1 (%-predicted), and suspected arteriosclerosis population ($p < 0.05$).

Forty-two men and 26 women were classified into the higher SWT results group and 31 men and 50 women were classified into the lower SWT results group. Among men, there were significant differences between higher and lower SWT results groups in age, BMI, 10-m walk time, TUG score, SMI, FVC (L), FVC (%-predicted), FEV_1 (L), and FEV_1 (%-predicted) ($p < 0.05$). In women, there were significant differences between higher and lower SWT results groups in age, TUG score, handgrip strength, FVC (L), FVC (%-predicted), FEV_1 (L), and FEV_1 (%-predicted) ($p < 0.05$).

In the multivariate logistic regression analysis, variables that remained in the final step of the regression model were considered to be significantly correlated with a higher SWT result. In men, these were 10-m walk time ($p = 0.001$), and FEV_1 ($p < 0.001$), whereas in women, age ($p < 0.001$) was the only significantly correlated variable (Table 2).

Discussion

We analyzed the association between SWT results and age, body composition, motor function, lung function, and cardiovascular function in community-dwelling elderly people. We found that younger age, higher FEV_1, and shorter 10-m walk time were associated with higher SWT results in men, and that younger age associated with higher SWT results in women. To date, there are few studies of the relationship between lung function and SWT results in community-dwelling elderly people. The results of the present study suggest that maintaining better lung function and walk speed is the key to preserving endurance in community-dwelling elderly men.

It has been previously shown that a decrease in FEV_1 increases dyspnea during exercise and results in decreased walk speed and endurance in patients with airflow limitation [13, 30, 31]. We considered that in community-dwelling elderly populations, a lower capacity for lung function would increase subjects' dyspnea during the SWT test, resulting in decreased walk speed and SWT results. According to the American College of Chest Physicians guidelines [32], it is still unclear which lung function is improved by pulmonary rehabilitation in airflow limitation patients. Moreover, there are only a few studies that report that pulmonary rehabilitation improves lung function among community-dwelling elderly people. Therefore, we consider that pulmonary exercises, such as improving thorax and respiratory muscle mobility, and employing breathing techniques, may sustain better lung function and preserve endurance performance in this demographic.

Table 1 Comparison of demographic characteristics and measurements

	Men				Women				*p* value**
	All ($n = 73$)	Higher level SWT ($n = 42$)	Lower level SWT ($n = 31$)	*p* value*	All ($n = 76$)	Higher level SWT ($n = 26$)	Lower level SWT ($n = 50$)	*p* value*	
General characteristics									
Age, years (SD)†	73.7 (4.6)	72.3 (4.1)	75.6 (4.7)	0.002	73.4 (4.3)	70.2 (3.5)	75.1 (3.7)	<0.001	0.71
BMI, kg/m^2 (SD)†	23.4 (3.1)	24.1 (3.0)	22.6 (3.1)	0.048	23.3 (2.7)	22.6 (2.3)	23.7 (2.8)	0.09	0.81
Smoking-pack-years index (SD)†	29.0 (30.0)	27.2 (33.7)	29.9 (24.6)	0.81	0 (0)	0 (0)	0 (0)	–	<0.001
Motor function									
10-m walk time, s (SD)†	7.3 (1.0)	6.9 (0.7)	7.8 (1.1)	<0.001	7.3 (1.3)	6.9 (0.8)	7.5 (1.5)	0.06	0.81
TUG, s (SD)†	6.4 (1.1)	6.1 (0.9)	7.0 (1.0)	<0.001	6.9 (1.1)	6.4 (0.8)	7.2 (1.1)	0.004	0.008
Handgrip strength, kg (SD)†	33.4 (5.9)	34.4 (5.8)	32.4 (5.9)	0.09	23.0 (3.8)	24.3 (3.1)	22.3 (3.9)	0.02	<0.001
Body composition									
SMI, kg/m^2 (SD)†	7.3 (0.7)	7.5 (0.7)	7.0 (0.6)	0.01	5.8 (0.6)	6.0 (0.6)	5.7 (0.5)	0.02	<0.001
Lung function									
FVC, L (SD)†	3.2 (0.6)	3.4 (0.5)	3.0 (0.4)	<0.001	2.2 (0.5)	2.5 (0.4)	2.1 (0.5)	<0.001	<0.001
FVC, %-predicted (SD)†	96.2 (13.8)	99.1 (12.7)	92.2 (14.3)	0.03	97.6 (16.0)	104.5 (15.6)	94.0 (15.1)	0.01	0.56
FEV$_1$, L (SD)†	2.3 (0.6)	2.5 (0.5)	2.0 (0.5)	<0.001	1.6 (0.5)	1.9 (0.4)	1.5 (0.4)	<0.001	<0.001
FEV$_1$, %-predicted (SD)†	88.1 (18.4)	92.5 (17.3)	82.1 (18.4)	0.02	96.9 (21.1)	105.5 (20.2)	92.4 (20.3)	0.01	0.007
FEV$_1$/FVC, % (SD)†	71.0 (10.5)	72.7 (8.9)	68.8 (12.1)	0.11	72.6 (11.2)	75.5 (11.9)	71.1 (10.6)	0.10	0.39
Cardiovascular function									
Suspected arteriosclerosis, %††	72.6	71.4	74.2	0.79	48.6	34.6	56.0	0.08	0.003
Suspected PAD, %††	5.5	0	0	–	1.3	0	2.0	0.47	0.56

BMI body mass index, *TUG* Timed Up and Go, *SMI* skeletal mass index, *FVC* forced vital capacity, *FEV$_1$* forced expiratory volume in 1 s, *PAD* peripheral artery disease

† *t* test

†† χ^2 test

* Comparison between higher and lower level of SWT

** Comparison between men and women

Table 2 Multivariate logistic regression model with stepwise selection to determine the association with shuttle walking test level

	Odds ratio	95 % CI	*p* value
Men			
10-m walk time (s)	0.24	0.11–0.54	0.001*
FEV_1 (L)	12.80	3.05–53.70	0.001*
Women			
Age	0.69	0.57–0.82	<0.001**

CI confidence interval, FEV_1 forced expiratory volume in 1 s

* $p < 0.05$

** $p < 0.001$

Further investigation, such as measuring dyspnea following the SWT, is needed to prove this hypothesis. In addition, we demonstrated an association between lung function and endurance exclusively among men. This may be attributed to the difference in smoking history between men and women in our study. As shown in Table 1, compared to women, men had a significantly higher pack-years index and significantly lower FEV_1. Smoking is one of the strongest risk factors for respiratory disease [33]. Our results in community-dwelling elderly men indicate that smoking may decrease lung function, resulting in lower SWT results. To better understand the association between lung function and endurance in community-dwelling elderly women, further research should be conducted in another population that includes women with a history of smoking.

We have shown that age associates with SWT results in women. Reports indicate that age can adversely affect a person's cardiovascular function and endurance level [34, 35]. Moreover, it is possible to separate factors that affect endurance according to utilization theory and presentation theory [36]. Utilization theory acts on the premise that endurance is determined by the oxygen (O_2)-consuming parties, while presentation theory states that it is determined by the O_2-supplying party. Saltin et al. [36] showed that endurance is more markedly affected by O_2 presentation than by utilization. In the present study, lung function, considered to be a presentation theory component, affected endurance performance more so than SMI, cardiovascular function, and motor function, which are components of the utilization theory. We also considered that our findings, with regard to age, may be associated with low cardiac function, which could potentially yield decreased SWT results. It would have been beneficial to additionally measure cardiovascular function parameters, such as stroke volume and pulse.

There are several limitations to the scope of our research. First, because this is a cross-sectional study, the causal relationship between endurance and lung function, walk speed, or age is uncertain. Moreover, the study sample did not include women with a history of smoking. As smoking history has great impact on lung function, this may be a source of sampling bias; therefore, the scope of our investigation should be extended to subjects in other communities. Another source of study limitation is that we were unable to assess other SWT-affecting factors, although these may indeed affect SWT results. In addition to cardiovascular function and dyspnea factors, previous studies have shown that step length can affect SWT or 6-min walk test results [7, 37]. Thus, further analysis should be undertaken to identify additional factors that may be of importance to endurance performance.

Conclusion

We found a significant association between lung function, walk speed, and SWT results in community-dwelling elderly men, and between age and SWT results in women. In this society, prevention for bedridden and taking care is an important issue in terms of medical economics. Elderly men with a high level of expiratory function display high endurance performance. Although this is a cross-sectional study, our results may help advise physicians of ways in which they can promote endurance performance among the elderly, through focusing and adapting community exercise programs. However, further investigation is required to assess the impact of cardiovascular function on SWT results in community-dwelling elderly populations.

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Conflict of interest None.

Human and Animal Rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and with the 1964 Helsinki declaration and its later amendments. This article does not contain any studies with animals performed by any of the authors.

Informed consent Informed consent was obtained from all individual participants included in the study.

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資料5：

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ORIGINAL ARTICLE

The physiological characteristics of community-dwelling elderly Japanese with airflow limitation: a cross-sectional study

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Abstract
Background and aims The aim of this study was to investigate the physiological characteristics of community-dwelling elderly subjects, aged ≥65 years, with airflow limitation in the Japanese community.
Methods Subjects were recruited through local press advertisement, and 180 individuals were enrolled. Data on age, body mass index (BMI), gender, smoking history, and past medical history were obtained, as were pulmonary function parameters, skeletal muscle mass index, and physical activity.
Results The final study population comprised 161 participants from whom we obtained valid spirometry results. The mean age of this population was 73.4 ± 4.4 years, and 78 participants (48.4 %) were men. The prevalence of airflow limitation was 29.2 % ($n = 47$). Subjects with airflow limitation were significantly older ($P = 0.01$) and had poorer pulmonary function ($P < 0.01$), lower BMI ($P < 0.01$), and lower skeletal muscle mass index ($P = 0.03$) than healthy elderly subjects. Furthermore, skeletal muscle mass index was significantly correlated with the percentage of predicted forced vital capacity ($r = 0.45$, $P < 0.05$) and forced expiratory volume in 1 s ($r = 0.50$, $P < 0.05$) only in men with airflow limitation.
Conclusions We found that the skeletal muscle mass index was significantly reduced in community-dwelling elderly with airflow limitation, and the skeletal muscle mass index was correlated with pulmonary function only in men with airflow limitation.

Keywords Airflow limitation · Pulmonary function · Skeletal muscle mass index · Community-dwelling elderly · Japanese

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation [1] that is usually progressive and irreversible [2]. Today, COPD is a global health problem and is predicted to become the fifth most common cause of disability in the world by 2020 [3] and the third largest cause of death by 2030 [4]. The prognosis of COPD is strongly influenced by the severity level of the airflow limitation [5]. The Nippon COPD Epidemiology (NICE) Study reported that Japan has an estimated 5.3 million subjects with airflow limitation [6]. Of them, 5 million (95 %) remain undiagnosed within the community, and only some patients received treatment in the hospital. Therefore, early detection of subjects with airflow limitation in the community is very important.

Early detection of cases has the potential to reduce the future burden of COPD for both morbidity and mortality [7]. However, COPD is frequently diagnosed at a relatively late stage of the disease, probably because early symptoms of the disease are subtle and unrecognized due to individual perception and interpretation. Early symptoms of the disease may not be evident, even though spirometry reveals airflow limitation. Therefore, even if there are no subjective clinical symptoms, early detection of community-dwelling elderly subjects with airflow limitation using spirometry is a major social issue that should be tackled immediately.

To date, many previous studies focused on physiological characteristics have investigated COPD patients. It is known that COPD has a negative influence not only on respiratory function but also on the whole body, being associated with systemic inflammation, cardiovascular disease, osteoporosis, and changes in body composition such as weight loss [8]. Although many studies report on the association between body composition and exercise function in COPD patients [9, 10], skeletal muscle wasting is of particular interest in that because it directly influences exercise performance [11] and is associated with poor health-related quality of life [12]. Ju and Chen [13] demonstrated that total-body skeletal muscle mass was significantly decreased in COPD patients compared with controls. In addition, Ischaki et al. [14] demonstrated that lean total skeletal muscle mass is associated with pulmonary function. Although these effects have been well described in COPD patients, no studies have been published on such physiological characteristics related to an adverse prognosis in community-dwelling elderly Japanese, aged ≥65 years, with airflow limitation.

Therefore, the purpose of this study was to investigate physiological characteristics of community-dwelling elderly Japanese with airflow limitation aged ≥65 years.

Materials and methods

Participants

Elderly community-dwelling subjects aged ≥65 years were recruited through local press advertisement, and 180 participants were enrolled. The inclusion criteria were age ≥65 years, living in the community, and the ability to walk independently (or with a cane). The exclusion criteria were cognitive impairment, severe cardiac or musculoskeletal disorders, previously diagnosed pulmonary disease, and hearing impairment. Written informed consent was obtained from each participant in accordance with the guidelines of the Kyoto University Graduate School of Medicine and the Declaration of Human Rights, Helsinki, 1995. This study protocol was approved by the ethical committee of the Kyoto University Graduate School of Medicine.

Measurements

Demographic data

Data on age, body mass index (BMI), gender, smoking history, and past medical history (hypertension, hyperlipidemia, diabetes mellitus, cardiovascular disease, and osteoporosis) were obtained. All subjects completed a self-reported questionnaire on smoking history and past medical history. All data were collected at study onset. Furthermore, the pack-year index was calculated for each subject by multiplying the number of cigarette packs smoked per day by the number of smoking years [15].

Pulmonary function tests

All subjects underwent spirometric evaluation. Pulmonary function tests were carried out according to the guidelines of the Japanese Respiratory Society [16]. In the recent global initiative for chronic obstructive lung disease (GOLD) guideline, all values for forced expiratory volume in 1 s (FEV_1) refer to post-bronchodilator FEV_1, but our values were obtained without a bronchodilator. Forced vital capacity (FVC), FEV_1, and peak flow were measured by spirometry (Spiro Sift SP-370; Fukuda Denshi Co., Ltd, Tokyo, Japan). After that, we calculated FVC % predicted and FEV_1 % predicted, corrected by height and age. The formulae for calculating FVC % predicted and FEV_1 % predicted were derived from the Japanese criteria [17]. Airflow limitation was defined as a ratio of FEV_1/FVC of <70 % [18]. The severity of airflow limitation was based on FEV_1 % predicted, in accordance with the GOLD criteria ($FEV_1 \geq 80$ % predicted, mild; FEV_1 50–79 % predicted, moderate; FEV_1 30–49 % predicted, severe; $FEV_1 < 30$ % predicted, very severe) [19].

Skeletal muscle mass index (SMI)

A bioelectrical impedance data acquisition system (Inbody 430; Biospace Co., Ltd, Seoul, Korea) was used to determine bioelectrical impedance. This system applies a constant current of 800 mA at 50 kHz through the body. Participants stood on 2 metallic electrodes and held metallic grip electrodes. Appendicular skeletal muscle mass was determined using segmental body composition and muscle mass, and the value for the appendicular skeletal muscle mass was determined and used for the present analysis. SMI was obtained by dividing the appendicular skeletal muscle mass by the square of height (kg/m^2) [20].

Table 1 Distribution according to the severity of airflow limitation

	Mild ($FEV_1 \geq 80$ % predicted)	Moderate (50 % $\leq FEV_1 < 80$ % predicted)	Severe (30 % $\leq FEV_1 < 50$ % predicted)	Very severe ($FEV_1 < 30$ % predicted)	Total
Gender					
Overall	15 (31.9)	29 (61.7)	3 (6.4)	0 (0.0)	47
Male	3 (12.0)	20 (80.0)	2 (8.0)	0 (0.0)	25
Female	12 (54.5)	9 (40.9)	1 (4.6)	0 (0.0)	22

Values are shown as *n* (%); *FEV_1* forced expiratory volume in 1 s

Physical activity

We distributed pedometers and note paper to participants for recording physical activity. Participants were asked to wear the pedometer in the pocket of their dominant leg for 14 consecutive days except when bathing, sleeping, and performing water-based activities. The pedometers had 30-day data storage capacity. The reproducibility and validity of the pedometers in counting walking steps have been previously established in healthy people [21]. The pedometers and note papers were sent to our laboratory by mail after 2 weeks. We calculated averages of daily step counts for 2 weeks.

Statistical analyses

The participants were divided into two groups: those with airflow limitation and those who were healthy. We statistically analyzed the differences between the 2 groups using the unpaired *t* test for age, pulmonary function, body composition, and physical activity, and the χ^2 test for gender, smoking history, and past medical history. The correlation between SMI and pulmonary function was analyzed using Pearson's correlation analysis. Additionally, partial correlation analysis controlling for the variable of age was carried out subsequently to assess the influence of age on SMI and pulmonary function. All statistical analyses were performed with SPSS version 20.0 software (SPSS Inc., Chicago, IL, USA). The level of statistical significance was set at $P < 0.05$ for all analyses.

Results

Prevalence of airflow limitation

Of 180 initially selected community-dwelling elderly Japanese aged ≥65 years, 19 were excluded owing to invalid spirometry results. Thus, the study population comprised 161 community-dwelling elderly. The mean age of this population was 73.4 ± 4.4 years, and 78 (48.4 %) participants were men. Undiagnosed Airflow limitation existed in 29.2 % ($n = 47$) of the study population. According to the GOLD stage classification, 31.9 % ($n = 15$) of participants were classified as mild, 61.7 % ($n = 29$) as moderate, and 6.4 % ($n = 3$) as severe; no participants were classified as very severe (Table 1). Regarding smoking history, the smoking rate was 39.8 % ($n = 64$) in the entire population and 34.0 % ($n = 16$) in airflow limitation subjects.

Comparison of characteristics between airflow limitation subjects and healthy older subjects

Demographic characteristics for the airflow limitation subjects and healthy elderly subjects are shown in Table 2. Subjects with airflow limitation were older ($P = 0.01$) and had poorer pulmonary function (FVC % predicted, $P = 0.03$; FEV_1, FEV_1 % predicted, FEV_1/FVC, and peak flow, $P < 0.01$) and lower BMI ($P < 0.01$) than healthy elderly subjects. In addition, the SMI of those with airflow limitation was 6.3 ± 0.9 kg/m^2, whereas that of healthy elderly subjects was 6.6 ± 1.0 kg/m^2; this difference was statistically significant (Fig. 1, $P = 0.03$). Furthermore, physical activity of those with airflow limitation was 6,601 ± 2,650 steps/day, whereas that of healthy elderly subjects was 7,553 ± 3,237 steps/day; although the difference in physical activity was not significant, it tended to be lower in those with airflow limitation.

Correlation between SMI and pulmonary function

SMI was significantly positively correlated with FVC % predicted ($r = 0.45$, $P < 0.05$) and FEV_1 % predicted ($r = 0.50$, $P < 0.05$) in men with airflow limitation, but no correlation was found in women with airflow limitation. This significant correlation in men with airflow limitation was apparent after controlling for age using partial correlation analysis (FVC % predicted, $r = 0.48$; FEV_1 % predicted, $r = 0.48$). By contrast, there was no correlation between SMI and pulmonary function in healthy elderly subjects, as shown in Table 3.

Discussion

This cross-sectional study provides two new findings. First, compared with healthy elderly subjects, SMI was

Table 2 Comparison of demographic characteristics and measurements between airflow limitation subjects and healthy elderly subjects

	Airflow limitation subjects ($n = 47$)	Healthy elderly subjects ($n = 114$)	*P* value
Age (year)	74.8 ± 4.3	72.9 ± 4.3	0.01[b]
Gender[a]			0.45
Male	25 (53.2 %)	53 (46.5 %)	
Female	22 (46.8 %)	61 (53.5 %)	
Pack-year index[a]			0.87
0–24	35 (74.5 %)	83 (72.8 %)	
25–49	7 (14.9 %)	16 (14.0 %)	
50+	5 (10.6 %)	15 (13.2 %)	
Pulmonary function			
FVC(L)	2.6 ± 0.7	2.8 ± 0.7	0.82
FVC % predicted	97.4 ± 20.2	104.5 ± 17.7	0.03[b]
FEV_1 (L)	1.5 ± 0.4	2.2 ± 0.5	<0.01[c]
FEV_1 % predicted	71.4 ± 17.1	103.1 ± 18.9	<0.01[c]
FEV_1/FVC (%)	57.9 ± 10.2	77.9 ± 5.0	<0.01[c]
Peak flow (L)	2.3 ± 1.5	4.6 ± 2.0	<0.01[c]
Body composition			
BMI (kg/m^2)	21.8 ± 2.9	23.7 ± 2.8	<0.01[c]
SMI (kg/m^2)	6.3 ± 0.9	6.6 ± 1.0	0.03[b]
Physical activity			
Steps/day	6601 ± 2650	7553 ± 3237	0.08
Complication[a]			
Hypertension	15 (31.9 %)	47 (42.0 %)	0.16
Hyperlipidemia	4 (8.5 %)	19 (17.0 %)	0.13
Diabetes	6 (12.8 %)	13 (11.6 %)	0.91
Cardiac disorder	5 (10.6 %)	9 (8.0 %)	0.76
Osteoporosis	8 (17.0 %)	6 (5.4 %)	0.03[b]

Data are shown as *n* (%) or mean ± standard deviation; Pack-year index was calculated for each subject by multiplying the number of cigarette packs smoked per day by the number of smoking years

BMI body mass index, *FEV_1* forced expiratory volume in 1 s, *FEV_1 % predicted* FEV_1 as percentage of predicted, *FVC* forced vital capacity, *FVC % predicted* FVC as percentage of predicted, *SMI* skeletal muscle mass index

[a] χ^2 test

[b] $P < 0.05$

[c] $P < 0.01$

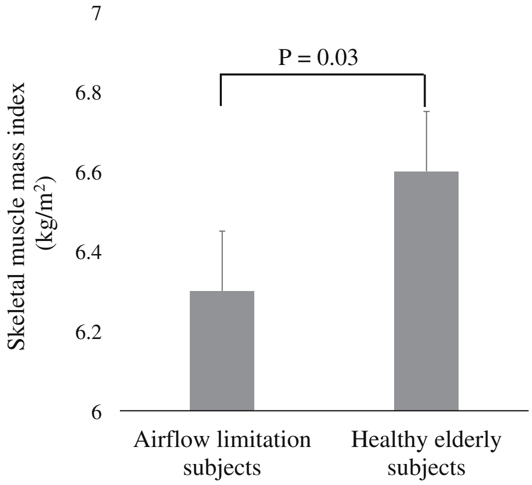

Fig. 1 The difference [mean ± standard error (SE)] in skeletal muscle mass index between airflow limitation subjects and healthy elderly subjects. Airflow limitation was defined as a ratio of forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) of <70 %

Table 3 Single and partial correlation between skeletal muscle mass index and pulmonary function

	Skeletal muscle mass index		Skeletal muscle mass index (controlling for age)	
	Men	Women	Men	Women
Airflow limitation subjects				
FVC % predicted	0.45[a]	−0.25	0.48[a]	−0.31
FEV_1 % predicted	0.50[a]	−0.11	0.48[a]	−0.19
Healthy elderly subjects				
FVC % predicted	0.16	0.10	0.16	−0.05
FEV_1 % predicted	0.23	0.15	0.23	0.05

FVC % predicted forced vital capacity as percentage of predicted, *FEV_1% predicted*, forced expiratory volume in 1 s as percentage of predicted

[a] Correlation is significant at the 0.05 level

significantly decreased in those with airflow limitation. Second, SMI was significantly correlated with pulmonary function in men with airflow limitation.

Airflow limitation was found in 29.2 % of our participants. Previous epidemiological studies for 40 years or more in Japan have reported the prevalence of airflow limitation to be approximately 10 % [6, 22]. However, Akamatsu et al. [23] reported that the prevalence of airflow limitation exceeded 15 % in elderly subjects aged 60–69 years and 28 % in those aged >70 years. The difference in prevalence means that the prevalence of airflow limitation increases with aging, and the association between aging and prevalence of airflow limitation has been reported by a previous study [24]. Therefore, our results for subjects aged ≥65 years (mean age was 73.4 ± 4.4 years) are in accordance with the results of a previous study [23], and we believe that our study did not overestimate or underestimate the spirometry measurements. However, a limitation of the process is that the participants might not yield the real picture of airflow limitation, because we excluded subjects with cognitive impairment. Previous study reported that cognitive impairment has been associated with poor pulmonary function [25]. However, we excluded patients with cognitive impairment as they were unable to perform accurately a spirometry measurement because a previous study reported that reproducibility of spirometric measurements was definitely poor in subjects with cognitive impairment [26].

To the best of our knowledge, this is the first study to indicate a reduction in skeletal muscle mass in community-dwelling subjects with airflow limitation. The mechanisms of skeletal muscle wasting are not precisely understood; however, inactivity [27] and systemic inflammation [28] are considered to be major factors in skeletal muscle wasting. We found that the difference in physical activity was not significant compared with healthy elderly subjects, but it tended to be lower in subjects with airflow limitation. Pitta et al. [29] reported that daily physical activity values in COPD patients were significantly lower than those in healthy controls. This previous study targeted patients with mild to very severe COPD, but because we targeted airflow limitation subjects with few symptoms and no consultation history in the community, the possibility that there are no significant differences in physical activity in comparison with healthy older subjects is high. However, the trend of reduced physical activity in subjects with airflow limitation is consistent with the results of a previous study in COPD patients [29]. Therefore, there is a possibility that the decrease in physical activity is associated with skeletal muscle wasting. On the other hand, pulmonary function disorders are often associated with a systemic inflammatory state [30]. Although age [31], gender [32], and smoking history [33] have been reported to accelerate systemic inflammation, we found a significant difference only for age between airflow limitation subjects and healthy elderly subjects. Therefore, the reduction in SMI in subjects with airflow limitation may be dependent on systemic inflammation related to older age.

The present study found a significant correlation between SMI and pulmonary function in men with airflow limitation after controlling for age using partial correlation analysis. This relationship might be a consequence of the high resting energy expenditure due to the increased work of breathing [34], inadequate dietary intake, physical inactivity [35], and excessive apoptosis of skeletal muscle due to increased systemic inflammation [36]. However, with the exception of physical activity, our data do not support these hypotheses. To our knowledge, we believe that the recognized gender differences are a reflection of systemic inflammation. Previous studies reported in cross-sectional and longitudinal analyses that systemic inflammation is negatively correlated with both FEV_1 and FVC in men but not in women [32, 37, 38]. That is, it is possible that systemic inflammation contributed to both skeletal muscle wasting and poor pulmonary function in men with airflow limitation. Because the prognosis for elderly people with decreased skeletal muscle mass and pulmonary function is generally adverse, it is important to detect airflow limitation at an early stage in the community.

There are several limitations that warrant mention in this study. First, because the participants were recruited through local press advertisements, there may be a selection bias. The participants may have been highly health conscious; on the other hand, the subjects with health problems might not participate in this study. Second, self-reported questionnaires may not always provide precise data due to recall bias. Third, because we performed only a simple pulmonary function test to detect airflow limitation in the community-dwelling elderly in our study, we were not able to examine pulmonary function in detail. Fourth, because this study was cross-sectional, a cause–effect relationship between SMI and pulmonary function remains unknown. Further investigations, including prospective studies, are required to confirm our discussion.

Conclusions

To the best of our knowledge, this is the first study to investigate the physiological characteristics of community-dwelling elderly Japanese with airflow limitation aged ≥65 years. We found a significant reduction in SMI in subjects with airflow limitation compared with healthy elderly subjects. Furthermore, we found a significant correlation between SMI and pulmonary function in men with airflow limitation, but not in women. Additional studies are needed for the early detection of subjects with airflow limitation and to determine the characteristics of community-dwelling elderly Japanese, aged ≥65 years, with airflow limitation.

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Conflict of interest None of the authors have conflicts of interest or financial disclosures.

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ORIGINAL ARTICLE

Rehabilitation Program After Mesenchymal Stromal Cell Transplantation Augmented by Vascularized Bone Grafts for Idiopathic Osteonecrosis of the Femoral Head: A Preliminary Study

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Abstract
Objective: To determine the feasibility and safety of implementing a 12-week rehabilitation program after mesenchymal stromal cell (MSC) transplantation augmented by vascularized bone grafting for idiopathic osteonecrosis (ION) of the femoral head.
Design: A prospective case series.
Setting: University clinical research laboratory.
Participants: Participants (N=10) with ION who received MSC transplantation augmented by vascularized bone grafting.
Intervention: A 12-week exercise program, which included range-of-motion (ROM) exercises, muscle-strengthening exercises, and aerobic training.
Main Outcome Measures: Measures of ROM, muscle strength, Timed Up and Go test, and Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) were collected before surgery and again at 6 and 12 months after surgery.
Results: All participants completed the 12-week program. External rotation ROM as well as extensor and abductor muscle strength significantly improved 6 months after treatment compared with that before treatment (*P*<.05). Significant improvements were also seen in physical function, role physical, and bodily pain subgroup scores of the SF-36 (*P*<.05). No serious adverse events occurred.
Conclusions: This study demonstrates the feasibility and safety of a multiplex rehabilitation program after MSC transplantation and provides support for further study on the benefits of rehabilitation programs in regenerative medicine.
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Idiopathic osteonecrosis (ION) of the femoral head is a painful disorder that progresses to femoral head collapse and osteoarthritis of the hip joint.[1,2] This disease mainly affects individuals aged 30 to 40 years.[3] The exact pathologic mechanism of ION remains unknown; however, obstruction of blood flow to the femoral head, which causes death of bone-forming cells, is a hallmark of this condition. Without bone-forming cells, bone tissue gradually loses

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its mechanical properties and eventually collapses, causing articular surface deformities.[1-3]

Recently, surgical treatment has become more common than nonsurgical treatment for ION in the United States.[4] Conservative treatment to offload forces by limiting weight-bearing, activity modification, and physical therapy is thought to have limited success in preventing disease progression.[3,4] If the disease progresses, the patient eventually requires total hip arthroplasty (THA).[1-3] Although the survival rate of THA has improved markedly, individuals with ION are typically young, and THA durability is limited; therefore, joint-preserving treatment is preferred. However, recent data indicate that joint-preserving procedures are performed less often than THA.[3]

Regenerative medicine using cell transplantation is a promising treatment for patients with refractory disease. Mesenchymal stromal cell (MSC) transplantation, for example, is a promising new treatment for joint preservation in ION. MSCs can differentiate into cells of osteogenic, chondrogenic, and adipogenic lineages in vitro.[5-7] During early-stage ION, treatment with MSCs in combination with core decompression surgery has resulted in significant delay and even prevention of femoral head collapse.[8-12] However, in more advanced stages, the result of this procedure has not been satisfactory.[12-14] Because bone marrow pressure is elevated in the early stage of ION,[15] core decompression to reduce the pressure is required. However, in advanced-stage disease, when subchondral bone fractures occur, initial strengthening, instead of decompression, is needed to prevent collapse.[16]

We designed a protocol using a combination of MSCs and vascularized bone grafts for treating advanced stages of ION.[17] Because ION is caused by loss of blood supply and bone-forming cells as well as mechanical vulnerability, vascularized bone grafting is, theoretically, a reasonable treatment for this condition.[16,17] Although MSC transplantation is a promising therapeutic strategy, rehabilitation interventions after surgery may have a significant effect on the ultimate treatment result. However, detailed information about rehabilitation programs after cell transplantation has not yet been reported.[8-14] Moreover, the effect of rehabilitation alone on ION is controversial.[18,19] This study aimed to determine the feasibility and safety of a rehabilitation program that was performed in a clinical trial of MSC transplantation augmented by vascularized bone grafting for ION.

Methods

The current study was a prospective case series of subjects enrolled in a clinical trial. Details of this prospective, open-labeled, proof-of-concept clinical trial, conducted at Kyoto University Hospital, have been previously reported.[17] The study protocol was approved by the Ethics Committee of Kyoto University Graduate School and Faculty of Medicine and was conducted according to the Declaration of Helsinki. For this clinical trial, participants were recruited via the website page of Kyoto University Hospital and the University Hospital Medical Information Network (UMIN) Clinical Trials Registry.

List of abbreviations:

ION	**idiopathic osteonecrosis**
MSC	**mesenchymal stromal cell**
RM	**repetition maximum**
ROM	**range of motion**
SDIC	**Specific Disease Investigation Committee**
SF-36	**Medical Outcomes Study 36-Item Short-Form Health Survey**
THA	**total hip arthroplasty**

Assessment of necrotic lesion and radiographic stage

Necrotic lesion type and size were assessed using the radiographic classification proposed by the Specific Disease Investigation Committee (SDIC) in Japan (appendix 1).[20] Staging of ION proposed by the SDIC in Japan is a modified version of the system proposed by the Association Research Circulation Osseous Committee.[20]

Inclusion criteria

Patients aged 20 to 50 years with radiographic stage 3A or 3B, according to SDIC staging,[20] were eligible for enrollment. Written informed consent was obtained from all participants in the clinical trial.

Exclusion criteria

Exclusion criteria were a history of transplantation on the affected part of the hip, heavy smoking (Brinkman index >600), current use of warfarin, diabetes mellitus (defined as hemoglobin A1c >9.0%), arteriosclerosis obliterans, pregnancy, malignant disease, myocardial infarction, brain infarction, rheumatoid arthritis, dialysis use, hematologic disease (leukemia, myeloproliferative disorder, myelodysplastic disorder), limited life expectancy, hepatitis B, hepatitis C, human immunodeficiency virus infection, syphilis, hypotension (systolic blood pressure <90mmHg), low body weight (<40kg), loss of marrow function (neutrophil count $<1500/mm^3$, hemoglobin level <11.0g/dL [men] or <10.0g/dL [women], platelet count $<100{,}000/mm^3$), change in medication (bisphosphonates or steroids) within 3 months of the study, and ineligibility determined by a doctor.

MSC transplantation augmented by vascularized bone grafting

Under general anesthesia, 100mL of bone marrow was obtained from the posterior iliac crest. Mononuclear cells containing MSCs were cultured for approximately 2 weeks under 20% partial pressure of oxygen (Po_2) and 5% partial pressure of carbon dioxide (Pco_2) conditions at 37°C.

MSC transplantation was augmented by vascularized bone grafting. Briefly, participants were placed on the table in the supine position. A curved skin incision (modified Smith-Peterson approach) was made from the iliac crest to the anterior aspect of the proximal thigh.[17] The rectus femoris was released, and the anterior aspect of the femoral neck was explored. Then, a cortical window (1.5×4cm) was prepared, through which a bony trough connecting the necrotic area was created under both fluoroscopic and endoscopic guidance. MSCs ($0.5-1.5\times10^8$) premixed with β-tricalcium phosphate granules (Osferion[a]) were transplanted into the cavity created by curettage. Tricortical iliac crest bone was harvested with a vascular pedicle and grafted into the bone trough.[16] Then, the joint capsule and rectus femoris were sutured.

Rehabilitation program

Rehabilitation was performed at a hospital for 12 weeks. During the initial 4 weeks, rehabilitation was performed at an acute care hospital (table 1). Participants continued rehabilitation at a special rehabilitation hospital for 8 additional weeks. During the first 4 weeks,

Table 1 Rehabilitation program

Time Course After Treatment	Side	Day 1	Day 3	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 8	Week 10	Week 12	Discharge
Rest level		Bed rest		Wheelchair	Walk on crutch						→	Walk on T-cane	
Weight-bearing		NWB						→	1/3 WB	1/2 WB	2/3 WB	FWB	
ROM exercise	Transplant				Passive F, E								→
						Passive Ab							→
									Passive R				→
												Active F, E, Ab, R	
	Nontransplant		Passive & active F, E, Ab, R										→
Muscle strength exercise	Transplant								Isotonic (Straight leg raising, no weight)				→
											Isotonic (Straight leg raising, 2-kg weight)		
									Isokinetic F, E				→
										Isokinetic Ad			→
											Isokinetic R		→
												Isokinetic Ab Squat & heel raise	
	Nontransplant		Isometric F, E, Ab, R										→
												Isokinetic F, E, Ab, R	
									Squat & heel raise				→
				Muscle strength exercise of upper limb									→
Aerobic training											Aerobike		→

Abbreviations: Ab, abduction; Ad, adduction; E, extension; F, flexion; FWB, full weight-bearing; NWB, non—weight-bearing; R, rotation; WB, weight-bearing.

physical therapy was performed for 40 minutes at a time, once a day, 5 days a week. After the initial 4 weeks, it was performed for 60 minutes at a time, twice a day, 6 days a week. The entire rehabilitation program was supervised by skilled physiotherapists, and the specific therapy received was recorded in the participant's medical record.

Participants were kept non−weight-bearing for 6 weeks after transplantation surgery, followed by one-third weight-bearing, one-half weight-bearing, and two-thirds weight-bearing, progressing at 2-week intervals (see table 1). Full weight-bearing was permitted 12 weeks after treatment.

Before performing range-of-motion (ROM) exercises, pain level was assessed using a numeric rating scale. Passive flexion and extension ROM exercises were initiated 2 weeks after treatment on the transplant side. Passive adduction was initiated 3 weeks after treatment, and passive rotation ROM exercise was initiated 6 weeks after treatment. Active ROM exercise in all directions was initiated 12 weeks after treatment (see table 1). Passive and active ROM exercises in all directions were initiated 3 days after treatment on the nontransplant side (see table 1).

For isotonic flexion muscle-strengthening exercise, straight leg raising with no weight was started 6 weeks after treatment on the transplant side (see table 1). Straight leg raising with 2-kg weight was started after 10 weeks. The intensity of exercise was defined by pain level. Each position was held for 5 seconds and performed 5 times. For isokinetic flexion and extension muscle-strengthening exercises, resistance training was started 6 weeks after treatment on the transplant side. The intensity of exercise was increased by increasing the load by 40% to 80% of 10-repetition maximum (RM). Isokinetic adduction exercise was added at 8 weeks, rotation exercise at 10 weeks, and adduction exercise at 12 weeks after treatment. Isokinetic rotation exercise was performed using Coxa Link.[b] Squat and heel raise exercises were performed 12 weeks after treatment. On the nontransplant side, isometric and isokinetic exercises were started 3 days after treatment. If muscle weakness was present, the intensity of exercise was increased by increasing the load by 70% to 100% of 10RM for muscular hypertrophy. If muscle weakness was not present, exercise loading was increased by 60% to 70% of 15RM for muscular endurance. Nontransplant side squat and heel raise exercises were started 6 weeks after treatment. Upper limb muscle-strengthening exercises were performed using Shoulder Link[b] 1 week after treatment (see table 1).

Aerobic training was started 8 weeks after treatment. The intensity of exercise was defined as a target heart rate of 220×(age×0.6) by using an Aerobike Ai[c] for 30 minutes. After discharge, participants continued home exercises and were assessed once a month. Patients were allowed to resume sports and work 6 months after confirmation of bone ossification (see table 1).

Assessment

All participants underwent assessment before treatment and 6 and 12 months after treatment. Passive hip flexion, extension, abduction, and external rotation angles were measured using universal goniometry. Hip flexor, extensor, and abductor strengths were measured using a handheld dynamometer[d] during isometric contraction for 3 seconds with manual resistance. Knee extensor and flexor strengths and lower limb load were assessed using the Iso Force GT-330.[e] Torque was expressed as a percentage of body weight (Nm/kg). Values of lower limb load force were normalized to body weight (N/kg). In the Timed Up and Go test, the time (in seconds) that a participant required to stand from an armless chair (chair seat height, 45cm), walk a distance of 3m, turn, walk back to the chair, and sit down was measured. Health-related quality of life was evaluated using the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).[21]

Adverse events

Compliance with the rehabilitation program and adverse events were recorded in each participant's medical record. Adverse events were monitored by the Department of Clinical Trial Design and Management Translational Research Center. Serious adverse events were assessed by the External Data Monitoring Committee.

Statistical analysis

ROM, muscle strength, and SF-36 score were presented as the median with 25% to 75% quartiles. For follow-up assessment of changes in each outcome over time, the Friedman test was used to identify overall significant differences at 3 different time points (before treatment and 6 and 12mo after treatment) for each variable. Post hoc Scheffe test was used to assess which time points showed significant differences. A P value of <.05 was considered statistically significant for all analyses.

Results

Between November 2007 and June 2009, 10 participants were recruited into the clinical trial. All participants were men with an average age of 31.7 years (range, 20−48y). A history of steroid treatment was found in 4 participants (table 2). The pretreatment radiographic stage was 3A in 6 hips and stage 3B in 4 hips (see table 2). During the rehabilitation period (6mo after surgery), there was no progression of disease. At 1 year after surgery, 6 hips with stage 3A and 2 hips with stage 3B did not progress, but 2 hips with stage 3B (cases 3 and 7) progressed to stage 4.[17]

Hip ROM

While nearly all ROM measures improved after treatment, the only significant improvements were transplant-side external rotation at 6 months ($P<.05$) and nontransplant-side flexion at 12 months ($P<.01$) (table 3).

Muscle strength and function

While nearly all muscle strength measures improved after treatment, the only significant improvements were transplant-side extensor and abductor strength at 12 months after treatment ($P<.05$) (table 4).

On the nontransplant side, there was significant improvement in lower limb load strength ($P<.05$) (see table 4). The remaining subgroup scores showed posttreatment improvements that did not reach statistical significance.

SF-36 subgroup score

There were significant improvements in physical function, role physical, and bodily pain subgroup scores between the 3 time points (before treatment and 6 and 12mo after treatment) ($P<.05$) (table 5). There was also a significant difference in each score between values before and 12 months after treatment ($P<.05$).

Table 2 Baseline data of patients

Case	Age (y)	Sex	Height (cm)	Weight (kg)	Affected Side	Steroid Use	Class*	Stage†	History
1	27	M	170.9	66.5	R	Y	C2	3B	Nephritis
2	23	M	171.0	56.6	L	Y	C2	3A	Cushing syndrome
3	48	M	174.7	87.5	R	N	C2	3B	Meningioma
4	20	M	174.2	76.8	R	Y	C1	3A	Hepatitis
5	35	M	178.8	70.0	L	N	C2	3A	None
6	28	M	169.2	58.3	R	N	C2	3A	None
7	39	M	183.1	85.2	R	Y	C2	3B	Leukemia
8	26	M	175.1	66.4	R	N	C2	3B	None
9	33	M	174.2	61.0	R	N	C2	3A	None
10	38	M	166.7	52.9	R	N	C2	3A	None

Abbreviations: L, left; M, male; N, no; R, right; Y, yes.
* Radiographic clinical classification proposed by Japanese Investigation Committee.
† Radiographic staging score by Japanese Investigation Committee.

Adverse events

All participants completed the 12-week rehabilitation program. There were 5 cases of muscle pain, 2 cases of muscle stiffness, and 1 case of ankle pain on initiation of load bearing, but no serious adverse events were associated with rehabilitation. Radiography showed no evidence of progression in femoral head collapse during the rehabilitation period.

Discussion

In the current study, we designed a rehabilitation program that focused on 3 aspects: (1) improving hip joint function, (2) avoiding collapse of the femoral head, and (3) promoting bone formation from transplanted cells by using a physical therapy protocol.

In the field of rehabilitation, the relationship between pursuing functional improvement and risk reduction becomes a trade-off in some cases, but compatibility between them is important. To accomplish this trade-off, it is helpful to simultaneously assess the etiologic factors and radiologic findings of these patients in order to treat ION.[22,23] Further, lesion size, lesion location, and radiographic staging can help determine the natural course of ION.[22] In our patients, necrotic lesion size was broad, and radiographic stage had progressed (see table 2). The prognosis for steroid-induced ION is better than that for ION associated with sickle cell anemia.[22] In our study, among the 10 participants, 4 had a history of steroid use, while the other 6 had idiopathic ION (see table 2). The rehabilitation program in patients with ION should consider these aspects and should be planned carefully to avoid collapse of the femoral head.

Weight-bearing was prohibited until 6 weeks after treatment (see table 1), and full-weight sitting-to-standing actions were prohibited until 12 weeks after treatment because of the high pressure placed on the top of the femoral head.[24-26] Not only weight-bearing, but also muscle activity increases the acetabular contact pressure. Isometric hip extension and active hip flexion generate high pressure on the femoral head, equal to weight-bearing and walking.[25,26] By comparison, the pressure generated by isotonic and isokinetic exercises is much less.[25,26] Such joint-

Table 3 Comparison of hip ROM between pretreatment, 6 months after treatment, and 12 months after treatment (N=10)

Hip ROM	Pretreatment	6mo After Treatment	Effect Size (Pre/6mo)	12mo After Treatment	Effect Size (Pre/12mo)	*P* at 3 Time Points (Pre/6mo/12mo)
Flexion (deg)						
Transplant side	97.5 (95.0–107.5)	107.5 (96.3–110.0)	.58	107.5 (100–113.8)	.74	.19
Nontransplant side	101.0 (100.0–110.0)	112.5 (100.0–113.8)	.31	112.5 (101.3–120.0)*	.47	<.01
Extension (deg)						
Transplant side	20.0 (15.0–20.0)	20 (16.3–20.0)	.12	15.0 (15.0–18.8)	.47	.34
Nontransplant side	20.0 (16.3–20.0)	20.0 (15.0–20.0)	.01	17.5 (15.0–20.0)	0	.92
Abduction (deg)						
Transplant side	30.0 (21.3–35.0)	35.0 (30.0–40.0)	.52	35.0 (30.0–38.8)	.38	.24
Nontransplant side	35.0 (31.3–38.8)	37.5 (31.3–40.0)	.23	35.0 (35.0–35.0)	.11	.53
External rotation (deg)						
Transplant side	45.0 (37.5–53.8)	50.0 (41.3–60.0)†	.43	50.0 (42.5–53.8)	.31	.09
Nontransplant side	40.0 (37.5–53.8)	50.0 (45.0–60.0)	.46	50.0 (45.0–60.0)	.42	.38

NOTE. Values are median (25%–75% quartiles) or as otherwise indicated. *P* values at 3 time points were calculated by Friedman test. Multiple comparison test was performed by Scheffe test.
* $P<.01$.
† $P<.05$ as calculated by comparison with pretreatment.

Table 4 Comparison of physical function between pretreatment, 6 months after treatment, and 12 months after treatment (N=10)

Measure	Pretreatment	6mo After Treatment	Effect Size (Pre/6mo)	12mo After Treatment	Effect Size (Pre/12mo)	*P* at 3 Time Points (Pre/6mo/12mo)
Hip flexor strength (Nm/kg)						
Transplant side	1.39 (1.01–1.65)	1.49 (1.35–1.86)	0.74	1.79 (1.58–1.91)	0.70	.12
Nontransplant side	1.30 (1.05–1.50)	1.82 (1.38–1.96)	1.14	1.73 (1.68–2.03)	1.12	.08
Hip extensor strength (Nm/kg)						
Transplant side	0.56 (0.43–0.78)	1.48 (0.84–1.56)	0.98	1.28 (0.86–1.69)*	1.00	<.05
Nontransplant side	0.64 (0.37–0.80)	1.13 (0.82–1.49)	1.18	1.61 (0.96–1.77)	1.62	.08
Hip abductor strength (Nm/kg)						
Transplant side	0.67 (0.51–1.29)	1.20 (0.81–1.43)	0.58	1.28 (1.05–1.78)*	0.86	<.05
Nontransplant side	0.66 (0.52–1.37)	1.21 (0.88–1.66)	0.53	1.28 (1.21–1.85)	0.71	.20
Knee flexor strength (Nm/kg)						
Transplant side	1.36 (1.18–1.79)	1.55 (1.32–1.81)	0.38	1.63 (1.37–1.71)	0.47	.15
Nontransplant side	1.36 (1.11–1.70)	1.50 (1.12–1.66)	0.29	1.55 (1.27–1.58)	0.37	.07
Knee extensor strength (Nm/kg)						
Transplant side	2.77 (2.24–3.37)	2.97 (2.42–4.09)	0.46	3.22 (2.93–3.69)	0.56	.10
Nontransplant side	2.71 (2.50–4.00)	3.38 (2.98–3.83)	0.49	3.51 (2.72–4.10)	0.36	.19
Lower limb load (N/kg)						
Transplant side	10.61 (8.01–14.58)	15.78 (9.16–20.02)	0.99	15.34 (12.04–19.74)	0.98	.06
Nontransplant side	14.16 (10.36–20.65)	17.61 (12.49–21.72)	0.47	18.04 (14.12–23.50)*	0.70	<.05
Timed Up and Go test (s)	7.06(5.82–7.31)	6.11 (4.96–7.00)	0.51	5.40 (5.00–6.50)	0.77	.15

NOTE. Values are median (25%–75% quartiles) or as otherwise indicated. *P* values at 3 time points were calculated by Friedman test. Multiple comparison test was performed by Scheffe test.
* *P*<.05, as calculated by comparison with pretreatment.

preserving, muscle-strengthening exercise has been reported in physical therapy for osteoarthritis.[27,28] We designed the rehabilitation program so that isotonic and isokinetic exercises could be performed on the transplant side before isometric exercises (see table 1). All participants completed the 12-week rehabilitation program without excessive pain. Functional improvement was observed, and there were no serious adverse events associated with rehabilitation. These results suggest that the first 2 aims of our study were achieved.

Although we could not show clear evidence that the current rehabilitation program promotes bone formation, mechanical stimulation may be important for bone formation of transplanted cells. Lack of mechanical loading causes bone loss and fractures in the elderly.[29] During physical activity, mechanical forces are placed on the bones through ground reaction forces and the contractile activity of muscles.[30,31] Adapting physical forces to bone structure results in maintenance and prevention of fractures in the elderly.[30] Fluid flow, strain, and hydrostatic pressure are mechanotransducers of physical force to osteocytes.[29,31,32] Stimulated mechanoreceptors on osteocytes activate the prostaglandin and Wnt pathways.[33] Mechanical loading stimulates not only osteocytes but also osteoblasts[34,35] and MSCs.[36,37] Oscillatory fluid flow promotes the proliferation and differentiation of marrow MSCs.[37] Furthermore,

Table 5 Comparison of SF-36 subgroups scores between pretreatment, 6 months after treatment, and 12 months after treatment (N=6)

SF-36 Subgroups	Pretreatment	6mo After Treatment	Effect Size (Pre/6mo)	12mo After Treatment	Effect Size (Pre/12mo	*P* at 3 Time Points (Pre/6mo/12mo)
Physical function	45 (36.3–65)	90 (78.8–95)	1.54	92.5 (78.8–95)*	1.58	<.05
Role-physical	40.6 (36.3–78.1)	68.8 (57.8–93.8)	0.71	96.9 (93.8–100)*	1.63	<.05
Bodily pain	52 (51.3–52)	72 (64.5–72)	2.83	73 (64.5–81.5)*	3.18	<.05
General health	59.5 (49.5–77)	77 (61.8–90.8)	0.66	79.5 (62–88)	0.72	.31
Vitality	71.9 (54.7–84.4)	68.8 (62.5–84.4)	0.22	71.9 (62.5–85.9)	0.11	.58
Social function	31.3 (25–84.4)	100 (71.9–100)	0.90	93.8 (78.2–100)	1.00	.21
Role-emotion	50 (37.5–87.5)	100 (100–100)	0.89	100 (100–100)	1.15	.13
Mental health	80 (71.2–88.8)	90 (82.5–90)	0.52	80 (80–83.4)	0.44	.27

NOTE. Values are median (25%–75% quartiles) or as otherwise indicated. *P* values at 3 time points were calculated by Friedman test. Multiple comparison test was performed by Scheffe test.
* *P*<.05 as calculated by comparison with pretreatment.

mechanical signals inhibit adipogenesis and promote the anabolism of osteogenesis.[36] A report by Ambrosio et al[38] reveals important information about this issue. Treadmill running has a synergistic effect on healing injured skeletal muscle after muscle-derived stem cell transplantation,[38] in addition to the positive effects of improved weight management, cardiovascular health, and metabolic profile.[39] Our previous report[40] suggested that adequate exercise promotes muscle remodeling after bilateral broad necrosis of the soleus muscles. It is hypothesized that suitable mechanical stimulation drives the differentiation of MSCs, while the beneficial paracrine effect may induce a synergistic effect between MSC transplantation and rehabilitation. However, further basic and clinical research is required to prove this hypothesis.

Evaluation of the effect of nonsurgical procedures on ION is important. Mont et al[18] compared the effect of core decompression surgery with nonsurgical management of ION and reported a 63.5% satisfactory clinical result with core decompression, but only 22.7% with nonsurgical management. However, this study was not an adjusted case-control study but was a literature review. Therefore, etiologic factors and radiographic findings were not fully assessed.[18] In multicenter, randomized controlled studies, physical therapy has similar effects in ION patients with sickle cell disease as does core decompression surgery with physical therapy.[19,41] Basic studies to design the rehabilitation protocol and further clinical studies are needed, but the information provided from the current study may aid in the development of rehabilitation protocols after cell transplantation for the treatment of ION.

Study limitations

The current study has several major limitations. This was a small-scale, single-group, pre-post preliminary study. Case-control and large-scale studies are needed to demonstrate the efficacy of the rehabilitation protocol. The current study was based on the original clinical trial, so it is not an individual study. The population size of the clinical trial itself was limited because it was a feasibility study.

Conclusions

The present study demonstrated the feasibility and safety of an intensive multiplex rehabilitation program after MSC transplantation in individuals with ION. Despite this, future studies should investigate dosing and timing parameters, as well as the mechanistic basis for improvements in outcomes when a combination therapy is used.

Suppliers

a. Olympus Terumo Biomaterials Co.
b. Senoh Co.
c. KONAMI Co.
d. Nihon Medix Co Ltd.
e. OG Giken Co Ltd.

Keywords

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Appendix 1 Assessment of Necrotic Lesions and Stages

Radiographic classification proposed by the SDIC in Japan[20]:

- Type A lesions occupied the medial one third or less of the weight-bearing portion.
- Type B lesions occupied the medial two thirds or less of the weight-bearing portion.
- Both types C1 and C2 lesions occupied more than the medial two thirds of the weight-bearing portion.
- Type C2 lesions extended laterally to the acetabular edge, but type C1 lesions did not.

The ION staging proposed by the SDIC used in Japan is a modified version of the system proposed by the Association Research Circulation Osseous Committee.[20]

- *Stage 1:* Specific findings of osteonecrosis are not observed on magnetic resonance imaging, bone scintigram, histology, or radiographs.
- *Stage 2:* Demarcating sclerosis is seen without collapse of the femoral head.
- *Stage 3:* Collapse of the femoral head, including the crescent sign, is seen without joint-space narrowing. Mild osteophyte formation of the femoral head or acetabulum may be seen.
  - *Stage 3A:* Collapse of the femoral head <3mm
  - *Stage 3B:* Collapse of the femoral head ≥ 3mm
- *Stage 4:* Osteoarthritic changes are seen.

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