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分担研究報告書

いわゆる動機づけ支援が運動習慣および動脈硬化におよぼす影響

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＜目的＞健康づくりのための運動基準 2006 を改定するための基礎資料を得るために、生活習慣改善支援（いわゆる動機づけ支援）が運動習慣および動脈硬化に及ぼす影響を検討した。

＜方法＞岡山県南部健康づくりセンターにおいて、1 年間隔でメディカルチェック（尿、血液検査）、ヘルスチェック（体力測定等）の健康度測定を受診し、薬物療法を受けていなかった男性 105 名、女性 110 名を対象とした。身体計測、脈波伝播速度(baPWV)、自記式問診票による運動習慣を調査した。健康度測定時には結果をもとに生活習慣改善支援（いわゆる動機づけ支援）を行った。

＜結果＞1 年間で、男性は体重、body mass index (BMI)、腹囲、女性は体重、BMI が有意に減少し、男女とも運動習慣者が増加した。運動習慣を獲得した者はそうでない者に比較すると baPWV の悪化が少なかった。

＜今後の展望＞いわゆる動機づけ支援により、運動習慣者は増加し、動脈硬化進展が抑制される可能性が示唆された。

A. 研究目的

現在、地域、職域において特定健診、保健指導が行われているが、必ずしも受診率は高くない。特に積極的支援では、かなりの費用、労力が必要であるため、その効果的な運用が望まれている。

一方、動機づけ支援は積極的支援に比較して、地域、職域において行いやすいが、その効果については十分検討されていない。そこで、今回私たちは、岡山県南部健康づくりセンター健康度測定受診者を対象に、生活習慣改善支援（いわゆる動機づけ支援）が運動習慣と動脈硬化進展に与える影響を検討した。

B. 研究方法と結果

対象は、岡山県南部健康づくりセンターでのメディカルチェック（尿、血液検査）、ヘルスチェック（体力測定、生活習慣状況調査等）の健康度測定を受診した成人男性 105 名、女性 110 名を対象とした（表１）。

測定項目は、身長、体重、腹囲、ヒップ囲、脈波伝播速度(brachial-ankle pulse wave velocity: baPWV)、自記式問診票による運動習慣（1 回 30 分、週 2 回、3 か月以上継続）の有無等であった。

なお、測定にあたっては各個人から書面による同意を得るとともに、岡山県健康づくり財団倫理委員会の承認を得た。

C. 結果

いわゆる動機づけ支援による1年間の変化を表1に示す。男性では、体重、body mass index (BMI)、腹囲が、女性では体重、BMIが有意に減少した。baPWVは男女とも有意な変化は認めなかったが、減少傾向であった。

また、運動習慣者の変化を検討すると、男女とも1年間で運動習慣者は有意に増加した（**表2**）。

ベースライン時に、運動習慣のなかった男性63名、女性77名でいわゆる動機づけ支援の効果を検討したところ、男性では、体重、BMI、腹囲が、女性では体重、BMIが有意に減少し、baPWVは男女とも減少傾向であった（**表3**）。

1年間で、運動習慣を獲得した者とそうでない者を比較すると（**表4**）、運動習慣を獲得した者のbaPWVの変化量は獲得できなかった者のbaPWVの変化量に比較すると低い傾向であり、動脈硬化の進展の抑制傾向が認められた。

D. コメント

私たちは、今回、いわゆる動機づけ支援の運動習慣およびbaPWVを指標にした動脈硬化への影響を検討した。

従来から、有酸素運動をはじめとした運動がbaPWV等を指標にした動脈硬化改善作用を示すことは多く示されている。また、積極的支援のように時間と人手をかけて介入することは、運動習慣の獲得や動脈硬化進展抑制に良いことが容易に予想される。しかしながら、今回、薬物療法をうけていないいわゆる健康な人を対象に、動機づけ支援の効果を検討した結果、運動習慣者が有意に増加し、運動習慣を獲得した者では動脈硬化進展が抑制される可能性を示すことができたことは、一般の地域、職域での生活習慣改善支援を行う有益なエビデンスを提供できたと思われる。

しかしながら、今回の対象者は、自ら健康度測定を受けた比較的健康意識の高い人が多いと思われるため、今後、さまざまな対象、地域、職域において実証する必要がある。

E.結論

いわゆる動機づけ支援によって、1年間で運動習慣者は増加し、動脈硬化進展が抑制できる可能性が示唆された。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

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2. 学会発表

なし

H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

表1　対象および1年間の変化

	前		後		
	平均値 ± 標準偏差		平均値 ± 標準偏差		*p*
男性					
症例数	105				
年齢	48.2	± 13.8			
身長 (cm)	170.5	± 6.0			
体重 (kg)	71.3	± 11.6	70.0	± 11.1	0.0003
Body mass index (kg/m^2)	24.5	± 3.7	24.1	± 3.4	0.0002
腹囲 (cm)	85.6	± 10.2	84.2	± 9.6	0.0033
ヒップ囲 (cm)	95.1	± 6.6	95.0	± 8.1	0.8221
baPWV (右) (cm/s)	1329.1	± 210.0	1326.8	± 198.5	0.8261
baPWV (左) (cm/s)	1333.4	± 217.9	1326.8	± 196.4	0.5129
baPWV (平均) (cm/s)	1331.2	± 212.4	1326.8	± 195.2	0.6529
女性					
症例数	110				
年齢	48.6	± 12.1			
身長 (cm)	157.5	± 5.0			
体重 (kg)	54.3	± 7.6	53.7	± 7.5	0.0171
Body mass index (kg/m^2)	21.9	± 3.1	21.7	± 3.0	0.0175
腹囲 (cm)	76.4	± 8.7	76.8	± 8.8	0.5053
ヒップ囲 (cm)	91.2	± 5.2	90.6	± 5.1	0.0623
baPWV (右) (cm/s)	1241.1	± 189.1	1231.9	± 182.8	0.3532
baPWV (左) (cm/s)	1258.6	± 198.7	1254.3	± 206.0	0.7391
baPWV (平均) (cm/s)	1249.9	± 192.0	1243.1	± 186.3	0.5147

表2　運動習慣の変化

		後		
		運動習慣(+)	運動習慣 (−)	*p*
男性				
前	運動習慣 (+)	36	6	0.0052
	運動習慣 (−)	38	25	
女性				
前	運動習慣 (+)	29	4	<0.0001
	運動習慣 (−)	25	52	

表３　ベースライン時運動習慣のなかった者の1年間の変化

	前		後		
	平均値 ± 標準偏差		平均値 ± 標準偏差		p
男性					
症例数	63				
年齢	45.4 ± 12.4				
身長 (cm)	171.9 ± 5.1				
体重 (kg)	73.5 ± 12.2		71.9 ± 11.8		**0.0013**
Body mass index (kg/m^2)	24.9 ± 4.0		24.3 ± 3.9		**0.0011**
腹囲 (cm)	87.4 ± 10.6		85.7 ± 10.5		**0.0092**
ヒップ囲 (cm)	96.5 ± 6.9		96.6 ± 9.5		0.8989
baPWV (右) (cm/s)	1313.4 ± 200.9		1302.7 ± 172.9		0.4220
baPWV (左) (cm/s)	1317.4 ± 207.6		1305.2 ± 22.9		0.3716
baPWV (平均) (cm/s)	1315.4 ± 202.3		1304.0 ± 175.3		0.3851
女性					
症例数	77				
年齢	49.0 ± 11.8				
身長 (cm)	157.7 ± 4.7				
体重 (kg)	54.6 ± 7.7		54.0 ± 7.3		**0.0357**
Body mass index (kg/m^2)	22.0 ± 3.2		21.8 ± 3.0		**0.0481**
腹囲 (cm)	76.3 ± 8.8		77.1 ± 8.9		0.1943
ヒップ囲 (cm)	91.0 ± 5.4		90.7 ± 5.1		0.3186
baPWV (右) (cm/s)	1256.1 ± 197.8		1241.6 ± 184.9		0.2160
baPWV (左) (cm/s)	1270.1 ± 203.6		1270.0 ± 217.4		0.9916
baPWV (平均) (cm/s)	1263.1 ± 198.6		1255.8 ± 190.4		0.5532

表４　運動習慣獲得の有無によるbaPWVの変化量の比較

	症例数	平均値 ± 標準偏差	p	p (年齢補正後)
男性				
運動習慣 (−) →(+)	38	-21.0 ± 99.0	0.3749	0.3204
運動習慣 (−) →(−)	25	3.0 ± 111.5		
女性				
運動習慣 (−) →(+)	25	-29.1 ± 101.1	0.2206	0.3462
運動習慣 (−) →(−)	52	3.2 ± 110.0		

研究成果の刊行に関する一覧表

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研究成果の刊行物・別刷

Geriatr Gerontol Int 2012; 12: 292–297

Association of 29C>T polymorphism in the transforming growth factor-β1 gene with lean body mass in community-dwelling Japanese population

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Aim: Sarcopenia is the significant degenerative loss of skeletal muscle mass and strength associated with aging, and it is one of the components of frailty. We previously reported an association between the 29C>T polymorphism in the transforming growth factor-β1 gene (rs1800470) and the prevalence of vertebral fractures in subjects with postmenopausal osteoporosis. The association was not attributable to bone mineral density, which suggests that polymorphism influences some aspects of bone quality that affects strength and/or frailty rather than bone strength itself. Thus, we examined the relationship between genetic polymorphism and lean body mass in a Japanese population.

Methods: A total of 479 adults comprising 143 men and 336 women, age 23 to 85 years, participated in the present study. Fat-free mass was measured by dual energy X-ray absorptiometry, and the relative skeletal muscle index was calculated as the ratio of appendicular (sum of arms and legs) fat-free mass to the square of height.

Results: Total, leg, and appendicular fat-free mass as well as the relative skeletal muscle index were significantly lower in male subjects with CT/TT genotypes compared to those with CC genotype. Female subjects did not show any genotype-dependent differences when analyzed as a group, but when those without menstruation (postmenopausal women) were analyzed, arm fat-free mass was significantly lower in the CT/TT genotypes than in the CC genotype.

Conclusions: T allele of the 29C>T polymorphism in the transforming growth factor-β1 gene might be a risk factor of sarcopenia in a Japanese population. **Geriatr Gerontol Int 2012; 12: 292–297.**

Keywords: genetic polymorphism, genetic susceptibility, lean body mass, sarcopenia, transforming growth factor-β1.

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Introduction

Sarcopenia, refers to the significant loss of lean tissue, particularly skeletal muscle mass, associated with aging. Loss of muscle mass is correlated to loss of strength and functional impairment and disability common among

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the elderly. Measuring lean body mass (LBM) with dual-energy X-ray absorptiometry (DXA) is one of the best ways to determine the quantity of skeletal muscle.[1] LBM is genetically determined, with heritability ranging from 52% to 84%.[2–4] Recently, Liu *et al.* reported that two single nucleotide polymorphisms (SNP), rs16892496 and rs7832552, within the thyrotropin-releasing hormone receptor gene were significantly associated with LBM by genome-wide association study.[5] However, most of the gene's underlying variations in LBM are largely unknown.

Transforming growth factor-β1 (TGFB1) is a multifunctional cytokine, and its gene is located on chromosome 19q13.2. There are several commonly known (potentially) functional polymorphisms in this gene. One of the polymorphisms, designated as 29C>T, which results in a Pro to Leu substitution at amino acid position 10, has been related to a variety of disease conditions including cardiovascular diseases, neoplasms and osteoporosis.[6–8]

We previously reported a cooperative effect between serum 25-hydroxyvitamin D concentration and the TGFB1 29C>T genetic polymorphism on the prevalence of vertebral fractures in postmenopausal osteoporosis.[9] The protective effect of the C allele against fracture could not be attributed to bone mineral density, suggesting that the polymorphism may influence some aspects of bone quality such as strength and/or frailty (e.g. a predisposition to falls) rather than bone strength itself. Thus, we examined the relationship between the 29C>T polymorphism and LBM as well as various anthropometric values in community-dwelling Japanese women and men.

Methods

Subjects

A total of 479 adults comprising 143 men and 336 women, age 23 to 85 years, participated in the present study. The subjects were recruited from the community around the National Institute of Health and Nutrition in Tokyo, Japan. All subjects answered a medical history questionnaire and were assessed as free of severe chronic disease. All assessments were conducted at the National Institute of Health and Nutrition between April 2007 and August 2008. Written consent was obtained from each subject, and the study was approved by the Ethics Committees of the National Institute of Health and Nutrition and Tokyo Metropolitan Institute of Gerontology. The study was performed in accordance with the guidelines of the Declaration of Helsinki.

Anthropometry analyses

Body weight and height were measured to the nearest 0.1 cm and 0.1 kg, respectively, and BMI (kg/m^2) was calculated by dividing the body weight (kg) by the square of height (m^2). After 10 min of quiet rest in the supine position, subjects were studied in the supine position. Bilateral brachial and ankle blood pressures were simultaneously measured with a vascular testing device, form PWV/ABI (Omron Colin, Kyoto, Japan). Bilateral brachial and ankle arterial pressure waveforms were stored for 10 s by extremity cuffs connected to a plethysmographic sensor and an oscillometric pressure sensor wrapped on both arms and ankles. The brachial-ankle pulse wave velocity (PWV) was calculated as the distance between the two arterial recording sites divided by the transit time.[10–12] The value of brachial-ankle PWV mainly reflects stiffness in the central arteries because, when using a catheter tip with a pressure manometer, it correlates well with the aortic PWV.[11,12] The mean value of right and left PWV was obtained for analysis. The day-to-day coefficient of variation was 3.4% for PWV in our laboratory.[12,13]

Measurement of body composition

Whole body bone mineral density, total body fat (fat mass) and total fat-free mass (FFM) were obtained from DXA (Hologic QDR-4500A scanner, Hologic, Waltham, MA, USA) using the previously described method.[14] Briefly, subjects were positioned for whole-body scans according to the manufacturer's protocol. Participants lay in the supine position on the DXA table with their limbs close to their bodies. The whole body FFM was divided into several regions, arms, legs, trunk and head, to estimate appendicular FFM (sum of arms and legs), leg FFM, arm FFM, and relative skeletal muscle index (RSMI), which was calculated as the ratio of appendicular FFM to the square of height. The body compositions were analyzed using manual DXA analysis software (version 11.2:3). The arm region was defined as the region extending from the head of the humerus to the distal tip of the fingers. The reference point between the head of the humerus and the scapula was positioned at the glenoid fossa. The leg region was defined as the region extending from the inferior border of the ischial tuberosity to the distal tip of the toes. The whole body was defined as the region extending from the shoulders to the distal tip of the toes. To minimize interobserver variation, all scans and analyses were carried out by well-disciplined investigators, and the day-to-day coefficient of variation of their observations was 2.95% for FFM in the whole body.

Genotyping

Total genomic DNA was extracted from the peripheral blood leukocytes using a QIAamp DNA Blood Mini Kit (Qiagen, Tokyo, Japan). Genotyping for rs1800470 (29C>T, Pro10Leu) in the TGFB1 gene was carried out

by Real Time Thermocycler (LightCycler 480, Roche Applied Science, Mannheim, Germany) using the TaqMan SNP genotyping assay method. This technique employs fluorogenic 5′ nuclease chemistry (also known as TaqMan probe-based chemistry) to enable detection of specific PCR product. C_22272997_10 was used as the SNP genotyping assay ID (Applied Biosystems, Foster City, CA, USA). The PCR reaction was carried out using 10-μL final volume that contained 5-μL TaqMan Genotyping Master Mix (2X) (Applied Biosystems), 0.5-μL 20X working stock of SNP Genotyping Assay (primer and probe; Applied Biosystems), and 1 μL (about 10 ng) genomic DNA and 1.0 μL deionized water. The thermocycler conditions used were an initial denaturation step at 95°C for 10 min, followed by 40 cycles of denaturation at 92°C for 15 s, and annealing/extension at 60°C for 1 min. The primers and probes used in the TaqMan SNP Genotyping Assays were chosen based on information available on the Applied Biosystems website. PCR 96-well plates were read on the LightCycler 480 using the end-point analysis mode. The allelic discrimination analysis was performed using LightCycler 480 software v. 1.5 (Roche Applied Science, Mannheim, Germany). All polymorphisms were successfully genotyped in all 479 subjects.

Statistical analyses

Values are expressed as means ± SD. Because the 29C>T (Pro10Leu) genotype in the TGFB1 gene was the T-dominant genetic model, data of measures for the CC genotype were compared with those for the CT/TT genotype using one-way ANOVA or ANCOVA, adjusting for age as a covariate using JMP v. 8 (SAS Institute Japan, Tokyo, Japan). The allele frequency was calculated, and a χ^2 test determined the deviation of the genotype distribution from Hardy–Weinberg equilibrium. A *P*-value of less than 0.05 was considered statistically significant.

Results

In this study, the percent frequency distribution of CC, CT and TT genotypes in the TGFB1 polymorphism was 25.6%, 51.1% and 23.3%, respectively, and the minor allele (T) frequency was 0.49. The genotype frequency distribution was within Hardy–Weinberg equilibrium.

The characteristics of the total study population are shown in Table 1. There were no significant differences in age, height, weight, BMI, total fat mass and whole body bone mineral density between subjects with the CC genotype and those with the CT/TT genotypes in both sexes. In contrast, total FFM, leg FFM, appendicular FFM and RSMI were significantly lower in male subjects with the CT/TT genotypes than those with the CC genotype. A statistical significance in the genotype-dependent difference of RSMI was still found ($P = 0.0315$) even after adjustment for age using ANCOVA. Furthermore, systolic blood pressure, diastolic blood pressure and PWV were significantly higher in male subjects with the CT/TT genotypes than those with the CC genotype. In contrast to male subjects, female subjects showed no significant difference by genotype with regard to any parameters presented in Table 1.

Table 1 Clinical characteristics of the study population ($n = 479$)

	Men ($n = 143$)				*P*	Women ($n = 336$)				*P*
	CC ($n = 43$)		CT/TT ($n = 100$)			CC ($n = 80$)		CT/TT ($n = 256$)		
	mean	SD	mean	SD		mean	SD	mean	SD	
Age (years)	46.6	13.4	48.3	13.3	0.3753	56.0	9.9	53.9	11.6	0.1526
Height (cm)	169.4	5.1	170.2	6.3	0.5037	156.3	5.8	156.3	6.0	0.9535
Weight (kg)	69.4	8.5	69.0	9.1	0.8035	55.0	7.7	55.0	8.3	0.9814
BMI (kg/m^2)	24.1	2.5	23.8	2.4	0.4145	22.6	3.3	22.5	3.1	0.8695
Total FM (kg)	15.5	8.0	15.0	4.4	0.6309	16.8	4.8	16.4	5.3	0.6024
Total FFM (kg)	57.6	9.3	54.8	6.2	**0.0356**	39.3	4.1	39.4	5.0	0.8206
Arm FFM (kg)	6.1	1.1	5.9	0.9	0.2006	3.6	0.5	3.6	0.6	0.9133
Leg FFM (kg)	19.4	3.4	18.4	2.6	**0.0384**	12.7	1.6	12.8	1.9	0.7867
Appendicular FFM (kg)	25.5	4.3	24.3	3.0	**0.0494**	16.3	2.0	16.3	2.4	0.8475
RSMI (kg/m^2)	8.9	1.2	8.4	0.8	**0.0062**	6.7	0.7	6.7	0.8	0.9749
Whole body BMD (g/cm^2)	1.16	0.11	1.15	0.11	0.5485	1.03	0.10	1.03	0.12	0.9556
SBP (mmHg)	118	11	124	15	**0.0112**	120	17	120	17	0.9065
DBP (mmHg)	72	9	77	10	**0.0138**	71	10	70	11	0.9158
PWV (cm/s)	1249	197	1345	243	**0.0227**	1290	247	1277	227	0.6637

Bold type represents *P*-values <0.05. BMD, bone mineral density; DBP, diastolic blood pressure; FFM, fat-free mass; FM, fat mass; PWV, pulse wave velocity; RSMI, relative skeletal muscle index; SBP, systolic blood pressure.

Table 2 Body composition by genotype in female with or without menstruation

	Women with menstruation				*P*-value	Women without menstruation				*P*-value
	CC (n = 23)		CT/TT (n = 99)			CC (n = 56)		CT/TT (n = 148)		
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Total FM (kg)	16.3	4.2	15.9	6.1	0.7500	16.9	5.1	16.8	4.7	0.8887
Total FFM (kg)	40.1	3.9	41.8	5.4	0.1765	39.0	4.2	38.0	4.2	0.1407
Arm FFM (kg)	3.6	0.4	3.8	0.6	0.0766	3.6	0.5	3.4	0.4	**0.0295**
Leg FFM (kg)	13.2	1.5	13.7	2.1	0.3346	12.5	1.7	12.2	1.6	0.2696
Appendicular FFM (kg)	16.8	1.8	17.5	2.6	0.2307	16.1	2.1	15.7	2.0	0.1650
RSMI (kg/m^2)	6.6	0.6	6.9	0.8	0.0700	6.7	0.8	6.5	0.7	0.0691

Bold type represents $P < 0.05$. FM, fat mass; FFM, fat-free mass; RSMI, relative skeletal muscle index.

Because the lack of significant difference by genotype in female subjects suggested an influence of estrogen on the interaction between body composition and genotype, we divided female subjects into two groups according to the menstruation status and re-analyzed. As shown in Table 2, in female subjects with menstruation, no significant difference was found in any of the body composition data by genotype. However, in female subjects without menstruation, arm FFM was significantly lower in subjects with the CT/TT genotypes than in those with the CC genotype. RSMI was also lower in subjects with the CT/TT genotypes than in those with the CC genotype albeit the difference was not statistically significant ($P = 0.0691$).

Discussion

The present study has demonstrated for the first time that the TGFB1 29C>T genetic polymorphism is associated with the indices of LBM, not just with some surrogate markers for cardiovascular diseases. Total, leg and appendicular FFM as well as RSMI were significantly lower whereas systolic blood pressure, diastolic blood pressure and PWV were significantly higher in community-dwelling Japanese male subjects with the CT/TT genotypes relative to those with the CC genotype (Table 1). Female subjects did not show any genotype-dependent difference in the indices of LBM when analyzed as a whole. However, when those without menstruation were exclusively analyzed, arm FFM was also significantly lower in the CT/TT genotypes than in the CC genotype (Table 2).

The TGFB1 29C>T genetic polymorphism, which results in a Pro to Leu substitution at amino acid position 10, is located in the signal peptide sequence,[15] which is thought to target newly synthesized protein molecules to the endoplasmic reticulum. Therefore, it is most likely that the polymorphism affects the signal peptide's function, possibly influencing synthesized protein's intracellular trafficking or export efficiency. In fact, transfections of hela cells with constructs encoding either the Pro or Leu forms at amino acid position 10 of TGFB1 and driven by the cytomegalovirus promoter indicated that the signal peptide with Pro10 caused a 2.8-fold increase in secretion compared with the Leu10 form.[7] Serum concentration of TGFB1 has also been reported to increase with the number of C alleles.[6,16] Therefore, it is conceivable that the genotype-dependent differences in the efficiency of de novo TGFB1 production may be related at least partly to the genotype-dependent differences in the clinical phenotype.

Recently, age-related changes in several inflammatory mediators have been implicated in the pathogenesis of sarcopenia.[17] Cross-sectional studies as well as a prospective cohort study have demonstrated that higher levels of inflammatory markers, such as tumor necrosis factor-α, are associated with lower muscle mass and strength.[18–20] TGFB1 is a pleiotropic cytokine that is involved in many different critical processes, such as embryonic development, cellular maturation and differentiation, wound healing, and immune regulation. It maintains immune homeostasis by acting as a potent immune suppressor by inhibiting the proliferation, differentiation, activation and effector functions of immune cells.[21] Therefore, it is plausible that the TGFB1 29C>T genetic polymorphism would affect a chronic inflammatory state by altering the efficiency of de novo TGFB1 synthesis, and the T allele-associated decrease in the TGFB1 production attenuates its immune suppressor function, which in turn facilitates inflammation-mediated reduction of muscle mass.

Premenopausal female subjects did not show any genotype-dependent differences in the indices of LBM. However, in postmenopausal subjects, arm FFM was found to be significantly lower in the CT/TT genotypes as compared to the CC genotype (Table 2). These observations suggest that estrogen could conceal the putative differential effect of the TGFB1 genetic polymorphism on muscle mass. It has already been hypothesized that menopause transition and the subsequent decline in estrogen may play a role in muscle mass

loss.[22] The mechanisms by which a decrease in estrogen levels may have a negative effect on muscle mass are not well understood, but it has been suggested that the decrease in estrogen concentrations may be associated with an increase in pro-inflammatory cytokines, such as tumor necrosis factor-α or interleukine-6.[23] According to these hypotheses, it is conceivable that during the premenopausal state when estrogen levels are sufficiently high, its anti-inflammatory effect may compensate for the weakened anti-inflammatory effect of TGFB1 in the T-allele carriers.

The association between the TGFB1 29C>T genetic polymorphism and blood pressure has been previously reported by Rivera *et al.* and He *et al.*[24,25] Rivera *et al.* found that, among European-Americans but not among African-Americans, the Pro10 homozygote (CC genotype) has a significantly higher systolic blood pressure than the Leu10 homozygote (TT genotype).[24] He *et al.* also found an association between the C allele and a higher risk of essential hypertension in the Kazakh and Han Chinese populations.[25] Our observation that the C homozygote in male subjects had significantly lower blood pressure than those who bear at least one T allele (CT/TT) contrasts with previous findings that the C allele is a risk allele for hypertension. The reason for this apparent discrepancy is unknown, but ethnicity and gender seems to variably affect the function of the TGFB1 genetic polymorphism. A similar kind of ethnicity-related discrepancy was also reported for this polymorphism with regard to risk of cerebrovascular diseases; Kim and Lee found that subjects carrying the TT genotype were susceptible to both ischemic stroke and vascular dementia in a Korean population,[26] whereas Sie *et al* found that a significantly increased risk of stroke was associated with the C allele in Dutch population.[27]

In conclusion, we found that the T allele of the TGFB1 29C>T genetic polymorphism might be a risk factor of sarcopenia in a Japanese population. The mechanistic basis of the polymorphism in determining muscle mass has not yet been elucidated, but the T allele-mediated attenuation of the anti-inflammatory property of TGFB1 may be at least partly attributed to the processes. It should be noted that the sample size of the present study was relatively small for this kind of genetic association study. Nevertheless, our findings give new insight into sarcopenia etiology and pathogenesis.

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Disclosure statement

No authors report any conflict of interest.

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Effects of resistance training on arterial stiffness: a meta-analysis

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ABSTRACT

Background Regular aerobic exercise prevents and reverses arterial stiffening, but the association between resistance training and arterial stiffness is unclear.

Aim This study was performed to conduct a systematic review and meta-analysis of randomised controlled clinical trials (RCTs) assessing the associations between resistance training and changes in arterial stiffness.

Methods MEDLINE and SPORTDiscus databases were searched from January 1980 through to April 2011. RCTs evaluating the ability of resistance training to increase arterial stiffness in comparison with a control group were included in the meta-analysis. Two independent reviewers extracted data and assessed the quality of the included studies. Data from 185 reports of eight RCTs (193 participants) were included. Pooled mean differences in arterial stiffness indices (carotid arterial β stiffness and pulse wave velocity (PWV)) between intervention and control groups were calculated using a random-effects model.

Results The overall association of resistance training versus control with relative changes in carotid β index or PWV (eight studies; 193 participants) was 10.7% (95% CI 3.4% to 18.0%; I^2, 89%; heterogeneity, $p<0.001$). Five studies indicated that resistance training in young subjects (n=115) was significantly associated with an increase in stiffness index of 14.3% (95% CI 8.5% to 20.1%; I^2, 71%; heterogeneity, $p<0.001$) compared with controls. However, three studies showed that resistance training in middle-aged subjects (n=78) was not associated with changes in arterial stiffness. In addition, although high-intensity resistance training (n=87) was significantly associated with an increase in stiffness of 11.6%, moderate-intensity resistance training (n=106) showed no such association.

Conclusion High-intensity resistance training is associated with increased arterial stiffness in young subjects with low baseline levels of arterial stiffness.

INTRODUCTION

Increases in arterial stiffness impair arterial buffering function and contribute to elevation of systolic blood pressure, left ventricular hypertrophy, coronary ischaemic disease and reduction of arterial baroreflex sensitivity.[1–3] Indeed, greater arterial stiffness is associated with a higher rate of mortality in patients with end-stage renal failure and essential hypertension,[4] as well as hypertension in normotensive men.[5 6] Therefore, prevention and treatment of pathological changes in arterial stiffness are of paramount importance.

Previous studies have demonstrated that regular aerobic exercise is efficacious in preventing and reversing arterial stiffening in healthy adults.[7–9] In recent years, resistance exercise, another common exercise modality, has gained widespread acceptance in exercise prescription and cardiopulmonary rehabilitation programmes, and has become an integral component of comprehensive health programmes endorsed by major health organisations.[10–13] These recommendations are based primarily on the documented impact of resistance training on the attenuation of osteoporosis and sarcopaenia and related risks, including falling and functional disability.[10 14] However, little information is available regarding the potential influence of resistance training on non-musculoskeletal components, in particular, cardiovascular function. In marked contrast to the favourable effects of regular aerobic exercise on arterial stiffness,[7–9] we and other groups have found that several months of resistance training 'increases' central arterial stiffness in healthy men.[15–21] On the other hand, no such changes were observed in several other studies.[22–25]

The small sample sizes in these studies may have been responsible, at least in part, for the observed discrepancies. Meta-analysis is especially appropriate when the number of studies is small and/or the number of subjects that can be enroled in any one study is small. To our knowledge, there have been no previous meta-analyses to examine the effects of resistance training on arterial stiffness. Therefore, this study was performed to conduct a systematic review and meta-analysis of the effects of resistance training on arterial stiffness.

METHODS

Search strategy and study selection

We searched the MEDLINE (accessed via PubMed) and SPORTDiscus electronic databases covering the period from January 1980 through April 2011. In addition, we searched the references of published studies manually. The initial search consisted of the terms (resistance or strength or weight) and training and (artery or arterial) and (compliance or stiffness) associated with a high-sensitivity strategy for the search of randomised control trials (RCTs). Only eligible full articles in English were considered for review.

Eligibility criteria

We included RCTs that compared any category of resistance exercise training with a control group that evaluated arterial stiffness as an outcome, and reported means or differences between means and respective dispersion values of arterial stiffness at baseline and after the intervention. Studies using outcomes other than pulse wave velocity (PWV) and carotid β stiffness index were excluded.[3 26 27]

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Data extraction

Titles and abstracts of retrieved articles were independently evaluated by two investigators (M. M. and N. T.). Abstracts that did not provide sufficient information regarding the inclusion and exclusion criteria were retrieved for full-text evaluation. Two reviewers independently evaluated full-text articles and determined the eligibility for this study. Moreover, they independently conducted data extraction from eligible studies. The major categories of variables encoded were (1) physical characteristics of subjects, (2) stiffness assessment characteristics, (3) training programme characteristics and (4) treatment effects (mean and SD values of changes in arterial stiffness for baseline and postintervention in training and control groups). The majority of studies included in this meta-analysis reported only mean±SD for baseline and postintervention. The corresponding authors of all five of these studies were contacted to obtain data regarding the treatment effects. Four of these five authors responded, and the treatment effects for the remaining one study were calculated in accordance with the previous study.[28]

Data analysis

Statistical analysis was performed with Review Manager Software (RevMan 5.0; Cochrane Collaboration, Oxford, UK). Absolute changes in carotid β index and PWV are reported as differences between arithmetic means before and after interventions. Moreover, relative (%) changes were also calculated. Pooled-effect estimates were obtained by comparing the least-squares mean percentage changes from baseline to the end of the study for each group, and were expressed as the weighted mean differences between groups. Calculations were performed using a random-effects model. In all analyses, $p<0.05$ was considered to indicate statistical significance. Subgroup analysis was performed according to age (young: <40 years old; middle-aged: ≥40 years old) and training intensity (high: >70% 1 repetition maximum (1RM); moderate: 40–70% 1RM). The cut-off point of training intensity was based on American Heart Associationreview in which high and moderate intensity were defined as ~80% and 30%–60% of 1RM, respectively.[29]

Statistical heterogeneity of the treatment effect among studies was assessed using the Cochran Q test. A threshold p value of 0.1 was considered statistically significant. The inconsistency I^2 test was performed and values >50% were considered indicative of high heterogeneity. Selection bias was examined visually using the funnel plot method.

RESULTS

Description of studies

From 185 potentially relevant citations retrieved from electronic databases and searches of reference lists, eight RCTs fulfiled the inclusion criteria. A flow diagram of search and selection is shown in figure 1. The included studies had a total of 193 participants. The characteristics of these studies are summarised in table 1.

Association of resistance training with arterial stiffness

The overall association of any resistance training versus control with relative changes in carotid β index or PWV (eight studies; 193 participants) was 10.7% (95% CI 3.4% to 18.0%; I^2, 89%; heterogeneity, $p<0.001$) (figure 2). A funnel plot of sample size against the effect size was examined. The plot did not show any asymmetry, indicating that significant publication bias was unlikely. From observations of data, for example, publication year, randomisation process and losses to follow-up, selection bias did not markedly affect the results of the present study. In addition, the related factors of age, sex, training intensity or volume, and BMI varied, and these factors were examined visually. The results detected biases by age and training intensity. Thus, subgroup analysis was performed according to age (young or middle-aged) and training intensity (high or moderate).

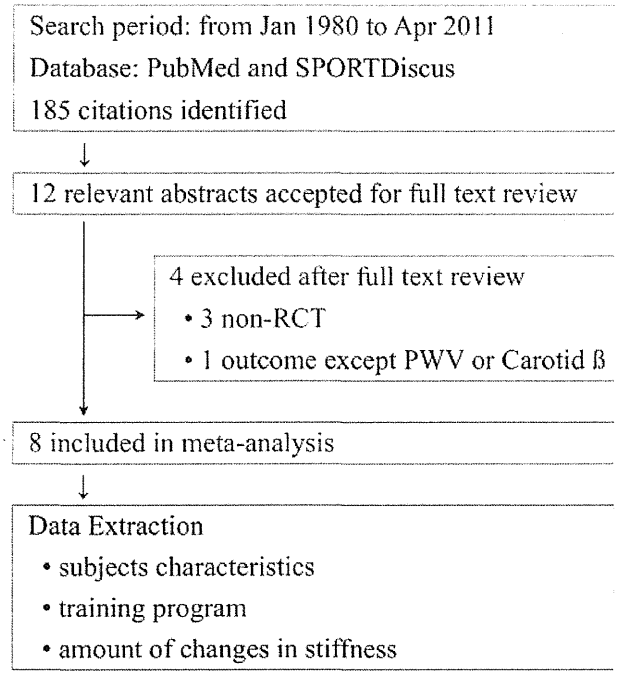

Figure 1 Selection of studies included in the meta-analysis.

Subgroup analysis

Five studies demonstrated that resistance training in young subjects (n=115) was significantly associated with an increase in stiffness of 14.3% (95% CI 8.5% to 20.1%; I^2, 71%; heterogeneity, $p<0.001$) in comparison with control (figure 2). Four of the five studies used high-intensity resistance training, while the other study used training of moderate intensity. On the other hand, three studies showed that resistance training in middle-aged subjects (n=78) was not associated with a change in arterial stiffness (mean difference: −0.6%, 95% CI −10.8% to 9.6%). All of the three studies used moderate-intensity training.

Although high-intensity resistance training (n=87) was significantly associated with an increase in stiffness of 11.6% (95% CI 7.3% to 15.9%; I^2, 54%; heterogeneity, $p<0.001$), moderate-intensity resistance training (n=106) showed no such association, because there was a large degree of variability between the studies (mean difference: 9.1%, 95% CI −5.9% to 24.2%).

DISCUSSION

Our systematic review and meta-analysis demonstrated that resistance training is associated with an increase of ~11.0% in arterial stiffness. Interestingly, resistance training in middle-aged subjects was not associated with an increase in arterial stiffness, but that in young subjects showed a significant association with an increase in stiffness compared with controls. To our knowledge, this is the first systematic review and meta-analysis to assess the association between resistance training and arterial stiffening.

Table 1 Characteristics of the studies included in the meta-analysis

		Control			Trained					
Authors	Year	N	Age (y)	Sex	N	Age (y)	Sex	Training intensity	Outcome	Effect
Miyachi *et al*[18]	2004	14	22	Male	14	22	Male	High	carotid β	Increase
Okamoto *et al*[19]	2005	9	19.9	Female	10	19.1	Female	High	baPWV	Increase
Kawano *et al*[17]	2006	16	22	Male	12	20	Male	Moderate	carotid β	Increase
Cortez-Cooper *et al*[23]	2008	12	54	Both	13	52	Both	Moderate	cfPWV	No change
Collier *et al*[15]	2008	15	49.8	Both	15	47	Both	Moderate	cfPWV	Increase
Okamoto *et al*[20]	2009	10	19.7	Male	10	19.6	Male	High	baPWV	Increase
Okamoto *et al*[21]	2009	10	20.1	Both	10	20.2	Both	High, upper limb	baPWV	Increase
Yoshizawa *et al*[25]	2009	12	49	Female	11	47	Female	Moderate	cfPWV	No change

high, >70% 1RM; moderate, 40%–70% 1RM; carotid β., carotid arterial β stiffness index.
baPWV, brachial-ankle pulse wave velocity; cfPWV, carotid-femoral pulse wave velocity; y, years.

The current guidelines endorsed by major health organisations recommend resistance training.[11–13] The present finding that resistance training is associated with arterial stiffening may discourage this practice. However, we should emphasise that the magnitude of the relative increase in arterial stiffness was only ~11%, the absolute increase in carotid β was 1.12 AU (95% CI 0.66 to 1.58 AU), and the increase in PWV was 72 cm/s (95% CI −3 to 148 cm/s). Such levels of arterial stiffening may not have clinically adverse effects, especially in young adults with low baseline levels of arterial stiffness.[26 27 30] In addition, although high-intensity resistance training (n=87) was significantly associated with an increase in stiffness of 11.6%, moderate-intensity resistance training (n=106) showed no such association. Furthermore, the blood pressure response during dynamic resistance exercise using large muscle groups may be attenuated in middle-aged men relative to young men.[31] Taken together, based on the role of resistance training on the maintenance of functional ability and the prevention of osteoporosis and sarcopaenia, 'properly prescribed' moderate-intensity resistance training based on evidence and guidelines should still be encouraged, particularly in middle-aged and older adults.

The critical question remains whether any type of high-intensity resistance training can be performed regularly without inducing arterial stiffening in young adults. Recent studies suggested that simultaneously performed aerobic exercise training, for example, walking and jogging for 30 min at moderate-intensity,[17] lower-limb resistance training[20] or eccentric resistance training[19] did not induce stiffening of central arteries. In contrast to resistance training, regular aerobic exercise is known to be efficacious for preventing and reversing arterial stiffening in healthy adults.[7 32–34] In fact, the current guidelines endorsed by the major health organisations recommend muscle-strengthening activity and moderate-intensity to vigorous-intensity aerobic activity.[10–12] Therefore, although further studies are necessary, simultaneous aerobic exercise (moderate-intensity walking or jogging for ~30 min) could prevent the stiffening of central arteries caused by high-intensity resistance training in healthy young adults.

The physiological mechanisms underlying the arterial stiffening associated with high-intensity resistance training are not yet clear. Intense resistance training is known to be a strong stimulus to increase sympathetic nervous system activity,[35 36] which may act to increase arterial stiffness by providing chronic restraint on the arterial wall via greater sympathetic adrenergic vasoconstrictor tone.[37] During each bout of high-intensity resistance exercise, arterial blood pressure is also known to increase to as high as ~320/250 mm Hg.[38] These acute intermittent elevations in arterial blood pressure during resistance exercise may alter the arterial structure, or arterial load-bearing properties or both. Further studies are required to determine the physiological

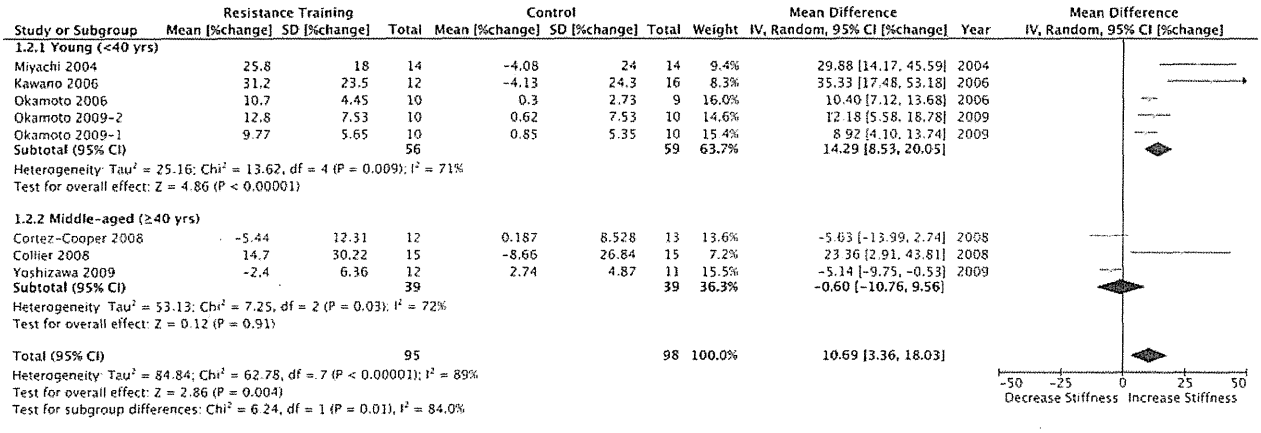

Figure 2 Relative changes in arterial stiffness in individual studies of resistance training versus no intervention. Relative changes in arterial stiffness index (%) of individual studies included in the meta-analysis of resistance exercise training versus no intervention. Studies with young (<40 years old) or middle-aged (≥40 years old) participants were evaluated as separate observations. Weights are from random-effects analysis.

mechanisms underlying the influence of resistance training on central arterial stiffness.

There were some limitations to this meta-analysis. First, although only RCTs were included in the analysis, the limitation may be acceptable as the quality of intervention studies may be affected by many confounding biases. Our systematic review identified three non-RCT intervention studies examining the effects of resistance training on arterial stiffness.[16 22 24] Second, publication bias is always a concern in meta-analyses. We performed electronic searches, including a manual search, and examined sample size against effect size by funnel plot analysis. The funnel plot suggested that there was little influence of publication bias on the effect size. Third, this analysis was confined to articles in the English language literature, and data extraction was unblinded, both of which are potential sources of bias. Fourth, this meta-analysis did not include studies regarding the effects of light-intensity (<30% 1RM) resistance training or those in older subjects (>65 years old), and further investigations are therefore necessary. Finally, the author of the present study is also the principal investigator of two articles selected in this meta-analysis.[17 18] However, this potential conflict did not affect the procedures or results of this meta-analysis because evaluation for eligibility and data extraction were performed by two independent reviewers.

CONCLUSIONS

High-intensity resistance training is associated with an increase in arterial stiffness in young participants with low baseline levels of arterial stiffness. Further studies are warranted to address whether the relatively small increase in arterial stiffness reported with high-intensity resistance training is relevant to cardiovascular health.

What is already known on this topic

- The current guidelines endorsed by major health organisations recommend resistance training.
- Regular aerobic exercise prevents and reverses arterial stiffening, but it is unclear and in controversy whether resistance training increases arterial stiffness.

What this study adds

- This meta-analysis indicates that resistance training is associated with an increase of ~11% in arterial stiffness.
- Although high-intensity resistance training is associated with increased arterial stiffness in young with low baseline levels of arterial stiffness, moderate-intensity resistance training in middle-aged was not.
- The prescribed moderate-intensity resistance training should be encouraged, particularly in middle-aged and older adults.

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