

mRNA expressions of peroxisome proliferator-activated receptor gamma coactivator 1 α , tumor necrosis factor- α , and interleukin-6 in paraspinal muscles of patients with lumbar kyphosis: a preliminary study

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Background: Kyphosis is a spine deformity that can lead to falls and reduced quality of life. Peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α) regulates mitochondrial biogenesis and is important for proper functioning of skeletal muscle, including the paraspinal muscles, which support and allow movement of the spine. The role of PGC-1 α in paraspinal muscles in lumbar kyphosis has not been examined. We also examined the expressions of the proinflammatory cytokines tumor necrosis factor (TNF)- α and interleukin (IL)-6.

Methods: We obtained paraspinal muscle specimens from 12 patients who underwent posterior lumbar surgery. RNA was isolated from these samples, and quantitative PCR was performed to compare the expression levels of PGC-1 α , TNF- α , and IL-6 mRNA between patients with decreased lumbar lordosis (LL) and normal LL patients.

Results: TNF- α and IL-6 mRNA expressions in paraspinal muscles were significantly higher in the decreased LL group than in the normal LL group ($P=0.048$ for both). PGC-1 α mRNA expression was slightly increased in the decreased LL group, but the difference was not significant. Age was significantly positively correlated with PGC-1 α mRNA expression ($P=0.010$). PGC-1 α mRNA expression was significantly positively correlated with TNF- α mRNA expression ($P=0.022$). LL was significantly negatively correlated with PGC-1 α , TNF- α , and IL-6 mRNA expressions ($P=0.015$, 0.036 , and 0.010 , respectively).

Conclusion: TNF- α and IL-6 mRNA expressions in paraspinal muscles were significantly higher in the decreased LL group than in the normal LL group. LL was significantly negatively correlated with PGC-1 α , TNF- α , and IL-6 mRNA expressions. PGC-1 α mRNA expression levels in paraspinal muscles may be affected by lumbar kyphosis.

Keywords: aging, PGC-1 α , TNF- α , IL-6, lumbar kyphosis

Introduction

Spinal deformities, especially kyphosis, due to aging and its related problems, are important concerns for spine surgeons.^{1,2} Kyphotic deformities negatively impact quality of life (QOL) and postural balance, leading to falls in elderly or osteoporotic patients.³⁻⁵ In particular, sagittal spinal malalignment has a greater impact on QOL scores than coronal malalignment in adult patients with spine deformities.^{6,7} Generally, degenerative kyphosis is related to back muscle atrophy and decreased back extensor strength,^{8,9} the latter of which is a risk factor for falls and poor QOL.^{5,10} On the other

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hand, back muscle atrophy and fatty degeneration are also observed in patients with chronic lower back pain.^{11,12} Back-strengthening exercises increase both back extensor strength and QOL scores in postmenopausal women.¹³

Age-related loss of skeletal muscle mass and function, that is, sarcopenia, is a serious health problem. The etiology of sarcopenia is considered to be multifactorial and includes disuse, changes in endocrine function, chronic diseases, inflammation, insulin resistance, and nutritional deficiencies.¹⁴ Peroxisome proliferator-activated receptor gamma coactivator 1 α (PGC-1 α) is a master regulator of mitochondrial biogenesis and a possible therapeutic target for age-related mitochondrial dysfunction in skeletal muscle. PGC-1 α can protect against skeletal muscle wasting by regulating autophagy and is also required for stabilization of the neuromuscular junction program.^{15–17} Furthermore, chronic inflammation due to a sedentary lifestyle is linked with many chronic diseases including musculoskeletal disorders. Normally, PGC-1 α expression in the skeletal muscle of older subjects is decreased, leading to loss of muscle function due to low mitochondriogenesis.^{18–20} Interestingly, PGC-1 α plays an important antiinflammatory role.²¹ In fact, skeletal muscle tissue in skeletal muscle-specific PGC-1 α knockout mice shows increased expressions of several proinflammatory genes such as tumor necrosis factor (TNF)- α and interleukin (IL)-6, and these mice also show elevated levels of circulating IL-6.²² In addition, chronic elevation of IL-6 and TNF- α results in skeletal muscle atrophy and inhibition of muscle regeneration.^{23–25} Administration of IL-6 or TNF- α to rats increases skeletal muscle protein breakdown, decreases protein synthesis and the amino acid concentration in skeletal muscle, and causes muscle wasting.^{26–29}

To our knowledge, no studies have reported the impact of PGC-1 α , TNF- α , and IL-6 expressions in paraspinal muscles on lumbar kyphosis. We hypothesized that decreased expression of PGC-1 α and increased expressions of TNF- α and IL-6 in paraspinal muscles are associated with lumbar kyphosis due to muscle dysfunction. Herein, we examined the relationship among PGC-1 α , TNF- α , and IL-6 expressions in paraspinal muscles and lumbar kyphosis in human subjects.

Materials and methods

Subjects

The study protocol was approved by the ethics committee of Akita University Graduate School of Medicine. Written informed consent was obtained from each patient. Twelve patients (seven males, five females; median age at the time

of surgery, 61 years, range, 18–89 years) requiring posterior lumbar surgery were enrolled in this study. Preoperative lumbar lordosis (LL) was measured using X-ray in the upright position (Table 1). Five patients were diagnosed with lumbar spinal stenosis (LSS), three were diagnosed with lumbar disc herniation, and one patient each was diagnosed with lumbar vertebral fracture, lumbar degenerative kyphosis, lumbar degenerative kyphosis with LSS and an old lumbar vertebral fracture, and osteoid osteoma of the lumbar spine.

Patients were divided into a decreased LL group (n=7), which was defined as less than $-2SD$ (33.8°) according to a previous study in the Japanese population,³⁰ and a normal LL group (n=5).

Preparation of muscle specimens, RNA isolation, and analysis of gene expression

All patients underwent posterior decompression with/without instrumented fusion except for the patient with osteoid osteoma who underwent tumor excision. Bilateral multifidus muscles were obtained during surgery, immediately placed in sterile tubes, frozen in liquid nitrogen, and stored at -80°C until analysis. Specimens were homogenized using ISOGEN (Nippon Gene, Toyama, Japan) and then centrifuged at $12,000\times g$ at 4°C for 10 minutes. Chloroform (200 μL) was added to the supernatant, and the mixture was centrifuged at $12,000\times g$ at 4°C for 15 minutes. Isopropanol was added to an equivalent amount of supernatant. Then, 1 mL ethanol was added to the pellet after the supernatant was discarded, and the mixture was centrifuged at $7,500\times g$ at 4°C for 5 minutes. The sediment was desiccated at room temperature, resuspended in 100 μL diethylpyrocarbonate-treated water, and quantified by spectrophotometry (A260/280). The RNA concentration was determined by absorbance at 260 nm using a U-2000 spectrophotometer (Hitachi Ltd., Tokyo, Japan). Isolated total RNA was treated with DNase I (Sigma-Aldrich, St Louis, MO, USA) according to the manufacturer's instructions. Then, cDNA was synthesized using the First Strand cDNA Synthesis Kit (GE Healthcare, Buckinghamshire, UK) according to the manufacturer's instructions. Specific primers for human PGC-1 α , TNF- α , and IL-6 (QIAGEN,

Table 1 Baseline characteristics of the study population

Variables	Mean	Median	Minimum	Maximum	SD
Age (years)	57.3	61	18	89	20.1
Male:female (n)	7:5				
Lumbar lordosis (degrees)	19.7	25	-25	56	24.1

Note: The angle was considered positive if the curve was lordotic and negative if the curve was kyphotic.

Tokyo, Japan) were used for quantitative polymerase chain reaction (qPCR). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was amplified as an endogenous control gene for normalization. GAPDH primers were synthesized by Greiner Japan in Tokyo. LightCycler 480[®] (Roche Diagnostics, Laval, QC, Canada) and LightCycler 480 SYBR Green 1 Master (Roche Diagnostics) were used for qPCR. Reaction conditions were as follows: 5 minutes at 95°C (denaturation step); 45 cycles of 10 seconds at 95°C, 10 seconds at 58°C, and 10 seconds at 72°C; 5 seconds at 95°C; 65°C–98°C at a rate of 2.2°C/s (melting curve analysis). The relative quantification method for gene expression was performed using the E-Method,³¹ and gene expression was analyzed as the mean value of both sides of the paraspinal muscles. PGC-1 α , TNF- α , and IL-6 mRNA expressions were normalized to GAPDH mRNA expression.

Statistical analysis

The statistical software package IBM SPSS for Mac Version 22.0 (IBM Corp., Armonk, NY, USA) was used for all data analyses. The Mann–Whitney *U* test was used for comparison of variables, and Fisher's exact test was used for comparison of categorical variables between the decreased LL group and the normal group. Relationships among variables were analyzed using Spearman's correlation coefficient. *P*-values <0.05 were considered statistically significant.

Results

TNF- α and IL-6 mRNA expressions in paraspinal muscle were significantly higher in the decreased LL group than in the normal LL group (*P*=0.048 for both; Table 2). The correlations between variables are shown in Table 3. LL was significantly negatively correlated with PGC-1 α , TNF- α , and IL-6 mRNA expressions. Age was significantly positively correlated with PGC-1 α mRNA expression and tended to be

negatively correlated with LL. PGC-1 α mRNA expression was significantly positively correlated with TNF- α mRNA expression and tended to be positively correlated with IL-6 mRNA expression.

Discussion

We predicted that age-related low levels of PGC-1 α mRNA expression in paraspinal muscles and an increase in TNF- α and IL-6 mRNA expressions may be associated with back muscle dysfunction and may lead to lumbar kyphosis. Contrary to our expectation, PGC-1 α mRNA expression in paraspinal muscles was not only positively correlated with age but also negatively correlated with LL. These results are different from previous studies which demonstrated that lower PGC-1 α mRNA expression is related to older age. Ghosh et al¹⁹ demonstrated reduced (by 42%) basal PGC-1 α mRNA levels in human vastus lateralis muscle in older (age \geq 65 years) subjects compared with younger (age 18–30 years) subjects (*P*<0.05). Lanza et al²⁰ also demonstrated that endurance-trained older (59–76 years old) subjects showed lower PGC-1 α protein expression in the vastus lateralis muscle than younger (18–30 years old) subjects. Interestingly, PGC-1 α protein expression is higher in both endurance-trained older and younger subjects than in sedentary older and younger subjects. In our study subjects, PGC-1 α mRNA expression was significantly positively correlated with TNF- α mRNA expression and tended to be positively correlated with IL-6 mRNA expression. In contrast, Handschin et al³² reported that PGC-1 α expression is negatively correlated with IL-6 expression (*r*=0.184, *P*=0.005) and TNF- α expression (*r*=0.137, *P*=0.016) in human vastus lateralis muscles. The reason for these discrepancies between our results and previous studies may be the different muscles examined. Paraspinal muscle activity is increased in lumbar kyphosis patients compared with age-matched LSS patients.³³

Table 2 Comparison of variables between the two groups

Variables	Decreased LL group (n=7)				Normal LL group (n=5)				P-value
	Mean	Median	Range	SD	Mean	Median	Range	SD	
Age (years)	62.9	62	33–89	17.2	49.6	55	18–75	23.4	0.432
Male:female (n)	3:4				4:1				0.293 ^a
LL (degrees)	4.6	2	–25–31	19.2	40.8	40	33–56	9.2	0.003
PGC-1 α	2.6	2.3	0.8–4.7	1.4	1.3	1.1	0.8–2.5	0.7	0.106
TNF- α	3.0	3.2	0.3–5.2	1.6	1.2	1.2	0.7–1.9	0.5	0.048
IL-6	1.2	0.9	0.1–2.5	0.9	0.3	0.3	0.2–0.6	0.2	0.048

Notes: The angle was considered positive if the curve was lordotic and negative if the curve was kyphotic. PGC-1 α , TNF- α , and IL-6 mRNA expressions were normalized to GAPDH mRNA expression. *P*<0.05 was considered statistically significant (nonparametric Mann–Whitney *U* test). ^aFisher's exact test.

Abbreviations: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IL-6, interleukin-6; LL, lumbar lordosis; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1 α ; TNF- α , tumor necrosis factor- α .

Table 3 Correlation between measured variables

Variables	LL (degrees)	PGC-1 α	TNF- α	IL-6
Age (years)				
r^s	-0.553	0.711	0.382	0.498
P-value	0.062	0.010	0.221	0.099
LL (degrees)				
r^s		-0.678	-0.608	-0.708
P-value		0.015	0.036	0.010
PGC-1 α				
r^s			0.650	0.546
P-value			0.022	0.066
TNF- α				
r^s				0.764
P-value				0.004

Notes: PGC-1 α , TNF- α , and IL-6 mRNA expressions were normalized to GAPDH mRNA expression. ^sSpearman's correlation coefficient.

Abbreviations: GAPDH, glyceraldehyde-3-phosphate dehydrogenase; IL-6, interleukin-6; LL, lumbar lordosis; PGC-1 α , peroxisome proliferator-activated receptor gamma coactivator 1 α ; TNF- α , tumor necrosis factor- α .

Chronic increased paraspinal muscle activity in our study subjects may have accelerated PGC-1 α mRNA expression in the paraspinal muscles. In fact, Pilegaard et al³⁴ demonstrated that PGC-1 α transcription and mRNA content in vastus lateralis muscles increase after exercise, especially in the trained leg compared with the untrained leg. In addition, exercise-induced upregulation of PGC-1 α is not limited by aging. Ghosh et al¹⁹ demonstrated that exercise increases PGC-1 α mRNA levels in older subjects by 2.6-fold compared with preexercise mRNA levels ($P < 0.05$). Cobley et al³⁵ also demonstrated that PGC-1 α mRNA expression increases significantly ($P = 0.002$) 3 hours after exercise in the vastus lateralis muscles of sedentary elderly males, and the increase is not influenced by age ($P = 0.604$) or training status ($P = 0.992$). Taken together, these observations suggest that kyphotic deformities of the spine induce upregulation of PGC-1 α mRNA expression in paraspinal muscles, regardless of aging.

Increased expressions of IL-6 and TNF- α mRNA in paraspinal muscles in the decreased LL group in this study may have affected back muscle dysfunction.²³⁻²⁹ However, the role of IL-6 in skeletal muscle is still controversial. Serrano et al reported that IL-6 is an essential regulator of satellite cells.³⁶ Moreover, IL-6 mRNA expression in human vastus lateralis muscle increases after exercise, but no significant increase in TNF- α mRNA expression was observed.^{37,38} Therefore, we cannot conclude whether the increased IL-6 mRNA expression in the decreased LL group was due to chronic inflammation or secondary changes due to increased paraspinal muscle activity.

One of our interests is a possible treatment strategy using pharmacological interventions that modulate PGC-1 α expression to prevent back muscle weakness in the elderly. The efficacy of PGC-1 α upregulation on muscle preservation

has been suggested by several studies. Wenz et al³⁹ reported that MCK-PGC-1 α mice (PGC-1 α driven by the muscle creatine kinase promoter) show preserved mitochondrial function, neuromuscular junctions, and muscle integrity during aging due to reduced apoptosis, autophagy, and proteasome degradation. Furthermore, these PGC-1 α transgenic mice exhibit improved endurance with conversion to slow-twitch, fatigue-resistant, muscle fibers.^{15,40} Qiao et al⁴¹ reported that adiponectin, which is an adipocyte-derived hormone that regulates energy homeostasis, enhances p38 mitogen-activated protein kinase (MAPK) phosphorylation, PGC-1 α expression, and mitochondrial biogenesis by suppressing MAPK phosphatase-1 expression in C2C12 myotubes. These results suggest the possibility of pharmacological treatment to enhance PGC-1 α expression in skeletal muscle. Okada-Iwabu et al⁴² identified "AdipoRon" as an adiponectin receptor agonist and demonstrated that adiponectin/adiponectin receptor 1 signaling improves metabolism and exercise endurance by increasing mitochondrial volume and function similar to physical activity via PGC-1 α upregulation. These data suggest that pharmacological interventions via modulation of adiponectin/adiponectin receptor 1 signaling may improve age-related muscle wasting.

Our study has some limitations. First, the number of participants in this study was small because this was a preliminary study. Second, to what degree paraspinal muscle activity influences mRNA expression in the decreased LL group is unclear because participants in this study did not undergo electromyography before surgery.

Conclusion

TNF- α and IL-6 mRNA expressions in paraspinal muscles were significantly higher in the decreased LL group than in the normal LL group. LL was significantly negatively correlated with PGC-1 α , TNF- α , and IL-6 mRNA expressions. Age was also significantly positively correlated with PGC-1 α mRNA expression in paraspinal muscles. Increased PGC-1 α mRNA expression in paraspinal muscles may be affected by lumbar kyphosis.

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Author contributions

All authors contributed toward data analysis, drafting, and critically revising the paper, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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