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Peroxisome proliferator-activated receptor gamma co-activator 1 gene Gly482Ser polymorphism is associated with the response of low-density lipoprotein cholesterol concentrations to exercise training in elderly Japanese

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Abstract Muscle peroxisome proliferator-activated receptor gamma co-activator 1 (PGC-1)α gene expression is influenced by the Gly482Ser gene polymorphism, which is a candidate genetic risk factor for diabetes mellitus and obesity. This study investigated the effects of PGC-1 gene Gly482Ser polymorphisms on alterations in glucose and lipid metabolism induced by exercise training. A 12-week intervention study was performed for 119 participants who were more than 65 years of age and completed exercise training at lactate threshold intensity. Total cholesterol and low-density lipoprotein cholesterol were significantly reduced in Gly/Gly but not in Gly/Ser and Ser/Ser participants after exercise. The Gly/Gly genotype of the PGC-1 gene Gly482Ser polymorphism influences the effects of moderate-intensity exercise training on low-density lipoprotein cholesterol and total cholesterol concentrations in older people.

Keywords Hyperlipidemia · Atherosclerosis · Diabetes mellitus · Moderate-intensity exercise · Mitochondria

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Introduction

Peroxisome proliferator-activated receptor gamma co-activator 1 (PGC-1)α is a master regulator of energy metabolism. PGC-1α acts as a strong activator of mitochondrial biogenesis and oxidative phosphorylation through effects on gene expression [1, 2], and increases oxidative metabolism in muscle fibers [3, 4]. In addition, PGC-1α increases lipid and glucose use via upregulation of glucose transporter-4 and cluster of differentiation 36 (FAT/CD36) [5–7]. Numerous studies have reported that PGC-1α expression increases in both rodent and human skeletal muscle following a single bout of exercise as well as with longer-term exercise training [8–11].

Skeletal muscle is the predominant organ of energy metabolism, not only during exercise but also under resting conditions. Skeletal muscle mass accounts for approximately 40 % of body mass [12], and the basal metabolic rate correlates with muscle mass [12]. More than half of the total body glycogen is stored in skeletal muscle [13–15]. Muscle mitochondrial content, enzyme activity, and expression of related genes and proteins have all been observed to decrease with obesity and type 2 diabetes [16–19]. These results suggest that muscle mitochondria influence systemic energy metabolism, and that an increase in muscle mitochondrial content and/or function is important for the prevention of obesity, diabetes, and hyperlipidemia. Therefore, PGC-1α plays an important role in the prevention of chronic diseases [20].

Moderate-intensity exercise training improves glucose [21] and lipid metabolism [22, 23] as well as aerobic capacity [24]. In a previous study, we demonstrated that the lactate threshold (LT) intensity is a crucial determinant of PGC-1α gene expression in human skeletal muscle [11]. Exercise-induced PGC-1α can act as a key regulator of

systemic metabolic adaptation [20, 25]. Like many other genes, PGC-1α gene expression is affected by genetic polymorphisms. The PGC-1 gene is located on chromosome 4 (4p15.1), and the genetic variation at position 1444 in exon 8 (rs8192678) results in a Gly482Ser substitution on the gene that influences PGC-1α and PGC-1β gene expression levels in human skeletal muscle in elderly people. Expression levels of these genes are higher in older people with the Gly/Gly genotype than in those with the Gly/Ser or Ser/Ser genotypes [26]. Gly482Ser has been reported as not only a candidate gene polymorphism for type 2 diabetes prevalence [27–30] but also for nonalcoholic fatty liver disease [31, 32] and obesity [33, 34]. PGC-1α can increase type-I skeletal muscle fibers [3, 4], and the Gly482Ser polymorphism of the gene influences exercise-induced skeletal muscle fiber-type transition [35]. A higher composition of type-I skeletal muscle fibers is favorable for the prevention of non-communicable diseases [36]. These findings suggest that the Gly482Ser polymorphism influences metabolic adaptation to exercise training, particularly changes in glucose and lipid metabolism, through regulation of PGC-1α and PGC-1β in skeletal muscle.

This study investigated whether Gly482Ser polymorphism in the PGC-1 gene influences the adaptation of glucose and lipid metabolism to exercise training.

Methods

Participants

Three hundred and twenty-eight Japanese people (112 men and 216 women) over 65 years of age were recruited to participate in the study. All participants were required to pass a medical check-up to ensure that they were of sufficient health to participate [24, 37]. The effects of exercise training among different genotypes were compared in participants who fulfilled inclusion criteria and were accepted into the intervention part of the study. Inclusion criteria for the intervention study were: (1) took part in the 12-week exercise training program; (2) performed exercise tests pre- and post-intervention; (3) recorded in full their at-home training in a logbook; and (4) provided a blood sample pre- and post-intervention. Of the 328 potential participants, 119 (49 men and 70 women) were included in the study.

Fifty-four of the study participants received no medication during the study, and the remaining 65 took medication for hypertension ($n = 42$), hyperlipidemia ($n = 22$), gastrointestinal disorders and constipation ($n = 18$), diabetes mellitus ($n = 6$), and other maladies ($n = 47$) including allergy, inflammation, difficulty sleeping, and osteoporosis. The prevalence of each disorder requiring

medication was compared with the genotype distribution in all 119 participants, and no significant between-genotype differences were detected (Table 1; Chi square test). No participant changed his or her medication status during the intervention.

Genotyping

Genomic DNA was obtained from ethylene-diaminetetraacetic acid–anticoagulated white blood cells using a blood DNA purification kit (GE Healthcare, Little Chalfont, UK). The PGC-1 gene Gly482Ser polymorphism of each individual was determined based on polymerase chain reaction (PCR) restriction fragment length polymorphism analysis, as previously described [38]. PCR products were run on a 3 % agarose gel containing ethidium bromide after digestion by MSP I (New England Biolab, Ispwich, MA, USA) for at least 12 h at 37 °C and were visualized under ultraviolet light.

Assessment of LT

Participants performed a sub-maximal, graded, bench-stepping exercise test using a 20-cm-high bench-stepping platform (StepWell; Combi, Tokyo, Japan) to assess their LT intensity. During the test, participants exercised for a total of 4 min per stage with a 2 min rest between each stage. The initial workload was 40 steps min^{-1}, and the workload was increased by 20 steps min^{-1} for each 4-min stage. The bench-stepping exercise test was concluded when one of two criteria were met: (1) a rating of perceived exertion above 15; or (2) a blood lactic acid concentration above 2 mM/L. Heart rate was obtained over the 30 s immediately prior to the end of each stage using a portable heart rate monitor (Polar Accurex Plus; Polar, Kempele, Finland). For measurement of lactic acid, a blood sample was obtained from the earlobe immediately after each stage using a portable blood lactate measuring device (Lactate Pro; Arkray, Kyoto, Japan). The LT was calculated as previously described [39] and metabolic equivalents at LT intensity were determined. All investigators performed their testing regimen while blind to the Gly482Ser polymorphism status of the participants.

Exercise training

All participants in the intervention study performed bench-stepping exercise training at LT intensity for 12 weeks, as previously described [24, 37]. Participants were instructed to exercise for at least 140 min per week every week. They performed the exercise training at their home and were observed for at least 20 min every week. After 6 weeks of training, participants performed an exercise test and their

Table 1 Conditions requiring medication and PGC-1 gene Gly482Ser polymorphisms

Medications (n)	Gly/Gly (n = 34)	Gly/Ser (n = 56)	Ser/Ser (n = 29)	χ^2	p value
No medications (54)	13	28	13	0.01	0.99
	(0.24)	(0.52)	(0.24)		
On medication (65)	21	28	16	0.01	1.00
	(0.32)	(0.43)	(0.25)		
Hypertension (42)	12	18	12	0.01	0.99
	(0.29)	(0.43)	(0.29)		
Hyperlipidemia (22)	8	8	6	0.05	0.97
	(0.36)	(0.36)	(0.27)		
Gastrointestinal disorders and constipation (18)	7	4	7	0.36	0.84
	(0.39)	(0.22)	(0.39)		
Diabetes mellitus (6)	1	3	2	0.11	0.95
	(0.17)	(0.50)	(0.33)		
Others (47)	15	17	15	0.05	0.97
	(0.32)	(0.36)	(0.32)		

The upper number is the number of participants in each category, and the lower number is the ratio of the number of participants with that polymorphism divided by the total number of participants with each condition. Prevalence was compared with genotype distribution in all 119 participants using the Chi square test

LT was evaluated to readjust their training intensity. They then exercised at the revised intensity for the next 6 weeks. The amount of exercise, including time spent exercising, was noted daily in their exercise training log.

Blood analysis

Blood samples were obtained from the antecubital vein. Sampling was carried out between 0800 and 1100 hours after at least a 12-h fast. Blood was centrifuged and plasma and serum were harvested immediately after collection. Whole blood was stored at 4 °C and plasma and serum were stored at −80 °C until analysis. Fasting glucose (FG), glycated hemoglobin (HbA1c), immune-reactive insulin (IRI), triglycerides (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) were measured using commercially available assays (SRL, Tokyo, Japan). For assessment of insulin resistance, the homeostatic model assessment insulin resistance (HOMA-IR) was used: HOMA-IR = fasting IRI (mU)/fasting plasma glucose (mg/dL)$_{/405}$). For sensitivity, the quantitative insulin sensitivity check index (QUICKI) was used: QUICKI = 1/(log[fasting IRI (mU)] + log[fasting plasma glucose (mg/dL)]) [40]. IRI and HbA1c were measured in 102 and 118 of the 119 participants, respectively, because we could not take a sufficient blood volume, or we had to exclude because of hemolysis in specimens. Low-density lipoprotein cholesterol (LDL-C) was calculated using Friedewald's formula [41].

Statistical analysis

The statistical software program PASW Statistics 18 (SAS Institute, Cary, NC, USA) was used for all statistical analyses. One-way analysis of variance (ANOVA) was used to compare baseline age, training time, height, weight, and body mass index (BMI) among genotypes. LT was adjusted by age and was then compared using analysis of covariance (ANCOVA) with post hoc Bonferroni testing. Two-factor repeated-measures ANOVA was used to determine the effect of genotype on changes in LT, body mass, and glucose and lipid profiles. Where there was an interaction between genotype and time, changes in variables were compared using ANCOVA with post hoc Bonferroni testing adjusted for age, gender, training time (min week^{-1}), LT, and baseline values. The significance of differences in responses to training was assessed using Student's paired t test to compare values at 0 and 12 weeks. Blood values were used after log-transformation, and the equality of variance between polymorphism groups was confirmed using Levene's test. In all instances, a P value <0.05 was considered to be statistically significant.

Results

Participant characteristics and distribution of the gene polymorphism

Participant characteristics are shown in Table 2. Distributions of the Gly482Ser polymorphism were 28.6, 47.1, and 24.4 % for Gly/Gly, Gly/Ser, and Ser/Ser, respectively.

Table 2 Characteristics, body mass, aerobic capacity, and glucose and lipid profiles before and after exercise training

(M/F)		Gly/Gly $n = 34$ (16/18)	Gly/Ser $n = 56$ (23/33)	Ser/Ser $n = 29$ (10/19)	All participants $n = 119$ (49/70)
Age (years)	0w	70 ± 6	71 ± 7	73 ± 6	71 ± 6
Height (cm)	0w	156.0 ± 8.4	155.8 ± 7.2	153.2 ± 7.6	155.2 ± 7.7
Training time (min/week)		145 ± 54	157 ± 57	165 ± 59	156 ± 57
Body mass (kg)	0w	58.9 ± 10.1	57.8 ± 10.4	55.2 ± 8.2	57.5 ± 9.8
	12w	58.1 ± 9.6*	57.2 ± 10.3*	54.7 ± 8.0[†]	56.9 ± 9.6[#]
BMI (kg/m^2)	0w	24.1 ± 2.5	23.8 ± 3.8	23.5 ± 2.8	23.8 ± 3.3
	12w	23.7 ± 2.4*	23.6 ± 3.9*	23.3 ± 2.7	23.5 ± 3.2[#]
LT (METs)	0w	4.4 ± 0.9[$]	4.5 ± 0.8[$]	3.8 ± 1.0	4.3 ± 0.9
	12w	5.1 ± 1.0*	5.4 ± 1.0*	5.0 ± 0.9*	5.2 ± 1.0[#]
FG (mg/dl)	0w	104 ± 14	103 ± 19	101 ± 20	103 ± 18
	12w	101 ± 16*	100 ± 16*	98 ± 19*	100 ± 17[#]
HbA1c (%)	0w	5.6 ± 0.6	5.6 ± 0.9	5.8 ± 0.9	5.8 ± 0.8
	12w	5.6 ± 0.5	5.7 ± 0.7	5.8 ± 0.6	5.7 ± 0.6
IRI (μU/ml)	0w	7.5 ± 4.5	7.6 ± 7.6	8.0 ± 7.8	7.6 ± 6.8
	12w	6.5 ± 3.6	7.6 ± 4.9	7.5 ± 7.1	7.3 ± 5.1
HOMA-IR	0w	1.9 ± 1.1	2.0 ± 2.2	1.7 ± 1.4	1.9 ± 1.8
	12w	1.6 ± 0.9	2.0 ± 1.4	1.8 ± 1.6	1.8 ± 1.3
QUICKI	0w	0.359 ± 0.037	0.370 ± 0.045	0.369 ± 0.039	0.367 ± 0.042
	12w	0.365 ± 0.029	0.363 ± 0.042	0.370 ± 0.043	0.365 ± 0.039
TG (mg/dL)	0w	119 ± 88	99 ± 43	113 ± 53	108 ± 62
	12w	127 ± 83	104 ± 43	111 ± 42	112 ± 58
TC (mg/dL)	0w	212 ± 33	214 ± 32	205 ± 24	211 ± 31
	12w	205 ± 34*	217 ± 33	212 ± 30	212 ± 33
HDL-C (mg/dL)	0w	58 ± 12	63 ± 15	59 ± 15	60 ± 14
	12w	58 ± 15	63 ± 16	61 ± 15	61 ± 15
LDL-C (mg/dL)	0w	130 ± 31	132 ± 30	124 ± 22	129 ± 28
	12w	122 ± 27*	134 ± 32	128 ± 29	129 ± 30

Values are mean ± SD

* $P < 0.05$ vs. week 0 within genotype

[†] $P = 0.068$ vs. week 0 within genotype

[#] $P < 0.05$ vs. week 0 within total group

[$] $P < 0.05$ vs. week 0 for Ser/Ser genotype

The distribution of the Gly482Ser polymorphism was in Hardy–Weinberg equilibrium. Gender, age, height, body mass, and BMI did not significantly differ among genotypes. Baseline values for FG, HbA1c, IRI, HOMA-IR, QUICKI, TG, TC, HDL-C, and LDL-C were not significantly different among genotypes. The Gly/Gly and Gly/Ser genotypes had a higher LT intensity at baseline (Table 2). Training times obtained from training logs did not significantly differ among the genotypes.

Exercise training effects and gene polymorphism

When all genotype groups were combined, body mass, BMI, and FG were lower, and LT intensity was higher, after 12 weeks of exercise compared with baseline. Although there were no differences in LDL-C and TC concentrations before and after exercise in combined genotypes ($P = 0.808$ and $P = 0.566$, respectively; paired t test), an interaction between genotype and time was found for LDL-C and TC ($F = 3.981$ and $P = 0.021$, $F = 3.246$ and $P = 0.042$, respectively; two-factor repeated-measures ANOVA). Only participants with the Gly/Gly genotype showed a significant reduction (Table 2). When changes in parameters over the 12-week intervention period were compared using ANCOVA, LDL-C concentrations in participants with the Gly/Gly genotype significantly differed from Gly/Ser and Ser/Ser ($F = 4.956$ and $P = 0.009$) participants (Fig. 1). TC concentrations in participants with
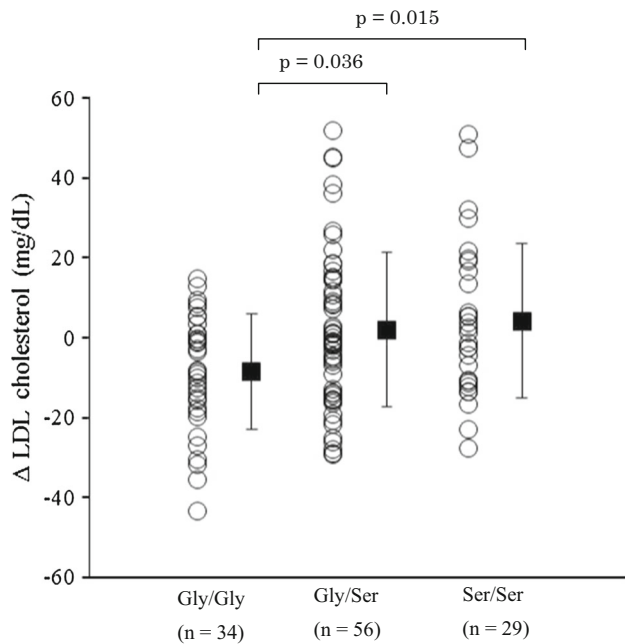
Fig. 1 Comparison of changes in plasma low-density lipoprotein cholesterol (LDL-C) concentrations after 12 weeks of exercise training at lactate threshold (LT) intensity. Log-transformed values were used for the statistical analysis. Changes in LDL-C concentrations after 12 weeks (ΔLDL-C) of exercise training at LT intensity were adjusted for age, gender, training time (min week^{-1}), and baseline values and were compared using analysis of covariance (ANCOVA) with Bonferroni post hoc testing. The change in LDL-C in participants with the Gly/Gly genotype significantly differed from changes in Gly/Ser and Ser/Ser ($F = 4.956$ and $P = 0.009$) participants. Post-exercise training LDL-C concentrations were significantly lower in participants with the Gly/Gly genotype than in those with the Gly/Ser and Ser/Ser genotypes. Values are mean ± SD
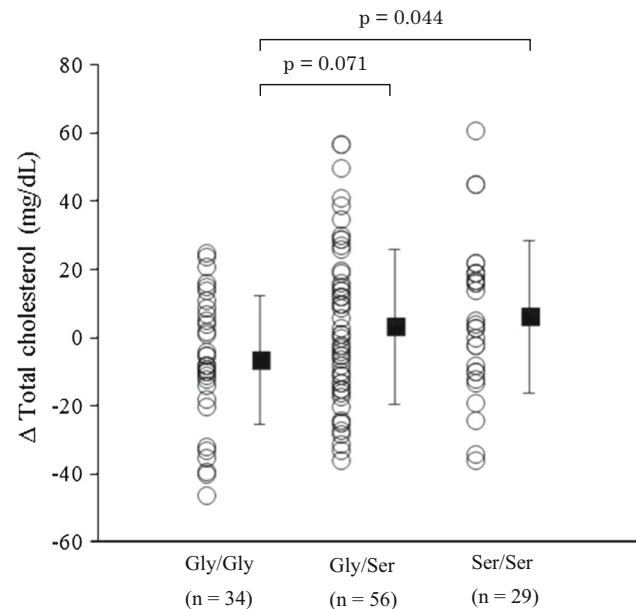

Fig. 2 Comparison of changes in plasma total cholesterol (TC) concentrations after 12 weeks of exercise training at lactate threshold (LT) intensity. Log-transformed values were used for the statistical analysis. Changes in TC concentrations after 12 weeks (ΔTC) of exercise training at LT intensity were adjusted for age, gender, training time (min week^{-1}), and baseline values and were compared using analysis of covariance (ANCOVA) with Bonferroni post hoc testing. The change in TC in participants with the Gly/Gly genotype significantly differed from changes in Gly/Ser and Ser/Ser ($F = 3.850$ and $P = 0.024$) participants. Values are mean ± SD

the Gly/Gly genotype also significantly differed from Gly/Ser and Ser/Ser ($F = 3.850$ and $P = 0.024$) participants (Fig. 2).

Discussion

This study investigated whether the Gly482Ser polymorphism of the PGC-1 gene influenced the effects of exercise on systemic glucose and lipid metabolism. We found, for the first time to the best of the authors' knowledge, that this gene polymorphism modulated the influence of exercise on LDL-C and TC concentrations in this population of older Japanese people.

Gly482Ser polymorphism of the PGC-1 gene is suspected to be a genetic risk factor for diabetes [27–30]. PGC-1α strongly stimulates mitochondrial biogenesis and increases mitochondrial function [1, 2]. The expression of genes associated with oxidative phosphorylation is regulated by PGC-1, and is lower in diabetic patients than in non-diabetics [17–19]. An increase in PGC-1 expression

could be a crucial factor for improvement of glucose metabolism.

We hypothesized that this gene polymorphism influences the improvements in insulin resistance and sensitivity seen with exercise training. However, our results do not indicate that this is the case. In this study, participants were older patients without diabetes mellitus. The treatment guide for diabetes edited by the Japan Diabetes Society [42] defines diagnostic criteria for diabetes mellitus and insulin resistance as: FG ≥126 mg/dL, HbA1c ≥6.5 %, and HOMA-IR ≥2.5. Baseline values for these parameters are shown in Table 2. In the current study, only 9, 7, and 21 of the 119 participants were over the diagnostic levels for FG, HbA1c, and HOMA-IR, respectively. If diabetic patients had been recruited, these associations would have been very different.

Moderate-intensity exercise training helps in the prevention and treatment of non-communicable diseases. However, previous exercise training studies carried out at LT intensity have not consistently shown the LDL-C-lowering effect of moderate exercise that we observed [43–45]. Furthermore, Durstine et al. [46] reported in their review that just 25 % of publications reported that exercise training had a lowering effect on TC and LDL-C

concentrations. Other meta-analyses [47] have also concluded that LDL-C concentrations are unchanged by exercise training. When all genotype groups in the current study were combined, LDL-C concentrations were not significantly different between before and after exercise training (Table 2). This result aligns with those of previous studies; however, we found that the change in LDL-C seen with exercise at LT intensity differed among the different PGC-1 gene Gly482Ser polymorphism genotypes. The reduction in TC concentration was higher in participants with the Gly/Gly genotype than in Ser/Ser participants. Although not statistically significant, it also tended to be higher than in those with the Gly/Ser genotype ($P = 0.064$; Bonferroni test). Both LDL-C ($P = 0.002$) and TC concentrations ($P = 0.049$) were reduced after exercise training only in participants with the Gly/Gly genotype, and changes in LDL-C and TC concentrations significantly correlated ($r^2 = 0.763$, 0.877, and 0.826 for Gly/Gly, Gly/Ser, and Ser/Ser genotypes, respectively; all $P < 0.01$). These findings suggest that the Gly482Ser polymorphism may account for the previously observed inconsistency in the effects of exercise on LDL-C and TC concentrations. Although further studies are required, it is suggested that the Gly482Ser polymorphism may be useful for predicting the effect of exercise intervention aimed at lowering LDL-C and TC concentrations.

The mechanism by which exercise-induced changes in LDL-C and TC concentrations are affected by the Gly482Ser polymorphism is unclear; however, the LDL receptor (LDLR) may play a role in this process. The LDLR is systemically expressed in the human body, including in the liver and skeletal muscle [48]. Cells take up LDL-C via the LDLR, and LDL-C then degrades to cholesterol in the lysosome. In the liver, cholesterol is used for bile acid biogenesis. Part of the bile acid produced is excreted with the feces, and this reduces LDL-C concentrations. Bile acid biogenesis is regulated by the rate limiting enzyme cholesterol 7-α-hydroxylase in the liver, and PGC-1α activates this enzyme [49]. Bile acid not only facilitates cholesterol excretion but also enhances LDLR gene expression [50]. It has not been clearly proven that PGC-1α gene expression levels in the liver differ among individuals with different Gly482Ser polymorphisms; however, previous studies have demonstrated that the Ser/Ser genotype is a risk factor for nonalcoholic fatty liver disease [31, 32], obesity [33, 34], and reduced clearance of non-esterified fatty acids [51]. These results suggest that the Gly482Ser polymorphism could influence PGC-1α gene expression in not only skeletal muscle but also in the liver and other organs.

The Gly482Ser polymorphism presents in the coding region of PGC-1 and changes the amino acid sequence. Although the mechanisms regulating this change are unclear, the Gly/Gly genotype is reported to show higher PGC-1α and PGC-1β gene expression in human skeletal muscle in the elderly [26]. If the gene polymorphism alone determines PGC-1α gene expression, the difference may be also identified in young people. Therefore, other factors that are influenced by aging may be working with the gene polymorphism. PGC-1α gene expression is regulated by members of the myocyte enhancer factor 2 (MEF2) family of transcriptional factors. PGC-1 activates MEF2 to bind to the PGC-1α promoter region [52] and regulates its own gene expression. It is possible that the amino acid replacement may affect the positive feedback loop and change the PGC-1a gene expression level.

The exercise protocol used in this study did not result in significant improvements in HDL-C and TG concentrations. Exercise-induced changes in HDL-C have been shown to depend on the amount of time spent exercising [44]. In this study, participants exercised for 145–165 min per week (this is consistent with an HDL-C concentration of approximately 42–46 mg/dL [44]), and the time spent training was not enough to increase HDL-C concentrations.

A limitation of the study was the small sample size. If patients with hypertriglyceridemia or low HDL-C had been recruited, then it is suggested that the observed differences would have been more prominent.

In conclusion, the results of the study suggest that, in general, exercise training for 12 weeks at LT intensity (mean training time of 145–165 min week^{-1}) had little effect on LDL-C and TC concentrations in this population. The Gly/Gly genotype of the PGC-1 gene Gly482Ser polymorphism may enhance the ability of exercise to lower LDL-C and TC concentrations in older people.

Author contributions A, B and F designed the study. A, B, C, D, and E performed experiments. A, E and F analyzed the data. A and F wrote the manuscript. All authors read and approved the final version of the manuscript.

Compliance with ethical standards

Disclosure of potential conflicts of interest The authors declare that they have no conflicts of interest.

Research involving human participants and/or animals All procedures performed in studies involving human participants were in

accordance with the ethical standards of the ethics committee of Hokkaido University School of Medicine and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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

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