Relationship between Angiotensin Converting Enzyme Gene I/D Polymorphism and Muscle Strength in Elderly

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Previous studies have indicated that the Angiotensin I converting enzyme (ACE) gene insertion/deletion (I/D) polymorphism could influence human physical performance. Furthermore, a study has suggested that ACE inhibitor treatment might decrease long-term decline in muscle strength in elderly women. Thus we hypothesized that the I allele of ACE gene I/D polymorphism, which relates to lower ACE activity, might be associated with slow-decline of muscle strength in the elderly. One hundred ninety elderly people aged 72 were recruited for this study. We assessed isometric knee extension strength, leg extension power and grip strength every year for 4 years. In the preliminary measurements, physical characteristics and muscle strength were not significantly different among three genotypes. Age-related changes of the isometric knee extension, leg extension power, grip strength were similar among three genotypes. The results of this investigation suggest that ACE gene I/D polymorphism does not affect age-related change of muscle strength in the elderly.

Keywords: Angiotensin I converting enzyme, Polymorphism, Aging

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1. Introduction

Age-related physical changes are affected by various factors. Especially, genetic factors are predominant in these changes. This is because aging speed and lifespan converge in the same species (Hekimi et al., 2003; Browner et al., 2004). One recent study investigating human longevity and genetic factors reports the angiotensin I converting enzyme (ACE) gene Insertion (I) Deletion (D)

polymorphism to be a candidate for important related factors (Schachter et al., 1994).

ACE is a key enzyme in the blood pressure regulation system which produces vasoconstrictor angiotensin II (Ang II) from angiotensin I (Ang I). Ang II stimulates water and sodium retention in order to facilitate aldosterone secretion in the adrenal glands. Furthermore, ACE inactivates the bradykinin (BK). As a result the enzyme increases blood pressure.

The human ACE gene is codified in 17q23. ACE gene I/D polymorphism is decided by the presence or absence of genes on intron 16 of 287 base pairs. ACE gene I/D polymorphism consists of three genotypes: I allele homozygous (I/I), D allele homozygous (D/D), and heterozygous (I/D). ACE activity of serum and tissue is significantly lower in I/I than D/D while I/D stands in the middle (Rigat et al., 1990; Danser et al., 1995).

Many reports indicate ACE gene I/D polymorphism as a genetic factor influential in physical performance (Montgomery et al., 1998; Gayagay et al., 1998; Hagberg et al., 1998; Woods et al., 2001). The finding in our previous study that ACE gene I/D polymorphism is one of the genetic factors determining human skeletal muscle fiber composition supports the phenomenon that this polymorphism is associated with physical performance (Zhang et al., 2003). Also, recent reports suggest an ACE inhibitor has an effect on improvement of physical performance (Vescovo et al., 1998) and that it inhibits decline of muscle strength with age (Onder et al., 2002). Thus, we hypothesize that chronically lower ACE activity prevents decline of age-related muscle strength.

The purpose of this study is to examine the relationship between ACE gene I/D polymorphism and age-related change of muscle strength by a follow-up study of the elderly.

2. Method

2.1. Subjects

We randomly selected 600 elderly living in Niigata Prefecture in Japan who turned 72 years old in 2000, and from that group we identified 190 subjects who fulfilled four years of physical examinations conducted in June every year from 2000 to 2004. We received informed consent from all the subjects. This study was approved by the Ethics Committee of the Faculty of Dentistry at Niigata University.

2.2. ACE gene polymorphism

We extracted genomic DNA from peripheral blood leukocytes and amplified the I and D allele of ACE gene I/D polymorphism by polymerase chain reaction (PCR). The PCR products of 490bp and 290bp were separated on 1.5% agarose gel and visualized by

ethidium bromide staining, as previously described by Zhang et al. (2003).

2.3. Muscle strength measurement

We evaluated isometric knee extension strength, leg extension power, and grip strength. For isometric knee extension strength, the subjects were asked to sit on a chair and attach both ankles to a belt that was connected to a loadcell. Strength was measured through maximum isometric tension when their knees were extended to ninety degrees. We measured leg extension power five times by a leg extension power measuring device (Anaeropress-3500, Combi: Japan) and used the means of the two greatest measurements. For grip strength, we measured right and left twice using a smedley hand dynamometer (DM-100s, Yagami: Japan) and took the maximum value.

2.4. Statistical analysis

ANOVA was used to compare the measured values of the first year with I/I, I/D, and D/D of ACE gene I/D polymorphism. Repeated 2-way ANOVA was used to compare the age-based changes of knee extension strength, leg extension power, and grip strength among the polymorphisms with a significance level less than 5%.

3. Result

The frequency of ACE gene I/D polymorphism was 77 (50 males and 27 females) in I/I, 85 (52 males and 33 females) in I/D, and 28 (18 males and 10 females) in D/D. Hardy-Weinberg equilibrium was established.

Height, weight, knee extension strength, leg extension power, and grip strength obtained in the measurement of the first year did not show any difference among the ACE gene I/D polymorphisms (**Table 1**). No significant difference was observed in the change of knee extension strength, leg extension power, and grip strength with time during four years among the ACE gene I/D polymorphisms (**Figure 1**).

4. Discussion

Many studies have reported a possibility of influence of the ACE gene I/D polymorphism on

Table 1 Characteristics and muscle strength at baseline of the subjects.

	I/I N = 77	I/D N = 85	D/D N = 28
Height (cm)	158.1 ± 8.2	158.2 ± 8.2	156.5 ± 7.0
Body weight (kg)	54.7 ± 9.8	56.4 ± 8.7	54.9 ± 8.0
Isometric knee extension strength (kg)	62.1 ± 22.2	57.6 ± 16.0	62.8 ± 15.0
Leg extension power (watts)	751.0 ± 326.3	765.2 ± 303.8	702.4 ± 286.6
Grip strength (kg)	35.2 ± 8.5	36.1 ± 9.0	35.3 ± 8.0

Values are given as mean ± SD

physical performance. Furthermore, two reliable studies suggest that the gene polymorphism may control lifespan and that long-term use of an ACE inhibitor may curb weakening of muscle strength with age. Thus, we examined if ACE gene I/D polymorphism, which has a great influence on ACE activity, might affect change of age-related muscle strength. Contrary to our hypothesis, knee extension strength, leg extension power, and grip strength did not show any differences among the polymorphisms.

Muscle strength declines with age (Gallagher et al., 1997). If ACE gene I/D polymorphism is a genetic factor strongly influential in the change of age-related muscle strength, some differences should have been recognized in 2000 when the subjects turned 72. The present study did not observe any differences either in the change of muscle strength in the first year or the four-year age-based change of muscle strength among the ACE gene I/D polymorphisms. From our longitudinal and lateral observation of the present study, there was no relation between ACE gene I/D polymorphism and the change of age-related muscle strength.

Onder et al., have suggested reduction in inflammatory responses to slow the decreases in muscle strength with age by prolonged use of an ACE inhibitor (Onder et al., 2002). The pathway of a decrease of inflammatory reactant, as they exemplified, includes increase of nitrogen monoxide (NO) through ACE inhibition-mediated BK

increase (De Caterina et al., 1995) and decrease of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) through inhibition of nuclear factor κB (NF-κB) from entering into the nucleus by a decrease of Ang II (Han et al., 1999; Ross, 1993). Because ACE activity is lower in I/I than D/D among the ACE gene I/D polymorphisms, BK is inactivated less and Ang II is produced less in I/I. In previous studies, however, no difference was observed between BK at rest and Ang II among the ACE gene I/D polymorphisms (Murphey et al., 2000; Lachurie et al., 1995). Thus, it demonstrates little possibility of influence of ACE gene I/D polymorphism on production of inflammatory reactant.

The result of the present study suggests that ACE gene I/D polymorphism is not the factor affecting the change of age-related muscle strength.

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Figure 1 Changes in muscle strength in I/I (---●---), I/D (---●---) and D/D (—○—) genotype of angiotensin I converting enzyme gene I/D polymorphism. Data are shown as mean and SE.

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