Original Paper

A Comparison of Anthropometry, Biochemical Variables and Plasma Amino Acids among Centenarians, Elderly and Young Subjects

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Key words: centenarians, elderly, young, anthropometry, biochemistry, plasma amino acids

Objective: Aging health is associated with nutritional changes which are not well understood and were therefore evaluated in this study by comparing the nutritional status of centenarians and elderly (in their 70s) relative to young subjects.

Subjects: The participants were 27 young subjects (10 males, 17 females), 40 healthy elderly (20 males, 20 females) and 32 centenarians (9 males, 23 females).

Methods: The activities of daily living (ADL), height, weight, body mass index (BMI), biochemical variables (total protein, albumin, triglycerides as well as total, HDL, LDL and VLDL cholesterol) and plasma amino acid profiles were evaluated.

Results: Compared with young subjects, lower ($p<0.05$) height, weight, total protein, albumin and albumin/globulin (A/G) ratio and total cholesterol for centenarians and height, albumin and A/G ratio for elderly were observed in both genders. Total cholesterol of male centenarians was lower than in young and elderly subjects and total and LDL cholesterol concentrations of female elderly were higher than those of young and centenarian subjects. However, the cholesterol concentrations of all the centenarians were within the reference range. The ratios of essential amino acids to nonessential amino acids were significantly lower ($p<0.05$) in the centenarians than the young subjects. Clear changes in individual amino acids with aging were lower ($p<0.05$) branched chain amino acids and methionine and higher proline and cystine, which are similar to the amino acid profiles in liver deterioration.

Conclusion: The results suggest that the centenarians had poor nutritional status, which may be due to their decreased metabolism and the possibility that only short, slender individuals with low lipids, protein and essential amino acids are those that tend to survive to be centenarians.

INTRODUCTION

The proportion and number of the aged have increased progressively in most countries. In Japan, the increase is remarkable, where about 15.1% of the population are aged 65 years or older [1]. Older individuals usually have various health problems. To ensure optimum quality of life and also to alleviate the financial and psychological burdens arising from aging for the individuals and their families and the society as a whole, good health is important. Nutrition is an important contributory factor in such problems. However, information about the nutritional status of very old people, such as centenarians, is limited, especially that assessed by biochemical variables, including amino acid profiles. Thus we are uncertain whether we can assume the elderly (in their 70s) and centenarians to be similar groups in their nutritional status.

Activities of daily living (ADL), anthropometry and biochemical variables, such as total protein, albumin, globulin, albumin/globulin (A/G) ratio [A/G ratio=albumin/difference of total protein and albumin] and various cholesterol values, are good indicators of nutritional status [2–12]. Plasma amino acid concentrations reflect all the factors influencing total body

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amino acid flux and, therefore, can also be good indicators of the nutritional status of the hosts [13–17]. In protein undernutrition, concentrations of essential amino acids (EAA) decreases and nonessential amino acids (NEAA) increases, hence EAA/NEAA ratio (E/N ratio) decreases [13]. Specific changes in some amino acids are also known in various diseases [18–21].

In this study, we assessed the nutritional status of the centenarians by the anthropometry, biochemical variables and plasma amino acid profiles and compared it with that of young subjects and elderly in their 70s.

MATERIALS AND METHODS

Subjects and Methods

Subjects in the study were 99 adult volunteers. Twenty-seven were young bank employees (10 males aged 26.3±0.8 years, 17 females aged 25.0±0.6 years), 40, healthy elderly (20 males aged 75.8±0.5 years, 20 females aged 76.3±0.8 years) and 32 centenarians (9 males aged 101.9±1.0 years, 23 females aged 102.0±0.5 years). The first two groups were citizens who went to the annual health examination of the prefecture and agreed to participate in this study. All centenarians living at home within an area possible for us to visit were contacted and 32 centenarians volunteered to take part in this study. The purpose and procedures of the study were explained to the subjects, and informed and written consent was obtained from all subjects. All subjects underwent a physical examination and blood tests (including liver and kidney function), and those who were taking medication or had chronic illness were excluded from this study. Height and weight were measured, and the body mass index (BMI) was calculated [weight (kg)/height (m^2)].

The Japanese average anthropometric values of the centenarians at 20 years of age in 1920 and the elderly at 20 years of age in 1948 are given here in order to appraise the present study's results. The average values were calculated based on percentile values of body weight and height classified by gender and age. It is assumed that healthy persons fall within a weight and height percentile range of 25 and 75 in the respective groups. The average height, body weight and BMI of Japanese when the centenarians were 20 years of age in 1920 were 150.9 cm, 49.3 kg and BMI 21.7 kg/m^2 for females and 162.4 cm, 54.4 kg and BMI 20.6 kg/m^2 for males, and the average height, body weight and BMI of the Japanese elderly were 154.0 cm, 51.4 kg and BMI 21.7 kg/m^2 for females and 163.7 cm, 55.3 kg and BMI 20.6 kg/m^2 for males in 1948 when the elderly were 20 [22].

Activities of daily living (ADL) were assessed by interviewing the subjects and the families of centenarians. Physical items (meal taking, bowel and bladder continence, standing ability, extent of general activities, bathing and dressing abilities), sensory items (auditory acuity and eyesight) and cognitive abilities (comprehension and self-expression) were included in the ADL. Each item was classified into five categories of self-sufficiency: completely independent, independent but slow, independent with difficulty, partially dependent and completely dependent, using a point score from 5 to 1, respectively [23].

Venous blood was withdrawn in the morning (after an overnight fast). Part of the blood was centrifuged at 2500 rpm for ten minutes to obtain serum for analyses of total protein, albumin, triglycerides and cholesterols (total, HDL, LDL and VLDL cholesterol). The remainder were dispensed into a heparinized tube, centrifugated and the plasma was stored at −80°C. The biochemical variables were analyzed at a commercial analytical service center (SRL Co., Okinawa, Japan).

Plasma (120 μL) was deproteinized by the addition of 30 μL 0.5m hydrochloric acid, to which a 150 μL internal standard (homoserine) was added. Protein was removed immediately by centrifuging at 8000 rpm for 30 minutes. Deproteinized supernatant (40 μL) was transferred to sample vials, and amino acid concentrations were analyzed by an automatic amino-acid analyzer (Hitachi 835-50, Tokyo, Japan) using the standard physiological program described in the manual. A lithium-loaded ion-exchange column was used. The column effluent was mixed with *o*-phthalaldehyde fluorescent derivatives of the primary amines. A calibrated mixture of amino acids supplied by Sigma Chemical Company, Tokyo, Japan, which contained most of the amino acids found in physiological specimens, was used to standardize the amino acid analysis procedure. Known amounts of tryptophan, ornithine, glutamine and the internal standard (homoserine) were added to the calibration mixture. A standard amino acid mixture was run before and after each batch. No more than five samples were analyzed sequentially in a batch.

Tryptophan, cystine and proline were analyzed by the use of a sodium loaded ion-exchange column, because they could not be measured by the lithium loaded ion-exchanged method. Plasma (20 μL) was deproteinized by the addition of 80 μL 0.2m hydrochloric acid, to which a 100 μL internal standard (nor-valine) was added. After deproteinization, the supernatant (40 μL) was transferred to sampler vials then analyzed as above, except that nor-valine was used as an internal standard (Ajinomoto Company, Tokyo, Japan).

Statistical Analysis

Data were analyzed by one-way ANOVA and expressed as mean±SEM. The differences between the young, elderly and centenarians of either gender were evaluated by Duncan's multiple range test [24]. A p value of <0.05 was considered significantly different.

RESULTS

Activities of Daily Living

The ADL of the centenarians are shown in Table 1. The physical activities of most centenarians were scored as the

Table 1. Activities of Daily Living in Centenarians

		Female (n=23)					Male (n=9)				
Scored point*		[5]	[4]	[3]	[2]	[1]	[5]	[4]	[3]	[2]	[1]
Physical activities	Meals taking	15**	4	4	0	0	7	1	1	0	0
	Bowel continence	14	5	4	0	0	9	0	0	0	0
	Bladder continence	12	5	6	0	0	8	1	0	0	0
	Standing ability	8	5	5	5	0	7	2	0	0	0
	Extent of general activities	5	4	7	7	0	2	2	2	3	0
	Bathing ability	5	4	7	7	0	2	2	3	2	0
	Dressing ability	9	6	4	4	0	3	3	2	1	0
Sensory functions	Auditory acuity	1	4	8	10	0	0	3	4	2	0
	Eyesight	6	5	7	5	0	4	2	3	0	0
Cognitive abilities	Comprehension	12	5	5	1	0	6	3	0	0	0
	Self-expression	12	5	5	1	0	7	2	0	0	0

* Each item was classified into five categories of self sufficiency, using a point score from 5 to 1, respectively: completely independent (5 points), independent but slow (4 points), independent with difficulty (3 points), partially dependent (2 points) and completely dependent (1 point).
** The numbers of centenarians which were scored as each category.

category of completely independent and independent but slow in both genders. The auditory acuity and eyesight of the centenarians were poor, but their cognitive abilities were still good. However, the elderly and young subjects had complete independence of physical activities, good sensory functions and cognitive abilities, therefore were not shown in this table.

Anthropometry

Fig. 1 shows the mean body weight, height and BMI values of the centenarians, elderly and young subjects. In male, height and body weight decreased with aging ($p<0.05$). The BMI of young, elderly and centenarians was not different. In females height decreased with age ($p<0.05$); the body weight of young and elderly subjects was similar and heavier ($p<0.05$) than that of centenarians. The BMI of elderly was significantly higher ($p<0.05$) than that of the young and centenarians.

Biochemistry

Table 2 shows the mean of the age and biochemical values of the female centenarians, elderly and young subjects. Total protein, albumin and A/G ratio decreased with age ($p<0.05$). Total and LDL cholesterol concentrations of the elderly were higher ($p<0.05$) than those of young and centenarian subjects. Table 3 shows the mean age and biochemical values of the male subjects. Total protein, albumin and A/G ratio decreased with age ($p<0.05$). The total cholesterol of centenarians was lower ($p<0.05$) than that of young and elderly subjects. However, all the cholesterol concentrations of centenarians were within the reference range in both genders.

Plasma Amino Acids Profiles

Figs. 2 and Fig. 3 show the concentrations of plasma essential and nonessential amino acids of female subjects. As

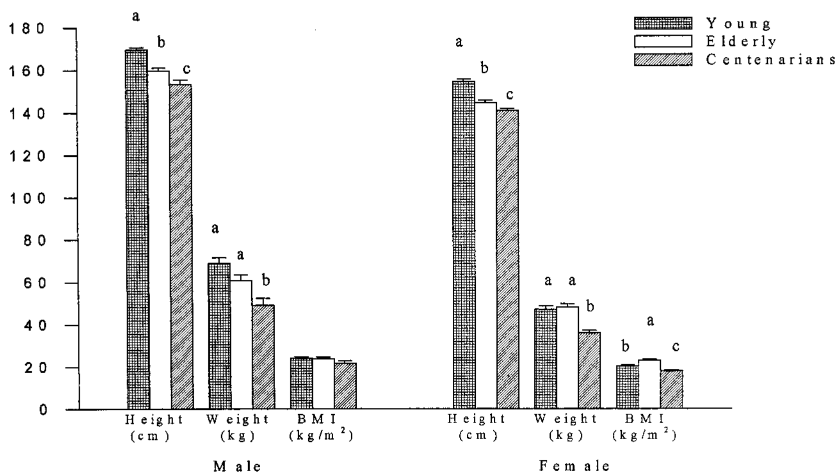

Fig. 1. Anthropometric values of centenarians, elderly and young subjects. Different letters indicate significant difference (a>b>c) by Duncan's multiple range test ($p<0.05$). Abbreviations: BMI=body mass index.

Table 2. Mean Age and Biochemical Values of Female Centenarians, Elderly and Young Subjects*

	Reference range**	Young	Elderly	Centenarians
n		17	20	23
Age (y)		25.0±0.6	76.3±0.8	102.0±0.5
Total protein (g/L)	68–82	76.5±1.1[a#]	72.2±1.2[b]	67.3±1.0[c]
Albumin (g/L)	41–59	49.8±1.0[a]	44.0±0.4[b]	36.4±1.1[c]
A/G (g/g)	1.5–2.5	1.90±0.04[a]	1.50±0.07[b]	1.20±0.05[c]
Total Chol (g/L)	1.50–2.19	1.74±0.08[b]	2.09±0.08[a]	1.65±0.08[b]
HDL Chol (g/L)	0.35–1.05	0.65±0.03[a]	0.59±0.02[a]	0.49±0.02[b]
LDL Chol (g/L)	0.70–1.51	0.98±0.07[b]	1.38±0.08[a]	0.98±0.06[b]
VLDL Chol (g/L)	0.03–0.33	0.11±0.02[b]	0.12±0.01[b]	0.18±0.02[a]
Triglycerides (g/L)	0.36–1.30	0.91±0.08	0.87±0.09	0.87±0.10

* Data are expressed as Means±SEM.
** Reference range reported by SRL Co. Japan [43].
[#] Different letters in a row indicate significant difference (a>b>c) by Duncan's multiple range test ($p<0.05$).
A/G ratio=albumin/globulin ratio; HDL=high-density lipoprotein; LDL=low density lipoprotein; VLDL=very low-density lipoprotein.

Table 3. Mean Age and Biochemical Values of Male Centenarians, Elderly and Young Subjects*

	Reference range**	Young	Elderly	Centenarians
n		10	20	9
Age (y)		26.3±0.8	75.8±0.5	101.9±1.0
Total protein (g/L)	68–82	76.1±1.9[a#]	72.4±1.2[a]	64.8±1.6[b]
Albumin (g/L)	41–59	50.2±1.0[a]	45.3±0.4[b]	35.7±1.5[c]
A/G (g/g)	1.5–2.5	2.00±0.09[a]	1.60±0.02[b]	1.30±0.13[c]
Total Chol (g/L)	1.50–2.19	1.81±0.07[a]	1.87±0.07[a]	1.54±0.08[b]
HDL Chol (g/L)	0.35–1.05	0.50±0.04	0.51±0.03	0.46±0.04
LDL Chol (g/L)	0.70–1.51	1.14±0.06	1.06±0.04	0.99±0.07
VLDL Chol (g/L)	0.03–0.33	0.17±0.02[ab]	0.21±0.03[a]	0.11±0.02[b]
Triglycerides (g/L)	0.36–1.30	1.07±0.10	1.14±0.13	0.88±0.08

* Data are expressed as Means±SEM.
** Reference range reported by SRL Co. Japan [43].
[#] Different letters in a row indicate significant difference (a>b>c) by Duncan's multiple range test ($p<0.05$).
A/G ratio=albumin/globulin ratio; HDL=high-density lipoprotein; LDL=low density lipoprotein; VLDL=very low-density lipoprotein.

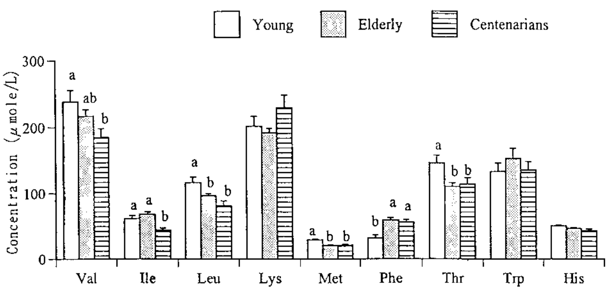

Fig. 2. Plasma essential amino acid concentrations of female subjects. Bars with a different letter or different letters in the same amino acid indicate significant difference (a>b) by Duncan's multiple range test ($p<0.05$). Abbreviations: Val=valine, Ile=isoleucine, Leu=leucine, Lys=lysine, Met=methionine, Phe=phenylalanine, Thr=threonine, Trp=tryptophan, His=histidine.

compared with young subjects, the centenarians had lower concentrations of valine, isoleucine, leucine, methionine, threonine and glutamine and higher concentrations of phenylalanine, arginine, cystine, ornithine and proline ($p<0.05$). However, the elderly had concentrations between those of the young and centenarian subjects for most of the amino acids.

The concentrations of plasma free amino acids of male subjects are shown in Fig. 4 and Fig. 5. As compared with young subjects, the centenarians had lower concentrations of leucine and glutamic acid and higher concentrations of cystine, glycine and proline ($p<0.05$). The elderly subjects had concentrations of most of the amino acids between those of the young and centenarians; however, most of the amino acids concentrations were not statistically different from those of 20 year olds.

Table 4 shows the EAA, NEAA, total amino acids (TAA: EAA plus NEAA), branched chain amino acid (BCAA: valine, leucine and isoleucine) and the EAA/NEAA (E/N) ratio. As compared with the young group, significant decreases were found in the EAA concentrations for the male and E/N ratio for both genders ($p<0.05$) in the centenarian group. BCAA concentrations gradually decreased with aging, but were not significant.

From data presented in Figs. 2 to 5 and Table 4, we concluded that the changes of plasma amino acids with aging were fundamentally similar for males and females and that the characteristic changes common for both genders were decreases of E/N ratio, BCAA and methionine concentrations and increases of proline and cystine concentrations.

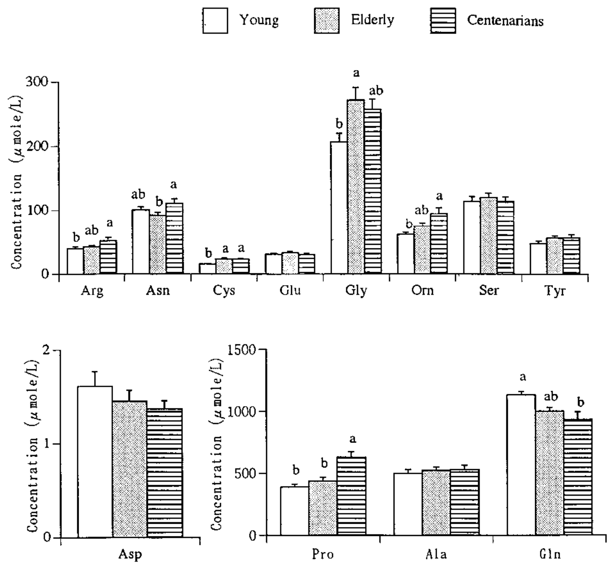

Fig. 3. Plasma nonessential amino acid concentrations of female subjects. Bars with a different letter or different letters in the same amino acid indicate significant difference (a>b) by Duncan's multiple range test ($p<0.05$). Abbreviations: Arg=arginine, Asn=asparagine, Cys=cystine, Glu=glutamic acid, Gly=glycine, Orn=ornithine, Ser=serine, Tyr=tyrosine, Asp=aspartic acid, Pro=proline, Ala=alanine and Gln=glutamine.

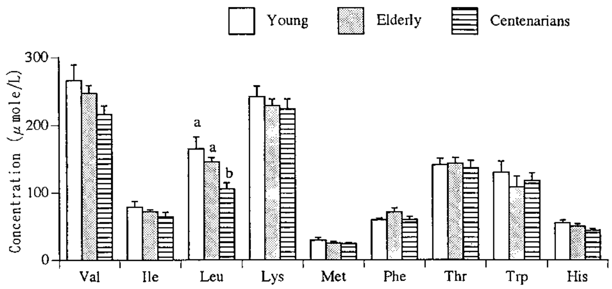

Fig. 4. Plasma essential amino acid concentrations of male subjects. Bars with a different letter or different letters in the same amino acid indicate significant difference (a>b) by Duncan's multiple range test ($p<0.05$). Abbreviations: Val=valine, Ile=isoleucine, Leu=leucine, Lys=lysine, Met=methionine, Phe=phenylalanine, Thr=threonine, Trp=tryptophan, His=histidine.

DISCUSSION

In this study we assessed the nutritional status of centenarians in comparison with subjects of 20 years and 70 years of age using various records. Age-related differences in nutritional parameters were fundamentally similar between males and females. ADL was an important index in characterizing our volunteer subjects. Our young and elderly subjects had no problems with their ADL, but centenarians had low ADL, especially to the extent of general activities, bathing and dressing abilities and sensory functions. However, none of them was

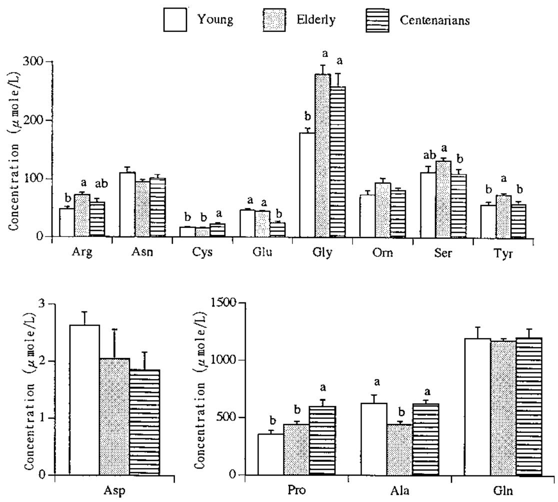

Fig. 5. Plasma essential amino acid concentrations of male subjects. Bars with a different letter or different letters in the same amino acid indicate significant difference (a>b) by Duncan's multiple range test ($p<0.05$). Abbreviations: Arg=arginine, Asn=asparagine, Cys=cystine, Glu=glutamic acid, Gly=glycine, Orn=ornithine, Ser=serine, Tyr=tyrosine, Asp=aspartic acid, Pro=proline, Ala=alanine and Gln=glutamine.

bedridden, and all could ambulate, indicating that they were a rather healthy group of centenarians [25].

Anthropometric measurements are the ones most affected by the aging process. The average height, body weight and BMI in Japan vary greatly. We appraised our results by comparing them with the Japanese average values when the centenarians and elderly were 20 years of age, in 1920 and 1948, respectively. In centenarians, the variation in height and weight with aging was greater than in the elderly; the height, weight and BMI of centenarians were lower than those of young and elderly subjects. The results showed that centenarians were shorter and thinner.

Albumin is produced in the liver and is reduced by major chronic diseases, particularly hepatic disease [2–4,26]. Decreased serum albumin concentration is due not only to loss in liver function, but also to loss of peripheral muscle tissue, which is referred to as "sarcopenia" [5–6]. This may be supported by the BMI results, since these reflect to some extent the muscle mass in the elderly [5] and that was low in our centenarian subjects. Therefore the low serum protein concentrations in our centenarian subjects might be due to the negative balance between protein synthesis and breakdown in liver and muscle. However, none of the centenarians had abnormal glutamate oxaloacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) values. These results suggested that the centenarians did not have a specific hepatic disease and the low values might be due to the reduced synthesis.

Total cholesterol concentration increases until about 50 to 70 years of age [27–28], then decreases with age [27,29]. A similar tendency was observed in our subjects. Lowering serum

Table 4. Effect of Aging on Amino Acid Profiles*

	Female			Male		
	Young	Elderly	Centenarians	Young	Elderly	Centenarians
n	17	20	23	10	20	9
EAA (mg/L)	10.1±0.7	9.6±0.7	9.1±0.7	11.6±0.3[a]	10.9±0.4[ab]	9.9±0.5[b]
NEAA (mg/L)	26.4±0.8	26.8±0.9	28.3±0.7	28.3±1.2	28.7±0.9	31.5±1.5
TAA (mg/L)	36.5±3.4	36.4±1.8	37.4±2.3	39.9±2.0	39.6±0.9	41.4±3.1
E/N (mg/mg)	0.38±0.02[a]**	0.36±0.01[ab]	0.32±0.02[b]	0.41±0.03[a]	0.38±0.02[ab]	0.31±0.03[b]
BCAA (mg/L)	4.2±0.4	3.8±0.4	3.1±0.6	5.1±0.6	4.6±0.3	3.8±0.9

* Data are expressed as Means±SEM.

** Different letters in a row within same gender indicate significant difference (a>b) by Duncan's multiple range test ($p<0.05$).

EAA=essential amino acid; NEAA=nonessential amino acid; TAA=total amino acid; E/N ratio=EAA/NEAA ratio; BCAA=branched chain amino acid.

cholesterol concentration is an effective way to reduce cardiovascular morbidity and mortality [7–11]. However, low serum cholesterol concentration is associated with high incidence of stroke in Japan, because the blood vessel of hypocholesterolemic patient is weak and easily fissured by high blood pressure [30]. The HDL cholesterol concentrations of the centenarian group were lower than those of the young group. The reduction of HDL cholesterol may accelerate the development of atherosclerosis by impairing the clearance of cholesterol from the arterial wall [9]. A negative correlation between HDL cholesterol and the development of coronary artery disease exists [10–11]. Since the major causes of death in the elderly in Japan are heart disease and stroke [1], moderate concentrations of serum cholesterol must be an important factor in the longevity of centenarians.

Amino acid profiles of our young subjects were similar to those of the previous reports [31–32]. E/N ratio decreased gradually with advance in age. This was due to the decrease of EAA and the increase of NEAA. The decrease in E/N ratio may indicate protein undernutrition [13]. Such a decrease in the elderly is usually due to poor intake of nutrients, especially protein, together with various metabolic changes [13–17]. With advancing age, protein synthesis declines [14], and the secretory rate changes for several hormones that affect amino acid metabolism or tissue protein synthesis [15–17]. Contribution of muscle to total body protein metabolism also declines; this diminishes the mobilization of amino acids from the peripheral tissues [33]. These changes affect each other and accelerate protein deficiency in the elderly. In our previous study, we evaluated the energy intakes of centenarians and elderly in their 70s and found there were similar energy intakes for the two age groups [34]. Therefore, the results of the E/N ratio suggest that the centenarians had poor nutritional status, which may be due to their decreased metabolism rather than the energy intake.

Rudman *et al.* [35] observed the decrease in BCAA with age as did our results. BCAA are oxidized peripherally and serve as a fuel source to decrease protein degradation and to stimulate protein synthesis in liver and muscle [36]. The diminished BCAA concentrations were observed in patients with advanced liver cirrhosis [18–19]. The supplements of BCAA have beneficial effects during an interval of stress, improving plasma amino acid imbalance and protein-energy malnutrition and achieving better nitrogen retention and positive nitrogen balance; these also increase the survival rate of cirrhotic and septic patients [36–38]. This information may suggest a decreased liver function of the centenarians.

We observed a clear increase in proline concentration with aging in this study. The result from Jeevanandam *et al.* [20] was contradictory to ours. However, in their study the number of subjects was small and the data of males and females were combined (eight elderly: four males, four females; ten young: five males, five females) and the ranges of age in each group were very broad (young group 27 to 57 years, geriatric group 61 to 80 years). Sarwar *et al.* [39] had results consistent with ours. They compared proline concentration between young subjects (14 males, 23 females; 30 to 35 years of age) and elderly subjects (11 males, 19 females; 80 to 89 years) and found concentrations between them which were similar to the results in our subjects of 20 years and 70 years. Based on this information, we may be able to conclude that our results on proline concentration were acceptable. Proline is an important energy-yielding and gluconeogenic amino acid that can neither be interconverted nor oxidized by muscle and is primarily metabolized in the liver [40]. Therefore the increase of plasma proline concentration in the centenarians might be related to the deterioration of liver function. Since proline is a major amino acid of collagen and composes over one-fifth of skin collagen [41], the higher levels of this amino acid in the centenarians have to be studied in terms of collagen metabolism in the future.

Animals synthesize cystine from methionine. The methionine concentrations of female centenarians was significantly lower than those of young subjects, whereas cystine concentrations were significantly higher than those in young subjects of both genders. Methionine and cystine are known to protect body tissues against oxidative damage and inflammation. The decreased concentration of methionine occurs in cirrhosis [21]. Plasma cystine was significantly elevated in patients with primary biliary cirrhosis and patients with other liver disease [42]. This may again indicate the decreased liver function in the centenarians.

As discussed above, clear changes of individual amino acids by aging were decreases of BCAA and methionine and increases of proline and cystine ($p < 0.05$), which were similar to those found in the amino acid profiles in liver deterioration [18,19,21,37,38,40,42]. However, the GOT and GPT concentrations of our centenarian subjects were within the reference range. These results suggest that the alteration of plasma amino acids in centenarians may indicate their gradual decline of liver function, rather than acute damage of liver cells.

Some amino acids also showed changes among the three age groups; however, they were rather small and not consistent between male and female; therefore, it was difficult to interpret the results in this study.

CONCLUSION

The present results may indicate that the centenarians had poor nutritional status, which may be due to their decreased metabolism and the possibility that only short, slender individuals with low lipids, protein and essential amino acids are those that tend to survive to be centenarians.

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