Table 2. Prevalence of "all" dietary supplement users in each user category and sociodemographic and lifestyle characteristics by user categories.

			User category (%)†			
		n	Any‡	Seldom§	Weekly‖	Daily¶
Sex	Males	1,152	55	23	14	18
	Females	1,107	61**	19*	16	26***
Age (year)	40-49	534	65	33	17	14
	50-59	580	55	23	15	17
	60-69	562	55	17	15	24
	70-	583	57*	11***	13*	33***
Smoking	Never	1,268	61	20	15	25
	Past	524	55	21	13	21
	Current	462	54	22	16	17
Subjective health status	Excellent/Good	573	55	26	12	18
	Usual	1,433	58	19	16	23
	Bad/Very bad	244	66**	20	18**	28*
Total sum of family annual income, million yen	-4.49	668	57	15	14	28
	4.50-9.99	1,012	57	24	14	20
	10.00-	513	61	24	18	19
Education	Less than high school	671	58	15	14	28
	High school or equivalent	923	57	20	16	22
	More than high school	655	60	28	15	17
Marriage status	Unmarried	58	50	24	14	12
	Married	1,944	57	21	15	22
	Separated/Divorced	51	67	31	20	16
	Widowed	202	63	13	17	33
Body mass index (kg/m^2)	<18.5	123	56	16	11	29
	18.5-24.9	1,588	59	21	16	22
	25.0-	547	56	21	14	21
Care of maintaining appropriate weight	Yes	1,375	60	20	16	24
	No	876	55*	22	14	20
Energy intake (kcal/day) ††	-1500	201	58	19	13	26
	1500-1999	926	60	19	15	26
	2000-2499	759	56	22	15	20
	2500-	225	58	27	16	15
Energy intake from fat (%) ††	<20	203	59	15	16	28
	20-24	639	56	19	14	24
	25-29	792	58	22	15	21
	30-	477	61	25	15	21
Total alcohol intake (g etanol/day) ††	<10	1,500	60	20	16	24
	10-19	265	56	21	12	23
	20-29	139	52	24	13	15
	30-	207	51	23	12	16

Participants using any dietary supplements were defined as any dietary supplement users during the previous year.

†: Dietary supplement users were categorized into three user groups:
Seldom; seldom users those who reported any dietary supplement use once a year or more but less than once a week for the past 12 months.
Weekly; weekly uses those who reported any dietary supplement use once a week or more but less than once a day for the past 12 months.
Daily; daily users those who reported any dietary supplement use once a day or more for the past 12 months.

‡: n=1,306 (628 males and 678 females)

§: n=470 (260 males and 210 females)

‖: n=335 (158 males and 177 females)

¶: n=501 (210 males and 291 females)

*p<0.05, **p<0.01, ***p<0.001: Sex distribution was tested by chi-squared test. Age distribution was tested by Cocran-Mantel-Haenszel chi-squared test adjusted for sex. Other variables were tested by Cocran-Mantel-Haenszel chi-squared test adjusted for sex and age

††: Intake was settled using 3-day diet record.

"all" dietary supplements were very few in both sexes. On the other hand, 90th percentile value of vitamin E, vitamin B group, vitamin C, and niacin intake exceeded respective nutrient intake from diet shown in the National Nutrition Survey; i.e. about 10 % or more of dietary supplement users took large amount of such nutrient from dietary supplement. "Excess users" existed for iron, magnesium (only the 6th Ed.), vitamin A, vitamin K (only the 6th Ed.), vitamin B_6, and niacin (only the 6th Ed.).

Energy and nutrient intake from dietary supplement by major category among "regular users" is shown in Table 5. Individuals with intake of some nutrients at the 90th percentile value were larger amount than that from diet by the National Nutrition Survey (vitamin category: vitamin E, vitamin B group, niacin, and vitamin C; Mineral category: calcium; Drink type category: vitamin B_1, vitamin B_2, vitamin B_6, and niacin; "other" category: vitamin E and vitamin B group). "Excess users" existed in vitamin

Table 3. Prevalence of dietary supplement users by major category and sub-category by user category (%) (1,152 males and 1,107 females)

		User category†							
		Any		Seldom		Weekly		Daily	
Category	Sub-category	Males	Females	Males	Females	Males	Females	Males	Females
1. Vitamin		23.1	30.2*	6.2	6.8	6.9	7.2	10.0	16.2*
	Multivitamin	14.6	15.5	4.4	4.4	5.4	4.4	4.8	6.6
	Vitamin C	4.7	8.0*	1.1	1.4	1.5	2.1	2.1	4.6*
	Vitamin E	4.0	6.8*	0.7	1.3	0.5	1.0	2.8	4.5*
	Vitamin B_2	2.0	2.8	0.8	1.1	0.4	0.5	0.9	1.2
	Vitamin B_{12}	2.3	2.4	0.6	0.6	0	0.4*	1.7	1.4
	Vitamin D	0.3	2.8*	0	0.1	0	0.5*	0.3	2.2*
	Vitamin A	0.4	1.1*	0.1	0.2	0.1	0	0.2	0.9*
	Vitamin B_1	0.5	0.8	0.2	0.1	0.2	0.2	0.2	0.5
	Pantothenic acid	0.2	0.8*	0	0.1	0.1	0.1	0.1	0.6*
	Vitamin B_6	0.4	0.3	0.1	0	0	0	0.3	0.3
	Vitamin K	0.1	0.5	0	0	0	0	0.1	0.5
	Folate	0.1	0	0	0	0	0	0.1	0
2. Mineral		2.7	7.6*	0.8	1.4	0.4	2.1*	1.5	4.2*
	Calcium	1.7	5.2*	0.4	0.6	0.3	1.3*	1.0	3.3*
	Iron	0.2	2.4*	0.2	0.6	0	1.0*	0	0.7*
	Magnesium	0.4	0.5	0.1	0.2	0.1	0	0.2	0.3
	Other minerals	0.5	0.5	0.2	0.1	0.1	0	0.3	0.4
3. Fatty acid		1.0	1.2	0.1	0.3	0.1	0.2	0.7	0.8
4. Amino acid		1.1	1.5	0.1	0.4	0.4	0*	0.6	1.2
5. Dietary fiber		0.1	0.5	0	0.1	0	0	0.1	0.5
6. Drink type		27.0	24.8*	17.5	14.0*	7.4	8.0	2.2	2.9
7. Medicine		12.0	9.7	10.0	8.2	1.6	0.9	0.4	0.5
8. Others		18.3	26.9*	3.0	4.6*	4.1	6.0*	11.3	16.4*

†: Dietary supplement users were categorized into three user groups:
Seldom; seldom users those who reported any dietary supplement use once a year or more but less than once a week for the past 12 months.
Weekly; weekly uses those who reported any dietary supplement use once a week or more but less than once a day for the past 12 months.
Daily; daily users those who reported any dietary supplement use once a day or more for the past 12 months.
Any; combined three groups.

*: $p<0.05$ by Chi square test

No subject used niacin or biotin sub-category dietary supplement.

Table 4. Energy and nutrient intake per day from "all" dietary supplements among "regular users".

		Males (n=361)								Females (n=446)							
	National Nutrition		90th per-	95th per-		Tolerable upper intake level †		Excess Users ‡ 6th edition	Excess Users ‡ 2005 edition		90th per-	95th per-		Tolerable upper intake level †		Excess Users ‡ 6th edition	Excess Users ‡ 2005 edition
Nutrient	Survey *	Median	centile	centile	Max.	6th edition	2005 edition			Median	centile	centile	Max.	6th edition	2005 edition		
Energy (kcal)	1930	0	16	30	363	-	-	-	-	0	30	60	237	-	-	-	-
Protein (g)	72.2	0	1	2	80	-	-	-	-	0	1	2	35	-	-	-	-
Fat (g)	54.4	0	trace §	1	20	-	-	-	-	0	1	1	17	-	-	-	-
Carbohydrate (g)	271.2	0	trace §	1	21	-	-	-	-	0	trace §	1	15	-	-	-	-
Calcium (mg)	546	0	126	256	1320	2500 (40-69 y.o.) - (70+ y.o.)	2300	0	0	0	226	400	2123	2500 (40-69 y.o.) - (70+ y.o.)	2300	0	0
Iron (mg)	8.1	0	trace §	2	129	40	55 (40-49 y.o.) 50 (50-69 y.o.) 45 (70+ y.o.)	1	1	0	1	5	93	40	40 (40-49 y.o.) 45 (50-69 y.o.) 40 (70+ y.o.)	1	1
Magnesium (mg)	259	0	9	30	808	700 (40-49 y.o.) 650 (50+ y.o.)	-	1	-	0	7	48	906	700 (40-49 y.o.) 650 (50+ y.o.)	-	1	-
Vitamin A (IU)	3130	0	1200	2900	10200	5000	10000	8	4	0	800	1500	11000	5000	10000	12	4
Vitamin D (IU)	328	0	26	120	726	2000	2000	0	0	0	40	140	678	2000	2000	0	0
Vitamin E (mg)	8.2	0	91	198	483	600	800 (40-69 y.o.) 700 (70+ y.o.)	0	0	0	112	210	483	600	700 (40-69 y.o.) 600 (70+ y.o.)	0	0
Vitamin K (μ g)	260	0	0	0	30000	30000	-	1	-	0	0	4	45000	30000	-	6	-
Vitamin B_1 (mg)	0.87	2	38	55	280	-	-	-	-	1	43	72	144	-	-	-	-
Vitamin B_2 (mg)	1.21	1	6	10	68	-	-	-	-	1	8	16	64	-	-	-	-
Vitamin B_6 (mg)	1.17	1	16	41	185	100	60	3	9	1	30	66	106	100	60	3	26
Vitamin B_{12} (μ g)	7.4	0	250	1000	2340	-	-	-	-	0	500	1044	1566	-	-	-	-
Niacin (mg)	14.8	2	34	43	128	30	300 ‖	41	0	0	26	44	140	30	300 ‖	43	0
Vitamin C (mg)	101	0	210	668	6482	-	-	-	-	0	500	1100	4400	-	-	-	-

'Weekly users" plus "daily users" were defined as "regular users".

Seven males and 22 females were excluded from the analysis because they reported uncertainty about the information on dietary supplement intake.

Some products in which nutrient content was not described were excluded when we developed the database and we did not calculate nutrient intake from these products.

* : Results from the National Nutrition Survey in Japan, 2002 (mean of the total).

† : Tolerable upper intake level of adults in 6th edition or 2005 edition of Nutrient-Based Dietary Reference Intakes in Japan.

- : Tolerable upper intake level of adults in 6th edition or 2005 edition of Nutrient-Based Dietary Reference Intakes in Japan was not shown.

‡ : Number of participants who daily consumed some nutrients at more than the tolerable upper intake level in the 6th Edition or 2005 Edition of Nutrient-Based Dietary Reference Intakes (DRIs) in Japan.

§ : Below display limit

‖ : The amount of mg of nicotinic acid amide was used.

Table 5. Energy and nutrient intake per day from dietary supplements by major category among "regular users".

	1. Vitamin†						2. Mineral‡						6. Drink type§						8. Others‖					
		90th	95th		Excess Users *			90th	95th		Excess Users *			90th	95th		Excess Users *			90th	95th		Excess Users *	
		per-	per-		6th	2005		per-	per-		6th	2005		per-	per-		6th	2005		per-	per-		6th	2005
Nutrient	Median	centile	centile	Max	edition	edition	Median	centile	centile	Max	edition	edition	Median	centile	centile	Max	edition	edition	Median	centile	centile	Max	edition	edition
Energy (kcal)	0	4	12	80	-	-	0	8	10	57	-	-	0	16	30	237	-	-	5	27	54	145	-	-
Protein (g)	0	0	0	2	-	-	0	0	0	1	-	-	0	0	trace¶	28	-	-	0	2	3	36	-	-
Fat (g)	0	0	0	2	-	-	0	0	0	trace¶	-	-	0	0	0	0	-	-	0	1	3	20	-	-
Carbohydrate (g)	0	0	0	9	-	-	0	0	1	2	-	-	0	0	0	13	-	-	0	1	2	21	-	-
Calcium (mg)	0	7	130	1040	0	0	126	600	920	1833	0	0	0	0	9	54	0	0	0	106	320	1200	0	0
Iron (mg)	0	0	0	12	0	0	0	4	5	10	0	0	0	0	0	4	0	0	0	4	6	129	2	2
Magnesium (mg)	0	0	0	36	0	-	0	125	300	906	1	-	0	0	0	42	0	-	0	20	60	205	0	-
Vitamin A (IU)	0	1,000	2400	8000	3	0	0	0	0	200	0	0	0	0	0	0	0	0	0	1,000	3,600	11000	12	8
Vitamin D (IU)	0	30	40	600	0	0	0	80	159	396	0	0	0	0	0	0	0	0	0	40	200	726	0	0
Vitamin E (mg)	2	182	285	483	0	0	0	0	0	10	0	0	0	0	trace¶	27	0	0	0	30	100	280	0	0
Vitamin K (μg)	0	0	0	45000	7	-	0	6	8	66	0	-	0	0	0	11	0	-	0	4	48	400	0	-
Vitamin B1 (mg)	2	58	78	280	-	-	0	0	0	6	-	-	1	5	6	20	-	-	0	10	20	68	-	-
Vitamin B2 (mg)	trace¶	8	12	64	-	-	0	0	trace¶	6	-	-	1	4	5	10	-	-	0	3	14	68	-	-
Vitamin B6 (mg)	1	48	66	185	5	34	0	0	0	4	0	0	1	5	6	25	0	0	0	2	10	61	0	1
Vitamin B12 (μg)	0	1008	1500	2340	-	-	0	0	0	4	-	-	0	0	0	10	-	-	0	9	30	62	-	-
Niacin (mg)	0	39	60	140	62	0	0	0	0	15	0	0	4	20	20	100	6	0	0	7	18	128	10	0
Vitamin C (mg)	0	700	1336	4400	-	-	0	40	50	1000	-	-	0	44	50	2500	-	-	0	90	360	1620	-	-

'Weekly users" plus "daily users" were defined as "regular users".

Because there were few "regular users", 3.fatty acid, 4.amino acid, 5.dietary fiber, and 8.medicine were omitted.

Seven males and 22 females were excluded from the analysis because they reported uncertainty about the information on dietary supplement intake.

Some products for which nutrient content was not described were excluded when we developed the database and we did not calculate nutrient intake from these products.

* : Number of participants who daily consumed some nutrients at more than the tolerable upper intake level (UL) in the 6th Edition or 2005 Edition of Nutrient-Based Dietary Reference Intakes (DRIs) in Japan.

† : n=451 (191 males and 260 females)

‡ : n=85 (21 males and 64 females)

§ : n=232 (110 males and 122 females)

‖ : n=302 (129 males and 173 females)

- : Tolerable upper intake limit of adults in 6th edition or 2005 edition of Nutrient-Based Dietary Reference Intakes in Japan was not shown.

¶ : Below display limit

category (vitamin A, vitamin K, vitamin B6, and niacin), in the mineral category (magnesium), in drink type (niacin), and in the "others" category (iron, vitamin A, vitamin B6, and niacin). In the other major categories, there were no "excess users" for any nutrients.

According to the 6th Ed. UL, 20 people were "excess users" of vitamin A among "all" dietary supplement users (Table 4), 12 among the "others" category and 3 among vitamin category (Table 5). This indicates that 5 people consumed excess doses of vitamin A from more than one dietary supplement category. Some people consumed excess doses of magnesium (one participant), vitamin B6 (one participant), and niacin (six participants) from more than one dietary supplement category.

DISCUSSION

We conducted this study to evaluate the information on dietary supplement use and nutrient intake from these products in a random sample of a community-living population. Dietary supplements were used by more than half of the respondents in the previous year. The intake of some minerals and vitamins from these products were equal or more than the daily intake from food in the National Nutrition Survey.[16] Some users were found to take excess doses of minerals or vitamins from these products.

The prevalence of "all" dietary supplement use among "any users" in the previous year in our study was more than 50 % among both sexes. This is relatively high in comparison to those reported from Japan,[21,23] but it is almost the same as the prevalence found in studies that were conducted in the US.[2,20,22] However, differences in the definition of dietary supplements, dietary supplement users, duration of the study period (e.g., not specified or previous one year), and survey method (e.g., questionnaire only or including interview) among these studies make direct comparisons difficult.

In the National Nutrition Survey in Japan (J-NNS) in 2001,[23] dietary supplements were defined only as products which contained vitamins and minerals, and a concrete study period was not specified. Under this condition, 17.0 % of males and 23.6 % of females reported usual use of dietary supplements. In the subgroup of the Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Disease Cohort II,[21] dietary supplement was investigated in a questionnaire survey. In this study, dietary supplement was classified into multivitamins, beta-carotene, vitamin C, vitamin E, and others, and dietary supplement users were defined as subjects who used a dietary supplement one or more times a week for a year or longer. In this situation, the prevalence of dietary supplement use was 10.9 %.

Survey method (e.g., questionnaire only or including interview) may be another methodological factor to affect the prevalence of the dietary supplement intake. Third National Health and Nutrition Examination Survey in 1999-2000 (NHANES III)[22] in the US was conducted by household interviews. In NHANES III, dietary supplements included non-vitamin and non-mineral products, the duration of the study period was the previous month. Under this condition, the prevalence of dietary supplement use was 52 %, and it was similar to our results. It is possible that relatively high prevalence of dietary supplement use found in NHANES III and our study may result from the use of survey methods including interview.

At present, there have been a few studies on dietary supplement assessment methodology.[5-7,11,21,24-27] It is important to develop generally accepted assessment method in the dietary supplement study to make direct comparison.

We clarified the characteristics of dietary supplement users for the first time in Japan. Many studies conducted in the US and European countries reported that dietary supplement use was related to many aspects of appropriate lifestyles and a high health status.[6,9,13,28-33] In contrast, dietary supplement users in this study were likely to feel less healthy than nonusers. Dietary supplement users might have been more careful of maintaining an appropriate weight than nonusers, whereas other characteristics (i.e., smoking, education, marriage status, BMI, energy intake from food, and alcohol intake) were not significantly associated with dietary supplement use or nonuse in this study. The characteristics of dietary supplement users in our study might have been different from the characteristics of dietary supplement users in other countries. Such characteristics may depend on sex, age, and ethnicity.[7-9,28] Furthermore, some characteristics were different between frequencies of use of dietary supplements. For example, "seldom users" were prevalent among middle-aged subjects and were more likely to be males, whereas "daily users" were prevalent among older people and more likely to be females in our study. The association between dietary supplement use and other characteristics may be affected by the frequency of use of dietary supplements.

Multivitamin, vitamin C, and vitamin E were the popular dietary supplements in the vitamin category, and calcium was the most popular dietary supplement in the mineral category in our study. In the US, approximately 40% of subjects was reported to be users of some vitamin or mineral supplements in the NHANES III.[8] About 40 to 80% of adults was reported to be users of some vitamin or mineral supplements. Multivitamins were the most popular dietary supplements, and vitamin C, vitamin E, vitamin A, and calcium were commonly used in vitamins and mineral supplements.[8,9,13,28,29,31,34-36] Many studies reported the prevalence of combined dietary supplement use (vitamins and mineral). The prevalence of use of each dietary supplement was not determined; however, our results (vitamin plus mineral: males 25.8%, females; 37.8%) would be broadly comparable to the results of those studies.

Schaffer et al[33] reported that the prevalence of non-vitamin and non-mineral dietary supplement use was 32.7% (participants were the members of a large group in a model health plan, the duration of the study period was the past 12 months, and dietary supplement use was assessed by a questionnaire). The prevalence of non-vitamin and non-mineral dietary supplement users in our study ("all" - vitamin - mineral: males; 28.7%, females; 23.5%)

was close to the results of Schaffer et al. Radimer et al[32] reported that non-vitamin and non-mineral dietary supplements included many herbal supplements in NHANES III, and the term "herbal" is often used loosely, including non-plant dietary supplement (i.e., enzymes, glandular extracts, choline, and fish oils). Herbal supplements were most commonly used because they were considered "healthy or good for you",[14,34,37,38] and consumers may perceive plant products as more natural than manufactured medicines.[38] Furthermore, some studies reported that herbal supplement use is accelerating, and some products might have adverse health effects.[8,32,33,38] We could not determine the reason why some individuals chose "others" types of dietary supplements. As the prevalence of "others" types of dietary supplement use was high in our study, it will be important to estimate the prevalence of this kind of product (non-vitamin and non-mineral dietary supplements) and to clarify the health effects of these products.

In our study, the prevalence of drink type dietary supplement was high, especially in males, and more than 60 % of drink type dietary supplement users were "seldom users". Hakura et al[14] also reported that high prevalence of drink type dietary supplement was observed in Japan, and many of the occasional dietary supplement users took this kind of dietary supplements to maintain or recover health. However, drink type dietary supplement was not usually described in the studies reported from the Western countries.[32-34,38] The high prevalence of drink type dietary supplement use might be one of the characteristics observed in Japan, and might be caused by broad accessibility that people can get drink type dietary supplements easily at supermarkets and convenience stores when they feel weary.

The purpose of dietary supplement use may be to compensate the shortage of nutrients from foods, but some users had excessive intake of some nutrients. The median values of Vitamin B_1 and 90 percentile values of vitamin E, Vitamin B_2, B_6, B_{12}, niacin, and vitamin C from dietary supplements in this study were more than that from food, according to the results of J-NNS 2002.[16] Some dietary supplement users consumed huge amounts of nutrients from dietary supplements.

Regarding overdoses, this study had two important findings. The first was that overdoses sometimes occurred for non-target nutrients from dietary supplements, when the primary nutrient in the dietary supplement was defined as the target nutrient. For example, according to the 6th Ed. UL, only three persons took an excess dose of vitamin A among vitamin supplement users, whereas 12 people consumed an excess dose of vitamin A among the "others" type of supplement users (Table 5). The second was that overdose sometimes occurred in users of "multiple" dietary supplements. In this study, according to the 6th Ed. UL, five people consumed an excess dose of vitamin A from "multiple" dietary supplements which belonged to different categories.

Stewart et al[31] reported that there was a wide range of intake of vitamins from dietary supplements. Subjects who took more than 10 times the Recommended Dietary Allowances (RDAs) in the US were observed for vitamin B group, vitamin C, vitamin E, niacin, and pantothenic acid intakes. Other studies reported that some dietary supplement users consumed excess doses of some nutrients as compared to the RDAs.[6-9,39,40] Rock et al[2] noted that a few women consumed potentially toxic levels of vitamin A, vitamin B_6, iron, and zinc from dietary supplements. People need to be aware that excessive use of some dietary supplements may produce undesirable health effects.[41,42] Because we did not include fortified foods and modified foods among dietary supplements in this study, nutrient intake from those foods was not included the estimation of total nutrient intake. We are apprehensive that excessive levels of nutrient intake could be more common people with in a combination of fortified foods, modified foods and dietary supplement use.

The main strength of this study is the development of the nutrient content database of more than 900 dietary supplements, and the use of this database to calculate nutrient intake from these products for more than 2,000 middle-aged and older people. Although our database of dietary supplements is extensive, a lack of information on some dietary supplements still exists. Information on the nutrient content of some products available in the marketplace had not been obtained even by the producer and/or was difficult to get,[6,7,43-45] because dietary supplements except for medicines are not required to show their nutrient contents.

APPENDIX

We succeeded in constructing the database of more then 1500 dietary supplement products in April 2006. The database has been regularly updated according to the study. We will make latest dietary supplement database generally available, but for non-profit use only, in the internet website (http://www.nils.go.jp/department/ep/index-j.html) of our institute, without a need for permission. The authors, however, request that this article be cited when a study in which the data, or even a part of it, were used is published or open to the public. We expect that this database will be useful for the prevention of excess intake of dietary supplements and contribute to the development of research on nutritional epidemiology.

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3. 高齢者の生活習慣はどこまで是正すべきか（Pro）

下方　浩史

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第47回日本老年医学会学術集会記録
〈老年医療における Controversy〉

3. 高齢者の生活習慣はどこまで是正すべきか（Pro）

下方　浩史

要　約　健康長寿を目指すためには生活習慣の改善が最も重要である．喫煙や飲酒のコントロール，肥満防止，栄養改善，運動習慣などの生活習慣の改善は，寝たきりを防止して健康寿命を延ばしていくためには不可欠である．生活習慣の是正は小児期から必要であり，青年期，中年期から老年期まで，生涯にわたって必要であるが，ライフステージごとに方法や目標は異なる．75歳以上の後期高齢者では肥満よりも痩せの危険が高いことを認識し栄養指導を行うことが必要である．喫煙による循環器疾患や呼吸器疾患への影響としては急性の不整脈の誘発や，末梢血管の収縮，気道への刺激などもあり，禁煙は高齢者でも有用と考えられる．また代謝予備力が落ちているために飲酒量も減らすことが望ましい．運動習慣は高齢者の身体活動能力を維持するだけでなく，代謝機能を高め，鬱を予防するなど心身の健康維持に重要であり，運動教室などを利用して積極的な介入を行っていくべきであろう．

Key words：生活習慣，老年病，予防，栄養，喫煙

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高齢者の生活習慣への介入

生活習慣病は，食事，肥満，身体活動，喫煙，飲酒などの生活習慣に起因する疾患であり日本人の死因の大部分を占めるがん，心臓病，脳卒中がその代表的疾患である[1]．また高齢者に多い痴呆や骨粗鬆症も生活習慣が重要な因子である場合が多い．生活習慣病は，性別や年齢，遺伝的素因，さらには職業や教育など社会的要因が相互に作用しあって発症する．したがって，これらの背景要因を考慮し，生活習慣への介入を行って疾病の発症予防，進行の予防，そして再発の予防を行うことが重要である．

生活習慣病の予防には小児期，青年期，中年期，老年期のそれぞれのライフステージに応じたストラテジーが必要である（図1）．小児期，青年期には将来の疾患発症を予防するための一次予防に重点を置いた指導が行われる．小児期には基本的な生活習慣が形作られるため，それに対応しての家庭や学校での健康教育が重要である．塩味や油の多い食事への嗜好なども小児期に形成される．青年期には栄養や運動など一生にかかわる生活習慣が確立する．また喫煙や飲酒の習慣もこの頃から始まることが多い．中年期には疾患の早期発見・早期治療を目指す二次予防も重要となる．効率的な健診の体制作りが必要だろう．さらに老年期には再発の予防を中心とした三次予防も重要である．

75歳未満の前期高齢者は元気である．多くの人が職

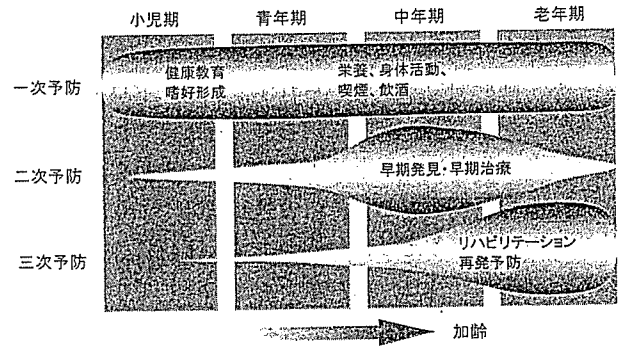

図1　ライフステージ別にみた生活習慣病の予防
生活習慣病の予防には小児期，青年期，中年期，老年期のそれぞれのライフステージに応じたストラテジーが必要である．

についており，また積極的に社会参加をしている．喫煙や飲酒のコントロール，肥満防止，栄養改善，運動習慣などの生活習慣の改善は，寝たきりを防止して健康寿命を延ばしていくためには不可欠である．一方，75歳以上の後期高齢者では加齢による身体機能の変化に対応し，10年先，20年先のことよりも現在の生活の質（Quality of life；QOL）を考慮した生活習慣への介入が必要だろう．

肥満と老化

食餌制限と寿命との関係については，1930年代のMcCayによるラットを使った有名な実験があり[2]，自由

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無制限の食餌を与えたラットより食餌を制限したラットの方が長生きするという結果は基礎老化の研究者の間ではよく知られている[3)4)]．

人間ではやせていればいるほど健康にいいのか．もしそうでないなら，どの程度の体重であるのが医学的には理想なのか．Andresは米国の生命保険会社のデータから，体重（kg）を身長（m）の二乗で割って求めたBody Mass Index（BMI）を身長とは無相関の肥満の指標として用い，各年代ごとに最も死亡率の低いBMIをもとめた[5)]．この結果死亡率を縦軸，BMIを横軸にとった時，きれいなU字を描くことを示した．BMIの小さいやせた人では，肺炎や結核などの感染症の発病率が高く，BMIの大きな太った人では糖尿病や心臓病などの発病率が高くなる．男女別に，各年齢毎にこのようなグラフを作成し，死亡率の最も低い肥満度を求めてみると，この理想的な肥満度の値は加齢とともに大きくなっている[6)]．男女で大きな差はなく年齢とともにほぼ直線的に理想的なBMIの値が大きくなっていく．

BMIによる高齢者の肥満評価には，加齢に伴う椎間の狭小化，椎骨の圧迫骨折による脊椎前弯の増強などにより身長が年齢とともに低下し，BMIは本来あるべき値よりも，大きくなっていることにも留意せねばならない．

予備力が低下している後期高齢者では無理な減量はかえって健康を害することが多い．しかし複数の代謝性合併症を有するメタボリック・シンドローム，下肢の骨関節障害を有する高度肥満，睡眠時無呼吸症候群を有する高度肥満などでは高齢者においても減量は必要であると考えられる[7)]．

一方で，高齢者では骨格筋萎縮に伴う基礎代謝の低下，味覚などの感覚器機能低下，ジギタリス製剤等の食欲を低下させる副作用のある薬物の使用，味気ない減塩食や老人食，ACE阻害剤などの薬剤による亜鉛欠乏症等により，食欲が低下していることが多い．慢性的に栄養不良の高齢者も多く，肥満よりもむしろやせのリスクに注意する必要がある[8)]．

喫煙と老年病

喫煙により消化器の運動が低下する．口腔の衛生状態が悪くなり，歯周病のため歯牙が脱落する．喫煙で口がまずい，味覚障害などから食欲も低下する．1本のタバコを吸うと約10キロカロリーが使われる[9)]．1パック20本の喫煙では200キロカロリーが消費される．これは1時間の歩行とほぼ同等のエネルギー消費である．このため喫煙は体重減少の要因となる．

喫煙はさまざまな老年病の危険因子でもある．アルツハイマー病についてはハワイ在住日系人ではリスクは2.4倍と報告されている[10)]．喫煙による痩せ，エストロゲン抑制，骨カルシウム代謝障害などが骨粗鬆症の要因になる[11)]．また喫煙は老人性難聴[12)]，老人性白内障[13)]，加齢に伴う記銘力障害[14)]の要因でもある．慢性気管支炎，肺気腫の閉塞性肺疾患は高齢者に多くみられ，また喫煙との関連が強い．多くの化学物質が直接に気道に作用し，刺激により炎症反応を引き起こす．慢性閉塞性肺疾患による肺機能低下は禁煙によって回復しないが，禁煙をすることで，それ以上の悪化を防ぐことはできる．むしろ禁煙が進行を予防する唯一の手段である．

一般にがんは発がん物質に曝露されてから，実際にがんが見つかるまでの期間が長い．このため若い頃から喫煙を継続している高齢者が禁煙をしても，若い成人と同じようにがんのリスクを下げるような効果があるかどうかは不明である．

喫煙による循環器疾患や呼吸器疾患への影響は急性の不整脈の誘発や，末梢血管の収縮，気道への刺激など急性の影響もあり，禁煙は，高齢者でも有用と考えられる．しかしFramingham Studyでの18年間の観察で65歳以上の群では禁煙による虚血性心疾患のリスク低下は認められなかったとする報告もある[15)]．

喫煙者の近くで，副流煙・排出煙を吸わされる受動喫煙は，主流煙を吸う喫煙者本人よりも有害である．家族，主として夫の喫煙による妻への影響，あるいは子どもや孫への影響も重要である．特に小さな子どもや妊婦への影響は大きい．大家族で暮らすことの多い日本では，高齢者の喫煙に関して，こうした家庭での環境についても考慮が必要であろう．

高齢者の飲酒

適量の飲酒は，血清脂質，耐糖能，インスリン抵抗性を改善させる．しかし少量の飲酒でも高血圧の要因となりうるので要注意である．飲酒は高齢者の脳出血のリスクを上げる．加齢に伴いアルコール代謝機能が低下し，顔面紅潮などの頻度が高くなる．飲酒量を一般成人よりも減らすことも重要であろう．もちろん慢性肝炎・肝硬変では高齢者でも禁酒は必要であろう．

高齢者の身体活動

身体活動は加齢に伴う耐糖能を改善させ，骨粗鬆症を予防し，高齢者の循環器機能を維持するためきわめて重要である．我々は高齢者の身体活動が，うつを予防する効果のあることを報告している[16)]．

高齢者の身体機能の維持・改善，QOLの向上を目指し，介護予防を行っていくためにも生涯にわたっての介入が望ましい．積極的なソーシャル・サポートや家族からの支えによって，閉じこもりや，寝たきりを防止していくことも重要であろう．

しかし運動指導には，高齢者に多い循環器疾患，骨関

節疾患，呼吸器疾患などに留意し，個人ごとの対応が必要である．

おわりに

健康長寿を目指すためには，人の一生を通じて生活習慣の是正が欠かせない．しかし，その目標や方法は加齢の進行によって異なる．特に75歳以上の後期高齢者では現在のQOLを重視した生活指導が行われるべきである．高齢者では肥満よりも痩せが問題になる．健康の維持のためには食欲の低下による栄養不良，体重減少を予防していくことが必要であり，食事の制限や減塩などはどうしても必要な場合に限るべきであろう．喫煙は高齢者でも避けるべきであり，過度の飲酒も好ましくない．また，高齢者では心身の健康の維持のために運動習慣への積極的な介入が必要である．

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How far should life-style be corrected in the elderly?

Hiroshi Shimokata

Abstract

To ensure a healthy elderly population, correction of life-style is one of the most important approaches. Smoking cessation, regulation of alcohol intake, prevention of obesity, improvement of nutrition, promotion of physical activity are key factors for prevention of bed-ridden and extension of healthy life span. Although corrections of life-style are essential in childhood, adolescence, and the middle-aged and elderly periods, the methods and purpose are different in each life stage. The risks of emaciation and malnutrition are more important rather than that of obesity in the elderly aged 75 years or over. As for the influence of smoking in cardiovascular and respiratory diseases, smoking can be a trigger for arrhythmia, peripheral vascular constriction, and irritation of the respiratory tract in the elderly. Smoking cessation is necessary even among elderly people. It is also necessary to decrease the amount of alcohol intake, because the ability of metabolize alcohol is limited in the elderly. Physical activity in the elderly people is fundamental not only to maintain the ability of daily living, but also to improve metabolic function and to prevent depression. Vigorous intervention to increase physical activity such as exercise class is recommended, especially in the elderly.

Key words: *Life-style, Geriatric disease, Prevention, Nutrition, Smoking*
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Association of alcohol dehydrogenase 2*1 allele with liver damage and insulin concentration in the Japanese

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Abstract The Japanese have a polymorphism in the alcohol dehydrogenase 2 gene (*ADH2*). The alleles of *ADH2* (*ADH2*1* and *ADH2*2*) encode more active and less active forms for ethanol metabolism, respectively. We examined whether liver damage and the insulin–glucose axis vary according to *ADH2* genotype in the Japanese. The 2,232 subjects (1,126 men and 1,106 women) were recruited from a population-based prospective cohort study. Clinical evaluations including alcohol consumption, percentage of alcohol drinkers, plasma glucose, HbA1c, insulin, AST, ALT, γ-GTP, and prevalence of diabetes were compared among the *ADH2* genotypes. The percentage of drinkers, alcohol consumption, AST, ALT, and γ-GTP were higher in group *ADH2*1/1* than in group *ADH2*1/2* or *ADH2*2/2* (all $P<0.05$). Hence, *ADH2*1/1* is associated with excess alcohol intake and liver disorders. However, the prevalence of diabetes did not differ among the three groups. For the glucose–insulin axis, we examined subjects who did not receive insulin therapy or oral anti-diabetes medication. While amounts of alcohol consumed and glucose levels were nearly the same between *ADH*1/2* and *ADH2*2/2*, insulin concentrations were lower in *ADH2*2/1* than in *ADH2*2/2* ($P<0.05$ in men). This finding suggests that the *ADH2*1* allele is associated with a lower insulin concentration when alcohol intake is light or moderate. It also suggests that the genetic effect of *ADH2*1* plays an important role in alcohol drinking behavior and in the occurrence of liver injury, but the effect is so mild that it does not influence the glucose–insulin axis or prevalence of diabetes.

Keywords Alcohol dehydrogenase 2 · ADH2 · Diabetes · Insulin resistance · Liver dysfunction · Alcohol · Prospective cohort study

Abbreviations: ALDH: Aldehyde dehydrogenase · ADH: Alcohol dehydrogenase · PCR: Polymerase chain reaction

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Introduction

A reduced incidence of type 2 diabetes has been observed among drinkers in several large prospective studies. Conigrave et al (2001) reported a 12-year prospective study in a cohort of 46,892 US male health professionals, in which 1,571 new cases of type 2 diabetes were reported. The frequency of alcohol consumption was inversely associated with diabetes. Hu et al (2001) reported a large cohort study of 84,941 female nurses from 1980 to 1996, in which abstinence from alcohol use was associated with a significantly increased risk of diabetes. In contrast, other studies (Holbrook et al 1990) have shown an increased risk of diabetes among a proportion of subjects in the top alcohol consumption category. In Japanese men, Tsumura et al (1999) reported that heavy drinking is associated with an increased risk of type 2 diabetes, while moderate drinking is associated with a decreased risk of type 2 diabetes, showing a U-shaped relationship.

The genotypes involved in ethanol metabolism are now known to be associated not only with drinking, but also with longevity and oxidative stress parameters (Ohsawa et al 2003). In Japanese, the pharmacokinetics of alcohol metabolism have been well studied. Alcohol dehydrogenase (ADH) is one of the key enzymes in alcohol metabolism. Class I ADH isoenzymes, encoded

by *ADH1*, *ADH2* and *ADH3*, form dimers among the isoenzymes and oxidize ethanol and other small aliphatic alcohols (Borson et al 1988). About 85% of the Japanese population are carriers of the β2-subunit encoded by the *ADH2*2* allele, while isoenzymes with the β2-subunit have been found in only 5% or less of Europeans and white Americans. The β1- and β2-subunits differ by only one amino acid residue: Arg-47 in the NAD(H) pyrophosphate-binding site is substituted with His-47 in the β2-subunit. ADH2 functions as a dimer and the β2β2 dimer exhibits about 100 times more catalytic activity for ethanol oxidation than the β1β1 dimer at physiological pH (Borson et al 1988), whereas the β1β2 heterodimer exhibits nearly the same activity as the β1β1 homodimer. Thus, relative enzymatic activities of *ADH2*1/1:ADH2*1/2:ADH2*2/2* can be estimated as 1:26:100 if a dimer were to form between the subunits of ADH2*1 and ADH2*2 (Borson et al 1988; Yoshida et al 1984).

Several studies (Higuchi et al 1996; Yamauchi et al 2001) have reported that the *ADH2* genotype is associated with excess alcohol intake and alcohol-related disorders in the Japanese population. We have previously reported that the *ADH2* genotype affected LDL-cholesterol levels and the occurrence of cerebral infarction in a community-dwelling Japanese population (Suzuki et al 2004). We therefore examined whether the glucose–insulin axis or prevalence of diabetes is associated with the *ADH2* genotype in the same Japanese population.

Research design and methods

The National Institute for Longevity Sciences–Longitudinal Study of Aging (NILS–LSA), a population-based prospective cohort study of aging and age-related diseases, was begun in 1997 (Ohsawa et al 2003; Shimokata et al 2000; Yamada et al 2002). All participants were independent residents of the Aichi prefecture in Japan. Residents aged 40–79 years old were randomly selected from the register in co-operation with the local government.

The area of study is located in the south of Nagoya City. It is a commuter town and contains an industrial area belonging to the Toyota group, but it has many orchards and farms, so it has both urban and rural characteristics. This area is geographically located in the center of Japan, and its climate is average for Japan. We examined a representative sample of the area's population via a national postal questionnaire of prefecture-stratified random samples of 3,000 households from all prefectures in Japan, and previously showed that the lifestyle of people in this area was the most typical of all areas in Japan.

The sample consisted of 2,232 subjects (1,126 men and 1,106 women) who were randomly recruited. We refer to them as "subjects-1." Subjects-1 was stratified by both age and sex. Randomly selected men and women were invited, by mail, to attend an explanatory meeting. At the meeting, the procedures for each examination and follow-up schedule were fully explained. Written informed consent to the entire procedure was obtained from each participant. Participants in the present study were recruited from subjects examined in 1997–1999. The study protocol was approved by the Committee on the Ethics of Human Research of National Chubu Hospital and the National Institute for Longevity Sciences.

Descriptions of the physical examinations performed have been published before (Ohsawa et al 2003; Shimokata et al 2000; Yamada et al 2002). In brief, lifestyle, medical history and prescribed drugs were examined by questionnaire. Anthropometric measurements were taken by a physician. A drinker is defined as a subject who has drunk more than 5 g of alcohol on average per day during the past year. Amounts of alcohol consumed were carefully examined by taking pictures before and after drinking as well as with questionnaires. The percentage of non-smokers to smokers was also noted.

Venous blood was collected early in the morning after at least 12 h fasting. The mean of two determinations of blood chemistry data was obtained for each participant. Clinical evaluations included gender, age, height, body-mass index, smoker status, alcohol consumption, percentage of alcohol drinkers, and blood chemistry (fasting plasma glucose (FPG), HbA1c, insulin, AST, ALT, and γ-GTP levels). Diagnosis of diabetes was based on medical records, or it was defined as a FPG concentration greater than 126 mg/dl or an HbA1c of more than 6.5%, and/or if medication was taken to lower the blood glucose level. Namely, not all subjects whose FPG level was greater than 110 mg/dl did not receive the 75 g oral glucose tolerance test according to the criteria of the Japan Diabetes Society. In the analysis of glucose–insulin associated parameters, to exclude the effect of medications, the diabetic patients who received insulin therapy or oral medications for diabetes were excluded from subjects-1, and the remaining subjects were defined as the "subjects-2" group.

Genotyping of *ADH2*

Samples of DNA were isolated from peripheral blood cells. Genotypes were determined with a fluorescence-based allele-specific DNA primer-probe assay system (Toyobo Gene Analysis, Tsuruga, Japan). To determine the genotype with the G214A substitution (Arg-47-His), the polymorphic region of *ADH2* was amplified by polymerase chain reaction (PCR) with an antisense primer labeled at the 5′ end with biotin (5′-GATGGTGGCTGTAGGAATCTG-3′) and a G allele-specific sense primer labeled with FITC (5′-CCACGTGGTCATCTGTNCG-3′) or A allele-specific sense primer labeled with Texas red (5′-AACCACGTGGTCATCTGTNTG-3′).

Table 1 Comparison of parameters among three groups of men (subjects-1), divided according to *ADH2* genotype. Right columns indicate *P*-values of statistical differences between two groups

Variables	Men			*P*-value		
ADH genotype	2/2	1/2	1/1	2/2 vs. 1/2	2/2 vs. 1/1	1/2 vs. 1/1
Subjects-1 $n=$	689	378	59			
Age (years)	59.5 ± 0.4	58.9 ± 0.6	58.0 ± 1.4	n.s.	n.s.	n.s.
Height (cm)	164.4 ± 0.2	164.7 ± 0.3	164.6 ± 0.8	n.s.	n.s.	n.s.
BMI	23.0 ± 0.1	22.8 ± 0.1	22.9 ± 0.4	n.s.	n.s.	n.s.
Smoking (%)	61/39	63/37	63/37	n.s.	n.s.	n.s.
Alcohol (g/day)	28.8 ± 1.4	29.5 ± 1.9	44.5 ± 4.8	n.s.	0.0049**	0.0102**
Drinkers (%)	67.0	67.1	85.5	($P < 0.0175$)		
AST (IU/l)	26.6 ± 0.7	26.6 ± 0.9	33.6 ± 2.3	n.s.	0.0038**	0.0049**
ALT (IU/l)	27.1 ± 0.9	26.8 ± 1.2	34.3 ± 3.0	n.s.	0.02*	0.02*
γ-GTP (IU/l)	58.2 ± 3.1	57.3 ± 4.1	80.3 ± 10.5	n.s.	0.04*	0.04*
Diabetics (%)	13.3	13.3	13.6	n.s.	n.s.	n.s.

AST 2/2 ± 1/2 vs. 1/1, $P < 0.0033$; ALT 2/2 ± 1/2 vs. 1/1, $P < 0.02$; γ-GTP 2/2 ± 1/2 vs. 1/1, $P < 0.04$; drinkers 2/2 ± 1/2 vs. 1/1, $P < 0.005$; alcohol 2/2 ± 1/2 vs. 1/1, $P < 0.005$

*$P < 0.05$

**$P < 0.01$

Statistical analysis

Data are presented as means ± SE. The statistical significance of any difference in mean values and frequencies was determined with the Student's *t*-test or the Tukey–Kramer test. We used a one-way analysis of variance to test for overall differences among multiple groups, and the Fisher LSD post hoc test to identify which group differences accounted for the significant *P*-value. The significance of deviation from Hardy–Weinberg equilibrium was analyzed using the chi-square test. A *P*-value of < 0.05 was considered statistically significant.

Results

Influence of *ADH2* genotypes on drinking behavior and liver function

Among the 2,232 subjects, 1,355 (men 689, women 666) had the *ADH2*2/2* genotype, 759 (men 378, women 381) had the *ADH2*2/1* genotype, and 118 (men 59, women 59) had the *ADH2*1/1* genotype. The *ADH2*2/2*, *ADH2*2/1*, and *ADH2*1/1* genotypes were in Hardy–Weinberg equilibrium. There was no gender difference.

First, we compared the percentage of drinkers dependent upon *ADH2* genotype. The percentage of drinkers was significantly higher in both men and women in the *ADH2*1/1* group, showing overall differences among the groups (Table 1 and Fig. 1a). The difference was statistically significant according to the Fisher LSD post hoc test in men ($P < 0.0175$), women ($P < 0.0166$), and total subjects-1 ($P < 0.0033$) (Table 1). Moreover, amounts of alcohol consumed were much higher in the *ADH2*1/1* group than the other *ADH2* groups in men and total subjects-1 ($P < 0.01$ in *ADH2*2/2* vs. *ADH2*1/1* and $P < 0.05$ in *ADH2*1/2* vs. *ADH2*1/1*) (Tables 1, 3 and Fig. 1b). On the other hand, no significant difference in alcohol consumption among *ADH2*1/1* and the other groups was found in women, probably because much less alcohol was consumed by women than men (Table 2 and Fig. 1b). For smoking (percentage of non-smokers to smokers), there was no difference according *ADH2* genotype in men and in women.

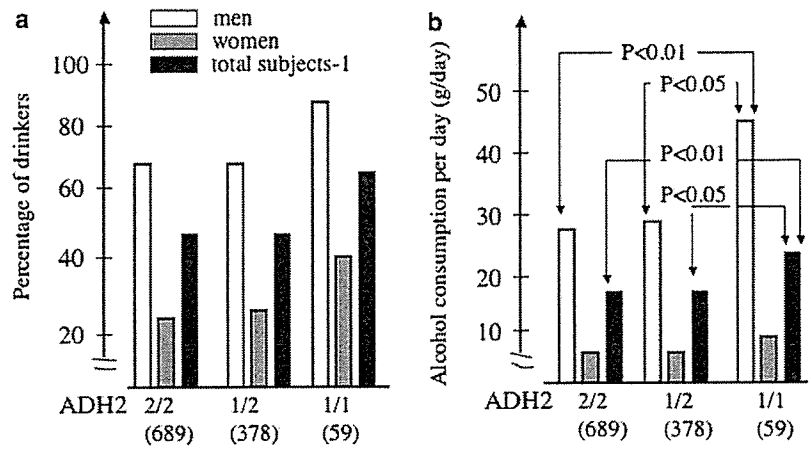

Fig. 1a, b Correlation of *ADH2* genotype with alcohol drinking behavior. **a** Percentage of drinkers in three groups based on *ADH2* genotype. Values in parentheses indicate the total number of subjects (*white bars* men, *gray bars* women, and *black bars* total subjects). **b** Average amounts of alcohol consumed per day. Subjects in the *ADH2*1/1* group drink more alcohol than those in the *ADH2*2/2* and *ADH2*1/2* groups

Table 2 Comparison of parameters among three groups of women (in subjects-1), divided according to the three *ADH2* genotypes. Right columns indicate *P*-value of statistical difference between each two group

Variables	Women			*P*-value		
ADH genotype	2/2	1/2	1/1	2/2 vs. 1/2	2/2 vs. 1/1	1/2 vs. 1/1
Subjects-1 $n=$	666	381	59			
Age (years)	59.4 ± 0.4	59.1 ± 0.6	60.0 ± 1.4	n.s.	n.s.	n.s.
Height (cm)	151.3 ± 0.2	151.1 ± 0.3	151.1 ± 0.8	n.s.	n.s.	n.s.
BMI	23.0 ± 0.1	22.7 ± 0.2	23.1 ± 0.4	n.s.	n.s.	n.s.
Smoking (%)	93/7	93/7	92/8	n.s.	n.s.	n.s.
Alcohol (g/day)	5.2 ± 0.6	5.4 ± 0.8	6.4 ± 2.0	n.s.	n.s.	n.s.
Drinkers (%)	22.9	25.5	39.7	< 0.0166		
AST (IU/l)	24.5 ± 0.6	23.5 ± 0.7	23.3 ± 1.8	n.s.	n.s.	n.s.
ALT (IU/l)	21.2 ± 0.8	20.1 ± 1.0	18.9 ± 2.5	n.s.	n.s.	n.s.
γ-GTP (IU/l)	27.9 ± 1.1	28.5 ± 1.4	29.4 ± 3.6	n.s.	n.s.	n.s.
Diabetics (%)	9.16	10.5	6.78	n.s.	n.s.	n.s.

Drinkers 2/2 ± 1/2 vs. 1/1, $P < 0.01$

Next, we compared blood parameters of liver function, namely AST, ALT, and γ-GTP activities. In men, levels were significantly higher in the *ADH2*1/1* group than the other two *ADH2* groups (Table 1, AST; $P < 0.01$ in *ADH2*2/2* vs. *ADH2*1/1* and $P < 0.01$ in *ADH2*1/2* vs. *ADH2*1/1*. ALT; $P < 0.05$ in *ADH2*2/2* vs. *ADH2*1/1* and $P < 0.05$ in *ADH2*1/2* vs. *ADH2*1/1*. γ-GTP; $P < 0.05$ in *ADH2*2/2* vs. *ADH2*1/1* and $P < 0.05$ in *ADH2*1/2* vs. *ADH2*1/1*), indicating that more alcohol intake in the *ADH2*1/1* group causes damage to the liver. On the other hand, no significant difference was found in women (Table 2); nevertheless the *ADH2*1/1* group consumed more alcohol than the other groups, probably because women drink less than men.

In subjects-1, the percentage of those with diabetes was compared among the three ADH2 genotypic groups. However, there was no statistical difference in the prevalence of diabetes among the three groups (men; *ADH2*2/2*:13.3%, *ADH2*1/2*:13.3%, and *ADH2*1/1*:13.6%, women; *ADH2*2/2*:9.2%, *ADH2*1/2*:10.5%, and *ADH2*1/1*:6.8%, total subjects-1; *ADH2*2/2*:11.2%, *ADH2*1/2*:11.9%, and *ADH2*1/1*:10.2%) (Tables 1, 2, 3).

Influence of *ADH2* genotype on fasting insulin concentration

We tried to clarify the correlation of insulin concentration with *ADH2* genotype. To exclude the effect of medication, subjects were limited to those (subjects-2) not treated with insulin therapy and/or with oral medications for diabetes. Although habits or behaviors generally depend upon genetic factors, we would like to distinguish the genetic effects from the secondary results of alcohol consumption. Since the frequency of drinking and the amountsof alcohol consumed were the same in the *ADH2*1/2* and *ADH2*2/2* groups (Fig. 1 and Tables 1, 2, 3), we compared fasting insulin concentrations between these two groups. Insulin levels were lower in the *ADH2*1/2* than *ADH2*2/2* group in total subjects-2 ($P < 0.02$). In men, insulin levels were lower in the *ADH2*1/2* than *ADH2*2/2* group ($P < 0.05$), while in

Table 3 Comparison of parameters among three groups of total subjects-1 divided according to *ADH2* genotype. Right columns indicate *P*-values of statistical differences between two groups

Variables	Total (men + women)			*P*-value		
ADH genotype	2/2	1/2	1/1	2/2 vs. 1/2	2/2 vs. 1/1	1/2 vs. 1/1
Subjects-1 $n=$	1,352	756	118			
Age (years)	59.4 ± 0.3	59.0 ± 0.4	59.0 ± 1.0	n.s.	n.s.	n.s.
Height (cm)	158.2 ± 0.2	158.1 ± 0.3	156.8 ± 0.8	n.s.	n.s.	n.s.
BMI	23.0 ± 0.1	22.7 ± 0.1	23.1 ± 0.3	n.s.	n.s.	n.s.
Smoking (%)	77/23	78/22	78/22	n.s.	n.s.	n.s.
Alcohol (g/day)	17.2 ± 0.9	17.6 ± 1.1	24.9 ± 2.8	n.s.	0.0089**	0.0158**
Drinkers (%)	45.4	45.6	62.0	< 0.0033		
AST (IU/l)	25.6 ± 0.4	25.0 ± 0.6	28.3 ± 1.4	n.s.	n.s.	0.0383**
ALT (IU/l)	24.2 ± 0.6	23.4 ± 0.8	26.5 ± 2.0	n.s.	n.s.	n.s.
γ-GTP (IU/l)	43.3 ± 1.7	42.9 ± 2.3	54.4 ± 5.7	n.s.	n.s.	n.s.
Diabetics (%)	11.2%	11.9%	10.2%	n.s.	n.s.	n.s.

Drinkers 2/2 ± 1/2 vs. 1/1, $P < 0.001$; alcohol 2/2 ± 1/2 vs. 1/1, $P < 0.01$
*$P < 0.05$
**$P < 0.01$

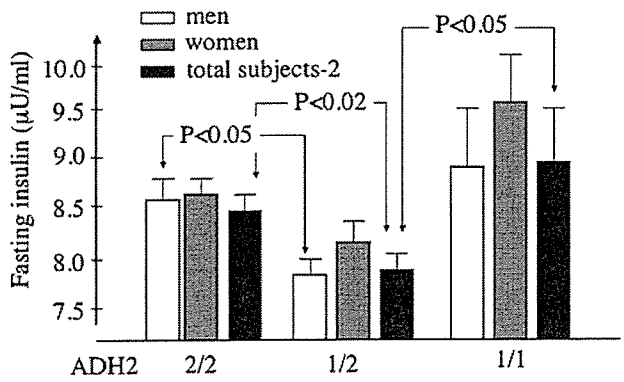

Fig. 2 Correlation of *ADH2* genotype with fasting insulin concentration in subject-2 group. Fasting insulin concentration (μU/ml): a significant difference was found between *ADH2*2/2* and *ADH2*1/2* in men (8.56±0.24 vs. 7.77±0.32, $P<0.05$), and between *ADH2*2/2* and *ADH2*1/2* in total subjects-2 (8.44±0.15 vs. 7.84±0.20, $P<0.02$). A significant difference was found between *ADH2*1/2* and *ADH2*1/1* in total subjects-2 (7.84±0.20 vs. 8.92±0.50, $P<0.05$)

women, the *ADH2*1/2* group tended to have lower insulin concentrations (Fig. 2 and Table 4). This suggests that the *ADH2*1* allele has a lowering effect on the concentration of insulin.

Next, we compared the concentration of insulin between *ADH2*1/2* and *ADH2*1/1*. The concentration tended to be higher in the *ADH2*1/1* group than the *ADH2*1/2* group in men, women and total subjects-2, but a significant difference was only found in total subjects-2 (insulin, *ADH2*1/2*: 7.84±0.20 μU/ml, *ADH2*1/1*: 8.92±0.50 μU/ml, $P<0.05$, Table 3 and Fig. 2). Because the *ADH2*1/1* group is small, the difference may have become statistically insignificant in men or in women.

In subjects-2, while the difference was statistically insignificant, the average level of HbA1c tended to be lower in the *ADH2*1/2* group than the *ADH2*1/1* or *ADH2*2/2* group (Fig. 3 and Table 4). For instance, in total subjects-2, HbA1c was 5.20±0.02%, 5.17±0.02%, and 5.23±0.05%, respectively, in the *ADH2*2/2*, *ADH2*1/2*, and *ADH2*1/1* groups. Therefore, low insulin levels in the *ADH2*1/2* group seem to parallel low HbA1c levels, showing a U-shaped relationship with *ADH2* genotype as in Figs. 2 and 3.

Discussion

By examining the correlation between *ADH2* genotype and drinking behavior, we confirmed the previous observation that *ADH2* genotype influences the amount of alcohol consumed in a Japanese population (Higuchi et al 1996). In addition to alcohol consumption and percentage of drinkers, men from the *ADH2*1/1* group had the highest levels of AST, ALT, and γ-GTP, suggesting that they drink so much alcohol that their livers become damaged. This coincides with the observation of Tanaka et al (1996), supporting the idea that *ADH2* polymorphisms play an important role in alcoholic liver diseases.

In terms of the mechanism involved, since carriers of *ADH2*1/1* have less enzymatic activity for ethanol than carriers of *ADH2*2/1* or *ADH2*2/2*, the slow rate of ethanol clearance could damage the liver, but this is unlikely because ethanol is less toxic than acetaldehyde. Alternatively, it is possible that the slow rate of ethanol clearance protects the subjects from the uncomfortable feeling caused by acetaldehyde, thereby causing them to drink too much alcohol and leading to liver damage.

Interestingly, concentrations of insulin were higher in the *ADH2*1/1* than the *ADH2*1/2* group. Onishi et al (2003) reported that excess alcohol intake can induce insulin resistance with enhanced PI3-kinase activation. Therefore, in the *ADH2*1/1* group, excess alcohol intake may cause insulin resistance, resulting in hyperinsulinemia. Otherwise, some liver dysfunction caused by excess alcohol intake may cause a high glucose output from liver, thereby inducing hyperinsulinemia.

Table 4 Comparison of glucose–insulin axis parameters among three groups of subjects-2 divided according to the three *ADH2* genotypes

Variables				*P*-value		
ADH genotype	2/2	1/2	1/1	2/2 vs. 1/2	2/2 vs. 1/1	1/2 vs. 1/1
Men $n=$	640	346	57			
FPG (mg/dl)	103.3±0.7	102.6±0.9	103.3±2.2	n.s.	n.s.	n.s.
HbA1c (%)	5.24±0.02	5.22±0.03	5.27±0.08	n.s.	n.s.	n.s.
Insulin (μU/ml)	8.46±0.22	7.69±0.31	8.47±0.75	0.0452*	n.s.	n.s.
Women $n=$	623	354	57			
FPG (mg/dl)	98.6±0.6	99.3±0.8	99.2±2.1	n.s.	n.s.	n.s.
HbA1c (%)	5.15±0.02	5.11±0.03	5.17±0.06	n.s.	n.s.	n.s.
Insulin (μU/ml)	8.42±0.19	8.00±0.26	9.36±0.65	n.s.	n.s.	n.s.
Total $n=$	1,263	700	114			
FPG (mg/dl)	101.0±0.46	101.0±0.6	101.2±1.5	n.s.	n.s.	n.s.
HbA1c (%)	5.20±0.02	5.17±0.02	5.23±0.05	n.s.	n.s.	n.s.
Insulin (μU/ml)	8.44±0.15	7.84±0.20	8.92±0.50	0.018*	n.s.	0.045*

*$P<0.05$
**$P<0.01$

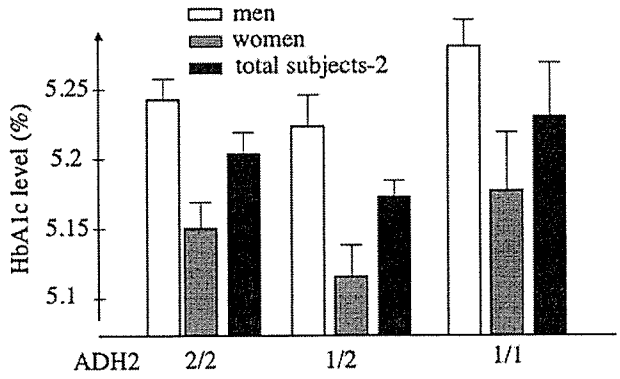

Fig. 3 Correlation of *ADH2* genotype with HbA1c level in subject-2. A significant difference was not found between the three groups. However, the HbA1c level showed a U-shaped relationship as if correlated to the insulin level

Next, we tried to focus on the *ADH2*'s genetic effects on the insulin–glucose axis. Because alcohol produces complicated effects, it is generally difficult to distinguish the genetic effects from the influence of alcohol drinking behavior. Interestingly, alcohol consumption or percentage of drinkers did not differ between the *ADH2*1/2* and *ADH2*2/2* groups (Tables 1, 2, 3 and Fig. 1a, b). This enabled us to compare the insulin concentration, dependent upon the difference in ADH2 activity itself, based on the *ADH2* polymorphism, almost independently from alcohol intake. Among subjects-2, we found that fasting insulin concentrations were significantly lower in the men and total subjects-2 with the *ADH2*1/2* genotype than those with the *ADH2*2/2* genotype (Table 4 and Fig. 2). A similar trend was seen in women, suggesting that this trend is reproducible irrespective of gender.

Thus, this study suggests that *ADH2*1* has a biphasic effect on the insulin concentration, a lowering effect with *ADH2*1/2*, and a raising effect with *ADH2*1/1* on excess alcohol intake. Interestingly, the average levels of HbA1c in subjects-2 tended to be lower in the *ADH2*1/2* group than the *ADH2*1/1* or *ADH2*2/2* groups. These two parameters seem to exhibit a U-shaped relationship (Figs. 2, 3). In nondiabetic subjects, a low insulin concentration together with a low HbA1c level usually coincides with low insulin resistance. Therefore, the above relationship suggests that light-to-moderate drinkers with the *ADH2*1* allele are likely to have reduced insulin resistance. Interestingly, this coincides with numerous other observations (Conigrave et al 2001; Hu et al 2001; Tsumura et al 1999) in terms of the notion that light drinking could benefit glucose tolerance.

Alcohol dehydrogenase catalyzed the first step in the metabolism of ethanol but has a wide range of substrates, including both aliphatic and aromatic alcohols, aldehydes, sterols, and ω-hydroxy fatty acids. We previously reported that, in the same population study, the *ADH2*1* allele is associated with increased levels of LDL-cholesterol and high blood pressure, and an increased risk of cerebral infarction (Suzuki et al 2004). The concentration of insulin or resistance to insulin could be affected by sex hormones, sex hormone-binding globulin or obesity (Falkner et al 1999; Collison et al 2000). Therefore, as another possibility, the interaction of the *ADH2*1* allele with several hormones associated with sex or lipids may decrease the insulin resistance in target tissues (Harada et al 1998).

However, in this study, the prevalence of diabetes did not differ among the three *ADH2* genotypes in subjects-1. Therefore, the effect of *ADH2* genotype on insulin resistance may be so mild or complex that it did not influence the prevalence of diabetes in the community-dwelling Japanese population. Alternatively, since all of the subjects whose FPG levels were higher than 110 mg/dl were not confirmed by the oral glucose tolerance test, if the subjects who had postprandial hyperglycemia had been included in subject-1, the result could have been different. To clarify this, a further study will be needed.

It is well known that drinking behavior is influenced more by *ALDH2* (aldehyde dehydrogenase 2) genotype than *ADH2* genotype (Higuchi et al 1996). However, although a similar investigation was performed on the correlation between *ALDH2* genotypes and their phenotype, no genetic effect of *ALDH2* was found in insulin–glucose axis and liver dysfunction (Ohsawa et al 2003). Thus, amounts of alcohol consumed would not simply depend upon insulin level.

In conclusion, this is the first paper to propose an effect of *ADH2* genotype on insulin concentrations in the Japanese. The effect seems small, although it was statistically significant due to the large number of subjects. The effect is possibly too small to have a significant bearing on the prevalence of diabetes. However, this finding provides several insights into the complex relationship between alcohol metabolism, genetic background, change in alcohol drinking behavior, the insulin–glucose axis, and the prevalence of diabetes and liver dysfunction.

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Association of SH-2 Containing Inositol 5′-Phosphatase 2 Gene Polymorphisms and Hyperglycemia

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Objectives: SH-2 containing inositol 5′-phosphatase 2 (SHIP2) is a family of inositol 5′-phosphatases, which possess the 5′-phosphatase activity that hydrolyzes phosphatidylinositol-3, 4, 5-trisphosphate to phosphatidylinositol-3, 4-bisphosphate and is suspected to negatively regulates the metabolic signaling of insulin. To clarify the possible involvement of SHIP2 in physiological abnormalities, we examined the human SHIP2 gene polymorphism in a Japanese cohort.

Methods: We searched single-nucleotide polymorphisms (SNPs) on the human SHIP2 gene promoter and 5′-untranslated region (5′-UTR) and investigated their relationship with impaired fasting glycemia (IFG) in a Japanese cohort. Next, the effect of the SNPs on promoter activity was examined in HeLa and HL60 cells.

Results: Among the several SNPs detected on the human SHIP2 gene promoter and 5′-UTR, 3 SNPs (−405 C/A, +57 G/A, and +334 C/T) formed the haplotypes CGC and AAT and were found at a relatively high frequency in the Japanese population. The frequency of genotypes (+334 CT and TT) was significantly higher in the group with IFG than in the normal group ($P < 0.0001$, odds ratio = 2.23, 95% confidence interval = 1.50 − 3.32). This association was not affected by age and gender. Furthermore, one haplotype (+57 A, +334 T) which was inserted into a luciferase reporter plasmid and existed more frequently in the IFG group than in the normal group exhibited increased promoter activity in the culture cells compared with the other haplotype (+57 G, +334 C).

Conclusions: The SNPs in the SHIP2 gene promoter and the 5′-UTR may account partly for the IFG and may be a marker for the risk of diabetes.

Key Words: SHIP2, SNP, diabetes, cohort study, promoter analysis

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Stimulation of the insulin receptor leads to the recruitment and activation of insulin receptor substrates (IRS-1 and IRS-2), which are responsible for inducing several distinct signaling pathways, including the phosphatidylinositol-3 kinase (PI3K)-Akt pathway. PI3K is a lipid kinase that phosphorylates phosphatidylinositol-4, 5-bisphosphate [PI(4, 5)P2], producing phosphatidylinositol-3, 4, 5-trisphosphate [PI(3, 4, 5)P3]. PI(3, 4, 5)P3 serves as a membrane binding site for the Akt family of serine-threonine kinases, which are activated upon translocation to the membrane by phosphoinositide-dependent protein kinase (PDK1).[1−3]

SH-2 containing inositol 5′-phosphatase 2 (SHIP2) is a family of inositol 5′-phosphatases, which possess the 5′-phosphatase activity that hydrolyzes PI(3, 4, 5)P3 to PI(3, 4)P2.[4−6] SHIP2 was reported to negatively regulate the metabolic signaling of insulin via its 5′-phosphatase activity and, therefore, to be important for the regulation of the insulin-induced activation of molecules downstream of PI3K, leading to glucose uptake and glycogen synthesis.[7,8]

The enhanced expression of SHIP2 was observed in the skeletal muscle and fat tissue of diabetic db/db mice.[9] Analysis with mice lacking the SHIP2 gene revealed that the loss of SHIP2 leads to an increased sensitivity to insulin, which was characterized by severe neonatal hypoglycemia, deregulated expression of genes involved in gluconeogenesis, and perinatal death.[10] However, the targeting construct used in this study left the first 18 exons encoding SHIP2 intact, generating a $SHIP2^{EX19\text{-}28-/-}$ mouse, and apparently also deleted a second gene, Phox2a. New SHIP2 knockout ($SHIP2^{-/-}$) mice, which were null for SHIP2 mRNA and protein, were viable, had normal glucose and insulin levels, and had normal insulin and glucose tolerance; however, they were highly resistant to weight gain when placed on a high-fat diet.[11] These findings suggested a positive interaction between the deregulated expression of SHIP2 and the diabetic pathology of insulin resistance and/or obesity.

SHIP2 is in human chromosome 11q13-14, which has been suggested to be linked to type 2 diabetes with insulin resistance and hypertension.[12−14] Thus, it is possible that SHIP2 is involved in the pathogenesis of insulin resistance of type 2 diabetes mellitus in humans.[15] A recent report has shown that some polymorphisms of SHIP2 found in British and French type 2 diabetes are associated with metabolic syndrome, including type 2 diabetes and hypertension.[16] Furthermore, another cohort study in a Japanese population has shown that some single-nucleotide polymorphisms (SNPs), mainly in coding sequence of SHIP2, are implicated, at least in part, in type 2 diabetes.[17]

We recently characterized the regulation of human SHIP2 gene expression and determined the transcription start sites (TSSs) of the human SHIP2 gene.[18] In the present study,

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