

15. Waters D, Pedersen TR Review of cholesterol-lowering therapy: coronary angiographic and events trials. *Am J Med*. 1996;101:4A34S–A38S; discussion A39S.
16. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ*. 2003;326:1423.
17. LaRosa JC, He J, Vupputuri S. Effect of statins on risk of coronary disease: a meta-analysis of randomized controlled trials. *JAMA*. 1999;282:2340–2346.
18. Durrington P. Dyslipidaemia. *Lancet*. 2003;362:717–731.
19. Kita T, Kume N, Minami M, Hayashida K, Murayama T, Sano H, Moriwaki H, Kataoka H, Nishi E, Horiuchi H, Arai H, Yokode M. Role of oxidized LDL in atherosclerosis. *Ann NY Acad Sci*. 2001;947:199–205; discussion 205–206.
20. Steinberg D, Witztum JL. Is the oxidative modification hypothesis relevant to human atherosclerosis? Do the antioxidant trials conducted to date refute the hypothesis? *Circulation*. 2002;105:2107–2111.
21. Kume N, Kita T. New scavenger receptors and their functions in atherogenesis. *Curr Atheroscler Rep*. 2002;4:253–257.
22. Sawamura T, Kume N, Aoyama T, Moriwaki H, Hoshikawa H, Aiba Y, Tanaka T, Miwa S, Katsura Y, Kita T, Masaki T. An endothelial receptor for oxidized low-density lipoprotein. *Nature*. 1997;386:73–77.
23. Kume N, Murase T, Moriwaki H, Aoyama T, Sawamura T, Masaki T, Kita T. Inducible expression of lectin-like oxidized LDL receptor-1 in vascular endothelial cells. *Circ Res*. 1998;83:322–327.
24. Kume N, Moriwaki H, Kataoka H, Minami M, Murase T, Sawamura T, Masaki T, Kita T. Inducible expression of LOX-1, a novel receptor for oxidized LDL, in macrophages and vascular smooth muscle cells. *Ann NY Acad Sci*. 2000;902:323–327.
25. Moriwaki H, Kume N, Kataoka H, Murase T, Nishi E, Sawamura T, Masaki T, Kita T. Expression of lectin-like oxidized low density lipoprotein receptor-1 in human and murine macrophages: upregulated expression by TNF-alpha. *FEBS Lett*. 1998;440:29–32.
26. Minami M, Kume N, Kataoka H, Morimoto M, Hayashida K, Sawamura T, Masaki T, Kita T. Transforming growth factor-beta(1) increases the expression of lectin-like oxidized low-density lipoprotein receptor-1. *Biochem Biophys Res Commun*. 2000;272:357–361.
27. Murase T, Kume N, Korenaga R, Ando J, Sawamura T, Masaki T, Kita T. Fluid shear stress transcriptionally induces lectin-like oxidized LDL receptor-1 in vascular endothelial cells. *Circ Res*. 1998;83:328–333.
28. Li DY, Zhang YC, Philips MI, Sawamura T, Mehta JL. Upregulation of endothelial receptor for oxidized low-density lipoprotein (LOX-1) in cultured human coronary artery endothelial cells by angiotensin II type I receptor activation. *Circ Res*. 1999;84:1043–1049.
29. Kataoka H, Kume N, Miyamoto S, Minami M, Moriwaki H, Murase T, Sawamura T, Masaki T, Hashimoto N, Kita T. Expression of lectinlike oxidized low-density lipoprotein receptor-1 in human atherosclerotic lesions. *Circulation*. 1999;99:3110–3117.
30. Kataoka H, Kume N, Miyamoto S, Minami M, Morimoto M, Hayashida K, Hashimoto N, Kita T. Oxidized LDL modulates Bax/Bcl-2 through the lectinlike Ox-LDL receptor-1 in vascular smooth muscle cells. *Arterioscler Thromb Vasc Biol*. 2001;21:955–960.
31. Kume N, Kita T. Apoptosis of vascular cells by oxidized LDL: involvement of caspases and LOX-1, and its implication in atherosclerotic plaque rupture. *Circ Res*. 2004;94:269–270.
32. Li D, Liu L, Chen H, Sawamura T, Ranganathan S, Mehta JL. LOX-1 mediates oxidized low-density lipoprotein-induced expression of matrix metalloproteinases in human coronary artery endothelial cells. *Circulation*. 2003;107:612–617.
33. Chen M, Kakutani M, Naruko T, Ueda M, Narumiya S, Masaki T, Sawamura T. Activation-dependent surface expression of LOX-1 in human platelets. *Biochem Biophys Res Commun*. 2001;282:153–158.
34. Murase T, Kume N, Kataoka H, Minami M, Sawamura T, Masaki T, Kita T. Identification of soluble forms of lectin-like oxidized LDL receptor-1. *Arterioscler Thromb Vasc Biol*. 2000;20:715–720.
35. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley and Sons Inc; 1989.
36. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. *Radiology*. 1983;148:839–843.
37. Newby LK, Christenson RH, Ohman EM, Armstrong PW, Thompson TD, Lee KL, Hamm CW, Katus HA, Cianciolo C, Granger CB, Topol EJ, Califf RM. Value of serial troponin T measures for early and late risk stratification in patients with acute coronary syndromes: the GUSTO-IIa Investigators. *Circulation*. 1998;98:1853–1859.
38. Muller-Bardorff M, Hallermayer K, Schroder A, Ebert C, Borgya A, Gerhardt W, Remppis A, Zehelein J, Katus HA. Improved troponin T ELISA specific for cardiac troponin T isoform: assay development and analytical and clinical validation. *Clin Chem*. 1997;43:458–466.
39. Fuster V, Stein B, Ambrose JA, Badimon L, Badimon JJ, Chesebro JH. Atherosclerotic plaque rupture and thrombosis: evolving concepts. *Circulation*. 1990;82(suppl II):II-47–II-59.
40. Cominacini L, Fratta Pasini A, Garbin U, Pastorino A, Rigoni A, Nava C, Davoli A, Lo Cassio V, Sawamura T. The platelet-endothelium interaction mediated by lectin-like oxidized low-density lipoprotein receptor-1 reduces the intracellular concentration of nitric oxide in endothelial cells. *J Am Coll Cardiol*. 2003;41:499–507.
41. Iwai-Kanai E, Hasegawa K, Sawamura T, Fujita M, Yanazume T, Toyokuni S, Adachi S, Kihara Y, Sasayama S. Activation of lectin-like oxidized low-density lipoprotein receptor-1 induces apoptosis in cultured neonatal rat cardiac myocytes. *Circulation*. 2001;104:2948–2954.
42. Li L, Roumeliotis N, Sawamura T, Renier G. C-reactive protein enhances LOX-1 expression in human aortic endothelial cells: relevance of LOX-1 to C-reactive protein-induced endothelial dysfunction. *Circ Res*. 2004;95:877–883.
43. Tsimikas S, Witztum JL. Measuring circulating oxidized low-density lipoprotein to evaluate coronary risk. *Circulation*. 2001;103:1930–1932.

Serum Lipid Survey and Its Recent Trend in the General Japanese Population in 2000

Hidenori Arai¹, Akira Yamamoto², Yuji Matsuzawa³, Yasushi Saito⁴, Nobuhiro Yamada⁵, Shinichi Oikawa⁶, Hiroshi Mabuchi⁷, Tamio Teramoto⁸, Jun Sasaki⁹, Noriaki Nakaya¹⁰, Hiroshige Itakura¹¹, Yuichi Ishikawa¹², Yasuyoshi Ouchi¹³, Hiroshi Horibe¹⁴, and Toru Kita¹⁵, on behalf of the Research Group on Serum Lipid Level Survey 2000 in Japan*

¹ Department of Geriatric Medicine, Kyoto University School of Medicine, Kyoto, Japan.

² National Cardiovascular Center, Osaka, Japan.

³ Department of Internal Medicine, Osaka University Osaka, Japan.

⁴ Department of Internal Medicine, Chiba University, Chiba, Japan.

⁵ Department of Internal Medicine, Tsukuba University, Ibaraki, Japan.

⁶ Department of Internal Medicine, Nippon Medical School, Tokyo, Japan.

⁷ Department of Internal Medicine, Kanazawa University, Ishikawa, Japan.

⁸ Department of Internal Medicine, Teikyo University, Tokyo, Japan.

⁹ International University of Health and Welfare, Fukuoka, Japan.

¹⁰ Fussa Hospital, Tokyo, Japan.

¹¹ Ibaraki Christian University, Ibaraki, Japan.

¹² Faculty of Health Sciences, Kobe University, Hyogo, Japan.

¹³ Department of Geriatric Medicine, University of Tokyo, Tokyo, Japan.

¹⁴ Keisen Clinic, Hyogo, Japan.

¹⁵ Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan.

* Members are listed in Appendix.

To determine the recent serum lipid levels and other serum variables in the general Japanese population and trends in their changes over the past 40 years, a nationwide survey of serum lipid levels was conducted in 36 institutes from various districts around Japan in 2000. The total number of subjects was 12,839, aged 4 through 99 years. The mean total cholesterol level was 201 mg/dl; 202 mg/dl in men and 200 mg/dl in women. The mean HDL-cholesterol level was 59 mg/dl; 55 mg/dl in men and 65 mg/dl in women. The mean LDL-cholesterol level was 118 mg/dl; 121 mg/dl in men and 115 mg/dl in women. The mean triglyceride level was 118 mg/dl; 136 mg/dl in men and 92 mg/dl in women. The total cholesterol level slightly increased by 5 mg/dl in 10 years. Although the triglyceride level in women did not change, the triglyceride level in men increased over 10 years, especially in the 30s through 70s age bracket, indicating a possible increase in metabolic syndromes in the future. The present results will become the standard serum lipid level data for the Japanese people, and succeeding 10-year surveys will clarify the trends of lipid levels in this country. *J Atheroscler Thromb*, 2005; 12: 98-106.

Key words: Hyperlipidemia, Cholesterol, Triglyceride, Life style, Coronary heart disease

Address for correspondence: Hidenori Arai, Department of Geriatric Medicine, Kyoto University School of Medicine, 54 Kawahara-cho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.

E-mail: harai@kuhp.kyoto-u.ac.jp

Received October 1, 2004.

Accepted for publication November 2, 2004.

Introduction

It has been well established that hyperlipidemia is a major risk factor for coronary heart disease (CHD) (1, 2). Numerous studies have shown that the reduction of serum lipid levels by dietary or drug treatment results in a

decrease in both the incidence of and the mortality from CHD (3–7). In contrast to the sharp decline in both serum cholesterol and mortality from CHD in the United States and Western Europe, remarkable increases in serum cholesterol levels as well as CHD mortality have been anticipated in the Asian-Pacific region, due to industrialization and modernization. Epidemiological studies indicate that changes in lifestyle have a great influence on the risk factors for atherosclerosis (8–10). Among the Asian-Pacific countries, Japan was found to have lower than average serum cholesterol values and a correspondingly lower incidence of CHD. Japanese in the 1960s consumed very little dietary fat, and both cholesterol levels and the incidence of CHD were low. Japanese who migrated to Hawaii and California, however, showed higher levels of serum cholesterol and a higher incidence of CHD than people in Japan (10). Thus, dietary habits and other environmental factors rather than genetic background affect serum cholesterol levels and CHD mortality in the population. In the United States, during the period of 1900 through 1991, many changes in nutritional lifestyle and medical therapeutic factors may have decreased serum total cholesterol levels among American adults (11). On the other hand, Japanese have adopted mixed dietary habits of a traditionally low fat and low cholesterol diet and a western style diet of relatively high fat and high cholesterol. As a result the serum cholesterol levels in the Japanese populations were found to have gradually increased over the 30 years from 1960 to 1990 according to 10-year-interval national surveys of serum cholesterol levels conducted in 1960, 1970, 1980, and 1990 (12–14). This study is the fifth survey and reveals the most recent serum lipid levels as well as fasting glucose, hemoglobin A1c (HbA1c), insulin, and uric acid levels in the general Japanese population, and the trends of serum lipid levels over the 40 years from 1960 to 2000.

Methods

Designs and data collection

The Research Group for Serum Lipid Level Survey 2000 in Japan co-ordinated members of 36 institutes from various areas in Japan. The project was designed to produce representative data of serum lipid, insulin, and uric acid plasma glucose and HbA1c levels in the civilian Japanese population. The subjects were people receiving annual health examinations in the general community, companies, and schools, and not patients visiting hospitals. The total number of subjects was 12,839, consisting of 7,658 men and 5,179 women (two of them were unknown for sex).

Laboratory methods

All serum and plasma samples were obtained in the fasting state except participants less than 20 years old, be-

cause it was hard to obtain permission to sample blood from children in a fasting state. All lipid and other analyses were conducted on venous blood samples within one week of collection at BML (Saitama, Japan). Serum cholesterol and triglyceride levels were measured by enzymatic assay. HDL-cholesterol and LDL-cholesterol were measured enzymatically by a kit from Daiichi Kagaku Co. Ltd (Tokyo, Japan). The results of lipid analyses in the four surveys were indirectly standardized according to the criteria of the CDC Lipid Standardization Program (11). There were no differences between the data obtained by Zak-Henly's method in 1960 and 1970, and those by the enzymatic methods used in 1980 through 2000. Thus, the cholesterol levels in these five surveys appear to be comparable. In the present survey, we also measured remnant-like particles (RLP)-cholesterol with a kit from Japan Immunoresearch Laboratories (Gunma, Japan). Plasma glucose was determined enzymatically and HbA1c was determined using a kit from Kyowa Medex Co. Ltd (Tokyo, Japan). Serum insulin was determined by immunoradiometric assay (Abbott Laboratories, Abbot Park, IL, USA).

Data analyses

The statistical analyses of the present data were performed by SAS statistical. The study was designed by the Research group, which organized 36 institutions from various districts of Japan from the extreme North (Hokkaido) to the furthest South (Okinawa islands).

Results

Table 1 shows the age-specific means and standard deviations of serum total cholesterol levels by age group in all the participants as well as in men and women. The mean total cholesterol level in this survey was 201 mg/dl, which is 5 mg/dl higher than that in 1990. In men, the age-specific mean serum cholesterol levels gradually increased from 185 mg/dl in the 0- to 9-year-old age group to 207 mg/dl in the 50- to 59-year-old age group. There was a slight decrease after age 60. In women, the mean cholesterol levels gradually rose from 186 mg/dl in the 0- to 9-year-old age group to 218 mg/dl in the 50- to 69-year-old age groups, and fell to 208 mg/dl after age 80.

Table 2 shows the age-specific means and standard deviations of serum triglyceride levels in all the participants as well as in men and women. The mean triglyceride level in this survey was 118 mg/dl, which was 13 mg/dl higher than that in 1990. The age-specific mean triglyceride values were highest in 30- to 49-year-old age group in men. In contrast, in women, the age-specific mean triglyceride levels increased gradually from 59 mg/dl in the 0- to 9-year-old age group to 117 mg/dl in the 60- to 69-year-old age group, and then declined to 105 mg/dl above 80 years of age. Although the triglyceride

level in women did not change in ten years, the triglyceride level in men has markedly increased, especially 30- to 39-year-old to 70- to 79-year-old age groups over the last ten years.

Table 3 shows the age-specific means and standard deviations in serum HDL-cholesterol levels in all the participants as well as in men and women. The mean HDL-cholesterol level in this survey was 59 mg/dl, which is 5

mg/dl higher than that in 1990. The age-specific mean HDL-cholesterol levels in men gradually decreased from 70 mg/dl in the 0- to 9-year-old age group to 54 mg/dl in the 30- to 39-year-old age group, and remained at this level up to 89 years old age. The mean HDL-cholesterol levels in woman remained constant from the 0- to 9-year-old age group to the 50- to 59-year-old age group, and gradually decreased thereafter. Figure 1 summarizes the

Table 1. List of the institutes enrolled for this survey from each district around Japan.

Area	Name of Institute	
Hokkaido	Sapporo Medical University	
	Hokkaido University	
	Asahikawa Red Cross Hospital	
Tohoku	Yamagata University	
	Hirosaki University	
	Mizusawa General Hospital	
Kantou	Tsukuba University	
	Teikyo University	
	St. Luka's International Hospital	
	Chiba University	
	National Defense Medical College	
	Tokyo University	
	Toranomon Hospital	
	Nihon Medical School	
	Nihon University	
	Hokuriku/Tokai	Hamamatsu Social Insurance Hospital
		Kanazawa University
University of Fukui Faculty of Medical Sciences		
Himi Municipal Hospital		
Nagoya University		
Sugiyama Jogakuen University	Sugiyama Jogakuen University	
	Nagoya City University	
	Kinki	National Cardiovascular Center
		Osaka University
Kyoto Center for Preventive Medicine		
Kobe University		
Chugoku/Shikoku	Egusa Clinic	
	Yamaguchi University	
	Chugoku Central Hospital	
	Udajima Social Insurance Hospital	
Kyushu/Okinawa	National Hospital Organization	
	Kumamoto Medical Center	
	Fukuoka University	
	Saga University Faculty of Medicine	
	Kagosima University	
	Miyazaki Prefectural Nichinan Hospital	
University of Ryukyus		

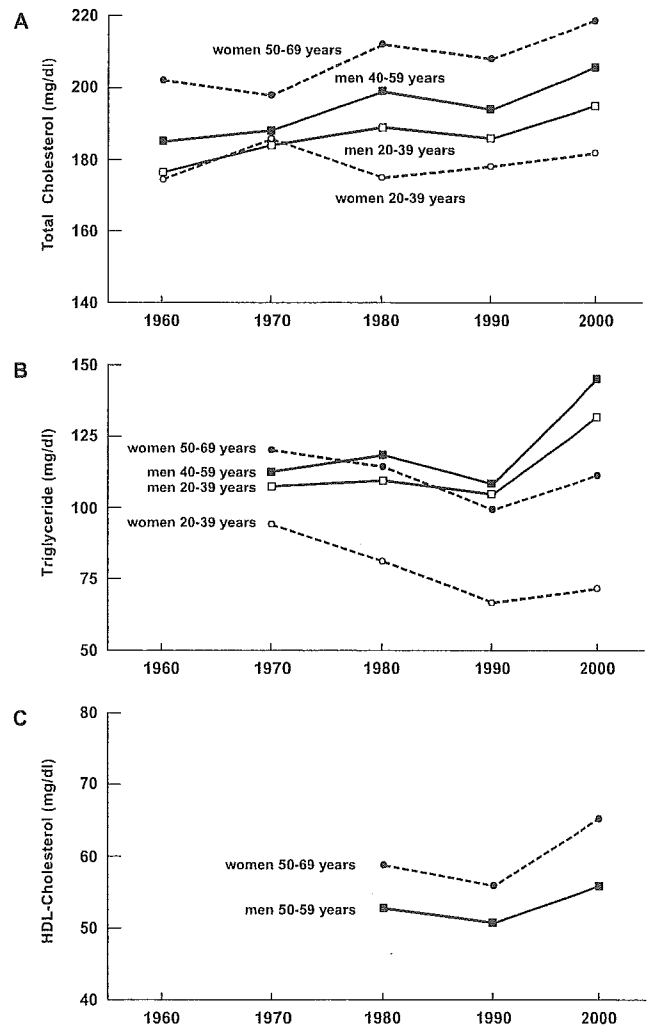


Fig. 1. Trends of serum lipid levels in Japanese in 40 years from 1960 to 2000. Results of the surveys carried out by the members of Japan Atherosclerosis Society. A. The mean cholesterol level in men and women of 20–39 years, men of 40–59 years, and women of 50–69 years from 1960 to 2000. B. The mean triglyceride level in men and women of 20–39 years, men of 40–59 years, and women of 50–69 years from 1970 to 2000. C. The mean HDL-cholesterol level in men and women of 50–59 years from 1980 to 2000.

Table 2. Serum total cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	186	27	102	185	26	114	186	27
10-19	465	181	28	196	178	28	269	183	27
20-29	1,256	180	31	394	181	32	861	180	31
30-39	1,642	195	34	1,101	200	34	541	185	31
40-49	3,564	201	33	2,399	204	32	1,165	195	32
50-59	3,467	211	34	2,328	207	33	1,139	218	34
60-69	1,625	209	34	844	200	34	780	218	32
70-79	551	206	33	271	198	32	280	214	32
80-89	53	197	33	23	181	29	30	208	32
Total	12,839	201	34	7,658	202	34	5,179	200	35

Table 3. Serum triglyceride (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	56	30	102	53	30	114	59	30
10-19	465	67	36	196	66	39	269	68	33
20-29	1,256	83	65	394	105	74	861	73	58
30-39	1,642	118	109	1,101	142	123	541	70	42
40-49	3,564	129	103	2,399	150	112	1,165	87	63
50-59	3,467	129	102	2,328	139	115	1,139	108	66
60-69	1,625	123	83	844	128	98	780	117	64
70-79	551	118	63	271	123	67	280	113	59
80-89	53	100	44	23	93	38	30	105	47
Total	12,839	118	96	7,658	136	109	5,179	92	62

recent trend of the mean total cholesterol, triglyceride, and HDL-cholesterol levels in young and middle-aged men and women from 1960 to 2000. The trend indicates a gradual increase in the total cholesterol level in men and women in almost all generations over the last 40 years in Japan. The trend of the triglyceride level was somewhat different from that of the total cholesterol level. The triglyceride level in women, especially in young women, has tended to decrease over the last 30 years, while the level in men dramatically has increased in the last 10 years. The level of HDL-cholesterol increased both in men and women in the last 10 years.

Table 4 shows the age-specific means and standard deviations in serum LDL-cholesterol levels in all the participants as well as in men and women. LDL-cholesterol was measured directly, not by Friedewald equation. The mean LDL-cholesterol level in this survey was 118 mg/dl, which is almost the same as that in 1990. The age-specific mean LDL-cholesterol levels in men gradually increased from 101 mg/dl in the 0- to 19-year-old age

group to 125 mg/dl in the 50- to 59-year-old age group. The age-specific mean LDL-cholesterol level in women increased from 93 mg/dl in the 20- to 29-year-old age group to 135 mg/dl in the 60- to 69-year-old age group, and then decreased slightly thereafter.

In this survey we also measured RLP-cholesterol levels to assess the level of remnant particles. Table 5 shows the age-specific means and standard deviations in serum RLP-cholesterol levels in all the participants as well as in men and women. The mean RLP-cholesterol level in this survey was 4.5 mg/dl. The mean RLP-cholesterol level in men was significantly higher than that in women, and the age-specific mean RLP-cholesterol values were highest in 30- to 49-year-old age group in men as found in the triglyceride levels. The trends in age-specific means were similar to those of the triglyceride level. As expected, the RLP-cholesterol level correlated with the triglyceride level. (data not shown, $R = 0.878$, $p < 0.0001$).

Table 6 shows the age-specific means and standard deviations in plasma fasting glucose levels in all the par-

ticipants as well as in men and women. The mean fasting glucose level in this survey was 95 mg/dl. The mean glucose level was slightly higher in men than in women. The glucose level had a tendency to gradually increase

according to age in both men and women. HbA1c levels also had a tendency to gradually increase according to age in both men and women. However, the mean HbA1c levels in men and women were almost the same in each

Table 4. Serum HDL-cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	69	15	102	70	15	114	68	16
10-19	465	65	14	196	63	14	269	66	13
20-29	1,255	64	14	393	56	13	861	68	14
30-39	1,637	58	15	1,096	54	14	541	67	14
40-49	3,545	58	15	2,380	55	14	1,165	65	15
50-59	3,434	59	16	2,295	56	15	1,139	65	16
60-69	1,614	57	14	833	55	14	780	60	14
70-79	551	57	15	271	55	15	280	60	15
80-89	53	58	16	23	54	12	30	61	18
Total	12,770	59	15	7,589	55	14	5,179	65	15

Table 5. Serum LDL-cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	154	104	22	70	101	22	84	106	22
10-19	162	103	24	51	101	21	111	104	25
20-29	713	97	24	240	105	26	472	93	22
30-39	751	112	29	484	119	29	267	101	25
40-49	1,179	121	30	750	124	31	429	116	29
50-59	1,243	127	30	733	125	30	510	130	30
60-69	726	129	31	387	124	30	338	135	29
70-79	246	126	28	117	120	27	129	130	28
80-89	32	123	29	10	113	27	22	127	30
Total	5,206	118	31	2,842	121	30	2,362	115	31

Table 6. Serum RLP-cholesterol (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	265	1.9	0.6	70	2.0	0.6	84	1.9	0.7
10-19	161	2.5	1.2	51	2.5	1.1	110	2.5	1.3
20-29	712	3.5	3.1	240	4.5	4.2	471	2.9	2.2
30-39	762	5.0	6.0	493	6.2	6.9	269	2.7	2.6
40-49	1,211	5.2	7.7	774	6.2	8.7	437	3.2	4.9
50-59	1,322	4.8	6.2	791	5.2	7.4	531	4.3	3.7
60-69	662	4.6	7.3	363	5.1	9.4	298	4.1	3.5
70-79	206	4.1	3.7	98	4.3	4.4	108	4.0	2.9
80-89	28	3.7	2.5	8	2.4	1.6	20	4.2	2.7
Total	5,218	4.5	6.2	2,888	5.4	7.6	2,328	3.4	3.5

age group (Table 7). We also measured the serum insulin level in this survey. The serum insulin level was almost constant except in the 20- to 29-year-old age group and the mean insulin level in this survey was 7.3 μ U/ml (Table 8). The mean insulin level was slightly higher in

women than in men.

Finally, we determined uric acid levels. The mean uric acid level in this survey was 5.4 mg/dl. The mean uric acid level was significantly higher in men than in women (Table 9). Although the level of uric acid in men was al-

Table 7. Fasting glucose (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	158	88	7	74	88	7	84	87	6
10-19	170	85	6	57	87	7	113	85	6
20-29	996	88	16	340	89	20	655	87	13
30-39	1,281	92	15	886	93	14	395	90	18
40-49	2,865	95	18	2,018	97	19	847	90	12
50-59	2,909	99	20	2,002	101	20	907	94	19
60-69	1,489	98	21	752	102	25	737	95	15
70-79	531	98	16	257	99	16	274	97	15
80-89	52	103	27	22	104	36	30	102	20
Total	10,451	95	19	6,408	98	20	4,042	92	16

Table 8. HbA1c for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	155	4.7	0.2	72	4.7	0.2	83	4.7	0.2
10-19	171	4.7	0.3	58	4.7	0.3	113	4.6	0.3
20-29	1,147	4.6	0.4	374	4.6	0.6	772	4.6	0.3
30-39	1,261	4.7	0.5	871	4.7	0.5	390	4.7	0.4
40-49	2,536	4.9	0.6	1,844	4.9	0.7	692	4.8	0.5
50-59	2,676	5.1	0.7	1,879	5.1	0.7	797	5.1	0.7
60-69	1,141	5.2	0.8	614	5.3	0.9	527	5.2	0.6
70-79	443	5.3	0.7	209	5.3	0.7	234	5.4	0.8
80-89	52	5.4	0.8	22	5.4	1.0	30	5.3	0.6
Total	9,582	4.9	0.7	5,943	5.0	0.7	3,638	4.9	0.6

Table 9. Serum insulin (μ U/ml) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	216	6.7	5.2	102	6.5	6.2	114	6.9	4.1
10-19	463	7.1	7.2	196	6.1	5.1	267	7.9	8.3
20-29	1,171	11.4	12.9	382	9.9	10.6	788	12.1	13.8
30-39	1,410	8.2	9.0	942	8.3	8.9	468	8.0	9.2
40-49	2,734	6.7	5.5	1,877	6.7	5.0	857	6.6	6.4
50-59	2,636	6.4	5.6	1,731	6.0	4.2	905	7.3	7.5
60-69	1,118	6.1	5.3	589	5.9	5.3	528	6.4	5.2
70-79	440	6.2	14.8	211	5.2	5.6	229	7.1	19.7
80-89	53	5.8	4.6	23	6.1	5.8	30	5.6	3.6
Total	10,241	7.3	8.0	6,053	6.8	6.2	4,186	8.0	10.0

most constant in all age groups, the uric acid level in women gradually increased according to age (Table 10).

Discussion

In this survey we found that the mean total cholesterol level in the Japanese general population increased by 5 mg/dl in the last 10 years. This increase, however, is attributed to the increase in HDL-cholesterol, but not to LDL-cholesterol. The triglyceride level has also increased in the last 10 years. This increase is attributed to the increase in middle-aged men, making us anticipate a further increase in the incidence of hypertriglyceridemia in the future. The significance of triglyceride as a risk factor for CHD has recently obtained more attention world-wide, and its relationship with hyperinsulinemia and glucose intolerance is emphasized (15,16). In the analysis by Yamamoto *et al.* on the survey in 1990, they concluded that the most important cause of hypertriglyceridemia is overweight. According to the survey conducted by the Ministry of Health, Labor and Welfare, the body mass index increased from 1980 to 2000 only in men, but not women. Therefore, the increase in triglyceride levels in Japanese men correlates with the increase of obese men. RLP-cholesterol is implicated as an atherogenic lipoprotein and our data showed a correlation of RLP-cholesterol with the triglyceride level. Therefore, we also should pay attention to the level of RLP-cholesterol. The importance of RLP-cholesterol in the prevention of CHD, such as being a marker for postprandial hyperlipidemia, should be determined in a future trial. Thus to reduce the triglyceride levels, we need to encourage lifestyle changes, such as more exercise and consuming a traditional Japanese diet instead of a modern 'western' diet in the Japanese general population, especially amongst men. Unless we can change our lifestyle in Japan, more people will die from cardiovascular disease in the 21st century.

In spite of the dramatic increase in the triglyceride level in men in the last 10 years, the HDL-cholesterol level also increased in the last 10 years. This is a somewhat unexpected finding, because hypertriglyceridemia is generally associated with a decrease in the HDL-cholesterol level. In this survey we changed the method of measuring HDL-cholesterol from the precipitation method to the enzymatic method. However, we have confirmed that this change of method does not affect the level of HDL-cholesterol. Therefore, we have at the moment no idea why both triglyceride and HDL-cholesterol increased in the last 10 years only in men.

Guidelines for the proper management of risk factors, and for targeting the prevention and treatment of atherosclerotic disease, have been established in the United States (17,18) and Europe (19). The Japan Atherosclerosis Society also published a guideline for the management of hyperlipidemia for the prevention of CHD in 2002. As in the American and European guidelines, the Japanese guideline also emphasized the importance of the management of high risk patients, such as patients with multiple risk factors or diabetes as well as those with established CHD (20). Although our survey shows no increase in LDL-cholesterol level, the triglyceride level was significantly increased in the last 10 years. Especially, the mean triglyceride level of men in their 40s is 150 mg/dl, indicating about half of the participants have hypertriglyceridemia. Because hypertriglyceridemia is one criteria of metabolic syndrome, our result implies that the number of the patients with metabolic syndrome will increase in Japan. Therefore, in the next survey in 2010, we will investigate the incidence of the metabolic syndrome in the general Japanese population after establishing guidelines for the management of metabolic syndrome in Japan. This survey also indicates that we, as the members of the Japan Atherosclerosis Society, have to make every effort to call more clinical attention to the

Table 10. Serum uric acid (mg/dl) for each 10-year group in Japanese.

Age	All			Men			Women		
	N	Mean	S.D.	N	Mean	S.D.	N	Mean	S.D.
0-9	0	-	-	0	-	-	0	-	-
10-19	3	6.7	0.7	3	6.7	0.7	0	-	-
20-29	410	4.7	1.4	137	6.1	1.3	273	4.0	0.8
30-39	927	5.6	1.5	714	6.0	1.3	213	4.0	0.9
40-49	2,425	5.5	1.5	1,763	6.1	1.3	662	4.1	0.9
50-59	2,459	5.5	1.4	1,762	6.0	1.3	697	4.3	0.9
60-69	1,141	5.2	1.4	618	5.8	1.3	523	4.5	1.0
70-79	296	5.1	1.5	152	5.8	1.4	144	4.4	1.1
80-89	25	4.9	1.6	8	5.0	0.9	17	4.9	1.8
Total	7,686	5.4	1.4	5,157	6.0	1.3	2,529	4.3	1.0

management of dyslipidemia for prevention of CHD.

Currently approximately 4 million people are taking statins for hyperlipidemia in Japan. In this survey about 5% of the participants were taking lipid-lowering drugs, most of which are supposed to be statins. The mean total cholesterol level of the participants without lipid lowering drugs was 209 mg/dl, which is slightly higher than the mean total cholesterol levels of all the participants. In this sense, the participants in this survey represent the general population in Japan. Use of lipid-lowering drugs such as statins would be more important for the treatment of high risk patients to prevent CHD.

In 2000, another survey was conducted by the Ministry of Health, Labor, and Welfare. In this study, more subjects were selected from rural, agricultural, and mountainous areas, and the results showed no rise in serum cholesterol in the last 10 years (from 1990 to 2000). In this study carried out by the members of the Japan Atherosclerosis Society, more subjects from urban areas were included. In both studies, the cholesterol levels were significantly lower in the agricultural and mountainous districts than in the districts including large cities like Tokyo and Osaka in 1980. In 1990, the difference in serum cholesterol levels was no longer significant between urban, rural, and mountain village areas. Therefore, it is not clear why these studies show a different trend in the cholesterol level. However, Kuzuya et al also found an increase in total cholesterol levels from 1989 to 1998 in Aichi Prefecture in the central region of Japan (21).

In this survey we also determined fasting glucose, insulin, and HbA1c levels of approximately 10,000 participants. We think that this is the largest survey of glucose metabolism in Japan. Our data indicate that the glucose and HbA1c levels gradually increased according to age in both sexes. However, the plasma insulin levels are almost constant in all age groups. We also showed that the uric acid level was significantly higher in men than in women. This is consistent with the data that the incidence of hyperuricemia and gout is higher in males than in females. Alcohol consumption would contribute to the higher level of uric acid in men. According to the database from the Ministry of Health, Labor, and Welfare (<http://www.mhlw.go.jp/toukei/>), the incidence of hyperuricemia in men and women is increasing in Japan. Because hyperuricemia is related to obesity, hypertension, and insulin resistance, and eventually to the incidence of CHD, controlling the uric acid level would be important for the prevention of CHD in Japan.

Thus this report tells us the importance of the prevention and treatment of hyperlipidemia for the prevention of CHD in Japan. We need to establish guidelines for lifestyle change to prevent the further increase of dyslipidemia in the future.

Acknowledgements: This study was supported by re-

search grants for health sciences from the Japanese Ministry of Health and a grant from the Japan Atherosclerosis Society. We also thank Osaka Pharmaceutical Manufactures Association for supporting our work. We also thank Nobuo Shirahashi (Osaka City University Medical School) for his advice on statistical analysis.

Appendix

Research Group on Serum Lipid Survey 2000 in Japan

Chairman: Toru Kita, Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine

Principal investigators: Akira Yamamoto, National Cardiovascular Center, Osaka, Japan.

Yuji Matsuzawa, Department of Internal Medicine, Osaka University, Osaka, Japan.

Yasushi Saito, Department of Internal Medicine, Chiba University, Chiba, Japan.

Shin-ichi Oikawa, Department of Internal Medicine, Nippon Medical School, Tokyo, Japan.

Noriaki Nakaya, Fussa Hospital, Tokyo, Japan.

Jun Sasaki, International University of Health and Welfare, Fukuoka, Japan.

Hiroshi Mabuchi, Department of Internal Medicine, Kanazawa University, Ishikawa, Japan.

Nobuhiro Yamada, Department of Internal Medicine, Tsukuba University, Ibaraki, Japan.

Hiroshige Itakura, Ibaraki Christian University, Ibaraki, Japan.

Yuichi Ishikawa, Faculty of Health Sciences, Kobe University, Hyogo, Japan.

Tadayoshi Ouchi, Department of Geriatric Medicine, University of Tokyo, Tokyo, Japan

Hiroshi Horibe, Keisen Clinic, Hyogo, Japan.

Tamio Teramoto, Department of Internal Medicine, Teikyo University, Tokyo, Japan.

Hidenori Arai, Department of Geriatric Medicine, Kyoto University, Kyoto, Japan

Co-principal investigators (institutes): Kazuaki Shimamoto (Sapporo Medical University), Takao Koike (Hokkaido University), Akizuki Morikawa (Asahikawa Red Cross Hospital), Makoto Tominaga (Yamagata University), Toshihiro Suda (Hiroshima University), Nobuyuki Sugawara (Mizusawa general hospital), Hideo Hamaguchi (Tsukuba University), Saburo Hori (St. Luke's International Hospital), Hideaki Bujo (Chiba University), Fumitaka Osuzu (National Defense Medical College), Koichi Kozaki (Tokyo University), Toshiro Murase (Toranomon Hospital), Katsuji Senda (Hamamatsu Social Insurance Hospital), Tomoo Okada (Nihon University), Akihiro Inazu and Toshinori Higashikata (Kanazawa University), Isamu Miyamori and Koji Oida (University of Fukui Faculty of Medical Sciences), Susumu Miyamoto (Himi Municipal Hospital), Akihisa Iguchi (Nagoya University), Nagahiko Sakuma (Nagoya City University), Taku Yamamura (National Cardiovascular Center), Shizuya Yamashita (Osaka University), Toshiko Kawakita and Atsuhiko Sato (Kyoto Center for preventive medicine), Mitsuhiro Yokoyama (Kobe University), Genshi Egusa (Egusa clinic), Masunori Matsuzaki (Yamaguchi University), Masayoshi Kihata (Chugoku Central Hospital), Hitoshi Kukida (Udazima Social Insurance Hospital), Shoji Kohori (National Hospital organization Kumamoto Medical Center), Kyosuke Yamamoto (Saga University Faculty of Medicine), Sadatoshi Birou (Kagosima University), Takao Ota (University of Ryukyus), Masato Ageta (Miyazaki Prefectural Nichinan Hospital)

References

- (1) Anderson KM, Castelli WP, and Levy D: Cholesterol and mortality. 30 years of follow-up from the Framingham study. *JAMA*, 1987; 257: 2176–2180
- (2) Stamler J, Wentworth D, and Neaton JD: Is relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). *JAMA*, 1986; 256: 2823–2828
- (3) The Lipid Research Clinics Coronary Primary Prevention Trial results. I. Reduction in incidence of coronary heart disease. *JAMA*, 1984; 251: 351–364
- (4) Holme I: Cholesterol reduction and its impact on coronary artery disease and total mortality. *Am J Cardiol*, 1995; 76: 10C–17C
- (5) Ericsson CG, Hamsten A, Nilsson J, Grip L, Svane B, and de Faire U: Angiographic assessment of effects of bezafibrate on progression of coronary artery disease in young male postinfarction patients. *Lancet*, 1996; 347: 849–853
- (6) Shepherd J, Cobbe SM, Ford I, Isles CG, Lorimer AR, MacFarlane PW, McKillop JH, and Packard CJ: Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. *N Engl J Med*, 1995; 333: 1301–1307
- (7) Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, and Braunwald E: The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and Recurrent Events Trial investigators. *N Engl J Med*, 1996; 335: 1001–1009
- (8) Levy RI and Moskowitz J: Cardiovascular research: decades of progress, a decade of promise. *Science*, 1982; 217: 121–129
- (9) Vartiainen E, Puska P, Pekkanen J, Tuomilehto J, and Jousilahti P: Changes in risk factors explain changes in mortality from ischaemic heart disease in Finland. *BMJ*, 1994; 309: 23–27
- (10) Marmot MG, Syme SL, Kagan A, Kato H, Cohen JB, and Belsky J: Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan, Hawaii and California: prevalence of coronary and hypertensive heart disease and associated risk factors. *Am J Epidemiol*, 1975; 102: 514–525
- (11) Johnson CL, Rifkind BM, Sempos CT, Carroll MD, Bachorik PS, Briefel RR, Gordon DJ, Burt VL, Brown CD, Lippel K, Kajiyama G, Kokubu T, Uzawa H, Mimura G, and Shimada O: Declining serum total cholesterol levels among US adults. The National Health and Nutrition Examination Surveys. *JAMA*, 1993; 269: 3002–3008
- (12) Konishi T: Total Serum Cholesterol Levels in Normal Subjects in Japan. *Jpn Circ J*, 1965; 29: 505–510
- (13) Sekimoto H, Goto Y, Goto Y, Naito C, Yasugi T, Okido M, Kuzuya F, Takeda R, Yamamoto A, and Fukuzaki H: Changes of serum total cholesterol and triglyceride levels in normal subjects in Japan in the past twenty years. Research committee on familial hyperlipidemia in Japan. *Jpn Circ J*, 1983; 47: 1351–1358
- (14) Current state of and recent trends in serum lipid levels in the general Japanese population. Research Committee on Serum Lipid Level Survey 1990 in Japan. *J Atheroscler Thromb*, 1996; 2: 122–132
- (15) Gaziano JM, Hennekens CH, O'Donnell CJ, Breslow JL, and Buring JE: Fasting triglycerides, high-density lipoprotein, and risk of myocardial infarction. *Circulation*, 1997; 96: 2520–2525
- (16) Yamamoto A, Yamamura T, Kawaguchi A, Kameda K, and Matsuzawa Y: Triglyceride and glucose intolerance as a risk factor for coronary heart disease. *Cardiology*, 1991; 78: 185–193
- (17) Lauer MS and Fontanarosa PB: Updated guidelines for cholesterol management. *JAMA*, 2001; 285: 2508–2509
- (18) Grundy SM: United States Cholesterol Guidelines 2001: expanded scope of intensive low-density lipoprotein-lowering therapy. *Am J Cardiol*, 2001; 88: 23J–27J
- (19) Wood D, De Backer G, Faergeman O, Graham I, Mancia G, and Pyorala K: Prevention of coronary heart disease in clinical practice: recommendations of the Second Joint Task Force of European and other Societies on Coronary Prevention. *Atherosclerosis*, 1998; 140: 199–270
- (20) Hata Y, Mabuchi H, Saito Y, Itakura H, Egusa G, Ito H, Teramoto T, Tsushima M, Tada N, Oikawa S, Yamada N, Yamashita S, Sakuma N, and Sasaki J: Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese adults. *J Atheroscler Thromb*, 2002; 9: 1–27
- (21) Kuzuya M, Ando F, Iguchi A, and Shimokata H: Changes in serum lipid levels during a 10 year period in a large Japanese population. A cross-sectional and longitudinal study. *Atherosclerosis*, 2002; 163: 313–320