Table 6. Mutations in the apoC-II gene in Japanese patients with apoC-II deficiency.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Author	References
intron 2	93+1 G→C	Tokyo	G→C at 93+1	5' splice signal	Okubo M	Atherosclerosis 130: 153–160, 1997
exon 3	108delC	Japan	deletion of C at 108	frame shift	Xiong WJ	Am J Hum Genet 48: 383–389, 1991
exon 3	W26R	Wakayama	T→C at 180	Trp→Arg at 26	Inadera H	Biochem Biophys Res Commun 193: 1174–1183, 1993

Table 7. Mutation in the hepatic lipase gene in a Japanese subject.

Position	Mutation	Nucleotide Change	Effect on Coding Sequence	Author	Reference
exon 2	C53G	T→G at 230	Cys→Gly at 53	Ikeda Y	Atherosclerosis XI: 777–788, 1998

Table 8. Mutations in the apolipoprotein E gene in Japanese subjects.

Exon	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
3	E3K	E-5	G→A at 28	Glu→Lys at 3	E-5	Tajima S	J Biochem (Tokyo) 104: 48–52, 1988
3	R25C	E2 Kyoto	C→T at 94	Arg→Cys at 25	LPG	Moriyama K	Kidney Int 56: 421–427, 1999
3	Q46H[§]		G→C at 159	Gln→His at 46	NR	Hisaki M	Domyakokuka 23: 891, 1996
4	135-142 ins[†]	E-5	insertion of 24 bp from codon 135	duplication of 135-142	E-5	Yamanouchi Y	J Hum Genet 46: 633–639, 2001
4	141-143 del[†]	E-Tokyo	deletion of 9 bp from codon 141	deletion of 141-143	LPG	Konishi K	Nephron 83: 214–218, 1999
4	141-146 del[†]	E-Maebashi	deletion of 18 bp from codon 141	deletion of 141-146	LPG	Ogawa T	Pediatr Nephrol 14: 149–151, 2000
4	R142S[†§]	E-1		Arg→Ser at 142	type III (d)	Sakuma N	Domyakokuka 29:252, 2001
4	K146E	E-1	A→G at 457	Lys→Glu at 146	type III (d)	Moriyama K	Biochim Biophys Acta 1128: 58-64, 1992
4	R145H	E-2 Kochi	G→A at 465	Arg→His at 145	type III (d)	Suehiro	—
4	156-173 del[†]	E-1	deletion of 54 bp from codon 156	deletion of Q156-G173	LPG	Ando M	Kidney Int 56: 1317–1323, 1999
4	Q187E	E2 Toranomon	C→G at codon 187	Gln→Glu at 187	type III (d)	Okubo M	Atherosclerosis 140: 187–190, 1998
4	A216V[§]	E3 Nananuma	C→T at 668	Ala→Val at 216	type III (d)	Matsunaga A	Domyakukoka 23: 846, 1996
4	R224Q	E2 Fukuoka	C→A at 692	Arg→Gln at 224	type III (d)	Moriyama K	Biochim Biophys Acta 1301: 185–190, 1989
4	E244K, E245K	E7 Suita	G→A at 751, 754	Glu→Lys at 244, 245	E-7	Tajima S	J Biochem (Tokyo) 105: 249–253, 1989
4	R145P	E2 Sendai	G→C at 445	Arg→Pro at 145	LPG	Oikawa S	J Am Soc Nephrol 8: 820–823, 1997

(d): dominant, LPG: lipoprotein glomerulopathy.
[†]: Mutation reported after the closing of registration to the Research Committee in 1998.
[§]: Mutation reported in an abstract form in Japanese.

Sterol storage disorders (cerebrotendinous xanthomatosis and sitosterolemia)

Sterol storage disorders are characterized by accumulation of plant sterols and massive xanthoma similar to those in homozygous FH, such as cerebrotendinous xanthomatosis (CTX, accumulation of cholestanol) and sitosterolemia (accumulation of sitosterol) (33). These disorders do not belong to primary hyperlipidemia but are recognized as related disorders, and one such patient has been registered with the Research Committee (2). CTX is caused by mutations in sterol 27 hydroxylase (Cyp27) (33), and sitosterolemia by mutations in the ATP-binding cassette transporter G5 or G8 (34). Some mutations have been identified in Japanese patients with sterol storage disorders (Table 14).

Discussion

In the present report, 190 mutations in 15 genes were described. The numbers of the described mutations were

Table 9. Mutations in the cholesteryl ester transfer protein gene in Japanese subjects.

Position	Mutation	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
promoter	(– 69)G→A†	G→A at (– 69)	promoter	deficiency	Nagano M	Arterioscler Thromb Vasc Biol 21: 985–990, 2001
exon 5	L151P†	T→C at codon 151	Leu→Pro at 151	deficiency	Nagano M	J Lipid Res 43: 1011–1018, 2002
exon 6	G181X	G→T at 722	Gly→Stop at 181	deficiency	Arai T	J Lipid Res 37: 2145–2154, 1996
exon 9	R282C†	C→T at codon 282	Arg→Cys at 282	deficiency	Nagano M	J Lipid Res 43: 1011–1018, 2002
exon 10	Q309X	C→T at 1106	Gln→Stop at 309	deficiency	Gotoda T	Biochem Biophys Res Commun 194: 519–524, 1993
intron 10	1111 + 2 T→G	T→G at 1111+2	5' splice signal	deficiency	Sakai N	J Lipid Res 37: 2065–2073, 1996
intron 14	1451 + 1 G→A	G→A at 1451+1	5' splice signal	deficiency	Brown ML	Nature 342: 448–451, 1989
intron 14	1451 + 3 ins T§	insertion of T at 1451+3	5' splice signal	deficiency	Inazu A	J Jpn Atheroscler Soc 21: 73, 1993
exon 15	D442G	A→G at 1506	Asp→Gly at 442	deficiency	Takahashi K	J Clin Invest 92: 2060–2064, 1993

†: Mutation reported after the closing of registration to the Research Committee in 1998.
§: Mutation reported in an abstract form in Japanese.

Table 10. Mutations in the lecithin:cholesterol acyltransferase gene in Japanese subjects.

Exon	Mutation	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
1	N5I	A→T at 15	Asn→Ile at 5	deficiency	Okubo M	Int J Clin Lab Res 26: 250–254, 1996
1	124insC	insertion of C at 124	frame shift after Pro 10	deficiency	Bujo H	Biochem Biophys Res Commun 181: 933–940, 1991
2	G30S§	G→T at 188	Gly→Ser at 30	deficiency	Yo S	J Jpn Atheroscler Soc 23: 179, 1995
3	R99C†§	C→T at codon 99	Arg→Cys at 99	FED	Shinoda Y	J Jpn Atheroscler Soc 24: 690, 1997
4	T123I§	C→T at 418	Thr→Ile at 123	FED	Nishioka K	J Jpn Atheroscler Soc 23: 179, 1995
4	R140C§	C→T at 518	Arg→Cys at 140	deficiency	Aragane K	J Jpn Atheroscler Soc 23: 847, 1996
4	G141ins	insertion of GGC from 521	insertion of Gly 141	deficiency	Gotoda T	Lancet 388: 778–781, 1991
6	N228K	C→A at 784	Asn→Lys at 228	deficiency	Gotoda T	Lancet 388: 778–781, 1991
6	P250R§	C→G at 852	Pro→Arg at 250	deficiency	Aragane K	J Jpn Atheroscler Soc 23: 180, 1995
6	873delG	deletion of G at 873	frame shift after Val 264	deficiency	Moriyama K	J Lipid Res 36: 2329–2343, 1995
6	M293I	G→A at 979	Met→Ile at 293	deficiency	Maeda E	Biochem Biophys Res Commun 178: 460–466, 1991
6	T321M	C→T at 1065	Thr→Met at 321	deficiency	—	—
6	G334S	G→A at 1130	Gly→Ser at 344	deficiency	Moriyama K	J Lipid Res 36: 2329–2343, 1995

†: Mutation reported after the closing of registration to the Research Committee in 1998.
§: Mutation reported in an abstract form in Japanese.
FED : fish eye disease.

larger than those in the annual reports of the Research Committee published in 1996–1998 (2, 35, 36), because mutations reported in academic meetings and/or those published in journals until 2003 were added to the database of the Research Committee. Although some genetic polymorphisms might be included in these mutations, most mutations are thought to be responsible for the disorders.

Table 11. Mutations in the apolipoprotein A-I gene in Japanese subjects.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	References
promoter	– 27A→C		A→C at (-27)	TATA box	deficiency	Matsunaga A	Arterioscler Thromb Vasc Biol 19: 348–355, 1999"
exon 3	78delA[§]		deletion of A at 693 (codon -5)	frame shift after Arg (– 5)	deficiency	Itoh T	Domyakukoka 24: 287, 1996
exon 3	105insC	Tsukuba	insertion of C at 105	frame shift after Glu5	deficiency	Nakata K	Biochem Biophys Res Commun 196: 950–955, 1991
exon 3	W8X		G→A at 729	Trp→Stop at 8	deficiency	Takata K	Arterioscler Thromb Vasc Biol 15: 1866–1874,1995
exon 3	D13Y	Yame	G→T at 743	Asp→Tyr at 13		Takada Y	J Lipid Res 32: 275–280, 1991
exon 3	A37T		G→A at 815	Ala→Thr at 37		Araki K	Biochim Biophys Acta 1214: 272–278, 1994
exon 4	D51V	Kaho	A→T at 1447	Asp→Val at 51		Moriyama K	J Atheroscler Thromb 3: 12–16, 1996
exon 4	335ins23bp	Sasebo	insertion of 23 bp from 1779	frame shift after Gly 81	deficiency	Moriyama K	Arterioscler Thromb Vasc Biol 16: 1416–1423, 1996
exon 4	Q84X		C→T at 1545	Gln→Stop at 84	deficiency	Matsunaga T	Proc Natl Acad Sci USA 88: 2793–2797, 1991
exon 4	A95D	Hita	C→A at 1579	Ala→Asp at 95		Araki K	Biochim Biophys Acta 1214: 272–278, 1994
exon 4	Y100H	Karatsu	T→C at 1593	Tyr→His at 100		Moriyama K	Clin Genet 49: 79–84, 1996
exon 4	K106 del	Nanakuma	deletion of AAG at 1601–1606	deletion of Lys 106 or 107		Moriyama K	Atheroscler Thromb 3: 12–16, 1996
exon 4	W108R	Tsushima	T→C at 1617	Trp→Arg at 108		Araki K	Biochim Biophys Acta 1214: 272–278, 1994
exon 4	E110K	Fukuoka	G→A at 1623	Glu→Lys at 110		Takada Y	Biochim Biophys Acta 1043: 169–176, 1990
exon 4	V156E	Oita	T→A at 1762	Val→Glu at 156	deficiency	Huang W	Arterioscler Thromb Vasc Biol 18: 389–396, 1998
exon 4	H162Q	Kurume	T→G at 1781	His→Gln at 162		Moriyama K	Clin Genet 49: 79–84, 1996
exon 4	2100delC[†]		deletion of C at codon 184	frame shift after Glu 183		Yokota H	Atherosclerosis 162: 399–407, 2002
exon 4	E235 del	Nichinan	deletion of GAG at 1995–2000	deletion of Gln 235	low HDL	Han H	Arterioscler Thromb Vasc Biol 19: 1447–1455, 1999

[†]: Mutation reported after the closing of registration to the Research Committee in 1998.
[§]: Mutation reported in an abstract form in Japanese.

Table 12. Mutation in the apolipoprotein A-II gene in a Japanese subject.

Position	Mutation	Name	Nucleotide Change	Effect on Coding Sequence	Class	Author	Reference
intron 3	243 + 1 G→A	Hiroshima	G→A at 243 + 1	5' splice signal	deficiency	Deeb SS	Am J Hum Genet 46: 822–827, 1990

Table 13. Mutations in ATP-binding cassette transporter-1 gene in Japanese patients.

Disorder	Mutation	Nucleotide Change	Effect on Coding	Author Sequence	References
FHD	A255T	G→A at 1158	Ala→Thr at 255	Nishida Y	Biochem Biophys Res Commun 290: 713–721, 2002
TD	N935H	A→C at 3198	Asn→His at 935	Guo Z	J Hum Genet 47: 325–329, 2002
TD	N935S	A→G at 3199	Asn→Ser at 935	Guo Z	J Hum Genet 47: 325–329, 2002
FHD	3787del4bp	deletion of CGCC from 3787	premature stop at 1224	Huang W	Biochim Biophys Acta 1537: 71–78, 2001
TD	D1229N	G→A at 3805	Asp→Asn at 1229	Huang W	Biochim Biophys Acta 1537: 71–78, 2001
FHD	N1611D	A→G at 5226	Asn→Asp at 1611	Nishida Y	Biochem Biophys Res Commun 290: 713–721, 2002
TD	R1680W		Arg→Trp at 1680	Ishii J	J Hum Genet 47: 366–369, 2002
FHD	R1851X	C→T at 5946	Arg→Stop at 1851	Nishida Y	Biochem Biophys Res Commun 290: 713–721, 2002
TD	R2021W	C→T at 6181	Arg→Trp at 2021	Huang W	Biochim Biophys Acta 1537: 71–78, 2001
TD	In12–In14 del	deletion of 1221 bp	deletion of exons 13, 14	Guo Z	J Hum Genet 47: 325–329, 2002
TD	In16–In31 del	deletion of 19.9 kb	deletion of exons 17–31	Guo Z	J Hum Genet 47: 325–329, 2002

All mutations have been reported after the closing of registration to the Research Committee.
FHD: familial high-density lipoprotein deficiency, TD: Tangier disease.

Table 14. Mutations in Japanese patients with sterol strage disorders.

Disorder	Gene	Mutation	Nucleotide	Effect on Coding Change	Author Sequence	References
CTX	Cyp27	R104W†	C→T at codon 104	Arg→Trp at 104	Nakashima N	J Lipid Res 35: 663–668, 1994
CTX	Cyp27	E162X	G→T at codon 162	Glu→Stop at 162	Wakamatsu N	J Neurol Neurosurg Psychiatry 67: 195–198, 1999"
CTX	Cyp27	R362H	G→A at codon 362	Arg→His at 362	Chen W	Biochim Biophys Acta 1317: 119-126, 1996
CTX	Cyp27	P368R	G→C at codon 368	Pro→Arg at 368	Okuyama E	J Lipid Res 37: 631–639, 1996
CTX	Cyp27	R372Q	G→A at codon 372	Arg→Gln at 372	Chen W	J Lipid Res 38: 870–879, 1997
CTX	Cyp27	intron 7+1G→A	G→A at intron 7+1	5' splice signal	Shiga K	J Neurol Neurosurg Psychiatry 67: 675–677, 1999
CTX	Cyp27	R441W	C→T at codon 441	Arg→Trp at codon 441	Kim KS	J Lipid Res 35: 1031–1039, 1994
CTX	Cyp27	R441Q	G→A at codon 441	Arg→Gln at codon 441	Kim KS	J Lipid Res 35: 1031–1039, 1994
Sitosterolemia	ABCG5	R419H	G→A at 1396	Arg→His at 419	Lee MH	Nat Genet 27: 79–83, 2001
Sitosterolemia	ABCG5	exon 3 del	deletion of exon 3		Lu K	Am J Hum Genet 69: 278–290, 2001
Sitosterolemia	ABCG5	R408X	C→T at 1362	Arg→Stop at 408	Lu K	Am J Hum Genet 69: 278–290, 2001
Sitosterolemia	ABCG5	R389H	G→A at 1306	Arg→His at 389	Lu K	Am J Hum Genet 69:278–290, 2001
Sitosterolemia	ABCG5	R550S	A→C at 1791	Arg→Ser at 550	Lu K	Am J Hum Genet 69:278–290, 2001

ABCG5: ATP-binding cassette transporter subfamily G member 5, CTX: cerebrotendinous xanthomatosis, CYP27: sterol 27-hydroxylase.
†: Mutation resistered to the Research Committee

So-called "common mutations" have been described in Japanese patients with FH, CETP deficiency and LPL deficiency. It has been reported that in patients with CETP deficiency (activity) < 75% of control), 65.7% had one of the 2 common mutations (1,451 + 1G > A and D442G) or both, and that in patients with marked HALP (HDL-cholesterol > 100 mg/dl), 57.5% had at least one of these common mutations (25), suggesting that genetic diagnosis could be feasible in CETP deficiency. On the other hand, prevalence of common mutations in the LDLR gene is relatively low (3, 4), indicating that genetic diagnosis of patients with FH may not be feasible.

FCHL is speculated to be the most prevalent disorder in genetic hyperlipidemia, however, the molecular mechanism has not been clarified. Similarly, the cause of FH-like syndrome, characterized by hypercholesterolemia, premature atherosclerosis and tendon xanthoma without reduction in LDLR activity, is also unknown. Further investigation should be performed to elucidate the molecular mechanisms of such disorders.

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Journal of Atherosclerosis and Thrombosis Vol. 11, No. 3
Original Articles

Clinical Features of Familial Hypercholesterolemia in Japan in a Database from 1996–1998 by the Research Committee of the Ministry of Health, Labour and Welfare of Japan

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Familial hypercholesterolemia (FH) is one of the most common primary hyperlipidemias, characterized by a heterozygous or homozygous phenotype for a severe serum low-density lipoprotein (LDL)-cholesterol level and advanced atherosclerosis, leading to coronary artery diseases (CAD). Various kinds of mutations in the LDL receptor gene responsible for the genetic disease have been identified since the human LDL receptor gene has been identified. In this study, the clinical features of FH were investigated using a database based on nationwide surveillance for primary hyperlipidemia and related disorders by the Research Committee on Primary Hyperlipidemia. The clinical features and the frequencies of accompanying vascular diseases in 660 cases of FH homozygotes and heterozygotes showed that the incidence of CAD was negatively associated with plasma HDL-cholesterol levels, but not with plasma LDL-cholesterol levels, in 641 FH heterozygotes. Risk factor analyses revealed that hypertension, male, smoking, low HDL-cholesterol levels, age > 50 y, diabetes mellitus, and hypertriglyceridemia were positive risk factors for CAD. The summarized gene analysis in FH heterozygotes showed at least 4 mutations in the LDL receptor gene as common mutations in Japan. The average serum lipids and frequency of CAD based on each common mutation suggested that their clinical features are in part determined by responsive mutations in the LDL receptor gene. *J Atheroscler Thromb, 2004; 11: 146–151.*

Key words: Database, LDL receptor, Mutation, Heterozygote

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Introduction

Various gene abnormalities causing primary hyperlipidemia have been identified in our country. Surveillance for the current gene analysis has been started by the Research Committee on Primary Hyperlipidemia (Chairperson: Professor Toru Kita, Kyoto University), organized

by the Ministry of Health, Labour and Welfare in 1996 (1).

Familial hypercholesterolemia (FH) is one of most frequent primary hyperlipidemias. The underlying gene abnormalities have been identified on the low-density lipoprotein (LDL) receptor gene locus. A previous investigation based on the database created by the Research Committee on Primary Hyperlipidemia reported that approximately 80 mutations have been identified in various regions in the LDL receptor gene in Japan, and some of them may be more prevalent than others, comprising the so-called "common mutations" (2–4). Furthermore, the possibility of different responses of mutations against cholesterol-lowering therapy was suggested in FH (5). In this study, the clinical features of FH in Japan were investigated using the above database for mutations in Japanese patients with primary hyperlipidemia and related disorders. Additionally, the clinical phenotypes in FH with the common mutations were studied using three databases based on different areas in Japan.

Methods

The database for mutations in Japanese patients with primary hyperlipidemia and related disorders by the Research Committee on Primary Hyperlipidemia organized by the Ministry of Health, Labour and Welfare was used for the analysis in this study (2–4). The analyses of phenotypes for the common mutations were performed based on the databases provided by Drs. Maruyama and Yamashita (Osaka University), Drs. Kajinami and Mabuchi (Kanazawa University) and Drs. Bujo and Saito (Chiba University). The results are shown as mean ± SD for each index. Comparison of data was performed using the Student's *t*-test and/or ANOVA, and a value of $p < 0.05$ was considered significant. Logistic analyses were performed to obtain odds ratios for coronary artery disease (CAD).

Results

Clinical profile of familial hypercholesterolemia in Japan

The clinical features of 660 registered cases of FH (19 cases of homozygotes including two compound heterozygotes, and 641 cases of heterozygotes) were analyzed (Table 1). Both in homozygotes and heterozygotes, more women were registered than men (63% and 54%, respectively). The average age of cases for homozygotes and heterozygotes was 26 y (4–49 y) and 51 y (1–85 y), respectively. The average serum total cholesterol (TC) and LDL-cholesterol (LDL-C) of homozygous FH was 686 mg/dl and 582 mg/dl, respectively. The average serum TC and LDL-C of heterozygous FH was 324 mg/dl and 248 mg/dl, respectively. The proportion of type IIb hyperlipidemia in the WHO classification, which indicates hypertriglyceridemia as well as hypercholesterolemia, was 22% for homozygotes and 23% for heterozygotes. The serum high density lipoprotein-cholesterol (HDL-C) level was 35 mg/dl in homozygotes.

The occurrence of arcus cornea was 85% in homozygotes and 38% in heterozygotes. Tendon xanthoma was observed all in homozygotes and in 82% of heterozygotes. The occurrences of skin xanthoma were not as frequent as those of tendon xanthoma: 13% in homozygotes and 8% in heterozygotes. The occurrences of xanthelasma were 31% in homozygotes and 9% in heterozygotes. There was a history of CAD in 73% of homozygotes and 24% of heterozygotes. Other atherosclerotic diseases, cerebrovascular diseases (CVD) and arteriosclerosis obliterans (ASO), were not observed in homozygotes, and observed at 3% and 2% in heterozygotes, respectively.

Serum lipids and CAD in heterozygous FH

In heterozygous FH, the clinical profiles of the 296 male cases were compared with those of the 345 female cases (Table 2). The average age of the male and female cases was 49 y and 54y, respectively. The average body mass index (BMI) of the male and female cases was 23.5 kg/m^2 and 22.6 kg/m^2, respectively. The average serum cholesterol levels of heterozygous FH were not significantly different between the males and females. The TG and

Table 1. Clinical features of FH in Japan.

	Homozygotes	Heterozygotes
n	19 (2:comp.hetero)	641
Sex (M/F)	7/12	296/345
Age (y)	26 ± 14 (19)	51 ± 15 (548)
BMI (kg/m^2)	17.2 ± 3.3 (8)	23.0 ± 3.3 (566)
TC (mg/dl)	686 ± 250 (19)	324 ± 71 (568)
LDL-C (mg/dl)	582 ± 132 (15)	248 ± 67 (512)
TG (mg/dl)	157 ± 117 (17)	132 ± 85 (551)
HDL-C (mg/dl)	35 ± 21 (16)	47 ± 14 (517)
IIa/IIb	14/4	430/130
Arcus cornea (%)	85% (13)	38% (498)
Xanthoma (%)	100% (16)	87% (556)
Xanthelasma (%)	31% (16)	9% (556)
Skin (%)	13% (16)	8% (556)
Tendon (%)	100% (16)	82% (556)
CAD (%)	73% (15)	24% (538)
CVA (%)	0% (3)	3% (477)
ASO (%)	0% (3)	2% (475)

Mean ± SD, Numbers in parentheses show the cases for analysis.

HDL-C levels were significantly higher in the males than in the females; the proportion of type IIb hyperlipidemia was higher in the males than in the females. There were no significant differences between the males and females in the occurrence of arcus cornea, skin xanthoma, or tendon xanthoma.

Figure 1 shows the relationships between serum lipids and occurrence of CAD in heterozygous FH. There was no obvious relationship between TC, LDL-C or triglyceride (TG), and CAD occurrence. However, the occurrence was most frequent in cases with LDL-C of more than 320 mg/dl or TG of more than 250 mg/dl. Notably, there was a clear negative tendency in the relationship between CAD occurrence and HDL-C; an increased HDL-C level was associated with a decreased CAD occurrence, and the occurrence at an HDL-C level of more than 60 mg/dl was reduced to about one-fifth of that at less than 35 mg/dl.

Males with FH showed a significantly higher occurrence of CAD than females (Fig. 2). There was no significant difference in CVD occurrence. Males with FH showed a higher tendency of occurrence of ASO than females, although not significant by. Further analysis of the heterozygotes was performed separately for type IIa and IIb hyperlipidemia, in order to determine the significance of accompanying hypertriglyceridemia for the occurrence of CAD (Fig. 3). There was no significant difference in CAD occurrence between the two types in the males. In the females, the cases with type IIb showed an obviously increased CAD occurrence compared to the cases with

Table 2. Clinical features of FH heterozygotes in Japan.

	Males	Females
n	296	345
Age (y)	49 ± 13 (244)	54 ± 16 (304)
BMI (kg/m²)	23.5 ± 3.3 (260)	22.6 ± 3.2 (306)
TC (mg/dl)	324 ± 70 (261)	325 ± 72 (307)
LDL-C (mg/dl)	249 ± 132 (261)	248 ± 69 (279)
TG (mg/dl)	153 ± 99 (256)	114 ± 65 (295)**
HDL-C (mg/dl)	42 ± 12 (237)	50 ± 15 (280)**
IIa/IIb	179/81	230/49*
Arcus cornea (%)	40% (229)	36% (269)
Xanthoma (%)	88% (254)	88% (302)
Xanthelasma (%)	6% (254)	10% (302)
Skin (%)	11% (254)	10% (302)
Tendon (%)	82% (254)	83% (302)

Mean ± SD, Numbers in parentheseis show the cases for analysis.
**: $p < 0.001$, *: $p < 0.0001$, vs male

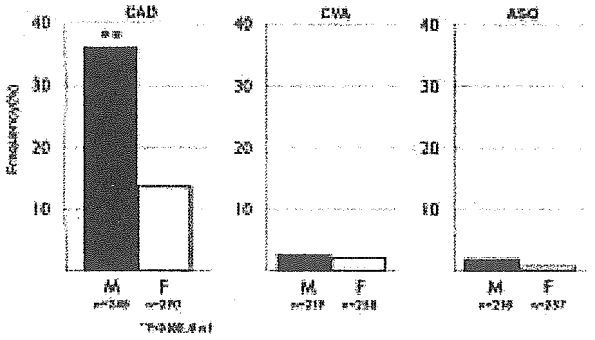

Fig. 2. Occurrence of vascular complications in FH heterozygotes.

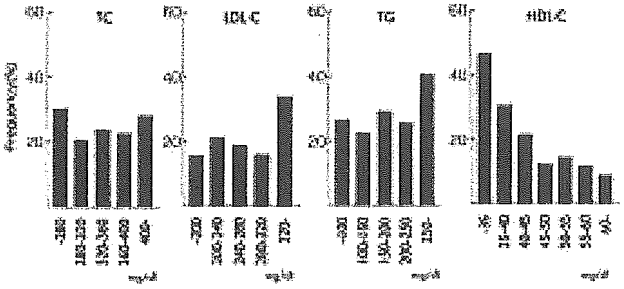

Fig. 1. Serum lipids and occurrence of CAD in FH homozygotes and heterozygotes.

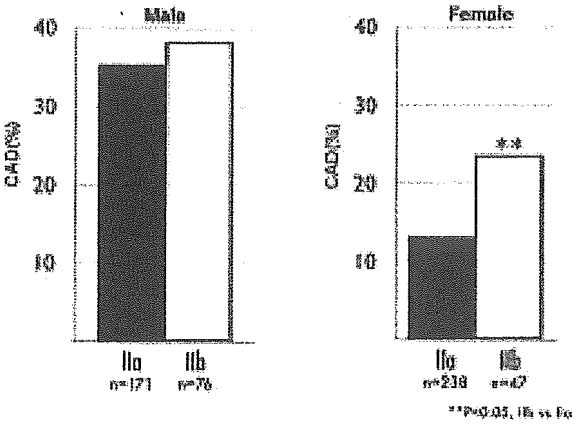

Fig. 3. Occurrence of CAD in the presence or absence of TG > 150 mg/dl in FH heterozygotes.

type IIa. Next, the significance of hypoalphalipoproteinemia (HDL-C of less than 40 mg/dl) was analyzed (Fig. 4). The cases with hypoalphalipoproteinemia showed increased CAD occurrence in males. Together with the results in Figure 1, serum HDL-C level seems to be rather well or related with CAD occurrence in FH heterozygotes.

Logistic regression analyses for CAD revealed that male, age > 50 y, smoking, hypertension, diabetes mellitus, TG > 150 mg/dl and HDL < 40 mg/dl were associated with an increased risk of CAD (Fig. 5). The cumulative incidence of CAD is shown in Fig. 6. Males with FH developed CAD 10-20 years earlier than females with FH.

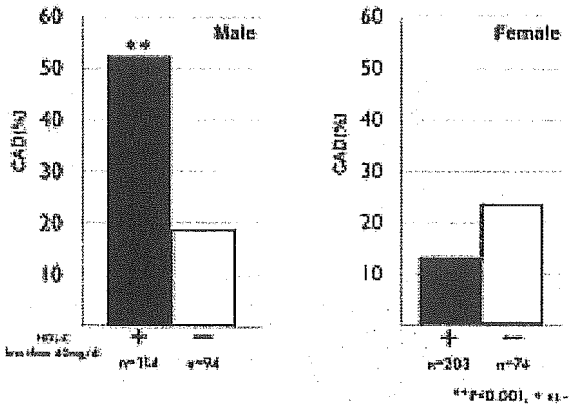

Fig. 4. Occurrence of CAD in the presence or absence of HDL-C < 40mg/dl in FH heterozygotes.

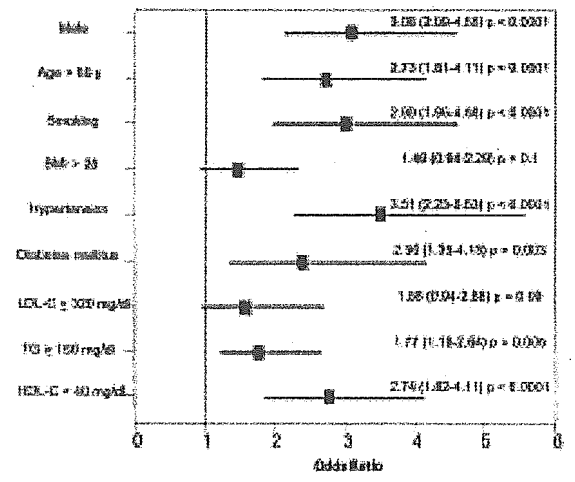

Fig. 5. Association between occurrence of CAD and conventional coronary risk factors in FH heterozygotes.

Phenotype of heterozygous cases with the "common mutations" in the LDL receptor gene

Common mutations in the LDL receptor gene have been suggested to exist in FH heterozygotes in Japan (6–8). The common mutations consist of four mutations: K790X in exon 17, C317S in exon 7 (FH Wakayama), P664L in exon 14 (FH Kanazawa-2) and 1845 + 2 T to C (FH Niigata). Previous studies have suggested that the total number of cases with the four mutations accounts for about 30% of heterozygous FH in Japan (6, 7). In order to determine the frequencies and clinical features of cases with the common mutations in various areas in Japan, the four mutations were intensively analyzed in the cases with FH in the Chiba area, and the frequencies and phenotypes were analyzed in comparison with previous data from other areas. The occurrences of the four mutations in the 154 cases of heterozygous FH in Chiba were observed as 5.8%, 4.5%, 5.2% and 1.9% for 1847TC, K790X, P664L and C317S, respectively (Table 3). The frequencies in Chiba were about one-half and one-third to-fourth for 1847TC and C317S, respectively, compared to those in the Osaka area. The frequencies of K790X and P664L were almost the same between both areas. The frequencies of P664L in both areas were also similar to that in the Kanazawa area. The frequency of cases with the four mutations was up to 17.5% of all FH cases analyzed in the Chiba area.

The clinical features of FH with the common mutations were analyzed next. The serum levels of both TC and LDL-C in the cases with the common mutations were increased compared to the average levels of the 641 cases with heterozygous FH (Table 4). The summarized data of the Chiba and Osaka areas (provided by Drs. Maruyama and Yamashita) showed that cases with any

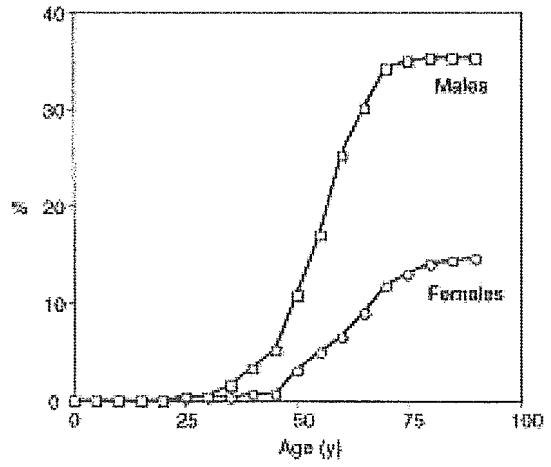

Fig. 6. Cumulative incidence of CAD in FH heterozygotes.

of the common mutations showed increased average TC and LDL-C levels compared to those in the data of heterozygous FH (Table 5). The frequencies of CAD occurrence were 52%, 54%, 36% and 54% for 1847TC, K790X, P664L and C317S, respectively. These occurrences in the cases with the common mutations were increased compared to those in the data of heterozygous FH, although the average age was younger in the cases with the common mutations. However, the average levels of TC and LDL-C of the cases with P664L (FH Kanazawa 2) in the Kanazawa area (provided by Drs. Kajinami and Mabuchi) were obviously decreased compared to the summarized levels (Table 6).

Discussion

The clinical features of FH in Japan were investigated using a database mutations in Japanese patients with primary hyperlipidemia and related disorders. Additionally, clinical phenotypes in FH with the common mutations were studied using three databases based on different areas in Japan. The clinical features and the frequencies of accompanying vascular diseases in 660 FH homozygotes and heterozygotes suggested that the occurrence of CAD has increased in males, and has not changed much in females, compared to that in the database from 1986, respectively (9). However, it is impossible to compare the occurrence exactly as the criteria for the definition of FH is not the same between the previous and current studies. There was no clear relationship between CAD occurrence and TC level in the annual report of the research group for primary hyperlipidemia in 1986, which is not clearly different from the results of this study. However, the annual report in 1986 showed a relationship between TG and CAD, which was not obviously observed in this study. The relationship

Table 3. Frequencies of common mutations in 3 areas in Japan.

Mutation	Chiba (n = 154)	Osaka (n = 120)	Kanazawa (n = 201)
1847TC	5.8% (9)	13.3% (16)	
K790X	4.5% (7)	6.7% (8)	
P664L (Kanazawa 2)	5.2% (8)	3.3% (4)	3.0% (6)
C317S	1.9% (3)	6.7% (8)	
Tonami 1			5.0% (10)
Tonami 2			5.5% (11)
Total	17.5% (27)	30.0% (36)	13.4% (27)

Table 4. Clinical features of FH heterozygotes with common mutations in the Chiba area.

Mutation	K790X	P664L	1847TC	C317S
n	7	8	9	3
Age (y)	50 ± 12	50 ± 17	50 ± 5	33 ± 20
Sex (M/F)	5/2	2/6	4/5	2/1
BMI (kg/m^2)	23.2 ± 2.7	22.8 ± 2.7	21.3 ± 4.1	20.8 ± 1.6
TC (mg/dl)	406 ± 25	398 ± 73	384 ± 35	349 ± 70
LDL-C (mg/dl)	335 ± 40	323 ± 77	329 ± 43	292 ± 65
TG (mg/dl)	164 ± 86	146 ± 54	118 ± 57	133 ± 39
HDL-C (mg/dl)	38 ± 11	46 ± 13	44 ± 14	31 ± 4
ATT (max, mm)	14 ± 8	11 ± 5	19 ± 7	8 ± 1
Xanthoma (%)	20	17	25	0
CAD (%)	40	43	50	33

Mean ± SD, Xanthoma does not include Achilles tendon thickness.

Table 5. Clinical features of FH heterozygotes with common mutations in 3 areas (National Cardiovascular Center, Osaka University, Chiba University).

Mutation	K790X	P664L	1847TC	C317S
n	13	16	29	13
Age (y)	44 ± 14	43 ± 18	44 ± 14	41 ± 14
Sex (M/F)	6/7	4/12	12/17	7/6
BMI (kg/m^2)	23.2 ± 1.7	22.7 ± 2.4	21.1 ± 2.9	22.2 ± 2.2
TC (mg/dl)	414 ± 90	377 ± 63	355 ± 74	381 ± 67
LDL-C (mg/dl)	346 ± 99	300 ± 64	282 ± 74	320 ± 63
TG (mg/dl)	149 ± 68	131 ± 55	140 ± 78	134 ± 55
HDL-C (mg/dl)	40 ± 12	51 ± 12	45 ± 14	34 ± 7
CAD (%)	54	36	52	54

Mean ± SD.

Table 6. Clinical features of FH heterozygotes with common mutations in the Kanazawa area.

Mutation	Kanazawa 2	Tonami 1	Tonami 2
n	15	22	34
Age (y)	40 ± 16	48 ± 19	52 ± 21
TC (mg/dl)	309 ± 45	338 ± 42	310 ± 69
LDL-C (mg/dl)	251 ± 43	272 ± 43	222 ± 61
TG (mg/dl)	126 ± 51	97 ± 41	158 ± 126
HDL-C (mg/dl)	35 ± 14	46 ± 12	40 ± 11

Mean ± SD.

observed between HDL-C and CAD was almost the same in both reports. The importance of accompanying hypertriglyceridemia in females and hypoalphalipoproteinemia in males for an increased occurrence of CAD was clarified in FH. Risk factor analyses revealed that hypertension, male, smoking, low HDL-cholesterol levels (< 40 mg/dl), age > 50 y, diabetes mellitus, and hypertriglyceridemia (> 150 mg/dl) were positive risk factors for coronary heart disease. The cumulative incidence of CAD showed that males with FH developed CAD 10–20 years earlier than females with FH.

A summarized gene analysis for hyperlipidemia showed at least four mutations in the LDL receptor gene as common mutations in Japan (6,7). The increased average serum lipids and frequencies of CAD suggested the differing phenotypic severity among FH cases based on various mutations. Further analysis of the clinical features of cases with the common mutations should be performed to determine the clinical severity in these cases.

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Journal of Atherosclerosis and Thrombosis Vol. 12, No. 2
Original Articles

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

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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

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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, because 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
	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

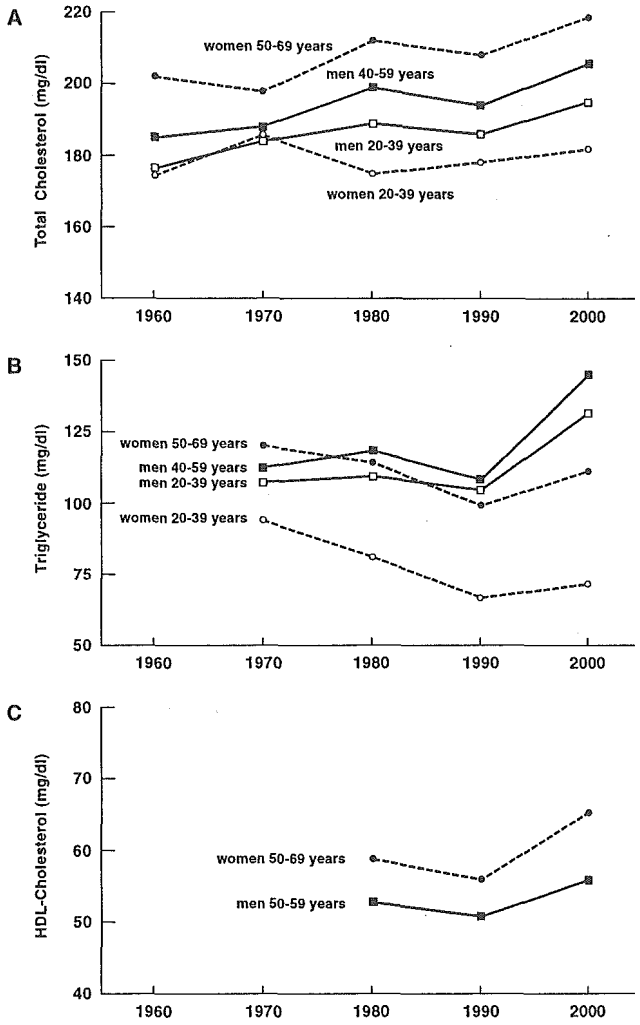

Fig. 1. Trends of serum lipid levels in Japanese in 40 years from 1960 to 2000. Results of the surveys carried out by the members of Japan Atherosclerosis Society. A. The mean cholesterol level in men and women of 20–39 years, men of 40–59 years, and women of 50–69 years from 1960 to 2000. B. The mean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

	All			Men			Women		
Age	*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.

	All			Men			Women		
Age	*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- 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.

	All			Men			Women		
Age	*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.

	All			Men			Women		
Age	*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.

	All			Men			Women		
Age	*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 μU/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.

	All			Men			Women		
Age	*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.

	All			Men			Women		
Age	*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 (μU/ml) for each 10-year group in Japanese.

	All			Men			Women		
Age	*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.

	All			Men			Women		
Age	*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