

Report of the Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Treatment of Hyperlipidemia in Japanese Adults

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Total Cholesterol and LDL-cholesterol

Hypercholesterolemia has been shown to be a major risk factor for coronary heart disease (CHD) by studies in Japan¹⁻⁶⁾ such as those by the Research Committee on "Primary Hyperlipidemia" of the Ministry of Health and Welfare of Japan as well as in western countries⁷⁻¹⁰⁾. With westernization of the lifestyle, especially the diet, the serum total cholesterol level in Japanese has been increasing. A survey of circulatory diseases by the Ministry of Health and Welfare of Japan revealed an increase in the mean serum total cholesterol level in both males aged ≥ 30 years (from 180 mg/dl in 1980 to 199 mg/dl in 1990) and females aged ≥ 30 years (from 191 mg/dl to 207 mg/dl) and a marked increase in the percentage of persons showing a level > 220 mg/dl (from 17% in 1980 to 31% in 1990)¹¹⁾. In such a status, an increase in patients with CHD is also expected in Japan.

In western countries where CHD is a leading cause of death, a reduction in serum total cholesterol level has been considered to be important in the treatment and prevention of CHD, and active measures have been taken. The treatment principles have been published as the Adult Treatment Panel (ATP) I¹²⁾ and II¹³⁾ of the National Cholesterol Education Program (NCEP) in the U.S. and as the guidelines of the European Atherosclerosis Society (EAS)¹⁴⁻¹⁷⁾ in Europe. The Japan Atherosclerosis Society Consensus Conference (1987) proposed a serum total cholesterol level of 220 mg/dl, a serum triglyceride level of 150 mg/dl, and an HDL-cholesterol level of 40 mg/dl as the levels for initiating treatment¹⁸⁾. To establish a guide-

line for the treatment of hyperlipidemia based on accumulated recent evidences in Japan, the Working Committee on JAS Guideline for Diagnosis and Management of Hyperlipidemia for Prevention of Atherosclerosis was organized in 1995 and has assessed the evidences. A guideline for serum total cholesterol is proposed below. The desirable range, the level for diagnosing hypercholesterolemia, and the treatment goal level proposed in this guideline are values for distinguishing pathological conditions and used as reference principles for the prevention and treatment of CHD that is most closely associated with serum total cholesterol. These values may differ from the reference range of serum total cholesterol in Japanese (range between the upper and lower limits of the middle part including 95% of standard levels shown by healthy individuals) that are clinicopathologically used.

I. Pathogenesis of hypercholesterolemia

Cholesterol is very important *in vivo* as a precursor of cell membrane components, hormones (steroid hormones, sex hormones), and bile acids. The *in vivo* cholesterol is derived from diets or produced in the body (endogenous cholesterol). Endogenous cholesterol is produced in the liver, incorporated into very low density lipoprotein (VLDL), and transported via the blood. Triglyceride in VLDL is hydrolyzed by lipoprotein lipase, changing VLDL to cholesterol-rich low density lipoprotein (LDL). LDL is taken up via LDL receptors by peripheral tissues such as the liver and is metabolized. Since 60-70% of serum total cholesterol is contained in LDL, a highly positive correlation is observed between LDL cholesterol and serum total cholesterol. Among lipoproteins, LDL has the most marked atherosclerosis-promoting effects. Concerning the general pathogenesis of hypercholesterolemia, abnormal LDL metabolism mediated by dysfunction of LDL receptors and excessive VLDL production by the liver are important. Hypercholesterolemia is classified as primary or secondary. Secondary hypercholesterolemia occurs

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secondary to hypothyroidism, diabetes mellitus, or nephrotic syndrome, and the treatment of the underlying disease is the most important. Five percent and 15% of primary hypercholesterolemia are attributed to familial hypercholesterolemia and familial combined hyperlipidemia, respectively, both of which are hereditary diseases and tend to induce CHD (See supplementary matters for treatment). Idiopathic hypercholesterolemia accounts for the other 80%. Though this type is most frequently encountered in clinical practice, its definite cause is unknown at present. In the treatment of patients with hypercholesterolemia, the differentiation between primary and secondary hypercholesterolemia is necessary. In patients with primary hypercholesterolemia, the possibility of hereditary types should be also considered.

II. Desirable range of serum total cholesterol in Japanese in terms of prevention and treatment of CHD

In Japan, there have been few detailed epidemiological studies that provide useful data for the determination of the desirable range of the serum total cholesterol level. Fig. 1, which is the results of meta-analysis on collected data of previous studies¹⁻⁶, shows the relative risk when the incidence or complication rate of CHD at a serum total cholesterol level of 200 mg/dl was regarded as 1, which represents the relationship between the serum total cholesterol level and CHD in Japanese. The risk of CHD markedly increases when the serum total cholesterol level exceeds 200 mg/dl.

Fig. 2 compares the above relationship between the serum total cholesterol level and CHD in Japan shown in Fig. 1 with that observed in the Multiple Risk Factor Intervention Trial (MRFIT)⁸ that uses the death rate from CHD in patients with a serum total cholesterol level of 193-202 mg/dl as the standard. The death rate from CHD markedly differed between Americans and Japanese. However, the relationship between serum total cholesterol and the relative risk of CHD showed a similar pattern, suggesting a similar relationship in both Japan and the U.S. The Research Committee on Serum Lipid Level Survey 1990 in Japan showed that the serum total cholesterol level of 200 mg/dl corresponds to about the 50-60 percentile value in Japanese aged ≥ 20 years⁹. The NCEP proposed that the desirable range of serum total cholesterol should be < 200 mg/dl¹² because the increase in the death rate from CHD was gradual at a serum total cholesterol level of 150-200 mg/dl but acute above this level in the survey by the MRFIT. The EAS (principles in 1994) also proposed < 200 mg/dl as the desirable range¹⁷.

Based on the results of epidemiological studies in Japan and the status overseas, the desirable range of serum total cholesterol in terms of prevention of CHD may be < 200 mg/dl.

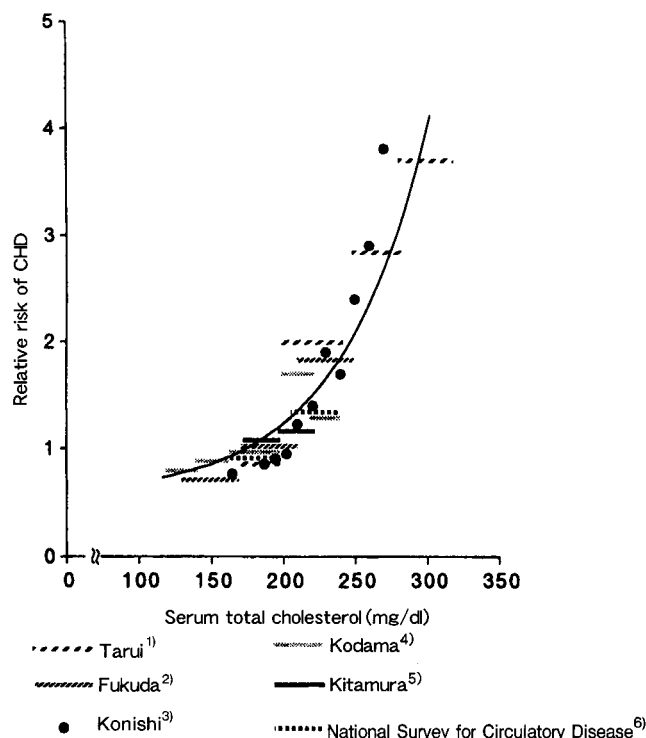


Fig. 1. Relationship between the serum total cholesterol level and the relative risk of CHD in Japanese.

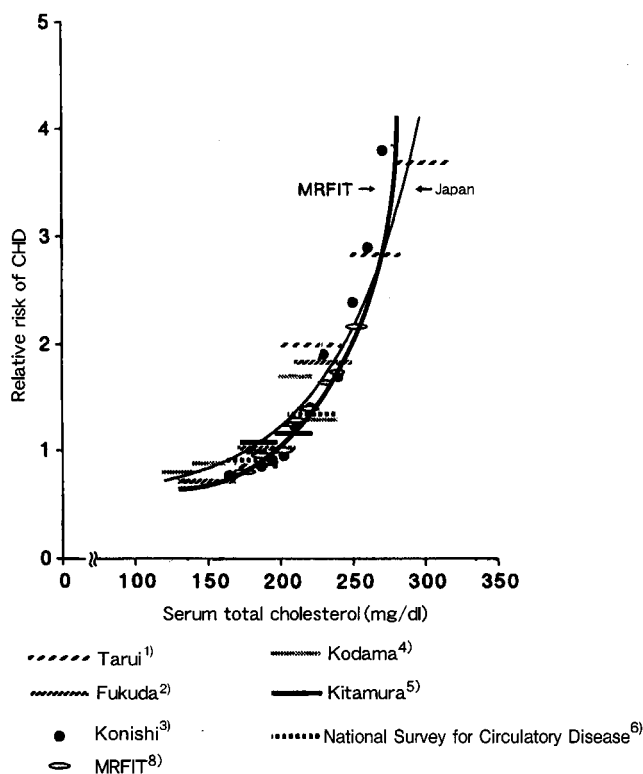


Fig. 2. Relationship between the serum total cholesterol level and the relative risk of CHD. Comparison between Japan and the U.S.

III. Level for diagnosing hypercholesterolemia in Japanese in terms of prevention and treatment of CHD

Concerning the level for diagnosing hypercholesterolemia, ≥ 220 mg/dl has been conventionally used in Japan. This value was proposed in 1987 at the Consensus Conference of the Japan Atherosclerosis Society¹⁸⁾. This value was not determined based on the results of a large-scale epidemiological study, but was accepted as the consensus of specialists. The relative risk of CHD at a serum total cholesterol level of 220 mg/dl is 1.5 times that at 200 mg/ml as shown in Fig. 1. This fact provides one of the bases for the appropriateness of ≥ 220 mg/dl as the level for diagnosing hypercholesterolemia. On the other hand, the NCEP-ATPI and II proposed ≥ 240 mg/dl as the level for diagnosing hypercholesterolemia for the following reasons: 1) The MRFIT showed that the death rate from CHD at a serum total cholesterol level of 240–300 mg/dl was 4 times that at < 200 mg/dl. 2) The serum total cholesterol level of 240 mg/ml corresponded to the 80 percentile value of the cholesterol distribution in the U.S. population. Though the EAS guidelines in 1994 determined treatment principles according to the lipid level and classified the serum total cholesterol level into 4 grades with the upper limit of mild hypercholesterolemia being at 230 mg/dl¹⁷⁾. Thus, western countries used a cutoff level at which the risk of CHD considerably increased.

In Japan, if a serum total cholesterol level of 220 mg/dl is used as the cutoff level for diagnosing hypercholesterolemia, the following problems may occur.

- 1) The death rate from CHD is 197 per 100,000 population in the U.S., 288 in England, but only 42 in Japan²⁰⁾, being very low in Japan compared with western countries. Therefore, it is questionable whether the use of a level lower than 240 mg/dl, which was proposed by the ATP II, in Japan has any significance. Serum total cholesterol level of 240 mg/dl, which increases the relative risk of CHD twice high as that of 200 mg/dl might be more appropriate.
- 2) A cutoff diagnostic level that differs from that in western countries lacks international conformity.
- 3) When this cutoff level is used in clinical settings, about 45–50% of examinees are diagnosed as having hypercholesterolemia at present, which makes management difficult. Since the serum total cholesterol level is increasing in the Japanese, patients with hypercholesterolemia will markedly increase using this cutoff level.

On the other hand, the use of a total cholesterol level of 220 mg/dl as the cutoff has the following advantages.

- 1) In the U.S., the opinion that the total cholesterol level of 240 mg/dl is too high as the cutoff is beginning to arise.
- 2) Since a national average of total cholesterol is gradu-

ally increasing in this country, the lower cutoff level of total cholesterol at 220 mg/dl will help keeping nation's cholesterol level within a desirable range below 200 mg/dl.

- 3) The change in the reference value of 220 mg/dl to 240 mg/dl will cause many troubles not only in daily practice but also in clinical and basic studies, risk statistics, comparative epidemiology, and drug development in the lipid field, because all the data so far collected have been classified according to this reference value of 220 mg/dl and analysis has been made based upon this criteria.
- 4) If the cutoff is increased to 240 mg/dl, people with a total cholesterol value of 220–239 mg/dl who have a considerably high risk will possibly be left untreated.
- 5) Beside CHD, cerebral infarction of cortical artery type and arteriosclerosis obliterans also have a close relationship with dyslipidemias, whose total cholesterol level however is mostly below 240 mg/dl. Therefore, a cutoff level higher than 220 mg/dl may disregard lipid disorders of these important atherosclerotic diseases.
- 6) There is no adequate basis for increasing the cutoff for diagnosing hypercholesterolemia from the present value.

For these reasons, it may be appropriate to use a serum cholesterol level ≥ 220 mg/dl as the level for diagnosing hypercholesterolemia in the present guideline.

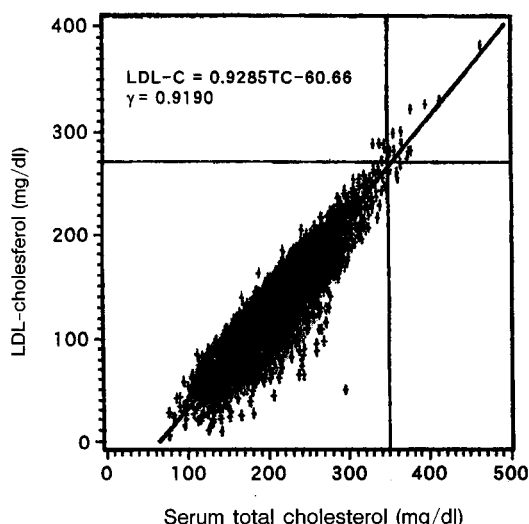
When ≥ 220 mg/dl is used for diagnosing hypercholesterolemia, the borderline range becomes ≥ 200 mg/dl– < 220 mg/dl. In the ATP II, the borderline range is ≥ 200 mg/dl– < 240 mg/dl. The determination of the borderline range is important as a buffer zone where the effects of stepwise treatment, especially corrections in the lifestyle, are evaluated. This range also gives flexibility to treatment and also can be a buffer zone for differences of cholesterol level among institutions.

LDL-cholesterol has been suggested to be more closely related to CHD than serum total cholesterol. Therefore, importance should be also placed in LDL-cholesterol in the present guideline. LDL should be isolated by ultracentrifugation and its cholesterol content measured. However, in the general clinical setting, LDL-cholesterol is often calculated from serum total cholesterol, HDL-cholesterol, and triglyceride values using Friedewald's formula ($\text{LDL-cholesterol} = \text{serum total cholesterol} - \text{HDL-cholesterol} - \text{serum triglyceride}/5$)²¹⁾. To evaluate the validity of Friedewald's formula in Japan, Hata *et al.* analyzed the relationship between the LDL-cholesterol level determined by ultracentrifugation and that estimated by Friedewald's formula in 920 Japanese subjects with a serum triglyceride level ≤ 400 mg/dl and observed their high correlation (correlation coefficient, 0.8468). Therefore, estimation of the LDL-cholesterol level using Friedewald's formula and its use as a clinical index may present no problems in Japanese subjects with a serum

Table 1. Desirable cholesterol level range and the level for diagnosing hypercholesterolemia in Japanese in terms of prevention and treatment of CHD.

	Serum total cholesterol	LDL-cholesterol
Desirable cholesterol range	<200 mg/dl	<120 mg/dl
Borderline cholesterol range	200~219 mg/dl	120~139 mg/dl
Hypercholesterolemia	≥220 mg/dl	≥140 mg/dl

1. Even when the cholesterol level is in the desirable range, treatment is sometimes necessary in the presence of other risk factors of atherosclerosis.
2. In patients with CHD, strict management is necessary, and therefore, the serum total cholesterol level for initiating treatment is ≥180 mg/dl (LDL-cholesterol ≥100 mg/dl).

**Fig. 3.** Relationship between the serum total cholesterol level and the LDL-cholesterol level obtained using Friedewald's formula in Japanese adults ($n=31,796$).

triglyceride level ≤ 400 mg/dl. The value $k=5$ has been applied in the original VLDL-cholesterol estimation formula (serum triglyceride/ k). However, $k=4$ has been suggested to be more practical in Japanese who tend to show a lower serum triglyceride level than Caucasians because the error between the estimated and observed LDL-cholesterol levels is 9% with $k=5$ but 4% with $k=4$ ²²⁾. Fig. 3 shows the relationship between LDL-cholesterol level obtained using Friedewald's formula and serum total cholesterol level in 31,796 Japanese adults based on the results of a survey in Japanese by the Research Committee on Serum Lipid Level Survey 1990 in Japan. The relationship was expressed as the following formula: (LDL-cholesterol = $0.9285 \times$ serum total cholesterol - 60.66). In this relationship, serum cholesterol levels of 200, 220, and 240 mg/dl corresponded to LDL-cholesterol levels of 120, 140, and 160 mg/dl, respectively. The desirable cholesterol range and the level for diagnosing hypercholesterolemia were determined according to serum total cholesterol and LDL-cholesterol levels as shown in Table 1. As Fig. 3 indicates, some adults showed a desirable serum total cholesterol level but

hyper-LDL-cholesterolemia due to changes in serum triglyceride or HDL-cholesterol while others showed a desirable LDL-cholesterol level but hypercholesterolemia. Therefore, importance should be placed in LDL-cholesterol level as an index of hyperlipidemia.

IV. Guideline for the treatment of hypercholesterolemia in Japanese in terms of prevention and treatment of CHD

1. Risk factors of atherosclerosis other than hypercholesterolemia

Risk factors are defined as factors that accelerate the progression of coronary atherosclerosis after exposure to them. There are many risk factors of atherosclerosis in addition to hypercholesterolemia. Among them, the established risk factors were used in this guideline (age, family history of CHD, smoking habit, hypertension, abnormal glucose tolerance, and obesity).

1) Factors that can not be improved :

(1) Age

The number and degree of atherosclerosis risk factors as well as the incidence of CHD increase with age. In Japanese, the death rate from CHD is higher in males than in females^{4,6)}. It is unclear at which age the risk of CHD increases in Japanese males. Since the NCEP (ATP II) showed a high incidence of CHD in males aged ≥ 40 years, age ≥ 45 years was regarded as the age requiring strengthening of the treatment for hypercholesterolemia¹³⁾.

(2) Gender

In females, the risk of CHD increases after menopause. Menopause occurs by the age of 56 years in 90% of Japanese females²³⁾, and therefore, this age is a point for strengthening the treatment of hypercholesterolemia.

(3) Family history of CHD

Caution is necessary when relatives in the first degree have a history of sudden death or premature CHD.

2) Risk factors that can be improved :

(1) Smoking habit

Smoking is an important risk factor for CHD²⁴⁾. Smoking induces lipoprotein abnormalities (an increase in LDL-cholesterol, a decrease in HDL-cholesterol), vascular spasm, enhancement in blood coagulation, and damage in vascular endothelial cells, promoting atherosclerosis. A

study in Hisayama-cho revealed that the risk of CHD in smokers (≥ 10 cigarettes/day) is 2.8 times that in non-smokers without hypertension²⁵.

In Japanese males aged ≥ 20 years, the percentage of smokers is 53.2%²⁶, which is higher than that in western countries (30–40%). The percentage of smokers is the highest in Japan among developed countries. Smoking cessation is very important in preventing CHD.

(2) Hypertension

Hypertension together with smoking is an important risk factor for CHD in Japanese. The above-described study in Hisayama-cho revealed that the risk of CHD in the hypertensive group (systolic pressure ≥ 160 mmHg and/or diastolic pressure ≥ 90 mmHg) was 3.2 times higher, and that in the hypertensive smoker group was 5.5 times higher than that in the non-hypertensive non-smoker group²⁵. Konishi *et al.* followed up males aged 35–54 years for 6 years and observed the lowest incidence of CHD irrespective of the serum total cholesterol level in the non-hypertensive group, followed in order by the non-smoker group, the hypertensive group (≥ 160 mmHg and/or ≥ 95 mmHg) and the smoker group, and the hypertensive smoker group³. The national nutritional survey in 1993 showed hypertension (≥ 160 mmHg and/or ≥ 95 mmHg) in 24% of Japanese males and 20% of Japanese females²⁶. In 1993, a joint committee of the WHO and the International Hypertension Society revised the guideline and proposed that mild hypertension should be defined as a systolic pressure ≥ 140 mmHg and/or a diastolic pressure ≥ 90 mmHg²⁷, describing that management of hypertension should be started from the stage of mild hypertension.

(3) Abnormal glucose tolerance

In diabetes mellitus (fasting blood glucose level ≥ 126 mg/dl and/or blood glucose level at 2 hours in 75 g GTT ≥ 200 mg/dl²⁸), abnormal lipid metabolism or hypertension is often observed, and coronary atherosclerosis tends to progress. In mild impairment of glucose tolerance (borderline type: fasting blood glucose level, ≥ 110 mg/dl– <140 mg/dl; blood glucose level at 1 hour in 75 g GTT, ≥ 160 mg/dl; that at 2 hours, ≥ 120 – <200 mg/dl)²⁸, the degree of atherosclerosis in the carotid artery has been shown to be similar to that in diabetes mellitus²⁹. In addition, the incidence of CHD in patients with IGT (fasting blood glucose level, <140 mg/dl; blood glucose level at 2 hours in 75 g GTT, ≥ 140 mg/dl– <200 mg/dl) has been reported to be similar to that in patients with diabetes mellitus³⁰. Even in patients with mild abnormal glucose intolerance, the accumulation of atherosclerosis risk factors such as obesity, hypertension, hyperinsulinemia, and hyperlipidemia is higher compared with subjects with normal glucose tolerance³¹. Thus, all categories of abnormal glucose tolerance including the borderline type should be regarded as an atherosclerosis risk factor.

In Japanese adults aged ≥ 40 years, the incidence of

diabetes mellitus is 10%³², and there are also about 10,000,000 adults (≥ 40 years) with the borderline type that is considered to be as important as definite diabetes mellitus as a risk factor for atherosclerosis. Many cases of abnormal glucose tolerance can be controlled by diet and exercise, and therefore, the importance of these basic treatment should be emphasized.

(4) Obesity

Westernization of the lifestyle is associated with obesity in Japanese. The body mass index (BMI: body weight (kg)/height (m)²) during the 10 years from 1983 to 1993 decreased in females aged <50 years, which reflects their concern about the diet, but increased in males in all age groups from 20–69 years except the group aged 40–49 years²⁶. The Japanese Society of Obesity defined a BMI index of 20– <25 as $\geq$, and ≥ 25 as obesity³³.

Obesity is an important factor that increases insulin resistance and a risk factor for the development of diabetes mellitus. Obesity also induces multiple risk factors of atherosclerosis such as abnormal lipid metabolism represented by hypertriglyceridemia and hypo HDL-cholesterolemia, and hypertension. The visceral fat accumulation has a greater impact on the accumulation of multiple risk factors than the subcutaneous fat accumulation type³⁴. Thus a reduction in body weight by restriction of the energy intake and exercise is important for prevention of CHD.

(5) Others

In recent years, the importance of apoprotein in lipoprotein metabolism has been clarified, and measurement of apoprotein is considered to be useful for evaluating the risk of CHD³⁵. Attention has been also paid to the atherosclerosis-inducing action of remnants as an intermediate metabolic product of chylomicrons and VLDL³⁶ and small dense LDL³⁷. In addition, Lp(a) has been shown to be a risk factor for atherosclerosis that not only causes cholesterol deposition in the arterial wall but also inhibits the fibrinolysis system. A high Lp(a) level has been reported to be associated with CHD and cerebral infarction³⁸.

2. Levels for initiating treatment of hypercholesterolemia and treatment goal levels

The progression of coronary atherosclerosis is also accelerated by the accumulation of risk factors other than hypercholesterolemia. In patients who already have CHD, strict management of hypercholesterolemia is necessary as secondary prevention. Thus, it may be more practical to determine the level for initiating the treatment of hypercholesterolemia and the treatment goal according to the presence or absence of CHD or atherosclerosis risk factors other than hypercholesterolemia. In this guideline, the level for initiating the treatment of hypercholesterolemia and the treatment goal were proposed according to the following 3 categories: Category A) absence of

CHD and atherosclerosis risk factors other than hypercholesterolemia, Category B) absence of CHD but presence of atherosclerosis risk factors other than hypercholesterolemia, and Category C) presence of CHD. Due to recent advances in the diagnostic techniques for atherosclerosis, asymptomatic CHD has been increasingly detected. This guideline includes not only symptomatic but also asymptomatic CHD.

Category A: Absence of CHD and atherosclerosis risk factors other than hypercholesterolemia

As mentioned above, we proposed 220 mg/dl as a cutoff level for diagnosing hypercholesterolemia in Japanese. In patients with a serum total cholesterol level ≥ 220 mg/dl (LDL-cholesterol ≥ 140 mg/dl), lifestyle modification and dietary therapy should be applied as a fundamental treatment. The effects of dietary therapy should be evaluated for at least several months. When the serum total cholesterol remains ≥ 240 mg/dl (LDL-cholesterol ≥ 160 mg/dl) after dietary therapy, drug treatment is considered. However, the timing of its initiation should be carefully determined, considering the sex and age of the patient. The relative risk of coronary atherosclerosis at a serum total cholesterol level of 240 mg/dl is twice that at 200 mg/dl. We proposed that the desirable range of the serum total cholesterol level to be < 200 mg/dl, but this range may include many young patients with hypercholesterolemia but not other risk factors. Thus, the appropriate treatment goal may be a serum total cholesterol level < 220 mg/dl (LDL-cholesterol < 140 mg/dl), but careful observation of its changes is necessary.

Category B: Absence of CHD but presence of atherosclerosis risk factors other than hypercholesterolemia

The level for initiating treatment and the treatment goal level should be set lower in patients who also have the following atherosclerosis risk factors other than hypercholesterolemia than in patients with hypercholesterolemia alone classified as Category A: age (≥ 45 years in males, after menopause in females), family history of CHD, smoking habit, hypertension (systolic pressure ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg), obesity (BMI ≥ 25), and abnormal glucose tolerance (borderline type, diabetes mellitus according to the criteria of the Japan Diabetes Society). Sasaki *et al.* performed a cross-sectional study on the coronary artery stenosis in patients with hypercholesterolemia (serum total cholesterol ≥ 220 mg/dl) according to the smoking habit, hypertension ($\geq 150/90$ mmHg), hyperuricemia (uric acid ≥ 7.5 mg/dl), hyperglycemia (fasting blood glucose ≥ 120 mg/dl), and obesity (BMI ≥ 27). They observed a higher prevalence of patients with $\geq 75\%$ stenosis in the group with these risk factors than the group without them. Thus the findings revealed that the strict control is necessary in patients with atherosclerosis risk factors other than hypercholesterolemia³⁹⁾ Since these risk factors differ in the degree of importance, different treatment principles

should be used according to their combinations. However, to discuss detailed treatment principles, there have been no data by intervention studies in Japanese. Therefore, in this guideline, patients with one or more atherosclerosis risk factors other than hypercholesterolemia were included in the same category. Many patients with hypercholesterolemia also have other risk factors and may be classified in this category. The treatment goal of serum total cholesterol level in this category is < 200 mg/dl (LDL-cholesterol < 120 mg/dl). At a serum total cholesterol level ≥ 200 mg/dl (LDL-cholesterol ≥ 120 mg/dl), lifestyle modification and dietary therapy are initiated. It should be constantly noted that some patients in Category B might improve to Category A without drug treatment by strict dietary therapy, smoking cessation, and exercise. When the serum total cholesterol level remains ≥ 220 mg/dl (LDL-cholesterol ≥ 120 mg/dl) even after these management for several months, drug treatment is considered.

Concerning management of atherosclerotic diseases other than CHD, ATP II reported that the presence of peripheral artery diseases or symptomatic carotid artery diseases increases the risk of CHD four- to sixfold^{40,41)}, and therefore, recommended that the management of hypercholesterolemia in patients with these conditions should be as strict as those in patients with CHD. In Japan, coronary stenosis on angiograms was reported to be 57% of patients with arteriosclerosis obliterans⁴²⁾. However, hypercholesterolemia is not an important established risk factor for cerebral infarction or peripheral artery diseases. In this guideline, we considered it appropriate that all patients with atherosclerotic diseases other than CHD are included in this category, and their course should be carefully observed.

Category C: Presence of CHD

In patients with CHD, hypercholesterolemia should be treated more strictly than in patients without CHD. Since these patients often have other risk factors such as hypertension and abnormal glucose tolerance, management of these risk factors is also important. Shibuya *et al.* reported that LDL-cholesterol level ≥ 100 mg/dl persisted in 95% of patients showing progression of coronary stenosis after re-examination of coronary angiography⁴³⁾. The ATP II proposed that both LDL-cholesterol level for initiating treatment and the goal should be ≤ 100 mg/dl. A study on secondary prevention by coronary angiography showed that a more marked decrease in coronary stenosis after aggressive reduction in LDL-cholesterol (≤ 100 mg/dl), which is attainable by treatment¹³⁾. When ≤ 100 mg/dl is used as the LDL-cholesterol level for initiating treatment and the goal in Japanese patients with CHD, the corresponding serum total cholesterol level indicated in Fig. 3 is about 180 mg/dl. Lifestyle modification and dietary therapy are performed in patients with a serum total cholesterol ≥ 180 mg/dl. As shown in Fig. 1, the relative risk of CHD increases at a serum total cholesterol

Table 2. Criteria for management of Japanese adult patients with hypercholesterolemia in terms of prevention and treatment of CHD

Category	Level for initiating lifestyle modification and dietary therapy ^(note 1)	Level for initiating drug treatment ^(note 2)	Treatment goal
A: CHD ⁽¹⁾ (–) Other risk factors ⁽²⁾ (–)	LDL-C ≥ 140 mg/dl (TC ≥ 220 mg/dl)	LDL-C ≥ 160 mg/dl (TC ≥ 240 mg/dl)	LDL-C < 140 mg/dl (TC < 220 mg/dl)
B: CHD ⁽¹⁾ (–) Other risk factors ⁽³⁾ (+)	LDL-C ≥ 120 mg/dl (TC ≥ 200 mg/dl)	LDL-C ≥ 140 mg/dl (TC ≥ 220 mg/dl)	LDL-C < 120 mg/dl (TC < 200 mg/dl)
C: CHD (+)	LDL-C ≥ 100 mg/dl (TC ≥ 180 mg/dl)	LDL-C ≥ 120 mg/dl (TC ≥ 200 mg/dl)	LDL-C < 100 mg/dl (TC < 180 mg/dl)

1) CHD

(1) myocardial infarction, (2) angina pectoris, (3) asymptomatic myocardial ischemia (such as ischemic ECG abnormalities), (4) significant stenosis on angiograms

2) Major risk factors of atherosclerosis other than hypercholesterolemia

(1) aging (males, ≥45 years old; females, after menopause) (2) family history of CHD (3) smoking habit (4) hypertension (≥140 and/or 90 mmHg) (5) obesity (BMI ≥ 25) (6) abnormal glucose tolerance (Japan Diabetes Society Criteria, borderline type, diabetic type) (7) hypertriglyceridemia (≥150 mg/dl) (8) hypo-HDL-cholesterolemia (<40 mg/dl)

Note 1: Lifestyle modification and dietary therapy are basic treatment in all categories (A, B, C). In A, the course should be observed for at least several months with lifestyle modification and dietary therapy. In B, attention should be paid to possible improvement to A after stricter management of other risk factors.

Note 2: Use of drug treatment should be carefully evaluated based on the clinical background, pathological condition (including familial hypercholesterolemia, type III hyperlipidemia, and familial combined hyperlipidemia), and habits of each patient.

Note 3: Patients with atherosclerotic diseases other than CHD such as peripheral atherosclerotic disease, symptomatic carotid artery disease, or cerebral infarction should be included in category B with a high risk for CHD even when there are no other risk factors.

level >200 mg/dl. Drug treatment is considered when a serum total cholesterol level ≥200 mg/dl even after lifestyle intervention. However, the application of drug treatment is carefully considered in aged patients, and patients with severe heart failure and malignant tumors.

The criteria for the management of patients with hypercholesterolemia is summarized in Table 2. This guideline provides reference principles in clinical settings and expected to be used flexibly based on the condition of patients at the discretion of the physician.

3. Supplementary matters concerning treatment of hyperlipidemia

(1) Japan Atherosclerosis Society Guideline for Diagnosis and Management of Hyperlipidemia for Prevention of Atherosclerosis was proposed for adults aged 20–<65 years in principle. Hyperlipidemia in children and the aged subjects has not been adequately studied and remains as a future problem.

(2) As hereditary hyperlipidemia showing hypercholesterolemia, familial hypercholesterolemia, familial combined hyperlipidemia, and familial type III hyperlipidemia are important. Familial hypercholesterolemia, which is transmitted as an autosomal dominant trait, is caused by abnormal catabolism of LDL due to abnormal LDL receptors⁽⁴⁴⁾. The heterozygote is observed in 1 of 500 population, and the homozygote in 1 of 1,000,000. The mean serum total cholesterol level (±SD) in patients with familial hypercholesterolemia is 338 (±63) mg/dl in hetero-

zygotes and 713 (±122) mg/dl in homozygotes⁽⁴⁵⁾. Tendinous xanthomas are present, and juvenile CHD develops. Dietary therapy alone does not have adequate effects, and drug treatment is important.

Familial combined hyperlipidemia (FCHL)⁽⁴⁶⁾ showing autosomal dominant inheritance occurs in about 1% of Japanese, which is higher than the percentage of patients with familial hypercholesterolemia⁽⁴⁷⁾. Patients with this disease accounted for 30% of those with myocardial infarction. In the same family of FCHL, there are hypercholesterolemia, hypertriglyceridemia, and their combined hyperlipidemia. In addition, the same individuals change the phenotype of hyperlipidemia such as hypercholesterolemia or hypertriglyceridemia. Investigation of the family is indispensable for diagnosis. The cause of the disease is still uncertain, but excessive production of VLDL and elevated apo B levels are discussed⁽⁴⁸⁾.

Familial type III hyperlipidemia is a rare condition developing in the presence of the genetic predisposition of the homozygote of apoprotein E2 lacking receptor binding ability and is characterized by accumulation and elevated levels of β -VLDL in the blood. Both serum total cholesterol and triglyceride are increased. Since electrophoresis reveals β -VLDL between LDL and VLDL, a broad β -band appears from the pre β to β area. Palmar linear xanthomas are sometimes observed, and juvenile CHD and peripheral atherosclerosis tend to develop. The degree of hyperlipidemia is often increased by diabetes mellitus and obesity as complications. This disease

Table 3. Diagnosis of hereditary hyperlipidemia showing hypercholesterolemia (Research Committee on Primary Hyperlipidemia)

1) Familial hypercholesterolemia

[Major criteria]

- (1) In principle, serum cholesterol level ≥ 260 mg/dl, IIa or IIb phenotype
- (2) Presence of tendinous xanthomas* or skin nodular xanthomas; Evaluation of thickening of the Achilles tendon by soft X-ray examination* or xeroradiography (maximum axis on the lateral plane, ≥ 9 mm) is useful.
- (3) Decreased or abnormal LDL receptor activity.

[Minor criteria]

- (1) Xanthelasmas
- (2) Juvenile (<50 years old) arcus corneae
- (3) Juvenile (<50 years old) onset of ischemic heart disease

Definite diagnosis with 2 major criteria or more.

Suspected diagnosis with 1 major criterion and 1 or more minor items. However, a definite diagnosis can be made even only with 1 major criterion when a definite diagnosis is observed in a relative in the first degree.

2) Familial combined hyperlipidemia

[Major criteria]

- (1) Presence of either of the 3 phenotypes^(note), IIb, IIa, or IV
- (2) There is a relative in the first degree showing either of these phenotypes and at least one relative including the patient showing type IIb or IIa.
- (3) Familial hypercholesterolemia can be excluded.

[Minor criteria]

- (1) Serum cholesterol ≤ 300 mg/dl in many patients
- (2) Changes among types IIa, IIb, and IV occur during the course.
- (3) Aggravation of hyperlipidemia after puberty.
- (4) Absence of tendinous xanthomas

Definite diagnosis with all major criteria

Minor criteria are used for further confirmation of diagnosis.

3) Familial type III hyperlipidemia

[Major criteria]

- (1) Increases in both serum cholesterol and serum triglyceride
- (2) Electrophoresis of plasma lipoprotein shows a broad β pattern that is continuous from VLDL to LDL.
- (3) Electrophoresis of apolipoprotein demonstrates abnormalities of apolipoprotein E (such as E2/2, E deficiency).

[Minor criteria]

- (1) Xanthomas (especially palmar linear xanthomas)
- (2) Increased serum apolipoprotein E concentration (apolipoprotein E/total cholesterol ratio ≥ 0.05)
- (3) VLDL cholesterol/serum triglyceride ratio ≥ 0.25
- (4) Decreased LDL cholesterol
- (5) Complicated by atherosclerotic diseases such as arteriosclerosis obliterans and ischemic heart disease

Definite diagnosis with all the 3 major criteria.

Suspected diagnosis with 2 major criteria and one or more minor criteria.

responds well to dietary therapy, and some patients show a dramatic improvement after caloric restriction.

Table 3 shows the diagnostic criteria for these diseases proposed by the Research Committee on Primary Hyperlipidemia, Intractable Diseases, of the Ministry of Health and Welfare of Japan.

(3) Studies on the effects of dietary therapy in Japan have shown a 10–30 mg/dl reduction in serum total cholesterol after 3–6 months. Childhood hyperlipidemia should be managed by dietary therapy and exercise therapy as much as possible. Further careful studies are required on the necessity for drug treatment in children.

(4) Low serum total cholesterol levels increase the risk of cerebral hemorrhage. An epidemiological study in

Japan showed an increase in the incidence of cerebral hemorrhage in subjects with a serum total cholesterol level ≤ 140 mg/dl³⁾. These results may be applied when the appropriate degree of the reduction in the cholesterol level is considered for prevention of CHD.

(5) Cost-effectiveness and cost-benefit of treatment for hyperlipidemia

The cost-effectiveness of the treatment for hyperlipidemia is an index representing the number of patients who can survive during a certain period after treatment for hyperlipidemia (life-saving effect), the medical cost (such as drugs) required for the life-saving, prolongation of the life in treated patients with hyperlipidemia compared with untreated patients (life-prolongation effect), and the

medical cost (such as drugs) required for the prolongation. Cost-benefit is an index of changes in the total medical cost required for treatment of atherosclerotic diseases after treatment of hyperlipidemia as a risk factor for atherosclerotic diseases such as CHD.

Many studies in western countries on cost-effectiveness and cost-benefit in the treatment of hyperlipidemia have shown that treatment of hyperlipidemia requires a certain medical cost but reduces the total medical cost due to its prevention of atherosclerotic diseases⁵⁴⁻⁵⁷. However, the cost-effectiveness and cost-benefit of the treatment of hyperlipidemia depend on the characteristics of diseases in each country such as the incidence of atherosclerotic diseases developing in the presence of hyperlipidemia, the medical cost required for the treatment of atherosclerotic diseases, and the cost of drugs. Therefore, the results obtained in western countries can not be directly applied to Japan.

There has been only one study on the cost-effectiveness and cost-benefit of the treatment of hyperlipidemia in the present status of Japan. Fujino *et al.*⁵⁸ evaluated the treatment with pravastatin for secondary prevention and obtained results similar to those in western countries though the incidence of atherosclerotic diseases is low in Japan. However, their analysis was not based on results of intervention study in Japanese with hyperlipidemia and also ignored secondary preventive effects that have recently been shown with HMG-CoA reductase inhibitors. In addition, there have been no studies in Japan or other countries in which the cost-effectiveness and cost-benefit of the treatment of hypertriglyceridemia or hypo-HDL-cholesterolemia were calculated. Thus, evaluation of the cost-effectiveness and cost-benefit of the treatment for hyperlipidemia has been insufficient in Japan. Therefore, establishment of this guideline based on these indices must be clarified further.

4. Important notice in the use of this guideline

In this guideline, (1) the desirable range of the serum total cholesterol level in Japanese and the level for diagnosing hypercholesterolemia and (2) the level for initiating treatment and the goal level were separately determined. The diagnostic level of serum total cholesterol provides the criteria for screening but does not represent the level for initiating treatment. In the treatment of hypercholesterolemia, a comprehensive evaluation of not only the serum cholesterol level but also other risk factors for atherosclerosis is necessary.

5. Future prospects

In this guideline as reference principles of the prevention and treatment of CHD, the desirable range of the serum total cholesterol level, the level for diagnosing hypercholesterolemia, the level for initiating treatment for hypercholesterolemia, and the goal level were proposed. There are three major points in the guideline for the

diagnosis and management of hyperlipidemia, i.e., (1) diagnosis of hyperlipidemia and detection of patients (Detection), (2) detailed analysis of hyperlipidemia and evaluation of other risk factors (Evaluation), and (3) treatment such as lifestyle guidance, dietary therapy, and drug treatment (Treatment). This guideline is concerned with "Detection" among the three points. Concerning "Evaluation" and "Treatment", we intend to perform further studies and propose principles that are useful in daily clinical practice.

To improve this guideline, further evaluation is necessary on many unsolved problems described in the supplementary matters in treatment.

Triglyceride

When serum triglyceride level is evaluated in association with development and progression of diseases, consideration should be paid to two diseases. One is atherosclerotic diseases such as myocardial infarction and cerebral infarction, and the other is pancreatic diseases such as acute pancreatitis.

Concerning the association between hypertriglyceridemia and acute pancreatitis, investigators have the following same opinion. A serum triglyceride level >600 mg/dl in fasting blood samples is a warning sign of acute pancreatitis. Patients with a level >1,000 mg/dl are at a high risk and require examination of pancreatic function and immediate correction of the serum triglyceride level^{1,2}.

The association between the serum triglyceride level and the development and progression of atherosclerotic diseases has been extensively discussed for more than 30 years³⁻¹². No definite association as observed between the serum cholesterol level and coronary heart diseases (CHD) has been established between the serum triglyceride level and atherosclerotic diseases. However, the clinical importance of the serum triglyceride level as a risk factor for atherosclerotic diseases has been gradually clarified. Recent angiographic studies have shown the importance of the serum triglyceride level as an independent coronary risk factor¹³⁻¹⁷.

In March, 1995, the Japan Atherosclerosis Society Working Committee on Guideline for Diagnosis and Management of Hyperlipidemia for the Prevention of Atherosclerosis was organized and began to discuss the serum lipid level for diagnosing hyperlipidemia. We report the diagnostic principles for hypertriglyceridemia proposed by this committee and present epidemiological results that provided a basis for this proposal and various phenomena associated with hypertriglyceridemia among Japanese. In addition, we describe problems caused by evaluation of the development and progression of atherosclerotic diseases based on the serum triglyceride level and the importance of hypertriglyceridemia as a part of risk management.

I. Level for diagnosing hypertriglyceridemia

Epidemiological studies such as the Research Committee on Serum Lipid Level Survey, 1990 in Japan in 17,348 Japanese¹⁸⁾ revealed that the mean serum triglyceride level in Japanese adults is 88–110 mg/dl in males and 63–105 mg/dl in females^{19–25)}. On the other hand, cross-sectional surveys showed a higher serum triglyceride level (158–180 mg/dl) in patients with CHD^{21,23,24)}. In patients with familial hypercholesterolemia (FH) or other types of hypercholesterolemia, the incidence of CHD is increased at a serum triglyceride level ≥ 150 mg/dl²⁶⁾. In addition, in patients with diabetes mellitus, CHD tends to develop at even a lower serum triglyceride level^{27,28)}. A retrospective survey by the Uwajima Social Insurance Hospital revealed a serum triglyceride level ≤ 190 mg/dl in more than 50% of patients with CHD. A prospective survey by the same institution (Fig. 4) showed a 3.7-fold increase in the incidence of CHD at a serum triglyceride level ≥ 150 mg/dl with an acute increase over the level of 150 mg/dl^{25,29)}.

These results show that the serum triglyceride level in the group with atherosclerosis is higher than that in the normal group by about 50 mg/dl. Therefore, it may be valid to initiate certain treatment at a serum triglyceride level ≥ 150 mg/dl in terms of prevention of atherosclerosis though not all cases of hypertriglyceridemia are associated with atherosclerotic diseases. In addition, cases should be more closely evaluated for treatment in association with decreased HDL-C, increased remnants, appearance of small dense LDL, and fibrinolytic abnormalities induced by hypertriglyceridemia. In patients with multiple coronary risk factors such as diabetes mellitus (see the items for classification of serum cholesterol levels) since the incidence of CHD begins to increase even at a level <150 mg/dl, prevention and treatment may be necessary in patients with a lower serum triglyceride level.

Based on these facts, we propose that the fasting serum triglyceride level for diagnosing hypertriglyceridemia should be ≥ 150 mg/dl (Table 4). In patients with a serum triglyceride level ≥ 150 mg/dl, dietary and exercise therapy are initiated. However, in high-risk patients, drug treatment as well as dietary and exercise therapy should be initiated.

II. Clinical importance of hypertriglyceridemia and the basis for determination of the serum triglyceride level for its diagnosis

1) Diseases causing hereditary hypertriglyceridemia

The diseases inducing hypertriglyceridemia include hyperchylomicronemia (hyper-CM-emia) due to lipoprotein lipase deficiency or apo CII deficiency²⁾, familial combined hyperlipidemia (FCHL)³⁰⁾, familial hypertriglyceridemia (FHTG)³⁰⁾, and familial type III hyperlipidemia^{31,32)}. In families with FCHL and familial type III hyperlipidemia,

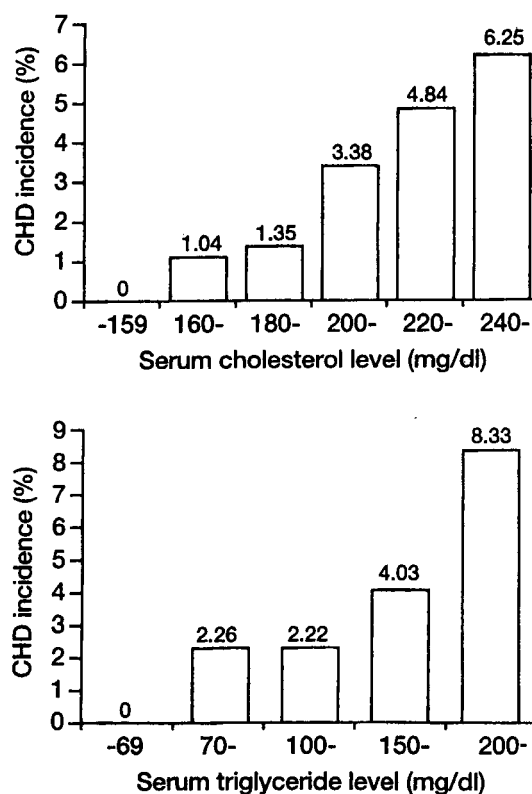


Fig. 4. Incidence of CHD and serum lipids²⁵⁾. (Prospective study reported by Kikuta H *et al.*)

Table 4. Level for diagnosing hypertriglyceridemia

	Fasting triglyceride level
Hypertriglyceridemia	≥ 150 mg/dl

a high incidence of CHD is known³³⁾. However, the incidence of CHD in patients with hereditary hyper-CM-emia (type I hyperlipidemia) or families with FHTG are similar to that in controls though these diseases also induce hypertriglyceridemia³⁴⁾ (Fig. 5). Thus, attention should be paid to CHD as a complication in patients with hypertriglyceridemia while hypertriglyceridemia is not always involved in the development and progression of CHD.

2) Hypertriglyceridemia and remnant lipoprotein

Remnant lipoprotein^{35,36)} (remnant particles or remnants) is rich in apo E and an intermediate metabolite in the blood of triglyceride-rich lipoproteins, such as CM or very low density lipoprotein (VLDL). Therefore, increased remnants also cause hypertriglyceridemia. The above-described familial type III hyperlipidemia³⁷⁾, FCHL, and diabetic hypertriglyceridemia^{38,39)} show increased blood remnants and are frequently complicated by atherosclerotic lesions. In diabetic patients with type V hyperlipidemia due to poor control, increased remnant particles in the blood and eruptive xanthomas formed by aggrega-

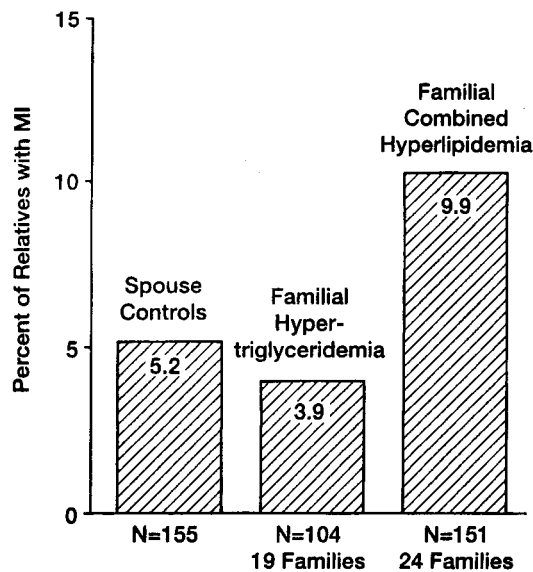


Fig. 5. Familial hyperlipidemia showing hypertriglyceridemia and the risk of developing myocardial infarction (MI)³⁴⁾ (Brunzell JD. *et al.* Metabolism, 1976)

tion of cholesterol-rich foam cells are observed, but these xanthomas disappear with a decrease in remnant particles after strengthening of insulin therapy⁴⁰⁾.

Remnant particles are lipoproteins that transport both triglyceride and cholesterol. The total amount of cholesterol transported into the arterial wall intima by remnant particles is larger than that transported by LDL. In a study, more than one-third of lipoproteins recovered from the human atherosclerotic lesions were VLDL and IDL, which were large size apo E-rich lipoproteins¹⁷⁾. *In vitro* experiment, remnant particles, even when not degenerated, are incorporated by macrophages ($M\phi$), as is oxidized and modified LDL⁴¹⁾, forming foam cells⁴¹⁻⁴⁶⁾. Thus, increased remnant particles in the blood lead to formation of early atherosclerotic lesions such as fatty streaks. Recently, Shimada *et al.*⁴⁷⁾ administered an atherogenic diet to LDL-receptor knockout mice for 8 weeks and found the increased blood remnant particles and formation of marked fatty streaks. In the same mice, the increased blood remnant particles were markedly reduced by overexpression of lipoprotein lipase, resulting in a reduction in fatty streak lesions to 1/18.

3) Insulin resistance and hypertriglyceridemia

Many epidemiological studies have demonstrated that hyperinsulinemia is a risk factor for atherosclerotic diseases⁴⁸⁻⁵⁹⁾. Patients with hyperinsulinemia show insulin resistance, a mixture of mild glucose tolerance abnormality, obesity, hypertension, hypertriglyceridemia, hypo-HDL-cholesterolemia⁵¹⁾, and pathological conditions with multiple risk factors such as visceral fat syndrome⁵²⁾, syndrome X⁵³⁾, deadly quartet⁵⁴⁾, and insulin resistance syndrome^{55,56)}. From all aspects, hypertriglyceridemia is

considered to be an important sign.

In a recent method of determining the degree of visceral fat, the distribution of visceral fat (V) and that of subcutaneous fat (S) are evaluated based on abdominal CT scan images at the navel level and expressed in terms of their ratio (V/S). By this method, a V/S ratio ≥ 0.4 was regarded as visceral fat obesity⁵⁷⁾. Fig. 3 shows the relationship between the V/S ratio and serum lipids. The serum triglyceride level is positively correlated with the V/S ratio, and a V/S ratio of 0.4 corresponds to a serum triglyceride level of 150 mg/dl.

4) Effects of hypertriglyceridemia on other lipoproteins

(1) Effects on HDL-C

Hypertriglyceridemia is accompanied by decreased HDL-C^{6,25,58-60)}. In lipoprotein metabolism, when triglyceride-rich lipoprotein is catabolized by lipoprotein lipase, HDL is produced from its surface components. Therefore, in hypertriglyceridemia due to impaired catabolism of triglyceride-rich lipoprotein, more triglyceride enters HDL particles in exchange for cholesteryl ester via cholesteryl ester transfer protein (CETP) activity, and a resulting decrease in cholesteryl ester in the core components of HDL particles induces hypo-HDL-cholesterolemia.

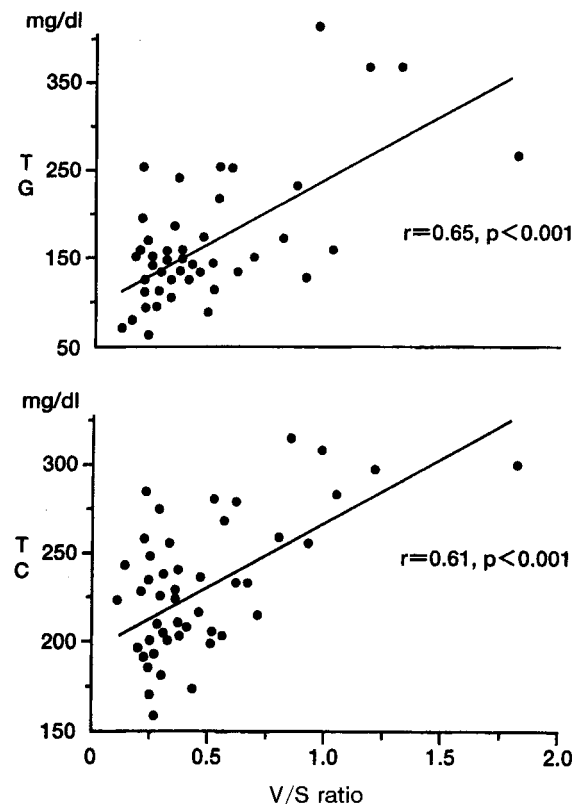


Fig. 6. Relationship between the V/S ratio and the serum triglyceride (TG) or serum cholesterol (TC) level. V/S ratio ≥ 0.4 , visceral fat obesity; V/S ratio < 0.4 , subcutaneous fat obesity (Kaoru Takemura *et al.* Gendai Iryo, 1996)

lemia. HDL is a lipoprotein that plays an important role in reverse cholesterol transport, and a decrease in HDL-C is involved in the progression of atherosclerotic lesions (See the report by the HDL-cholesterol subcommittee).

Thus, there is an inverse relationship between the serum triglyceride level and the HDL-C level. However, as the results of previous large-scale epidemiological surveys (Table 5) show, this inverse relationship is not so marked as to allow estimation of the serum triglyceride level by the HDL-C level alone, and whether an increased serum triglyceride level is an independent risk factor for CHD should be determined. The Framingham study showed that the incidence of CHD increases with an increase in the serum triglyceride level independently from the HDL-C level⁶¹.

Murase⁶², who evaluated the relationship between decreased HDL-C and the serum triglyceride level in patients with diabetes mellitus, found a rapid increase in the percentage of patients with hypo-HDL-cholesterolemia when the serum triglyceride level exceeded 150 mg/dl (Fig. 7).

(2) Effects on LDL

Hypertriglyceridemia is also involved in the polymorphism of LDL particles. LDL particles undergo remodeling, and therefore, small dense LDL is increased in hypertriglyceridemia^{63,64} (Fig. 8). Small dense LDL readily enters the intima of the arterial wall and is easily oxidized and incorporated by macrophages, and is therefore considered to be a lipoprotein that promotes atherosclerosis⁶⁵⁻⁶⁷.

5) Effects on the blood coagulation-fibrinolysis system

In hypertriglyceridemia, factor VII is activated, and factor VII bound to phospholipids is increased, and plasmin activity is decreased. A positive correlation between the serum triglyceride level and the PAI-1 level was also reported. In hypertriglyceridemia, blood coagulation ability of factor X is amplified, and production of thrombin from fibrinogen is promoted. Thus, in hypertriglyceridemia, in addition to increased blood viscosity, thrombosis is also promoted by activation of coagulation fac-

Table 5. Correlation between the serum triglyceride and the HDL-C levels in each epidemiological study

Study	Subjects	Correlation coefficient
Honolulu Heart Study, 1976	Men	-0.36
Framingham Study, 1977	Men	-0.35
	Women	-0.43
Modesto, California 1980	Men and Women	-0.32
Lipid Research	Men	-0.23 to -0.55
Clinics Prevalence Study, 1980	Women	-0.21 to -0.65

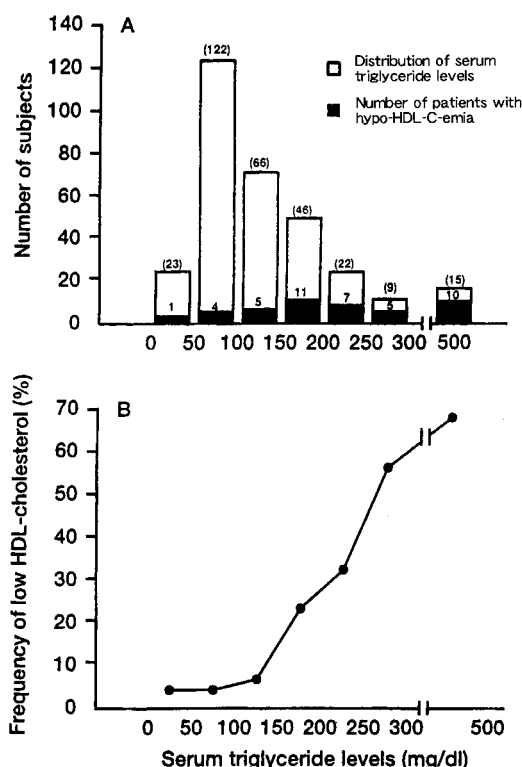


Fig. 7. Relationship between the serum triglyceride level and hypo-HDL-C-emia in males with diabetes mellitus.

A. Distribution of serum triglyceride levels

B. Number of patients with hypo-HDL-cholesterolemia (Murase T *et al.* Churchill Livingstone Japan, 1994)⁶²

tors^{35,68-72}.

Morishita⁷³ evaluated the relationship between these blood coagulation-fibrinolysis factors and the serum triglyceride level and observed a positive correlation between the serum triglyceride level and factor VII, factor X, and active type PAI-1 (Fig. 9). From this aspect, lower serum triglyceride levels are more desirable.

6) Importance of the serum triglyceride level evaluated by epidemiological studies

Noma⁷⁴ reported the distribution of serum lipid levels in 240 normal Japanese males (Fig. 10). The distribution of serum cholesterol or HDL-C levels showed normal distribution while that of serum triglyceride levels was deviated to low values, trailing the skirt toward high values. This distribution curve of serum triglyceride levels is composed of some different curves, and the border between the first peak and the second peak is present at the serum triglyceride level of 150 mg/dl. Next, the clinical importance of the serum triglyceride level evaluated by epidemiological studies is briefly described below.

(1) Relationship between the serum triglyceride level and CHD (reports in Japan)

(a) Report of the Research Committee on Primary Hyperlipidemia (1986)

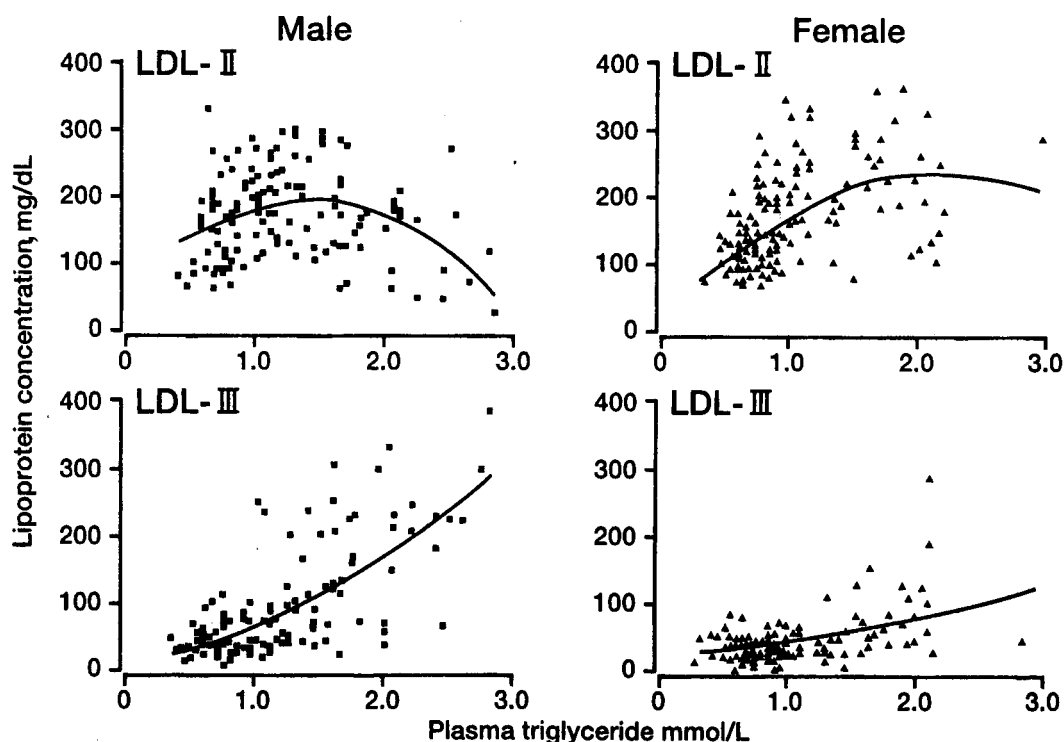


Fig. 8. Small dense LDL (LDL-III) and serum triglyceride levels (McNamara JR *et al.* Arterioscler Thromb 1992)⁶³⁾

A cross-sectional survey of 10,313 subjects revealed no association between the serum triglyceride level and the development of CHD. However, in patients with FH, the incidence of cardiovascular diseases increased, depending on the serum triglyceride level; the incidence of CHD in subjects with a serum triglyceride level ≥ 150 mg/dl was 3 times that in those with a serum triglyceride level < 150 mg/dl⁷⁵⁾.

(b) Report of the Research Committee on Primary Hyperlipidemia (1987)

A cross-sectional survey in 419 patients with severe hyperlipidemia revealed an increased incidence of atherosclerotic diseases in patients with a serum triglyceride level ≥ 300 mg/dl⁷⁶⁾.

(c) The association between coronary angiographic findings and the levels of serum lipids and serum apoprotein was evaluated in age-matched males. The group with significant angiographic findings showed significantly higher levels of serum triglyceride (166 ± 65 vs 112 ± 53 mg/dl, mean $\pm$ SD) and apo B and significantly lower levels of HDL-C, apo AI, and apo AII than in the normal controls.²³⁾

(d) In addition, in an epidemiological survey to clarify risk factors for the development of CHD, the χ^2 test suggested the usefulness of the high serum cholesterol and triglyceride level as risk factors²⁵⁾.

(e) A family survey of patients with CHD showed a significantly higher serum triglyceride level in the patients

than in the controls (178 ± 80 vs 111 ± 46 mg/dl, $p < 0.01$) and in male relatives of the patients than in male non-relatives (167 ± 98 vs 103 ± 51 mg/dl, $p < 0.01$)²¹⁾.

(f) Epidemiological surveys of Japanese Americans living in the U.S. (Hawaii or Los Angeles) and Japanese living in Hiroshima have also been performed. Among them, the following studies suggested the involvement of high serum triglyceride level.

i) Robertson *et al.*⁷⁷⁾ evaluated coronary risk factors and suggested the involvement of obesity, the serum cholesterol level, uric acid level, systolic blood pressure, and diastolic blood pressure as risk factors in Japanese-Americans living in Hawaii and the serum cholesterol level and blood pressure in Japanese living in Japan. The serum triglyceride level was slightly higher in patients with CHD.

ii) A study on the relationship between ECG abnormalities and various parameters in 1,095 Japanese-Americans living in Hawaii and Los Angeles showed a significantly higher serum triglyceride level in the group with ECG abnormalities than in the group with normal ECG (171 ± 90 vs 126 ± 103 mg/dl, $p < 0.01$)²⁴⁾. When the subjects were stratified according to the serum lipid level, ECG abnormalities were significantly more frequently observed in subjects with a serum triglyceride level ≥ 300 mg/dl. In addition, in the group with a serum cholesterol level ≥ 250 mg/dl, the number of subjects with ECG abnormalities at a serum triglyceride level ≥ 150 mg/dl

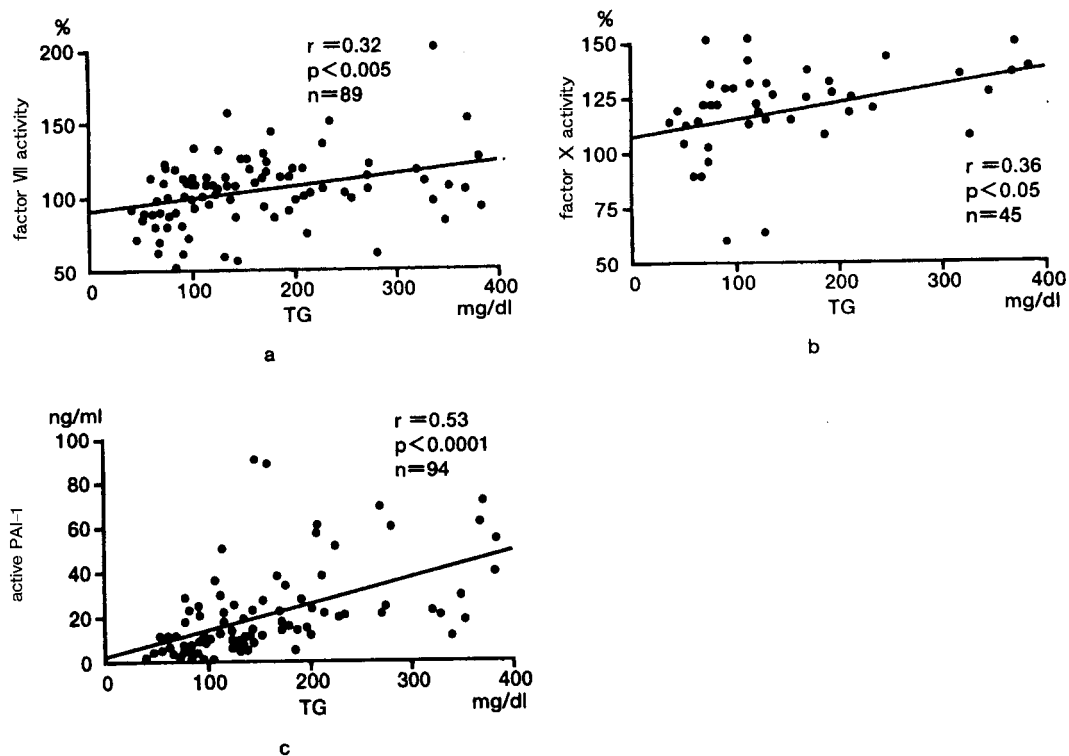


Fig. 9. Relationship between serum triglyceride and coagulation-fibrinolysis factors. a : Correlation between serum triglyceride and factor VII activity, b : Correlation between serum triglyceride and factor X activity, c : Correlation between serum triglyceride and active PAI-1 (Eriko Morishita, Gendai Iryo, 1996)

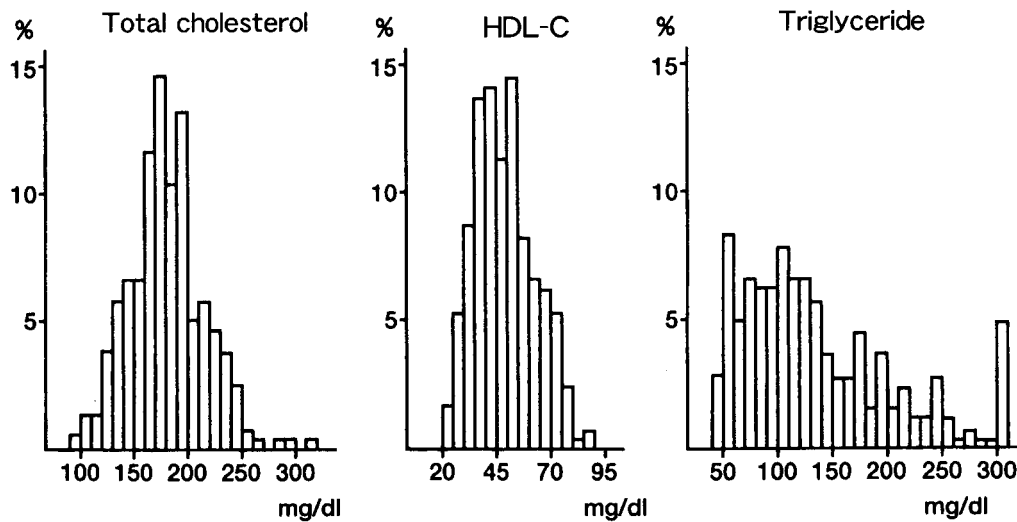


Fig. 10. Distribution of serum lipids concentrations in Japanese (240 males) (Akio Noma, Gendai Iryo, 1996)

was twice that at a serum triglyceride level <150 mg/dl. In the group with a serum cholesterol level ≥ 200 mg/dl, the number of subjects with ECG abnormalities increased with the serum triglyceride level, showing a significant increase at a serum triglyceride level ≥ 300 mg/dl.

(g) Retrospective and prospective surveys on the relationship between CHD and serum lipids performed by the Uwajima Social Insurance Hospital revealed the following results^{21,23,25,29}.

i) Retrospective studies

The serum triglyceride level was higher in the CHD group than in the non-CHD group (180 ± 32 mg/dl vs 112 ± 52 mg/dl, $p < 0.01$). Therefore, when the serum triglyceride level of 190 mg/dl (as 95% value) was used as the cut-off value, 49% of the patients with CHD had hypertriglyceridemia. In other words, 51% of the patients with CHD showed a triglyceride level ≤ 190 mg/dl.

ii) Prospective studies

Setting the occurrence of myocardial infarction or angina pectoris as the end points, 1,110 normal subjects were observed for 12 years. During the follow-up period, 19 subjects showed end points. The mean triglyceride level was 136 mg/dl in the patients with myocardial infarction or angina pectoris but 116 mg/dl in the controls. The incidence of myocardial infarction and angina pectoris in subjects with a serum triglyceride level < 150 mg/dl (1.12%) was 3 times that in those with a level ≥ 150 mg/dl (4.09%).

(h) Kameda *et al.*³⁷⁾ evaluated serum lipids in 97 patients who developed myocardial infarction according to sex. In the group who developed myocardial infarction, the serum triglyceride level was 158 mg/dl in males and 161 mg/dl in females, while in the control group, the serum triglyceride level was 116 mg/dl and 82 mg/dl, respectively.

(i) Cross-sectional survey by the Research Institute of Diabetes Mellitus, Asahi Mutual Life Insurance Co., Ltd.

A cross-sectional survey by this institution in 880 patients with type 2 diabetes mellitus showed 71 patients who developed myocardial infarction and 27 who developed cerebrovascular disease. The serum triglyceride level was 151 mg/dl in the group with myocardial infarction (control group, 133 mg/dl, ns) and 177 mg/dl in the group with cerebrovascular disease (control group, 133 mg/dl, $p < 0.001$). In these patients with type 2 diabetes mellitus, the serum triglyceride level was ≤ 100 mg/dl in 32.4% of the patients with myocardial infarction and 22.2% of those with cerebrovascular disease, and the serum triglyceride level was ≤ 150 mg/dl in 57.7% of the former and 40.7% of the latter. There have been no results showing direct contribution of correction of the serum triglyceride value to improvement in the prognosis of atherosclerotic diseases in patients with diabetes mellitus. However, in patients with diabetes mellitus, it should be recognized that atherosclerotic diseases develop even at a relatively low serum triglyceride level.

(j) Results from Institutions for the Research of Radiological Effects

Comparison between Japanese living in Hiroshima and those living in Hawaii showed a high incidence of fatal CHD in the latter and the involvement of the high blood pressure, glucose intolerance, smoking, and the amount of alcohol ingestion (negative correlation), but no significant difference in the serum triglyceride level⁷⁸⁾.

(2) Relationship between the serum triglyceride level and CHD (studies overseas)

In 1959, Albrink and Mann who carried out a case control study, suggested the relationship between the serum triglyceride level and myocardial infarction⁷⁹⁾.

Austin^{3,4)} and Hamsten⁵⁾ reviewed in detail the epidemiological studies in various countries, mainly western countries, on the association between the serum triglyceride level and CHD. In all of 17 case-control studies and cross-sectional surveys between 1959 and 1989 on the association between the serum triglyceride level and CHD in males, simple correlation analysis revealed their relationship. Of these studies, all 6 in which correction for serum cholesterol or LDL-C was performed also showed a relationship between increased triglyceride and development of CHD. This relationship was also observed in 3 of 4 studies in which correction for HDL-C was performed. Many of 16 prospective surveys performed between 1965 and 1990 confirmed the relationship between increased serum triglyceride and development of CHD by simple correlation analysis. However, when these results were corrected for the serum cholesterol or LDL-C level, the association between the serum triglyceride level and CHD decreased. Of 5 studies in which correction for HDL-C was performed, only one still confirmed the relationship between the serum triglyceride level and CHD. These results are supported by the reciprocal relationship between the serum triglyceride and HDL-C levels. On the other hand, evaluation of the association between the serum triglyceride level and CHD in females showed their closer association than in males.

In the Western Collaboration Group Study⁶⁾ performed in 2,966 subjects, the relative risk of the serum triglyceride level for CHD was 1.35, but their association disappeared after correction for serum cholesterol, HDL-C, and BMI. Carlson *et al.*⁷⁾ performed a secondary prevention test of myocardial infarction and reported a decrease in the incidence of new cases of myocardial infarction by reducing the serum triglyceride level. In an angiographic study by Freedman *et al.*⁸⁾, a serum triglyceride level ≥ 196 mg/dl increased the incidence of CHD independently from other risk factors including serum cholesterol. The Paris Prospective Study⁹⁾ suggested the importance of serum triglyceride as an independent risk factor for CHD in females including those with an HDL-C ≤ 40 mg/dl. Similarly, the Lipid Research Clinic Follow-up Study⁸⁰⁾ showed an increase in deaths from CHD at a serum triglyceride level ≥ 180 mg/dl, suggesting the importance of the serum triglyceride level as an independent risk factor. In addition, the Stockholm Prospective Study⁸¹⁾ indicated the serum triglyceride level as a risk factor for fatal myocardial infarction in both males and females. Comprehensive evaluation of these results suggested a 2% decrease in the incidence of CHD by a 1% decrease in the serum triglyceride level⁸²⁾. A recent report of results of coronary bypass surgery suggested the impor-

tance of the triglyceride level as a factor predicting re-infarction of the bypassed arteries⁸³. In contrast, Pocock *et al.* using 7,000 subjects and the Helsinki Heart Study refuted the association between the serum triglyceride level and CHD⁸⁴⁻⁸⁶.

Thus, a review of epidemiological studies in various countries suggests that the importance of serum triglyceride as a coronary risk factor can not be ignored though some studies have refuted the relationship between the serum triglyceride level and CHD.

The European Society of Atherosclerosis proposed an optimal serum triglyceride level ≤ 200 mg/dl and a treatment goal level ≤ 200 mg/dl⁸⁷⁻⁸⁹. This may be mainly based on the increased deaths from CHD at a serum triglyceride level ≥ 180 mg/dl in the LRC Prevalence Study and the results of the above Freedman's study. However, Criqui observed an increased risk of CHD at a serum triglyceride level $\geq 4-6$ mmol/L (354-531 mg/dl), and Barbir *et al.* proposed a serum triglyceride level ≥ 5 mmol/L (443 mg/dl) as a warning for an increase in CHD⁹⁰.

(3) Relationship between the serum triglyceride level and cerebrovascular diseases

Many studies have refuted the involvement of the serum triglyceride level in cerebral infarction^{11,91,92}. However, the Glostrup Study in aged subjects⁹³ showed cerebrovascular diseases that can not be classified in many females with hypertriglyceridemia. The Honolulu Heart Study showed a positive correlation between the degree of extension of atherosclerosis in the small arteries in the circle of Willis and the serum triglyceride level, and multivariate analysis confirmed this relationship. Rösner *et al.* evaluated 61 patients aged 21-55 years with ischemic cerebrovascular disease and found hypertriglyceridemia in 18% of the males and 17% of the females⁹⁴. Daniel *et al.* evaluated 8 children with thrombotic cerebrovascular disease of unknown cause that was accompanied by serum lipid abnormalities, and observed hypertriglyceridemia and decreased HDL-C in many of them⁹⁵. Mathew *et al.*⁹⁶ studied the relationship between cerebral infarction lesions observed by angiography and serum lipids 25 days after attacks and found a significantly high incidence of type IV hyperlipidemia in the group with atherosclerotic lesions (type IV hyperlipidemia was observed in 42% and type II hyperlipidemia in 9% of the patients with extracranial major vessel disease while type IV hyperlipidemia was observed in 35.8% and type II hyperlipidemia in 8.4% of those with intracranial major vessel disease.) Pedro-Betet *et al.* reported increased remnant particles in ischemic cerebrovascular disease; triglyceride and cholesterol in VLDL and IDL, triglyceride in LDL, and serum Lp(a) were increased, but HDL-C was decreased in 100 males with ischemic cerebrovascular diseases compared with 100 age-adjusted controls⁹⁷.

One of the influences of hypertriglyceridemia on the

development of cerebral infarction is increased large particle lipoproteins and a resulting increase in blood viscosity since triglyceride is present in large particle lipoproteins. A study with gemfibrozil showed that a decrease in VLDL-triglyceride resulted in improvement in cerebral circulation measured with Xenon 133 in patients with cerebrovascular diseases, leading to improvement in their cognition ability⁹⁸.

III. Problems and matters to be addressed in establishment of the serum triglyceride level for diagnosing hypertriglyceridemia

Though the serum triglyceride level for diagnosing hypertriglyceridemia was proposed in this study, this value was obtained by blood collection after fasting for at least 10 hours. The state of blood collection is important. Therefore, when a level higher than the diagnostic level is observed, treatment should not be initiated immediately. Instead, explanation of dietary therapy and exercise therapy is given, and re-examination is performed after fasting for more than 10 hours and abstention from alcohol on the previous day of examination. When a level higher than the diagnostic level is obtained again, treatment is initiated. However, except for patients with a serum triglyceride level $\geq 1,000$ mg/dl, the course is observed with strict dietary and exercise therapy for 2-3 months, avoiding early initiation of drug treatment. At present, treatment with fibrates, nicotinic acid derivatives, or EPA preparations reduces the incidence of CHD and deaths from CHD but does not significantly reduce the total number of deaths.

IV. Future problems of triglycerides

Evaluation of hypertriglyceridemia as a risk factor for CHD is important. We hope that the triglyceride level for diagnosing hypertriglyceridemia proposed in this study will be tolerable to the use by clinicians who aim to prevent the development and progression of CHD. However, there have been few large-scale prospective epidemiological studies on the relationship between hypertriglyceridemia and the development and progression of hypertriglyceridemia in Japan. We have a responsibility to make efforts to determine more practical serum triglyceride levels based on results of future studies.

HDL-cholesterol

Many epidemiological surveys have shown a decreased cholesterol level in the high-density lipoprotein (HDL) fraction (HDL-C) in patients with atherosclerotic diseases represented by coronary heart disease (CHD) and a correlation between the incidence of these diseases and the serum HDL-C level¹⁻⁵. Therefore, hypo-HDL-cholester-

olemia is widely accepted as a risk factor for CHD that is independent of other risk factors such as the cholesterol level (LDL-C) in the low-density lipoprotein (LDL) fraction. Hereditary diseases showing markedly decreased HDL-C are often complicated by lipid accumulation signs such as corneal opacity or juvenile atherosclerotic diseases. A previous study reported inhibition of the progression of atherosclerosis after intravenous HDL injection to animals⁶⁾. HDL appears to have anti-atherosclerotic effects. Therefore, in the presence of hypo-HDL-cholesterolemia, atherosclerosis such as ischemic heart disease should be suspected, and close examination of signs and symptoms and management are necessary. The Japan Atherosclerosis Society organized a committee to produce a guideline for the diagnosis and management of adult hyperlipidemia based on previous results in Japan. This report summarizes the discussion in the HDL-cholesterol subcommittee on the desirable HDL-C level in Japanese.

I. Pathogenesis of hypo-HDL-cholesterolemia

The basis for the negative correlation between hypo-HDL-cholesterolemia and the development of CHD has not adequately been clarified. However, recent experimental study by biochemical methods have shown that HDL promotes efflux of cholesterol from foam cells accumulated in atherosclerotic lesions⁷⁾. This anti-atherosclerotic action of HDL has been supported by experimental studies in animal models^{6,8)}.

HDL has the highest density and comprises of the smallest particles among various lipoproteins. HDL is produced and secreted by the liver and small intestine.

HDL immediately after secretion is disk-like particles called nascent HDL. HDL removes cholesterol accumulated in the peripheral tissue, and esterification of the removed cholesterol by lecithin : cholesterol acyltransferase (LCAT) results in formation of cholesteryl ester, which is incorporated into the core of HDL particle. With an increase in cholesteryl ester in the particles, HDL becomes spherical, increasing its diameter. Cholesteryl ester in the inner part of HDL is transferred by cholesteryl ester transfer protein (CETP) to very low density lipoprotein (VLDL) or LDL. These proteins that received cholesteryl ester are taken up by the liver. In addition, a pathway by which HDL directly transfers cholesterol from peripheral tissue to the liver has been suggested. A part of cholesterol incorporated into the liver is used again, and another part is excreted as bile acid into the bile. These pathways are the so-called reverse cholesterol transport system⁹⁾, which is considered to prevent cholesterol accumulation in tissues.

As shown in Table 6, hypo-HDL-cholesterolemia occurs in association with various factors including very rare hereditary HDL deficiency¹⁰⁾ (such as Tangier disease, familial LCAT deficiency, fish eye disease, apo A-I/C-III deficiency, and isolated apo A-I deficiency) and secondary hypo-HDL-cholesterolemia with a relatively high incidence that is associated with certain types of diseases or drug administration. In patients with hereditary HDL deficiency, premature CHD often develops, and signs of lipid accumulation such as corneal opacity or hepatosplenomegaly are sometimes observed. The HDL-C level is generally higher in females than in males, and the serum HDL-C level secondarily decreases due to factors

Table 6. Diseases and factors causing hypo-HDL-cholesterolemia

Disease
Hereditary HDL deficiency
Tangier disease, familial LCAT deficiency, fish eye disease, Apo A-I/C-III deficiency, isolated apo A-I deficiency
Hypertriglyceridemia
Obesity
Diabetes mellitus
Hyperthyroidism
Liver cirrhosis or liver diseases accompanied by jaundice
Myeloma
Chronic renal failure
Patients on hemodialysis
Other factors
Sex (males)
Diets rich in polyunsaturated fatty acid and saturated fatty acid
High carbohydrates diet
Physical inactivity
Smoking
Hypotensive drugs (thiazides, β blockers (ISA (–)))
Probucol
Oral hypoglycemic drugs (SU drugs)
Hormone drugs (androgen, progesterone)
Immunosuppressants

shown in Table 6. In general, hypertriglyceridemia is often accompanied by hypo-HDL-cholesterolemia. The HDL-C level is decreased in diabetes mellitus, hyperthyroidism, liver cirrhosis, and chronic renal failure and also decreases due to obesity caused by excessive calory intake, smoking, physical inactivity, and some drugs (probucol, β -blockers, anabolic steroids). Concerning the types of fatty acids in meals, studies have shown decreases in both LDL-C and HDL-C after a diet containing a high concentration of polyunsaturated fatty acids¹¹⁻¹³. However, another study reported no decrease in HDL-C when the intake of saturated fatty acid was reduced by replacing with polyunsaturated fatty acids¹⁴. HDL-C decreases after a high-carbohydrate diet.

II. Level for diagnosing hypo-HDL-cholesterolemia

In western countries, the Framingham Study¹⁵⁻¹⁷ and Multiple Risk Factor Intervention Trial (MRFIT)¹⁸ have shown a higher incidence of CHD with a lower serum HDL-C level and a lower incidence of CHD with a higher serum HDL-C level. In males, the total number of deaths in the group with an HDL-C level ≤ 35 mg/dl was 1.9 times that in the group with an HDL-C level ≥ 54 mg/dl, and the number of deaths from ischemic heart disease in the former was 4.1 times that in the latter. Gordon *et al.*¹⁹ reported a 2-3% increase in the incidence of ischemic heart disease with a 1 mg/dl decrement in HDL-C. When only the HDL-C level is low (isolated low HDL-cholesterolemia)²⁰ in the absence of hypercholesterolemia or hypertriglyceridemia, the risk of atherosclerosis was reported to increase. Conversely, a slightly high HDL-C level is considered to be a negative risk factor for CHD.

In Japan, similar results have been obtained in the general population though few large-scale surveys have been performed. A long-term prospective study by Kitamura *et al.* at the Osaka Medical Center for Cancer and Cardiovascular Diseases showed that the relative risk of CHD was 1.80 in subjects with an HDL-C level of 1.45-1.65 mM (56.1-63.8 mg/dl, 75 percentile) compared with those with an HDL-C level over 1.66 mM (64.2 mg/dl), 1.61 in those with an HDL-C of 1.24-1.44 mM (48.0-55.7 mg/dl), and 4.17 in those with an HDL-C < 1.24 mM (< 48.0 mg/dl), confirming the high risk of CHD in hypo-HDL-cholesterolemia²¹. When these data were analyzed again according to 5 mg/dl increments in the HDL-C level (Fig. 11), the incidence of CHD was increased at HDL-C levels lower than 40 mg/dl.

Retrospective studies in Japanese patients with CHD have also shown a decrease in the mean HDL-C level and a mean HDL-C level ≤ 40 mg/dl in males²²⁻²⁷. Decreased serum HDL-C has been also reported in patients with cerebral infarction or transient cerebral ischemic attacks^{24,28,29}. A cross-sectional survey by the Research Committee on Primary Hyperlipidemia (Chairman, Seiichiro Tarui), Intractable Diseases, of the Ministry of Health and Welfare of Japan (Fig. 2) analyzed the association between the HDL-C level and vascular complications in patients with hyperlipidemia and observed an increase in the complication rate of ischemic heart disease in the group with an HDL-C level ≤ 40 mg/dl compared with the group with an HDL-C of 41-55 mg/dl and similar tendency of a slighter degree for the complication rate of cerebrovascular diseases.

Based on these results in Japanese, what is the desirable range of HDL-C in Japanese? The National Cho-

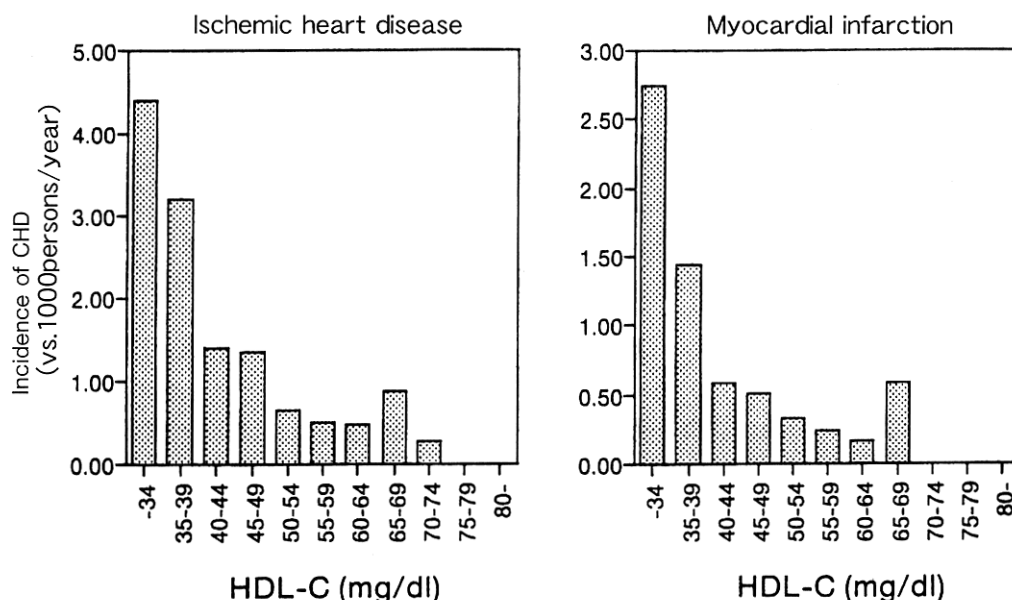


Fig. 11. HDL-cholesterol levels and the incidence of CHD (re-analysis of data reported by Kitamura *et al.*, *Circulation*, 89 : 2533-2539, 1994).

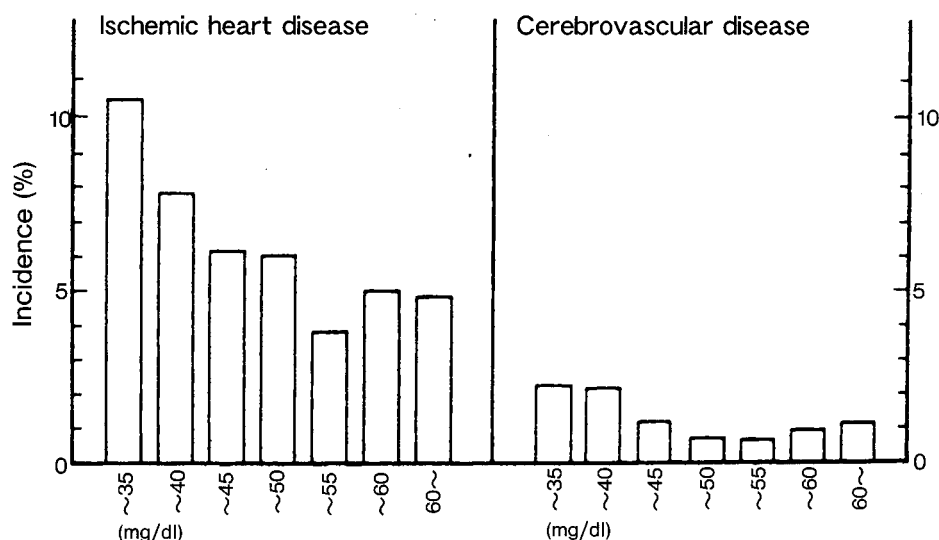


Fig. 12. HDL-cholesterol levels and the incidence of vascular complications (Research Committee on Primary Hyperlipidemia).

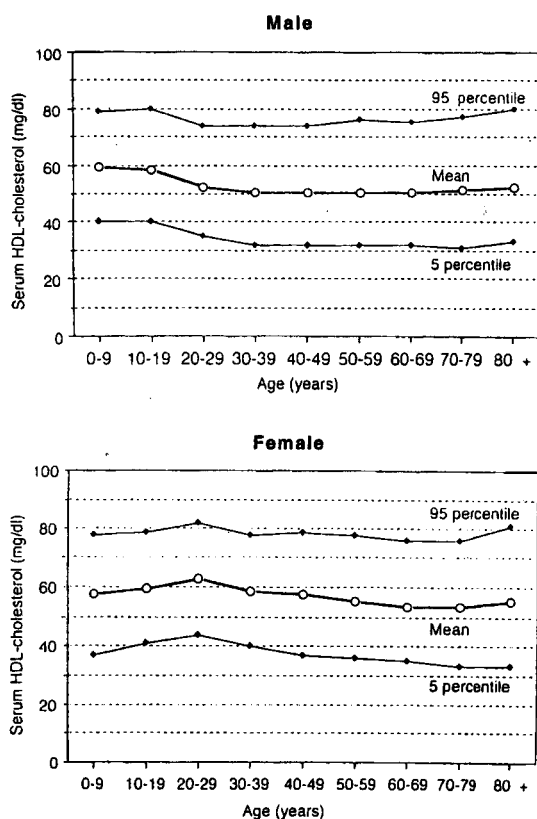


Fig. 13. Serum HDL-cholesterol levels according to age in Japanese (Research Committee on Serum Lipid Survey 1990 in Japan).

lesterol Education Program (NCEP) in the U.S.^{31,32}, which has often been used as a reference, proposed an HDL-C level ≤ 35 mg/dl for initiating treatment. Regarding the change of HDL-C level according to age and sex, there is

a report by the Research Committee on Serum Lipid Level Survey 1990 in Japan³³ (Fig. 13). As shown in Fig. 14, the mean HDL-C level at each age in males and females shows that the level in the females is higher than that in the males by about 5–10 mg/dl (Fig. 5). In the males, the HDL-C level in this report was higher than that in the U.S.³² by about 5 mg/dl (mean) in each age group (Fig. 15). No marked difference was observed between the two countries in the females. When these results in Japanese are also taken into consideration, a serum HDL-C level < 40 mg/dl may be a risk of CHD (Table 7). In such patients, detailed examinations for the presence or absence of atherosclerotic diseases should be performed, and treatment in the direction to increase HDL-C is necessary. The treatment principles will be evaluated in future studies. Concerning the border between normal and abnormal HDL-C levels in females, there is an opinion that a value about 5 mg/dl higher than that in males may be necessary. However, since a border value of 35 mg/dl in females complicates the diagnosis, we also propose the borderline of 40 mg/dl in females.

III. Supplementary matters concerning HDL-C

1) Method of measuring HDL-C

The basic method for measuring serum HDL-C is ultracentrifugation, but the precipitation method (fractionation method) and the direct method are frequently used in the daily clinical setting. In the precipitation method, lipoproteins other than HDL (such as VLDL and LDL) are precipitated with fraction reagents, and cholesterol concentration in the supernatant fraction (HDL) is measured by the enzymatic methods. The methods of fractionation include heparin/Mn²⁺, heparin/Ca²⁺, polyethylene glycol 6000, phosphotangstate/Mg²⁺, and dex-

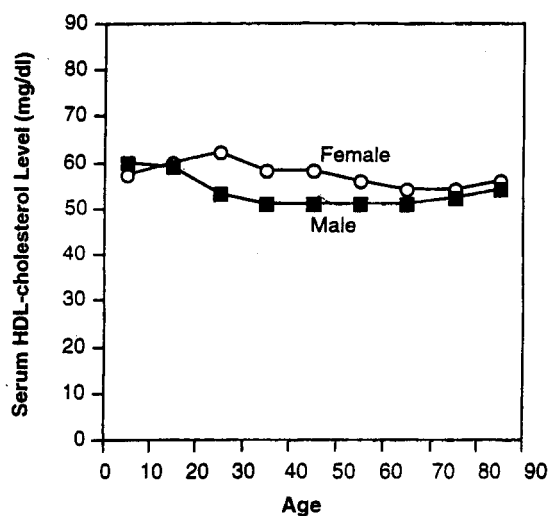


Fig. 14. Sex difference in the serum HDL-cholesterol level in Japanese (Research Committee on Serum Lipid Level Survey 1990 in Japan)

tran sulfate/Mg²⁺. These methods are readily performed and are international standards for HDL-C measurements but can not be used in chyliform samples. In addition, there are some technical errors according to types of precipitation reagents, and the fractionation procedure is not automated. Recently, the HDL-C direct quantification method has become used at institutions nation wide. In the direct method, HDL-C is directly measured without precipitation of lipoprotein containing apo B. This method has rapidly spread because automation is possible. However, a marked dissociation from data obtained by the conventional precipitation method is sometimes observed (especially in hypo-HDL-cholesterolemia). This dissociation depends on the content of

Table 7. HDL-cholesterol level for diagnosing hypo-HDL-cholesterolemia.

HDL-C < 40 mg/dl

apo-E-rich HDL particles in samples. Since hypo-HDL-cholesterolemia discussed in this report is based upon values obtained by the conventional precipitation method, further studies are necessary on their conformity with epidemiological data that will be obtained by the direct method that is becoming the main current in Japan.

2) Management of patients with hyper-HDL-cholesterolemia

Hyper-HDL-cholesterolemia³⁴⁾, i.e., markedly increased serum HDL-C (HDL-C ≥ 100 mg/dl) is a syndrome caused by various factors. Homozygous patients with CETP deficiency, the most frequent HDL metabolic disease in Japan, often show an HDL-C level ≥ 100 mg/dl [172 ± 45 mg/dl (mean $\pm$ SD, $n=24$) in patients with intron 14 splice abnormality]³⁴⁾. Hyper-HDL-cholesterolemia due to CETP deficiency or hepatic lipase deficiency, corneal arcus, ischemic heart disease, cerebrovascular disease are sometimes observed as complications^{35,36)}. An epidemiological study in Omagari in Akita Prefecture where there are many cases of CETP deficiency³⁷⁾ showed that hyper-HDL-cholesterolemia due to CETP deficiency is not a longevity syndrome, but is often complicated by CHD. Fushimi *et al.* performed carotid artery echography and measured the pulse wave velocity in patients with hypo-HDL-cholesterolemia (mostly CETP deficiency) in Yokote City near Omagari in Akita Prefecture and observed a significantly higher incidence of atherosclerotic lesions in the carotid artery in the patients with hyper-HDL-cholesterolemia than in the controls³⁸⁾. Concerning the atherogenicity of CETP deficiency, a

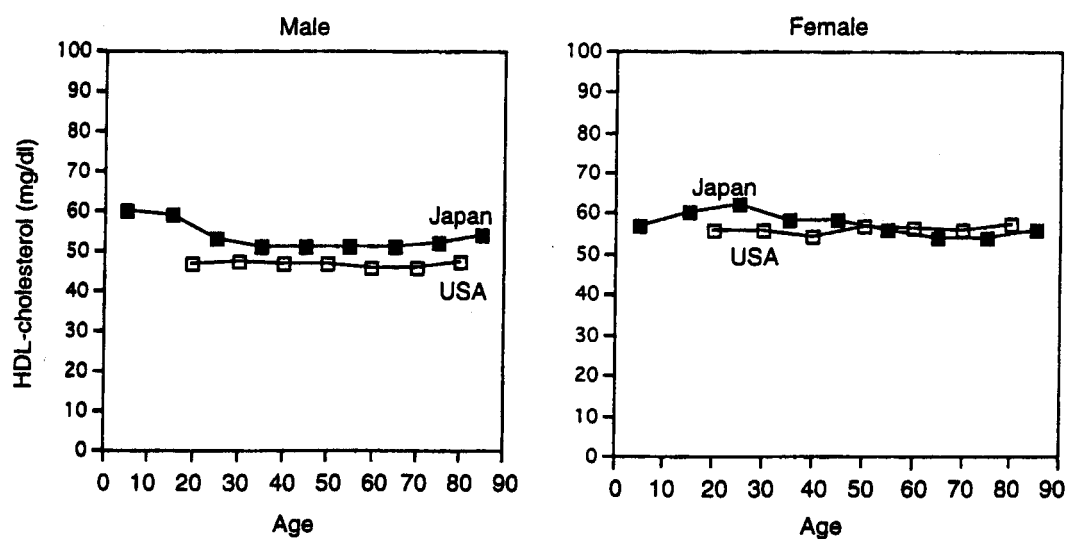


Fig. 15. Comparison of serum HDL-cholesterol levels between Japan and United States.

recent survey of Japanese-Americans by Tall *et al.*³⁹⁾ suggested a negative correlation between the incidence of CHD and the HDL-C level in all subjects but a higher incidence of CHD in the group with CETP deficiency (especially with an HDL-C level of 41–60 mg/dl) than in the control group. At a serum HDL-C level ≥ 100 mg/dl, abnormalities in HDL metabolism should be suspected, and analysis of the cause and extensive examination for the presence or absence of atherosclerosis as a possible complication should be performed.

Summary

This paper described the Guideline for Diagnosis and Management of Hyperlipidemias for Prevention of Atherosclerosis proposed by The Japan Atherosclerosis Society (JAS) Guideline Investigating Committee (1,995–2,000) under the auspices of the JAS Board of Directors.

1) The guideline defines the diagnostic criteria for serum total cholesterol (Table 1), LDL-cholesterol (Table 1), triglycerides (Table 4) and HDL-cholesterol (Table 7). It also indicates the desirable range (Table 1), the initiation levels of management (Table 2) and the target levels of treatment (Table 2) for total and LDL-cholesterol.

2) Though both total and LDL-cholesterol are shown as atherogenic parameter in the guideline, the use of LDL-cholesterol, rather than total cholesterol, is encouraged in daily medical practice and lipid-related studies, because LDL-cholesterol is more closely related to atherosclerosis.

3) Elevated triglycerides and low HDL-cholesterol are included in the risk factors, since no sufficient data have been accumulated to formulate the guideline for these two lipid disorders.

4) Emphasis is laid on evaluation of risk factors of each subject before starting any kind of treatment (Table 2).

5) This guideline is applied solely for adults (age 20–64). Lipid abnormalities in children or the youth under age 19, and the elderly with an age over 65 have to be evaluated by their own standard.

6) This part of the guideline gives only the diagnostic aspects of hyperlipidemias. The part of management and treatment will follow in the second section of the guideline that will be published in future.

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