Figure 3. a, Immunofluorescence study for F4/80 in glomeruli of nonoperated WT and KO and renal-ablated WT and KO mice. Right panel shows representative F4/80 staining in a glomerulus. Immunohistochemical analysis revealed increased number of glomerular infiltrating F4/80-positive macrophages in KO mice after subtotal nephrectomy. b, The mRNA levels of proteins associated with macrophage infiltration and inflammation. c, The mRNA levels of proteins associated with glomerular and tubulointerstitial fibrosis. d, The mRNA levels of NADPH oxidase components. After subtotal nephrectomy, the mRNA levels of VCAM-1, MCP-1, TNF-α, TGF-β1, collagen I, collagen III, gp91^{phox}, p47^{phox}, and p67^{phox} in the remnant kidney were significantly higher in KO mice than in WT mice. #P<0.05 for control WT mice. *P<0.05 for renal-ablated WT mice.

subtotal nephrectomy (33.9±10.6 mg/g Cr versus 102.3±16.2 mg/g Cr; P<0.01, Figure 4b). In contrast, no differences were observed in urinary albumin excretion between WT/Ad-β gal and WT/Ad-APN after subtotal nephrectomy (29.7±7.6 mg/g Cr versus 35.5±9.8 mg/g Cr; NS, Figure 4b). Furthermore, Ad-APN-treated subtotal nephrectomized-KO mice had significantly smaller glomerular cross-sectional area (Figures 4c and 5e through 5h), lower number of intraglomerular cells (Figures 4d and 5e through 5h), smaller area of tubulointerstitial fibrosis (Figures 4e and 5e through 5h), lower number of F4/80 positive cells, and lower mRNA levels of F4/80. CD68. VCAM-1, MCP-1. TNF-α. TGF-β1, collagen I, collagen III, gp91^{phox}, p47^{phox}, and p67^{phox} in the remnant kidney (supplemental Figure III), compared with Ad-β gal–treated subtotal nephrectomized-KO mice. In contrast, no differences were observed in those levels between WT/Ad-β gal and WT/Ad-APN after subtotal nephrectomy (Figures 4c through 4e and 5a through 5d; supplemental Figure III).

Discussion

The major findings of the present study are the following: (1) renal injury was associated with accumulation of adiponectin in glomeruli and tubular interstitium; (2) Subtotal nephrectomized-adiponectin KO mice exhibited more severe glomerular hypertrophy, increased number of intraglomerular cells, wider tubulointerstitial fibrosis, lower levels of nephrin mRNA, higher urinary albumin excretion and overexpression of VCAM-1, MCP-1, TNF-α, TGF-β1, collagen I/III, and NADPH oxidase components mRNA levels in the remnant kidney, compared with subtotal nephrectomized-WT mice; (3) Adiponectin treatment ameliorated albuminuria, glomer-

ular hypertrophy, and tubulointerstitial fibrosis, and reduced mRNA levels of VCAM-1, MCP-1. TNF-α. TGF-β1, collagen I, III, NADPH oxidase components in the remnant kidney of subtotal nephrectomized-adiponectin KO mice relative to Ad-β gal-treatment in the same mice.

There is an increasing body of evidence that obesity itself can damage the kidney, even in otherwise healthy subjects.[1] There appears to be an interesting parallel between the effects of obesity and those of diabetes on the kidney. Firstly, increases in renal blood flow and glomerular filtration rate (GFR) have been described in obesity and, secondly, microalbuminuria is reported to be related to obesity.[19,20] These 2 processes are known to predict future renal dysfunction in diabetes. Experimental and clinical evidence suggests that inflammation and oxidative stress play a role in the pathogenesis of diabetic nephropathy, in addition to, or in concert with, the associated hemodynamic and metabolic changes.[21] Microalbuminuria, defined as urine albumin to urine creatinine ratio of 30 to <300 μg/mg,[22] is an established risk factor for cardiovascular morbidity and mortality in individuals with hypertension and diabetes mellitus and even in healthy subjects.[23,24] Dysfunction of the vascular endothelium, chronic low-grade inflammation, and oxidative stress are common pathophysiological findings in microalbuminuria and cardiovascular disease.[16,25] In the present study, subtotal nephrectomy worsened urinary albumin excretion, which was accompanied by glomerular and interstitial changes, although it is difficult to define the abnormal levels of excretion in mice. Mounting evidence indicates that these renal structural abnormalities are a consequence of concerted actions of mechanical stress, caused by glomerular hypertension and hypertrophy,[26] oxidative stress, and inflammatory changes comprising cell infiltration or proliferation and accumulation of extracellular
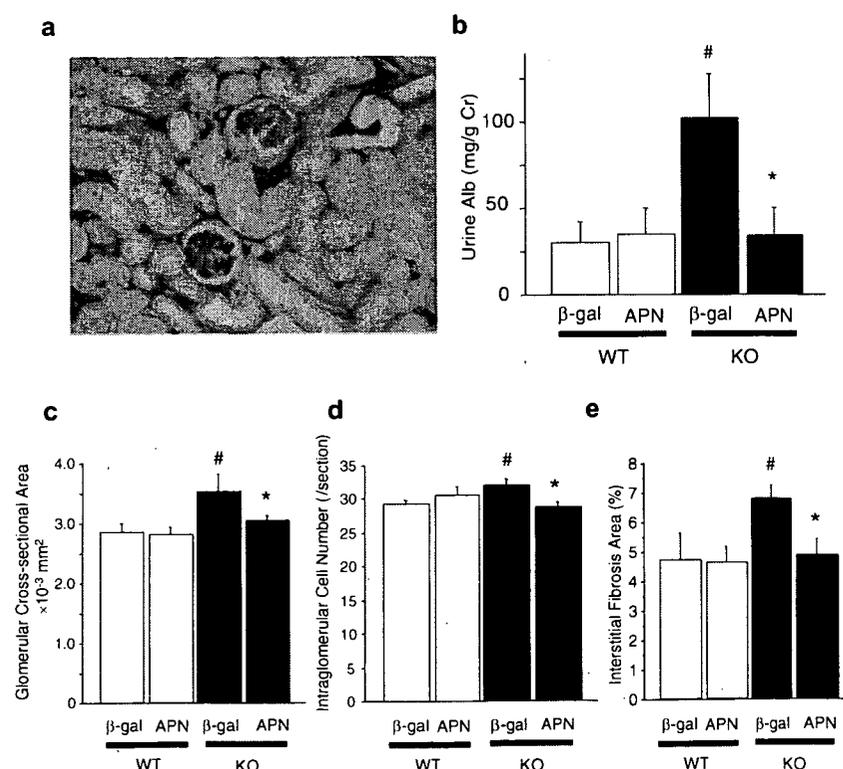
a   b

c   d   e

Figure 4. a, Representative results of immunohistochemical analyses for adiponectin in Ad-APN-treated KO mice after subtotal nephrectomy. Accumulation of adiponectin in glomeruli and tubulointerstitium originated from the blood stream. Magnification ×200. b, Urinary excretion of albumin/Cr (mg/g Cr) in KO and WT mice treated with Ad-APN or Ad-β gal. Ad-APN treatment significantly decreased urinary excretion of albumin/Cr (mg/g Cr) in KO than in KO/Ad-β gal after subtotal nephrectomy, whereas no differences were observed between WT/Ad-β gal and WT/Ad-APN after subtotal nephrectomy. The mean area of glomerular cross-section (c), number of intraglomerular cells (d), and area of interstitial fibrosis (e) in KO and WT mice treated with Ad-APN or Ad-β gal are shown. The mean glomerular cross-sectional area, number of intraglomerular cells, and tubulointerstitial fibrotic area were significantly lower in Ad-APN–treated KO mice than Ad-β gal–treated KO mice. #P<0.05 for Ad-β gal–treated WT mice. *P<0.05 for Ad-β gal–treated KO mice.
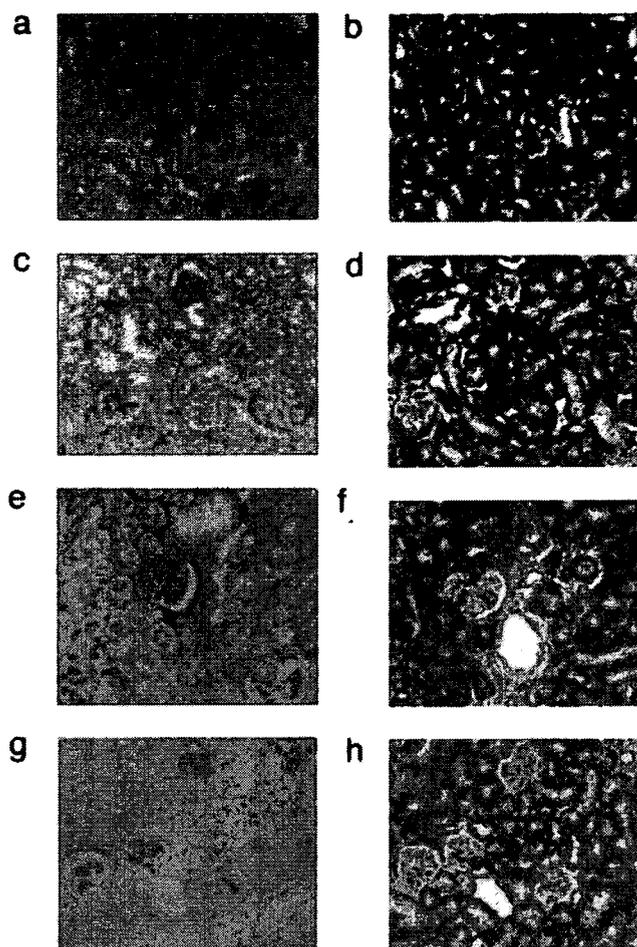
Figure 5. a through h, Histology of kidneys of WT/Ad-β gal (a and b), WT/Ad-APN (c and d), KO/ Ad-β gal (e and f) and KO/Ad-APN (g and h) after renal ablation. Representative periodic acid-Schiff (PAS)-stained sections (a, c, e, and g) and Masson trichrome stained sections (b, d, f, and h).

matrix.[27] Moreover, a causal relationship appears to exist between these phenomena, because distention of glomerular walls by intracapillary hypertension could trigger the local release of reactive oxygen species (ROS) and cytokines and growth factors.[28-30]

We and others have reported that adiponectin has antiinflammatory and antioxidative properties.[7,30,31] Clinically, hypoadiponectinemia is closely associated with increased levels of inflammatory markers such as C-reactive protein and IL-6.[28] In vitro, recombinant adiponectin suppressed TNF-α–induced expressions of endothelial adhesion molecules and TNF-α in macrophages, and selectively increased the expression of TIMP-1, which protects vascular wall from plaque rupture, in human monocyte-derived macrophages through induction of IL-10, an antiinflammatory cytokine.[3-6] We hypothesized that the protective effects of adiponectin against renal fibrosis are mediated by the antioxidative and antiinflammatory effects of adiponectin. Because our study showed that blood pressure levels and serum creatinine, creatinine clearance, and blood urea nitrogen concentrations were not different among WT and KO mice with or without renal ablation, factors other than hemodynamics should account for the renal fibrosis in APN-KO mice. In

this regard, adiponectin treatment reversed urinary albumin excretion and renal fibrosis, which were further upregulated in KO mice after subtotal nephrectomy compared with WT mice. These findings clearly show that the lack of adiponectin exacerbates renal damage after subtotal nephrectomy, and that adiponectin accumulation in the remnant kidney may have protective properties against glomerular and tubulointerstitial injury via its antiinflammatory and antioxidative effects.

Adipo R1, Adipo R2, and T-cadherin are reported to function as adiponectin receptors.[32,33] Adipo R1 and R2 mediate increased AMP-activated protein kinase, peroxidase proliferators-activated receptor-α (PPAR-α) ligand activities, and glucose uptake and fatty-acid oxidation by adiponectin.[32] T-cadherin, which is expressed in endothelium and smooth muscle, has been identified as an adiponectin-binding protein with preference for high molecular weight (HMW) adiponectin multimers.[33] On the other hand, the mechanism between adiponectin receptors and antiinflammatory, antioxidative effects of adiponectin is not entirely clarified. Recently, it has been reported that adiponectin protects the organism from systemic inflammation by promoting the clearance of early apoptotic cells by macrophages.[34] This activity was mediated by calreticulin expressed on the phagocytic cell surface and not by any of the previously identified adiponectin receptors such as Adipo R1, Adipo R2, and T-cadherin.[34] The glomerular infiltrations of macrophages were significantly increased in KO mice after subtotal nephrectomy in the present study. It is therefore possible that the increased inflammation and oxidative stress in KO mice might be mediated by the impaired clearance of early apoptotic cells, although further studies are necessary to elucidate the precise mechanism.

In conclusion, we demonstrated for the first time accumulation of adiponectin in the injured glomeruli, and that the lack of adiponectin promotes albuminuria, glomerular hypertrophy and tubulointerstitial fibrosis in a subtotal nephrectomy mouse model. Our results suggest that hypoadiponectinemia could contribute to the exacerbation of renal injury through a proinflammatory mechanism and that adiponectin supplementation might be therapeutically beneficial in renal disorders.

Disclosures

None.

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Committee Report 2

Diagnostic Criteria for Dyslipidemia
— Executive Summary of Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese

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Committee for Epidemiology and Clinical Management of Atherosclerosis

Epidemiological studies have shown that the incidence of coronary artery disease increases as the LDL-C, TC[1-9], and TG[10, 11] levels rise and the HDL-C level lowers[5, 8, 12] both in Japan and in Western countries (**Fig. 1**). At present, prevalence of coronary artery disease in Japan is much lower than that in Western countries[13-16]. However, recent increases in the LDL-C and TC levels in Japanese associated with so-called Westernization of diet implies future increases in coronary artery disease. In this guideline, therefore, criteria for the diagnosis of dyslipidemia were defined as in **Table 1**, with a greater emphasis on the prevention of coronary artery disease.

The first step in this diagnostic procedure is to measure TC, TG, and HDL-C levels after overnight fasting. LDL-C level is then calculated by use of the Friedewald equation (LDL-C = TC − HDL-C − TG/5). The LDL-C level may be measured by a homogenous method especially in the case of postprandial examination or when the TG level is 400 mg/dL or higher.

1. High-LDL-Cholesterolemia

Results of many epidemiological studies conducted in Western countries, including the Framingham study, have shown that the morbidity and mortality of coronary artery disease increase with elevations in the TC level (LDL-C level). Also in Japan, the relative risk of coronary artery disease has been confirmed to increase continuously with-rise in the LDL-C and TC levels by epidemiological studies such as NIPPON DATA 80, the Hiroshima/Nagasaki Study[7], Ministry of Health and Welfare Primary Hyperlipidemia Study[17], 3M Study, an epidemiological study at 76 workplaces[3, 4],

Okinawa Cohort Study[9], and Ehime Epidemiological Study[11].

In NIPPON DATA 80, a prospective epidemiological study in Japan, the relative risk of death due to coronary artery disease has been shown to increase 1.4, 1.7, 1.8, and 3.8 times when the TC level is 200-219, 220-239, 240-259, and 260 mg/dL or higher, respectively, compared with the group with a TC level of 160-179 mg/dL with males and females combined (**Fig. 1a**)[1].

Since the relationship between TC and the morbidity and mortality of coronary artery disease is continuous over a broad range of TC levels without clear threshold, it is difficult to define a borderline for hypercholesterolemia.

On the other hand, it has been shown in Western countries that cholesterol lowering therapy including lifestyle improvement can significantly reduce the incidence of cardiovascular diseases. Also in Japan, results of large-scale clinical studies have recently been reported[18-21], demonstrating preventive effect of LDL-Lowering against artherosclerotic diseases.

On the basis of the relationship between the TC level and mortality due to coronary artery disease shown by the MRFIT[22], the NCEP, which is a guideline for lipid management in the United States, defines a TC level of 240 mg/dL, at which the relative risk of coronary artery disease doubles compared with that at 200 mg/dL, as a criterion of hypercholesterolemia[23].

In consideration of these evidences, we adopted a TC level of 220 mg/dL, at which the relative risk of coronary artery disease increases 1.5 times compared with that at 160-179 mg/dL according to NIPPON

Table 1. Diagnostic criteria for dyslipidemia (Serum sampled after overnight fasting)

LDL-cholesterol	≥140 mg/dL
HDL-cholesterol	<40 mg/dL
Triglycerides	≥150 mg/dL

Diagnosis of dyslipidemia is made when either type of lipid abnormalities is present.

These diagnostic criteria are not intended for the beginning of drug therapy.

It is important to consider the indications of drug therapy only after evaluation of other risk factors.

LDL-C is evaluated bacically by calculation with the Friedewald equation.

[LDL-C = TC − HDL-C − TG/5 (when TG is <400 mg/dL)]

When the TG is ≥400 mg/dL or non-fasting state, the LDL-C should be determined by direct measurement.

DATA 80, as a screening criterion for Japanese from a preventive viewpoint, and set an LDL-C level of 140 mg/dL, which corresponds to this TC level, as a criterion for high-LDL-cholesterolemia.
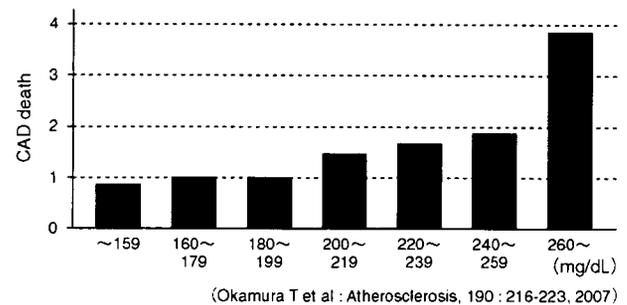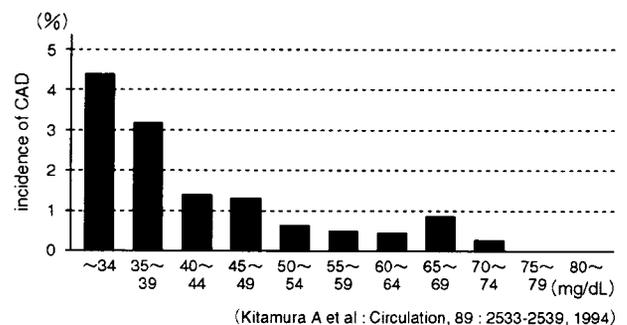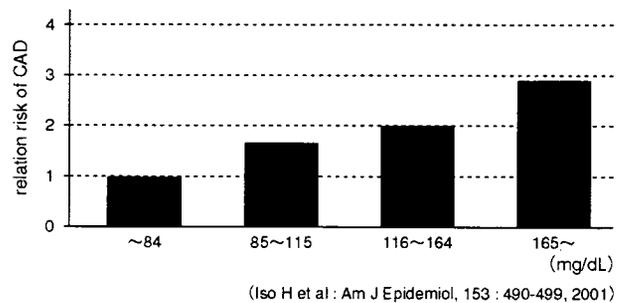
2. Low-HDL-Cholesterolemia

A significant negative correlation between the HDL-C level and the risk of coronary artery disease has been established not only in Western countries[24-28] but also in Japan[5-8, 12, 29]. However, there is no threshold HDL-C level for the relationship between HDL-C levels the morbidity of coronary artery disease is contiuous over a broad range of LDL-C, and it is difficult to define a borderline for low-HDL-C, similarly to high-LDL-C. A Japanese epidemiological study reported that the risk of coronary artery disease increases rapidly as the HDL-C level decreases to the level less than 40 mg/dL (**Fig. 1b**). The NCEP-ATPIII defines an HDL-C level below 40 mg/dL as low-HDL-C[30, 31].

In consideration of these reports, the current guideline defines an HDL-C level below 40 mg/dL as low-HDL-C. While the HDL-C level is generally higher in females than in males, there is insufficient evidence concerning the relationship between the gender difference in HDL-C and the risk of coronary artery disease. Therefore, this guideline applies the single criterion to both males and females. Low-HDL-C is a risk factor of coronary artery disease, and the risk of coronary artery disease decreases as the HDL-C level increases.

3. Hypertriglyceridemia

Although there have been a number of reports on the positive correlation between the TG level and mor-

a) TC levels and CAD death

(Okamura T et al : Atherosclerosis, 190 : 216-223, 2007)

b) HDL-C levels and CAD incidence

(Kitamura A et al : Circulation, 89 : 2533-2539, 1994)

c) TG levels and CAD incidence

(Iso H et al : Am J Epidemiol, 153 : 490-499, 2001)

Fig. 1. Incidence of coronary artery disease(CAD) increases as the LDL-C, TC, TG, HDL-C.

bidity of coronary artery disease in Japan[10, 11, 32] as well as in Western countries[33-38], the issue remains controversial. Particularly, disappearance of the association after correction for the HDL-C level has been reported in a number of studies[39]. Recently, significant association between the TG level and coronary artery disease has been suggested by 2 Japanese cohort studies (**Fig. 1c**)[10, 32]. A Japanese epidemiological study showed that the morbidity of coronary artery disease increases when the TG level is 150 mg/dL or higher[11].

Also in the United States, a TG level of 150 mg/dL or higher is regarded as hypertriglyceridemia on the basis of the Framingham study[40].

In consideration of these results, the current guideline defines a TG level of 150 mg/dL or above as hypertriglyceridemia. However, hypertriglyceridemia often has other important implications such as an increase in remnant lipo-protein, increase in small dense LDL, and complication of low-HDL-C. Therefore, possible association of these metabolic abnormalities should be kept in mind upon management of elevated TG level.

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Committee Report 3

Goals of Dyslipidemia Management
— Executive Summary of Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese

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Committee for Epidemiology and Clinical Management of Atherosclerosis

Introduction

Concerning the prevention of atherosclerotic diseases, there are risk factors those require intervention such as cigarette smoking, hypertension, diabetes mellitus, as well as dyslipidemia, and their comprehensive management is absolutely essential. There are guidelines concerning hypertension and diabetes mellitus introduced by Japanese medical associations specializing in these disorders, and patients should be treated according to the management goals of these guidelines. In addition, smoking cessation is the most essential management item for the prevention of atherosclerotic diseases.

It must also be sufficiently understood that dyslipidemia does not always require drug therapy. Particularly, lifestyle modification is important for the management of low HDL-cholesterol(HDL-C) and high triglyceride(TG), and sufficient correction of dyslipidemia is expected by itself. However, high TG may require drug therapy if the TG level is 500 mg/dL or higher in order to prevent acute pancreatitis. Also, patients with TG≥300 mg/dL are accompanied frequently by various abnormalities of lipoprotein metabolism, and medical intervention is often necessary.

Herein, the background and rationale of patient categorization according to risk and management goals for various categories of dyslipidemia are discussed.

1. Categorization Based on Risk Factors

Management goals for categories based on the risk factors of atherosclerosis were set as management criteria for patients diagnosed as dyslipedemia (Table 1).

First, the patients must be classified into those who have not developed coronary artery disease (for primary prevention) and those who have a history of coronary artery disease (CAD) (for secondary prevention). Treatment for atherosclerosis is considered necessary for the latter, and the patients must be approached differently from the former patients. For secondary prevention, the management goals of LDL-C is set at a low level (LDL-C<100 mg/dL), and the appropriate initiation of drug therapy is necessary without delay along with lifestyle modification.

4S[1] showed that the total mortality as well as mortality due to CAD can be lowered by reducing a high LDL-C level, and that lowering the LDL-C level is essential for secondary prevention. Thereafter, large-scale clinical studies (CARE[2] and LIPID[3]) showed that, for secondary prevention, reducing even an average LDL-C level is effective for the prevention of recurrence of CAD, reduction of total mortality, and reduction of stroke. Subsequently, the J-LIT, in which Japanese patients treated for hypercholesterolemia were followed up, reported the effect of lowering LDL-C levels for secondary prevention. J-LIT research group described that, in the patients with CAD, the recurrence of CAD was reduced by decreasing the LDL-C level to 100 mg/dL. Recently, also, the MUSASHI-AMI[4], another Japanese clinical study, reported that the recurrence of cardiovascular events could be reduced by the administration of statin in patients with acute myocardial infarction. These reports suggest that aggressive drug therapy accompanied by lifestyle modification should be recommended for secondary prevention. Recently, it has also been reported by large-scale clinical studies in Western countries that even more aggressive

Table 1. Lipid management goals based on risk assessment

Principle of therapeutic strategy	Category		Lipid management goals (mg/dL)		
		Major risk factors other than LDL-C*	LDL-C	HDL-C	TG
Primary prevention	I (Low-risk group)	0	<160		
Lifestyle should be changed before consideration of drug therapy.	II (Intermediate-risk group)	1~2	<140		
	III (High-risk group)	3 or more	<120	≥40	<150
Secondary prevention Both drug therapy and lifestyle modification are considered.	History of coronary artery diseases		<100		

Management of serum lipids as well as intervention of other risk factors (smoking, hypertention or diabetes) is necessary.
*Major risk factors other than LDL-C
Aging (male ≥45 years, female ≥55 years), hypertension, diabetes (including impaired glucose tolerance), smoking, family history of coronary artery disease, low HDL cholesterol (<40 mg/dL)
• Category III, if complicated by diabetes mellitus, cerebral infarction or arteriosclerosis obliterans.

LDL-C reducing therapy is effective for the prevention of progression and recurrence of acute coronary syndrome. Similar results have been reported by the ESTABLISH[5], performed in Japan.

In primary prevention, the main object is to prevent the future development of CAD in persons without history of such diseases, patients are categorized into low-, intermediate, and high-risk groups (Categories I, II, and III, respectively) according to the number of concurrent risk factors other than LDL-C. The concurrence of risk factors was also shown to be closely related to the occurrence of CAD by the Framingham study. The NIPPON DATA80[6-9] and J-LIT[10-12], which are conducted in Japan, have also established the importance of the concurrence of risk factors in the occurrence of CAD.

Major coronary risk factors other than LDL-C those have been confirmed to date are male gender, age, hypertension, diabetes mellitus (including abnormal glucose tolerance), cigarette smoking, family history of CAD, and low HDL-C. Whether diabetes mellitus should be regarded as a more important risk factor than the others is controversial. We classified diabetic patients in the high-risk group (category III), considering diabetes mellitus to be more important than other risk factors, because: 1) patients with type 2 diabetes mellitus are increasing rapidly, and the prognosis of established CAD is poor in diabetic patients; 2) the JDCS[13], which is a prospective study of patients with type 2 diabetes mellitus being conducted in Japan, showed that the incidence of CAD is similar to, or higher than, that of cerebral infarction, and that the LDL-C level is a top risk factor of CAD; 3) the UKP-DS[14] and other studies have concluded that treatment of hyperglycemia has not been sufficiently established

in order to prevent the CAD in patients with type 2 diabetes mellitus.

Also, patients with cerebral infarction and arteriosclerosis obliterans were classified in the high-risk group (Category III), because they have already developed atherosclerotic disorders in vessels other than the coronary artery.

2. Goals of Dyslipidemia Management

For primary prevention, indications of drug therapy should be evaluated after making efforts to modify the lifestyle for a period long enough to assess its effects. At the initiation of drug therapy, its indications must be evaluated by sufficiently examining each patient for risk factors of atherosclerosis. It must be emphasized that the necessity of drug therapy is considerably lower in the low-risk group (**Fig. 1**). LDL-C goals should be less than 160 mg/dL without a major risk factor [Category I (low-risk group)], less than 140 mg/dL with 1 or 2 major risk factors [Category II (intermediate risk group)], and less than 120 mg/dL with 3 or more risk factors [Category III (high-risk group)]. Achievement of these goals are recommended, but it does not mean that the achievement is obligatory.

No consensus has been reached as to the goals of LDL-C level in patients with familial hypercholesterolemia (FH). This guideline proposes an LDL-C level of less than 100 mg/dL as a goal similarly to secondary prevention, because FH patients have a long history of high LDL-C from childhood and so are under serious risk of CAD. However, as sufficient management of LDL-C by drug therapy is often impossible in patients with such genetic disorders, it may be deserved as a goal to reduce LDL-C by more than 30%.
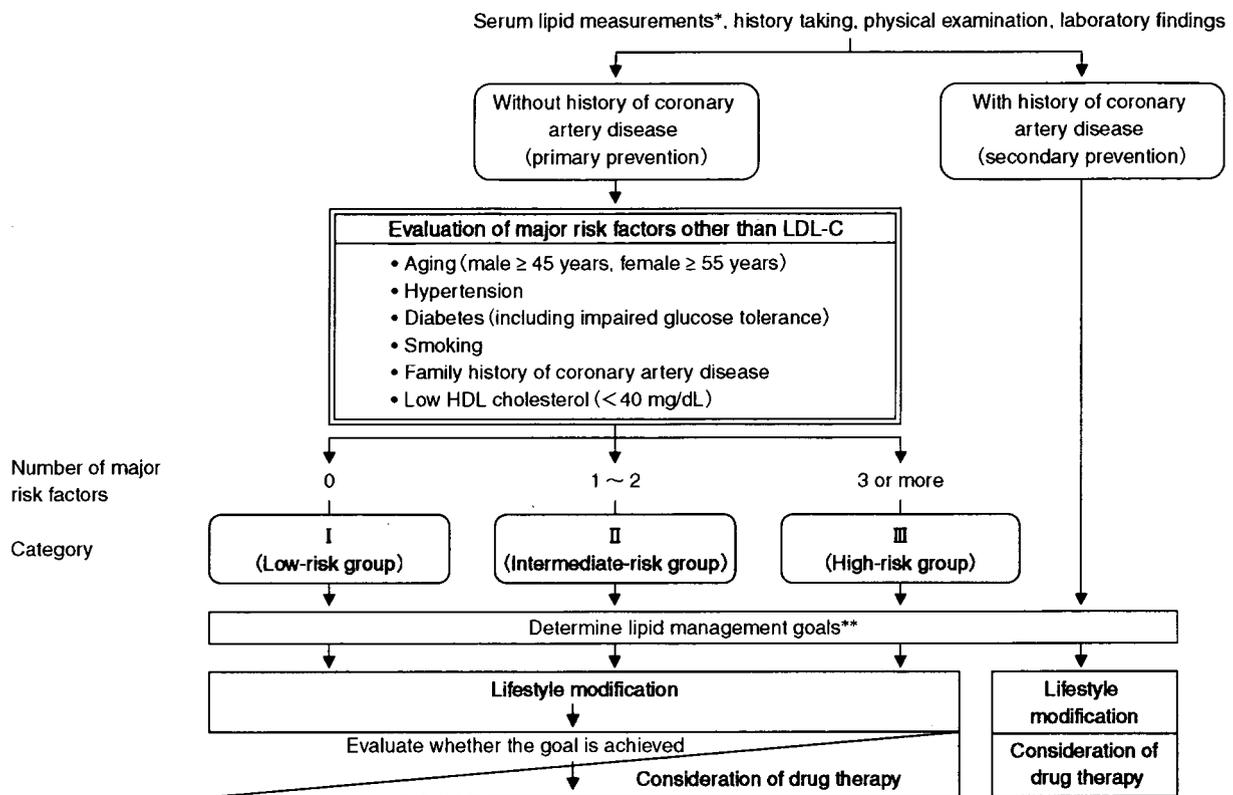
Serum lipid measurements*, history taking, physical examination, laboratory findings

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                    ┌──────────────────────┐              ┌──────────────────────┐
                    │ Without history of   │              │  With history of     │
                    │ coronary             │              │  coronary            │
                    │ artery disease       │              │  artery disease      │
                    │ (primary prevention) │              │ (secondary prevention)│
                    └──────────────────────┘              └──────────────────────┘
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Evaluation of major risk factors other than LDL-C

- Aging (male ≥ 45 years, female ≥ 55 years)
- Hypertension
- Diabetes (including impaired glucose tolerance)
- Smoking
- Family history of coronary artery disease
- Low HDL cholesterol (<40 mg/dL)

Number of major risk factors	0	1 ~ 2	3 or more
Category	**I** (Low-risk group)	**II** (Intermediate-risk group)	**III** (High-risk group)

Determine lipid management goals**

Lifestyle modification

Evaluate whether the goal is achieved

Consideration of drug therapy

Lifestyle modification

Consideration of drug therapy

Fig. 1. Therapeutic strategies based on the categories and management goals

*Measurement of blood lipid levels: TC, LDL-C, HDL-C, and TG in serum after overnight fasting. See Appendix.

**Lipid management goals: See Table 1

Note: A patient with diabetes, cerebral infarction or arteriosclerosis obliterance is categorized into III even without other risk factors.

Since the treatment of FH patients is often difficult, and as they are at very high risk for developing atherosclerotic complications, we recommend consultation with an expert.

This guideline is originally prepared for the application to adults aged less than 65 years. However, it can also be applied to those aged 65-74 years. Also, as the incidence of CAD is low in females, females with high LDL-C must be managed with greater attention to other risk factors.

It might be proposed to set the goal for high LDL-C as a percent decrease in the LDL-C level rather than an absolute value. Since meta-analysis of studies in Western countries has shown that cardiovascular events decrease by 23% with a reduction in the LDL-C by 1 mmol/L (38.6 mg/dL), LDL-C must be controlled at a low level for the prevention of CAD[15]. However, in patients with markedly high LDL-C level, typically FH, the goal proposed in this guideline may be difficult to achieve. The NCEP suggests that such patients should be treated with a 30-40% decrease in the LDL-

C level as an alternative goal[16]. Also, the results of the MEGA[17], which is a large-scale clinical study on primary prevention in Japan, suggest that coronary artery events can be reduced by about 30% by an approximate 20% reduction in the LDL-C level. On the basis of the above evidence, this guideline proposes a decrease in the LDL-C level of 20-30% in addition to an absolute level of LDL-C as possible treatment goals for primary prevention.

The HDL-C level should be managed to 40 mg/dL or above primarily through modification of lifestyle. The TG level, on the other hand, should be managed with sufficient consideration of background factors. Particularly, it should be managed strictly with less than 150 mg/dL as a goal if hypertriglyceridemia is accompanied by low HDL-C.

In this guideline, the LDL-C is used as an index of the management target. But there also is an argument that the non-HDL-C level (TC - HDL-C) is more convenient for the management of dyslipidemia in those who have high TG as a notable feature, such

as in metabolic syndrome. The NCEP sets the criterion for the non-HDL-C level at 30 mg/dL higher than that for the LDL-C level[16]. This criterion should be referred to when treatment is conducted using the non-HDL-C level as an index.

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Appendix. Diagnostic criteria for dyslipidemia (Serum sampled after overnight fasting)

LDL-cholesterol	≥ 140 mg/dL
HDL-cholesterol	< 40 mg/dL
Triglycerides	≥ 150 mg/dL

Diagnosis of dyslipidemia is made when either type of lipid abnormalities is present.

These diagnostic criteria are not intended for the beginning of drug therapy.

It is important to consider the indications of drug therapy only after evaluation of other risk factors.

LDL-C is evaluated basically by calculation with the Friedewald equation.

[LDL-C = TC - HDL-C - TG/5 (when TG is < 400 mg/dL)]

When the TG is ≥ 400 mg/dL or non-fasting state, the LDL-C should be determined by direct measurement.

Committee Report 4

Risk Factors of Atherosclerotic Diseases

— Executive Summary of Japan Atherosclerosis Society (JAS) Guideline for Diagnosis and Prevention of Atherosclerotic Cardiovascular Diseases for Japanese

Tamio Teramoto, Jun Sasaki, Hirotsugu Ueshima, Genshi Egusa, Makoto Kinoshita, Kazuaki Shimamoto, Hiroyuki Daida, Sadatoshi Biro, Kazuhiko Hirobe, Tohru Funahashi, Koutaro Yokote, and Masayuki Yokode

Committee for Epidemiology and Clinical Management of Atherosclerosis

The risk factors of coronary artery disease (CAD) used for the categorization and setting of management targets have been established on the basis of evidence accumulated over a long time (**Table 1**). According to a 14-year follow-up in NIPPON DATA80 conducted in Japan, also, factors related to CAD were the TC level, age, systolic blood pressure, blood glucose level, and cigarette smoking (**Reference 1-A, B**)[1]. Similar results have been obtained by a 19-year follow-up, in which the hazard level was 2.11 (95% confidence interval: 0.92-4.84) at a TC level of 200-219 mg/dL, 2.17 (0.89-5.25) at 220-239 mg/dL, and 3.74 (1.44-9.76) at 240-259 mg/dL in males when the hazard level at a TC level of 160-179 mg/dL is defined as 1[2].

Also, while the TG level is an important factor clearly related to CAD, evidence that indicates their direct relationship is insufficient. Therefore, it was not used for categorization and was included as a management target alone. In addition, consideration of some risk factors that have been clarified recently (**Table 2**) is necessary in the setting of management targets in the future. These risk factors are discussed below.

1. Hypertension

Hypertension is a strong risk factor of conditions including cerebral hemorrhage not based on atherosclerosis, but it is also a clear risk factor of atherosclerotic diseases. In Western countries, studies including the Framingham study[3], MRFIT[4], and Honolulu Heart Program[5] showed that hypertension can also be a risk factor of CAD. Hypertension based on the diastolic pressure is also a clear risk factor[6]. Furthermore, a 19-year follow-up in NIPPON DATA80 showed sig-

nificant increases in the hazard ratio of death due to cardiovascular diseases with blood pressure elevations in elderly people aged 75 years or above as well as those aged 30-64 and 64-74 years[7].

According to the Hisayama Study in Japan, a significant increase in the incidence of cerebral infarction at a blood pressure of 140/90 mmHg was observed[8]. NIPPON DATA80 demonstrated that the systolic pressure is a significant risk factor of death due to CAD[1, 7, 9]. In males of the 3M (Morbidity of Myocardial Infarction Multicenter Study in Japan) study, hypertension increased the risk of myocardial infarction 3.1 times[10, 11]. In the J-LIT, (Japan Lipid Intervention Trial) the relative risk of CAD in the target population for primary prevention was 2.5 times higher in hypertensive females and 2.3 times higher in hypertensive males compared with non-hypertensives[12-14].
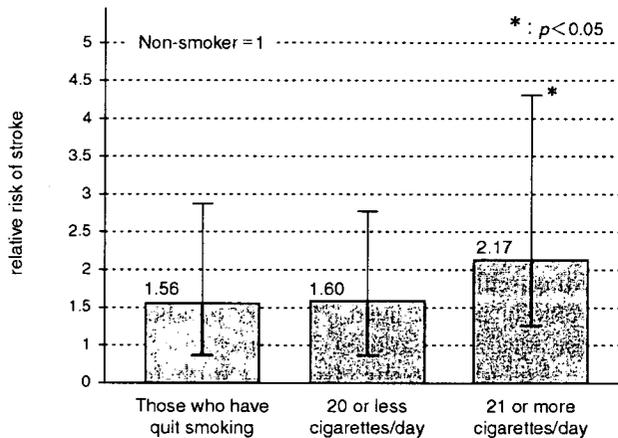
2. Cigarette smoking

Cigarette smoking has been reported to be a risk factor of CAD and stroke through many studies including the Framingham study, MRFIT, and Honolulu Heart Program[5, 15-20]. This has also been proven in Japan by the Hisayama Study[21]. According to NIPPON DATA80, also, habitual smoking was a risk factor of death due to both stroke and CAD[1], and the risk of death due to stroke compared with that in non-smokers was 1.60 and 2.17 times higher in males smoking 20 or less and 21 or more cigarettes a day, respectively. The risk of death due to cerebral infarction was 2.97 and 3.26 times higher, respectively (**Fig. 1**)[1]. In females, also, the risk of death due to stroke was 1.42 and 3.91 times higher in those smoking 20 or less and

Table 1. Major risk factors other than LDL-cholesterol

- Low HDL-cholesterol
- Age (males ≧45 years, females ≧55 years)
- Diabetes mellitus (including impaired glucose tolerance)
- Hypertension
- Cigarette smoking
- Family history of coronary artery disease

Hypertriglyceridemia must also be considered.

Table 2. Other risk factors that require consideration

- Lp(a)
- Remnant lipoproteins
- Homocysteine
- Small dense LDL
- Acute-phase proteins (C-reactive protein, serum amyloid A protein, etc.)
- Coagulation and fibrinolytic factors (tissue plasminogen activator <t-PA>, plasminogen activator inhibitor 1, fibrinogen, etc.)

Fig. 1. Smoking and relative risk of death due to stroke.

Results of a follow-up of 51,774 males in NIPPON DATA80[1]
Adjusted for age, systolic blood pressure, BMI, TC level, drinking, and diabetes.
(Prepared on the basis of Ueshima H, et al: Stroke, 2004; 35:1836-1841)

Fig. 2. Cigarette smoking and relative risk of death due to coronary artery disease

Results of a follow-up of 51,774 males in NIPPON DATA 80[1]
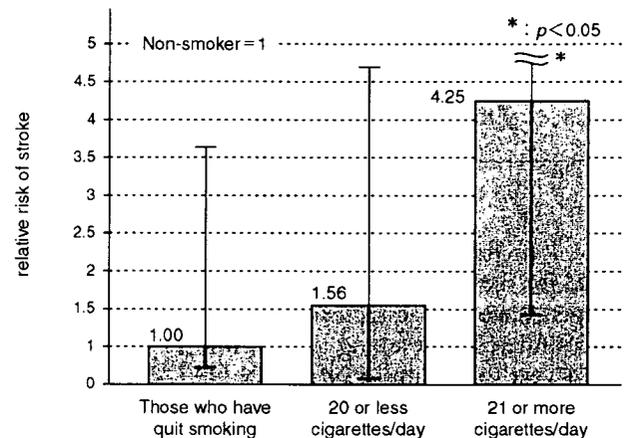Adjusted for age, systolic blood pressure, BMI, TC level, drinking, and diabetes.
(Prepared on the basis of Ueshima H, et al: Stroke, 2004; 35:1836-1841)

21 or more cigarettes a day than in non-smokers, and the risk of death due to cerebral infarction was 1.75 and 2.31 times higher, respectively. The risk of death due to CAD in males was 1.56 and 4.25 times higher, respectively, than in non-smokers (**Fig. 2**).

A multi-purpose cohort study conducted by the Ministry of Health, Labor and Welfare also indicated that smoking was a risk factor of stroke and increased the risk of subarachnoid hemorrhage 4 times[22]. Furthermore, the risk of CAD was about 4 and 3 times higher in male and female smokers, respectively[23], than in non-smokers, similarly to NIPPON DATA80. In addition, quitting smoking has been found to reduce the risk of death due to cardiovascular diseases rapidly within 2 years to the level of non-smokers[1, 24]. It has been also demonstrated that quitting smoking has been demonstrated to be beneficial for the secondary prevention of CAD. After myocardial infarction, the mortality rate can be reduced to 30-60% by quit-

ting smoking[25, 26]. In Japanese males with a history of myocardial infarction, the relative risk of recurrence is 3.1 times higher in those who continued to smoke than in those who quit[27]. According to the J-LIT, the relative risk of CAD in a target population of primary prevention was 2.2 times higher in female smokers and 1.2 times higher in male smokers than in non-smokers, indicating that the effect of smoking is stronger in females than in males[12-14].

Furthermore, smoking is well known to be a risk factor of arteriosclerosis obliterans[28-30].

3. Diabetes Mellitus

Diabetes has been established by many studies in Japan and abroad to be a risk factor of atherosclerotic diseases. In Western countries, the risk of CAD has been reported to be 2-6 times higher in diabetics than in non-diabetics[31-34]. About a 2-fold increase in the

risk was also reported by NIPPON DATA80[9].

In Japan, the Hisayama Study showed that the incidence of initial CAD was about 2.6 times higher in diabetics than in non-diabetics[35]. Moreover, the risk of atherosclerotic diseases has been reported to increase significantly at an LDL-C level of 120 mg/dL or higher in diabetics[36]. In the J-LIT, in which hypercholesterolemic patients were followed up after treatment, the relative risk of CAD was about 3.0 and 1.7 times higher in female and male diabetics, respectively, than in non diabetics in a target population of primary prevention[12-14]. In the 3M Study, the risk of CAD was 3.5 times higher in males (aged 30-65 years) with a fasting glucose level of 110 mg/dL or higher than in those with a fasting glucose level of less than 110 mg/dL[10, 11].

Whether diabetes mellitus should be regarded as more important than other coronary risk factors is controversial. According to the ATPIII of the NCEP, the risk of being diabetic was regarded as comparable to the risk of already having CAD[3, 38]. In Western countries, there is evidence that supports this view[39], and the American Diabetes Association sets a target LDL-C level at 100 mg/dL or less for patients with diabetes mellitus type 2[39]. In Japan, however, there is no evidence that diabetes mellitus is a risk factor comparable to secondary prevention (a history of CAD). The results of the J-LIT indicate that diabetes mellitus is a risk factor comparable to hypertension and smoking[12-14]. Recently, a large-scale Scottish study showed that the risk of CAD was significantly lower in patients with diabetes mellitus type 2 than in those with a history of CAD[40], and diabetes is also estimated in Western countries to be a risk factor not necessarily comparable to secondary prevention.

This guideline classified diabetic patients in the high-risk group (Category III), because: 1) patients with diabetes mellitus type 2 are rapidly increasing, and the prognosis of CAD is poor in diabetic patients; 2) the JDCS (Japan Diabetes Complications Study) being conducted in Japan has shown that diabetes mellitus type 2 is complicated by CAD as often as, or more often than, by cerebral infarction, and LDL-C was identified as a leading risk factor; and 3), according to the UKPDS (United Kingdom Prospective Diabetes Study) and other studies, treatment of hyperglycemia in patients with diabetes mellitus type 2 has not been sufficiently confirmed to be effective for the prevention of CAD.

In addition to diabetes mellitus, impaired glucose tolerance has been shown to increase the incidence of cardiovascular disorders, with cerebral infarction and CAD combined, 1.9 times[35]. Although further evaluation is necessary concerning whether impaired glucose tolerance is a risk factor comparable to diabetes mellitus, impaired glucose tolerance was included as a risk factor at present.

4. Age

Age is a strong risk factor of atherosclerotic diseases similarly in Western countries[41, 42] and Japan. Concerning CAD, the mortality and morbidity rates begin to increase after the age of 45 years in males and 55 years in females according to data in the United States[43], "Trends of Health of the Japanese"[44], Hiroshima/Nagasaki study[45], 3M study based on workplaces[10], and Takashima Study, Shiga[46].

In female, the risk of atherosclerotic diseases is considered to increase after menopause in females, but the exact point of menopause is difficult to determine by health screenings. Therefore, an age of 55 years, when most Japanese females have experienced menopause[47], or above was regarded as a risk factor. However, conditions such as bilateral ovariectomy should be considered risk factors even in females aged less than 55 years.

5. Familial History of Coronary Artery Disease

In Western countries, a familial history of CAD has been reported to be a risk factor of the disease since the 1970s[48-56]. A familial history of CAD, particularly that in the first degree relatives or that of early onset CAD (before 45 years in males and 55 years in females), is a strong risk factor of CAD.

The Framingham Study reported that the age-adjusted odds ratio of the risk of CAD increases 2.6 times in males and 2.3 times in females when at least 1 parent has CAD, and 2.0 times in males and 1.7 times in females also on multivariate analysis[57]. Although there has been no large-scale study on the familial history in Japan, the J-LIT showed that a familial history of CAD increases the relative risk of the disease by about 3 times[58].

Known risk factors (high LDL-cholesterol, low HDL-cholesterol, hypertension, diabetes mellitus, and smoking) are affected by genetic factors and family habits. Therefore, the familial history of CAD is considered to include known genetic and environmental risk factors. In addition, while factors such as Lp(a), small dense LDL, and homocysteine have begun to attract attention, these are all under genetic influence. However, as the familial history remains a strong independent risk factor even after adjustment for all

known risk factors by methods such as multivariate analysis[49, 50, 54, 57, 59], it is estimated to include many unknown genetic and environmental factors[60].

Thus, most studies on familial history have concluded that the familial history of CAD is an independent risk factor of the disease. Particularly, individuals with a familial history of early onset (age of onset: <55 years in males and <65 years in females) CAD should be regarded as a high-risk group.

6. Low HDL-Cholesterolemia

A low HDL-C level is a risk factor of arteriosclerotic diseases, and the risk decreases with increases in the HDL-C level[13, 14, 60]. The recent results of NIPPON DATA90 clearly showed a significant negative correlation between the HDL-C level and total mortality over an observation period of 9.6 years[62]. Also, in the J-LIT, the relative risk was 1.30 times higher in the target population of primary prevention and 1.60 times higher in the target population of secondary prevention at an HDL-C level of less than 40 mg/dL compared with 40-49 mg/dL. Therefore, we regarded an HDL-C level of less than 40 mg/dL as a risk factor.

A serum lipid investigation performed in Japan in 2000 showed that the HDL-C level was higher in females than in males[63], but whether different HDL-C level criteria should be applied to males and females remains as an important issue to be addressed in the future. Conditions called high HDL-C in Japan include cholesteryl ester transfer protein defect, which is observed in 8-10% of the population[64, 65]. This disorder should be considered when the HDL-C level is 100 mg/dL or higher. High HDL-C due to this defect may not reduce the risk[66, 67]. Also, hypercholesterolemia detected by screening includes that due to high HDL-C, and the condition is not an indication of treatment unless the LDL-C level is high.

7. Hypertriglyceridemia

There have been a number of reports in Japan[68-70] as well as in Western countries[1-6] on a positive correlation between the TG level and incidence of CAD, but many other reports refute this relationship. Particularly, there are also reports that the relationship disappears after correction for the HDL-C level[7]. Recently, a significant correlation between the TG level and CAD was reported by 2 cohort studies in Japan[68, 70]. Concerning epidemiological studies in Japan, there is a report that the incidence of CAD increases when the TG level is 150 mg/dL or higher[69]. In the United States, also, a TG level of 150 mg/dL or

higher is regarded as hypertriglyceridemia on the basis of the Framingham Study[78]. In addition, hypertriglyceridemia is often accompanied by an increase in remnant lipoproteins, an increase in small dense LDL, and low HDL-C, which may have other important implications. Therefore, factors associated with increases in the TG level need sufficient evaluation.

8. Other Risk Factors that Require Attention

New risk factors other than the established ones above have been proposed (**Table 2**), and evidence is being accumulated.

As lipoprotein-related markers related to the occurrence and progression of arteriosclerosis, oxidized LDL, Lp(a), remnant lipoproteins, and small dense LDL are attracting attention.

Oxidized LDL is considered to be generated as LDL is exposed to oxidative stress in the body and to be involved in a wide range of atherosclerotic processes including damage to vascular endothelial cells and foam cell formation. Recently, as the measurement of plasma levels of oxidized LDL became possible, oxidized LDL has been suggested to be closely involved in acute coronary artery events[79] and to be a possible predictive factor of coronary artery events even in healthy males with no history of CAD or diabetes mellitus[80].

Lp(a) is a lipoprotein with the same structure as LDL, to which apo(a) is bound by a disulfide bond. Its plasma level has been reported to be related to CAD[81-85]. The amino acid sequence of apo(a) is highly homologous to that of plasminogen[86], and the relationship of Lp(a) to CAD is considered to be due to interference by Lp(a) with physiologic roles of plasminogen in the fibrinolytic system. Moreover, Lp(a) is speculated to promote arteriosclerosis by inducing cholesterol deposition in the vascular wall, proliferation of vascular wall cells, and binding of cholesterol to oxidized phospholipids[87, 88].

The relationship between postprandial hyperlipidemia and CAD is attracting attention, and the lipoproteins involved in this relationship are remnant lipoproteins[89]. Remnant lipoproteins are intermediate metabolites of chylomicrons and VLDL resulting from their triglyceride-hydrolysis by lipoprotein lipase. When they accumulate in a stagnant bloodstream, they are considered to be deposited in the vascular intima and to induce the progression of arteriosclerosis[90]. Diseases in which remnant lipoproteins increase include familial combined hyperlipidemia, familial type III hyperlipidemia, and diabetes mellitus.

Small dense LDL[91, 92] is a small-size and high-

density fraction of LDL particles and has been reported to be related to CAD by many authors. Small dense LDL particles are atherogenic, reportedly because they are likely to be oxidized[93], and they are disposed of as they bind to the cell membrane surface by means other than LDL receptors[94]. Small dense LDL is also related to hypertriglyceridemia and low HDL-C[95], characteristically observed in metabolic syndrome, and closely related to insulin resistance[96].

An increase in the blood homocysteine concentration has been reported to be a risk factor of not only CAD but also cerebral and peripheral arteriosclerosis[97, 98]. In the Physicians' Health Study, which is a prospective study in 14,916 males, the relative risk of myocardial infarction was 3.1 in those with a high compared with normal blood homocysteine level[99].

Inflammatory reactions are considered to play an important role in the formation of atherosclerotic lesions[100, 101]. C-reactive protein (CRP) is an acute-phase protein and is used as a marker of inflammation. Recently, however, it has been shown to serve as a marker for the primary and secondary prevention of CAD[102-104]. Amyloid A protein, another acute-phase protein, has also been reported to serve as a marker[105, 108].

Plaque rupture and subsequent thrombus formation have been found to be important in the pathogenic mechanism of CAD[109]. There have been a number of reports that fibrinogen, a coagulation factor, is involved in cardiovascular diseases[110-113]. Fibrinolytic factors such as t-PA[111] and PAI-1[89] are also involved. Particularly, PAI-1 is reportedly related to visceral fat and insulin resistance and to affect CAD[114, 115]. These factors are considered to participate in the establishment of atherosclerotic lesions while they cross-talk with one another[116].

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