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Relatioship Between Serum 7-Ketocholesterol Concentrations and Coronary Artery Disease

Takashi Hitsumoto and Kohji Shirai
The Department of Internal Medicine, Sakura Medical Center,
School of Medicine, Toho University, Chiba,
Japan

1. Introduction

Coronary artery disease is a major health problem and a major cause of death in most industrialized and developing countries. On the other hand, recent basic and clinical studies have illustrated that oxidative stress plays an important role in the progression of coronary atherosclerosis (Kunsch C & Medford RM., 1999; Azumi H et al., 2002). Oxidative stress leads to oxidation of products in vivo and numerous oxidation products have been investigated and their significance examined in atherosclerotic disease (Steinberg D et al., 1997; Ehara S et al., 2001). 7-Ketocholesterol is known to be a major component of the cholesterol oxidation product, oxysterols, and is found in high concentrations in atherosclerotic plaques which contribute to the development of atherosclerosis (Brown AJ & Jessup W., 1998; Smith LL et al., 1996). Thus, 7-ketocholesterol is considered to be an important target factor in the prevention of coronary events and reflects the pathogenesis of coronary artery disease, and therefore has clinical applications. However, the clinical significance of blood 7-ketocholesterol concentrations (7KCHO) are not fully understood, because it is difficult to analyze these concentrations accurately. In the present study, we established a measuring system for serum 7-ketocholesterol concentrations (s-7KCHO) using gas chromatography mass spectrometry technique and attempted to clarify the clinical significance of s-7KCHO in the progression of coronary atherosclerosis using coronary angiography and intra-vascular ultrasound (IVUS).

2. Measurement of s-7KCHO

7KCHO was purchased from Sigma Chemicals Co. (St. Louis, MO, USA). 24,25,25,25,26,26,26,-d7-7-Ketocholesterol (d7-7KCHO) was prepared by Isotec (Miamisburg, OH, USA), and used as an internal standard. Dried pyridine was purchased from Merck (Darmstadt, Germany). Serum blood samples were stored immediately at −80°C , and were used as samples for the s-7KCHO assay within 1 week. A 500 µl aliquot of serum was mixed with 50 µl internal standard stock solution (10 µg/ml of d7-7KCHO dissolved in 1 ml toluene/ethyl acetate = 1:1, v/v), and 3 ml of diethyl ether/hexane (2:3, v/v) containing 0.01% BHT. The mixture was flushed with nitrogen gas and mixed in a rotary shaker for 30 min at room temperature. After centrifugation at 2000 × *g* for 15 min, the organic phase was collected and dried under nitrogen gas. The residue was dissolved in 1 ml of

toluene/ethyl acetate (1:1, v/v), and applied to 3 ml "Diol" extraction columns (Bakerbond Spe, J.T. Baker Inc., Phillipsburg, NJ) that had been conditioned with the same solvent. After collection of the first eluted fraction under mild vacuum, the columns were eluted with another 2 ml of the same solvent. Three ml the of eluent was dried under nitrogen gas, and the residues were dissolved in 2 ml of diethyl ether, following which 500 µl of 20% potassium hydroxide dissolved in methanol was added. After mixing in a rotary shaker for 3 h, the mixture was neutralized by 20% acetic acid. To separate the organic phase from the aqueous phase, 1 ml of water was added and centrifuged. The organic phase was s eparated, added again to 1 ml of water, and centrifuged. The pooled organic fractions were dried under nitrogen gas. Dried samples were derivatized with 200 µl of *o*-methylhydroxylamine/hydrochloride dissolved in dried pyridine at 70°C for 2 h, and 100 µl of *N,O*-bis(trimethyl-silyl)trifluoroacetamide (BSTFA) at 70°C for 2 h. Then 1 µl aliquots were injected into a Varian GC/MS system consisting of a gas chromatography (CP-3800), an ion trap mass spectrometry (Saturn-2000), and an auto-sampler (CP-8400). The whole instrument set was controlled by a computer. The column used was a commercial product "WCOT Fused Silica (30 m × 0.25 mm i.d.) Coating CP-SIL 8 CB Low Bleed/MS" (Varian Inc., Palo Alto, CA, USA). Helium was used as carrier gas at a flow rate of 0.8 ml/min. The injection temperature was set at 270 °C (split ratio 1:4) and the initial column temperature at 60 °C. The analysis was run by holding the initial temperature for 1 min, and then increasing it at a rate of 20°C/min up to 280°C and 10°C/min up to 300°C. Thereafter the temperature was held at 300 °C for 10 min and was then increased again at a rate of 15 °C/min until 330 °C. The total running time was 31 min. The transfer line was maintained at 250 °C and the ion source at 220 °C. The electron ionization was performed by 70 eV ionized energy. The number of monitoring ions used was 471 for 7KCHO and 478 for internal standard (d7-7KCHO). In this assay system, recovery test was 95%, intra-assay coefficients of variation were <5%, and the detection limit of the assay was 6.2ng/ml.

3. Angiographic study

3.1 Study population

One hundred and thirty-nine subjects with coronary artery disease (CAD; subjects with stable angina pectoris or acute myocardial infarction) and 43 subjects with normal coronary arteries were enrolled. We examined relation of s-7-KCHO and findings of coronary angiography or coronary risk factors.

3.2 Methods of coronary angiography

Coronary angiography was performed by transfemoral or transbrachial approaches using a standard technique. Two experienced angiographers who were single blinded to the study reviewed all coronary angiograms. The severity of coronary stenosis was assessed with a worst-view projection. The percentage of luminal narrowing was recorded according to the American Heart Associations reporting system. Significant stenotic lesion was defined as ≥75% diameter stenosis, and the extent of coronary atherosclerosis was classified by the number of vessels with significant stenotic lesions. Lesions in the left main trunk were not observed in the present study. Of the study population, 68 subjects suffered from acute myocardial infarction (AMI). All AMI subjects had confirmed culprit lesion, which was a total or subtotal occlusion by coronary angiography. Diagnosis of AMI was based on: (1) a

clinical history of central chest pressure pain, or tightness for 30 min or more, (2) ST-segment elevation greater than 0.1 mV in at least one standard or precordial lead, and (3) a rise in the serum creatine kinase concentration to more than twice the normal laboratory value. All subjects with normal coronary artery (NCA) were performed coronary angiography for evaluation of chest pain and/or abnormality of electrocardiograph and NCA was defined as the absence of significant stenosis and spastic reaction which was provoked by intracoronary administration of acetylcholine.

3.3 Results

Patient characteristics are shown in Table 1. Age, proportion of male subjects, diabetes mellitus and smoking were significantly higher in subjects with CAD than in those with NCA. Considering the serum lipid concentrations, there were significantly higher TC, LDL-C and triglyceride concentrations in subjects with NCA than in those with CAD; however, the serum lipid data were similar in subjects without antihyperlipidemic treatment (data not shown). HDL-C concentrations were significantly lower in subjects with CAD than in those with NCA. hs-CRP concentrations were significantly higher in subjects with CAD than in those with NCA.

	NCA (n=43)	CAD (n=139)
Age (yrs)	62±9	66±10*
Sex (male/female)	21/22	105/33**
Hypertension	16 (37)	70 (51)
Diabetes mellitus	5 (12)	45 (33)**
Obesity (BMI ≧25)	12 (28)	44 (32)
Smoking	12 (28)	68 (49)*
Family history of CAD	6 (14)	18 (13)
Total cholesterol (mg/dl)	217±38	189±34**
LDL-cholesterol (mg/dl)	127±36	114±30*
Triglyceride (mg/dl)	142±103	114±53*
HDL-cholesterol (mg/dl)	55±13	45±13*
Antihyperlipidemic treatment	8 (19)	73 (53)**
Statin use	5 (11)	63 (45)**
High sensitive CRP (mg/L)	0.9±0.7	1.8±1.7*

Data are expressed mean ± SD( ): %
*p<0.05 vs NCA, **p<0.01 vs NCA
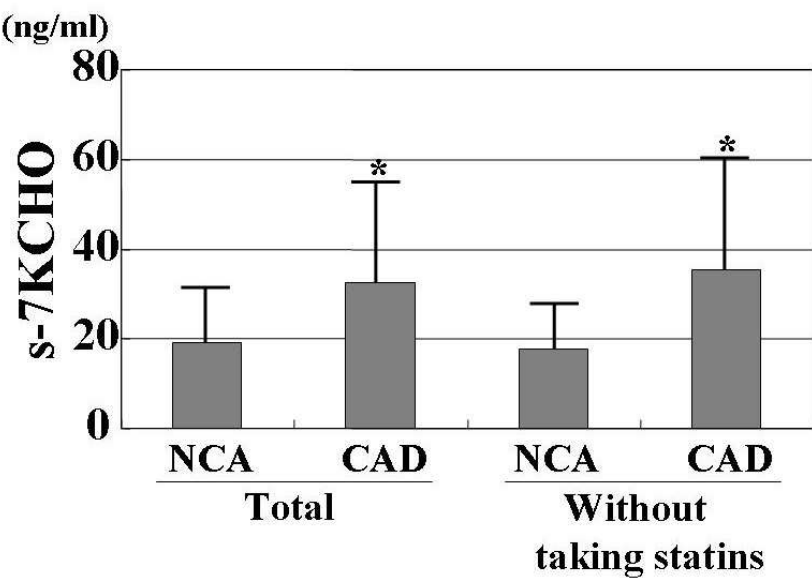NCA: Normal coronary artery
CAD: Coronary artery disease
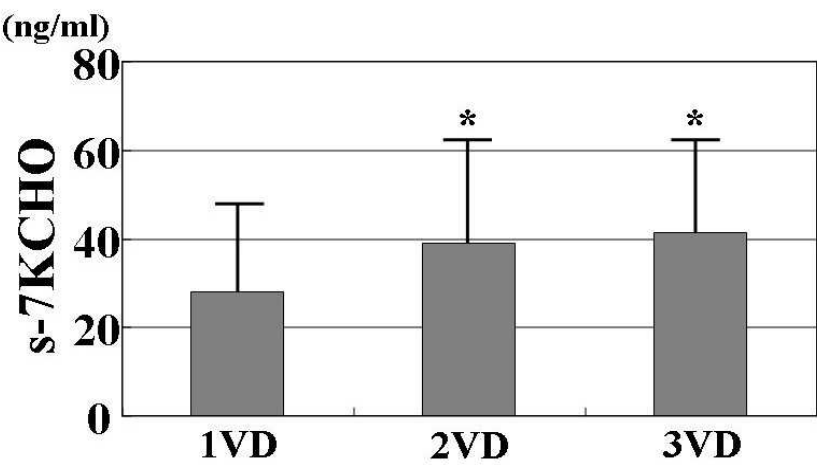BMI: body mass index
LDL: low-density lipoprotein
HDL: high-density lipoprotein

Table 1. Baseline clinical characteristics

Data are expressed mean ± SD *p<0.01 vs NCA

Fig. 1. Comparisons of 7-ketocholesterol concentrations between subjects with normal coronary artery and coronary artery disease
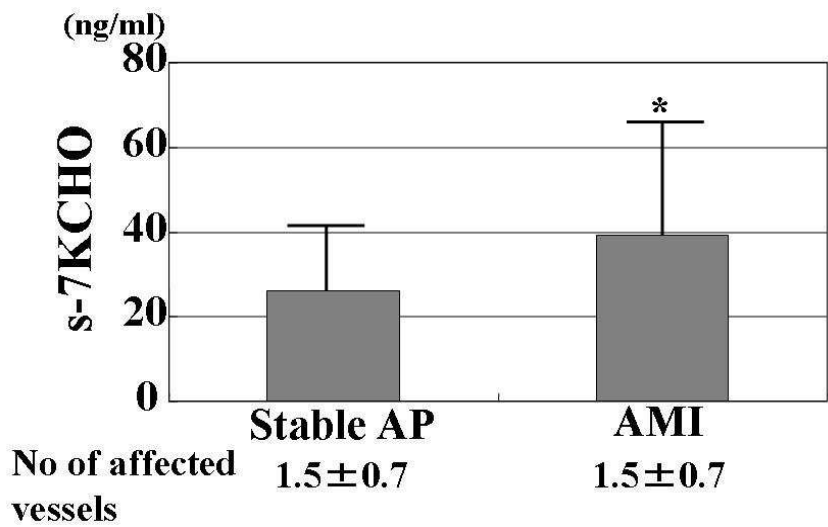

Data are expressed mean ± SD
*p<0.05 vs 1VD
1VD (n=85): 1-vessel disease
2VD (n=36): 2-vessel disease
3VD (n=18): 3-vessel disease

Fig. 2. Relation of 7-ketocholesterol concentrations and number of affected vessels.

Comparisons of s-7KCHO between NCA and CAD subjects are shown in Fig. 1. s-7KCHO were significantly higher in subjects with CAD than in those with NCA ($p < 0.01$) (NCA: 19.0 ± 11.3 ng/ml, CAD: 32.4 ± 23.1 ng/ml). We also examined s-7KCHO in subjects without taking statins. s-7KCHO were significantly higher in subjects with CAD than in those with NCA ($p < 0.01$) (NCA: 17.7 ± 9.6 ng/ml, CAD: 35.4 ± 25.4 ng/ml). The relationship between s-7KCHO and the number of affected vessels is shown in Fig. 2. s-7KCHO were significantly higher in subjects with 2 or 3 vessel disease than those with single vessel disease ($p < 0.05$, p

< 0.05, respectively) (1-vessel disease: 28.0 ± 21.1 ng/ml, 2-vessel disease: 39.0 ± 25.6 ng/ml, 3-vessel disease: 41.3 ± 23.2 ng/ml). Comparisons of s-7KCHO between subjects with stable angina pectoris and those with AMI are shown in Fig. 3. s-7KCHO were significantly higher in subjects with AMI than in those with stable angina pectoris even though the number of affected vessels were similar in the two groups (p < 0.01) (Stable angina pectoris: 26.1 ± 15.2 ng/ml, AMI: 39.1 ± 27.7 ng/ml).

Data are expressed mean ± SD
*p<0.01 vs stable AP
Stable AP (n=69): stable angina pectoris
AMI (n=68): acute myocardial infarction

Fig. 3. Comparisons of 7-ketocholesterol concentrations between subjects with stable angina pectoris and acute myocardial infarction.

	r	p value
Total cholesterol	-0.03	NS
LDL-cholesterol	-0.04	NS
Log-Triglyceride	0.01	NS
HDL-cholesterol	-0.23	<0.01
Log-hs-CRP	0.24	<0.01

Table 2. Correlation between 7-keto cholesterol concentration and serum parameters.

Correlation between serum parameters and s-7KCHO in CAD subjects were shown in Table 2. There were no significant correlations between TC or LDL cholesterol concentrations and s-7KCHO. Conversely, s-7KCHO had significant correlations with HDL-cholesterol and hs-CRP concentrations. Other coronary risk factors such as age, sex, hypertension, diabetes mellitus,

obesity, smoking, and family history of CAD were not related to s-7KCHO (data not shown). We also examined relationship between statin use and s-7KCHO. Subjects with statin use showed higher s-7KCHO than those without statin use, although the difference was not significant (p=0.09) (without statin use: 28.9 ± 19.9 ng/ml, statin use: 35.4 ± 25.7 ng/ml).

Multivariate analysis revealed that s-7KCHO were selected as an independent variable for CAD (p < 0.01, Table 3). In CAD subjects, the presence of acute myocardial infarction, number of affected vessels, and high sensitive C-reactive protein concentrations strongly correlated with s-7KCHO (p < 0.01, < 0.05, < 0.05, respectively, Table 4).

	OR (95%CI)	p value
s-7KCHO	1.06 (1.02-1.09)	<0.01
Age	1.08 (1.03-1.13)	<0.01
Sex (male)	5.04 (1.81-13.98)	<0.01
Diabetes mellitus	2.29 (0.85-6.13)	NS
HDL-cholesterol	0.97 (0.94-1.01)	NS
Smoking	1.66 (0.62-4.42)	NS
hs-CRP	1.10 (0.36-3.41)	NS

OR: odds ratio, CI: confidence interval, (n=182)

Table 3. Results of multivariate logistic regression analysis for coronary artery disease.

	Standard regression coefficent	t value	p value
Explanatory factor			
AMI	0.32	3.9	<0.01
No of affected vessels	0.25	3.0	<0.05
hs-CRP	0.24	2.9	<0.05
Subordinate factor			
s-7KCHO (actual value)			

R2=0.27, F value=3.8, p<0.0001, (n=139)

Table 4. Results of multiple regression analysis for 7-ketocholesterol concentrations in subjects with coronary artery disease.

Our angiographic study indicated that high s-7KCHO were closely associated with acute myocardial infarction. On the other hand, recent clinical studies using IVUS have clarified that coronary artery plaque already exists in subjects with normal coronary artery, which is

diagnosed by coronary angiography. Furthermore, it has been reported that almost 70% of culprit lesion on acute myocardial infarction, now called acute coronary syndrome, which is highly correlated with mortality, occurs in less than 50% of angiographic stenosis (Falk E et al., 1995). Therefore, it is difficult to predict the occurrence of acute coronary syndrome and it is important that we consider the presence of coronary atherosclerosis; especially presence of vulnerable plaque, before angiographic stenosis. IVUS studies have clarified the future of plaque on acute coronary syndrome; plaque volume is large and shows abnormal plaque quality (Yamagishi M et al., 2000; Namiki N et al., 1999; Kotani J et al., 2003) such as eccentricity, lipid pool and mild calcified lesions. Therefore, next, we examined relation of s-7KCHO and coronary plaque in angiographic normal stage using IVUS.

4. IVUS study

4.1 Study population

66 subjects with normal coronary artery diagnosed by coronary angiography were enrolled. Proxymal range of left anterior descending coronary artery was observed by intravascular ultrasound using auto-pullback methods and examined relation of s-7KCHO and coronary plaque.

4.2 Methods of IVUS study

Coronary angiography was performed the transfemoral approach using a standard technique. Two experienced angiographers reviewed all coronary angiograms and confirmed that there were no stenotic lesion, and consequently performed IVUS study. To avoid spasm, 1 to 2 mg of nitroglycerin was administrated before insertion of the 0.014-inch coronary guidewire and IVUS catheter through a coronary guiding catheter. After the IVUS catheter was inserted more than 20 mm beyond proximal of left descending coronary artery (LAD), a motorized auto pullback was performed at 1 mm/second velocity and the percent plaque volume was calculated for 20 mm length of LAD proximal side as plaque quantity. We also evaluated plaque quality, such as eccentricity, calcification and lipid pool into plaque. Eccentricity was identified when the minimum dimension of plaque thickness/dimension of the other side plaque thickness at max plaque area was less than 0.5. Calcification was defined when a high echo area with back reflection was detected and lipid pool was defined as when echo lucent zone was detected during the observation period.

4.3 Results

There were significantly positive correlation between s-7-KCHO and %Plaque volume (r=0.37, p<0.001, Fig. 4.); furthermore, multiple regression analysis showed that high s-7-KCHO were selected as independent variables for %Plaque volume (p<0.05). On the other hand, subjects with high s-7-KCHO ($\geqq$20ng/ml, n=33) were detected high incidence of abnormal plaque quality such as eccentric plaque (76%), mild calcified lesion (64%) and lipid pool (30%) (Table 5). Fig. 5. shows the relationship of high s-7-KCHO and degree of calcification. Subjects with high s-7-KCHO had mild degree and plural number of calcification into plaque.
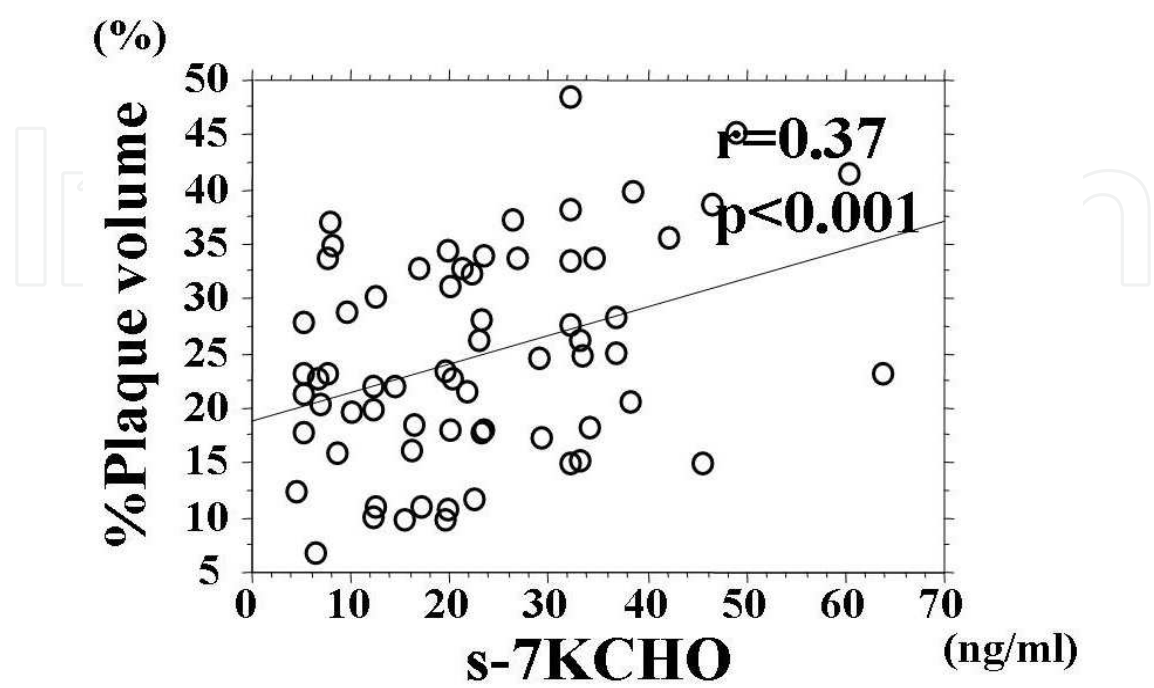
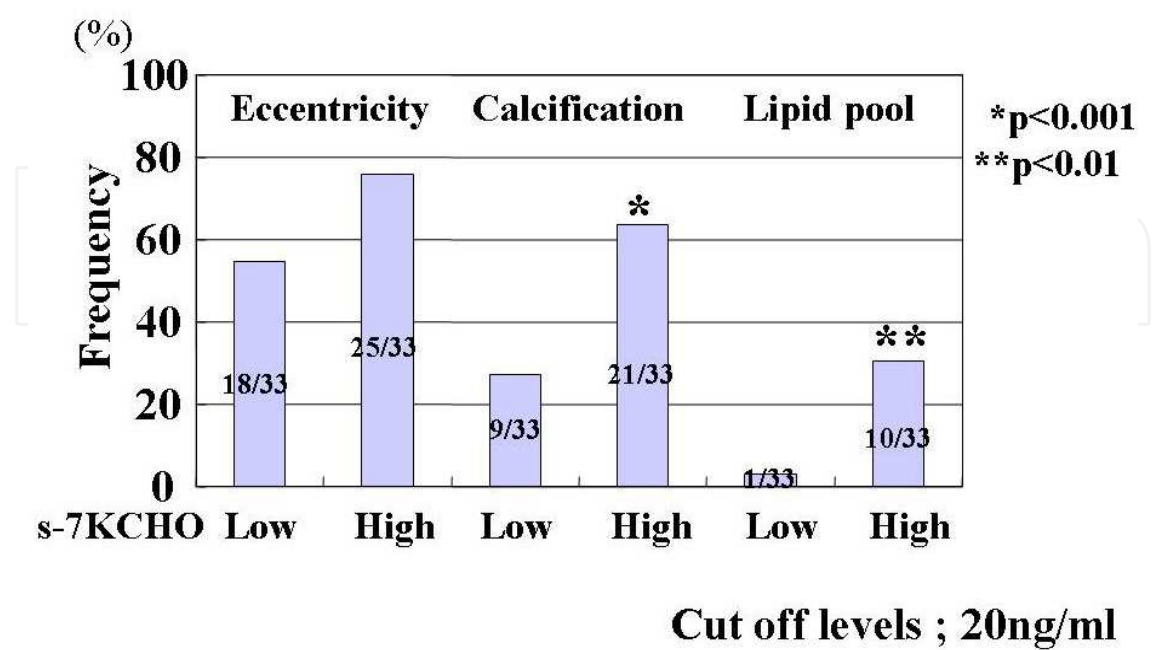Fig. 4. Correlation between 7-keto cholesterol concentration and %Plaque volume.

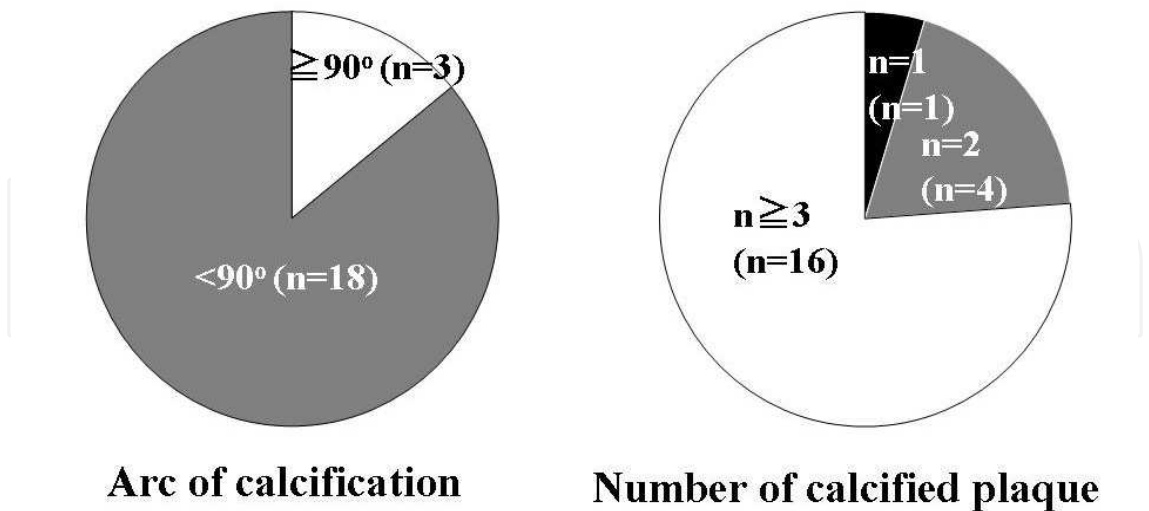Table 5. 7-ketocholesterol concentrations and abnormality of plaque quality.

Fig. 5. Feature of calcification in subjects with high 7-ketocholesterol concentrations.

5. Discussion

In angiographic study, s-7KCHO were significantly higher in subjects with CAD than in those with NCA; furthermore, multiple regression analysis revealed that s-7KCHO were selected as independent variable for the presence of CAD as a subordinate factor. The presence of AMI, number of affected vessels, and hs-CRP concentrations strongly correlated with s-7KCHO in CAD subjects. Furthermore, IVUS study indicated that s-7KCHO reflected vulnerable coronary plaque which is not detectable by coronary angiography.

7KCHO is excessive in advanced atherosclerotic plaques (Brown AJ & Jessup W., 1998), and contributes to the development of atherosclerosis (Smith LL et al., 1996). Furthermore, 7KCHO causes apoptosis (Miyashita Y et al., 1997) and inhibits migration of smooth muscle cells (Oyama T et a.l, 2001). These findings suggest that accumulation of 7KCHO in atherosclerotic lesions may decrease the amount of cells and render atherosclerotic plaques unstable. Thus, 7KCHO is important not only in the progression of coronary atherosclerosis but is also the cause of plaque rupture which is a major factor of AMI. In the present study, s-7KCHO reflected the severity of coronary atherosclerosis, estimated by coronary angiography; furthermore, s-7KCHO strongly correlated with presence of AMI and vulnerable coronary plaque. Therefore, s-7KCHO may reflect 7KCHO in the coronary artery plaque and is expected to be a predictor of AMI occurrence which is strongly associated with mortality.

Hypercholesterolemia is established as one of the most important coronary risk factors; however, the average serum TC or LDL-C concentration in subjects with CAD often appears to be within the normal range. The present study also indicated that serum TC or LDL-C concentrations were not higher in CAD subjects than in NCA subjects. Furthermore, there is no relationship between serum TC or LDL-C concentrations and s-7KCHO. Another study also indicated that blood 7KCHO had no relationship with blood cholesterol concentrations in CAD subjects (Tomasik A et al., 2000). Therefore, these results suggest that s-7KCHO is a different marker from blood cholesterol concentrations even though 7KCHO were oxidation

products of cholesterol. This allows us to predict coronary events which are not detectable by serum TC or LDL-C concentrations if we can measure s-7KCHO in the clinic. In a basic study, degenerative LDL such as small sized LDL or glycated LDL was shown to be easily oxidized (de Graaf J et al., 1991; Lyons TJ., 1992), consequently, promoting atherosclerotic lesion. Some clinical studies emphasized an increase in degenerative LDL in CAD (Austin MA & Krauss RM., 1984; Krauss RM., 1994). 7KCHO may relate to oxidation products of degenerative LDL, however, the relationship is not fully understood. Therefore, further studies are required to investigate the significance of s-7KCHO from the perspective of precise lipid profiles.

Among the serum lipid concentrations, only HDL-C had significant relationship with s-7KCHO. A number of studies reported that low HDL-C concentrations were inversely related to the risk of cardiovascular disease (Castelli WP et al., 1986; Rhoads GG et al., 1976) and the present study may indicate that HDL retards the progression of coronary atherosclerosis by decreasing 7KCHO in the coronary vessel wall or blood flow. The relationship between HDL-C concentrations and s-7KCHO in coronary atherosclerosis is not fully understood. Recently, however, Terasaka reported that HDL exerted a protective effect against apoptosis induced by 7KCHO using ATP-binding cassette transporter ABCG1+/+ mice (Terasaka N et al., 2007). The ATP-binding cassette transporter ABCG1 was recently shown to promote efflux of cholesterol from macrophage to HDL and reverse the relationship between HDL-C concentrations and s-7KCHO. This may be partly explained by the role of ATP-binding cassette transporter ABCG1.

In the present study, there was a significant correlation between s-7KCHO and hs-CRP concentrations in CAD subjects. Furthermore, these two factors had a significant association with each other after adjustment of related factors. Thus, this result suggests that s-7KCHO are closely associated with inflammation in coronary atherosclerosis. Recent clinical investigations showed that inflammation plays an important role in the progression of atherosclerosis (Ross R., 1999; Libby P et al., 2002) and epidemiological studies clarified the link between high levels of CRP concentration and cardiovascular events (Ridker PM et al., 2002; Matsumoto K et al., 2003). Paul et al. showed that CRP is present in the human arterial intima of the atherosclerotic lesion by histological examination (Paul A et al., 2004); furthermore, Kobayashi et al. reported that, by using a sample of directional coronary atherectomy, expression of CRP was colocalized with p22phox and CRP directly induced p22phox expression generating reactive oxygen species in cultured smooth muscle cells (Kobayashi S et al., 2003). Therefore, CRP may promote the production of 7-KCHO in coronary artery plaques; consequently, increasing s-7KCHO. However, some reports indicate that oxysterol influences proinflammatory properties (Wang N et al., 1996; Liu Y et al., 1997). Joffre et al. reported that 7KCHO enhanced interleukin-8 gene expression using porcine retinal pigment epithelial cells (Joffre C et al., 2007). Interleukin-8 is a proinflammatory and chemotactic cytokine which might play a crucial role in the recruitment of monocytes and T lymphocytes into the arterial subendothelial space, consequently, promoting atherosclerotic lesion (Terkeltaub R et al., 1998). Furthermore, interleukin-8 could have a potential atherogenic role by inhibiting the local tissue inhibitor of metalloproteinase-1 expression, thereby leading to an imbalance between matrix metalloproteinases and metalloproteinase-1 at focal sites of atherosclerotic plaque, and to local extracellular degradation, causing the rupture

of atheromatous plaques (Moreau M et al., 1999). Thus, 7KCHO and inflammation in coronary atherosclerosis are closely associated with each other and may promote vulnerable plaque formation.

In IVUS study, calcification was frequently detected in subjects with high s-7KCHO compared with low s-7KCHO.

Calcification into plaque is vulnerable and has been controversial. However, some clinical studies have shown that coronary calcification, which is detected by computed tomography is a powerful predictor for cardiac events (Kondos GT et al., 2003; Greenland P et al., 2004). Raggi et al (Raggi P et al., 2003) reported that coronary calcification identified by electron-beam computed tomography was highly prevalent in patients with acute myocardial infarction; thus, coronary calcification might be indicated in the presence of vulnerable plaque. Furthermore, a recent IVUS study (Ehara S et al., 2004) reported that culprit lesion on acute coronary syndrome had significantly high incidence of mild calcification than those with stable angina pectoris. Therefore, our results can be interpreted as follows: from the viewpoint of calcification, subjects with high s-7KCHO already have vulnerable plaque in early stage coronary atherosclerosis.

6. Conclusion

Our data which is accurately measured s-7KCHO indicate that high s-7KCHO are closely associated with not only progression of coronary atherosclerosis but also formation of vulnerable plaque. To achieve the clinical usefulness, simple and reliable methods to measure blood 7KCHO concentrations are needed and examination of many clinical studies investigating the significance of s-7KCHO in diagnosis and treatment are required.

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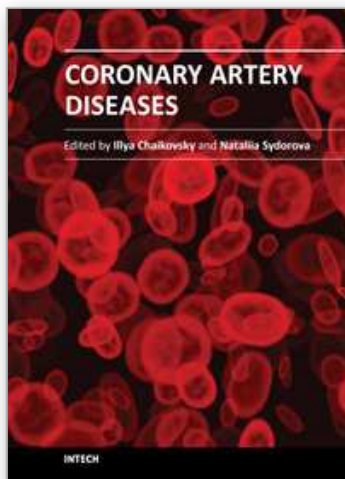
Coronary Artery Diseases

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This book has "wide geography" both literally and figuratively. First of all, this book brings together contributions from around the world, both from post-industrial countries and developing world. This is natural, because coronary artery disease is becoming pandemic worldwide. CAD is the single most frequent cause of death in developed countries, causes about 1 in every 5 deaths. Mortality from cardiovascular disease is predicted to reach 23.4 million in 2030. Moreover, in the developing world, cardiovascular disease tends to affect people at a younger age and thus could negatively affect the workforce and economic productivity. The morbidity, mortality, and socioeconomic importance of CAD make its diagnosis and management fundamental for all practicing physicians. On another hand, the book widely represents "geography" of CAD itself, i.e. many various aspects of its pathophysiology, epidemiology, diagnosis, treatment are touched in this book. This book does not pretend on complete and integral description of the Coronary artery disease. Rather, it contains selected issues on this complex multifactorial disease. Nevertheless, we hope that readers will find Coronary Artery Disease useful for clinical practice and further research.

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Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821