Fasting Triglyceride is a Significant Risk Factor for Coronary Artery Disease in Japanese Middle-aged Men: Results from10-Year Cohort Studies

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Running title: Fasting Triglyceride and Coronary Artery Disease

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Background: It has been well established that dyslipidemia is a significant risk factor for coronary artery disease (CAD), however, fasting triglyceride (TG) is controversial. The objective of this study was to elucidate the relation between fasting TG and CAD in Japanese middle-aged men.

Methods and Results: A cohort study of 6,966 Japanese middle-aged men (mean±SD: 46.6± 5.2 years) with 10-year follow-up was conducted to identify risk factors for the occurrence of CAD. 111 cases of CAD were identified during the follow-up. The Cox proportional hazard model was used to identify the independent risk factors for CAD. Adjustment was made for variables including age, body mass index, smoking habit, alcohol intake, duration of sleeping, systolic blood pressure, uric acid, total cholesterol, high-density lipoprotein cholesterol, fasting plasma glucose, and TG. Fasting TG was identified as an independent risk factor for CAD. Adjusted hazard ratio (HR) of TG for CAD was 3.07 (95% confidence interval (CI): 1.01-9.35, p ＜0.05). Additionally, serum TG concentration level greater than 78 mg/dl was a significant risk

for CAD.

Conclusions: Using the long term follow-up data of Japanese middle-aged men, fasting TG was identified as a significant risk factor for CAD.

Key word: Coronary artery disease; Total cholesterol; High-density lipoprotein cholesterol; Triglyceride

Introduction

A number of previous studies have established the relationship between high total cholesterol (TC) and low high-density lipoprotein cholesterol (HDL-C) and the development of coronary artery disease (CAD) [1-6]. In contrast, the association between triglyceride (TG) and the occurrence of CAD is controversial [7, 8]. Previous studies have demonstrated that triglyceride is a significant risk factor for CAD by the univariate analysis [9-12]. On the contrary, other studies have shown that this relation was not statistically significant after adjusting with TC and HDL-C by using the multivariate regression analyses [13-15]. However, these studies have been performed in the Western countries and might not be directly applicable to the Japanese population because the incidence of CAD has been reported to be lower in Japan compared to that in Europe and the United States [16]. Although one study reported that nonfasting TG could predict the occurrence of CAD in Japanese population [17], the relation between fasting TG and the risk for CAD has not been established. Therefore, the purpose of the present study was to

elucidate the relationship between fasting TG and the development of CAD among 6,966 Japanese middle-aged men using the database obtained from the cohort study with the follow-up period of 10 years.

Methods

Study Subjects

The study subjects included 7,403 male workers, 33-59 years old, in a company in Hokkaido, Japan, from1995-2005. 215 subjects who had not physical examination at baseline and 26 subjects who had already diagnosed as having CAD were excluded from the present study. 196 subjects left the company during follow-up were also excluded. Thus, a total of 6,966 subjects were included in the analysis of the present study in 1995. During the follow-up of 10 years, 81 had non-CAD death and 8 had CAD death were included in the present study. The study protocol was approved by the ethical committee of NTT East Japan Sapporo Hospital.

Data Collection

At baseline, blood samples were obtained in the morning after an overnight fast. Blood sample was obtained from antecubital vein and serum was separated. After precipitation by heparin-manganese, total cholesterol (TC) and high-density lipoprotein cholesterol (HDL-C) were

measured by the phosphotungstate method. Triglyceride (TG) and uric acid (UA) were measured enzymatically. Fasting plasma glucose (FPG) was enzymatically determined by the hexokinase method. Baseline blood pressure (BP) was measured by a trained nurse using a standard mercury sphygmomanometer with the participant in the sitting position after at least a 5-minute rest. Body weight and height were measured in the morning in the fasting state. Body mass index (BMI) was calculated as body weight (kilograms) divided by squared height (meters squared). Smoking habit, alcohol intake, and duration of sleeping were determined by using a self-reported questionnaire. Subjects who had never smoked and ex-smokers were classified as “nonsmokers”. Subjects were divided into two groups, that is over 5 hours of sleep or not.

Outcome Measures

During the follow up period of 10 years (mean±SD: 9.5±0.8 years), sick leave subjects were immediately informed at the company’s health management center. The occurrence of CAD was identified annually between 1995 and 2005 after we examined details of a subject’s clinical chart.

CAD was identified as acute myocardial infarction and angina pectoris. The criteria for CAD were modified from World Health Organization Expert Committee [18]. Angina pectoris was defined as repeated episodes of chest pain during effort and usually disappearing rapidly after the cessation of effort or on use of sublingual nitroglycerin. Additionally, subjects with angina pectoris had coronary stenosis greater than 75% of the luminal diameter by coronary angiography [19]. Acute myocardial infarction was defined by the presence of at least two of the following criteria: a history of prolonged discomfort or anginal equivalent, ECG changes consistent with ischemia or necrosis, and elevated cardiac enzymes.

Statistical Analysis

Continuous variables were expressed as mean±SD, TG was described as a median (and interquartile range) for variables with a skewed distribution, smoking habit and duration of sleeping were described as a percentage. The differences of variables between two groups were examined by the Student unpaired t test for approximately normal distributed variables, or by the

Wilcoxon rank-sum test for TG, and by the Fisher's exact test for the proportion of smoking habit and duration of sleeping. The Cox proportional hazard model was used to examine the relationship between risk factors and CAD and to access the unadjusted and adjusted hazard ratio (HR) of events. The principle model included candidate variables for age (years), smoking habit (non and current smokers), alcohol consumption (g/day), duration of sleep (less and more than 5 hours), BMI, systolic BP (mmHg), TC (mg/dl), HDL-C (mg/dl), log TG, FPG (mg/dl), and UA (mg/dl). Age and BMI were indicated per additional one increase. Systolic BP was indicated per additional 10 mmHg increase. TC and FPG were indicated per additional 10 mg/dl increase. HDL-C was indicated per additional 5 mg/dl increase. TG was calculated as a log-transformed. A p value of less than 0.05 was considered to indicate statistical significance. All statistical analyses were performed using the SPSS statistical package for Windows version 12.0 (Chicago, IL, USA) [20].

Results

During the follow-up of 10 years, 111 subjects had CAD; 74 subjects had acute myocardial infarction and 37 subjects had angina pectoris. The age at baseline was 46.6±5.2 years, ranging from 33 to 55 years and that at onset of CAD were 51.6±5.7 years, ranging from 36 to 59 years.

The baseline characteristics of the subjects with and without CAD are shown in Table 1. Subjects with CAD were more likely smokers and less likely drinkers. They had greater BMI, systolic BP, TC, TG, and FPG levels, and lower HDL-C level. There were no significant differences in other variables such as age, duration of sleep, UA between these 2 groups of subjects.

By using the Cox proportional hazard models, smoking habit, systolic BP, TC, TG, FPG, and low HDL-C were identified as significant independent risk factors for CAD (Table 2). The HR of CAD adjusting for risk factors with smoking habit was 5.59 (95% confidence interval (CI): 2.85-10.96, $p < 0.001$), with 10 mmHg increase in systolic BP was 1.01 (95%CI: 1.02-1.25, $p <$

0.05), with 10 mg/dl increase in TC was 1.14 (95%CI: 1.07-1.21, p＜0.001), with one increase in log TG was 3.07 (95%CI: 1.01-9.35, p＜0.05), with 5 mg/dl increase in HDL-C was 0.80 (95%CI: 0.73-0.89, p＜0.001), with 10 mg/dl increase in FPG was 1.05 (95%CI: 1.01-1.10, p＜0.05), respectively.

By using the Cox proportional hazard models, TG was identified as a significant independent risk factor for CAD (Table 3). The unadjusted HR of CAD for TG was 23.74 (95%CI: 10.10-55.81, p＜0.001). TG was an independent risk factor for CAD even after the adjustment with such unfounding variables such as TC and HDL-C. The adjusted HR of CAD was 3.07 (95%CI: 1.01-9.35, p＜0.05).

Hazard ratios for CAD were further assessed with in the quartile levels of TG ranging ≦78, 79-110, 111-161, and≧162 mg/dl (Table 4). There was a dose-response relation between TG and the risk of CAD. Compared the lowest to the second low quartile level of TG, the unadjusted HR was 7.22 (95%Cl;2.15-24.20, p＜0.01). After adjusting for TC, HDL-C, and other variables, the

adjusted HR of CAD was 4.13 (95%Cl; 1.22-14.00, p＜0.05).

HDL-C values in the quartile levels of TG are shown in Figure 1. There was a negative relation between the quartile levels of TG and HDL-C values. The quartile levels of TG from the lowest to highest had HDL-C values (mean±SD), which were 63.8±17.6, 55.6±14.8, 50.1±13.5, and 43.8±11.6 mg/dl, respectively.

Hazard ratios for CAD were further assessed by the combination of TG and HDL-C levels (Table 5). We divided into 3 groups, which were low TG and high HDL-C (group1), high TG and high HDL-C (group 2), and high TG and low HDL-C (group 3). Considering group 1 as a reference, the adjusted HR of CAD in group 2 and group 3 was 5.52 (95%CI: 1.71-17.85, p＜0.01) and 12.59 (95%CI: 3.82-41.46, p＜0.001), respectively.

Discussion

The present study indicated that fasting TG is significantly associated with the development of CAD in Japanese middle-aged men. Serum TG concentration level greater than 78 mg/dl is a significant risk for CAD. To our knowledge, this is the first epidemiological study to demonstrate a significant relation between fasting TG and CAD among Japanese men.

The relationship between dyslipidemia and CAD risk has been well established [3, 21, 22]. Previous studies have demonstrated that high TC increases the risk for CAD and a 1% reduction in serum TC concentration reduces CAD risk by 2% [1]. The present study has shown that a 10 mg/dl increase in TC increase CAD risk by 14%. Even though hyperlipidemia is an established risk factor for CAD, about 40% of CAD patients had TC level below normal range and most of these patients had low levels of HDL-C, regardless with the levels of TG [23]. Recently, International Diabetes Federation (IDF) showed that other lipoproteins such as HDL-C and TG could be the potential therapeutic targets [24]. Low level of HDL-C is a well-established risk

factor for the development of CAD. Previous studies demonstrated that 1% increase in HDL-C is associated with a 2% to 3% reduction in the risk of CAD [5]. The present study similarly demonstrated that a decrease of CAD risk was 20% by 5mg/dl increase of HDL-C.

Previous studies have reported inconsistent results regarding the association between TG and CAD [7-17]. The Copenhagen Male Study, which followed 2906 white men over 8 years, found that fasting TG was independently associated with the incidence of CAD. However, when adjusted for the HDL-C and low-density lipoprotein (LDL) cholesterol levels, TG did not increase the risk for CAD [9]. In most studies, the relationship between TG and CAD risk is not statistically significant especially in men [9, 25]. The present study demonstrated that fasting TG is dose-dependent relationship with the development of CAD, with adjusting for HDL-C, TC and other risk factors. The previous study demonstrated a close correlation of remnant-like particles (RLP)-cholesterol levels with TG levels in Japanese population [26]. RLP-cholesterol contributed to atherogenesis by directly affecting the vascular cells, endothelial cells and smooth muscle cells

[27]. That's because fasting TG might be an independent risk factor for CAD in our population. Additionally, the analysis of quartile levels of TG indicated that TG greater than 78 mg/dl was a significant risk for CAD. By comparing two groups which are greater or less than 78 mg/dl, the adjusted HR of CAD was 4.18 (95%Cl; 1.35-14.24, p=0.014) (data not shown) and the same result was indicated.

TG and HDL-C are inversely correlated and mechanistically linked means of lipid transfer activities [28]. In our population, the increase of serum TG concentration affected the decrease of serum HDL-C concentration. These results demonstrated that subjects who had higher levels of TG could have another risk factor such as low HDL-C and might have more risk for CAD. The present study demonstrated that subjects who had high TG level and low HDL-C level had significantly higher risk for CAD than those who had high TG level and normal HDL-C level.

Hypertriglycemia is associated with increased concentrations of factor Ⅶ and plasminogen activator inhibitor, which may accelerate thrombotic processes [29]. Hyperglycemia is also

closely associated with small, dense LDL, which is increased entry into and retention in the arterial wall because of a low affinity for LDL receptors and susceptibility to oxidation and this is considered to be more atherogenic than larger LDL particles [29-33]. However, it is difficult to assess LDL particle size directly. These results have indicated that the measurement of TG is considered to be important to predict the risk for the development of CAD.

Study limitations

Our study subjects included only male and age ranged from 33 to 55 years old. Thus, we need to be cautious to extend the present result to general population. Recently, metabolic syndrome was a significant risk factor for the development of CAD and abdominal obesity and insulin resistance were crucial problems. These risk factors were not investigated in the present study and further examinations using these variables were needed. However, this study design enables us to enroll and perform the long-term follow-up studies in many subjects.

In conclusion, the present study demonstrated that fasting triglyceride is an independent risk

factor for CAD among Japanese middle-aged men.

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Table 1 Baseline characteristics for subjects with and without coronary artery disease during 10-year follow up.

Variable	CAD (n=111)	No CAD (n=6855)	P value
Age (years)	46.6±5.2	46.7±5.2	0.48
Body mass index	24.9±3.2	23.4±2.9	＜0.01
Smokers (%)	82.9	62.3	＜0.01
Alcohol (g/day)	22.08±20.7	26.38±22.7	＜0.05
Duration of sleep (less than 5hours) (%)	3.3	2.7	0.44
Systolic BP (mmHg)	132.2±18.3	126.6±17.5	＜0.01
TC (mg/dl)	219.3±32.0	201.9±32.7	＜0.01
TG (mg/dl)	157 (113-207)	110 (78-159)	＜0.01
HDL-C (mg/dl)	43.6±12.2	53.5±16.3	＜0.01
FPG (mg/dl)	108.0±40.3	97.4±22.4	＜0.01
UA (mg/dl)	5.9±1.3	5.9±1.4	0.49

Data are as mean±SD. TG was expressed as a median and interquartile range due to its skewed distribution.

P-value＜0.05 considered to be significant.

CAD, coronary artery disease; BP, blood pressure; TC, total cholesterol; TG, triglyceride;

HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; UA, uric acid;

Table 2　Hazard ratios for coronary artery disease with confidence intervals for risk factors with adjustment for all variables

Variable	Adjusted HR	95%CI	P value
Age	1.00	0.96–1.03	0.81
Body mass index	1.05	0.99–1.12	0.12
Smoking	5.59	2.85–10.96	＜0.001
Alcohol	0.92	0.88–0.96	0.05
Duration of sleep	1.00	0.97–1.02	0.87
Systolic BP	1.01	1.02–1.25	0.03
TC	1.14	1.07–1.21	＜0.001
log TG	3.07	1.01–9.35	＜0.05
HDL-C	0.80	0.73–0.89	＜0.001
FPG	1.05	1.01–1.10	0.03
UA	0.86	0.74–1.00	0.05

P-value＜0.05 considered to be significant.

CI, confidence interval; HR, hazard ratio; BP, blood pressure; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; FPG, fasting plasma glucose; UA, uric acid;

Table 3 Hazard ratios for coronary artery disease with confidence intervals for triglyceride levels

	Hazard ratio	95%CI	P value
Model 1	23.74	10.10−55.81	＜0.001
Model 2	10.16	3.81−27.08	＜0.001
Model 3	6.63	2.34−18.76	0.001
Model 4	3.07	1.01−9.35	＜0.05

Model 1, unadjusted

Model 2, adjusted for age, BMI, smoking, alcohol, duration of sleeping, systolic BP, FPG, UA, and TC

Model 3, adjusted for age, BMI, smoking, alcohol, duration of sleeping, systolic BP, FPG, UA, and HDL-C

Model 4, adjusted for age, BMI, smoking, alcohol, duration of sleeping, systolic BP, FPG, UA, TC, and HDL-C

P-value＜0.05 considered to be significant.

CI, confidence interval;

Table 4　Hazard ratios for coronary artery disease with confidence intervals according to quartile levels of triglyceride

Quartile (Q) of triglycerides	Q1	Q2	Q3	Q4
No. of cases (%)	2.7	18.9	30.6	47.7
Model 1				
HR	1.0	7.22	11.44	18.75
95%CI		2.15−24.20	3.51−37.24	5.85−60.03
P value		＜0.01	＜0.01	＜0.01
Model 2				
HR	1.0	5.57	7.41	10.31
95%CI		1.65−18.75	2.24−24.46	3.12−34.05
P value		＜0.01	＜0.01	＜0.001
Model 3				
HR	1.0	6.78	9.24	11.38
95%CI		1.49−16.98	1.94−21.31	2.40−26.96
P value		＜0.05	＜0.05	＜0.05
Model 4				
HR	1.0	4.13	4.44	4.87
95%CI		1.22−14.00	1.32−14.93	1.42−16.69
P value		＜0.05	＜0.05	＜0.05

Q1,2,3,and 4 are TG levels ≦78, 79-110, 111-161, and ≧162 mg/dl, respectively.

Model 1, 2, 3, and 4 are shown in Table 3. P-value＜0.05 considered to be significant.

HR, hazard ratio; CI, confidence interval;

Table 5　Hazard ratios for coronary artery disease with confidence intervals according to the combination of triglyceride and high-density lipoprotein cholesterol

	Low TG and High HDL-C group	High TG and High HDL-C group	High TG and Low HDL-C group
Unadjusted HR	1.0	6.21	19.62
95%CI		1.45−26.57	4.83−79.69
P value		＜0.05	＜0.001
Adjusted HR	1.0	5.52	12.59
95%CI		1.71−17.85	3.82−41.46
P value		＜0.01	＜0.001

TG level was divided into high or low group, which was more or less than 78 mg/dl.

HDL-C level was divided into high or low group, which was more or less than 40 mg/dl.

P-value＜0.05 considered to be significant.

HR, hazard ratio; CI, confidence interval; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol;

Figure 1.

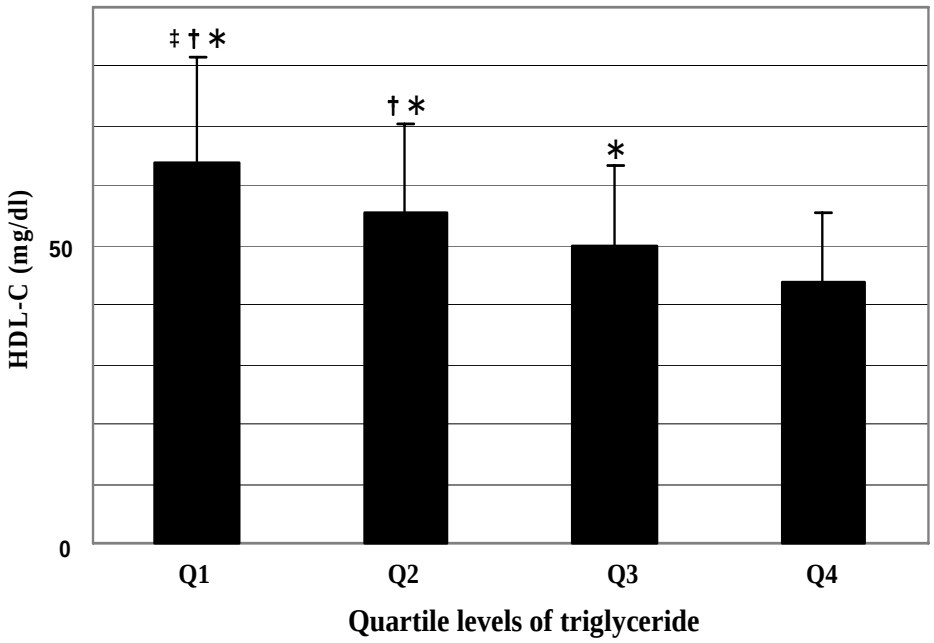

Figure legend

Figure 1. High-density lipoprotein cholesterol values in the quartile levels of triglyceride

Q1,2,3,and 4 are TG levels ≦78, 79-110, 111-161, and ≧162 mg/dl, respectively.

***:** $p<0.01$ compared with Q4, †:$p<0.01$ compared with Q3, ‡:$p<0.01$ compared with Q2