Original Article

Fatty Liver and Uric Acid Levels Predict Incident Coronary Heart Disease but Not Stroke among Atomic Bomb Survivors in Nagasaki

Takeshi BABA[1),2)], Yasuko AMASAKI[2)], Midori SODA[3)], Ayumi HIDA[2)],

Misa IMAIZUMI[2)], Shinichiro ICHIMARU[2)], Eiji NAKASHIMA[4)],

Shinji SETO[1),2)], Katsusuke YANO[1),2)], and Masazumi AKAHOSHI[2)]

Relationships between fatty liver and coronary heart disease (CHD) and stroke risk remain ill defined. We investigated whether fatty liver is a predictor of CHD and stroke risk. Until December 2000 we followed 2,024 atomic bomb survivors (775 men: 62.0±9.9 years old; 1,249 women: 63.2±8.4 years old) who had basic examinations between November 1990 and October 1992 for clinical and laboratory CHD risk factors and fatty liver and who were initially free of CHD and stroke. Forty-nine cases of CHD and 84 cases of stroke were observed. At the time of the baseline examinations, significant clinical associations were found between fatty liver and obesity ($p<0.001$), hypertension ($p<0.001$), dyslipidemia ($p<0.001$), and glucose intolerance ($p<0.001$). A slight but nonsignificant association was found between fatty liver and hyperuricemia ($p=0.07$) as well. By using multiple Cox regression analyses, age (relative risk [RR] 1.05, 95% confidence interval [CI] 1.01–1.08), smoking (RR 2.20, 95% CI 1.02–4.74), hyperuricemia (RR 2.30, 95% CI 1.08–4.89), and fatty liver (RR 2.53, 95% CI 1.06–6.06) were shown to be significant predictors of CHD, whereas age (RR 1.08, 95% CI 1.06–1.10), smoking (RR 2.06, 95% CI 1.14–3.72), and hypertension (RR 2.14, 95% CI 1.38–3.30) predicted stroke risk. Fatty liver, which clusters clinical and laboratory CHD risk factors, is an independent predictor of CHD, but not of stroke. Fatty liver should be followed as a feature of metabolic syndrome, with the aim of preventing CHD. (*Hypertens Res* 2007; 30: 823–829)

Key Words: **atomic bomb, cardiovascular disease, thrifty genotype, follow-up studies, liver**

Introduction

Visceral fat accumulation plays a central role in the development of the insulin resistance syndrome (*1–3*). This clinical syndrome, presently defined as the metabolic syndrome, represents the clustering of obesity, insulin resistance, dyslipidemia, glucose intolerance, and hypertension (*4–6*). Visceral fat accumulation induces the deposition of triglycerides in the liver, which is a histological characteristic of fatty liver (*7, 8*). Non-alcoholic fatty liver also is highly related to insulin resistance, obesity, dyslipidemia, glucose intolerance, and hypertension (*9–12*). Therefore, non-alcoholic fatty liver may be considered an additional feature of the metabolic

syndrome (*11*, *12*).

The insulin resistance syndrome, *i.e.*, metabolic syndrome, has been reported to predict coronary heart disease (CHD) (*5*, *6*, *13*, *14*). On the other hand, the natural history of non-alcoholic fatty liver has been extensively studied with respect to liver cirrhosis and liver-related death (*15–17*), but recently, there has been a focus on the association between non-alcoholic fatty liver and CHD risk (*18–21*). It has been reported that indicators of liver function such as γ-glutamyltransferase and alanine aminotransferase, surrogate markers of non-alcoholic fatty liver, predicted the future CHD risk (*18–20*), although there have been only a few studies examining the association between non-alcoholic fatty liver detected by ultrasonography and future CHD risk to confirm this association (*21*).

We conducted baseline examinations to clarify the association between fatty liver detected by ultrasonography and metabolic CHD risk factors in 2,083 Nagasaki atomic bomb survivors from November 1990 through October 1992. We prospectively followed 2,024 survivors who were free from CHD (myocardial infarction and angina pectoris) or stroke (intracranial hemorrhage and cerebral infarction) at baseline examination until December 2000 and identified incident cases of CHD and stroke to examine whether fatty liver predicts CHD and stroke risk.

Methods

Subjects

A total of 7,564 atomic bomb survivors (3,374 men and 4,190 women) have undergone biennial examinations in Nagasaki since 1958 as part of the follow-up program of the Radiation Effects Research Foundation (RERF, formerly the Atomic Bomb Casualty Commission). A detailed description of this program has been published elsewhere (Atomic Bomb Casualty Commission, Technical Report (*22*) and Radiation Effects Research Foundation, Research Plan for RERF Adult Health Study, Hiroshima and Nagasaki, RERF Research Protocol 2-75, 1975). This program was approved by the Research Protocol Review Committee and the Human Investigation Committee at RERF in 1975.

At the baseline period, from November 1990 through October 1992, 2,083 subjects (810 men and 1,273 women) underwent clinical examination, biochemical measurement, and abdominal ultrasonographic examination to detect fatty liver. Because 59 subjects (35 men and 24 women) already had CHD (myocardial infarction and angina pectoris) and/or stroke (intracranial hemorrhage and cerebral infarction) at baseline examination, the remaining 2,024 subjects (775 men and 1,249 women) were followed until December 2000.

Baseline Examination

At each examination, a trained nurse collected medical infor-mation and information about smoking (non-smoker or smoker, with the latter category including past or current smokers) and drinking (non-drinker or drinker, with the latter including past or current drinkers) habits.

Sitting blood pressure (mmHg) was measured on the left arm with a sphygmomanometer after a sufficient sedentary period. The first and fifth Korotkoff phases, respectively, were used for systolic (SBP) and diastolic blood pressure (DBP). Mean blood pressure (MBP) was calculated as DBP plus pulse pressure divided by three. A subject was classified as having hypertension if his or her MBP was 107 ($\approx 90 + (140 - 90)/3$) mmHg or more. Standing height (in m) and body weight (in kg) were measured without socks and without outer clothing. Body mass index (BMI, kg/m^2) was calculated from the body weight divided by the square of the standing height. Obesity was defined as a BMI of 26.0 or more, in accordance with the definition of Ikeda and Ohno (*23*). A standard 12-lead electrocardiogram was obtained by the regular procedure.

Fasting blood samples were drawn for biochemical measurements. Serum total cholesterol (mg/dL), high-density lipoprotein cholesterol (HDL-cholesterol, mg/dL), serum triglyceride (mg/dL), fasting blood glucose (FBG, mg/dL), and uric acid (mg/dL) were measured by an automated procedure (Hitachi 7050; Hitachi Ltd., Tokyo, Japan) with quality control monitored by the College of American Pathologists (Northfield, USA). Hypercholesterolemia was defined as a serum total cholesterol level of 220 mg/dL or more, low HDL-cholesterol as a serum HDL-cholesterol level below 40 mg/dL, hypertriglyceridemia as a serum triglyceride level of 150 mg/dL or more, and hyperuricemia as a serum uric acid level of 7.0 mg/dL or more. Subjects with an FBG of 110 mg/dL or more and those undergoing medical treatment for diabetes mellitus or impaired glucose tolerance were defined as having glucose intolerance.

A radiologist (Y.A.) conducted consecutive abdominal ultrasonographic examinations using an Aloka SSD-650 (ALOKA Co., Ltd., Tokyo, Japan) without making reference to the subject's history of liver disease, clinical findings or biochemical data. Fatty liver was diagnosed when there was accentuation of liver-kidney contrast, blurring of the hepatic vessel wall or deep attenuation of echogenicity (*24*). Ultrasonography has 83% sensitivity and 100% specificity in cases with fatty change of over 30% in the hepatic lobule (*24*) and 80% sensitivity in cases with fatty change of up to 25% of the liver parenchyma (*25*).

Follow-Up

All subjects visited RERF biennially and underwent the same clinical, biochemical and ultrasonographic examinations as at baseline examination. Diagnoses of CHD and stroke were confirmed at every visit and stored in a database according to the International Classification of Disease, ninth version (ICD9). The follow-up began on the date of the baseline

Table 1. Basic Characteristics of the Study Population

| | With fatty liver | | Without fatty liver | | *p* value with *vs*. without fatty liver | |
	Male	Female	Male	Female	Male	Female
Number	41	80	734	1,169		
Age (years)	55.2±8.4	61.4±7.2	62.3±9.9	63.3±8.5	<0.001	<0.001
Smoking (%)	95.2	15.0	73.0	10.0	0.60	0.16
Drinking (%)	68.2	18.8	77.7	19.3	0.17	0.90
BMI (kg/m^2)	25.9±2.9	25.9±3.0	22.1±2.9	22.8±3.2	<0.001	<0.001
MBP (mmHg)	100.0±11.9	101.4±13.1	97.6±12.2	94.4±13.0	0.23	<0.001
T-chol (mg/dL)	216.1±29.5	231.7±37.2	191.0±32.1	213.3±34.8	<0.001	<0.001
HDL-C (mg/dL)	44.0±11.3	48.6±12.4	52.4±14.8	56.6±14.3	<0.001	<0.001
TG (mg/dL)	220.9±179.9	176.9±110.0	121.1±74.9	110.1±52.1	<0.001	<0.001
FBG (mg/dL)	112.7±40.2	116.9±50.2	100.0±22.7	98.2±21.6	<0.001	<0.001
Uric acid (mg/dL)	6.0±1.7	5.3±1.2	5.7±1.3	4.6±1.2	0.023	<0.001

BMI, body mass index; MBP, mean blood pressure; T-chol, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; TG, triglyc-
erides; FBG, fasting blood glucose. Age, BMI, MBP, T-chol, HDL-C, TG, FBG, and uric acid are expressed as the mean±SD. Smoking
and drinking are expressed as percentage.

**Table 2. Age, Sex, Smoking, and Drinking Adjusted Relationship between Fatty Liver and Coronary Risk Factors at Baseline
Examination**

	With fatty liver	Without fatty liver	*p* value
Obesity (%)	48.8 (59/121)	12.3 (235/1,903)	<0.001
Hypertension (%)	32.2 (39/121)	19.0 (362/1,903)	<0.001
Hypercholesterolemia (%)	57.0 (69/121)	31.9 (608/1,903)	<0.001
Low HDL-cholesterol (%)	32.2 (39/121)	14.3 (273/1,903)	<0.001
Hypertriglyceridemia (%)	50.4 (61/121)	19.2 (366/1,903)	<0.001
Glucose intolerance (%)	25.6 (31/121)	10.1 (193/1,903)	<0.001
Hyperuricemia (%)	11.6 (14/121)	8.2 (156/1,903)	0.07

Values are expressed as percentage and numbers appear in parentheses. HDL, high-density lipoprotein.

examination during the period from November 1990 through
October 1992, and ended on the date of occurrence of CHD
and/or stroke, or December 31, 2000, whichever came first.
Deaths other than from CHD and stroke were treated as cen-
sored cases.

Diagnose of CHD (myocardial infarction and angina pecto-
ris) and stroke (intracranial hemorrhage and cerebral infarc-
tion) were based on the same methods used previously;
namely, self-report, electrocardiographic findings, and infor-
mation provided from the physician in charge (*26*). Two car-
diologists (T.B. and M.A.) reviewed the electrocardiographic
findings of all subjects. Myocardial infarction was confirmed
by the presence of one or more of the following conditions:
typical electrocardiographic evidence of myocardial infarc-
tion compared with previous electrocardiographic findings;
chest pain with typical electrocardiographic changes; eleva-
tion of myocardial enzymes; and coronary arteriographic
(CAG) findings. Angina pectoris was confirmed by the pres-
ence of one or more of the following conditions: a positive
result in an exercise electrocardiogram; chest pain with typi-
cal electrocardiographic changes; effectiveness of medical

treatment for the disorder; and CAG findings. Stroke was
defined as rapid onset of a new neurological deficit in the
absence of underlying potentially important nonvascular
causes and lasting at least 24 h. Brain CT images and other
diagnostic tests were also used to determine stroke. Two car-
diologists (T.B. and M.A.) reviewed the diagnosis of CHD
and stroke without knowledge of whether the subject had
been diagnosed with fatty liver.

RERF followed the vital status of all participants using
Japan's family registration system. We collected all death
certificates of subjects who died between baseline examina-
tion, from November 1990 through October 1992, and
December 31, 2000. The primary cause of death was classi-
fied according to the ICD9. Death certificate data were also
used to identity subjects with a history of myocardial infarc-
tion or stroke.

During the follow-up period, we identified a total of 49
CHD cases, including 28 myocardial infarction cases and 21
angina pectoris cases, and a total of 84 stroke cases, including
21 intracranial hemorrhage cases and 63 cerebral infarction
cases. Seven of 28 myocardial infarction cases, 7 of 21 intra-

cranial hemorrhage cases, and 10 of 63 cerebral infarction cases were ascertained by death certificate only, without clinical data.

Statistical Analysis

Differences in baseline characteristics between controls and subjects with fatty liver were assessed by the χ^2 and Wilcoxon rank sum tests. Multivariate logistic regression analysis was used to evaluate the association between fatty liver and metabolic CHD risk factors. The Cox proportional hazard regression model was used to estimate the relative risk (RR) and 95% confidence interval (CI) of fatty liver and each metabolic CHD risk factor for incident CHD and stroke. All the analyses were conducted using UNIX SAS (SAS Institute, Cary, USA) (27). The data were expressed as the mean±SD. A *p* value less than 0.05 was considered statistically significant.

Results

At baseline examination, there were 121 fatty liver cases, of which the preponderance were females (Table 1). Although the prevalences of smoking and drinking were higher in males than in females, the prevalences of smoking and drinking did not differ between fatty liver cases and controls in either sex. Levels of BMI, MBP, serum total cholesterol, serum triglyceride, FBG, and uric acid were higher in fatty liver cases than in controls, regardless of sex, although these differences were not always significant. By contrast, levels of HDL-cholesterol were lower in fatty liver cases than in controls, regardless of sex.

Fatty liver was related to obesity, hypertension, hypercholesterolemia, low HDL-cholesterol, hypertriglyceridemia, and glucose intolerance, and a moderate but non-significant association was identified between fatty liver and hyperuricemia as well, after controlling for age, sex, smoking, and drinking (Table 2).

Predictive variables for CHD risk were age (RR 1.04, 95% CI 1.01–1.07), glucose intolerance (RR 2.00, 95% CI 1.02–3.91), hyperuricemia (RR 2.59, 95% CI 1.26–5.34), and fatty liver (RR 2.54, 95% CI 1.06–6.05) (Table 3). Independent predictive variables for CHD risk were identified using multiple Cox regression analyses that included variables for which the *p* values were less than 0.1 (glucose intolerance, hyperuricemia, and fatty liver) in addition to age, sex, smoking, and drinking. The following variables were found to be predictive: age (RR 1.05, 95% CI 1.01–1.08), smoking (RR 2.20, 95% CI 1.02–4.74), hyperuricemia (RR 2.30, 95% CI 1.08–4.89), and fatty liver (RR 2.53, 95% CI 1.06–6.06).

Predictive variables for stroke risk were age (RR 1.08, 95% CI 1.05–1.10), smoking (RR 2.02, 95% CI 1.13–3.61), and hypertension (RR 2.22, 95% CI 1.44–3.40) (Table 4). Independent predictive variables for stroke risk were identified using multiple Cox regression analyses that included variables for which the *p* values were less than 0.1 (obesity and hypertension) in addition to age, sex, smoking, and drinking. The following variables were found to be predictive: age (RR 1.08, 95% CI 1.06–1.10), smoking (RR 2.06, 95% CI 1.14–3.72), and hypertension (RR 2.14, 95% CI 1.38–3.30).

Discussion

It is well known that fatty liver is associated with insulin resistance. The clinical counterpart of insulin resistance is the metabolic syndrome. In the present study, fatty liver was closely related to clinical and laboratory risk factors of the metabolic syndrome, which clusters obesity, hypertension, hypercholesterolemia, low HDL-cholesterol, hypertriglyceridemia, and glucose intolerance (9, 10).

The association between fatty liver and abnormal levels of uric acid is controversial (10, 12, 28). In the present study, uric acid levels were shown to be higher in fatty liver cases than in those of the controls, although a slight but nonsignificant association between fatty liver and hyperuricemia was suggested, after controlling for age, sex, smoking, and drinking. This observation is consistent with the suggestion that fatty liver and uric acid levels are clinically associated (12, 28). In several studies, different diagnostic criteria for hyperuricemia were used for males and females; that is, the uric acid level defining hyperuricemia was higher in males than in females (29, 30). However, in the present study, we used the same uric acid levels to define hyperuricemia in both males and females. This may be related to the fact that a slight but nonsignificant association between fatty liver and hyperuricemia was suggested in the present study.

It is well known that insulin resistance syndrome is predictive of CHD development (5, 6, 13, 14). A pattern of central body fat distribution is now generally considered to play an important role in this syndrome. Lakka *et al*. reported that abdominal obesity, as assessed by waist-to-hip ratio and waist circumference, can estimate risk for CHD (31). Visceral fat accumulation induces fatty liver (7, 8), and fatty liver is an additional feature of insulin resistance syndrome (9–12). It is reasonable to suggest, therefore, that fatty liver predicts increased CHD risk as well. Many studies have reported that indicators of liver function such as γ-glutamyltransferase and alanine aminotransferase, surrogate markers of fatty liver, were predictive of future CHD risk, suggesting that fatty liver itself is predictive of future CHD risk (14, 18, 19). Although ultrasonography is a reliable and noninvasive method for diagnosis of fatty liver (9, 24, 25), few studies have examined the association between ultrasonographically detected fatty liver and future CHD risk (21). In the present study, we used ultrasonography to detect fatty liver and clarified that fatty liver, with its constellation of clinical and laboratory risk factors closely linked to insulin resistance, appears to be predictive of CHD. Because radiation dose did not predict CHD risk (data not shown) in the present study cohort of atomic bomb survivors, the present result that fatty liver predicts CHD risk could be applied to the general Japanese population. Fatty

Table 3. Relative Risk of Classic Risk Factors and Fatty Liver for Coronary Heart Disease Development

	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Age (years)	1.04 (1.01–1.07)	<0.01	1.05 (1.01–1.08)	<0.01
Sex (female)	0.85 (0.37–1.93)	0.70	0.88 (0.38–2.04)	0.76
Smoking	2.11 (0.99–4.47)	0.05	2.20 (1.02–4.74)	0.04
Drinking	0.70 (0.35–1.39)	0.30	0.72 (0.36–1.45)	0.36
Obesity	1.21 (0.56–2.58)	0.63		
Hypertension	1.34 (0.71–2.51)	0.36		
Hypercholesterolemia	1.38 (0.77–2.46)	0.27		
Low HDL-cholesterol	0.96 (0.46–1.99)	0.91		
Hypertriglyceridemia	0.91 (0.47–1.79)	0.79		
Glucose intolerance	2.00 (1.02–3.91)	0.04	1.59 (0.76–3.34)	0.22
Hyperuricemia	2.59 (1.26–5.34)	<0.01	2.30 (1.08–4.89)	0.03
Fatty liver	2.54 (1.06–6.05)	0.04	2.53 (1.06–6.06)	0.04

RR, relative risk; CI, confidence interval; HDL, high-density lipoprotein. Multiple Cox regression analysis was conducted using variables with *p* value less than 0.1 (glucose intolerance, hyperuricemia, and fatty liver), in addition to age, sex, smoking, and drinking.

Table 4. Relative Risk of Classic Risk Factors and Fatty Liver for Stroke Development

	Univariate analysis		Multivariate analysis	
	RR (95% CI)	*p*	RR (95% CI)	*p*
Age (years)	1.08 (1.05–1.10)	<0.01	1.08 (1.06–1.10)	<0.01
Sex (female)	0.62 (0.33–1.16)	0.13	0.63 (0.32–1.21)	0.16
Smoking	2.02 (1.13–3.61)	0.02	2.06 (1.14–3.72)	0.02
Drinking	0.79 (0.48–1.31)	0.37	0.83 (0.50–1.38)	0.47
Obesity	1.72 (0.99–3.00)	0.06	1.43 (0.81–2.53)	0.22
Hypertension	2.22 (1.44–3.40)	<0.01	2.14 (1.38–3.30)	<0.01
Hypercholesterolemia	1.38 (0.88–2.16)	0.17		
Low HDL-cholesterol	1.42 (0.87–2.32)	0.16		
Hypertriglyceridemia	1.26 (0.78–2.04)	0.34		
Glucose intolerance	1.54 (0.90–2.65)	0.12		
Hyperuricemia	1.07 (0.53–2.16)	0.85		
Fatty liver	1.33 (0.53–3.31)	0.54		

RR, relative risk; CI, confidence interval; HDL, high-density lipoprotein. Multiple Cox regression analysis was conducted using variables with *p* value less than 0.1 (obesity and hypertension), in addition to age, sex, smoking, and drinking.

liver is easily detected by abdominal ultrasonography, and its prevalence is considered to be approximately 20% of the general population in Japan and in Western countries (*9*, *15*, *32*). Fatty liver, along with other clinical and laboratory CHD risk factors, should be treated and followed not only as a hepatic disease but also as a feature of the metabolic syndrome, with the aim of preventing the development of CHD.

Although some of the results coming from different epidemiological studies have been contradictory, most studies concluded that an abnormal level of serum uric acid is a risk factor for CHD (*33–35*). In the present study, uric acid, which had a weak association with fatty liver, also predicted incident CHD independently from fatty liver. In univariate analysis, glucose intolerance was considered a future CHD risk, while in multivariate analysis, glucose intolerance was not consid-

ered an independent future CHD risk. This may reflect indirect effects of glucose intolerance on CHD risk through other variables.

Epidemiological analyses of case-control and prospective cohort studies have provided substantial evidence that insulin resistance is associated with increased risk for ischemic stroke (*36*, *37*). However, in the present study, fatty liver was not a predictive variable for incident stroke, which included both intracranial hemorrhage (21 cases) and cerebral infarction (63 cases). When we analyzed the predictive value of fatty liver for incident cerebral infarction after controlling for age, sex, smoking, and drinking, the predictive value increased only slightly and insignificantly to an RR value of 1.49 (95% CI 0.54–4.15). The reason why fatty liver did not predict stroke in the present study is not clear. However, it has

been reported that the predictive value of insulin resistance factor for stroke was not significant from 5 to 10 years of follow-up but was significant from 15 to 22 years of follow-up (*13*). This may partly explain the reason why fatty liver was not a predictive variable for stroke, because the maximum follow-up period was only approximately 10 years in the present study. Further follow-up of our cohort is necessary to confirm the presence of any association.

Study Limitations

1) Atomic bomb survivors were selected "healthy survivor" subjects who might be resistant to atomic bomb radiation or atomic bomb disaster. A "healthy survivor" selection effect on non-cancer death rates is observed in atomic bomb survivors; *i.e.*, baseline (zero dose) non-cancer mortality in proximal survivors was lower than that in distal survivors for a few years after the bombing, while the difference diminished steadily over the first two decades of follow-up (*38*, *39*). If the "thrifty genotype," which is advantageous for survival during a period of starvation but unfavorably causes obesity and diabetes mellitus during a time of affluence (*40*, *41*), is partly involved in this "healthy survivor" selection, there may exist a possible selection bias in the present study. That is, the present cohort of atomic bomb survivors might be endowed with a "thrifty genotype" and prone to develop obesity and diabetes mellitus, and ultimately fatty liver in these days of affluence.

2) Twenty five percent (7/28) of the diagnoses of myocardial infarction, 33% (7/21) of those of intracranial hemorrhage, and 16% (10/63) of those of cerebral infarction were based on death certificates, leading to possible misclassification for the diagnosis of CHD and stroke. However, this was unlikely to have biased our results, since the potential for misclassification bias was not different between fatty liver cases and controls.

3) The present results suggest the possibility that treatments of fatty liver with medication and/or life style intervention might have beneficial effects on CHD. However, further studies will clearly be needed to confirm this.

In conclusion, fatty liver was found to be associated with a cluster of related clinical entities—namely, obesity, hypertension, dyslipidemia, and glucose intolerance. Fatty liver and hyperuricemia appear to be independent predictors of CHD, but not of stroke. Because fatty liver is easily detected by abdominal ultrasonography and its prevalence is approximately 20% of the general population in Japan and in Western countries, fatty liver might well be used to identify and to monitor the metabolic syndrome, with the aim of preventing CHD.

Acknowledgements

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