Original Article

Correlation between Fatty Liver and Coronary Risk Factors: a Population Study of Elderly Men and Women in Nagasaki, Japan

Masazumi AKAHOSHI, Yasuko AMASAKI, Midori SODA, Tan TOMINAGA, Shinichiro ICHIMARU, Eiji NAKASHIMA*, Shinji SETO**, and Katsusuke YANO**

The relation between fatty liver, detected by ultrasonography as a marker of visceral fat accumulation, and coronary risk factors was studied in 810 elderly men and 1,273 elderly women in Nagasaki, Japan from 1990 to 1992. The prevalence of fatty liver was 3.3% in the male and 3.8% in the female non-obese participants (BMI, body mass index $< 26.0 \text{ kg/m}^2$) and 21.6% in the male and 18.8% in the female obese participants ($26.0 \text{ kg/m}^2 \leq \text{BMI}$). Fatty liver was significantly ($p < 0.01$) related to hypercholesterolemia and hypertriglyceridemia in the men and to hypertension, hypercholesterolemia, low-HDL cholesterol, hypertriglyceridemia and diabetes mellitus or impaired glucose tolerance (DM+IGT) in the women independent of age, obesity, smoking and drinking. Non-obesity with fatty liver, rather than obesity with or without fatty liver, had the highest odds ratio for hypertension and low-HDL cholesterol in the men and for hypercholesterolemia, low-HDL cholesterol, hypertriglyceridemia and DM+IGT in the women. The prevalence of fatty liver is the same in elderly men and women, and fatty liver is an independent correlate of coronary risk factors in the elderly. (*Hypertens Res* 2001; 24: 337–343)

Key Words: fat distribution, liver, obesity, risk factors

Introduction

Vague classified obesity into male (upper body obesity) and female (lower body obesity) patterns, and reported that the former is closely related to an increased insulin level, diabetes mellitus and atherosclerosis (1). Since that report, the correlation between fat distribution and coronary risk factors has been shown, and fat distribution has been evaluated with anthropometric indexes such as the waist/hip circumference ratio (WHR) in many studies. WHR, which gives a useful estimation of the proportion of upper body fat, is related to

serum cholesterol, serum triglyceride, serum glucose, serum insulin and blood pressure levels (2, 3). Abdominal obesity with increased WHR is considered an independent (4), and a better predictor of cardiovascular disease than the degree of adiposity (5).

Computed tomography (CT) has been used to distinguish between abdominal obesity caused by visceral fat accumulation and that caused by subcutaneous fat accumulation, and a number of CT study findings confirm the importance of visceral fat accumulation in coronary risk factors (6–8). Visceral fat accumulation is associated with higher levels of serum cholesterol, serum triglyceride and serum glucose than is

From the Department of Clinical Studies, Radiation Effects Research Foundation, Nagasaki, Japan, * Department of Statistics, Radiation Effects Research Foundation, Hiroshima, Japan, and ** the Third Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, Japan. This publication is based on research performed at the Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan. RERF is a private foundation funded equally by the Japanese Ministry of Health and Welfare and the US Department of Energy through the National Academy of Science.

Address for Reprints: Masazumi Akahoshi, M.D., Department of Clinical Studies, Radiation Effects Research Foundation, Nakagawa 1–8–6, Nagasaki 850–0013, Japan. E-mail: akahoshi@rerf.or.jp

Received December 11, 2000; Accepted in revised form March 2, 2001.

subcutaneous fat accumulation (6, 7). Moreover, the ratio of the visceral fat area to the subcutaneous one is related positively to systolic and diastolic blood pressure (7, 8).

CT studies have shown a relationship between visceral fat accumulation and coronary risk factors, but there are several limitations with these findings: 1) the sizes of these cohorts were small; 2) participants were limited to one sex; and 3) few of the studies included non-obese normal controls (6–8). The relation between visceral fat accumulation and coronary risk factors has thus not been fully clarified. A community-based study is needed, but CT cannot be used in such a study.

Of the anthropometric indexes, WHR is a candidate for evaluation of visceral fat accumulation in community-based studies because it is correlated with the ratio of visceral fat area to subcutaneous fat area in Caucasian males and females (9). Waist and hip circumference measurements, however, are prone to operator bias. Moreover, WHR is not correlated with the ratio of visceral fat area to subcutaneous fat area in Japanese females (8). Liver fat is reported to be related to WHR (10) and visceral fat accumulation (11, 12), and ultrasonography is seen as a sensitive and reasonably accurate diagnostic tool for assessing fat infiltration of the liver (96% accuracy with 83% sensitivity and 100% specificity in comparison to histology and 85% accuracy with 100% sensitivity and 56% specificity in comparison to CT) (13, 14). We therefore used fatty liver, as diagnosed by abdominal ultrasonography, as the marker of visceral fat accumulation and evaluated the relationship between this marker and coronary risk factors in a community-based sample from Nagasaki, Japan.

Subjects and Methods

General Procedure

A total of 7,564 participants (3,374 men and 4,190 women) have received biennial examinations in Nagasaki since 1958 as part of the follow-up program of the Radiation Effects Research Foundation (formerly the Atomic Bomb Casualty Commission). A detailed description of this program has been published (Atomic Bomb Casualty Commission (15) and Radiation Effects Research Foundation, Research Plan for RERF Adult Health Study, Hiroshima and Nagasaki, RERF Research Protocol 2-75, 1975). At each examination, sitting blood pressure (mmHg) was measured with a sphygmomanometer placed on the left arm after a sufficient sedentary period. Standing height (in m) and body weight (in kg) were measured without socks and outer clothing. Fasting blood samples were drawn for blood biochemistry. The first and fifth Korotkoff phases, respectively, were used for the systolic and diastolic blood pressures. Mean blood pressure (MBP) was calculated as diastolic blood pressure plus pulse pressure divided by three. Hypertension was defined as an MBP of 107 ($\approx 90 + (140 - 90) / 3$) mmHg or more. The

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 kg/m^2 or more.

Ultrasonographic Examination

From November 1990 through October 1992, 2,083 persons (810 men and 1,273 women) underwent an abdominal ultrasonographic examination in addition to the physical examination and biochemical measurements. A radiologist (Y.A.) conducted consecutive abdominal ultrasonographic examinations with an Aloka SSD-650 (ALOKA Co., Ltd., Tokyo, Japan) without reference to the participant'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 (13), resulting in fatty liver being diagnosed in 123 subjects.

Biochemical Measurements

Serum cholesterol (mg/dl), high density lipoprotein cholesterol (HDL-cholesterol, mg/dl), serum triglyceride (mg/dl), fasting blood glucose (FBG, mg/dl), glutamate oxaloacetate transaminase (GOT, IU/l), glutamic pyruvic transaminase (GPT, IU/l), γ -glutamyl transpeptidase (γ -GTP, U/l) and albumin (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 cholesterol level of 220 mg/dl or more, low HDL-cholesterol as an HDL-cholesterol level below 40 mg/dl, and hypertriglyceridemia as a serum triglyceride level of 150 mg or more. Participants with an FBG of 110 mg/dl or more and those undergoing medical treatment for diabetes mellitus (DM) or impaired glucose tolerance (IGT) were defined as having DM or IGT (DM + IGT).

Smoking and Drinking Habits

From January 1986 through December 1990, information about smoking (non-smoker or smoker including current or past smoker) and drinking (non-drinker or drinker including current or past drinker) habits was collected by trained nurses. Although the period of inquiry about smoking and drinking habits mainly preceded the period of ultrasonographic examination, we used the data to evaluate the relationship between smoking and drinking habits and fatty liver.

Statistical Analysis

The 2,083 participants were divided into four groups according to BMI and ultrasonographic findings: 1) non-obesity ($\text{BMI} < 26.0 \text{ kg/m}^2$) without fatty liver ($n = 1,718$), 2) non-obesity with fatty liver ($n = 64$), 3) obesity ($26.0 \leq \text{BMI}$) with-

Table 1. Basic Characteristics of the Study Population

	Sex	Non-obesity		Obesity	
		Without fatty liver	With fatty liver	Without fatty liver	With fatty liver
Number	Male	698	24	69	19
	Female	1,020	40	173	40
Fatty liver (%)	Male		3.3		21.6
	Female		3.8		18.8
Mean age (years) $\pm$ SD	Male	62.8 $\pm$ 9.7	55.5 $\pm$ 8.2*	59.0 $\pm$ 10.0	54.7 $\pm$ 9.0
	Female	63.3 $\pm$ 8.6	62.5 $\pm$ 7.0	64.1 $\pm$ 7.5	58.5 $\pm$ 8.2
Mean BMI (kg/m ²) $\pm$ SD	Male	21.6 $\pm$ 2.4	23.5 $\pm$ 1.4*	27.6 $\pm$ 1.5	28.4 $\pm$ 1.7
	Female	21.9 $\pm$ 2.4	23.6 $\pm$ 1.6*	28.0 $\pm$ 1.9	28.3 $\pm$ 2.1
Mean GOT (IU/l) $\pm$ SD (normal range: 6–38)	Male	24.7 $\pm$ 15.4	27.7 $\pm$ 9.5	24.8 $\pm$ 12.5	30.0 $\pm$ 15.0
	Female	21.8 $\pm$ 10.1	29.6 $\pm$ 20.1*	23.3 $\pm$ 14.5	23.8 $\pm$ 6.7
Mean GPT (IU/l) $\pm$ SD (normal range: 4–34)	Male	19.9 $\pm$ 15.4	29.5 $\pm$ 12.8	25.1 $\pm$ 16.1	32.6 $\pm$ 22.8
	Female	16.1 $\pm$ 13.2	32.7 $\pm$ 23.9*	19.0 $\pm$ 13.2	25.6 $\pm$ 9.4 [†]
Mean γ -GTP (U/l) $\pm$ SD (normal range: 0–61)	Male	49.4 $\pm$ 59.3	41.3 $\pm$ 25.9	55.6 $\pm$ 51.2	85.1 $\pm$ 101.2
	Female	21.5 $\pm$ 22.1	48.1 $\pm$ 48.8*	25.8 $\pm$ 22.6	45.0 $\pm$ 42.9 [†]
Mean albumin (mg/dl) $\pm$ SD (normal range: 4.0–5.2)	Male	4.4 $\pm$ 3.0	4.6 $\pm$ 2.4*	4.4 $\pm$ 2.7	4.6 $\pm$ 1.9
	Female	4.4 $\pm$ 2.6	4.5 $\pm$ 2.6*	4.4 $\pm$ 2.7	4.5 $\pm$ 2.0
Smoker (%)	Male	78.1	82.6	73.9	84.2
	Female	10.1	17.5	11.0	12.5
Drinker (%)	Male	77.8	69.6	79.7	63.2
	Female	19.8	22.5	16.2	15.0

Abbreviations used: BMI, body mass index; GOT, glutamate oxaloacetate transaminase; GPT, glutamic pyruvic transaminase; γ -GTP, γ -glutamyl transpeptidase. Non-obesity was defined as BMI of less than 26.0 kg/m². Obesity was defined as BMI of 26.0 kg/m² or more. *Significance ($p < 0.05$) vs. non-obesity without fatty liver. [†]Significance ($p < 0.05$) vs. obesity without fatty liver.

out fatty liver ($n = 242$) and 4) obesity with fatty liver ($n = 59$). The biochemical measurements related to liver functions (GOT, GPT, γ -GTP and albumin), age and BMI of all the groups were compared using the Kruskal-Wallis test. The proportion of men, smokers and drinkers in the groups were compared using the chi-square test, and the age-adjusted coronary risk factors (MBP, serum cholesterol, HDL-cholesterol, serum triglyceride and FBG) were compared using the analysis of covariance. The relationship of fatty liver and obesity to coronary risk factors was evaluated by multiple logistic analyses. Odds ratios of coronary risk factors in each group were calculated using the non-obesity without fatty liver group as the reference category group. All analyses were done with the Statistical Analysis System package of programs for personal computers (16). Findings were expressed as the means $\pm$ SD. Values of $p < 0.05$ and $0.05 \leq p < 0.1$ were considered statistically significant and suggestive, respectively.

Results

The basic characteristics of the four groups are shown in Table 1. The prevalence of fatty liver did not differ between males and females in the non-obese (3.3 vs. 3.8 %) or obese (21.6 vs. 18.8 %) groups. Although the participants with fatty liver were younger than those without it, a statistical sig-

nificance was found only for non-obese males. In the obese persons, BMI did not differ between those with and without fatty liver, whereas in the non-obese ones, BMI was higher in those with fatty liver. The frequency of smoking and drinking did not differ between participants with and without fatty liver in the non-obese or obese groups, irrespective of gender. Logistic analysis showed that in terms of sex, age, BMI, smoking and drinking, age and BMI were related to fatty liver, whereas smoking and alcohol intake were not. Although biochemical measurements related to liver functions (GOT, GPT and γ -GTP) were higher in subjects with fatty liver in both the non-obese and obese groups, irrespective of gender, except for γ -GTP for the obese males, all the mean values for those with fatty liver were within the normal range.

All the risk factors were worsened in persons with fatty liver, in comparison to those without fatty liver in both the non-obese and obese groups, irrespective of gender, but a statistical significance was not always found (Table 2). When the values of the non-fatty liver participants were compared for the non-obese and obese groups, MBP and HDL-cholesterol were significantly worsened in the male obese participants, and all the risk factors, except serum cholesterol, were worsened in female obese participants. In contrast, when the values of those with fatty liver were compared between the non-obese and obese groups, serum triglyc-

Table 2. Age-Adjusted Mean Values of Blood Pressure, Serum Cholesterol, HDL-Cholesterol, Serum Triglyceride and Fasting Blood Glucose among Four Groups

Factor	Sex	Non-obesity		Obesity	
		Without fatty liver	With fatty liver	Without fatty liver	With fatty liver
Mean blood pressure (mmHg)	Male	97.2 ± 12.1	99.8 ± 12.1	100.6 ± 12.1 ‡	101.6 ± 12.1
	Female	93.4 ± 12.8	97.6 ± 12.8	99.7 ± 12.8 ‡	105.8 ± 12.8 †
Serum cholesterol (mg/dl)	Male	190.7 ± 31.9	206.6 ± 32.0 *	194.8 ± 31.9	224.0 ± 32.0 †
	Female	212.9 ± 34.8	232.0 ± 35.0 *	216.6 ± 35.0	232.2 ± 35.0 †
HDL-cholesterol (mg/dl)	Male	52.9 ± 14.5	41.9 ± 14.6 *	45.0 ± 14.5 ‡	43.9 ± 14.6
	Female	57.3 ± 14.0	48.0 ± 14.0 *	53.0 ± 14.0 ‡	48.7 ± 14.0
Serum triglyceride (mg/dl)	Male	119.9 ± 82.1	190.5 ± 82.4 *	138.5 ± 82.2	241.7 ± 82.4 †,§
	Female	107.1 ± 56.5	184.0 ± 56.5 *	127.8 ± 56.6 ‡	172.5 ± 56.6 †
Fasting blood glucose (mg/dl)	Male	99.9 ± 24.0	101.2 ± 24.1	103.0 ± 24.0	126.9 ± 24.1 †,§
	Female	97.3 ± 24.3	121.8 ± 24.2 *	104.2 ± 24.2 ‡	112.1 ± 24.2 †,§

Non-obesity was defined as body mass index (BMI) of less than 26.0 kg/m². Obesity was defined as BMI of 26.0 kg/m² or more. Data are expressed as the means ± SD. *Significance ($p < 0.05$) vs. non-obesity without fatty liver. †Significance ($p < 0.05$) vs. obesity without fatty liver. ‡Significance ($p < 0.05$) vs. non-obesity without fatty liver. §Significance ($p < 0.05$) vs. non-obesity with fatty liver.

Table 3. Age- and Smoking- and Drinking-Adjusted Odds Ratios of Obesity and Fatty Liver for Coronary Risk Factors

Coronary risk factor	Sex	Odds ratio of obesity	95% Confidence interval	Odds ratio of fatty liver	95% Confidence interval
Hypertension	Male	1.252	(0.742–2.110)	1.923 *	(0.961–3.846)
	Female	1.845 ***	(1.290–2.639)	2.075 ***	(1.238–3.472)
Hypercholesterolemia	Male	1.066	(0.607–1.873)	4.132 ***	(2.096–8.130)
	Female	1.029	(0.756–1.401)	2.336 ***	(1.447–3.774)
Low HDL-cholesterol	Male	1.949 **	(1.170–3.247)	1.938 *	(0.965–3.891)
	Female	1.508 *	(0.986–2.304)	3.115 ***	(1.808–5.348)
Hypertriglyceridemia	Male	2.183 ***	(1.333–3.584)	2.857 ***	(1.447–5.650)
	Female	1.721 ***	(1.209–2.451)	4.098 ***	(2.519–6.667)
Diabetes mellitus or impaired glucose tolerance	Male	1.969 **	(1.119–3.460)	1.435	(0.631–3.268)
	Female	1.664 **	(1.041–2.660)	3.571 ***	(2.012–6.329)

* Relationship is suggestive ($0.05 \leq p < 0.1$). ** Significance of $p < 0.05$. *** Significance of $p < 0.01$.

eride and FBG were significantly worsened in the obese males, whereas no risk factor was significantly worsened in the obese females.

Obesity was significantly related to low HDL-cholesterol, hypertriglyceridemia and DM+IGT in the men, and to hypertension, hypertriglyceridemia and DM+IGT in the women (Table 3). A relationship between obesity and low HDL-cholesterol was suggested in the women. Fatty liver was significantly related to hypercholesterolemia and hypertriglyceridemia, a relationship suggestive of hypertension and low HDL-cholesterol in the men; whereas, in the women fatty liver was significantly related to all the risk factors. A comparison between the odds ratio of obesity and fatty liver showed that fatty liver had a higher odds ratio for hypertension, hypercholesterolemia and hypertriglyceridemia in the men and for all the risk factors in the women. Although not shown in the table, fatty liver-sex interaction was suggested in hypercholesterolemia and DM+IGT; *i.e.*, fatty liver appeared to have more adverse effects on hypercholesterolemia

in the men than in the women and on DM+IGT in the women than in the men.

Table 4 shows age- and the smoking- and drinking-adjusted odds ratio for coronary risk factors in each group. The male non-obese participants with fatty liver had the highest odds ratio of hypertension and low HDL-cholesterol, and the odds ratios of hypercholesterolemia and hypertriglyceridemia were higher than those in obese men without fatty liver. Of the women, non-obese participants with fatty liver had the highest odds ratios of hypercholesterolemia, low HDL-cholesterol, hypertriglyceridemia and DM+IGT.

Discussion

In our cohort, which included both male and female non-obese and obese persons, all the risk factors were worsened in persons with fatty liver, although a statistical significance was not always observed, and fatty liver was related to hypertension, hypercholesterolemia, low HDL-cholesterol and

Table 4. Adjusted Odds Ratios of Non-Obesity with Fatty Liver, Obesity without Fatty Liver and Obesity with Fatty Liver for Coronary Risk Factors

Coronary risk factor	Sex	Non-obesity		Obesity	
		Without fatty liver	With fatty liver	Without fatty liver	With fatty liver
Hypertension	Male	1	2.481 *	1.395	1.805
	Female	1	1.626	1.727 **	4.525 **
Hypercholesterolemia	Male	1	3.922 **	1.036	4.651 **
	Female	1	2.469 **	1.044	2.283 *
Low HDL-cholesterol	Male	1	3.165 **	2.358 **	2.242
	Female	1	5.128 **	1.859 **	3.077 **
Hypertriglyceridemia	Male	1	3.067 *	2.247 **	5.747 **
	Female	1	9.174 **	2.252 **	3.484 **
Diabetes mellitus or impaired glucose tolerance	Male	1	0.664	1.639	4.329 **
	Female	1	5.952 **	2.110 **	4.000 **

Non-obesity was defined as body mass index (BMI) of less than 26.0 kg/m². Obesity was defined as BMI of 26.0 kg/m² or more. In this analysis, the results were adjusted for age and smoking and drinking habits. The non-obesity without fatty liver group is the reference category group for the odds ratio calculations. *Significance of $p < 0.05$. **Significance of $p < 0.01$.

hypertriglyceridemia in the men and to hypertension, hypercholesterolemia, low HDL-cholesterol, hypertriglyceridemia and DM+IGT in the women, independent of obesity, age, and whether or not the person was a smoker or drinker. Ikai *et al.* (17) reported that systolic blood pressure, serum cholesterol, serum triglyceride and the insulin response to an oral 75 g glucose tolerance test were significantly higher in persons with hepatic steatosis, as detected by ultrasonography, than in normal persons. GPT, as a marker of fatty liver, is significantly related to serum cholesterol, serum triglyceride, FBG and fasting insulin (18). In addition, steatosis of the liver, as evaluated by CT or biopsy, is positively correlated with systolic blood pressure, serum triglyceride, FBG and fasting plasma insulin, and negatively with HDL-cholesterol (10–12). These findings are similar to our present result that fatty liver was related to blood pressure, dyslipidemia, and glucose metabolism.

Fatty liver is not a single clinical entity; rather, it is characterized by histological change, infiltration into and accumulation of fat within the liver due to various causes, such as obesity and alcohol intake (19–21). Banerji *et al.* who studied black men with non-insulin-dependent DM (11), and Goto *et al.* who studied non-diabetic obese and non-obese Japanese (12), reported that the liver fat score assessed by CT is correlated with the visceral adipose tissue mass. Visceral adipose tissue is metabolically active, releasing free fatty acid into the portal vein by lipolysis (22, 23), and thereby leading to the stimulation of triglyceride synthesis in the liver (20, 24). Deposition of triglyceride is a histological characteristic of fatty liver (20, 25). Increases in plasma-free fatty acids and liver fat decrease hepatic insulin clearance, leading to hyperinsulinemia and peripheral insulin resistance (11, 22, 26). Hyperinsulinemia or insulin resistance is closely related to dyslipidemia and hypertension (27, 28). It follows that liver fat deposition is an additional manifestation

of the metabolic insulin resistance syndrome that consists of peripheral insulin resistance, hyperinsulinemia, dyslipidemia, hypertension and increased visceral adipose tissue. Banerji *et al.* confirmed that the liver is an important member of the “triumvirate” in the metabolic insulin resistance syndrome: visceral adipose tissue mass, insulin action and liver fat (11). Fatty liver, as detected by ultrasonography, is reported not to be related to alcohol intake (17), which also was the case in our study. Although we did not examine the association between fatty liver and visceral fat accumulation in the present study, we consider that fatty liver in our participants is another manifestation of visceral fat accumulation.

Sex hormones affect the fat distribution (29). In men fat accumulates in the upper body with an increase in weight that produces an android fat pattern, whereas in women it accumulates in the lower body with an increase in weight that produces a gynoid fat pattern (1, 30). Android or visceral fat accumulation therefore is less common in premenopausal women than in men (31). The slope showing the relationship between age and visceral fat volume is gentle in premenopausal women as compared to men, but it becomes steep in postmenopausal women and is almost the same as in men (32). The android mass or visceral fat mass is therefore greater in postmenopausal women than in premenopausal ones (33, 34). This may explain why the prevalence of fatty liver in our study is the same for men and women, because in view of their ages almost all our female participants could be considered to be in the postmenopausal state.

There is increasing evidence that fat distribution rather than adiposity is closely related to the metabolic aberrations of dyslipidemia, insulin resistance and hypertension (2, 6–8) and a better predictor of coronary heart disease (35). When we compared the odds ratio of obesity and fatty liver with coronary risk factors, fatty liver had a higher odds ratio for all the risk factors, except low HDL-cholesterol and DM+

IGT, in the men and for all the factors in the women. Furthermore, non-obese men with fatty liver, rather than obese men with or without fatty liver, had the highest odds ratio of hypertension and low HDL-cholesterol. Moreover, the odds ratios of hypercholesterolemia and hypertriglyceridemia were higher in the non-obese male participants with fatty liver than in the obese male participants without it. Among the women, non-obese participants with fatty liver, rather than obese participants with or without fatty liver, had the highest odds ratio of hypercholesterolemia, low HDL-cholesterol, hypertriglyceridemia and DM+IGT. These findings are evidence that fatty liver, rather than obesity, is closely related to coronary risk factors.

Nonalcoholic fatty liver or steatohepatitis has been considered solely in the context of obesity but it should no longer been considered a disease predominantly observed in obese subjects (36, 37). This was also the case in our study, and the surprising finding was that the odds ratios of the coronary risk factors were high in non-obese participants with fatty liver. Although the reasons for this have yet to be shown, our findings support, at least in part, those of Larsson *et al.* that the highest incidence of coronary artery disease and related death occurs for low BMI and high WHR (5). We therefore think it is important to detect fatty liver and uncover the existence of multiple coronary risk factors in non-obese subjects.

The reliability of ultrasonography in the diagnosis of fatty liver has been assessed in many studies. Ultrasonography shows 83% sensitivity and 100% specificity in cases with fatty change of over 30% in the hepatic lobule (13) and 80% of sensitivity in cases with fatty change of up to 25% of the liver parenchyma (38). In comparison to CT findings, ultrasonography has 100% sensitivity and 56% specificity, and a good correlation between the grading of fatty infiltration based on ultrasonography and CT is observed (14). Ultrasonography is thus a reliable and noninvasive method for the diagnosis of fatty liver. In Japan, where ultrasonography is widely used in the fields of clinical and public health, detection of fatty liver by ultrasonography is a highly effective means of identifying patients with multiple coronary risk factors.

There are limitations in this study. Because the mean values of liver function tests in the cases with fatty liver were within the normal range, we believe that not only the severe fatty liver cases but also the mild to moderate cases were included in the analysis. However, because the severity of fatty liver was not assessed in comparison to CT findings, we could not negate the possibility that only severe fatty liver cases were selected and this contributed to the close relationship between fatty liver and coronary risk factors. Furthermore, although the present study revealed the close relationship between fatty liver and coronary risk factors, whether or not fatty liver is an independent risk factor for ischemic heart disease remains to be examined in future studies.

Conclusions

The prevalence of fatty liver is virtually identical in elderly men and women, and the close relationship of fatty liver to coronary risk factors is independent of obesity in both. Non-obese persons with fatty liver, rather than obese ones with or without fatty liver, have the highest odds ratios: two of the five coronary risk factors for men and four of the five factors for women. These findings confirm the greater importance of fatty liver and visceral fat accumulation, rather than obesity, as an independent correlate of coronary risk factors in the elderly.

Acknowledgements

We thank Kaoru Yoshida for preparing the manuscript.

References

1. Vague J: The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout, and uric calculous disease. *Am J Clin Nutr* 1956; **4**: 20–34.
2. Meigs JB, D'Agostino RB, Wilson PWF, Cupples LA, Nathan DM, Singer DE: Risk variable clustering in the insulin resistance syndrome: the Framingham offspring study. *Diabetes* 1997; **46**: 1594–1600.
3. Anderson AJ, Sobocinski KA, Freedman DS, Barboriak JJ, Rimm AA, Gruchow HW: Body fat distribution, plasma lipids, and lipoproteins. *Arteriosclerosis* 1988; **8**: 88–94.
4. Rexrode KM, Carey VJ, Hennekens CH, *et al*: Abdominal adiposity and coronary heart disease in women. *JAMA* 1998; **280**: 1843–1848.
5. Larsson B, Svärdsudd K, Welin L, Wilhelmsen L, Björntorp P, Tibblin G: Abdominal adipose tissue distribution, obesity, and risk of cardiovascular disease and death: 13 year follow up of participants in the study of men born in 1913. *Br Med J* 1984; **288**: 1401–1404.
6. Fujioka S, Matsuzawa Y, Tokunaga K, Tarui S: Contribution of intra-abdominal fat accumulation to the impairment of glucose and lipid metabolism in human obesity. *Metabolism* 1987; **36**: 54–59.
7. Nakamura T, Tokunaga K, Shimomura I, *et al*: Contribution of visceral fat accumulation to the development of coronary artery disease in non-obese men. *Atherosclerosis* 1994; **107**: 239–246.
8. Kanai H, Matsuzawa Y, Kotani K, *et al*: Close correlation of intra-abdominal fat accumulation to hypertension in obese women. *Hypertension* 1990; **16**: 484–490.
9. Seidell JC, Oosterlee A, Deurenberg P, Hautvast JGAJ, Ruijs JHJ: Abdominal fat depots measured with computed tomography: effects of degree of obesity, sex, and age. *Eur J Clin Nutr* 1988; **42**: 805–815.
10. Marceau P, Biron S, Hould FS, *et al*: Liver pathology and the metabolic syndrome X in severe obesity. *J Clin Endocrinol Metab* 1999; **84**: 1513–1517.

11. Banerji MA, Buckley MC, Chaiken RI, Gordon D, Lebovitz HE, Kral JG: Liver fat, serum triglycerides and visceral adipose tissue in insulin-sensitive and insulin-resistant black men with NIDDM. *Int J Obes* 1995; **19**: 846–850.
12. Goto T, Onuma T, Takebe K, Kral JG: The influence of fatty liver on insulin clearance and insulin resistance in non-diabetic Japanese subjects. *Int J Obes* 1995; **19**: 841–845.
13. Yajima Y, Ohta K, Narui T, Abe R, Suzuki H, Ohtsuki M: Ultrasonographical diagnosis of fatty liver: significance of the liver-kidney contrast. *Tohoku J Exp Med* 1983; **139**: 43–50.
14. Scatarige JC, Scott WW, Donovan PJ, Siegelman SS, Sanders RC: Fatty infiltration of the liver: ultrasonographic and computed tomographic correlation. *J Ultrasound Med* 1984; **3**: 9–14.
15. Atomic Bomb Casualty Commission: Research Plan for Joint ABCC-NIH Adult Health Study in Hiroshima and Nagasaki, Japan: ABCC Technical Report. 1962, pp11–62.
16. SAS/STAT: User's Guide, Release 6.03 Edition. Cary, SAS Inst. Inc., 1988.
17. Ikai E, Ishizaki M, Suzuki Y, Ishida M, Noborizaka Y, Yamada Y: Association between hepatic steatosis, insulin resistance and hyperinsulinaemia as related to hypertension in alcohol consumers and obese people. *J Hum Hypertens* 1995; **9**: 101–105.
18. Kawasaki T, Hashimoto N, Kikuchi T, Takahashi H, Uchiyama M: The relationship between fatty liver and hyperinsulinemia in obese Japanese children. *J Pediatr Gastroenterol Nutr* 1997; **24**: 317–321.
19. Ludwig J, McGill DB, Lindor KD: Metabolic liver disease: review: nonalcoholic steatohepatitis. *J Gastroenterol Hepatol* 1997; **12**: 398–403.
20. James OFW, Day CP: Non-alcoholic steatohepatitis (NASH): a disease of emerging identity and importance. *J Hepatol* 1998; **29**: 495–501.
21. James O, Day C: Non-alcoholic steatohepatitis: another disease of affluence. *Lancet* 1999; **353**: 1634–1636.
22. Björntorp P: "Portal" adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. *Arteriosclerosis* 1990; **10**: 493–496.
23. Pouliot MC, Després JP, Nadeau A, et al: Associations between regional body fat distribution, fasting plasma free fatty acid levels and glucose tolerance in premenopausal women. *Int J Obes* 1990; **14**: 293–302.
24. Kral JG, Lundholm K, Björntorp P, Sjöström L, Scherstén T: Hepatic lipid metabolism in severe human obesity. *Metabolism* 1977; **26**: 1025–1031.
25. Maruhama Y, Yanbe A, Tadaki H, et al: Liver lipids in patients with endogenous hypertriglyceridemia. *Tohoku J Exp Med* 1974; **114**: 247–252.
26. Svedberg J, Björntorp P, Smith U, Lonnroth P: Free-fatty acid inhibition of insulin binding, degradation, and action in isolated rat hepatocytes. *Diabetes* 1990; **39**: 570–574.
27. Després JP: Dyslipidaemia and obesity. *Baillieres Clin Endocrinol Metab* 1994; **8**: 629–660.
28. Laakso M: Insulin resistance and coronary heart disease. *Curr Opin Lipidol* 1996; **7**: 217–226.
29. Evans DJ, Hoffmann RG, Kalkhoff RK, Kissebah AH: Relationship of androgenic activity to body fat topography, fat cell morphology, and metabolic aberration in premenopausal women. *J Clin Endocrinol Metab* 1983; **57**: 304–310.
30. Björntorp P: Morphological classifications of obesity: what they tell us, what they don't. *Int J Obes* 1984; **8**: 525–533.
31. Enzi G, Gasparo M, Biondetti PR, Fiore D, Semisa M, Zurlo F: Subcutaneous and visceral fat distribution according to sex, age, and overweight, evaluated by computed tomography. *Am J Clin Nutr* 1986; **44**: 739–746.
32. Matsuzawa Y, Shimomura I, Nakamura T, Keno Y, Tokunaga K: Pathophysiology and pathogenesis of visceral fat obesity. *Ann N Y Acad Sci* 1995; **748**: 399–406.
33. Kirchengast S, Gruber D, Sator M, Hartmann B, Knogler W, Huber J: Menopause-associated differences in female fat patterning estimated by dual-energy X-ray absorptiometry. *Ann Hum Biol* 1997; **24**: 45–54.
34. Tchernof A, Poehlman ET: Effects of the menopause transition on body fatness and body fat distribution. *Obes Res* 1998; **6**: 246–254.
35. Björntorp P: Body fat distribution, insulin resistance and metabolic disease. *Nutrition* 1997; **13**: 795–803.
36. Teli MR, James OF, Burt AD, Bennett MK, Day CP: The natural history of non-alcoholic fatty liver: a follow-up study. *Hepatology* 1995; **22**: 1714–1719.
37. Bacon BR, Farahvash MJ, Janney CG, Neuschwander-Tetri BA: Nonalcoholic steatohepatitis: an expanded clinical entity. *Gastroenterology* 1994; **107**: 1103–1109.
38. Joseph AEA, Savarymattu SH, Al-Sam S, Cook MG, Maxwell JD: Comparison of liver histology with ultrasonography in assessing diffuse parenchymal liver disease. *Clin Radiol* 1991; **43**: 26–31.