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Increase in the prevalence of fatty liver in Japan over the past 12 years: analysis of clinical background

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Background. The aim of this investigation was to elucidate the time-course of changes in the prevalence of fatty liver, and to analyze its clinical backgrounds over the previous 12-year period. ***Methods.*** Thirty-nine thousand one hundred and fifty-one individuals who visited the Tokai University Hospital Health Checkup Center from 1989 to 2000 were examined for the presence of fatty liver, and their clinical backgrounds were analyzed. ***Results.*** In 1989, the prevalence of fatty liver was 12.6%, and it rose gradually thereafter, reaching 30.3% in 1998, corresponding to a 2.4-fold increase over the prevalence rate in 1989. The average prevalence was about twice as high in males (26.0%) as in females (12.7%). The prevalence was uniformly high in males in all ages, while the prevalence in females tended to rise gradually with age. Body mass index (BMI) was found to be the variable most closely related to the onset of fatty liver. On the other hand, nonobese individuals with a BMI of less than 25 kg/m^2 accounted for approximately half of all the patients with fatty liver, and this proportion remained almost unchanged during the 12-year survey period. It was therefore difficult to simply attribute the increase in the prevalence of fatty liver to the increased prevalence of obesity. In the 35 519 repeat examinees (repeaters), it was found that 5088 individuals (14.3%) developed fatty liver, and fatty liver resolved in 1248 individuals (3.5%). As fatty liver developed, the BMI increased by 1.0 ± 1.3 kg/m^2. As fatty liver disappeared, the BMI decreased by 1.0 ± 1.5 kg/m^2. ***Conclusions.*** These results suggest that the absolute value of the BMI, as well as the relative changes in the BMI in each individual, may be related to the onset of fatty liver.

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Introduction

The prognosis of fatty liver is generally considered to be good. Obesity, alcohol intake, and hyperlipidemia have been suggested to be predisposing factors for the onset of fatty liver. Because these conditions also serve as important risk factors for lifestyle-related diseases, such as arteriosclerosis and diabetes mellitus, it is necessary to review the significance of fatty liver in the context of the patient's entire clinical background. In recent years, several reports based on health checkup data have shown a trend towards an increased prevalence of fatty liver.[1–6] It would, however, be difficult to validate epidemiological trends based on these reports alone, because the subjects were limited to nonrandomized groups, the observation periods were of insufficient duration, and the data varied greatly among different medical facilities. It is noteworthy that, in our present study, we conducted annual observations at the same health checkup center over a fixed period of time. Data were analyzed to clarify changes in the prevalence of fatty liver over the previous 12-year period, as well as to access the degree of involvement of various factors in the onset of fatty liver during this period.

Subjects and methods

The subjects of our study were 39 151 individuals who visited the Tokai University Hospital Health Checkup Center for the first time during the 12-year period from 1989 to 2000 (Table 1). There were 23 819 males and 15 332 females, with a mean age of 45.4 ± 10.0 years (mean ± SD) for males, and 46.5 ± 10.2 years for

Table 1. Background of first examinees

Year	1989–1991	1992–1994	1995–1997	1998–2000	Total	*P* value
Sex						
Male (%)	9169 (62.5)	6780 (61.7)	4479 (58.8)	3391 (57.8)	23 819 (60.8)	$P < 0.0001$[a]
Female	5499 (37.5)	4211 (38.3)	3143 (41.2)	2479 (42.2)	15 332 (39.2)	
Daily alcohol intake						
None (%)	9246 (63.0)	7106 (64.7)	5199 (68.2)	4056 (69.1)	25 607 (65.4)	$P < 0.0001$[a]
Less than 60 g ethanol	4658 (31.8)	3357 (30.5)	2120 (27.8)	1593 (27.1)	11 728 (30.0)	
Over 60 g ethanol	764 (5.2)	528 (4.8)	303 (4.0)	221 (3.8)	1 816 (4.6)	
Total	14 668	10 991	7622	5870	39 151	
Year	1989–1991	1992–1994	1995–1997	1998–2000	Total	*P* value
Age (years; mean ± SD)	45.5 ± 9.7	45.3 ± 9.7	46.4 ± 10.5	47.0 ± 11.1	45.8 ± 10.1	NS[b]
BMI (kg/m^2)	22.4 ± 2.8	22.8 ± 2.9	22.8 ± 3.0	22.7 ± 3.1	22.6 ± 2.9	NS[b]

BMI, body mass index; NS, not significant
[a] Contingency table analysis
[b] Analysis of variance (ANOVA)

Table 2. Background of repeaters

Sex	
Male (%)	23 148 (65.2)
Female	12 371 (34.8)
Daily alcohol intake	
None (%)	22 582 (63.6)
Less than 60 g ethanol	11 513 (32.4)
Over 60 g ethanol	1 424 (4.0)
Total	35 519
Age (years; mean ± SD)	45.5 ± 9.7
BMI (kg/m^2)	22.4 ± 2.8
Survey period (years)	6.0 ± 3.4

females. Over the 12-year period, the proportion of females increased yearly, and the percentage of habitual drinkers decreased with time, although these changes were not significant. Neither the mean age nor the mean body mass index (BMI) changed during the survey period. Subjects who visited the facility two or more times during the survey period were defined as “repeaters”. Outcomes were analyzed in the 35 519 repeaters (Table 2).

In all cases, the diagnosis of fatty liver was based on abdominal ultrasonography. Ultrasound equipment used until 1994 included the Hitachi EUB340 (Hitachi, Tokyo, Japan), the Yokogawa RT2800 (GE Yokogawa Medical Systems, Tokyo, Japan), and the Yokogawa RT3000. After 1995, the Aloka SSD 650CL (Aloka, Tokyo, Japan) was used. Of the four known criteria used for the diagnosis of fatty liver (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring), the first two were used as definitive criteria, and the last two were taken into account as needed. In all cases, the diagnosis was confirmed separately by two specialists in gastroenterology. According to the WHO classification,[7] subjects with a BMI of 25–30 kg/m^2 were classified as the preobese group, and subjects with a BMI of over 30 kg/m^2 were classified as the obese group. The prevalence of fatty liver was analyzed in relation to the following seven factors associated with the onset of fatty liver: sex; age; BMI; level of alcohol intake; and fasting blood sugar (FBS), serum triglyceride (TG), and serum total cholesterol (TC) levels. To identify the cause of the increase in the prevalence of fatty liver during the 12-year survey period, we analyzed differences in the prevalence of each of the predisposing factors between the first 3-year period (1989–1991) and the last 3-year period (1998–2000) of the total 12-year survey period.

Contingency table analysis and analysis of variance were used for analyzing background variables (sex, age, BMI, and alcohol intake) of the subjects. The χ^2 was used for comparisons of the prevalence of fatty liver. Contingency table analysis was used for comparison of percentages. The unpaired *t*-test was used for comparison of each of the factors among different outcome groups. Logistic regression analysis was used for multivariate analysis.

Results

Prevalence of fatty liver

The prevalence of fatty liver among first-time examinees was 12.6% in 1989, and it rose gradually thereafter, with a 2.4-fold increase to 30.3% in 1998. The increase, however, declined after 1998, with the prevalence dropping to 28.4% in 2000. The average prevalence of fatty liver during the 12-year survey period was twice as high in males (26.0%) as in females (12.7%; $P < 0.0001$). A similar difference in prevalence between males and females continued to be seen each year during the 12-year

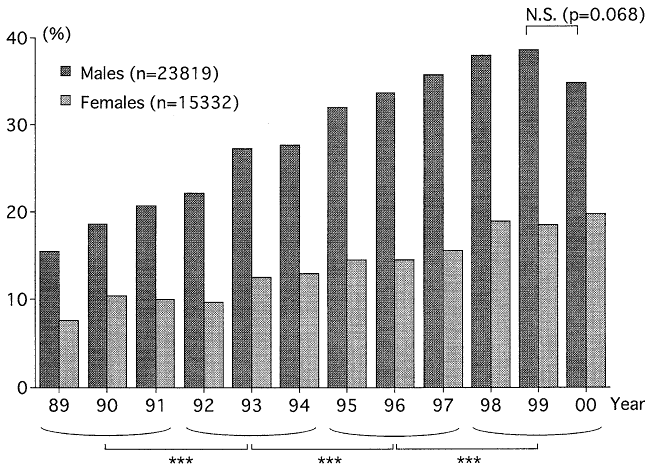

Fig. 1. The prevalence of fatty liver classified by year and sex among first-time examinees during the 12-year survey period. The prevalence was 12.6% in 1989, and it increased progressively to 30.3% in 1998. The average prevalence was twice as high in males (26.0%) as in females (12.7%) ($P < 0.0001$). In both males and females, the prevalence of fatty liver increased progressively from year to year ($P < 0.005$) (χ^2 test). ***$P <$ 0.001; *N.S.*, not significant

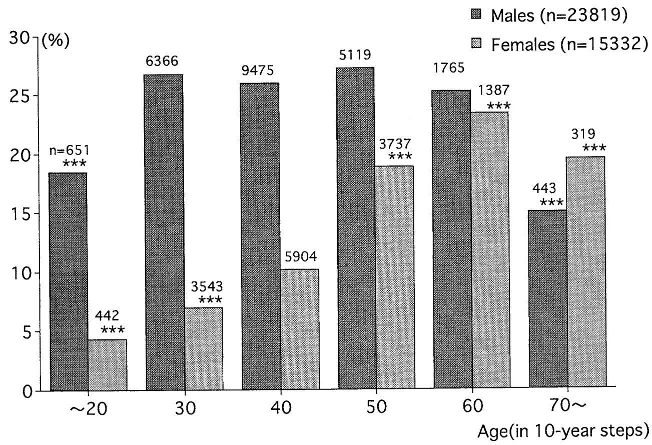

Fig. 2. The prevalence of fatty liver classified by age and sex among first-time examinees during the 12-year survey period. The prevalence in males in each age group between the ages of 30 and 60 years was equally high, ranging from 25% to 27%. In females, the prevalence increased gradually with age, with the peak incidence of 23.3% in the 60- to 69-year age group, which was 3.4 times as high as the incidence in the 30- to 39-year age group. (χ^2 test). ***$P < 0.0001$, significant as compared to prevalence in the 40- to 49-year age group

period. In both males and females, the prevalence of fatty liver increased yearly ($P < 0.005$). In males, the prevalence reached a peak (38.6%) in 1999 and decreased for the first time, to 34.9%, in 2000. The prevalence in females was 19.8% in 2000 (Fig. 1).

When analyzed by age, the prevalence of fatty liver among males was equally high (25%–27%) in all the age groups between the ages of 30 and 60 years. In females, on the other hand, the prevalence increased gradually with age, with a peak prevalence of 23.3% in the 60- to 69-year age group, which was 3.4 times as high as that in the 30- to 39-year age group. In the 70- to 79-year age group, the prevalence was higher in females (19.4%) than in males (14.9%; Fig. 2).

Factors related to the onset of fatty liver

The prevalence of fatty liver increased significantly with increasing grade of obesity, with prevalences of 12.8% recorded in the nonobese group, 51.4% in the preobese group (BMI less than $30\,kg/m^2$), and 80.4% in the obese group (BMI over $30\,kg/m^2$). When analyzed by level of alcohol intake, the prevalence was higher in habitual alcohol drinkers (ethanol intake about 60g per day) than in non-drinkers. The prevalence in the borderline diabetes group (FBS, 110–125mg/dl) was 43.7%, which was more than twice as high as that in the normal FBS group (18.6%), and the prevalence was higher still, at 53.3%, in the diabetes group (FBS, over 126mg/dl). As for TC and TG levels, two of the major factors involved in the development of arteriosclerosis, the prevalence was higher in subjects with elevated TC or TG levels, i.e., in those with hyperlipidemia (Fig. 3).

The nonobese group (BMI less than $25\,kg/m^2$) accounted for about half of all the cases of fatty liver. The percentage of nonobese subjects remained almost unchanged, at approximately 50%, during the first 3-year period (1989–1991) and the last 3-year period (1998–2000), even though the prevalence of fatty liver during the latter period was more than twice as high as that during the first 3-year period. This indicates that the increased prevalence of fatty liver cannot be completely explained by the increase in the prevalence of obesity alone. As for alcohol intake, the prevalence of fatty liver was higher in nondrinkers than in habitual alcohol drinkers. When analyzed in relation to the FBS, TG, and TC levels, the prevalence of fatty liver was found to be highest in the group with normal levels of these parameters. Thus, there were no marked changes in the prevalences of the predisposing factors that could explain the increased prevalence of fatty liver during the 12-year survey period (Fig. 4).

Multivariate analysis of factors

The degree of independent involvement of each factor in the onset of fatty liver was evaluated by multivariate analysis. The following cutoff levels were used: 40 years for age; 60g ethanol for alcohol intake; $25\,kg/m^2$ for BMI; and 110mg/dl for FBS, 150mg/dl for TG, and

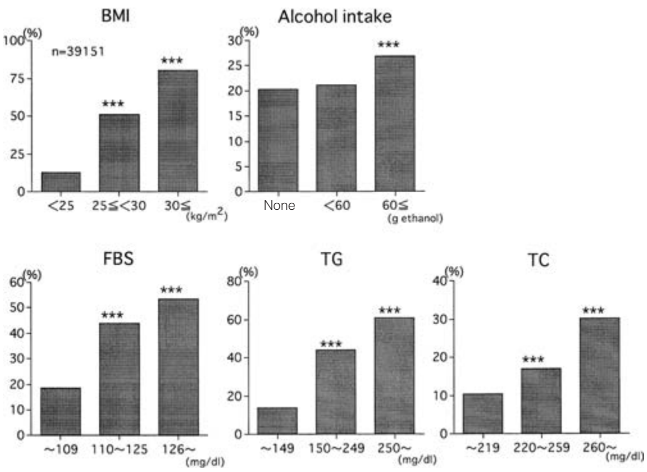

Fig. 3. The prevalence of fatty liver, classified by risk factors, among first-time examinees during the 12-year survey period. The prevalence of fatty liver increased markedly with increasing grade of obesity, the rates being 12.8% in the nonobese group, 51.4% in the preobese group (body mass index [*BMI*] less than 30 kg/m²), and 80.4% in the obese group (BMI over 30 kg/m²). The prevalence was higher in habitual alcohol drinkers than in nondrinkers. The prevalence was significantly higher in subjects with elevated fasting blood sugar (*FBS*), total cholesterol (*TC*), or triglyceride (*TG*) levels (χ^2 test). ***$P < 0.0001$, significant as compared to group without risk factors

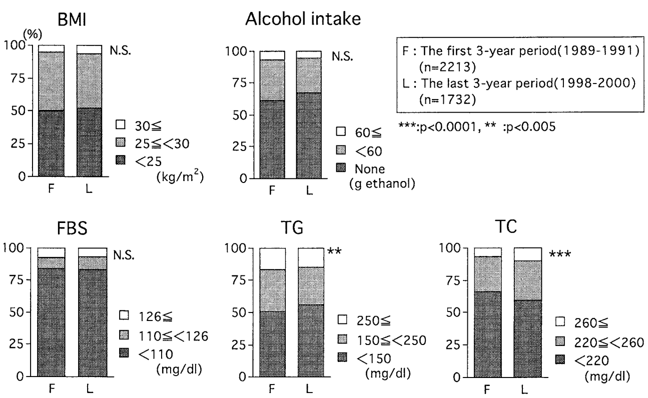

Fig. 4. Annual changes in the prevalence of each predisposing factor for fatty liver among first-time examinees with fatty liver. The nonobese group accounted for about half of all the cases of fatty liver. The percentage of nonobese subjects remained almost unchanged, at approximately 50%, during the first 3-year period and the last 3-year period. The prevalence of fatty liver was higher in nondrinkers than in habitual alcohol drinkers. When analyzed in relation to the FBS, TG, or TC levels, the prevalence of fatty liver was highest in the group with normal levels of these parameters (contingency table analysis)

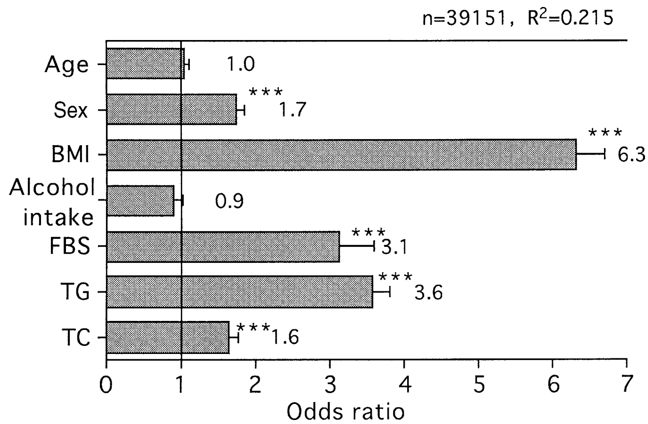

Fig. 5. The degree of independent involvement of each factor in the onset of fatty liver among first-time examinees. The odds ratio was highest for BMI (6.3), followed by that for TG levels (3.6) and FBS levels (3.1). The comparison between the first 3-year period and the last 3-year period revealed an increase in the odds ratio for BMI and TG levels, and a decrease in the ratio for FBS levels (logistic regression analysis). *** $P < 0.0001$

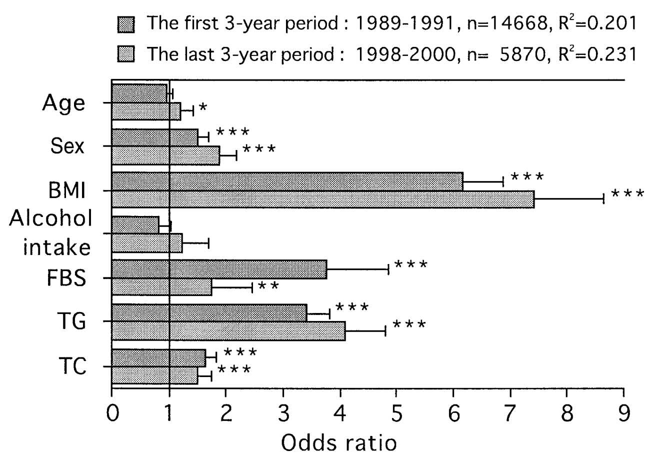

Fig. 6. A comparison of the odds ratios for each factor in the onset of fatty liver between the first 3-year period and the last 3-year period among first-time examinees. This comparison revealed an increase in the odds ratio for BMI and TG levels, and a decrease in the ratio for FBS levels (logistic regression analysis). *$P < 0.05$; **$P < 0.005$; ***$P < 0.0001$

220 mg/dl for TC levels. The odds ratio was highest for BMI (6.3), followed by that for TG levels (3.6) and FBS levels (3.1), as shown in Fig. 5. Alcohol intake was not found to have any independent relation to the onset of fatty liver. To follow the annual course of the odds ratio of each factor, the results of multivariate analysis were compared between the first 3-year period (1989–1991) and the last 3-year period (1998–2000). This comparison revealed an increase in the odds ratio for BMI and TG levels from 6.2 to 7.4 and from 3.4 to 4.1, respectively, and a decrease in the ratio for FBS levels from 3.8 to 1.7 (Fig. 6).

When the odds ratio for each factor was analyzed by sex, the odds ratio in males was highest for BMI (5.5), followed by that for TG level (3.3) and FBS level (2.6). In females, the ratio was highest for BMI (8.7), followed

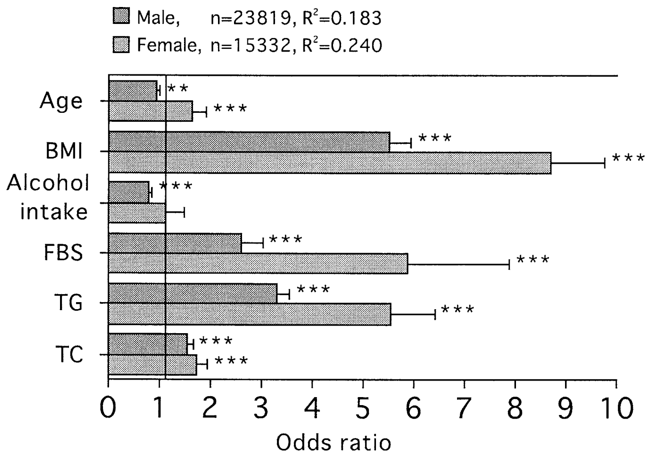

Fig. 7. The degree of independent involvement of each predisposing factor in the onset of fatty liver analyzed by sex among first-time examinees. The odds ratio in males was the highest for BMI (5.5), followed by that for TG level (3.3) and FBS level (2.6). In females, the ratio was highest for BMI (8.7), followed by that for FBS level (5.9) and TG level (5.6) (logistic regression analysis). $^{**}P < 0.05$; $^{***}P < 0.0001$

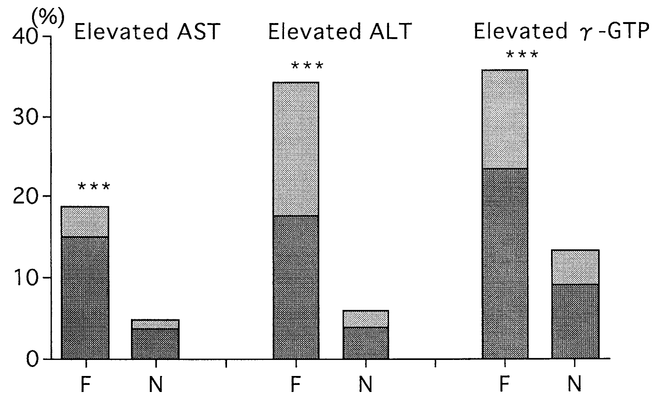

Fig. 8. Liver dysfunction in the presence/absence of fatty liver among first-time examinees. The incidence of elevated alanine aminotransferase (*ALT*) was 5.7% in subjects without fatty liver, but it was much higher in those with fatty liver (34.3%). Elevation of the γ-glutamyl transpeptidase (*γ-GTP*) levels was seen in 13.3% of subjects without fatty liver and 35.8% in those with fatty liver (χ^2 test). *Dark gray bars*, 31–50 IU/l; *light gray bars*, ≥51 IU/l. $^{***}P < 0.001$. *F*, fatty liver; N, normal liver

by that for FBS level (5.9) and TG level (5.6). Thus, the odds ratios for the three factors in females were about twice as high as those in males (Fig. 7).

Liver dysfunction

Liver function test data were analyzed in relation to the presence or absence of fatty liver. The percentage of patients with elevated asparate aminotransferase (AST; cutoff level, 30 IU/l) was 4.8% in the nonfatty-liver group and 18.9% in the fatty-liver group. Most of the subjects with fatty liver had an AST level of less than 50 IU/l. The incidence of elevated alanine aminotransferase (ALT; cutoff level, 35 IU/l) was 5.7% in the nonfatty-liver group, but it was much higher in the fatty-liver group (34.3%). Of patients with elevated ALT values, 17.7% showed a slight elevation (below 50 IU/l), and 14.3% showed a marked elevation (50–100 IU/l). Elevation of the γ-glutamyl transpeptidase (GTP) level (cutoff, 50 IU/l) was seen in 13.3% without fatty liver and in 35.8% with fatty liver (Fig. 8). The annual incidence of liver dysfunction did not change significantly during the 12-year survey period.

Changes of factors in repeaters

In the 35 519 repeaters between 1989 and 2000, fatty liver developed in 5088 subjects (14.3%), and resolved in 1248 subjects (3.5%). In these subjects, changes in the BMI, and in FBS, TG, and TC levels were analyzed in relation to the course of the fatty liver. The BMI rose to 1.0 ± 1.3 kg/m² as fatty liver developed, and decreased

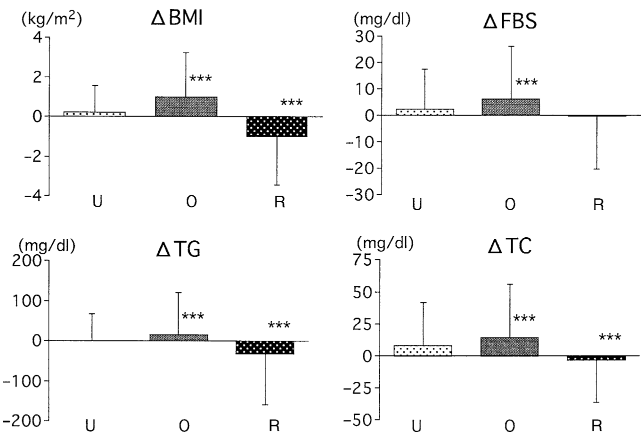

Fig. 9. Changes in factors analyzed by the course of fatty liver among repeaters. In the repeaters, fatty liver developed in 14.3% of subjects, and resolved in 3.5%. BMI rose to 1.0 ± 1.3 kg/m² as subjects developed fatty liver, and decreased to 1.0 ± 1.5 kg/m² as fatty liver resolved (unpaired *t*-test). $^{***}P <$ 0.0001, significant as compared to that in the uncharged group. *U*, unchanged group (n = 29 183); *O*, fatty liver onset group (n = 5088); *R*, fatty liver resolution group (n = 1248)

to 1.0 ± 1.5 kg/m² as fatty liver resolved (Fig. 9). These results suggest that not only the absolute level of BMI, but also the relative changes in BMI in each individual may be associated with the onset of fatty liver. The TG, FBS, and TC levels showed a similar course to that of the BMI. Relative changes in these parameters were associated with the onset or resolution of fatty liver.

Discussion

Several mechanisms are considered to be involved in the development of fatty liver, and some of the proposed mechanisms include (a) excessive inflow of substrates into the liver, (b) enhanced fatty acid synthesis, (c) impaired oxidation of fatty acids, and (d) disturbance of the synthesis and secretion of lipoproteins into the liver.[8,9] Obesity, diabetes mellitus, and alcohol intake have been regarded as risk factors for the onset of fatty liver, but the mechanisms of development of fatty liver differ depending on the underlying risk factors.[8,9] According to previous reports, the prevalence of fatty liver in the 1980s was 6%–14% in males and 4%–8% in females.[1–3] In the 1990s, the prevalence in males and females was reported to be 14%–19% and 5%–6%, respectively,[4–6] suggesting an increase in the prevalence of fatty liver in recent years. These studies, however, had limitations, such as reliance on data from particular populations, a short observation period, and large differences in facilities available, which make it difficult to reach definitive conclusions on the epidemiological trends of fatty liver. Therefore, it would be indispensable to investigate populations with the same background at various points of time.

The present study aimed at elucidating the time course of changes in the prevalence of fatty liver. The annual surveys were conducted over a 12-year period at a central area of Kanagawa Prefecture. The most important finding from the study was a marked increase in the prevalence of fatty liver during the survey period. The prevalence, which was 15.4% in males and 7.6% in females in 1989, increased gradually with time, to 38.1% in males and 19.0% in females in 1998. This increase was statistically significant, even after the data were corrected for age and sex. At present, the diagnosis of fatty liver is usually based on abdominal ultrasonography, which has been established as a simple and reliable means of screening for fatty liver, in combination with pathological examination.[10] Because it has been reported that the sensitivity of abdominal ultrasonography to detect fatty liver is as high as 89%, and the specificity is 93%,[11] abdominal ultrasonography is considered to be accurate for making a diagnosis of fatty liver at present.[12] We must bear in mind the possibility that advances in ultrasound equipment may affect the sensitivity and specificity of the diagnosis of fatty liver. However, because the make of the equipment was changed only once during our 12-year survey period, it is unlikely that the progressive increase in the prevalence of fatty liver from year to year would have been greatly affected by the change in the ultrasonographic equipment. The finding of an increased prevalence of fatty liver in these annual surveys may be interpreted as a general phenomenon. There have been no reports on the prevalence of fatty liver on health checkups in Western countries, but our results were higher by 10% than those of an Italian study, in which the prevalence was approximately 20% in patients who were randomly submitted to abdominal ultrasonography.[13]

Using multivariate analysis with logistic regression, we found that the highest odds ratio was for obesity (6.3 for BMI over 25 kg/m^2). The odds ratio for diabetes mellitus was also high (3.1 at an FBS of over 110 mg/dl). However, alcohol intake was not found to be a significant independent factor for the development of fatty liver, although simple comparison using the χ^2 test revealed that the prevalence of fatty liver was high in individuals who consumed 60 g ethanol or more per day. This suggests that the increased prevalence of fatty liver among drinkers probably represents the influence of some confounding factors, such as the high percentage of obese individuals among drinkers. We must also take into account the fact that individuals who are concerned about their health and undergo timely health checkups are less likely to be habitual drinkers or heavy drinkers. The result that alcohol consumption was not significantly related to the onset of fatty liver is consistent with previous reports from health checkups.[1,2] Regarding the involvement of hyperlipidemia, it was found that the risk of development of fatty liver increased 3.6-fold when the TG level was over 150 mg/dl, and 1.6-fold when the TC level was over 220 mg/dl. Hyperlipidemia can be both a cause and outcome of fatty liver.

Seven factors were analyzed in the present study, i.e., age; sex; BMI; level of daily alcohol intake; and FBS, TG, and TC levels. The coefficient of determination (R^2) in logistic regression was as low as 0.215. This indicates that these seven factors do not serve as sufficient explanatory variables for the onset of fatty liver. The percentage of subjects undergoing health checkups who did not have any of these factors was 46.1% among males and 62.0% among females, accounting for 16.9% and 17.2% of males and females with fatty liver, respectively. This strongly suggests that there are some as yet unknown factors determining the onset of fatty liver. The prevalence of obesity, and of elevated FBS, TG, and TC levels increased by several percent during the 12-year period, but none of these factors was found to adequately explain the twofold increase in the prevalence of fatty liver. It is, therefore, quite likely that the incidence of some unknown factors might have increased during the 12-year period. A recent study from Nagasaki University in Japan indicates that the etiology of fatty liver may be closely related to the percentage of body fat in nonalcoholic and nonoverweight patients with fatty liver, especially in females.[14]

Cases of the overnourished type of fatty liver, as seen in obese or diabetic patients, can be characterized by increased fatty acid release from fat tissues, as well as by excessive food ingestion. Of all types of fat tissue, visceral fat is the most metabolically active and plays a particularly important role in the development of fatty liver.[15] Visceral fat is more likely to be degraded in response to stimulation by catecholamines and other factors than subcutaneous fat, and is more likely to release free fatty acids following degradation.[16] Thus, visceral fat is considered to be a source of excess substrates for fat formation in the liver, and plays a significant role in the onset of fatty liver in both obese and nonobese individuals. In fact, it has been reported that the severity of fatty liver correlates with the area of visceral fat.[17] Therefore, the role of visceral fat in the mechanism of onset of fatty liver needs to be further clarified.

Visceral fat-type obesity has recently attracted close attention as a component of the "visceral fat syndrome" on the grounds that it is a more significant risk factor in arteriosclerotic diseases than subcutaneous fat-type obesity,[18] and because it is more frequently complicated by hypertension,[19] hyperlipidemia,[15] and diabetes mellitus.[15] It has been pointed out that fatty liver can serve as a risk factor for the development of arteriosclerotic diseases.[20,21] If fatty liver is attributable not only to obesity, diabetes mellitus, and alcohol abuse but also to visceral fat accumulation, we may say that unfavorable daily habits which cause lifestyle-related diseases may also serve as background risk factors for fatty liver.

When analyzed by sex, we found that the prevalence of fatty liver in males remained almost unchanged in the over-30-year age groups, while in females the prevalence gradually increased with age, with the rates eventually becoming equal in males and females in the 60- to 69-year age group. These results suggest the influence of female hormones. Estrogen is known to suppress visceral fat accumulation and to increase subcutaneous fat accumulation.[22] It is speculated that a decrease in estrogen activity may increase the amount of visceral fat accumulation, resulting in the onset of fatty liver. It has been reported that, in females, the ratio of the area of visceral fat to that of subcutaneous fat increases with age, and that after menopause, the absolute amount of fat, and the amount of visceral fat, increase markedly.[23] These data indicate that the amount of visceral fat may be closely associated with the development of fatty liver.

Our analysis of repeaters during the 12-year period revealed new-onset fatty liver in 14.3% of all subjects, and disappearance of fatty liver in 3.5%. The BMI increased by approximately 1 kg/m^2 subsequent to the onset of fatty liver, and decreased by 1 kg/m^2 following its resolution. These results suggest that not only absolute BMI indices of obesity but also relative changes in the BMI values for each individual may be involved in the onset of fatty liver in both obese and nonobese individuals. A BMI level of 1 kg/m^2 corresponds to 2–3 kg of body weight. Loss of body weight by this amount has been reported to be the first indicator of decreases in the amount of visceral fat. It is speculated that in visceral-fat-type obesity, dietary therapy may specifically reduce the amount of visceral fat, as it has been reported that visceral fat is degraded relatively easily.[24] Although the present study did not include direct observation of changes in the amount of visceral fat, our results may be interpreted as supporting the hypothesis that visceral fat may be involved in the development of fatty liver.

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