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Risk Factors for Liver Dysfunction in Middle Aged Men based on Four Year Health Examination Data

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Abstract: Risk Factors for Liver Dysfunction in Middle Aged Men based on Four Year Health Examination Data: Kumiko TAJIMA, *et al.* Department of Public Health, Gunma University School of Medicine—In order to develop a better lifestyle improvement program, the relationship between lifestyle and changes in liver function were compared through data-linkage of a self-administered questionnaire to the results of annual health examinations over 4 years. In this study, 2,511 male subjects aged 40–69 yr were asked to fill in the questionnaire. Of these, 824 subjects had a health examination in 1993. Two hundred and twenty-eight of these remained within the normal range in liver function tests (LFT) in each of annual health examinations between 1994 and 1996, whereas 63 had worsened LFT results after the initial examination and were therefore called the decreased liver function (DLF) group. Controls age-matched to the DLF group were chosen from the normal liver function group. Discriminant function analysis was carried out to identify the differences between the DLF group and the control group. The independent variables were selected from the variables which showed significant differences in the univariate analysis, considering multicollinearity. The independent variables used for the discriminant analysis were therefore alcohol consumption, diastolic blood pressure (DBP), BMI and "aggression" by THI. The Wilks' Lambda value was 0.787 (p value=0.0001). The overall correct identification rate in the discriminant analysis was 75.0%. The results of the present study suggest that men who are heavy drinkers, hypertensive, obese and aggressive had a high risk of developing liver dysfunction within a few years, even if their LFT values were within normal limits in any single year.
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Most studies of liver function focus on serious liver dysfunction and related diseases[1, 2]. There have been a few studies on sub-clinical or normal-range liver function decreases and their causal risk factors[3, 4]. A study of lifestyle risks and other factors that effect liver function is considered important not only from the standpoint of liver disease prevention but also for occupational health promotion based on evidence of lifestyle improvement.

Fortunately, extensive health check-up data have been accumulated over the past fifteen years in Japan. Starting in 1983, the Health and Medical Service Law for the Aged mandated a municipal health check-up service program for all citizens aged 40 yr or more, and the Ministry of Labor has instituted a health assessment program for the working population known as the Total Health Promotion plan (THP). These health check-up data include various kinds of liver function tests (LFTs), such as glutamate oxaloacetate transaminase (GOT), glutamate pyruvate transferase (GPT), and gamma-glutamyl transferase (γ-GTP). Analysis of this data along with the results of a lifestyle questionnaire should be helpful in order to extract risk factors which effect liver function at the sub-clinical level.

Recently, some follow-up studies have been carried out making use of fatal cases and their past health check-up data[5–9]. Yet there are few reports of changes in liver function and of risk factors related to lifestyle[3]. Some lifestyle studies have revealed relationships between obesity, blood pressure, and serum lipid levels[10], and some have been related to liver function change at the cross-sectional level[11, 12]. A few longitudinal studies analyzed the data to determine possible risk factors for liver function decrease, and the present study may provide some evidence to aid effective health guidance in occupational health settings.

In order to design an effective lifestyle improvement

program and carry out individual health counseling in occupational health, it is necessary to distinguish those at risk of liver function decrease from those who are not. Therefore, middle-aged men were asked to complete self-administered questionnaires to assess physical/mental symptoms and lifestyle, and the results were combined with their health check-up data. A case-control study was conducted in subjects with decreased liver function and in those whose liver function had not changed during the study period. Our objective was to develop a superior approach to preventing liver function decrease for company and community health professionals.

Materials and Methods

1. Subjects

Making use of health data from a cohort study of Komochi village in Gunma Prefecture, Japan, 2,511 male inhabitants aged 40–69 yr as of September, 1992 were asked to complete a Baseline Questionnaire Survey in January, 1993.

2. Data Collection

(1) *Baseline Questionnaire Survey*

The self-administered questionnaire designed by the authors was distributed and collected by the village municipal office. The survey contained items on occupation, health status, lifestyle, and the Todai Health Index (THI)[13, 14]. The THI has 130 items about physical and mental symptoms and complaints, which forms 12 scales and discriminant functions to identify neurosis and psychosomatic disease. This information is considered useful in quantitatively assessing the perceived health of the participants.

(2) *Health Examinations*

Data from health examinations carried out from 1993 to 1996 was used, based on a program mandated by the Health and Medical Service Law for the Aged. Komochi village has implemented community based health examinations once a year for all of the inhabitants over 40 yr old. Age, height and body weight were taken from the examination results. Body mass index (BMI) was calculated as body weight/(height)^2. A sphygmomanometer was used to measure blood pressure, with the subject seated. A public health nurse interviewed the subjects about their alcohol consumption (type and daily amount), smoking, current medical prescriptions, and history of chronic conditions including hepatitis and other liver disease, all of which were recorded and preserved as annual personal health records. Non-fasting blood samples were obtained and serum levels of GOT, GPT, γ-GTP, high density lipoprotein cholesterol (HDL-CHOL), triglyceride (TG) and total cholesterol (T-CHOL) were determined with the HITACHI 7250 autoanalyser.

Finally, the relationship between the results of the health examinations from 1993 to 1996 and the data collected through the Baseline Questionnaire Survey was analyzed.

3. Statistical Analysis

Subject Selection

The decreased liver function (DLF) group and the control group were selected from the responders to the questionnaire survey by using several criteria (Fig. 1). First, subjects who had abnormal initial GOT, GPT or γ-GTP values were excluded from the analysis due to the possibility of an existing liver disease. Subjects who were under medical treatment for other conditions were also excluded. Second, subjects who developed an abnormal result in any LFT between 1994 and 1996 were assigned to the DLF group. Third, subjects whose three LFTs for the three years remained within the normal range were assigned to the normal liver function group. We randomly selected one age-matched control (less than 5 yr difference) from the subjects in the normal liver function group for each man in the DLF group.

The normal ranges for LFTs used to define the two groups were GOT $\leqq$ 40U/*l*, GPT $\leqq$ 35U/*l*, and γ-GTP $\leqq$ 52U/*l*.

Univariate Analysis

The results of the questionnaire survey and the health examination for the DLF and control groups were

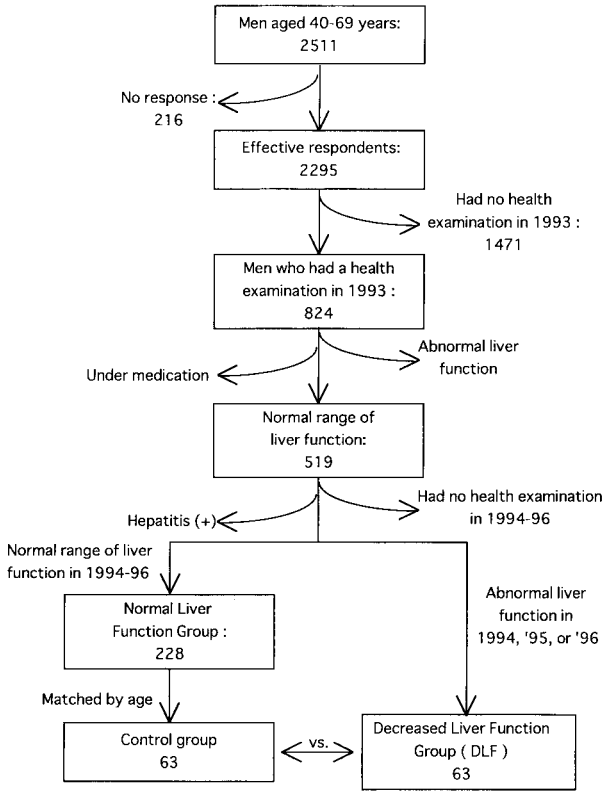

Fig. 1. Flow chart showing subject selection.

compared. Discrete variables, including questions on perceived health and lifestyle, were recategorized according to the distribution. For these variables, cross-tabulation and χ^2-tests were used for the comparison. The smoking index was calculated by multiplying daily cigarette consumption by the number of years of smoking. Alcohol consumption was expressed in "*gou*" (=180 m*l*), a Japanese traditional unit of "sake". One *gou* is approximately equivalent to one bottle of beer (633 m*l*), or about 25 g of ethanol. These data were obtained from the 1993 personal health records. For continuous variables such as BMI, *t*-tests were used for the comparison. The THI scale scores were also calculated and compared. One THI item related to alcohol consumption was omitted from the "aggression" scale score calculation because it was considered to overlap with the independent item of alcohol consumption mentioned above. Nevertheless, U-tests were used for GOT,GPT and γ-GTP in 1993, as their distribution in the two groups was considered to be skewed in 1993 when they were defined as in the normal range.

Multivariate Analysis

Discriminant analysis was used[15] to assess which variables were effective for identifying the DLF group from the control group. The dependent variable (external criteria) was defined according to whether the subjects belonged to the DLF group or the control group. The independent variables were selected from the variables which showed significant differences in the univariate analysis, including the age and excluding the variables which were multicollinear[15]. SPSS 6.1J for the Macintosh computer was used for the analysis.

Results

The questionnaire was submitted to 2,511 male residents of Komochi village aged 40–69 yr. A total of 2,295 men responded (response rate 91.4%) Their occupations were as follows: employed by a company (51.9%), self-employed (24.2%) and agriculture and forestry (21.6%). There were 969, 702 and 624 men respectively, in the 40–49, 50–59 and 60–69 age groups. Elderly people 70 years or older began to undergo health examinations not as a group but rather individually at family physician clinics in 1994, and therefore were not part of the study. Table 1 shows the number of men in Komochi village, according to age, who received health examinations between 1993 and 1996. The largest group participating each year were those in their 60s.

Of 2,295 subjects who responded to the questionnaire, 824 had health examinations in 1993. Of these, 643 had normal range LFT. Excluding men who were on medication, 519 men with normal range LFT in 1993 were selected as potential subjects. Of these, 228 had normal ranges LFT in all four years, and 63 had abnormal GOT, GPT or γ-GTP after 1994 (DLF group) (Fig. 1).

Table 1. Number of men undergoing health examinations, according to age, in Komochi village in 1993–1996.

Age	1993	1994	1995	1996
40–49	144	209	218	206
50–59	236	201	209	217
60–69	351	381	383	402
Total	731	791	810	825

One person who had had hepatitis was found in the 1993 health examination. He was excluded from subsequent analyses because he did not have any health examination after that year. A history of hepatitis was not reported in either group.

In order to exclude the influence of age, 63 participants in the control group aged-matched to the DLF group (1:1) were randomly selected from the 228 with the normal range LFT.

Univariate Analysis

There were no significant differences between the DLF and control groups in dietary habits in their 30s, current occupation or marital status. Table 2 shows the mean values and standard deviations (SD) for the continuous variables of alcohol consumption, smoking index, hours of sleep a day, THI scale scores, and biochemical data in 1993 for the DLF and control groups. The mean diastolic blood pressure (DBP), systolic blood pressure (SBP), alcohol consumption and BMI in the DLF group were notably higher than those in the control group. In particular, mean alcohol consumption in the DLF group, 1.4 *gou*/day, was twice as high as in the control group. There were no significant differences in the smoking index or hours of sleep. The mean "aggression" THI score (e.g., never become ill, not timid, etc.) was much higher in the DLF group. There were no notable differences between the two groups in the levels of T-CHOL and HDL-CHOL, but the mean levels of GOT, GPT and γ-GTP were significantly higher in the DLF group. In order words, differences between the two groups in these three variables were present at the time of the first health examination.

Multivariate Analysis

For the discriminant analysis, the independent variables were selected from the variables which showed significant differences in the univariate analysis (Table 2). An independent variable, SBP, was excluded, as DBP and SBP showed multicollinearity; so the independent variables used for the discriminant analysis were alcohol consumption, DBP, BMI, "aggression" by THI and age.

The results of the discriminant analysis are in Table 3. The Wilks' Lambda value was 0.787 (p value=0.0001). The overall correct identification rate in the discriminant

Table 2. Mean and standard deviation of continuous variables in the decreased-liver-function (DLF) and control groups (1993).

	DLF group n=63		Control group n=63		p-value
Age, years	52.4	(8.3)	52.6	(8.0)	0.905
Alcohol consumption, *gou*/day	1.4	(1.0)	0.7	(0.8)	0.000
Smoking index †	344.2	(353.4)	343.5	(361.8)	0.991
Sleep, hours/day	7.6	(1.1)	7.4	(1.1)	0.250
THI-SUSY §	28.9	(7.3)	27.7	(5.9)	0.318
THI-AGGR §	13.3	(2.2)	12.4	(1.9)	0.020
THI-LIFE §	16.6	(3.4)	16.1	(3.2)	0.433
BMI ‡, kg/m^2	23.7	(2.6)	22.6	(2.5)	0.018
SBP ‡, mmHg	141.4	(17.5)	134.4	(14.1)	0.014
DBP ‡, mmHg	86.4	(10.3)	81.4	(11.4)	0.011
T-CHOL ¶, mg/d*l*	190.5	(31.0)	184.3	(28.3)	0.245
HDL-CHOL ¶, mg/d*l*	45.9	(12.4)	43.3	(11.0)	0.217
TG ¶, mg/d*l*	169.9	(78.5)	157.1	(141.2)	0.530
GOT ¶, U/*l*	23.1	(5.7)	20.7	(4.2)	0.015
GPT ¶, U/*l*	21.7	(6.5)	16.9	(5.7)	0.000
γ- GTP ¶, U/*l*	31.2	(10.8)	17.7	(7.8)	0.000

The decreased-liver-function (DLF) group was defined as men who had levels of GOT $\leqq$40 U/*l*, GPT $\leqq$35 U/*l* and γ- GTP $\leqq$52 U/*l* in 1993, and were over the range in any year from 1994 to 1996. † smoking index: daily cigarette consumption multiplied by number of smoking years. § THI: Todai Health Index, SUSY: Vague complaints, LIFE: Irregularity of life, AGGR: Aggression. One item related to alcohol consumption was deleted from the AGGR scale score for the analysis. ‡ BMI: Body Mass Index, Weight/Height^2, SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure. ¶ T-CHOL: Total Cholesterol, HDL-CHOL: high density lipoprotein cholesterol, TG: triglyceride, GOT: glutamate oxaloacetate transaminase, GPT: glutamate pyruvate transferase, γ-GTP: gamma-glutamyl transferase.

Table 3. Results of the discriminant analysis (age included)

	Standardized discriminant function coefficient	p-value
Alcohol consumption, *gou*/day	0.633	0.003
BMI ‡, kg/m^2	0.309	0.169
DBP ‡, mmHg	0.437	0.050
THI-AGGR §	0.381	0.083
Correct identification ratio		
Control group	46/60 = 76.7%	
DLF group ¶	38/52 = 73.1%	
Total	84/112 = 75.0%	

Wilks' Lambda: 0.787, p=0.0001. ‡ BMI: Body Mass Index, Weight/Height^2; DBP: Diastolic Blood Pressure. § THI: Todai Health Index; AGGR: Aggression. One item related to alcohol consumption was deleted from the AGGR scale score for the analysis. ¶ DLF group: decreased-liver-function group.

analysis was 75.0%. The standardized discriminant function coefficient of alcohol consumption was the largest, and then DBP, "aggression" by THI, and BMI.

Discussion

Alcohol intake, obesity, viral infection, medication, and so on have been regarded as causes of decreased liver function[2–4, 11, 12, 16, 17]. A close relationship between the history of chronic hepatitis and liver dysfunction has been established[2, 18], but neither the hepatitis B nor C virus marker is checked routinely during company or community health examinations in Japan.

In this study, we combined lifestyle data and the results of annual health examinations for a four-year period and then analyzed the lifestyle factors which affect liver function. The subjects we analyzed initially had LFTs within the normal range, were not receiving medical treatment, and did not have a history of hepatitis. We tried to assess risk factors at the sub-clinical level. The subjects we analyzed had health examinations annually, so they may pay more attention to their health than the others[19]. But these findings can be utilized by professionals in those areas, because the blood tests such as GOT, GPT and γ-GTP taken during health examinations are commonly used in both occupational and community health services.

There is no consensus on how to identify decreased liver function in a population. In this study, decreased liver function cases were originally identified whenever a subject's LFT changed from normal (GOT $\leqq$ 40 U/*l*, GPT $\leqq$ 35 U/*l*, γ-GTP $\leqq$ 52 U/*l*) beginning in 1993 in at least one of the three follow-up years (1994, 1995 and 1996).

As a result, blood pressure, alcohol consumption, and BMI were notably higher for the DLF group than for the control group in the univariate analysis. This is consistent with past studies[3, 4, 12, 16, 17]. In addition, the THI "aggression" score was much higher. It has already been reported that the means of almost all of the THI scale scores are higher in the heavy drinker group than the light drinker group[20], which is consistent with the results of this study. In the discriminant analysis, alcohol consumption was positively correlated with decreasing liver function. It is worth noting that this factor was more significant than BMI and blood pressure. The overall correct identification rate was 75.0% in the discriminant analysis, which is considered to be sufficiently high.

It has been shown in a longitudinal study[21] and in a cross-sectional study[22] that serum lipid is related to obesity, alcohol consumption and physical exercise. Since BMI and blood pressure were significant in the univariate analysis in the present study, we thought they would yield an effect as large as alcohol consumption and lifestyle on liver dysfunction.

In 1993, the mean GOT, GPT and γ-GTP values in the DLF group were somewhat higher than those in the control group, although the DLF group was within the normal LFT range. In other words, some of the DLF group subjects may have been over the normal LFT range before 1993, having had latent mild liver dysfunction.

Medical staff would not pay attention to those who had normal liver function in the first year, but some developed abnormal results in the LFT during the three years (DLF group) of this study. In addition, the mean GOT, GPT and γ-GTP in the DLF group were significantly higher than those in the control group, though the results for both groups were within the normal range in 1993. This at-risk group had no history of hepatitis and they were not on medication.

A public or occupational health nurse can give health guidance by referring to the results of previous annual health examinations[23], but cases within the normal ranges of liver function tests are usually not noticed. This study suggests the possibility that men with hypertension, obesity and a heavy drinking habits or who are aggressive will be at a high risk of developing worsening liver function over a four year period, even if they have normal range LFT in any single year. Therefore, not only people who are over the normal range in the liver function screening test, but also those who have the related factors mentioned above, may need individual health counseling by professionals. In addition, those who showed only slight liver dysfunction should be asked if they have an inappropriate lifestyle that can be improved.

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