高めるという結果と一見矛盾する。そこで、女性も含めたアルコール性肝障害全体からマッチングを行って解析すると、肥満症例は非肥満症例よりも高血圧合併率が高く、女性の非肥満症例では高血圧の合併が認められなかった（データ省略）。アルコール性肝障害では肥満が高血圧に及ぼす影響について男女差が存在する可能性がある。今後、女性の症例数を増やして検証する必要があると考えられた。一方、非アルコール性脂肪性肝疾患と生活習慣病の関係に肥満は影響し、特に糖尿病の合併率を高めることが示唆された。

次に、アルコール性肝障害と非アルコール性脂肪性肝疾患の比較では肥満は生活習慣病との関係に影響を及ぼすことが示唆された。すなわち、非肥満症例では生活習慣病の合併率に疾患単一では差が認められなかったのに対し、肥満症例では高血圧と糖尿病で合併率に差（特に後者）が認められた。アルコール過多と栄養過多という2つの成因による脂肪性肝疾患は、単一の成因による脂肪性肝疾患とは、生活習慣病との関係からみて病態が異なると考えられた。非アルコール性脂肪性肝疾患は糖尿病を合併しやすいことはよく知られている2,3)。しかし、栄養過多による脂肪性肝疾患にアルコール過多が加わると糖尿病の発症が抑制されるように見える。非アルコール性脂肪性肝疾患における糖尿病の発症にはインスリン抵抗性の発現が重要である2)。一方、アルコール過多はインスリン抵抗性を有意には増大させないと報告されている4)。またアルコール摂取と糖尿病の発症に負の相関が認められたとの研究報告がいくつかある5, 6)。しかし逆の報告7)やBMI高値の場合には相関が認められないとの報告8)もあり、結論を出すには更なる研究が望まれる。アルコール過多は高血圧の危険因子であると報告9)されているが、肥満の影響については前述のごとく性差も含めた詳細な解析が必要である。

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E．研究発表

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F．知的財産権の出願・登録状況

1．特許取得

なし

2．実用新案登録

なし

3．その他

なし

表1 アルコール性肝障害の背景（男性）

	BMI <25 kg/m^2 (n = 29)	BMI ≥25 kg/m^2 (n = 29)	p *
年齢（歳）	61.7±10.4	58.8±15.2	0.407
BMI (kg/m^2)	20.8±2.7	27.5±2.3	<0.0001
線維化　有/無	10/19	12/17	0.588
収縮期血圧 (mmHg)	127±23	130±14	0.576
拡張期血圧 (mmHg)	75±11	79±11	0.140
AST (IU/L)	202±505	103±102	0.305
ALT (IU/L)	94±195	94±77	0.988
γ-GTP (IU/L)	432±536	252±182	0.092
血小板数 (×10^4/μL)	17.3±7.8	19.7±7.5	0.225
総コレステロール (mg/dL)	163±65	180±64	0.308
LDL コレステロール (mg/dL)	64±30	122±65	0.062
中性脂肪 (mg/dL)	250±298	208±323	0.612
空腹時血糖 (mg/dL)	144±79	113±27	0.056
HbA1c (JDS 値, %)	5.5±1.0	5.7±1.0	0.400

* t 検定またはχ^2検定.
BMI, body mass index; JDS, Japan Diabetes Society.

表2 アルコール性肝障害と生活習慣病（男性）

	BMI <25 kg/m^2 (n = 29)	BMI ≥25 kg/m^2 (n = 29)	p *
高血圧, n (%)	14 (48.3)	15 (51.7)	0.793
糖尿病, n (%)	8 (27.6)	7 (24.1)	1.000
脂質異常症, n (%)	8 (27.6)	10 (34.5)	0.777
高血圧 + 糖尿病, n (%)	5 (17.2)	6 (20.7)	1.000
高血圧 + 脂質異常症, n (%)	5 (17.2)	7 (24.1)	0.747
糖尿病 + 脂質異常症, n (%)	3 (10.3)	3 (10.3)	1.000
高血圧 + 糖尿病 + 脂質異常症, n (%)	3 (10.3)	3 (10.3)	1.000
2 疾患以上, n (%)	7 (24.1)	10 (34.5)	0.565

*χ^2検定またはFisher の正確検定.
BMI, body mass index.

表3 非アルコール性脂肪性肝疾患の背景（男性）

	BMI <25 kg/m^2 (n = 55)	BMI ≥25 kg/m^2 (n = 55)	p *
年齢（歳）	50.8±15.2	48.5±15.0	0.392
BMI (kg/m^2)	22.9±1.6	30.6±6.1	<0.0001
線維化　有/無	15/40	17/38	0.675
収縮期血圧 (mmHg)	125±16	129±14	0.203
拡張期血圧 (mmHg)	77±10	80±13	0.187
AST (IU/L)	55±70	57±36	0.812
ALT (IU/L)	89±114	90±61	0.971
γ-GTP (IU/L)	100±102	91±90	0.625
血小板数 (×10^4/μL)	21.1±6.7	20.6±6.1	0.713
総コレステロール (mg/dL)	187±40	198±38	0.158
LDL コレステロール (mg/dL)	117±39	120±40	0.759
中性脂肪 (mg/dL)	135±87	175±108	0.036
空腹時血糖 (mg/dL)	114±46	118±32	0.562
HbA1c (JDS 値, %)	5.9±1.4	6.2±1.2	0.370

* t 検定または χ^2 検定.
BMI, body mass index; JDS, Japan Diabetes Society.

表4 非アルコール性脂肪性肝疾患と生活習慣病（男性）

	BMI <25 kg/m^2 (n = 55)	BMI ≥25 kg/m^2 (n = 55)	p *
高血圧, n (%)	14 (25.5)	23 (41.8)	0.068
糖尿病, n (%)	16 (29.1)	28 (50.9)	0.037
脂質異常症, n (%)	23 (41.8)	28 (50.9)	0.339
高血圧 + 糖尿病, n (%)	7 (12.7)	14 (25.5)	0.087
高血圧 + 脂質異常症, n (%)	10 (18.2)	13 (23.6)	0.481
糖尿病 + 脂質異常症, n (%)	8 (14.5)	14 (25.5)	0.151
高血圧 + 糖尿病 + 脂質異常症, n (%)	4 (7.3)	9 (16.4)	0.237
2 疾患以上, n (%)	16 (29.1)	23 (41.8)	0.162

* χ^2 検定または Fisher の正確検定.
BMI, body mass index.

表5 脂肪性肝疾患の背景（男性）

	アルコール性肝障害 (n = 72)	非アルコール性脂肪性肝疾患 (n = 72)	p *
年齢（歳）	56.2±13.5	54.6±15.1	0.522
BMI (kg/m^2)	24.8±3.4	24.3±3.3	0.444
線維化　有/無	33/39	25/47	0.174
収縮期血圧（mmHg）	132±18	125±17	0.020
拡張期血圧（mmHg）	78±11	78±11	0.988
AST（IU/L）	94±78	57±41	0.0005
ALT（IU/L）	99±145	93±81	0.778
γ-GTP（IU/L）	321±277	112±107	<0.0001
血小板数（$\times 10^4/\mu L$）	19.1±8.1	20.4±6.8	0.290
総コレステロール（mg/dL）	178±63	193±44	0.105
LDL コレステロール（mg/dL）	96±54	122±43	0.024
中性脂肪（mg/dL）	195±172	147±73	0.032
空腹時血糖（mg/dL）	120±49	115±42	0.516
HbA1c（JDS 値，%）	5.6±1.1	6.0±1.3	0.151

* t 検定または χ^2 検定.

BMI, body mass index; JDS, Japan Diabetes Society.

表6 脂肪性肝疾患と生活習慣病（男性）

	アルコール性肝障害 (n = 72)	非アルコール性脂肪性肝疾患 (n = 72)	p *
高血圧，n（%）	30（41.7）	22（30.6）	0.165
糖尿病，n（%）	16（22.2）	26（36.1）	0.066
脂質異常症，n（%）	29（40.3）	32（44.4）	0.613
高血圧 + 糖尿病，n（%）	9（12.5）	13（18.1）	0.353
高血圧 + 脂質異常症，n（%）	16（22.2）	15（20.8）	0.839
糖尿病 + 脂質異常症，n（%）	6（8.3）	16（22.2）	0.019
高血圧 + 糖尿病 + 脂質異常症，n（%）	5（6.9）	10（13.9）	0.275
2 疾患以上，n（%）	21（29.2）	23（31.9）	0.718

* χ^2 検定または Fisher の正確検定.

表7 脂肪性肝疾患の背景（男性 BMI <25 kg/m²）

	アルコール性肝障害 (n = 42)	非アルコール性脂肪性肝疾患 (n = 42)	p *
年齢（歳）	52.8±11.8	52.8±15.0	0.994
BMI（kg/m²）	22.1±2.5	22.1±2.5	0.997
線維化　有/無	14/28	13/29	0.815
収縮期血圧（mmHg）	133±20	123±17	0.018
拡張期血圧（mmHg）	78±12	75±10	0.257
AST（IU/L）	100±76	62±81	0.028
ALT（IU/L）	100±177	95±124	0.878
γ-GTP（IU/L）	512±499	101±106	<0.0001
血小板数（×10⁴/μL）	20.6±9.9	19.6±6.5	0.591
総コレステロール（mg/dL）	169±45	178±46	0.399
LDL コレステロール（mg/dL）	72±36	107±41	0.047
中性脂肪（mg/dL）	200±206	124±89	0.035
空腹時血糖（mg/dL）	127±58	121±58	0.606
HbA1c（JDS 値，%）	5.8±1.3	6.1±1.7	0.407

* t 検定または χ^2 検定.
BMI, body mass index; JDS, Japan Diabetes Society.

表8 脂肪性肝疾患と生活習慣病（男性 BMI <25 kg/m²）

	アルコール性肝障害 (n = 42)	非アルコール性脂肪性肝疾患 (n = 42)	p *
高血圧，n（%）	16（38.1）	13（31.0）	0.491
糖尿病，n（%）	11（26.2）	14（33.3）	0.474
脂質異常症，n（%）	11（26.2）	15（35.7）	0.344
高血圧 + 糖尿病，n（%）	4（9.5）	7（16.7）	0.520
高血圧 + 脂質異常症，n（%）	6（14.3）	10（23.8）	0.405
糖尿病 + 脂質異常症，n（%）	2（4.8）	8（19.0）	0.089
高血圧 + 糖尿病 + 脂質異常症，n（%）	2（4.8）	5（11.9）	0.433
2 疾患以上，n（%）	8（19.0）	14（33.3）	0.135

* χ^2 検定または Fisher の正確検定.
BMI, body mass index.

表 9 脂肪性肝疾患の背景（男性 BMI ≥25 kg/m²）

	アルコール性肝障害 (n = 29)	非アルコール性脂肪性肝疾患 (n = 29)	p *
年齢（歳）	56.9±14.0	60.1±10.4	0.339
BMI (kg/m²)	27.4±2.4	27.7±1.8	0.642
線維化　有/無	12/17	10/19	0.588
収縮期血圧 (mmHg)	135±19	127±17	0.100
拡張期血圧 (mmHg)	82±11	77±12	0.073
AST (IU/L)	107±98	67±47	0.053
ALT (IU/L)	104±95	95±80	0.681
γ-GTP (IU/L)	262±168	100±119	<0.0001
血小板数(×10⁴/μL)	19.6±7.2	18.5±6.0	0.543
総コレステロール (mg/dL)	175±56	195±33	0.098
LDL コレステロール (mg/dL)	116±46	114±28	0.931
中性脂肪 (mg/dL)	234±324	207±94	0.672
空腹時血糖 (mg/dL)	117±29	131±54	0.222
HbA1c (JDS 値, %)	6.0±0.9	6.3±1.1	0.289

* t 検定または χ^2 検定.
BMI, body mass index; JDS, Japan Diabetes Society.

表 10 脂肪性肝疾患と生活習慣病（男性 BMI ≥25 kg/m²）

	アルコール性肝障害 (n = 29)	非アルコール性脂肪性肝疾患 (n = 29)	p *
高血圧, n (%)	16 (55.2)	11 (37.9)	0.187
糖尿病, n (%)	9 (31.0)	18 (62.1)	0.017
脂質異常症, n (%)	14 (48.3)	17 (58.6)	0.429
高血圧 + 糖尿病, n (%)	6 (20.7)	7 (24.1)	1.000
高血圧 + 脂質異常症, n (%)	10 (34.5)	7 (24.1)	0.565
糖尿病 + 脂質異常症, n (%)	4 (13.8)	7 (24.1)	0.123
高血圧 + 糖尿病 + 脂質異常症, n (%)	3 (10.3)	5 (17.2)	0.706
2 疾患以上, n (%)	14 (48.3)	14 (48.3)	1.000

* χ^2 検定または Fisher の正確検定.
BMI, body mass index.

研究成果の刊行に関する一覧

書籍

著者氏名	論文タイトル名	書籍全体の編集者名	書　籍　名	出版社名	出版地	出版年	ページ

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利國信行，福村　敦，林　伸彦，松江泰弘，湊　貴浩，齊藤　隆，土島　睦，有沢富康，堤　幹宏:	脂肪性肝疾患の成因と生活習慣病の関係における肥満の影響.	アルコールと医学生物学	32	印刷中	2013

Original Article

Comparison of the relationships of alcoholic and nonalcoholic fatty liver with hypertension, diabetes mellitus, and dyslipidemia

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We compared the relationships of alcoholic fatty liver and nonalcoholic fatty liver with hypertension, diabetes mellitus, and dyslipidemia. Using a nationwide Japanese survey, we collected data on subjects with biopsy-proven alcoholic fatty liver or nonalcoholic fatty liver. Multiple logistic regression analysis was performed to determine whether alcoholic fatty liver and nonalcoholic fatty liver are associated factors for these diseases. Data on 191 subjects (65, alcoholic fatty liver; 126, nonalcoholic fatty liver) were analyzed. Alcoholic fatty liver (odds ratio, 2.54; 95% confidence interval, 1.06–6.32; $p = 0.040$), age ≥55 years, and body mass index ≥25 kg/m² were correlated with hypertension, whereas nonalcoholic fatty liver (odds ratio, 2.32; 95% confidence interval, 1.08–5.20; $p = 0.035$) and serum γ-glutamyl transpeptidase levels ≥75 IU/l were correlated with dyslipidemia. Furthermore, we found that there were biological interactions between alcoholic fatty liver and body mass index ≥25 kg/m² in ≥55-year-old subjects (attributable proportion due to interaction, 0.68; 95% confidence interval, 0.19–1.17), as well as between alcoholic fatty liver and age ≥55 years in subjects with body mass index ≥25 kg/m² (attributable proportion due to interaction, 0.71; 95% confidence interval, 0.24–1.18). Alcoholic fatty liver was more strongly associated with hypertension than nonalcoholic fatty liver and nonalcoholic fatty liver was more strongly associated with dyslipidemia than alcoholic fatty liver. Moreover, alcoholic fatty liver, obesity, and older age may interact to influence hypertension status.

Key Words: **alcoholic fatty liver, nonalcoholic fatty liver, hypertension, diabetes mellitus, dyslipidemia**

Fatty liver disease (FLD) is the most prevalent form of liver disease worldwide.[1,2] Overnutrition and excessive alcohol consumption are 2 major causes of FLD.[3] Overnutrition can induce nonalcoholic fatty liver disease (NAFLD), a spectrum of conditions raging from simple steatosis [or nonalcoholic fatty liver (NAFL)] to nonalcoholic steatohepatitis and cirrhosis.[1,4] NAFLD is considered the hepatic manifestation of the metabolic syndrome,[5,6] and many studies have revealed strong relationships between NAFLD and hypertension (HT), type 2 diabetes mellitus (DM), and dyslipidemia (DL).[7] In contrast, excessive alcohol consumption can lead to alcoholic liver disease (ALD), which includes simple steatosis [or alcoholic fatty liver (AFL)], alcoholic hepatitis, hepatic fibrosis, and cirrhosis.[2] Less data are available on the relationship between ALD and HT, DM, and DL than that between NAFLD and such diseases. However, accumulating evidence indicates a positive relationship between excessive alcohol consumption and HT, DM, and DL.[8–11] These findings indicate that ALD may also be closely linked to these diseases.

In the comprehensive management of FLD, it is important to understand the relationships between FLD and HT, DM, and DL in detail. To the best of our knowledge, no study has analyzed these relationships according to the FLD type. The goal of the present study was to compare AFL and NAFL, the most common FLD types, using data from a nationwide Japanese survey on FLD.

Materials and Methods

A nationwide survey. We conducted a nationwide Japanese survey on the status of FLD between 2009 and 2010 by sending a questionnaire to 894 institutions that employed medical specialists in gastroenterology and hepatology. The questionnaire contained questions regarding how histories were taken to assess alcohol consumption and what values were used as the upper limit of alcohol consumption for the purpose of defining social drinking. We also sent data sheets for subjects with biopsy-proven AFL, NAFL, or nonalcoholic steatohepatitis. The data sheets included details regarding age, gender, anthropometric measurements, blood pressure, liver function tests, data regarding the presence or absence of HT, DM, and DL, and laboratory test values associated with these diseases. Data obtained around the time of liver biopsy were collected. Written informed consent was obtained from each patient at the time of biopsy. This study was performed in accordance with the Declaration of Helsinki.

Subjects. In this study, we analyzed data from subjects with AFL or NAFL. AFL was diagnosed according to the following criteria of the Alcohol and Liver Research Group of the Ministry of Education: alcohol consumption ≥60 g/day for >5 years for men and ≥40 g/day for >5 years for women.[12] For the diagnosis of NAFL, we adopted ≤20 g/day as the upper limit of alcohol consumption, a value that is accepted by most researchers.[5,13]

Criteria for HT, DM, and DL. The diagnosis of HT, DM, and DL was made on the basis of treatments for these diseases or their respective criteria defined below. HT was defined according to the following Japanese Society of Hypertension guidelines for the management of hypertension: a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg.[14] DM was defined by the following criteria of the Japan Diabetes Society: fasting blood glucose levels ≥126 mg/dl or random blood glucose levels ≥200 mg/dl.[15] DL was defined as serum low-density-lipoprotein (LDL) cholesterol levels ≥140 mg/dl, serum high-density-lipoprotein (HDL) cholesterol levels <40 mg/dl, or serum triglyceride levels ≥150 mg/dl, according to the criteria of the Japan Atherosclerosis Society.[16] Serum LDL cholesterol levels were calculated using the Friedewald equation (LDL cholesterol =

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total cholesterol − HDL cholesterol − triglycerides/5) for subjects with serum triglyceride levels <400 mg/dl.[17]

Statistical analysis. Data are expressed as medians (ranges) or percentages. The chi-square test or Fisher's exact probability test were used to compare categorical variables, and the Mann–Whitney *U* test was used to compare continuous variables. A multiple logistic regression analysis was performed to determine whether the FLD types were associated factors for HT, DM, DL or combinations thereof (HT + DM, HT + DL, DM + DL, HT + DM + DL, and all combinations of ≥2 of the 3 diseases). The following potential confounding variables were included in the analysis: age (≥55 years, <55 years), gender (male, female), body mass index (BMI) (≥25 kg/m², <25 kg/m²), serum aspartate aminotransferase (AST) levels (≥40 IU/L, <40 IU/L), and serum γ-glutamyl transpeptidase (γ-GTP) levels (≥75 IU/L, <75 IU/L). BMI ≥25 kg/m² is defined as obesity in Japan.[18] A p value <0.05 was considered statistically significant. If the FLD types and other variables were simultaneously identified as associated factors, stratified and biological interaction analyses were conducted. Three indices were employed to assess biological interaction: the relative excess risk due to interaction (RERI), the attributable proportion due to interaction (AP), and the synergy index (S).[19,20] Methods for calculating the indices and their 95% confidence intervals (CI) are described by Andersson *et al.*[21] RERI = 0, AP = 0, or S = 1 indicated an additive interaction; RERI >0, AP >0, or S >1 indicated a synergistic interaction; and RERI <0, AP <0, or S <1 indicated an antagonistic interaction.[22] Analyses were performed using STATA ver 11.1 (STATA Corp., College Station, TX).

Results

Answers to the questionnaire were obtained from 101 (11.3%) of the 894 institutions and data on FLD were obtained from 66 hospitals (7.4%). The numbers of patients with FLDs were as follows: AFL, 71; NAFL, 131; nonalcoholic steatohepatitis, 494. Of the 202 subjects with AFL or NAFL, 6 with AFL and 5 with NAFL were excluded because of a lack of anthropometric data or information on the presence/absence of HT, DM, and DL. Thus, this study was conducted using data for 191 subjects (65, AFL; 126, NAFL).

Table 1 shows the baseline characteristics of the subjects. The female-to-male ratio, BMI, and diastolic blood pressure were lower in subjects with AFL than in those with NAFL. Laboratory tests revealed that levels of serum AST, γ-GTP, and fasting blood glucose were higher in subjects with AFL than in those with NAFL, whereas levels of serum total cholesterol and LDL cholesterol were lower in subjects with AFL than in those with NAFL. There were no significant differences in prevalence of HT, DM, DL, HT + DM, HT + DL, DM + DL, HT + DM + DL, and any combination of ≥2 of the 3 diseases between subject groups.

Table 2 lists factors associated with HT, DM, or DL for the entire cohort. Regarding FLD types, AFL was an associated factor for HT whereas NAFL was one for DL. Age ≥55 years was identified as a significant factor for HT, DM, and all combinations of the diseases. BMI ≥25 kg/m² was significantly associated with HT and HT + DL. Serum γ-GTP ≥75 IU/L was another factor associated with DL.

Stratified analysis was performed with regard to the 3 associated

Table 1. Baseline characteristics of the subjects

	Total cohort (n = 191)	AFL (n = 65)	NAFL (n = 126)	p value*
Age, years	54 (15–85)	56 (23–80)	53.5 (15–85)	0.541
Gender, male/female	115/76	50/15	65/61	0.0007
BMI, kg/m²	24.9 (13.2–61.3)	24.4 (18.0–35.3)	25.4 (13.2–61.3)	0.026
Systolic blood pressure, mmHg	124 (84–186)	123 (100–186)	125 (84–168)	0.727
Diastolic blood pressure, mmHg	76 (46–114)	74 (58–114)	78 (46–107)	0.010
AST, IU/L	41 (15–675)	61 (17–675)	35 (15–310)	<0.0001
ALT, IU/L	49 (12–1123)	49 (12–1123)	48.5 (13–377)	0.827
γ-GTP, IU/L	72 (10–3028)	156 (24–3028)	50 (10–646)	<0.0001
Fasting blood glucose, mg/dL	103 (67–310)	111.5 (70–176)	100 (67–310)	0.005
Hemoglobin A1c, %	5.8 (3.7–10.6)	5.9 (3.7–9.1)	5.8 (4.4–10.6)	0.450
Total cholesterol, mg/dL	192 (37–454)	166 (37–454)	201 (88–349)	<0.0001
LDL cholesterol, md/dL†	114 (5–246)	89 (5–210)	119 (51–246)	<0.0001
HDL cholesterol, mg/dL	49 (3–131)	47 (3–131)	50 (20–129)	0.182
Triglycerides, mg/dL	118 (21.5–879)	110 (25–879)	120 (21.5–407)	0.731
HT, n (%)	60 (31.4)	25 (38.5)	35 (27.8)	0.132
untreated, n (%)	18 (30.0)	10 (40.0)	8 (22.9)	
under treatment, n (%)	42 (70.0)	15 (60.0)	27 (77.1)	
DM, n (%)	47 (24.6)	19 (29.2)	28 (22.2)	0.287
untreated, n (%)	18 (38.3)	10 (52.6)	8 (28.6)	
under treatment, n (%)	29 (61.7)	9 (47.4)	20 (71.4)	
DL, n (%)	71 (37.2)	21 (32.3)	50 (39.7)	0.318
untreated, n (%)	43 (60.6)	15 (71.4)	28 (56.0)	
under treatment, n (%)	28 (39.4)	6 (28.6)	22 (44.0)	
HT + DM, n (%)	26 (13.6)	12 (18.5)	14 (11.1)	0.184
HT + DL, n (%)	34 (17.8)	12 (18.5)	22 (17.5)	0.864
DM + DL, n (%)	26 (13.6)	6 (9.2)	20 (15.9)	0.267
HT + DM + DL, n (%)	16 (8.4)	5 (7.7)	11 (8.7)	1.000
≥2 of the 3 diseases, n (%)	53 (27.7)	20 (30.8)	33 (26.2)	0.503

AFL, alcoholic fatty liver; NAFL, nonalcoholic fatty liver; BMI, body mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase, γ-GTP, γ-glutamyl transpeptidase; HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; LDL, low-density lipoprotein; HDL, high-density lipoprotein. *AFL vs NAFL. Chi-square test or Fisher's exact probability test for categorical variables, Mann–Whitney *U* test for continuous variables †The Friedewald equation was used. Data excluded 4 subjects with AFL and 1 with NALF whose serum triglyceride levels were ≥400 mg/dL.

Table 2. Associated factors for HT, DM, DL or their combinations

Disease	Associated factors	*p* value	Adjusted odds ratio*	95% Confidence interval
HT	AFL	0.040	2.54	1.06–6.32
	Age ≥55 years	<0.0001	6.64	3.24–14.49
	BMI ≥25 kg/m²	0.012	2.49	1.23–5.17
DM	Age ≥55 years	<0.0001	5.46	2.55–12.62
DL	NAFL	0.035	2.32	1.08–5.20
	γ-GTP ≥75 IU/L	0.004	2.85	1.42–5.90
HT + DM	Age ≥55 years	0.0006	7.17	2.55–25.78
HT + DL	Age ≥55 years	0.001	4.20	1.81–10.72
	BMI ≥25 kg/m²	0.021	2.61	1.18–6.06
DM + DL	Age ≥55 years	0.002	5.14	1.95–15.64
HT + DM + DL	Age ≥55 years	0.006	8.51	2.22–56.32
≥2 of the 3 diseases	Age ≥55 years	0.0001	4.42	2.19–9.41

HT, hypertension; DM, diabetes mellitus; DL, dyslipidemia; AFL, alcoholic fatty liver; BMI, body mass index; NAFL, nonalcoholic fatty liver; γ-GTP, γ-glutamyl transpeptidase. *A multiple logistic regression analysis was performed on the basis of types of fatty liver disease, age, gender, BMI, and serum levels of aspartate aminotransferase and γ-GTP.

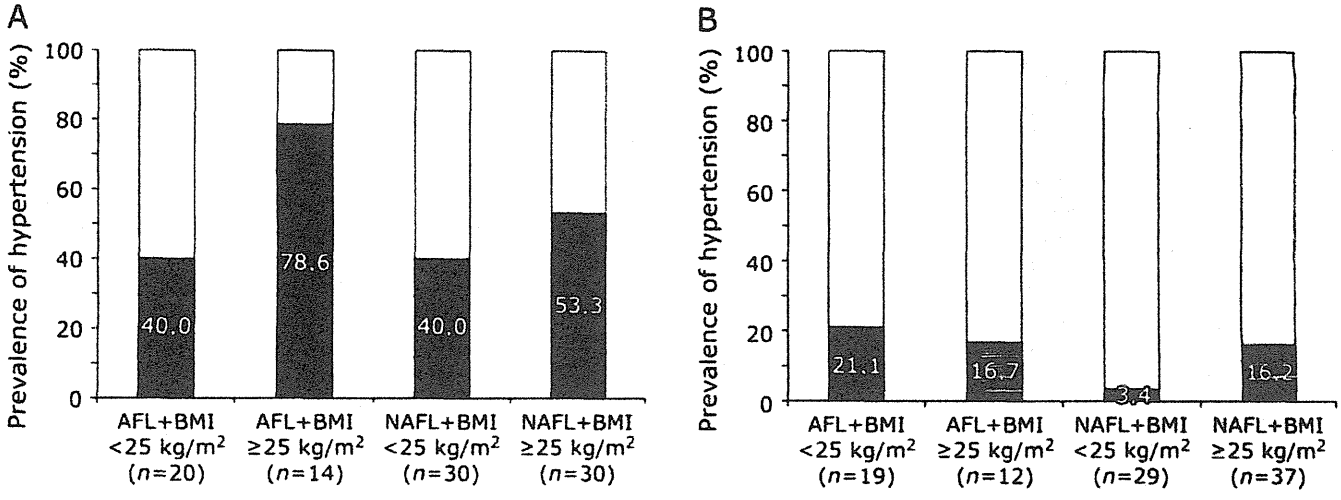

Fig. 1. Comparison of the prevalence of hypertension among subjects stratified by types of fatty liver disease and body mass index in each age subgroup. (A) Subjects aged ≥55 years. $p = 0.082$ (chi-square test). (B) Subjects aged <55 years. $p = 0.284$ (chi-square test). AFL, alcoholic fatty liver; NAFL, nonalcoholic fatty liver; BMI, body mass index ■, presence of hypertension; □, absence of hypertension.

factors (AFL, age ≥55 years, and BMI ≥25 kg/m²) for HT. First, the entire cohort was divided into 2 subgroups according to age (≥55 years, <55 years), and stratified analysis by FLD type and BMI was performed. Among subjects aged ≥55 years ($n = 94$), the prevalence of HT was the highest in subjects with AFL + BMI ≥25 kg/m² (Fig. 1A). After adjusting for other variables, AFL + BMI ≥25 kg/m² showed significantly higher odds ratio (OR) for HT compared with NAFL + BMI <25 kg/m² (Table 3). In interaction analysis between AFL and BMI ≥25 kg/m², AP (0.68, 95% CI, 0.19–1.17) was significant, whereas RERI and S were not. Among subjects aged <55 years ($n = 97$), the prevalence of HT was the highest in subjects with AFL + BMI <25 kg/m² (Fig. 1B). There were no significant differences between the relationship of each stratified group with HT (Table 3); moreover, neither RERI, AP, nor S was significant as per the interaction analysis.

We next divided the entire cohort into 2 subgroups according to BMI (≥25 kg/m², <25 kg/m²), and performed stratified analysis by FLD type and age. Among subjects with BMI ≥25 kg/m² ($n = 93$), the prevalence of HT was the highest in subjects with AFL + age ≥55 years (Fig. 2A). After adjusting for other variables, AFL + age ≥55 years and NAFL + age ≥55 years showed significantly higher ORs for HT compared with NAFL + age <55 years (Table 4). Regarding interaction analysis between AFL and age ≥55 years, AP (0.71, 95% CI, 0.24–1.18) was significant, whereas RERI and S were not. Among subjects with BMI <25 kg/m² ($n = 98$), the prevalence of HT was the highest in subjects with AFL + age ≥55 years (Fig. 2B). After adjustment for other variables, AFL + age ≥55 years and NAFL + age ≥55 years showed significantly higher ORs for HT compared with NAFL + age <55 years (Table 4). Neither RERI, AP, nor S was significant as per the interaction analysis.

The subjects were divided according to the FLD type and serum γ-GTP levels. The prevalence of DL was the highest in subjects with NAFL + γ-GTP ≥75 IU/L (Fig. 3). After adjusting for other variables, NAFL + γ-GTP ≥75 IU/L showed significantly higher ORs for DL than AFL + γ-GTP <75 IU/L (Table 5). A significant interaction between NAFL and γ-GTP ≥75 IU/L was not detected.

Discussion

To the best of our knowledge, this is the first study to analyze the relationships between FLD and HT, DM, and DL according to

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Table 3. Stratified and biological interaction analyses for hypertension in age subgroups

Subgroup	Stratification	*p* value	Adjusted odds ratio*	95% Confidence interval	Measures of interaction	Estimate	95% Confidence interval
Age ≥55 years (*n* = 94)	NAFL + BMI <25 kg/m²		1.00				
	NAFL + BMI ≥25 kg/m²	0.138	2.29	0.77–6.83	RERI	7.48	−9.59–24.56
	AFL + BMI <25 kg/m²	0.294	2.23	0.50–9.96	AP	0.68	0.19–1.17
	AFL + BMI ≥25 kg/m²	0.008	11.00	1.90–63.86	S	3.97	0.62–25.56
Age <55 years (*n* = 97)	NAFL + BMI <25 kg/m²		1.00				
	NAFL + BMI ≥25 kg/m²	0.127	5.46	0.41–72.11	RERI	−6.50	−27.33–14.33
	AFL + BMI <25 kg/m²	0.098	7.26	0.69–76.09	AP	−1.25	−5.50–3.01
	AFL + BMI ≥25 kg/m²	0.216	5.22	0.38–71.32	S	0.39	0.04–3.80

NAFL, nonalcoholic fatty liver; BMI, body mass index; AFL, alcoholic fatty liver; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index. *Odds ratios for hypertension were calculated after adjustment for gender and serum levels of aspartate aminotransferase and γ-glutamyl transpeptidase.

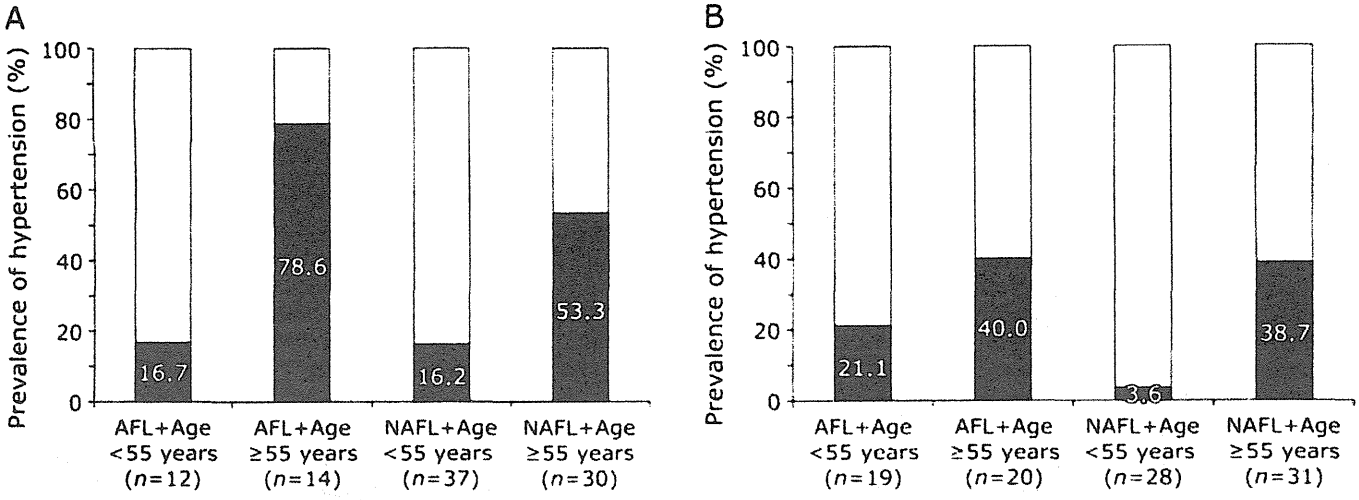

Fig. 2. Comparison of the prevalence of hypertension among subjects stratified by types of fatty liver disease and age in each body mass index (BMI) subgroup. (A) Subjects with BMI ≥25 kg/m². $p<0.0001$ (chi-square test). (B) Subjects with BMI <25 kg/m². $p = 0.006$ (chi-square test). AFL, alcoholic fatty liver; NAFL, nonalcoholic fatty liver; ■, presence of hypertension; □, absence of hypertension.

Table 4. Stratified and biological interaction analyses for hypertension in BMI subgroups

Subgroup	Stratification	*p* value	Adjusted odds ratio*	95% Confidence interval	Measures of interaction	Estimate	95% Confidence interval
BMI ≥25 kg/m² (*n* = 93)	NAFL + Age <55 years		1.00				
	NAFL + Age ≥55 years	0.004	5.83	1.79–19.05	RERI	14.43	−16.50–45.35
	AFL + Age <55 years	0.891	1.14	0.17–7.55	AP	0.71	0.24–1.18
	AFL + Age ≥55 years	0.0003	20.40	3.96–104.98	S	3.90	0.66–23.11
BMI <25 kg/m² (*n* = 98)	NAFL + Age <55 years		1.00				
	NAFL + Age ≥55 years	0.011	16.65	1.90–146.17	RERI	−1.21	−34.15–31.74
	AFL + Age <55 years	0.059	9.61	0.92–100.97	AP	−0.05	−1.46–1.36
	AFL + Age ≥55 years	0.006	24.05	2.44–237.10	S	0.95	0.24–3.84

BMI, body mass index; NAFL, nonalcoholic fatty liver; AFL, alcoholic fatty liver; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index. *Odds ratios for hypertension were calculated after adjustment for gender and serum levels of aspartate aminotransferase and γ-glutamyl transpeptidase.

the FLD type. Our results show that the FLD type influences the relationship between FLD and HT or DL. Thus, AFL was more strongly associated with HT than NAFL and NAFL was more strongly associated with DL than AFL. In contrast, the relationship between FLD and DM or the combinations of HT, DM, and DL were found not to be influenced by the FLD type.

Intensive studies have established excessive alcohol consumption as a risk factor for HT.[9] Because hepatic steatosis occurs in almost all subjects who consume alcohol excessively,[2,3] the close relationship between AFL and HT was expected. However, a full understanding of the influence of the FLD type on the relationship between FLD and HT is still lacking. Studies have revealed various mechanisms by which excessive alcohol consumption induces HT, including increased sympathetic nervous

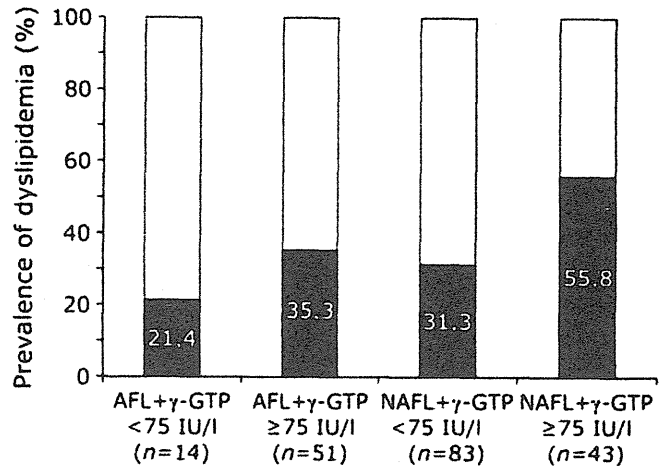

Fig. 3. Comparison of the prevalence of dyslipidemia among subjects stratified by types of fatty liver disease and serum γ-glutamyl transpeptidase level. $p = 0.027$ (chi-square test). AFL, alcoholic fatty liver; NAFL, nonalcoholic fatty liver; γ-GTP, γ-glutamyl transpeptidase; ■, presence of hypertension; □, absence of hypertension.

Table 5. Stratified and biological interaction analyses for dyslipidemia

Stratification	*p* value	Adjusted odds ratio*	95% Confidence interval	Measures of interaction	Estimate	95% Confidence interval
AFL + γ-GTP <75 IU/l		1.00				
AFL + γ-GTP ≥75 IU/l	0.298	2.13	0.51–8.91	RERI	2.30	−1.64–6.23
NAFL + γ-GTP <75 IU/l	0.482	1.65	0.41–6.61	AP	0.45	−0.07–0.97
NAFL + γ-GTP ≥75 IU/l	0.028	5.08	1.19–21.60	S	2.29	0.46–11.40

AFL, alcoholic fatty liver; γ-GTP, γ-glutamyl transpeptidase; NAFL, nonalcoholic fatty liver; RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index. *Odds ratios for dyslipidemia were calculated after adjustment for age, gender, body mass index, and serum aspartate aminotransferase levels.

system activity and stimulation of the renin–angiotensin–aldosterone system.[9] These mechanisms also have been reported to be involved in the metabolic syndrome, which is usually accompanied by NAFLD.[24,25] Insulin resistance, a key factor in the development of the metabolic syndrome,[26] is another mechanism in the pathogenesis of HT.[27] Recent studies have found that excessive alcohol consumption does not significantly increase insulin resistance.[28] Nevertheless, our study demonstrates that AFL is the FLD type more closely linked to HT. Potential differences in mechanisms of HT between the FLD types might influence planning therapeutic strategies for HT in subjects with such FLD types.

This study identified obesity and older age as other associated factors for HT. These factors are established risk factors for HT.[29,30] In stratified analysis, the combination of AFL and obesity in older subjects and that of AFL and older age in both obese and nonobese subjects showed a significant increase in the ORs for HT. In interaction analysis, the results differed according to the indices for biological interaction. According to the interaction analysis for AFL and obesity in older subjects, AP was significant, whereas RERI and S were not. The relationship between AFL and older age in obese subjects followed this same pattern. However, a study on interaction analysis published in 2006 demonstrates that AP is the most robust measure in a logistic regression model.[31] Hence our results could indicate that AFL, obesity, and older age interact to influence hypertension status.

Cross-sectional studies have suggested an interactive influence of excessive alcohol consumption and obesity on HT.[32,33] Moreover, in overweight men, combined intervention involving restricted alcohol and food consumption leads to decreases in blood pressure more effectively than either intervention alone.[34] We were unable to find any published studies examining the interaction between excessive alcohol consumption and older age in relation to HT. On the basis of the theory of biological interaction,[35] the interactions found in our present study may indicate the presence of at least a pathway toward HT in which AFL, obesity, and older age, are all involved. However, future prospective studies will be necessary to confirm these interactions.

We show here that NAFL and increased serum γ-GTP levels are associated factors for DL, and their combination is most strongly associated with DL. We could not confirm the DL types with which these factors were associated because we did not collect the relevant information. Generally, baseline serum LDL cholesterol levels were higher in subjects with NAFL than in those with AFL, although the results were calculated using data from untreated as well as treated subjects. This finding is consistent with the results in large-scale studies investigating the influence of alcohol consumption on serum lipid levels in which serum LDL cholesterol levels were inversely correlated with alcohol consumption.[36,37] Recent studies of subjects with DM have shown that serum γ-GTP levels are positively associated with DL.[38] Furthermore, elevation of serum γ-GTP levels has been identified as a predictor for cardiovascular diseases[39] as well as a marker of metabolic syndrome.[40] The complexes that form between γ-GTP forms and LDL lipoprotein facilitate the evolution of atherosclerotic plaques toward instability and rupture.[41] Given these findings, the magnitude of risk for cardiovascular diseases in subjects with NAFL with elevated serum γ-GTP levels should be investigated.

There are some limitations to this study. First, because of its cross-sectional design, this study could not determine causality between HT, DM, and DL and associated factors. Second, the number of subjects was relatively small, constraining statistical

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power. Third, data on FLD were obtained from only a limited number of institutions in Japan, which might limit generalizability of the findings. Fourth, this study lacked data on smoking, a potential confounder in particular for HT.[42] Since a close link of excessive alcohol consumption to smoking has been reported,[43] it is possible that in our cohort, the proportion of smokers was higher in subjects with AFL than in those with NAFL. A large-scale study, however, has demonstrated that smoking has a smaller impact on elevation of blood pressure than excessive alcohol consumption in men, no such effect was seen in women.[44] Therefore, although our results should be interpreted with caution, we feel confident in concluding that they would not have changed significantly if smoking had been included as a variable.

The present study demonstrates that the relationships between FLD and HT, DM, and DL partly depend on the FLD type. We believe that these findings may be helpful in managing subjects with FLD. Future studies are needed to confirm our results and clarify mechanisms responsible for the development of HT in which AFL, obesity, and older age play a role.

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Conflict of Interest

We have no financial disclosure or conflict of interest to report.

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生活習慣病に関するアルコール性脂肪肝と非アルコール性脂肪肝の比較検討

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1．目　　的

過栄養と過飲酒は脂肪肝の主な原因である．特に前者による脂肪肝，すなわち非アルコール性脂肪肝（nonalcoholic fatty liver）はメタボリック症候群の肝における表現型とされ，高血圧，糖尿病，脂質異常症といった生活習慣病との関連が多数報告されている[1]．一方，過飲酒と生活習慣病についても高血圧との関連を中心に報告されているが[2]，アルコール性脂肪肝（alcoholic fatty liver）と生活習慣病の関係という視点での研究報告は殆どない．脂肪肝に対する包括的な取り組みには，脂肪肝のタイプ別の特徴を把握しておくことが重要と考えられる．脂肪肝と生活習慣病の関連について，脂肪肝のタイプによる差異を検討した．

2．方　　法

厚生労働省研究班の「わが国における飲酒の実態把握およびアルコールに関連する生活習慣病とその対策に関連する総合的研究」に基づき，「アルコール性および非アルコール性脂肪肝症例に関する全国調査」（2009－2010年度の実態）を実施した．生検で確定診断された脂肪肝（simple steatosis）について有効回答が得られた191例（アルコール性脂肪肝　65例，非アルコール性脂肪肝126例）を解析の対象とした．脂肪肝のタイプ（アルコール性，非アルコール性），年齢（55歳以上，未満），性，body mass index（BMI）（25 kg/m^{2}以上，未満），血清AST値（40 IU/L以上，未満），血清γ-GTP値（75 IU/L以上，未満）を説明変数とし，高血圧，糖尿病，脂質異常症，およびそれらの組み合わせ2疾患（3パターン），3疾患，2疾患以上，合計8パターンの生活習慣病を目的変数として多重ロジスティック回帰分析を行い，脂肪肝のタイプが生活習慣病の関連因子であるか検討した．さらに，ある生活習慣病に対して脂肪肝のタイプを含め複数の因子が関連因子として同定された場合，層別解析を行った．また，relative excess risk due to interaction（RERI），attributable proportion due to interaction（AP），synergy index（S）の3指標を用いて，関連因子の生物学的交互作用（biological interaction）を検討した[3),4)]．すなわち，複数の関連因子が生活習慣病に対してどのように（相加的または相乗的）に作用するのかを調べた．RERI＞0，AP＞0，またはS＞1を相乗的（ただし，95％信頼区間下限がこれらの値を超える場合）とした．

3．結　　果

脂肪肝症例の背景を示す（表1）．アルコール性脂肪肝と非アルコール性脂肪肝では性，BMI，血清AST，血清γ-GTPに有意差が認められた．

Comparison of the relationships of alcoholic and nonalcoholic fatty liver with lifestyle-related diseases
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表1　脂肪肝症例の背景

	全体 (n = 191)	アルコール性脂肪肝 (n = 65)	非アルコール性脂肪肝 (n = 126)	P値*
年齢，歳	54 (15-83)	56 (23-80)	53.5 (15-85)	0.541
男/女	115/76	50/15	65/61	0.0007
BMI，kg/m²	24.9 (13.2-61.3)	24.4 (18.0-35.3)	25.4 (15.2-61.3)	0.026
収縮期血圧，mmHg	124 (84-186)	123 (100-186)	125 (84-168)	0.727
拡張期血圧，mmHg	76 (46-114)	74 (58-114)	78 (46-107)	0.010
AST，IU/l	41 (15-675)	61 (17-675)	35 (15-310)	<0.0001
ALT，IU/l	49 (12-1123)	49 (12-1123)	48.5 (13-377)	0.827
γ-GTP，IU/l	72 (10-3028)	156 (24-3028)	50 (10-646)	<0.0001
空腹時血糖，mg/dl	103 (67-310)	111.5 (70-176)	100 (67-310)	0.005
HbA1c，% (JDS 値)	5.45 (3.4-10.1)	5.5 (3.4-8.7)	5.4 (4.1-10.1)	0.449
総コレステロール，mg/dl	192 (37-454)	166 (37-454)	201 (88-349)	<0.0001
LDL コレステロール，mg/dl	114 (5-246)	89 (5-210)	119 (51-246)	<0.0001
HDL コレステロール，mg/dl	49 (3-131)	47 (3-131)	50 (20-129)	0.182
中性脂肪，mg/dl	118 (21.5-879)	110 (25-879)	120 (21.5-407)	0.731
高血圧，n (%)	60 (31.4)	25 (38.5)	35 (27.8)	0.132
糖尿病，n (%)	47 (24.6)	19 (29.2)	28 (22.2)	0.287
脂質異常症，n (%)	71 (37.2)	21 (32.3)	50 (39.7)	0.318
高血圧 + 糖尿病，n (%)	26 (13.6)	12 (18.5)	14 (11.1)	0.184
高血圧 + 脂質異常症，n (%)	34 (17.8)	12 (18.5)	22 (17.5)	0.864
糖尿病 + 脂質異常症，n (%)	26 (13.6)	6 (9.2)	20 (15.9)	0.267
高血圧 + 糖尿病 + 脂質異常症，n (%)	16 (8.4)	5 (7.7)	11 (8.7)	1.000
2 疾患以上，n (%)	53 (27.7)	20 (30.8)	33 (26.2)	0.503

*アルコール性脂肪肝 対 非アルコール性脂肪肝．カテゴリ変数は χ 二乗検定またはフィッシャーの正確検定．連続変数はマン・ホイットニーの検定．

表2　生活習慣病の関連因子

生活習慣病	関連因子	P値*	調整オッズ比	95%信頼区間
高血圧	アルコール性脂肪肝	0.040	2.54	1.06-6.32
	55 歳以上	0.0001	6.64	3.24-14.49
	BMI 25 kg/m² 以上	0.012	2.49	1.23-5.17
糖尿病	55 歳以上	<0.0001	5.46	2.55-12.62
脂質異常症	非アルコール性脂肪肝	0.025	2.32	1.08-5.20
	γ-GTP 75 IU/l 以上	0.004	2.85	1.42-5.90
高血圧 + 糖尿病	55 歳以上	0.0006	7.17	2.55-25.78
高血圧 + 脂質異常症	55 歳以上	0.001	4.20	1.81-10.72
	BMI 25 kg/m² 以上	0.021	2.61	1.18-6.06
糖尿病 + 脂質異常症	55 歳以上	0.002	5.14	1.95-15.64
高血圧 + 糖尿病 + 脂質異常症	55 歳以上	0.006	8.51	2.22-56.32
2 疾患以上	55 歳以上	0.0001	4.42	2.19-9.41

*多重ロジスティック回帰分析

生活習慣病の合併率にはいずれのパターンでも有意差が認められなかった．

多重ロジスティック回帰分析にて各生活習慣病およびそれらの組み合わせに対する関連因子を調べたところ，高血圧に対してはアルコール性脂肪肝，脂質異常症に対しては非アルコール性脂肪肝が関連因子として同定された（表2）．高血圧に対しては高齢（55 歳以上）と肥満（BMI 25 kg/m² 以上），脂質異常症に対しては血清 γ-GTP 高値（≥ 75 IU/l）も関連因子であった．

次に高血圧と脂質異常症について層別解析を行った．高血圧については年齢または BMI で 2 つのサブグループに分け，脂肪肝のタイプと BMI，脂肪肝のタイプと年齢でそれぞれ 4 つに層別化し，高血圧の合併率とオッズ比を計算した（表3，4）．年齢サブグループでは，高齢群において 2 つの関連因子を同時に持つ場合（アルコール性脂肪肝 + BMI 25 kg/m² 以上）に高血圧の合併率が最も高く，オッズ比も著しく上昇した．BMI サブグループでは，BMI 高値群および低値群の両群で，2 つの関連因子を同時に持つ場合（アルコール性脂肪肝 + 55 歳以上）に高血圧の合併率が最も高く，オッズ比も著しく上昇した．脂質異常症については脂肪肝のタイプと血清 γ-GTP で

表3　高血圧に対する年齢サブグループ別の層別解析

サブグループ	層別化	症例数	高血圧合併数（%）	P値*	調整オッズ比	95%信頼区間
55歳以上	非アルコール性脂肪肝 − BMI 25 kg/m² 未満	30	12（40.0）		1.00	
（n = 94）	非アルコール性脂肪肝 + BMI 25 kg/m² 以上	30	16（53.5）	0.138	2.29	0.77—6.83
	アルコール性脂肪肝 − BMI 25 kg/m² 未満	20	8（40.0）	0.294	2.23	0.50—9.96
	アルコール性脂肪肝 + 25 kg/m² 以上	14	11（78.6）	0.008	11.00	1.90—63.86
55歳未満	非アルコール性脂肪肝 − BMI 25 kg/m² 未満	29	1（3.4）		1.00	
（n = 97）	非アルコール性脂肪肝 + BMI 25 kg/m² 以上	37	6（16.2）	0.127	5.46	0.41—72.11
	アルコール性脂肪肝 − BMI 25 kg/m² 未満	19	4（21.1）	0.098	7.26	0.69—76.09
	アルコール性脂肪肝 + BMI 25 kg/m² 以上	12	2（16.7）	0.216	5.22	0.38—71.32

*多重ロジスティック回帰分析

表4　高血圧に対するBMIサブグループ別の層別解析

サブグループ	層別化	症例数	高血圧合併数（%）	P値*	調整オッズ比	95%信頼区間
BMI 25 kg/m² 以上	非アルコール性脂肪肝 − 55歳未満	37	6（16.2）		1.00	
（n = 93）	非アルコール性脂肪肝 + 55歳以上	30	16（53.3）	0.004	5.83	1.79—19.05
	アルコール性脂肪肝 − 55歳未満	12	2（16.7）	0.891	1.14	0.17—7.55
	アルコール性脂肪肝 + 55歳以上	14	11（78.6）	0.0003	20.40	3.96—104.98
BMI 25 kg/m² 未満	非アルコール性脂肪肝 − 55歳未満	28	1（3.6）		1.00	
（n = 98）	非アルコール性脂肪肝 + 55歳以上	31	12（38.7）	0.011	16.65	1.90—146.17
	アルコール性脂肪肝 − 55歳未満	19	4（21.1）	0.059	9.61	0.92—100.97
	アルコール性脂肪肝 + 55歳以上	20	8（40.0）	0.006	24.05	2.44—237.10

*多重ロジスティック回帰分析

表5　脂質異常症に対する層別解析

層別化	症例数	脂質異常症合併数（%）	P値*	調整オッズ比	95%信頼区間
アルコール性脂肪肝 − γ-GTP 75 IU/l 未満	14	3（21.4）		1.00	
アルコール性脂肪肝 − γ-GTP 75 IU/l 以上	51	18（35.3）	0.298	2.13	0.51—8.91
非アルコール性脂肪肝 − γ-GTP 75 IU/l 未満	83	26（31.3）	0.182	1.65	0.41—6.61
非アルコール性脂肪肝 + γ-GTP 75 IU/l 以上	43	24（55.8）	0.028	5.08	1.19—21.60

*多重ロジスティック回帰分析

4つに層別化し，脂質異常症の合併率とオッズ比を計算した（表5）．その結果，2つの関連因子を同時に持つ場合に脂質異常症の合併率，オッズ比が最も高かった．

層別解析に用いた2つの関連因子の組み合わせについて，生物学的交互作用を調べたところ，高血圧に関して，高齢群におけるアルコール性脂肪肝と肥満（AP 0.68，95％信頼区間 0.19−1.17），肥満群におけるアルコール性脂肪肝と高齢（AP 0.71，95％信頼区間 0.24−1.18），それぞれの組み合わせで相乗作用を示唆する結果が得られた（表6）．

表6　高血圧および脂質異常症に関する関連因子の生物学的交互作用

アルコール性脂肪肝と肥満（高血圧）	指標	値	95%信頼区間
55歳以上	RERI	7.48	9.59—24.56
	AP	0.68	0.19−1.17
	S	3.07	0.62−25.56
55歳未満	RERI	−6.50	−27.33—14.33
	AP	−1.25	−5.50—3.01
	S	0.39	0.04—3.80
アルコール性脂肪肝と高齢（高血圧）	指標	値	95%信頼区間
BMI 25 kg/m² 以上	RERI	14.42	−16.50—45.35
	AP	0.71	0.24—1.18
	S	3.90	0.68−23.11
BMI 25 kg/m² 未満	RERI	−1.21	−31.15−31.74
	AP	−0.05	−1.46−1.36
	S	0.95	0.24—3.84
非アルコール性脂肪肝と血清γ-GTP高値（脂質異常症）	指標	値	95%信頼区間
	RERI	2.30	1.64—6.23
	AP	0.45	−0.07—0.97
	S	2.29	0.46—11.40

RERI, relative excess risk due to interaction; AP, attributable proportion due to interaction; S, synergy index.

4．考　察

本研究によって，脂肪肝症例において脂肪肝のタイプは特定の生活習慣病の関連因子であることが示された．すなわち，高血圧に対してはアルコール性脂肪肝が強く関連し，脂質異常症に対しては

非アルコール性脂肪肝が強く関連していた．なお，糖尿病と複数の生活習慣病の組み合わせに対しては脂肪肝のタイプは関連因子ではなかった．

本研究は横断的研究であるため，生活習慣病と関連因子との直接的因果関係は示せない．しかし，過飲酒，高齢，肥満は既にそれぞれ高血圧の危険因子として報告されている[2),5),6)]．今回の検討ではこれら3因子が相乗的に作用して高血圧の合併率を高めていると考えられた．生物学的交互作用の理論によれば，これら3因子がすべて関わる高血圧発症経路の存在が示唆される[7)]．

近年，過飲酒と肥満の関係が注目されている．第一に，肥満はアルコール性肝障害における肝線維化の危険因子であると報告されている[8)]．第二に，本研究と同様，過飲酒と肥満の組み合わせは各因子単独と比較してより強く高血圧に関連するとの報告がある[9)]．日常診療においては過栄養に飲酒の影響がうかがわれる脂肪肝症例をしばしば経験する．こうした症例における肝線維化進展と高血圧を代表とする生活習慣病の危険性を前向き研究によって明らかにする必要がある．

5．結　　語

アルコール性脂肪肝と非アルコール性脂肪肝では生活習慣病（高血圧，糖尿病，脂質異常症）との関連性に一部差異が認められる．アルコール性脂肪肝，肥満，加齢は相乗的に作用して高血圧の発症に関与している可能性がある．

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