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Liver stiffness and arterial stiffness/abnormal central hemodynamics in the early stage of heart failure

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ABSTRACT

Background: It remains to be clarified whether liver stiffness is a direct risk factor for heart failure (HF) or whether its association with HF is mediated by vascular damage. We conducted cross-sectional and prospective longitudinal studies to examine whether fibrosis 4 score (FIB-4 score) is directly associated with the serum NT-pro-BNP levels or the association is mediated by arterial stiffness and/or abnormal central hemodynamics.

Methods and results: In 3040 health Japanese subjects with serum NT-pro-BNP levels < 125 pg/ml, the FIB-4 score was calculated, and the serum NT-pro-BNP levels, brachial-ankle pulse wave (baPWV) velocity and radial augmentation index (rAI) were measured. These parameters were measured again after a 3-year interval in 2135 subjects. Multivariate linear regression analysis demonstrated a significant cross-sectional association of the FIB-4 scores with the log-transformed the serum NT-pro-BNP levels (beta = 0.08, $p < 0.01$), but not with the baPWV or rAI. The change of serum NT-pro BNP levels during the study period was significantly higher in subjects with increase of the FIB-4 score during the study period (8.2 ± 22.5 pg/ml) than that in those with decrease/no change (5.4 ± 22.3 pg/ml) ($p < 0.05$).

Conclusion: Liver stiffness may have a significant direct association with the development of HF from the early stage, without the mediation of arterial stiffness and/or abnormal central hemodynamics. Therefore, the FIB-4 score appears to serve as a direct risk factor for HF from the early stage, and its association with HF may not be mediated by vascular damages.

1. Introduction

Heart failure (HF) is a heterogeneous condition with multiple pathophysiological bases in addition to intrinsic cardiac dysfunction, including vascular damage, renal dysfunction, neurohormonal factors, inflammation, oxidative stress, etc. [1]. The reduced liver blood flow and hepatic congestion associated with HF causes liver damage leading to liver sclerosis. On the other hand, the occurrence of such liver damage is thought to affect the prognosis of patients with HF [2–5]. Furthermore, it has been reported that in subjects without manifest cardiovascular disease, fibrosis 4 score (FIB-4 score), a marker of liver sclerosis, which can be simply calculated from the age, serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels, and blood platelet count (PLT), may serve as a predictor of the onset of HF [6]. Liver stiffness, such as that caused by non-alcoholic fatty liver disease, etc., is known to be associated with the progression of vascular damage, including arterial stiffening [7,8]. Such vascular damage may contribute to the new onset of HF via inducing cardiac ischemia and/or increasing the cardiac afterload [9,10], and also increase the risk of future cardiovascular (CV) events. However, it has not yet been clarified whether liver stiffness is a direct risk factor for the development of HF or the association of liver stiffness with HF is also mediated by vascular damage, similar to its association with other CV disorders.

Natriuretic peptide is released from the heart muscle, and its blood level is a marker of not only HF, but also CV events [11,12]. In our previous observational study, we demonstrated an association of the serum NT-pro-BNP levels with the markers of vascular damage (i.e., arterial stiffness and markers of central hemodynamics) [13]. We conducted the present prospective longitudinal and cross-sectional observational studies to examine whether the FIB-4 score was directly associated with the serum NT-pro-BNP levels or whether the association was

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mediated by arterial stiffness and/or abnormal central hemodynamics in subjects probably without apparent HF (i.e., serum NT-pro-BNP levels < 125 pg/ml) [14, 15].

2. Methods

The data of the present study, analytic methods, and study materials are not available to other researchers. Hirofumi Tomiyama has the right to query any aspect of the data directly, has full access to all the data in the study, and takes responsibility for the integrity of the data and the data analysis.

2.1. Study subjects

Fig. 1 shows the flow chart of the participant selection procedure. The present cross-sectional and longitudinal studies were conducted in a worksite cohort composed of the employees of a construction company located in downtown Tokyo (including the company headquarters and branch offices located in Tokyo). In Japan, all company employees are mandated by law to undergo annual health checkups. The study protocol has already been described in detail elsewhere [13, 16]. The annual health checkup examinations conducted in the mornings in fasting subjects included physical examination, blood pressure measurement (2 times) with the subject in the seated position, blood and urine examinations, electrocardiography, chest roentgenography, barium swallow, audiometry, vision testing, and measurements of the brachial-ankle PWV and radial augmentation index (AI).

In 2009 (the first examination) and 2012 (the second examination), in addition to these examinations, the serum NT-pro BNP levels were also measured in all of the study subjects. Informed consent was obtained from all the study participants prior to their enrollment in the study. The study was conducted in compliance with the Declaration of Helsinki and with the approval of the Ethical Guidelines Committee of the Tokyo Medical University. The follow-up protocol is described in detail elsewhere. In 2009 (the first examination), 3276 employees at the company headquarters and branch offices located in Tokyo underwent annual medical examinations; 2305 of these participants were successfully followed up until 2012 (the second examination). However, of the initial 3276 participants, 236 were excluded from this study because of the following issues: In 2009 and/or 2012; presence of atrial fibrillation, ankle/brachial systolic blood pressure index of <0.95, standard deviation of the radial AI of ≥6%, and/or a history of treatment for liver disease, chronic kidney disease, heart disease or stroke; In 2009 alone (first examination), serum NT-pro-BNP levels ≥125 pg/ml. Finally, data in the remaining 3040subjects were included for the cross-sectional study and the data of the remaining 2135 subjects were included for the longitudinal study.

2.2. Measurements

2.2.1. Pulse wave velocity

The brachial-ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan), in accordance with a previously described method [17]. In brief, occlusion cuffs, which were connected to both plethysmographic and oscillometric sensors, were tied around both the upper arms and ankles of the subjects lying in the supine position. The brachial and post-tibial arterial pressures were measured using the oscillometric sensor. The measurements were conducted after the subjects had rested for at least 5 min in the supine position, in a temperature-controlled room (24°C -26°C) designed exclusively for this purpose.

2.2.2. Augmentation index

Measurements of the blood pressure and radial AI were conducted after the subjects had rested for at least 5 min in the sitting position. The blood pressure was measured in the right upper arm using the oscillometric method (HEM-907; Omron Healthcare Co., Ltd., Kyoto, Japan). Immediately after this measurement, the left radial arterial waveform was recorded using an arterial applanation tonometry probe equipped with an array of 40 micropiezo-resistive transducers (HEM-9010AI; Omron Healthcare Co., Ltd., Kyoto, Japan). The HEM-9010AI device is programmed to automatically determine the pressure of the radial artery to yield the optimal radial arterial waveform [18]. Then, the first and second peaks of the peripheral systolic pressure (SBP1, a marker of the brachial systolic blood pressure, and SBP2, a marker of the CSBP) and peripheral diastolic pressure (DBP) were automatically detected using the fourth derivatives for each radial arterial waveform and averaged. The radial AI, a marker of the central AI, was calculated as follows: (SBP2 − DBP)/(SBP1 − DBP) × 100 (%) [18]. Pulse pressure 1 (PP1) = SBP1–diastolic blood pressure, and PP2 = SBP2–diastolic blood pressure, a marker of the CPP, were also calculated [18].

2.2.3. Laboratory measurements

Fasting serum concentrations of triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, creatinine (Cr), AST and ALT, and the fasting plasma glucose (FPG) concentrations were measured using enzymatic methods, and the PLT was measured using

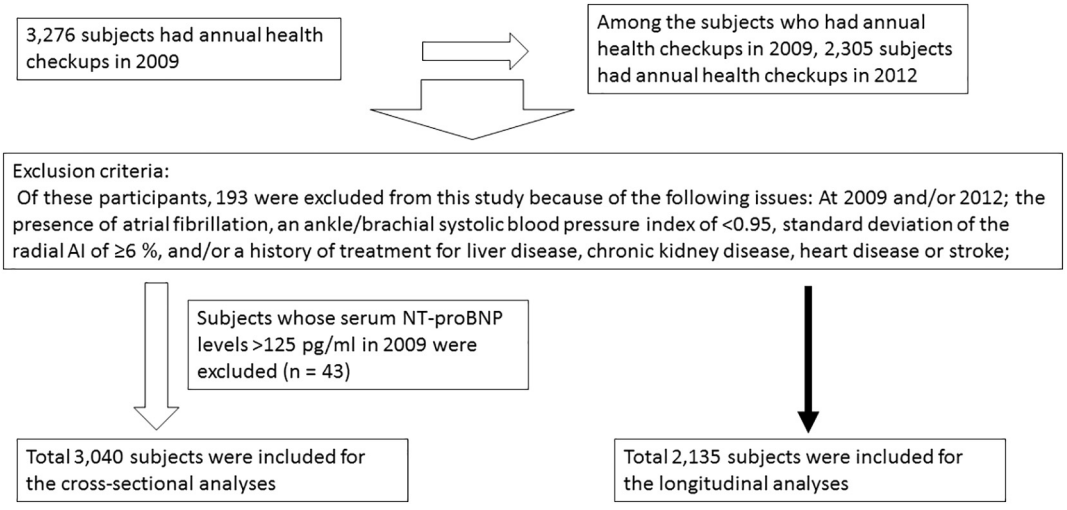

Fig. 1. Flow chart of the participant selection procedure.

Table 1
Clinical characteristics in study subjects at the first examination.

Parameter	
Number	3040
Age (y)	45 ± 9
Men/women (%)	2589/451 (85/15)
BMI (kg/m^2)	23.6 ± 3.2
Alcohol drinking (current), No. (%)	2562 (84)
Alcohol intake, ethanol g/day	9.8 ± 7.1
Smoking (current), No. (%)	781 (26)
SBP (mm Hg)	121 ± 15
DBP (mm Hg)	75 ± 11
Pulse rate (bpm)	69 ± 10
Hb (g/L)	146 ± 13
PLT (10^9/L)	232 ± 49
AST (U/L)	22.9 ± 9
ALT (U/L)	25.3 ± 18
TC (mmol/L)	5.4 ± 0.9
HDL(mmol/L)	1.7 ± 0.5
TG (mmol/L)	1.4 ± 1.2
FPG (mmol/L)	5.0 ± 0.7
Serum creatinine (μmol/L)	73 ± 12
NT- pro BNP (pg/ml)	27 ± 22
baPWV (cm/s)	1284 ± 197
rAI (%)	72 ± 14
SBP2 (mm Hg)	108 ± 16
PP2 (mm Hg)	33 ± 9
FIB4	0.98 ± 0.4
Medication history	
Hypertension: number of subjects (%)	290 (10)
Dyslipidemia: number of subjects (%)	106 (4)
Diabetes mellitus: number of subjects (%)	74 (2)

Abbreviations: BMI = body mass index; Alcohol drinking (current), No. = number of current drinking alcohol; Daily alcohol intake = ethanol intake volume per day; Smoking (current), No. = number of current smokers; SBP = systolic blood pressure; DBP = diastolic blood pressure; Hb = hemoglobin; PLT = Platelet; AST = aspartate aminotransferase; ALT = alanine aminotransferase; TC = serum total cholesterol; HDL = serum high density lipoprotein cholesterol; TG = serum triglycerides; FPG = fasting plasma glucose; NT-proBNP = serum N-terminal fragment of B-type natriuretic peptide; baPWV = brachial-ankle pulse wave velocity; rAI = radial augmentation index; SBP2 = second peak of the radial pressure waveform; PP2 = second peak of the radial pressure waveform – diastolic blood pressure; Medication history = number and percentage of subjects receiving medication(s).

the sheath flow method (Falco Biosystems Co., Ltd., Tokyo, Japan). Serum NT-proBNP levels were determined using a chemiluminescence immunoassay kit (Roche Diagnostics, Mannheim, Germany). All blood samples were obtained in the morning after the participants had fasted overnight. The FIB-4 score was calculated using the following formula: age ([yr] × AST [U/L])/(PLT [10^9/L]) × (ALT [U/L])$^{1/2}$) [19].

2.3. Statistical analysis

Data were expressed as means ± SD (the adjusted values obtained by a general linear model [GLM] analyses were expressed as means ± SE). The differences in the variables between the first and second examinations were assessed by paired *t*-tests or McNemar's non-parametric test. The delta changes of the variables during the study period were calculated as the values obtained at the second examination minus the values obtained at the first examination. For assessment of the differences in the status of each variable between the groups, post hoc comparison in a GML analysis was applied.

Since the serum NT-pro BNP levels were skewed rightward, log-transformation of the values was conducted for the analyses. The relationships among the variables were assessed by Pearson's correlation analysis and multivariate linear regression analysis with adjustments. Concerning the adjustments, the covariates used were the age, gender, body mass index, current smoking status, alcohol intake, heart rate, systolic blood pressure, TC, HDL, TG, Creatinine, FBG, and hemoglobin. In addition, "receiving medication" was also used as a covariate (i.e., receiving/not receiving medication for hypertension, dyslipidemia or diabetes mellitus was scored as follows: "receiving medication" = 1, and "not receiving medication" = 0, for each medication). All of the analyses were conducted using the IBM/SPSS software for Windows, version 24.0 J (IBM/SPSS Inc., Chicago, IL); $p < 0.05$ was considered as denoting statistical significance.

3. Results

Table 1 shows the clinical characteristics of study subjects at the first examination. Among the clinical variables, FIB-4 was significant correlated with age, current smoking status, heart rate, TC, HDL and gender, but not with systolic blood pressure, body mass index, serum creatinine, FBG, hemoglobin, alcohol intake and TG (Table 2). As shown in Table 2, analysis by calculation of Pearson's correlation coefficients revealed that FIB-4 score at the baseline was significantly correlated with the radial AI, SP2, PP2, baPWV, and log-transformed values of the serum NT-proBNP levels at the first examination. However, multivariate linear regression analysis conducted with adjustments identified the FIB-4 score as being significantly positively associated with the log-transformed

Table 2
Results of Pearson's correlation analysis and multivariate linear regression analysis performed to assess the association of the FIB-4 score with cardiovascular variables and clinical variables at the first examination.

Outcome variables	Pearson's correlation analysis		Multivariate linear regression			
	Correlation coefficient	*p*-Value	Total R-square	Standardized coefficient	Non-standardized coefficient (95% CI)	*p*-Value
LogBNP	0.23	<0.01	0.25	0.08	0.15 (0.08–0.22)	<0.01
baPWV	0.27	<0.01	0.59	0.03×10^{-1}	1.21 (−11.6–14.0)	0.85
rAI	0.23	<0.01	0.49	−0.06	−1.69 (−2.67 to −0.70)	<0.01
SBP2	0.23	<0.01	0.90	−0.02	−0.81 (−1.34 to −0.28)	<0.01
PP2	0.24	<0.01	0.67	−0.04	−1.24 (−1.28 to −0.25)	<0.01
SBP	0.16	<0.01	0.57	-0.02×10^{-1}	−0.08 (−1.36–1.19)	0.90
HR	−0.05	0.02	0.31	−0.09	−1.98 (−2.90 to −1.01)	<0.01
BMI	−0.05	<0.01	0.61	−0.02	−0.17 (−0.43–0.09)	0.21
Smoking (current)	−0.08	<0.01	0.32	−0.06	−0.06 (−0.10 to −0.02)	<0.01
TC	0.04	0.03	0.49	−0.15	−0.29 (−0.37 to −0.21)	<0.01
HDL	0.16	<0.01	0.65	0.17	0.17 (0.14–0.21)	<0.01
TG	−0.01	0.64	–	–	–	–
Serum creatinine	0.05	<0.01	0.63	0.01	0.36 (−0.54–1.27)	0.43
FBG	0.12	<0.01	0.39	−0.03	−0.05 (−0.12–0.01)	0.11
Gender	0.05	<0.01	0.57	0.02	0.02 (−0.01–0.04)	<0.01
Alcohol intake	−0.02	0.23	–	–	–	–
Hb	−0.06	<0.01	0.68	0.04×10^{-1}	0.01 (−0.09–0.11)	0.83
Age	0.57	<0.01	0.47	0.51	10.5 (9.9–11.0)	<0.01

Abbreviations: logBNP = log-transformed serum NT-proBNP levels; CI = confidence interval; other abbreviations are as described in the footnote for Table 1.

Table 3
Association of the FIB-4 score with the log-transformed values of the serum NT-proBNP levels by gender and by age.

	Outcome variables	Pearson's correlation analysis		Multivariate linear regression			
		Correlation coefficient	*p*-Value	Total R-square	Standardized coefficient	Non-standardized coefficient (95% CI)	*p*-Value
Men	Log BNP	0.28	<0.01	0.16	0.08	3.56 (1.60–5.50)	<0.01
Women	Log BNP	0.10	0.04	0.11	−0.04	−0.09 (−0.32–0.14)	0.46
Young age	Log BNP	0.12	<0.01	0.27	0.07	0.22 (0.05–0.39)	0.01
Elderly age	Log BNP	0.20	<0.01	0.24	0.10	0.19 (0.07–0.32)	<0.01

Abbreviations are as described in the footnote for Tables 1 and 2.

values of the serum NT-proBNP levels, but not with the radial AI, SP2, PP2 or baPWV, at the first examination.

Multivariate linear regression analysis with adjustments demonstrated that the association of the FIB-4 score with the log-transformed values of the serum NT-proBNP levels was significant in male subjects ($n = 2589$) On the other hand, the number of female subjects was relatively small ($n = 451$), and the significance of their association was not observed When subjects were divided into two groups by median of age (43 years old) (i.e., young and elderly), multivariate linear regression analysis with adjustments demonstrated that the association of the FIB-4 score with the log-transformed values of the serum NT-proBNP levels was significant in both groups. (Table 3).

As shown in Table 4, significantly higher values of the FIB-4 score, PP2, radial AI, baPWV, and serum NT-proBNP level were observed at the second examination as compared with the values recorded at the first examination. Change of the FIB-4 score during the study period was significantly associated with the change of the serum NT-pro BNP levels during the study period (Standard coefficient = 0.09, Non-standard coefficient = 1.02, 95% confidential intervals = 0.51–1.53, $p < 0.01$), but not with that of the radial AI, SP2, PP2 or baPWV, even after adjustments for changes in the values of the covariates during the study period (Table 5). When subjects were divided into two groups by the direction of change of the FIB-4 score during the study period {i.e., increase [FIB-4inc] ($n = 1497$) or decrease/no change [FIB-4dec] ($n = 638$)}, the change of the serum NT-pro BNP level during the study period was significantly higher in the FIB4inc group than in the FIB4dec group (Fig. 2A). This difference was observed in both genders (Fig. 2B,C).

Table 4
Clinical characteristics and changes in clinical parameters during the study period.

Parameter	First examination	Second examination
Number	2135	2135
Age (y)	44 ± 8	47 ± 8
Men/women (%)	1810/325(85/15)	
BMI (kg/m^2)	23.6 ± 3.2	23.8 ± 3.2*
Alcohol drinking (current), No. (%)	1793 (84)	1783 (84)
Alcohol intake, ethanol g/day	9.8 ± 7.0	17.1 ± 17.1*
Smoking, (current), No. (%)	536 (25)	457 (21)*
SBP (mm Hg)	120 ± 15	119 ± 15*
DBP (mm Hg)	75 ± 11	72 ± 11
Pulse rate (bpm)	69 ± 9	68 ± 9*
Hb (g/L)	146 ± 13	144 ± 12*
Plt (10^9/L)	232 ± 48	230 ± 48*
AST (U/L)	22.9 ± 9	23.4 ± 10*
ALT (U/L)	25.3 ± 18	23.4 ± 10*
TC (mmol/L)	5.4 ± 0.9	5.4 ± 0.9*
HDL (mmol/L)	1.7 ± 0.5	1.7 ± 0.4*
TG (mmol/L)	1.4 ± 1.3	1.3 ± 1.0*
FPG (mmol/L)	5.0 ± 0.7	5.0 ± 0.7*
Serum creatinine (μmol/L)	72.9 ± 11	71 ± 12*
NT- pro BNP (pg/ml)	26 ± 22	34 ± 27*
baPWV (cm/s)	1268 ± 184	1293 ± 202*
rAI (%)	71 ± 14	73 ± 13*
SBP2, (mm Hg)	107 ± 15	106 ± 15*
PP2, (mm Hg)	32 ± 8	34 ± 9*
FIB4	0.96 ± 0.4	1.0 ± 0.4*
Medication history		
Hypertension: number of subjects (%)	174 (8)	259 (12)*
Dyslipidemia: number of subjects (%)	65 (3)	118 (6)*
Diabetes mellitus: number of subjects (%)	50 (2)	72 (3)*

Abbreviations: * = $p < 0.01$ vs. first examination; other abbreviations are as described in the footnote for the Table 1.

4. Discussion

The present study is the first prospective observational study conducted to examine the cross-sectional and longitudinal associations of the FIB-4 score, a marker of liver sclerosis and the serum NT-pro-BNP levels, arterial stiffness and markers of central hemodynamics in subjects without apparent HF. The results revealed that the FIB-4 score was associated with the serum NT-pro-BNP levels, but not with the arterial stiffness or markers of central hemodynamics. In addition, the changes of the FIB-4 score during the study period were associated with those of the serum NT-pro-BNP levels.

Abnormal central hemodynamics and cardiac ischemia are key factors underlying elevation of the serum NT-pro-BNP levels [9,10]. Increase of the arterial stiffness and abnormal central hemodynamics, as assessed by the SP2/PP2, contribute to increase of the cardiac afterload [9,10]. Increase of the arterial stiffness also causes impaired coronary perfusion via decrease of the diastolic blood pressure. Several prospective studies have demonstrated that arterial stiffness and abnormal central hemodynamics are predictors of the onset of HF [20,21]. Furthermore, we previously reported a significant association of the serum NT-pro-BNP levels with the arterial stiffness and abnormal central hemodynamics in this same study cohort [13]. Several studies have already reported a significant association of liver sclerosis, especially in non-alcoholic fatty liver disease, with carotid atherosclerosis and arterial stiffness [7,8]. Vascular damage and abnormal central hemodynamics are known to be risk factors for future CV events. However, no study has examined the association of the FIB-4 score with the arterial stiffness and/or central hemodynamics. In the present study, no significant association of the FIB-4 score with the arterial stiffness/abnormal central hemodynamics could be confirmed; therefore, we concluded that the association of the FIB-4 score with the serum NT-pro-BNP levels was not mediated by arterial stiffness/abnormal central hemodynamics.

Hypertension is a major risk factor for HF [1], and high blood pressure has been reported to be associated with elevated serum NT-pro-BNP levels [9,10]. A recent experimental study has reported that elevated blood pressure is a determinant of liver stiffness [22]. In this study, even after adjustment for the blood pressure, the FIB-4 score showed a significant association with the serum NT-pro-BNP levels.

Liver dysfunction and cardiac dysfunction are thought to have a mutual interaction [2,3]. The reduced liver blood flow and hepatic congestion caused by cardiac dysfunction may provoke liver damage. Liver dysfunction also causes cardiac dysfunction via several mechanisms, such as abnormalities of the autonomic nervous system, plasma membrane fluidity, membrane calcium channels and/or neurohormonal factors [2]. In addition, liver stiffness may affect the cardiac preload abnormality associated with the splanchnic vasculature [3]. Regardless, abnormalities of the cardiac function and/or cardiac preload, both of which are related to liver stiffness, may affect the serum NT-pro-BNP

Table 5
Association of the FIB-4 score with the changes of the serum NT-BNP levels during the study period.

Explained variable	Outcome variables	Pearson's correlation analysis		Multivariate linear regression			*p*-Value
		Correlation coefficient	*p*-Value	Total R-square	Standardized coefficient	Non-standardized coefficient (95% CI)	
FIB41st	deltaNT-proBNP	-0.02×10^{-1}	0.92	0.05	0.03×10^{-1}	0.26 (−3.06–3.58)	0.88
deltaFIB4	deltaNT-proBNP	0.09	<0.01	0.06	0.09	1.02 (0.51–1.53)	<0.01

Abbreviations: FIB41st = FIB4 score at the first examination; deltaNT-proBNP = delta changes of serum NT-proBNP levels from the first to second examination (i.e., serum NT-proBNP levels at the second examination – serum NT-proBNP levels at the first examination); delta FIB4 = delta changes of FIB4 score from the first to second examination (i.e., FIB4 score at the second examination – FIB4 score at the first examination).

levels even from the early stage. In the present study, the FIB-4 score was directly associated with the serum NT-pro-BNP levels in the cross-sectional assessment, and a significant longitudinal association was also observed between the two. The present study was conducted in subjects with serum NT-pro-BNP levels < 125 pg/ml, which was considered to exclude subjects with HF who needed treatment [14,15]. This may mean that subjects with HF causing liver sclerosis were excluded from the analyses. Therefore, the findings of present study suggest that, between the early stages of liver sclerosis and cardiac dysfunction, the elevated serum NT-pro-BNP levels reflected cardiac dysfunction associated with liver stiffness rather that liver stiffness associated with cardiac dysfunction.

4.1. Clinical perspectives

The significance of liver abnormalities in the early stages of HF remains unclear. The present study findings suggest that liver stiffness is a risk factor for the development of HF. Further study is needed to examine whether the FIB-4 score can be used as an additional tool for natriuretic peptide-based screening and prevention of HF.

4.2. Study limitation

The present study had some limitations, as follows: 1) While other non-invasive markers are available for the assessment of liver sclerosis (e.g. transient elastography) [23], cardiac dysfunction (echocardiography) and atherosclerosis (carotid ultrasound examination), in the present study, we did not assess the association of liver stiffness with cardiac dysfunction/atherosclerosis using these other markers; 2) The present study was conducted in healthy Japanese subjects; therefore, further study is needed to examine the association in other ethnicities in the association; 3) Further studies are needed to clarify whether, in the early stages of liver dysfunction and cardiac dysfunction, liver disease and cardiac dysfunction have a bidirectional association or one-way causal association or confounders; 4) Some of the present study subjects were temporary employees, changed jobs or retired during the study period therefore, the follow-up rate was only 70%; 5) In the present study, the subjects with a history of treatment for liver disease were confirmed by questionnaire. However, the present study could not confirm the subjects with viral hepatitis by blood examination or those with fatty liver disease by abdominal ultrasound examination;

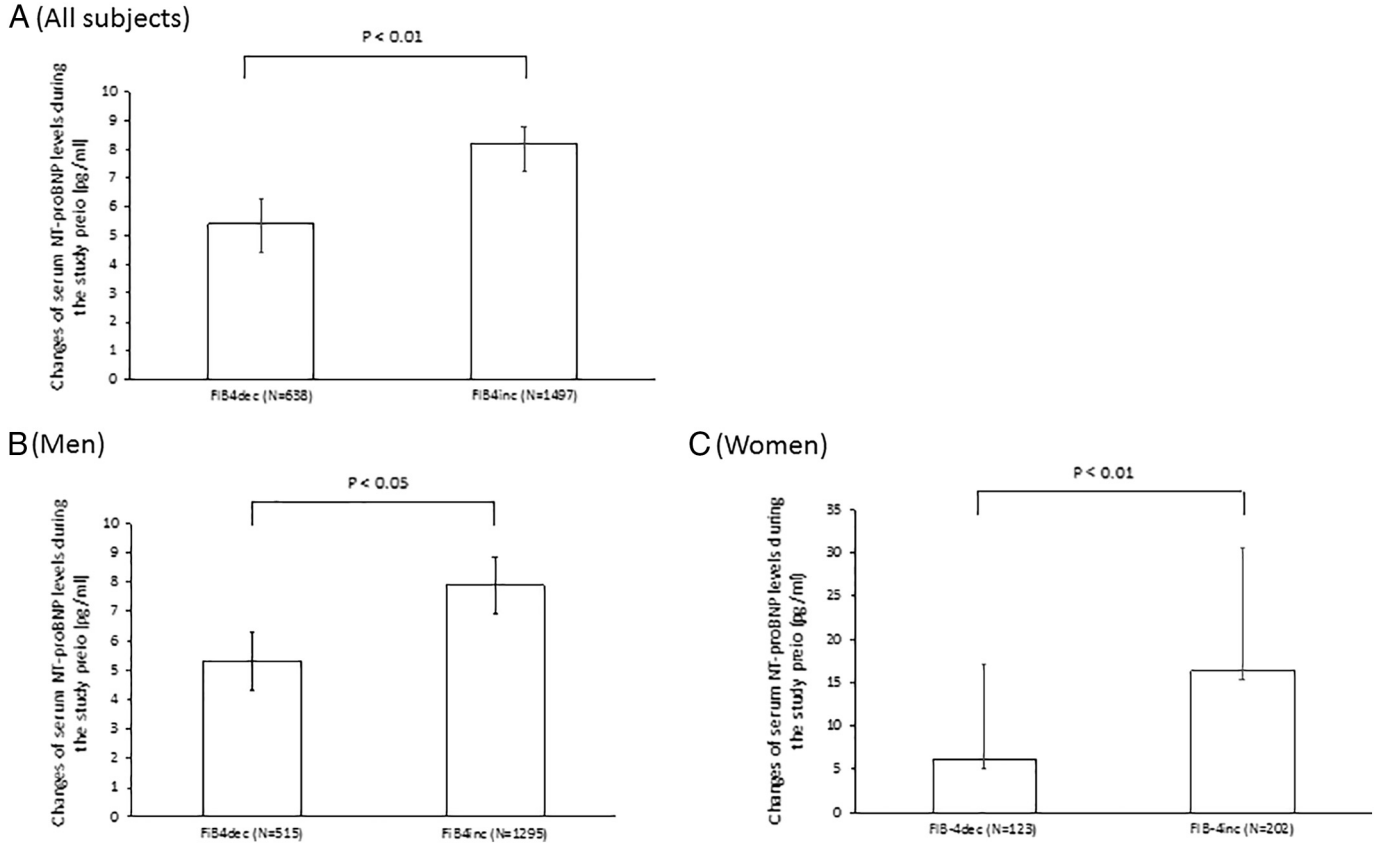

Fig. 2. Changes of the serum NT-pro BNP levels during the study period in the FIB4inc and FIB4dec groups in all subjects, in men and in women. Abbreviations: FIB4inc group = subjects with increase of the FIB-4 score during the study period; FIB4dec group = subjects with decrease/no change of the FIB-4 score during the study period.

6) Renal dysfunction is one of crucial factors for the progression of heart failure (i.e., cardiorenal syndrome). [24] In the present study, while serum creatine levels had no significant association with FIB-4 (Table 2), as a next logical step, the interaction between liver stiffness and renal dysfunction in the development of HF might be needed to be clarified; 7) Because the number of women was relatively small, the association of FIB4 with log-transformed serum NT-proBNP levels was not significant in women after the adjustment of covariates. However, even in women, the change of the serum NT-pro BNP level during the study period was significantly higher in the FIB4inc group than in the FIB4dec group (Fig. 2). Therefore, further study with increase the number of women is needed to confirm the significance of the association of FIB4 with serum NT-proBNP levels in women.

5. Conclusion

In subjects without apparent HF, the FIB-4 score was associated with the serum NT-pro-BNP levels, but not with the baPWV or markers of central hemodynamics. Thus, liver stiffness may show a significant direct association HF from the early stage, and the association may not be mediated by arterial stiffness and/or abnormal central hemodynamics. Therefore, the FIB-4 score may serve as a risk factor for HF from the early stage, and its association with HF may not be mediated by vascular damage.

Disclosure

The sponsor (Omron Health Care Company) assisted in the data formatting (i.e., the data of the brachial-ankle pulse wave velocity stored in the hard disc of the equipment used for measurement of the brachial-ankle pulse wave velocity was transferred to an Excel sheet). Other than this, however, the company played no role in the design or conduct of the study, that is, in the data collection, management, analysis or interpretation of the data, or in the preparation, review or approval of the manuscript. Other authors have no disclosures to make.

Conflicts of interest

Omron Health Care Company (Kyoto, Japan) and Asahi Calpis Wellness Company (Tokyo, Japan).

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