Fatty Liver is Associated with Low N-terminal pro-B-type Natriuretic Peptide in a Healthy Population: From the Kangbuk Samsung Health Study

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Abstract

Background

Fatty liver (FL), insulin resistance (IR), and obesity often coexist, but data on the independent impacts of these factors on N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels in healthy populations are scarce. We therefore examined the impact of FL, IR and obesity on NT-proBNP levels using a large set of cross-sectional data.

Methods

The associations of FL, IR and obesity with NT-proBNP were analyzed in 39,923 healthy adult participants using Kangbuk Samsung Health Study data. IR was estimated using homeostasis model assessment-estimated insulin resistance (HOMA-IR) index. A multivariable regression model that adjusted for factors that influence NT-proBNP was conducted to identify associations between NT-proBNP and FL on abdominal ultrasound.

Results

A total of 11,704 (29.3%) individuals had FL on abdominal ultrasound. FL, IR and obesity showed independent inverse associations with NT-proBNP after multiple adjustments for baseline characteristics. In a multivariable regression model adjusting for IR and obesity, FL was independently associated with lower levels of NT-proBNP (odds ratio 0.864, 0.849 - 0.880). The combination of FL and IR was a powerful dual predictor, lowering NT-proBNP levels approximately 25% in the generally healthy study population.

Conclusion

In this large sample of healthy individuals, FL was independently associated with lower NT-proBNP levels. FL and a high HOMA-IR index are a powerful predictor combination for lower NT-proBNP levels. Further research is needed to elucidate the mechanism underlying the association between FL and NT-proBNP.

Background

Levels of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) help to distinguish cardiac causes of dyspnea and are also useful in the prediction of prognosis and monitoring the treatment efficacy in patients with heart failure (1). In particular, the addition of NT-proBNP measurements to traditional risk assessment in individuals without cardiovascular disease (CVD) can increase the accuracy of the prediction of future CVD or cardiovascular events.

Novel metabolic functions of NPs, including lipolysis activation, lipid oxidation and mitochondrial respiration (2), have been identified in recent years. NPs can also ameliorate lipid-induced insulin resistance (IR) through improvements in hepatic (3) and muscular (4) lipid oxidation. These actions combine to enhance the browning and oxidative potential of white adipose tissue and protect individuals

against obesity and IR. Additionally, some data suggest that circulating glucose and insulin alter NP levels. In one study of obese subjects, hyperinsulinemia significantly reduced levels of NP by increasing the expression of the NP-clearance receptor in subcutaneous fat tissue (5). Based on previous observations, hyperglycemia and hyperinsulinemia may be the mechanisms underlying NP deficiency in obesity and diabetes.

Fatty liver (FL) is common in patients with obesity or IR. Both obesity and IR are associated with lower levels of NT-proBNP. Some studies have demonstrated that FL is associated with low NT-proBNP (6-8). Whether an IR or obesity-specific factor decreases NT-proBNP levels in FL populations or whether common pathological mechanisms exist in FL and IR/obesity which decrease NT-proBNP levels is currently uncertain. The availability of routine plasma NT-proBNP measurements and abdominal ultrasound (US) on >30,000 young individuals in the Kangbuk Samsung Health Study allows for a comprehensive investigation of the association of these variables and NT-proBNP levels. Therefore, we investigated associations of FL, IR and obesity with NT-proBNP levels in a large, relatively young, healthy and well-characterized occupational cohort.

Methods

Study population

Our study population (n = 44,066) consisted of individuals involved in a comprehensive health screening program that included NT-proBNP level measurement and abdominal US at Kangbuk Samsung Hospital, Seoul, Korea, from 2016 to 2018. The screening program aimed to promote health through early detection of chronic diseases and their risk factors. Additionally, the Korean Industrial Safety and Health Law requires employees to participate in an annual or biennial health examination. To minimize the effect of disease or medication on NT-proBNP levels, we excluded 4,143 subjects due to: hypertension (n = 2,180), coronary disease (n = 140), diabetes (n = 821), history of cancer (n = 1,285), NT-proBNP > 18,000 (n = 3) and missing information (n = 193). Some participants met multiple conditions of exclusion, and 39,923 participants were included in the final study.

Measurements

Data on demographic variables, health behaviors, educational background, past medical history and family history of CVD were collected using standardized, self-administered questionnaires (9). Anthropometric measurements and vital statistics were obtained by professional staff. The questionnaire asked about the frequency of alcohol consumption and the amount of alcohol consumed per consumption day recorded in standard units (10).

Following a minimum of 10 h of fasting, blood samples were obtained and analyzed in a single clinical core laboratory. The core clinical laboratory is certified by the Korean Association of Quality Assurance for Clinical Laboratories. Serum levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol

(LDL-C) and high-density lipoprotein cholesterol (HDL-C) were measured using Bayer Reagent Packs (Bayer Diagnostics, Leverkusen, Germany) on an automated chemistry analyzer (Advia 1650 Autoanalyzer; Bayer Diagnostics). Serum NT-proBNP levels were determined using an automated immunoassay analyzer (cobas e411; Roche Diagnostics, Tokyo, Japan). The inter-assay coefficients of variation for quality control specimens of lower levels and higher levels were 1.20–5.37% and 2.28–4.33%, respectively, during the study period.

The diagnosis of FL was based on abdominal US operated by experienced radiologists who were blinded to the aim of the present study. Ultrasonographic diagnosis of FL was determined based on standard criteria, including a diffuse increase of fine echoes in the liver parenchyma compared with kidney or spleen parenchyma, deep beam attenuation and bright vessel walls (11). The HOMA-IR was calculated as fasting insulin (mg/dL) x fasting glucose (mg/dL)/405. Individuals with HOMA-IR in the top quartile were considered to have IR (12). Obesity was defined as BMI ≥25 kg/m^2 in this Asian population.

Statistical analysis

Data are expressed as means [standard deviation (SD)] or as median (interquartile ranges) for continuous variables. Categorical data are expressed as numbers and percentages. Baseline variables were compared using Student's t-test, Wilcoxon rank-sum test or chi-square test as appropriate. Skewed variables were transformed into $\log_2$ to facilitate interpretation. Regression analyses were repeated using generalized linear models to accommodate variables (FL, HOMA-IR index and BMI) with $\log_2$-transformed NT-proBNP, using non-FL and low HOMA-IR index as the reference. Multivariate model 1 was adjusted for age, sex, waist circumference, systolic blood pressure, smoking status, physical activity, alcohol consumption, educational level and estimated glomerular filtration rate. To assess whether the association between FL and NT-proBNP level is mediated by IR, model 2 was adjusted for the variables in model 1 and BMI and HOMA-IR index. Reported p values were two-tailed, and < 0.05 was considered statistically significant. All statistical analyses were conducted using STATA version 16.1 (StataCorp LP, College Station, TX, USA).

Ethical considerations

This study was approved by the Institutional Review Board of Kangbuk Samsung Hospital, which exempted the requirement for informed consent because only retrospectively accessed de-identified data were utilized.

Results

A total of 39,923 individuals were included in the final analysis. Mean age of the population was 39.1 and 57.6% were male. 11,704 (29.3%) individuals had FL on abdominal US. Baseline characteristics according to the presence of FL are described in **Table 1**. Individuals with FL were older, were more likely to be

obese, consumed more alcohol and had higher LDL-cholesterol levels than the non-FL group. The non-FL group was associated with health-enhancing physical activity (HEPA) and better renal function. Liver enzymes were slightly higher in the FL group. The FL group showed a higher median HOMA-IR index (2.0 and 1.2 for the FL group and non-FL group, respectively). NT-proBNP level was significantly lower in the FL group (14.5 ng/dL for the FL group vs. 24.4 ng/dL for the non-fatty liver group).

Table 1
Baseline characteristics according to fatty liver on abdominal ultrasound

	Total	Fatty liver	No fatty liver	p value
Number	39,923	11,704	28,216	
Age	39.1±7.6	40.6±7.5	38.4±7.6	<0.001
IPAQ %				<0.001
Sedentary	19493 (48.83)	5602 (47.86)	13891 (49.23)	
Mild	14288 (35.79)	4500 (38.45)	9788 (34.69)	
HEPA	5998 (15.03)	1559 (13.32)	4439 (15.73)	
Unknown	141 (0.35)	43 (0.37)	98 (0.35)	
Current smoker, %	4814 (12.06)	2164 (18.49)	2650 (9.39)	<0.001
Alcohol intake (g/day)	4(1-13)	6(2-15)	4(1-11)	<0.001
High alcohol intake, %	3964 (10.58)	1394 (12.48)	2570 (9.78)	<0.001
BMI, kg/m^2	23.4±3.4	26.3±3.1	22.3±2.7	<0.001
Waist, cm	81.1±9.8	89.6±8	77.6±8.3	<0.001
Weight, kg	67±13.3	77.6±11.7	62.6±11.3	<0.001
Higher education, %	33449 (83.79)	9905 (84.63)	23544 (83.44)	0.012
SBP, mmHg	109±12.1	115.4±11.4	106.4±11.3	<0.001
DBP, mmHg	69.9±9.4	74.6±9.1	67.9±8.8	<0.001
Fasting glucose, mg/dl	93.7±10.9	98±13.9	92±8.7	<0.001
Total cholesterol, mg/dl	190.5±33.1	201.6±34.6	185.9±31.2	<0.001
LDL-C, mg/dl	127.1±32.1	140.9±32.3	121.4±30.3	<0.001
HDL-C, mg/dl	61.2±16.6	50.4±12.2	65.7±16.1	<0.001
Triglycerides, mg/dl	91(65-135)	140(101-197)	78(59-108)	<0.001
AST, IU/L	20 (16-24)	23 (19-30)	19 (16-22)	<0.001
ALT, IU/L	19 (13-28)	30 (21-45)	16 (12-22)	<0.001
rGTP, IU/L	20 (14-34)	34 (23-54)	17 (12-25)	<0.001
NT-proBNP	20.76(12.79-35.8)	14.5(8.99-23.5)	24.4(14.5-40.4)	<0.001
eGFR	104.1±13.2	101.1±13	105.3±13	<0.001
HOMA-IR	1.38(0.93-2.04)	2.03(1.41-2.92)	1.19(0.82-1.7)	<0.001

Numbers in the table are mean (standard deviation), median (interquartile range), or percentages.

ALT= alanine aminotransferase; AST= aspartate aminotransferase; BMI=body mass index; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; HDL-C=high-density lipoprotein cholesterol; HEPA=health enhancing physical activity; HOMA-IR= homeostasis model assessment-estimated insulin resistance; IPAQ= international physical activity questionnaire; LDL-C=low-density lipoprotein cholesterol; NT-proBNP=N-terminal pro-B-type natriuretic peptide; rGTP=γ-glutamyl transpeptidase; SBP=systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.

To assess the association between IR and NT-proBNP levels, we divided the overall population into two groups according to quartiles of HOMA-IR index. Individuals with HOMA-IR in the top quartile were considered to have IR. 9,980 (25.0%) of individuals were categorized as having IR (**Table 2**). Individuals without IR were older than individuals with IR. Individuals with IR had higher liver enzyme levels, BMI, and blood cholesterol levels. NT-proBNP was significantly lower in the IR group (22.8 for the non-IR group vs. 15.5 for the IR group). Nearly 60% of individuals in the IR group had FL (19.7% for the low HOMA-IR group vs. 58.2% for the high HOMA-IR group).

Table 2
Baseline characteristics according to HOMA-IR index

	Total	HOMAIR<75%	HOMA IR>=75%	p value
HOMA-IR, range	0.04-30.93	0.04-2.03	2.03-30.93	
Number	39,923	29,943	9,980	
Age	39.1±7.6	39.1±7.6	38.8±7.6	<0.001
IPAQ %				<0.001
sedentary	19501 (48.83)	14289 (47.71)	5212 (52.2)	
Mild	14293 (35.79)	10725 (35.81)	3568 (35.74)	
HEPA	6001 (15.03)	4835 (16.14)	1166 (11.68)	
Unknown	141 (0.35)	103 (0.34)	38 (0.38)	
Current smoker, %	4817 (12.06)	3387 (11.31)	1430 (14.32)	<0.001
Alcohol intake (g/day)	4(1-13)	4(1-11)	5(1-14)	<0.001
High alcohol intake, %	3967 (10.59)	2888 (10.29)	1079 (11.48)	0.001
BMI, kg/m^2	23.4±3.4	22.6±2.9	25.9±3.7	<0.001
Waist, cm	81.1±9.8	78.9±8.7	88±9.9	<0.001
Weight, kg	67±13.3	64.2±11.8	75.3±14	<0.001
Higher education, %	33462 (83.79)	25348 (84.63)	8114 (81.27)	<0.001
SBP, mmHg	109±12.1	107.2±11.5	114.7±12	<0.001
DBP, mmHg	69.9±9.4	68.6±9	73.5±9.5	<0.001
Fasting glucose, mg/dl	93.7±10.9	91.5±8	100.3±14.9	<0.001
Total cholesterol, mg/dl	190.5±33.1	188.6±32.3	196.2±34.7	<0.001
LDL-C, mg/dl	127.1±32.1	124.8±31.6	134.1±32.7	<0.001
HDL-C, mg/dl	61.2±16.6	63.9±16.5	53.3±14.3	<0.001
Triglycerides, mg/dl	91(65-135)	82(60-115)	134(94-193)	<0.001
AST, IU/L	20 (16-24)	19 (16-23)	22 (17-28)	<0.001
ALT, IU/L	19 (13-28)	17 (13-25)	27 (17-42)	<0.001
rGTP, IU/L	20 (14-34)	18 (13-29)	31 (19-52)	<0.001
NT-proBNP	20.77(12.79-35.8)	22.8(14.3-38.7)	15.5(9.82-26.86)	<0.001
eGFR	104.1±13.2	104.2±13	103.6±13.5	<0.001

Fatty liver, %	11,704 (29.3)	5,896 (19.7)	5,808 (58.2)	<0.001

Numbers in the table are mean (standard deviation), median (interquartile range), or percentages.

ALT= alanine aminotransferase; AST= aspartate aminotransferase; BMI=body mass index; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; HDL-C=high-density lipoprotein cholesterol; HEPA=health enhancing physical activity; HOMA-IR= homeostasis model assessment-estimated insulin resistance; IPAQ= international physical activity questionnaire; LDL-C=low-density lipoprotein cholesterol; NT-proBNP=N-terminal pro-B-type natriuretic peptide; rGTP=γ-glutamyl transpeptidase; SBP=systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.

When stratified by sex (**Table 3**), males were older; more likely to be obese; consumed more alcohol; and had higher blood pressure, glucose, cholesterol levels than females. Males showed a higher HOMA-IR index (1.5 for males vs. 1.3 for females) and had FL more frequently (43.0% for males vs. 10.6% for females) compared to females. NT-proBNP level was significantly higher in females than males (14.6 vs. 32.8 for males and females, respectively).

Table 3
Baseline characteristics according to sex

	Total	Male	Female	p value
Number	39,923	23,009 (57.63)	16,914 (42.37)	
Age	39.1±7.6	39.5±7.5	38.4±7.7	<0.001
IPAQ %				<0.001
sedentary	19501 (48.83)	9626 (41.83)	9875 (58.35)	
Mild	14294 (35.79)	9373 (40.73)	4921 (29.08)	
HEPA	6001 (15.03)	3950 (17.16)	2051 (12.12)	
Unknown	141 (0.35)	64 (0.28)	77 (0.45)	
Current smoker, %	4817 (12.06)	4625 (20.1)	192 (1.13)	<0.001
Alcohol intake (g/day)	4 (1-13)	7 (3-19)	2 (0-6)	<0.001
High alcohol intake, %	3967 (10.59)	3138 (14.06)	829 (5.47)	<0.001
BMI, kg/m^2	23.4±3.4	24.7±3	21.7±3.1	<0.001
Waist, cm	81.1±9.8	86±8	74.6±8.2	<0.001
Weight, kg	67±13.3	74.8±10.4	56.3±8.7	<0.001
Higher education, %	33462 (83.79)	20298 (88.2)	13164 (77.78)	<0.001
SBP, mmHg	109±12.1	113.8±10.9	102.6±10.4	<0.001
DBP, mmHg	69.9±9.4	73.2±8.8	65.3±8.1	<0.001
Fasting glucose, mg/dl	93.7±10.9	95.7±11.2	91.1±9.8	<0.001
Total cholesterol, mg/dl	190.5±33.1	195.8±33.3	183.3±31.3	<0.001
LDL-C, mg/dl	127.1±32.1	135.1±31.5	116.2±29.7	<0.001
HDL-C, mg/dl	61.2±16.6	55±13.9	69.7±16.3	<0.001
Triglycerides, mg/dl	91 (65-135)	112 (79-162)	71 (55-97)	<0.001
AST, IU/L	20 (16-24)	22 (18-27)	17 (15-20)	<0.001
ALT, IU/L	19 (13-28)	24 (18-35)	13 (11-18)	<0.001
rGTP, IU/L	20 (14-34)	28 (20-45)	13 (11-18)	<0.001
BNP	20.77(12.79-35.8)	14.6 (9.43-23.38)	32.8 (21.3-50.3)	<0.001
EGFR	104.1±13.2	100.4±12.7	109.1±12.2	<0.001
HOMA IR(median(IQR))	1.38 (0.93-2.03)	1.49 (1-2.2)	1.25 (0.84-1.82)	<0.001

Fatty liver, %	11,704 (29.3)	9,904 (43.0)	1,800 (10.6)	<0.001

Numbers in the table are mean (standard deviation), median (interquartile range), or percentages.

ALT= alanine aminotransferase; AST= aspartate aminotransferase; BMI=body mass index; DBP=diastolic blood pressure; eGFR=estimated glomerular filtration rate; HDL-C=high-density lipoprotein cholesterol; HEPA=health enhancing physical activity; HOMA-IR= homeostasis model assessment-estimated insulin resistance; IPAQ= international physical activity questionnaire; LDL-C=low-density lipoprotein cholesterol; NT-proBNP=N-terminal pro-B-type natriuretic peptide; rGTP=γ-glutamyl transpeptidase; SBP=systolic blood pressure.

High alcohol intake defined as >30 g/day for men and >20 g/day for women; higher education defined as college graduate or higher.

We evaluated the effect of each variable (FL, HOMA-IR index and BMI) on NT-proBNP levels using multivariable regression analysis (**Table 4**). Models were adjusted for sex, age, waist circumference, systolic blood pressure, activity level, smoking status, alcohol intake, educational level and estimated glomerular filtration rate. In a multivariable model (model 1), FL was associated with lower levels of NT-proBNP in the overall population (odds ratio 0.83, 0.82 - 0.85), and this inverse association was weaker in males. Similarly, higher HOMA-IR index was associated with lower NT-proBNP levels after multivariable adjustment (OR 0.86, 0.84-0.87). Obesity (as defined by BMI ≥ 25) was also associated with lower NT-proBNP levels (OR 0.95, 0.93-0.97). These trends for inverse association were observed in both sexes with identical patterns (weaker in males). We also made a multivariable regression model that adjusted for HOMA-IR score and BMI (model 2) to assess the independent effect of FL on NT-proBNP level; FL still showed inverse association with NT-proBNP level (OR 0.86, 0.85-0.88) in this model.

Table 4
Association between fatty liver, HOMA-IR index and BMI with NT-proBNP

	Total	Male	Female
	(n=39,923)	(n=23,009)	(n=16,914)
Fatty liver			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.833 (0.819-0.848)	0.831 (0.814-0.848)	0.795 (0.765-0.826)
Fatty liver*			
No	1 (reference)	1 (reference)	1 (reference)
Yes	0.864 (0.849-0.880)	0.849 (0.816-0.884)	0.856 (0.839-0.874)
HOMA IR			
75%<	1 (reference)	1 (reference)	1 (reference)
75% ≥	0.859 (0.844-0.874)	0.859 (0.841-0.877)	0.844 (0.820-0.869)
BMI			
BMI <25	1 (reference)	1 (reference)	1 (reference)
BMI ≥25	0.951 (0.931-0.971)	0.939 (0.916-0.962)	0.939 (0.9-0.978)

The multivariate model was adjusted for age, sex, waist circumference, systolic blood pressure, vigorous exercise (≥5 times/wk), smoking status, daily alcohol consumption, estimated glomerular filtration rate, and education level.

* The multivariate model was adjusted for age, sex, body mass index, systolic blood pressure, vigorous exercise (≥5 times/wk), smoking status, daily alcohol consumption, estimated glomerular filtration rate, education level and homeostasis model assessment-estimated insulin resistance index.

We determined whether or not the presence of FL or high HOMA-IR score affects NT-proBNP levels (**Table 5, Figure 1**). Using NT-proBNP of the group both without FL and having low HOMA-IR score as reference, high HOMA-IR scores and FL were associated with low levels of NT-proBNP. Individuals with both FL and high HOMA-IR index were associated with 25% reduction in NT-proBNP levels as compared to NT-proBNP levels in individuals without both FL and IR.

Table 5
Association of NT-proBNP with fatty liver and HOMA-IR score, accounting for obesity

	Total	Male	Female
	(n=39,923)	(n=23,009)	(n=16,914)
Fatty liver*- high HOMA IR index**			
No-No	1 (reference)	1 (reference)	1 (reference)
No-Yes	0.888 (0.868-0.908)	0.900 (0.871-0.929)	0.869 (0.842-0.897)
Yes-No	0.856 (0.838-0.874)	0.854 (0.834-0.875)	0.825 (0.783-0.869)
Yes-Yes	0.755 (0.737-0.773)	0.752 (0.732-0.773)	0.712 (0.783-0.869)
P for trend	<0.001	<0.001	<0.001

*Yes→ Presence of fatty liver on abdominal ultrasound

**Yes→ HOMA IR index≥□□□

The multivariate model was adjusted for age, sex, waist circumference, systolic blood pressure, vigorous exercise (≥5 times/wk), smoking status, daily alcohol consumption, estimated glomerular filtration rate, and education level.

The reference group was group of individuals both without fatty liver and high HOMA-IR index.

Discussion

The novel finding of our study was that FL is an independent predictor for lower NT-proBNP levels in a generally healthy population. After adjustment for baseline characteristics, FL, HOMA-IR index, and BMI were inversely associated with NT-proBNP level. FL had an independent association with NT-proBNP level in a multivariable regression model after adjustment for HOMA-IR index and BMI. Also, our data showed that the combination of FL and high HOMA-IR index is a powerful predictor combination, lowering NT-proBNP levels approximately 25% in our generally healthy population.

IR is a risk factor for diabetes or CVD due to its association with metabolic syndrome; this was demonstrated by Reaven et al. in 1988. The euglycemic clamping test is accurate and continues to be the gold standard procedure for measuring IR (13), but its complexity limits its application in daily medical practice. IR assessment using HOMA-IR has been the most frequently used technique both in clinical

practice and in epidemiological studies due to the simplicity of its determination and measurement. Obesity and FL can be used as other indicators of IR.

FL can be easily evaluated by abdominal US; and FL's association with metabolic syndrome, diabetes and CVD has been demonstrated, making the presence of FL a good surrogate marker. Also, FL is closely linked to hepatic IR as HOMA-IR index measures peripheral IR. One report provided evidence to support the causal relationship between hepatic fat accumulation and hepatic IR. This research group showed a dose response relationship between hepatic fat accumulation and hepatic IR, and preventing hepatic fat accumulation abrogated the development of hepatic IR (14).

Using a multivariable regression model adjusted for the HOMA-IR index, which is the most representative indicator of IR, we found that FL is associated with low NT-proBNP levels. An especially interesting finding of our study was that, when considering FL and HOMA-IR index together, these variables had synergistic effects on low NT-proBNP levels. The previous Dallas Heart Study supports our results. That study demonstrated an inverse association between BNP/NT-proBNP and liver fat using 1H-MR spectroscopy (15). In our study, this association remained significant after adjusting for BMI and HOMA-IR score, indicating that liver fat is associated with NT-proBNP levels regardless of obesity or IR. In addition, several other researchers have shown that NT-proBNP levels in individuals with magnetic resonance imaging- or computed tomography-defined non-alcoholic fatty liver disease were decreased significantly (7, 8). These findings are supported by the evidence that NT-proBNP levels are affected by circulating glucose or insulin levels. Hyperinsulinemia has been shown to decrease NP-binding receptors and increase clearance receptors in adipose tissues leading to lower circulating NP levels, while fasting causes the opposite effect (16). Since there is an abundance of data suggesting that increased NP levels are protective against IR (15), type 2 diabetes mellitus (17, 18) and CVD (19, 20), lower levels of NT-proBNP may have opposite effects on IR, diabetes and CVD. Besides the epidemiologic evidence, binding of NP to its receptors stimulates an increase in mitochondrial density, oxygen consumption and insulin sensitivity (21, 22), which leads to increased lipolysis in adipose tissue (23, 24). The biological explanation for the accumulation of fat associated with low NT-proBNP can be provided by these metabolic actions. These results indicate that higher levels of NT-proBNP may exert protective effects against many cardiovascular risk factors, and NT-proBNP may be a missing link between FL and increased risks of cardiovascular outcomes. Since FL can be easily diagnosed with US, identification of FL provides a potentially useful strategy for finding subjects at increased risk of diabetes or CVD in a healthy population.

There are strengths and limitations of our study that should be considered when interpreting our findings. We have excluded factors that can influence NT-proBNP to assess the precise association between IR and NT-proBNP, and this is one of the strengths of our research. The large number of individuals included, even after individuals with these factors have been excluded, is another strength of our study. Due to the cross-sectional design of our study, our results cannot be interpreted as a causal relationship and should be considered as hypothesis-generating. Presence of FL was assessed using abdominal US, but the sensitivity of US for detecting FL is limited to identification of > 25% fat infiltration (25). We have also

used HOMA-IR > 75% as a marker of IR because more sensitive or specific measurements of insulin sensitivity were not available in this cohort. Since KSHS includes relatively young individuals, there may be limitations in directly applying our results to elderly people. Further comprehensive study is needed to determine the underlying mechanism of lower NT-proBNP in subjects with FL.

Conclusions

In this large sample of healthy individuals, FL was independently associated with lower NT-proBNP levels. FL and a high HOMA-IR index remain a powerful predictor combination for lower NT-proBNP levels. Further research is needed to elucidate the mechanism underlying the association between FL and NT-proBNP.

Abbreviations

BMI = body mass index

BNP = B-type natriuretic peptide

CVD = cardiovascular disease

DBP = diastolic blood pressure

eGFR = estimated glomerular filtration rate

FL = fatty liver

HDL-C = high-density lipoprotein cholesterol

HEPA = health-enhancing physical activity

HOMA-IR= homeostasis model assessment-estimated insulin resistance

IR = insulin resistance

IQR = interquartile range

LDL-C = low-density lipoprotein cholesterol

NT-proBNP = n-terminal pro-b-type natriuretic peptide

SBP = systolic blood pressure

SD = standard deviation

Declarations

Ethics approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Kangbuk Samsung Hospital (Reference number: KBSMC 2018-06-001).

Consent for publication

The authors give full consent for publication of the present article.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request subject to the approval of the principal investigator.

Competing interests

The authors have no competing interests to declare.

Funding

The authors declare that the research was conducted in the absence of any commercial or financial relationships.

Authors’ contributions

CHI contributed substantially to conception and design, analysis and interpretation of data, and drafted the article. SKC contributed to design of the study, acquisition of data, revised the manuscript critically for important intellectual content, gave final approval of the version to be published, and agreed to act as guarantor of the work. LMY performed statistical calculations; all authors took part in interpreting the data. All authors read and approved the final manuscript.

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Figures

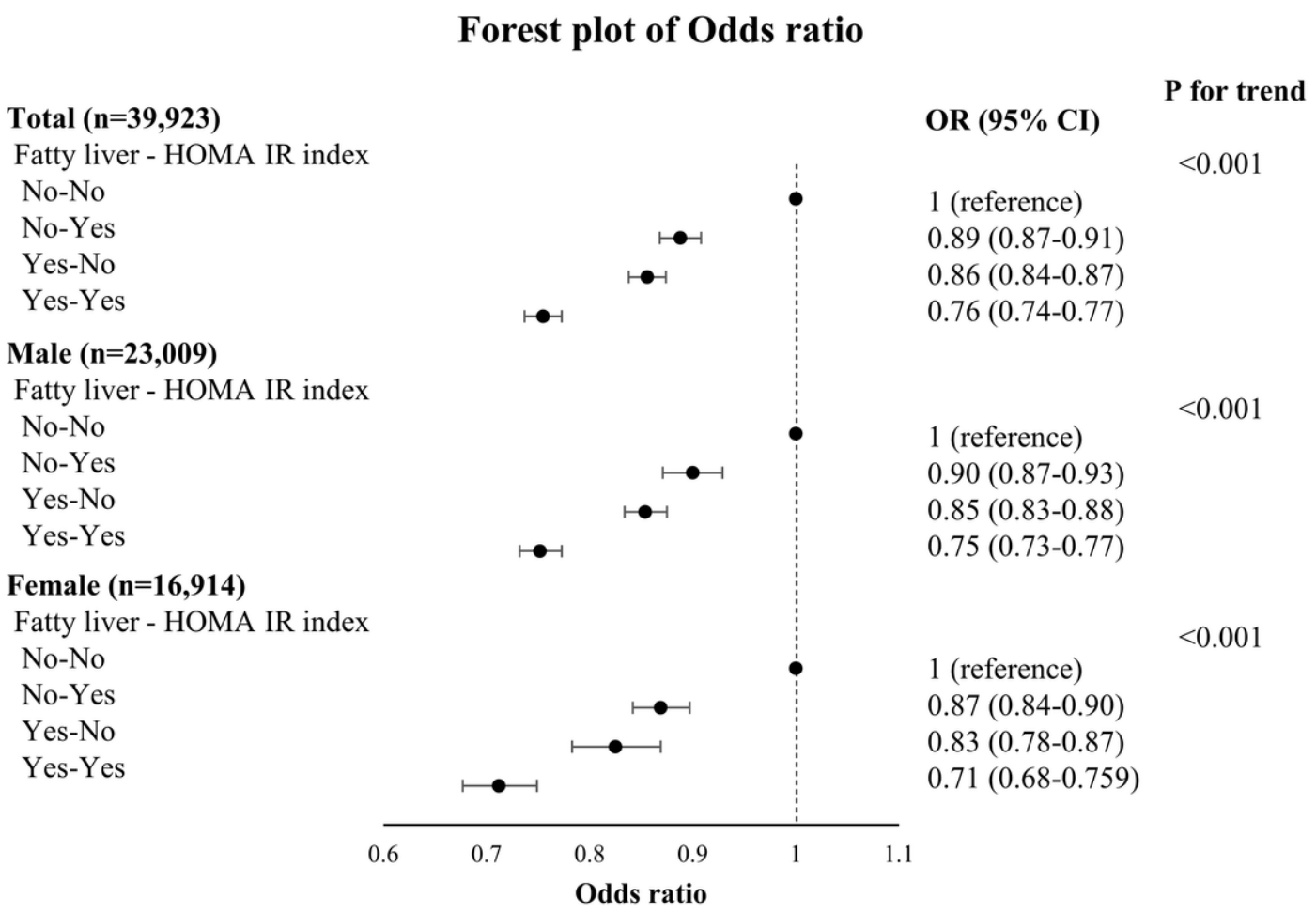

Figure 1

Forest plots are shown depicting the odds ratio (OR) for N-terminal pro-B-natriuretic peptide (NT-proBNP) levels in a multivariate logistic regression analysis. Fatty liver and HOMA-IR index (top quartile) were treated as categorical variables. Data points represent the OR ± the standard error. 95% CI indicates 95% confidence interval.