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Association of resting heart rate with nonalcoholic fatty liver disease in postmenopausal women

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Abstract

Resting heart rate, a simple and useful indicator of autonomic function, and its imbalance has emerged as an independent predictor of cardio metabolic diseases. Nonalcoholic fatty liver disease (NAFLD) is increasingly being diagnosed worldwide and is strongly associated with the features of cardiometabolic diseases. This study aimed to examine the association between resting heart rate and NAFLD in postmenopausal women.

The cross-sectional study included 1017 postmenopausal women aged ≥46 years, who attended a health examination program. Resting heart rate and NAFLD were measured in all subjects who underwent a medical examination. Resting heart rate quartiles were categorized as follows: Q1: 56 to 65, Q2: 66 to 71, Q3: 72 to 78, and Q4: 79 to 99 beats/min. The odds ratios and 95% confidence intervals for NAFLD were calculated after adjusting for confounding variables across resting heart rate quartiles using multiple logistic regression analysis.

The prevalence of NAFLD increased with increasing resting heart rate quartiles: 28.2% for Q1, 31.5% for Q2, 33.4% for Q3, and 38.1% for Q4 ($P < .001$). Compared to the 1st quartile, the odds ratio (95% confidence intervals) of NAFLD in the 4th quartile of resting heart rates was 2.11 (1.17–3.42) after adjusting for age, body mass index, cigarette smoking, regular exercise, blood pressure, total cholesterol, triglyceride, aspartate aminotransferase, and alanine aminotransferase levels.

Resting heart rate was positively associated with NAFLD in postmenopausal women, suggesting that it could be a useful additional measure to assess the risk for NAFLD in postmenopausal women.

Abbreviations: ANS = autonomic nervous system, BMI = body mass index, HDL = high density lipoprotein, NAFLD = nonalcoholic fatty liver disease.

Keywords: autonomic nervous system, inflammation, Insulin resistance, nonalcoholic fatty liver disease, resting heart rate

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) is characterized by a diffuse accumulation of triglycerides within hepatocytes and excludes excessive alcohol intake and other causes of liver disease. The prevalence of NAFLD has increased globally in recent decades, and NAFLD is the most common form of chronic liver disease worldwide, affecting 20% to 30% of the general population.[1,2] In postmenopausal women, a significant decrease in estrogen leads to weight gain and redistribution of body fat, including visceral fat accumulation,[3–5] which stimulates an influx of free fatty acids into the liver and hepatic steatosis. Thus, NAFLD is more prevalent in postmenopausal women than in premenopausal women.[6]

Resting heart rate, a global index of vital signs is a simple, cost-effective, and useful indicator of the status of the autonomic nervous system (ANS). A higher resting heart rate represents an imbalance in ANS activity, reflecting an increased sympathetic and decreased parasympathetic tone.[7–9] A growing amount of evidence indicates that a higher resting heart rate, even within the normal range, is an independent predictor of cardiovascular disease and metabolic syndrome.[8–13] Numerous cross-sectional and prospective studies have explored the association between increased sympathetic activity or decreased parasympathetic activity and cardiometabolic disease.[8–12] Therefore, an imbalance of the ANS activity may be involved in the pathogenesis of NAFLD.

However, it remains unclear whether a higher ratio of sympathetic to parasympathetic activity, manifested by a higher resting heart rate, is associated with NAFLD. Therefore, the purpose of the study was to examine the relationship between resting heart rate and NAFLD in postmenopausal women.

2. Methods

2.1. Study participants

We retrospectively reviewed the medical records of 1,315 postmenopausal women aged ≥46 years who underwent a medical examination at the Health Promotion Center of Gangnam

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Severance Hospital in Seoul, Korea, between November 2011 and July 2013. Natural menopause was defined as the final menstrual period and diagnosed when a woman had missed her period for 12 consecutive months. We excluded participants who met at least 1 of the following criteria: a history of exogenous estrogen or tamoxifen therapy; a history of induced menopause such as bilateral oophorectomy, radiation- or drug-induced menopause; a history of ischemic heart disease, arrhythmia, thyroid, respiratory, renal, hepatobiliary, or rheumatologic disease; subjects with an alcohol intake of 70 g/wk or more, a positive test for hepatitis B antigens or hepatitis C antibodies, hepatic enzyme higher than 2 times the upper limit of the reference range, resting heart rate ≤ 55 or ≥ 100 beats/min; leukocyte count $\geq 10{,}000$ cells/μ/l; missing data or not fasting for 12-h before testing. Following exclusion criteria, a total of 1,017 participants were included for the final analysis. The participants voluntarily visited the health promotion center regularly to undergo a health examination. Informed consent was obtained from each participant. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and approved by the Institutional Review Board of Yonsei University College of Medicine, Seoul, Korea.

2.2. Data collection

Each participant completed a self-report questionnaire regarding lifestyle and medical history to determine cigarette smoking status, alcohol consumption, and physical activity. Participants were categorized as non-smokers (people who had never smoked or smoked less than 100 cigarettes in their lifetime), ex-smokers (people who had smoked ≥ 100 cigarettes in their lifetime but did not smoke in the present), and current smokers (people who had smoked ≥ 100 cigarettes and smoked daily or occasionally in the present). Participants were asked about the type and frequency of leisure-time weekly physical activity levels. Regular exercise was defined as moderate or vigorous-intensity aerobic exercise activity for at least 30 minutes on $\geq$ 3 days/week. Body weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively, in light indoor clothing without shoes. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters (kg/m^2). Participants' resting heart rate was recorded during the baseline examination, using an automatic blood pressure monitor (FT-500, Jawon Medical Co. Ltd.). The automatic blood pressure monitor measured the frequency of the heartbeat and time duration while measuring the blood pressure, and the heart beats per minute were calculated. Systolic blood pressure and diastolic blood pressure were measured twice in the right arm using a standard mercury sphygmomanometer (Baumanometer, Copiague, NY). All blood samples were obtained from the antecubital vein after a 12-hour overnight fast. Fasting plasma glucose, total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transferase, alkaline phosphatase, and uric acid levels were measured through enzymatic methods using a Hitachi 7600 to 110 automated chemistry analyzer (Hitachi), and leukocyte counts were quantified using an automated blood cell counter (ADVIA 120, Bayer, NY).

Due to the large sample size and the ethical limitations for the routine use of liver biopsy in apparently healthy subjects, the diagnosis of fatty liver was based on abdominal ultrasonography with a 3.5-MHz transducer (HDI 5000, Philips, Bothell, WA). Ultrasonography was performed by 2 experienced radiologists who were unaware of the aims of the study and blinded to laboratory findings. The coefficients of variation for inter- and intra-operator reproducibility were 6.8% and 4.3%, respectively. The presence of hepatic steatosis was determined according to the findings of high hepatorenal echo contrast, bright liver, or attenuation of ultrasound in a deep area of the liver. Hepatic steatosis was graded according to the criteria described previously[14,15]: Mild, slight diffuse increase in bright homogenous echoes in liver parenchyma, with normal visualization of the diaphragm and portal and hepatic vein borders, and normal hepatorenal contrast; moderate, diffuse increase in bright echoes in liver parenchyma, with slightly impaired visualization of the peripheral portal and hepatic vein borders; and severe, marked increase in bright echoes at a shallow depth, with deep attenuation and impaired visualization of the diaphragm and marked vascular blurring. Liver with any degree of hepatic steatosis was considered NAFLD in the present study.

The modified National Cholesterol Education Program Adult Treatment Panel III definition of metabolic syndrome was used. As the waist circumference was not measured, we defined obesity as a BMI $\geq 25\ kg/m^2$, as suggested in the position statement of the American College of Endocrinology.[16] Metabolic syndrome was defined as the presence of 3 or more of the following risk factors: obesity with BMI $\geq 25.0\ kg/m^2$; elevated systolic blood pressure $\geq$ 130 mm Hg or diastolic blood pressure $\geq$ 85 mm Hg, or the use of anti-hypertensive medication; high fasting plasma glucose $\geq$ 100 mg/dL or the use of anti-diabetic medication; high triglyceride $\geq$ 150 mg/dL and low HDL cholesterol $<$50 mg/dL.

2.3. Statistical analysis

Resting heart rate was categorized into quartiles as follows: Q1: 56 to 65, Q2: 66 to 71, Q3: 72 to 78, and Q4: 79 to 99 beats/min. The clinical characteristics of the study population according to resting heart rate quartiles were compared using 1-way analysis of variance or the Kruskal-Wallis test for continuous variables according to the normality of distributions and chi-square test for categorical variables. Normal distribution was evaluated with the determination of skewness using the Kolmogorov-Smirnov test. Continuous data are presented as mean (standard deviation) or median (interquartile range), and categorical data are presented as frequencies. The odds ratios and 95% confidence intervals for NAFLD were calculated after adjusting for confounding variables across resting heart rate quartiles using multiple logistic regression analysis. All analyses were conducted using SAS statistical software (version 9.4; SAS Institute Inc., Cary, NC). All statistical tests were two-sided, and statistical significance was determined at $P < .05$.

3. Results

Table 1 shows the clinical and biochemical characteristics of the study population according to resting heart rate quartiles. The mean values for BMI, blood pressure, fasting plasma glucose, total cholesterol, leukocyte counts, and the median triglyceride levels were highest in the 4th quartile of resting heart rate. The proportion of regular exercise decreased, whereas metabolic syndrome increased in accordance with resting heart rate quartiles.

Figure 1 shows the prevalence of NAFLD according to resting heart rate quartiles. The overall prevalence of NAFLD was 33.9% and increased with increasing resting heart rate quartiles:

Table 1

Clinical and biochemical characteristics of the study population according to resting heart rate quartiles[*].

	Resting heart rate quartiles (beats/min)					
	Total	Q1 (56–65)	Q2 (66–71)	Q3 (73–78)	Q4 (79–99)	*P*- value
n	1017	249	277	241	250	
Age, yr	57.7 (6.8)	57.6 (6.8)	57.5 (6.6)	57.4 (6.6)	57.8 (6.7)	.177
BMI (kg/m^2)	23.5 (3.0)	23.3 (3.3)	23.5 (2.9)	23.6 (2.8)	23.8 (3.0)	.002
Systolic blood pressure (mm Hg)	124.9 (16.8)	121.0 (16.7)	124.2 (15.8)	124.8 (16.8)	129.4 (17.0)	<.001
Diastolic blood pressure (mm Hg)	77.0 (10.1)	73.6 (9.5)	76.7 (9.5)	77.4 (10.1)	80.2 (10.1)	<.001
Fasting plasma glucose (mg/dL)	96.2 (18.6)	92.5 (14.2)	94.5 (18.3)	95.7 (15.0)	101.9 (23.0)	<.001
Total cholesterol (mg/dL)	203.1 (35.5)	199.2 (34.4)	203.1 (34.4)	204.8 (36.7)	205.0 (36.2)	.002
Triglyceride (mg/dL)	103 (75–139)	99 (74–147)	100 (77–140)	101 (75–155)	112 (76–155)	.015
HDL-cholesterol (mg/dL)	55.5 (12.8)	55.9 (13.5)	54.9 (12.2)	55.5 (12.6)	55.6 (13.0)	.430
AST, U/L	21 (18–24)	20 (18–24)	21 (18–24)	20 (18–24)	21 (18–24)	.107
ALT, U/L	17 (14–23)	17 (14–23)	18 (14–24)	17 (14–22)	18 (14–22)	.291
GGT, U/L	17 (13–25)	17 (!3–24)	17 (13–26)	16 (13–23)	18 (1426)	.196
ALP, U/L	62 (52–76)	59 (52–71)	62 (51–78)	63 (52–75)	65 (53–79)	.002
Uric acid (mg/dL)	4.3 (0.9)	4.3 (0.9)	4.3 (0.9)	4.2 (1.0)	4.2 (1.0)	.451
Leukocyte, cells/μL	5680 (1462)	5411 (1372)	5641 (1491)	5693 (1383)	5949 (1349)	<.001
Current smoking[†] (%)	2.8	3.1	2.7	3.6	1.7	.117
Regular exercise[‡] (%)	41.4	47.8	47.1	38.5	31.9	<.001
Metabolic syndrome[§] (%)	29.5	26.8	27.1	30.0	33.9	.003

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index, HDL = high density lipoprotein. Data are expressed as the mean (SD), median (interquartile range, IQR), or percentage.

[*] P values were calculated using 1-way ANOVA test, Kruskal Wallis test, or chi-square test.

[†] Alcohol drinking ≥twice/wk.

[‡] Regular exercise ≥3 times/wk.

[§] Metabolic syndrome was defined by the presence of three or more of the following risk factors: obesity with BMI ≥25.0 kg/m^2, elevated systolic blood pressure ≥130 mm Hg, elevated diastolic blood pressure ≥85 mm Hg, or a current use of hypertension medication, and high fasting plasma glucose ≥ 100 mg/dL or a current use of diabetes medication, high triglycerides ≥150 mg/dL, low HDL cholesterol <50 mg/dL.

28.2% for Q1, 31.5% for Q2, 33.4% for Q3, and 38.1% for Q4 ($P < .001$).

Table 2 shows the results of multiple logistic regression analysis to assess the odds of predicting the presence of NAFLD in terms of resting heart rate quartiles. Compared to the referent 1st quartile, the odds ratio (95% confidence intervals) of NAFLD in the 4th quartile of resting heart rate was 2.11 (1.17–3.42) after adjusting for age, BMI, cigarette smoking, regular exercise, blood

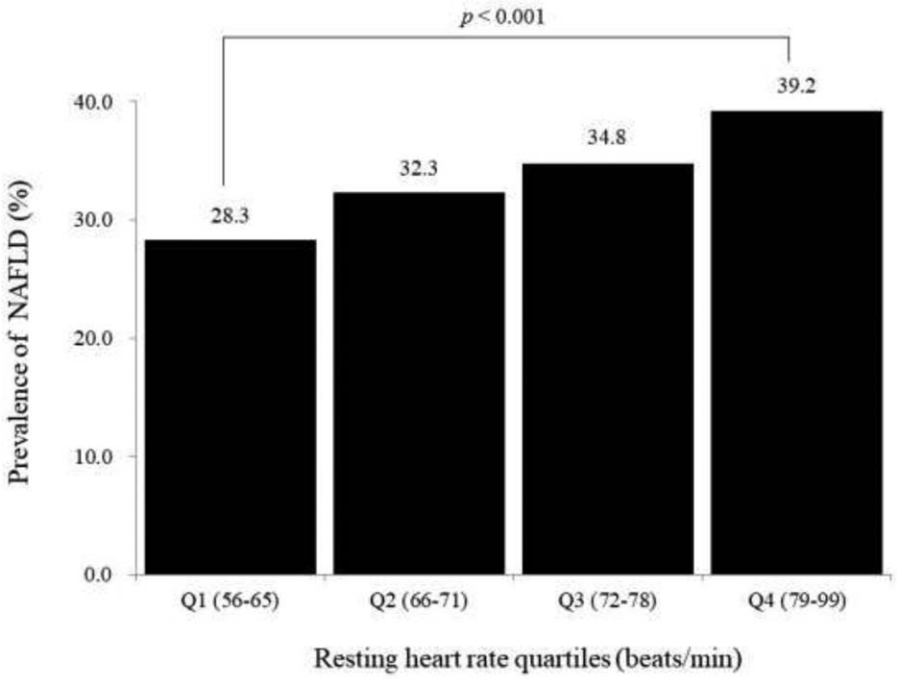

Figure 1. Prevalence of nonalcoholic fatty liver disease (NAFLD) according to resting heart rate quartiles in postmenopausal women (*P* value was calculated by analysis of variance (ANOVA) test).

Table 2

Odds ratios and 95% confidence for nonalcoholic liver disease according to resting heart rate quartiles.

	Resting heart rate quartiles (rate/min)				
	Q1 (56–65)	Q2 (66–71)	Q3 (73–78)	Q4 (79–99)	*P* for trend
Model 1[a]	1.00	1.27 (0.83–1.96)	1.44 (0.96–2.19)	2.30 (1.48–3.48)	<.001
Model 2[b]	1.00	1.30 (0.80–2.22)	1.33 (0.83–2.17)	2.11 (1.17–3.42)	.004
Model 3[c]	1.00	1.29 (0.78–2.16)	1.30 (0.82–2.16)	1.98 (1.19–3.29)	.009

Model 1: Adjusted for age and BMI.

Model 2: Adjusted for age, BMI, cigarette smoking, regular exercise, blood pressure, total cholesterol, triglyceride, AST, and ALT level.

Model 2: Adjusted for age, BMI, cigarette smoking, regular exercise, blood pressure, total cholesterol, triglyceride, AST, ALT, ALP levels, and leukocyte count.

ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, BMI = body mass index.

pressure, total cholesterol, triglyceride, aspartate aminotransferase, and alanine aminotransferase levels. We also assessed the association between resting heart rate and NAFLD after additionally adjusting for alkaline phosphatase level and leukocyte count. These positive associations were similar using model 3.

4. Discussion

In this cross-sectional study, a higher resting heart rate was independently and positively associated with NAFLD in postmenopausal women after adjusting for potential confounding variables. We believe that this is the first study to evaluate the association between resting heart rate and NAFLD. Some mechanisms could explain the significant relationships between resting heart rate and NAFLD. The current understanding of the development and progression of NAFLD involves the "2-hit hypothesis."[17,18] The "first hit" means insulin resistance associated with visceral obesity, which leads to high levels of circulating free fatty acids and excess fat accumulation in hepatocytes, resulting in fatty liver. The subsequent onset of oxidative stress acts as a "second hit" and results in hepatocyte injury, inflammation, and fibrosis. The liver damage may be modulated by additional insults, such as excessive free fatty acids in hepatocytes and other triggering factors.

A higher resting heart rate represents sympathetic overactivity and parasympathetic underactivity. Adrenergic stimulation and hypothalamic-pituitary-adrenal axis activation accompanied by sympathetic activation can contribute to insulin resistance. Moreover, sympathetic activation appears to play a synergistic causal role in obesity-associated insulin resistance through bidirectional interactions. Increased heart rate has been associated with obesity, cardiovascular disease, and metabolic syndrome in cross-sectional and longitudinal studies.[19–24] In a meta-analysis with seven longitudinal and ten cross-sectional studies, Lui et al determined that the pooled risk ratio of metabolic syndrome was 2.10 for the highest resting heart rate versus lowest resting heart rate and a 28% risk increase per 10 beats/min increment in resting heart rate.[25] In the present study, resting heart rate was also positively associated with metabolic syndrome and its components, other than HDL-cholesterol. Thus, a higher resting heart rate could be closely related to the "first hit" hypothesis. Reactive oxidative stress and low-grade inflammation could explain the significant relationship between resting heart rate and NAFLD, as suggested in the "second hit" hypothesis. A higher resting heart rate may reflect a higher rate of oxygen consumption and metabolic rate, leading to increased oxidative stress and elevation of pro-inflammatory cytokines, such as interleukin-6 and tumor necrosis factor-α.[26] This inflammatory cascade may inhibit insulin secretion in pancreatic β-cells and promote insulin resistance in the liver.[27] In the present study, leukocyte count gradually increased with the resting heart rate quartiles, which is in agreement with the previous results showing positive associations between resting heart rate and elevated inflammatory marker.[28,29]

Some limitations should be considered in the interpretation of this study. First, it had a cross-sectional design, suggesting that caution should be used in causal-effect interpretations. Future prospective research is warranted to elucidate the temporal relationship between resting heart rate and NAFLD. Second, we lacked information on insulin resistance, such as homeostasis model assessment of insulin resistance, and thus no direct relationship between resting heart rate and insulin sensitivity was demonstrated. Third, we did not take into consideration the effect of other potential confounding variables such as waist circumference, low-density lipoprotein cholesterol, HbA1C, C-reactive protein, and urine microalbumin. These variables were not fully adjusted for in the statistical model, causing a possible residual confounding effect. Fourth, we did not take into consideration the effect of medications, such as β-blockers, calcium channel blockers, and selective serotonin reuptake inhibitors on resting heart rate. Fifth, important confounders such as anemia, diabetes, hypertension, chronic kidney disease, and sleep-disordered breathing were missing in our study. Sixth, transient elastography, an easy and non-invasive method to identify NAFLD was not used. Transient elastography combined with ultrasonography could increase the positive predictive value for significant fibrosis compared to ultrasonography alone.[30] Lastly, although liver biopsy is the gold standard for the diagnosis of fatty liver, biopsy-proven NAFLD was not assessed in the present study. Liver biopsy is an invasive procedure dictated by the clinical setting, while ultrasonography is a non-invasive and widely available method for qualitative assessments of hepatic fat accumulation. Thus, ultrasonography is the preferred modality for mass screening for hepatic steatosis with reasonable accuracy (67%–94%).[31]

5. Conclusion

In the current study, resting heart rate was significantly associated with NAFLD in postmenopausal women, suggesting resting heart rate in postmenopausal women could be a useful additional measure in assessing the prevalence risk of NAFLD. Our findings support the hypothesis that a higher ratio of sympathetic to parasympathetic activity may be involved in the parthenogenesis of NAFLD.

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Author contributions

Hong-Bae Kim and Yong-Jae Lee designed the study, conducted statistical analyses, and interpreted the data. Hong-Bae Kim and Yong-Jae Lee wrote and edited the manuscript. Yong-Jae Lee, as the corresponding author, coordinated the study, interpreted the data, contributed to the discussion, and wrote the manuscript. All authors read and approved the final version of the manuscript.

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Drafting of the manuscript: Hong-Bae Kim.
Statistical analysis and interpretation: Yong-Jae Lee and Hong-Bae Kim.
Study concept and design: Yong-Jae Lee.
Study supervision: Yong-Jae Lee.

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