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Gender differences in the impact of anemia on subclinical myocardial damage and cardiovascular mortality in the general population: The Yamagata (Takahata) study

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ABSTRACT

Background: Anemia has been shown to worsen cardiovascular diseases. However, it is unclear whether there is a gender difference in the impact of anemia on subclinical myocardial damage and cardiovascular mortality in the general population.
Methods: A prospective cohort study was conducted in a community based on annual health checks. Serum heart-type fatty acid binding protein (H-FABP) levels, which is a marker for myocardial damage, and blood counts were measured at baseline in subjects without previous cardiovascular diseases (n = 3111).
Results: There were 343 subjects (11.0%) with anemia at baseline. H-FABP levels were inversely correlated with hemoglobin concentrations in male subjects, whereas there was no such correlation in female subjects, irrespective of the status of menopause. Prevalence of myocardial damage (H-FABP ≥4.3 ng/ml) was significantly higher in male subjects with anemia than those without, irrespective of the type of anemia (microcytic, normocytic, and macrocytic). Multivariate logistic regression analysis revealed that anemia was an independent predictor of myocardial damage after adjusting for confounders. During 10 years of follow-up, there were 204 all-cause deaths including 57 cardiovascular deaths. Kaplan–Meier analysis demonstrated that cardiovascular mortality was higher in male subjects with anemia than in those without. However, anemia was not associated with cardiovascular mortality in female subjects. Multivariate Cox proportional hazard analysis revealed that anemia was an independent predictor of all-cause and cardiovascular mortalities after adjusting for confounders.
Conclusion: Anemia was an independent predictor of all-cause and cardiovascular mortalities, and subclinical myocardial damage in male subjects, but not in female subjects.

1. Introduction

Subclinical myocardial damage has been reported to be associated with a risk of future cardiovascular mortality [1,2]. Therefore, detection of subclinical myocardial damage can help in identifying individuals at high risk for cardiovascular diseases, which may result in lowering of mortality. Heart type fatty-acid binding protein (H-FABP) is a small cytosolic protein which is released into the circulation when cardiomyocytes are damaged [3]. Therefore, H-FABP is considered a sensitive marker of ongoing myocardial damage [4,5]. We previously reported that circulating H-FABP levels can predict cardiovascular prognoses in the general population [1,6].

Anemia is a common disorder with worldwide prevalence [7–10]. It was reported that anemia is associated with unfavorable outcomes in patients with acute coronary syndrome [11] and those with chronic heart failure [12]. However, it remains to be determined whether anemia is an independent risk factor of cardiovascular death in apparently healthy subjects.

The aim of the present study was to investigate whether anemia is associated with subclinical myocardial damage as assessed by H-FABP and cardiovascular mortality in the general population.

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2. Methods

2.1. Study population

This study was based on community-based annual health check-ups of inhabitants of Takahata town in Yamagata, Japan (total population 26,026 in 2005). Community members, aged 40 years or older were invited to participate. Between 2004 and 2013, a total of 3520 subjects (1579 males and 1941 females) were enrolled in the study [13]. This study is a part of the Molecular Epidemiological Study and utilized the resources of Regional Characteristics of 21st Century Centers of Excellence (COE) Program and the Global COE Program in Japan. The methodology has been described previously [14]. The study was approved by the ethics committee of Yamagata University School of Medicine and all participants provided written informed consents. Subjects with insufficient blood data (n = 1) and those with severe renal disease (eGFR: estimated glomerular filtration rate < 30 ml/min/1.73 m^2) (n = 9) or previous cardiovascular diseases (n = 399) were excluded [15]. The data of the remaining 3111 subjects (1367 males and 1744 females) were analyzed. All procedures were performed in accordance with the guidelines of the Helsinki Declaration. Subjects used a self-report questionnaire to document their medical histories, history of smoking, current use of medications, and clinical symptoms.

2.2. Measurement of H-FABP

Serum concentrations of H-FABP were measured using a two-step sandwich enzyme-linked immunosorbent assay kit (MARKIT-M H-FABP, Dainippon Pharmaceutical Co. Ltd., Tokyo, Japan) as previously reported [6].

2.3. Definition of anemia and myocardial damage

Anemia was defined according to the World Health Organization classification of anemia: hemoglobin ≤13.0 g/dl in men and ≤12.0 g/dl in women.

Myocardial damage was defined as serum level of H-FABP ≥4.3 ng/ml in accordance with previous reports [16,17].

2.4. Other measurements and definitions

Blood samples were collected from the subjects after overnight fasting, and the samples were immediately transferred to chilled tubes. Serum concentrations of brain natriuretic peptide (BNP) were measured using a commercially available radioimmunoassay specific for human BNP (Shiono RIA BNP assay kit, Shionogi Co. Ltd., Tokyo, Japan) [18]. The lifetime severity of cigarette smoking was assessed using the smoking index, which is defined as the number of cigarette-years smoked. Blood pressure was measured using a mercury manometer after the subjects resting in a seated position for at least 5 min. Hypertension was defined as systolic blood pressures (SBP) ≥140 mm Hg, diastolic blood pressures (DBP) ≥90mm Hg, or the current use of antihypertensive medications. Dyslipidemia was defined as low density lipoprotein-cholesterol (LDL-C) ≥140 mg/dl, high density lipoprotein-cholesterol (HDL-C) <40 mg/dl, triglyceride (TG) ≥150 mg/dl, or the current use of lipid-lowering medications. Diabetes mellitus was defined as fasting blood glucose (FBG) ≥126 mg/dl, HbA1c ≥6.5%, or the use of antidiabetic medications. Metabolic syndrome was defined according to the modified National Cholesterol Educational Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (modified NCEP ATP III) [19]. In brief, subjects were deemed to have metabolic syndrome if they satisfied three or more of the following five criteria: 1) obesity, with body mass index (BMI ≥ 25 kg/m^2); 2) hypertriglyceridemia, with TG ≥ 150 mg/dl; 3) HDL-C < 40 mg/dl for men and <50 mg/dl for women; 4) hypertension, with SBP ≥ 130 mm Hg, DBP ≥ 85 mm Hg, or current use of antihypertensive drugs; and 5) glucose intolerance/diabetes mellitus, with FBG ≥ 110 mg/dl and/or current use of antidiabetic drugs. Estimated glomerular filtration rate (eGFR) was calculated using the modification of diet in renal disease (MDRD) equation with Japanese coefficient.

2.5. Endpoint and follow-up period

All subjects were prospectively followed up for a median period of 3376 days (interquartile range, 3040–3439 days) with all-cause and cardiovascular deaths as endpoints. The cause of death was determined by reviewing the death certificates through the end of 2013. The death code (International Classification of Disease, 10th Revision: ICD-10) and place of death were reviewed. Cardiovascular deaths were defined as deaths due to ICD-10 codes beginning with I in any position ("I00" to "I99").

2.6. Statistical analysis

All results are presented as mean ± SD for continuous variables and as percentages of the total number of subjects for categorical variables. Skewed variables are presented as medians and interquartile ranges. Student's unpaired *t*-test and chi-squared test were used for comparisons of continuous and categorical variables between two groups, respectively. If data were not distributed normally, the Mann–Whitney *U* test or Kruskal–Wallis test was used. Comparison among three or more groups was performed by one-way analysis of variance (ANOVA) followed by the Tukey–Kramer Honest Significance Difference test for parametric variables, or Steel–Dwass test for nonparametric variables. Logistic regression analysis was performed to identify independent predictors of subclinical myocardial damage. Significant variables on univariate analyses along with possible confounders were utilized for multivariate analyses in a stepwise manner. As BNP, H-FABP, and D-dimer were not distributed normally, we used $\log_{10}$BNP, $\log_{10}$H-FABP, and $\log_{10}$D-dimer for statistical analyses, respectively. A Cox proportional hazard regression analysis was performed to determine the independent predictors of all-cause and cardiovascular deaths. Significant variables on univariate analyses were selected and used in multivariate analyses. Survival curves were constructed with the Kaplan–Meier method and compared using log-rank tests. *P*-values of <0.05 were considered significant. All analyses were performed with a standard statistical program package (JMP version 10; SAS Institute Inc., Cary, North Carolina, USA).

3. Results

3.1. Baseline characteristics of the subjects stratified by gender

Table 1 shows the baseline clinical characteristics of the study subjects stratified by gender. Anemia was observed in 344 subjects (11.0%) and it was more prevalent in female subjects than in male subjects (14.4% vs. 6.8%, $P < 0.0001$). Higher prevalence of hypertension, diabetes mellitus, and atrial fibrillation (AF), and lower prevalence of dyslipidemia were observed in the male subjects than in female subjects. Male subjects had higher smoking index, alcohol consumption, SBP, DBP, $\log_{10}$H-FABP, albumin, hemoglobin, serum iron, and mean corpuscular volume (MCV) than female subjects. There were no differences in BMI, eGFR, prevalence of metabolic syndrome, and intake of vitamins B6 and B12, and folic acid between the genders.

3.2. Gender difference of anemia on subclinical myocardial damage

We analyzed the association between anemia and myocardial damage (Fig. 1A). Male subjects with anemia had higher prevalence of myocardial damage than those without anemia. However, there was no difference in the prevalence of myocardial damage between female subjects with and without anemia. There was a very weak but significant correlation between Log_{10}H-FABP levels and hemoglobin concentrations in male subjects ($r = -0.175$, $P < 0.0001$). In contrast, there was no correlation between hemoglobin concentrations and $\log_{10}$H-FABP levels in female subjects irrespective of the status of menopause (Fig. 1B).

Table 1
Baseline characteristics of subjects stratified by gender.

	Male n = 1367	Female n = 1744	*P* value
Age, years	62 ± 10	62 ± 10	0.1335
BMI, kg/m^2	23.5 ± 2.9	23.5 ± 3.4	0.8118
Hypertension, n (%)	802 (59)	912 (52)	0.0004
Dyslipidemia, n (%)	644 (47)	905 (52)	0.0064
Diabetes mellitus, n (%)	152 (11)	124 (7)	0.0001
Metabolic syndrome, n (%)	229 (17)	264 (15)	0.2226
Anemia, n (%)	93 (7)	251 (14)	<0.0001
Atrial fibrillation, n (%)	12 (0.9)	3 (0.2)	0.0041
Smoking index	360 (0–750)	120 (0–240)	<0.0001
Ethanol consumption, g/week	120 (0–240)	0 (0–0)	<0.0001
SBP, mm Hg	136 ± 16	133 ± 16	<0.0001
DBP, mm Hg	82 ± 10	78 ± 10	<0.0001
Laboratory data			
Log_{10}BNP	1.22 ± 0.38	1.31 ± 0.33	<0.0001
Log_{10}H-FABP	0.55 ± 0.19	0.52 ± 0.19	<0.0001
Albumin, g/dl	4.5 ± 0.3	4.5 ± 0.2	0.0060
Hb, g/dl	14.7 ± 1.2	13.0 ± 1.3	<0.0001
Iron, μg/dl	113.9 ± 39.4	98.9 ± 33.1	<0.0001
MCV, fl	95.0 ± 5.0	91.7 ± 5.6	<0.0001
eGFR, ml/min/1.73 m^2	82.6 ± 15.7	82.0 ± 16.2	0.2881
Vitamin B6 intake, mg/day	1.38 ± 0.63	1.34 ± 0.58	0.1839
Vitamin B12 intake, μg/day	10.7 ± 8.1	10.6 ± 7.7	0.7209
Folic acid intake, μg/day	375.8 ± 168.6	392.6 ± 173.5	0.0509

Data are expressed as mean ± SD, median (interquartile range), and number (percentage) of subjects. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; BNP, brain-type natriuretic peptide; H-FABP, heart-type fatty acid binding protein; Hb, hemoglobin; MCV, mean corpuscular volume; eGFR, estimated glomerular filtration rate.

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