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Fatty acid-binding protein 4 and incident heart failure: the Cardiovascular Health Study

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Aim To examine the association of plasma fatty acid-binding protein 4 (FABP4) with incident heart failure.

Methods and results In a prospective study of 4179 participants from the Cardiovascular Health Study, we measured plasma FABP4 on blood specimens collected between 1992 and 1993. Incident heart failure was adjudicated by an endpoint committee and we used a Cox proportional hazards model to calculate hazard ratios (HRs) of heart failure. The average age at baseline was 75 years. During a median follow-up of 10.7 years, 1182 cases of incident heart failure occurred. We observed a positive association between FABP4 and heart failure in the minimally adjusted models [HR 1.32, 95% confidence interval (CI) 1.25–1.38 per 1 SD higher FABP4] that was attenuated upon adjustment for potential confounders, mostly kidney function and body mass index (corresponding HR 1.09, 95% CI 1.01–1.17). In a subsample of heart failure cases with available data on LV systolic function, FABP4 was not associated with heart failure with or without preserved LV systolic function. Exclusion of people with unintentional weight loss and self-reported fair/poor health status did not alter the conclusion.

Conclusion An elevated plasma concentration of FABP4 was associated with a modestly higher risk of heart failure in older adults in the USA after adjustment for confounding factors.

Keywords Epidemiology • Adiposity • Heart failure • Fatty acid-binding protein 4

Introduction

In 2010, heart failure (HF) is estimated to account for $US39.2 billion spending in direct and indirect cost in the USA,[1] and remains the leading cause of hospitalization in the elderly. Over the past decades, HF incidence has remained stable.[2,3] Previous studies have reported a positive association between obesity and incident HF.[4–6] While it is possible that the increased risk of HF with obesity [as assessed by body mass index (BMI)] may be mediated by hypertension,[7,8] diabetes,[8–10] and coronary artery disease,[11] a direct relationship between adipokines and HF risk might also exist. Adipocytes produce a variety of bioactive molecules including fatty acid-binding protein 4 (FABP4),[12,13] with diverse functions including modulation of inflammation, thrombogenicity, insulin resistance, and other metabolic effects.[13,14] FABP4 (also referred to as aFABP or aP2) serves as a carrier protein for fatty acids and other lipophilic substances between extra- and intracellular membranes.[15–17] FABP4 has been shown to have a negative inotropic effect on cardiomyocytes.[18] In addition, expression of FABP4 in adipocytes has been positively associated with overall insulin resistance,[19–21] mortality,[22] metabolic syndrome,[23,24] incident diabetes mellitus,[25] greater coronary

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plaque burden,[26] and CAD.[27] These observations suggest that FABP4 may play a role in the development of HF. However, to our knowledge, this hypothesis has not been investigated in human populations. Because an elevated plasma concentration of FABP4 could be a consequence of renal insufficiency (leading to limited excretion of FABP4), it is important to determine whether an association of FABP4 with HF is independent of kidney function. Hence, the aim of the present study was to examine the association between plasma FABP4 and incident HF in older adults.

Methods

Study population

Study participants were drawn from the Cardiovascular Health Study (CHS), a prospective cohort consisting of 5888 men and women aged 65 years and older that were randomly selected from Medicare eligibility lists in four US communities (Forsyth County, NC; Washington County, MD; Sacramento County, CA; and Pittsburgh, PA). A detailed description of methods and procedures in the CHS has been published elsewhere.[28] Briefly, 5201 men and women aged $\geq$ 65 years were recruited between 1989 and 1990. In addition, a supplemental cohort of 687 predominantly African-American men and women was recruited in 1992–1993 from three of the same communities (except for Washington County) using the same sampling and recruitment methods. The institutional review board of each participating centre approved the study, and all participants gave informed written consent to participate in the study. Of the 5265 participants who attended the fifth clinic visit (1992–1993), we excluded from this analysis participants with prevalent HF ($n = 344$), missing plasma FABP4 measurement ($n = 495$), or missing covariate data ($n = 247$). The final analysis sample included 4179 participants.

Ascertainment of heart failure

Self-report of a physician diagnosis of HF was validated by the CHS Events Committee as previously described.[29,30] Briefly, HF validation required a constellation of symptoms (shortness of breath, fatigue, orthopnoea, paroxysmal nocturnal dyspnoea); chest X-ray findings (pulmonary oedema and increasing cardiomegaly); signs (oedema, pulmonary rales, gallop rhythm, displaced LV apical impulse); and treatment of HF (diuretics, digitalis, or vasodilators). Incident HF was ascertained upon review of pertinent data on hospitalization or outpatient visits such as medical history, physical examination, report of chest X-ray, and medications. HF was classified as systolic or diastolic HF based on LVEF. The estimated LVEF was obtained from an echocardiogram, cardiac catheterization, multiple gated cardiac pool imaging, or other modality. Records on LVEF were obtained by review from CHS investigators or the CHS adjudication committee. There were adequate data to estimate LVEF on 590 (50%) of the HF events in our sample, of whom 374 HF cases had LVEF $<$55% (systolic HF) and 216 HF cases had LVEF $\geq$ 55% (diastolic HF). The current analysis included validated HF up to 30 June 2008.

Measurement of fatty acid-binding protein 4

Plasma samples collected at the 1992–1993 examination were stored at −70°C until analysed at the Central Laboratory at the University of Vermont. Plasma FABP4 concentration was measured using standard enzyme-linked immunosorbent assay kits (Biovendor ELISA). The interassay coefficient of variation was 2.94–6.70%. Since blood samples were kept frozen at or below −70°C until they were thawed for measurements, it is unlikely that a meaningful degradation occurred during the storage time at extremely low temperatures.

Other variables

Comprehensive information on health-related factors was collected at baseline and, for some factors, annually thereafter in a standardized fashion. Age, sex, ethnicity, years of education, physical activity, smoking status, and alcohol consumption were based on self-reports. The leisure time activity (kcal/week) was assessed by using a modified Minnesota Leisure-Time Activities questionnaire.[21] Weight, waist circumference, and height were measured by using standardized protocols. BMI was calculated as weight in kilograms divided by height in metres squared. Smoking status and height to compute BMI were carried forward from previous years if missing for the first cohort.

Statistical methods

Distributions of baseline characteristics were summarized by sex-specific quartiles of FABP4. Continuous variables were presented as mean $\pm$ SD, and categorical variables as percentages. Incidence rates of HF were presented per 1000 person-years. Cubic splines were used to assess the shape of the FABP4–HF association.

Cox proportional hazards regression was used to estimate the association of FABP4 with incident HF. FABP4 was modelled as sex-specific quartiles, with the lowest quartile as the referent category, and continuously per standard deviation of FABP4. Follow-up continued up to 30 June 2008, and individuals were censored for death or loss to follow-up. A sequence of Cox models was evaluated. After an unadjusted model, we adjusted for age, ethnicity, sex, and clinic site (Model 1), with the addition of BMI, self-reported health status, education, kilocalories of physical activity, smoking status, alcohol intake categories, heart rate, and estimated glomerular filtration rate (eGFR) using cystatin C (Model 2). To evaluate intermediate pathways by which FABP4 might lead to HF, we additionally adjusted for AF by ECG, C-reactive protein, systolic blood pressure, hypertensive medication, prevalent diabetes, and coronary heart disease (Model 3). As a secondary analysis, we evaluated effect modification of the association of FABP4 with incident HF by ethnicity, age, sex, BMI, waist circumference, or diabetes using likelihood ratio tests.

In a further secondary analysis, we assessed the association of FABP4 with systolic and diastolic HF using competing risks methods.[31] There were 590 HF cases that could be classified as systolic or diastolic HF based on LVEF; those who could not be classified were censored. HF type was stratified, and estimates for the association of FABP4 and each outcome were obtained. A sensitivity analysis excluded people with unintentional weight loss (defined as self-reported loss of $\geq$ 10 lbs not due to diet or exercise during the past 12 months) or self-reported fair/poor health to assess further confounding in the data. A second sensitivity analysis included coronary heart disease as a time-varying covariate. Lastly, we accounted for competing risk of mortality and restricted follow-up time to 5 years.

Schoenfeld residuals were used to evaluate proportional hazards assumptions; there were no meaningful violations. Stata, version 11.1 (StataCorp LP, College Station, TX, USA) was used for all analyses, and P-values $<$0.05 were considered statistically significant.

Results

The mean age of study participants was 75 years (range 65–98). During a median follow-up of 10.7 years, 1182 participants developed HF. Baseline characteristics of the study population are shown in *Table 1*. Higher levels of FABP4 were associated with

Table 1 Characteristics of 4260 participants of the Cardiovascular Health Study according to quartiles of serum fatty acid-binding protein 4

	Sex-specific quartiles of FABP4 (ng/mL)			
	Q1 (1045)	Q2 (1045)	Q3 (1045)	Q4 (1044)
Quartile cut-off points				
Men	<18.398	18.398 to <23.09	23.09–29.9	>29.9
Women	<27.49	27.49 to <34.95	34.95–45.3	>45.3
Characteristics				
Age (years)	74.4 ± 4.7	74.5 ± 5.1	74.8 ± 5.3	75.0 ± 5.4
Body mass index (kg/m^2)	24.1 ± 3.5	26.0 ± 3.6	27.6 ± 4.1	29.6 ± 5.4
Waist circumference (cm)	90.0 ± 10.8	95.5 ± 10.8	99.2 ± 12.0	104.7 ± 13.9
Systolic blood pressure (mmHg)	134.4 ± 20.5	135.8 ± 21.7	137.2 ± 21.4	137.3 ± 21.4
Kilocalories of physical activity	1628 ± 1781	1506 ± 1786	1491 ± 1782	1170 ± 1560
eGFR by cystatin C (mL/min/1.73 m^2)	83.8 ± 16.7	77.3 ± 16.0	71.7 ± 15.4	60.7 ± 17.5
Cystatin C (mg/L)	0.96 ± 0.17	1.03 ± 0.19	1.10 ± 0.22	1.33 ± 0.49
HDL (mg/dL)	58.0 ± 15.2	54.3 ± 14.3	52.0 ± 13.6	49.6 ± 12.9
LDL (mg/dL)	125.3 ± 32.5	128.9 ± 33.7	130.1 ± 33.3	128.2 ± 35.7
Triglyceride (mg/dL)	114.3 ± 55.1	136.4 ± 78.0	151.9 ± 83.4	173.3 ± 104.6
C-reactive protein (mg/dL)	4.3 ± 10.2	4.4 ± 9.0	5.0 ± 6.7	7.3 ± 10.8
BNP (pg/mL)	213.2 ± 289.5	234.2 ± 545.7	268.8 ± 601.8	426.9 ± 1448.5
Heart rate	64.2 ± 10.7	65.2 ± 11.0	66.0 ± 10.4	67.4 ± 13.4
African-American	144 (13.8%)	145 (13.9%)	186 (17.8%)	195 (18.7%)
Male	428 (41.0%)	428 (41.0%)	428 (41.0%)	427 (40.9%)
Less than High School education	229 (21.9%)	255 (24.4%)	288 (27.6%)	305 (29.2%)
Oestrogens (among women)	120 (19.4%)	92 (14.9%)	75 (12.2%)	56 (9.1%)
Fair/poor self-reported health	171 (16.4%)	162 (15.5%)	197 (18.9%)	264 (25.3%)
Use of hypertension medication	386 (36.9%)	444 (42.5%)	533 (51.0%)	657 (62.9%)
Hypertension	502 (48.0%)	556 (53.3%)	623 (59.7%)	679 (65.1%)
Prevalent diabetes	94 (9.0%)	122 (11.7%)	153 (14.6%)	230 (22.0%)
Prevalent CHD	166 (15.9%)	185 (17.7%)	196 (18.8%)	240 (23.0%)
AF	17 (1.6%)	20 (1.9%)	25 (2.4%)	37 (3.5%)
Alcohol intake				
None	508 (48.6%)	534 (51.1%)	583 (55.8%)	626 (60.0%)
< 7 drinks/week	364 (34.8%)	371 (35.5%)	342 (32.7%)	319 (30.6%)
7–14 drinks/week	91 (8.7%)	88 (8.4%)	74 (7.1%)	50 (4.8%)
> 14 drinks/week	82 (7.8%)	52 (5.0%)	46 (4.4%)	49 (4.7%)
Smoking status				
Never smoked	468 (44.8%)	480 (45.9%)	492 (47.1%)	465 (44.5%)
Former smoker	444 (42.5%)	458 (43.8%)	451 (43.2%)	487 (46.6%)
Current smoker	133 (12.7%)	107 (10.2%)	102 (9.8%)	92 (8.8%)
LVEF (cohort 1)				
Normal	878 (95.7%)	873 (93.7%)	847 (94.4%)	818 (92.2%)
Borderline	27 (2.9%)	46 (4.9%)	36 (4.0%)	55 (6.2%)
Abnormal	12 (1.3%)	13 (1.4%)	14 (1.6%)	14 (1.6%)

Data are means (±SD) or *n* (%). There were missing data on waist circumference ($n = 4$), HDL ($n = 10$), LDL ($n = 80$), triglycerides ($n = 1$), BNP ($n = 450$), hypertension ($n = 4$), and LVEF for cohort 1 ($n = 29$).
LVEF is from the clinic visit in 1989–1990 for cohort 1 and not available for cohort 2 in 1992–1993.
CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; FABP4, fatty acid-binding protein 4.

female gender, higher measures of adiposity, dyslipidaemia, fair/poor self-reported health status, higher prevalent hypertension, diabetes, coronary disease, and AF, lower kilocalories of leisure time physical activity, higher cystatin C, and lower prevalence of current drinking and current smoking. Incidence rates of HF per 1000 person-years were 22.1, 22.0, 28.6, and 42.5 for the first to fourth quartiles of FABP4, respectively.

In a Cox proportional hazards model adjusting for age, ethnicity, gender, and clinic site, hazard ratios (HRs) of HF were 1 (reference), 1.00 [95% confidence interval (CI 0.84–1.20], 1.30 (95%

CI 1.09–1.54), and 1.97 (95% CI 1.68–2.32) from the lowest to the highest quartile of FABP4, *P* for trend <0.001. Each SD higher FABP4 (18.9 ng/mL) was associated with a HR of 1.32 (95% CI 1.25–1.38). However, additional adjustment for BMI, self-reported health status, education, kilocalories of physical activity, smoking, alcohol intake, heart rate, and eGFR using cystatin C attenuated this association (HR per 1 SD higher FABP4 was 1.09, 95% CI 1.01–1.17; *Table 2*). The eGFR using cystatin C followed by BMI were the most important confounders leading to the attenuation of the relative risk (*Table 3*). As expected, further adjustment for potential mediators of HF such as AF, systolic blood pressure, use of antihypertensive medications, diabetes, and coronary heart disease led to an attenuation of the effect measure (HR 1.05, 95% CI 0.97–1.13 per 1 SD higher FABP4).

In secondary analyses, similar associations were seen in African-Americans and Caucasians when analysed separately (data not shown) and there was no evidence for interaction between ethnicity and FABP4 on HF risk ($P = 0.9$). In addition, we did not observe any effect modification of the FABP4–HF relationship by age, sex, BMI, waist circumference, or prevalent diabetes (all *P*-values >0.2). In a subsample of HF cases ($n = 590$) with available data on LVEF, FABP4 was not associated with systolic (EF <55%) (HR 1.07, 95% CI 0.95–1.21) or diastolic HF (EF ≥ 55%) (HR 1.06, 95% CI 0.90–1.25). Further exclusion of people who reported unintentional weight loss or self-reported fair or poor health status ($n = 936$) did not alter the conclusions: the fully adjusted HR (95% CI) was 1.08 (95% CI 0.98–1.20) per 1 SD higher FABP4. Including coronary heart disease as time-varying covariate did not alter the results. Lastly, accounting for competing risks of death or restriction of analyses to the first 5 years of follow-up did not alter the conclusions (data not shown).

Table 2 Hazard ratios (95% confidence interval) for heart failure per standard deviation of fatty acid-binding protein 4 in the Cardiovascular Health Study[a]

Unadjusted model	Model 1[b]	Model 2[c]
1.18 (1.13–1.24)	1.32 (1.25–1.38)	1.09 (1.01–1.17)

[a]Standard deviation is 18.9 ng/mL.
[b]Adjusted for age, ethnicity, sex, and clinic site.
[c]Adjusted for age, ethnicity, sex, clinic site, body mass index, self-reported health status, education, log transformed kilocalories of physical activity, smoking, alcohol intake, heart rate, and estimated glomerular filtration rate by cystatin C.

Table 3 Influence of individual factors on the hazard ratios for heart failure per one standard deviation higher plasma fatty acid-binding protein 4

Adjusted for	HR (95% CI)
Model 1, adjusted for age, ethnicity, sex, and clinic site	1.32 (1.25–1.38)
Model 1 + eGFR by cystatin C	1.16 (1.09–1.24)
Model 1 + body mass index	1.27 (1.20–1.34)
Model 1 + self-reported health status	1.29 (1.23–1.35)
Model 1 + log-transformed kilocalories of physical activity	1.30 (1.24–1.36)
Model 1 + alcohol intake	1.30 (1.24–1.37)
Model 1 + heart rate	1.30 (1.24–1.37)
Model 1 + education	1.32 (1.25–1.38)
Model 1 + smoking	1.32 (1.26–1.38)

CI, confidence interval; eGFR, estimated glomerular filtration rate; HR, hazard ratio.

Discussion

In this prospective study among community-living older persons, we observed a positive association between plasma FABP4 and incident HF. Such an association was attenuated but remained statistically significant upon adjustment for traditional HF risk factors including BMI and eGFR, among others. Furthermore, there was no evidence of effect modification of the FABP4–HF association by ethnicity, age, sex, BMI, waist circumference, and diabetes status in this cohort of older US adults. The type of HF (systolic vs. diastolic) did not influence the FABP4–HF relationship.

To the best of our knowledge, this is the first study to examine the association between plasma FABP4 and the risk of HF in a prospective cohort of community-dwelling older men and women. Nevertheless, plasma FABP4 has been shown to predict cardiovascular mortality in people with coronary disease (HR 1.75, 95% CI 1.17–2.62 per unit increase in FABP4).[32] In addition, other investigators have examined the relationship of plasma FABP4 with HF risk factors. In healthy adults, FABP4 was associated with nearly a six-fold higher risk of metabolic syndrome comparing the highest with the lowest tertile of FABP4.[33] In the PREDIMED Study, plasma FABP4 concentration was associated with a higher incidence of atherogenic dyslipidaemia in women (HR 2.54, 95% CI 1.31–4.93 comparing the highest with the lowest tertile of FABP4).[34] Other investigators reported positive associations between FABP4 and HF risk factors including insulin resistance,[19–21] metabolic syndrome,[23,24,35] incident diabetes,[25] coronary disease,[20,26,27,36,37] and inflammation.[38] Despite these reports of associations between FABP4 and HF risk factors, our data are only consistent with a modest association between plasma FABP4 and incident HF after adjustment for adiposity measures and other confounders in the older community-living individuals studied here. This suggests that plasma FABP4 may not have a major influence on the risk of HF once major confounders are accounted for. In our analysis, it is noteworthy that adjustments for kidney function (using cystatin C to estimate the GFR) and BMI were responsible for a large proportion of the observed attenuation of the HRs. Such attenuation with adjustment for kidney function is consistent with a reported inverse relationship between FABP4 and eGFR in patients with coronary artery stenosis ($r = -0.41$, $P < 0.01$).[37]

In an experimental model, intervention with adipocyte-derived FABP4 from overweight and obese subjects led to reduced shortening amplitude as well as intracellular systolic peak Ca^{2+} in a dose-dependent manner in cardiomyocytes.[18] Those data suggest that FABP4 might be more associated with systolic than with

diastolic HF. However, in our data, the modest relationship of FABP4 with HF was not different for systolic or diastolic HF in a subsample of subjects with adequate data to estimate LVEF. It is important to acknowledge that we were underpowered to detect an association between FABP4 and HF subtype (systolic vs. diastolic HF) as we had information on LVEF for only 590 of the 1182 HF cases for classification.

It is important to acknowledge other limitations of our study. Given the observational study design, we cannot exclude residual or unmeasured confounding as an alternative explanation of our findings. The study sample consisted mainly of Caucasian older adults, thereby limiting the generalizability of our findings to other ethnic or age groups. In this cohort, we only had one measurement of plasma FABP4 obtained later in life (65+ years) and cannot exclude the possibility of a stronger relationship of plasma FABP4 with HF at younger ages. Furthermore, we were not able to account for change in plasma FABP4 over time in this study. We did not have data on LV function in all subjects with HF and, in participants with data on LVEF ($n = 590$), we acknowledge the heterogeneity in LVEF estimation (echocardiography and other imaging studies) as a limitation. We did not have adequate data to examine whether plasma FABP4 provides any incremental gain above and beyond currently recommended biomarkers for HF (i.e. natriuretic peptides).[39] Lastly, we did not have adequate information to examine whether the observed association differs by HF aetiology. On the other hand, our study has numerous strengths including a large number of study participants, data on both men and women, a representative US sample of older adults, use of a valid and reproducible method to assess plasma FABP4, a standardized and complete adjudication of HF and comorbidity, long-term follow-up, and availability of data on numerous potential confounders.

In conclusion, our study showed a positive yet modest association of plasma FABP4 with incident HF after adjustment for BMI, renal function, and other confounders in community-dwelling US older adults. If confirmed in future studies, plasma FABP4 might help improve early identification of people at risk of HF. Furthermore, FABP4 might also serve as a novel pharmacological target in HF management.

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