Heart Failure as a Risk Factor for Diabetes Mellitus

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Key Words

Heart failure · Diabetes mellitus · Risk factors

Abstract

Background: Diabetes mellitus (DM) is a well-recognized risk factor for heart failure (HF). We hypothesized that HF also increases the risk for DM. **Objective:** We explored the hypothesis that HF is a risk factor for DM. **Methods:** The Cardiovascular Health Study was a prospective cohort study of cardiovascular risk in ambulatory older adults. We used a limited-access dataset provided by the National Heart, Lung and Blood Institute. The impact of HF at baseline on DM after 3 or 4 years was examined in a cohort of 3,748 nondiabetic participants aged ≥ 65 years. The magnitude and significance of the association were evaluated using logistic regression models. Analyses were performed with and without adjustment for confounders and separately among subjects with normal and impaired fasting glucose at baseline. **Results:** Among subjects with normal fasting glucose at baseline, HF significantly increased the odds of developing impaired fasting glucose after 3 or 4 years [odds ratio (OR) 2.18, 95% confidence interval (CI) 1.03–4.61, $p = 0.043$] or overt DM (OR 4.78, 95% CI 1.84–12.4, $p < 0.001$). After adjusting for demographic and biomedical factors, HF remained significantly associated with a worsening DM status (OR 2.43, 95% CI 1.38–4.29, $p = 0.002$). **Conclusions:** In the elderly population, the presence of HF more than doubles the incidence of

DM within a few years. This association remains significant when adjusting for age, gender and cardiovascular comorbidities.

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Introduction

Diabetes mellitus (DM) is a well-recognized risk factor for many cardiovascular diseases. By accelerating atherosclerosis, DM facilitates the progression of ischemic heart disease, stroke and peripheral vascular disease. The relationship of DM with heart failure (HF) is less linear, but there is still plenty of evidence that these two conditions are connected. Specifically, incident HF occurs more commonly in patients with DM than in those with normal glucose metabolism [1]. In the Cardiovascular Health Study (CHS), incident HF occurred in 31 and 26% of matched participants with and without DM, respectively, over 13 years of follow-up [2].

Recently, there were several publications suggesting the reverse is also true, i.e. that HF precipitates the progression of DM. In a large Danish cohort study, which followed a nondiabetic population after acute myocardial infarction, those who developed HF as a result of ischemic cardiomyopathy were at a higher risk of new-onset DM, and the risk was proportionate to the severity of HF measured by the loop diuretic requirement [3]. The CHS

recorded both HF and the DM status of participants at different points in time, so we used this dataset to test the hypothesis that HF is also a risk factor for DM.

Methods

The CHS was a community-based prospective study of cardiovascular disease risk in ambulatory older adults. It was sponsored by the National Heart, Lung and Blood Institute (NHLBI). The purpose of the study was to investigate the risk factors for cardiovascular morbidity and mortality. The participants were recruited from random samples of Medicare beneficiaries aged ≥ 65 years in four different geographical areas of the USA, and who were expected to remain in the defined geographical area for at least 3 years. The original cohort of 5,201 community-dwelling individuals was recruited in 1989–1990 and a second cohort of 687 African-Americans was added in 1992–1993, giving a total of 5,888 participants [4]. Upon enrollment into the original study, subjects gave their informed consent. The study protocol was approved by the Institute's Committee on Human Research. No animal studies were conducted [5]. We used a deidentified, limited-access dataset from the CHS, provided to us by the NHLBI.

To determine the association between HF at baseline and risk of DM during follow-up, analyses were performed on 4,786 nondiabetic subjects for whom there was information on HF and DM status at baseline (fig. 1). Subjects being treated with insulin or oral hypoglycemic agents (known DM: $n = 498$) or if they had an 8-hour fasting plasma glucose level ≥ 126 mg/dl (newly diagnosed DM: $n = 448$) were excluded. Adjudication of HF was reviewed by the CHS Events Committee which classified all cardiovascular events. A self-report of a diagnosis of HF was followed by confirmation review of the participant's medical records.

Baseline independent measures included demographic and clinical characteristics [age, sex, race, educational level, self-reported health status, body mass index (BMI), smoking status, exercise and systolic and diastolic blood pressure], inflammatory biomarkers (fibrinogen, albumin and C-reactive protein), cardiovascular history besides HF and electrocardiographic variables [left-ventricular (LV) hypertrophy, estimated LV mass, atrial fibrillation and minor and major ST segment changes].

After the initial visit, nondiabetic participants were classified as having new-onset DM if they had elevated fasting glucose (≥ 126 mg/dl) or if insulin or oral hypoglycemic treatment had been initiated. Impaired fasting glucose was defined by a fasting blood glucose level of between 110 and 125 mg/dl. According to the CHS protocol, fasting glucose levels and new-onset DM were determined for all subjects only at 1 time point during follow-up, i.e. at 3 and 4 years after enrollment, for the original and additional cohorts, respectively. In other words, the incidence of DM was examined 3 years after baseline for cohort 1 and 4 years after baseline for cohort 2.

In this report, incident diabetes during follow-up is first examined separately for subjects with normal fasting glucose and impaired fasting glucose at baseline. The development of DM is also examined among subjects with impaired fasting glucose at baseline.

Statistical Analysis

Nondiabetic subjects at baseline, with either an available fasting glucose measurement or a known DM status after 3 or 4 years, were compared to other subjects at baseline for whom there was no DM information during follow-up. Differences in frequencies between demographic and lifestyle categorical groups were tested by χ^2 tests. When the expected number of subjects was < 5 in any cell, a Fisher's exact test was applied instead. When the variables were continuous, means were calculated and differences were tested by an independent two-sample t test. A multiple logistic regression identified the main factors associated with subjects included in the analysis.

Among the selected cohorts, a logistic regression model was fitted to examine how HF was associated with DM during follow-up. In addition to looking at all subjects, separate models were fitted for the subjects with normal fasting glucose and impaired fasting glucose at baseline. A logistic regression also examined the HF association with impaired fasting glucose during follow-up among subjects with normal fasting glucose at baseline. If the magnitude of the associations between HF and DM, or HF and impaired fasting glucose remained similar, the subgroups were combined by examining worsening DM status as an outcome and adjusting for whether or not the subject had had impaired fasting glucose at baseline. Worsening DM status was defined as going from normal fasting glucose (< 110 mg/dl) to either impaired fasting glucose or DM or, alternatively, when going from impaired fasting glucose to DM. Worsening DM was classified as a binary variable with a worsened DM status indicated by 1, and 0 indicating that the DM status was the same or improved.

In order to examine the cohort effect, an indicator variable was included in the models for the cohort to which the subject belonged. A hierarchical or blocked multiple logistic regression analysis was carried out to account for a wide range of potential confounders. The 1st block consisted of demographic, lifestyle and psychosocial factors, the 2nd included anthropometric factors and other diseases, the 3rd included medication and biological measures (e.g. potassium) and the 4th included other factors related specifically to HF. For each block of variables, a backward-selection criterion ($p < 0.10$) was applied to identify the most relevant factors associated with worsening DM. These variables were then added to the regression model. A final model was developed by retaining all variables that were associated ($p < 0.10$) in the previous multivariate regression model. Two-sided p values of < 0.05 were considered statistically significant. Analysis was performed using SAS 9.2 (SAS Institute Inc., Cary, N.C., USA) and SPSS 22.0 (IBM Corp., Armonk, N.Y., USA).

Results

From the original 4,010 subjects with normal fasting glucose at baseline and available baseline information, 3.7% were found to have had a history of HF. Of the 776 subjects with impaired fasting glucose, 4.4% had HF. Of the diabetic groups, 7.1% of the 448 who were newly diagnosed with DM had HF, and 10.4% of the 498 with known DM had HF. Further analysis excluded these sub-

Table 1. Demographic and lifestyle factors associated with available DM status information after 3- or 4-year follow-up among 4,786 nondiabetic subjects in the CHS

	Distribution of factors among subjects at 3 and 4 years, n (%)			Adjusted ORs for available DM status at 3 and 4 years as determined by multiple logistics regression		
	DM status not available	DM status available	p value	OR	95% CI	p value
Cohort						
Original (1989–1990)	884 (85.2)	3,425 (91.4)		1.00	ref.	
African-American (1992–1993)	154 (14.8)	323 (8.6)	<0.001	0.74	0.50–1.11	0.15
Congestive heart failure baseline						
No	949 (91.4)	3,653 (97.5)		1.00	ref.	
Yes	89 (8.6)	95 (2.5)	<0.001	0.33	0.24–0.45	<0.001
Gender						
Female	585 (56.4)	2,222 (59.6)		1.00	ref.	
Male	453 (43.6)	1,526 (40.7)	0.09	0.87	0.74–1.02	0.08
Race						
White	830 (80.0)	3,284 (87.6)		1.00	ref.	
Black	199 (19.2)	445 (11.9)		0.82	0.57–1.18	
Other	9 (0.9)	19 (0.5)	<0.001	0.58	0.25–1.38	0.31
Age, years						
65–70	324 (31.2)	1,717 (45.8)		1.00	ref.	
71–76	315 (30.3)	1,253 (33.4)		0.78	0.65–0.93	
>76	399 (38.4)	778 (20.8)	<0.001	0.41	0.34–0.50	<0.001
Education groups						
Some high school or less	416 (40.4)	913 (24.4)		1.00	ref.	
Technical college/some college	475 (46.1)	1,941 (51.9)		1.48	1.25–1.74	
4 years of college or more	129 (13.5)	888 (23.7)	<0.001	2.41	1.92–3.012	<0.001
Smoking status						
Never smoked	474 (45.7)	1,747 (46.7)		1.00	ref.	
Former smoker	397 (38.2)	1,566 (41.8)		0.97	0.83–1.15	
Current smoker	167 (16.1)	429 (11.5)	<0.001	0.64	0.51–0.80	0.003
Exercise						
None or low-intensity	695 (67.0)	1,963 (52.4)		1.00	ref.	
Moderate or high-intensity	342 (33.0)	1,784 (47.6)	<0.001	1.45	1.24–1.69	<0.001
BMI	26.2 (0.1)	26.3 (0.1)	0.54	1.01	0.99–1.03	0.41
Hypertension						
Normal	383 (39.9)	1,726 (46.1)		1.00	ref.	
Borderline	156 (15.0)	532 (14.2)		0.81	0.62–1.00	
Definite	499 (48.1)	1,484 (39.7)	<0.001	0.78	0.67–0.92	0.05

jects at baseline with either known or newly diagnosed DM.

At follow-up, 1,038 subjects did not have a fasting glucose measurement or information on DM status. Table 1 shows the factors associated with the availability of DM status. Not having a history of HF, being of younger age, having a higher level of education, being a current smoker and the absence of hypertension at baseline were significantly associated with the availability of DM status at follow-up.

Of the 3,748 subjects who had a follow-up visit after 3 or 4 years (fig. 1), 3,653 did not have HF at baseline and 95 did have HF at baseline.

Among the subjects with normal fasting glucose at baseline, HF significantly increased the odds of developing impaired fasting glucose [odds ratio (OR) 2.18, 95% confidence interval (CI) 1.03–4.61, $p = 0.043$] or overt DM (OR 4.78, 95% CI 1.84–12.4, $p < 0.001$) at follow-up (table 2). Among the subjects with impaired fasting glucose at baseline, HF also increased the odds of developing

Fig. 1. Study population. IFG = Impaired fasting glucose.

DM (OR 2.42; table 3). Since the magnitude of the associations across the different subgroups and comparisons remained similar, the groups were combined, and worsening DM was examined as an outcome. Baseline impaired fasting glucose was included in the model. Overall, HF significantly increased the odds of a worsening DM status after 3 or 4 years (OR 2.61, 95% CI 1.54–4.42, $p < 0.001$; table 4).

There was no cohort effect and the association persisted when adjusted for demographics, lifestyle, psychosocial and anthropometric features, comorbidities, medications, normal or impaired fasting glucose and factors

related specifically to HF at baseline (tables 3–5). LV mass at baseline was significantly associated with worsening DM, but not after adjusting for baseline BMI.

Discussion

In this study, we examined the relationship between HF and DM in an elderly population and demonstrated that a history of HF is associated with a 2-fold increase in the risk of new-onset DM within 3 or 4 years, compared to a population without prior HF. This association seems

Table 2. HF at baseline and in association with DM status after 3 or 4 years of follow-up among subjects with normal fasting glucose at baseline (n = 3,165)

Follow-up DM status among all subjects with normal fasting glucose at baseline (n = 3,165)	HF at baseline		OR (95% CI) for DM or impaired fasting glucose	p value
	no (n = 3,085)	yes (n = 80)		
Remained normal, n	2,882 (93.4%)	67 (83.8%)	1.00 (ref.)	
Impaired fasting glucose, n	158 (5.1%)	8 (10.0%)	2.18 (1.03–4.61)	0.043
DM, n	45 (1.5%)	5 (6.2%)	4.78 (1.84–12.4)	<0.001

Table 3. Multivariate logistic regression models of HF on worsening DM status after 3 or 4 years among nondiabetic subjects with and without adjustment for demographic, lifestyle, psychosocial, anthropometric and other disease factors

Predictors	Multivariate logistic regression of HF on DM status						
	model 1 adjustment adjusting for associated demographic, lifestyle and psychosocial factors (n = 3,736/3,748) ^a			model 2 adjustment adjusting for associated factors in model 1 as well as anthropometric factors and other diseases (n = 3,710/3,748) ^b			p value
	OR	95% CI	p value	OR	95% CI	p value	
HF at baseline							
No	1.00	ref.		1.00	ref.		
Yes	2.44	1.44–4.16	0.001	2.36	1.36–4.08		0.002
Gender							
Female	1.00	ref.		1.00	ref.		
Male	1.37	1.08–1.74	0.010	1.29	0.98–1.70		0.067
Low education							
No	1.00	ref.		1.00	ref.		
Yes (some high school or less)	1.39	1.08–1.89	0.011	1.26	0.97–1.63		0.082
Smoking status							
No	1.00	ref.		1.00	ref.		
Previously or currently	1.23	0.97–1.57	0.090	1.26	0.98–1.61		0.070
Impaired fasting glucose							
No, fasting glucose normal	–	–	–	1.00	ref.		
Yes	–	–	–	2.30	1.77–2.99		<0.001
BMI	–	–	–	1.11	1.07–1.14		<0.001
Waist-to-hip ratio, cm	–	–	–	3.56	0.57–22.2		0.17

^a Demographic (e.g. gender, age), lifestyle (e.g. smoking, exercise, alcohol consumption) and psychosocial factors (e.g. depression score, life-events score, social-network score) were determined for association ($p < 0.10$) with worsening DM status by backward-selection criteria.

^b Anthropometric (e.g. BMI, weight, height) and other diagnoses (e.g. ever diagnosed with cancer, hypertension, pneumonia, asthma) were interdependently determined for association ($p < 0.10$) with DM status: factors associated were added to demographic, lifestyle and psychosocial factors found to be associated in the model 1 adjustment.

to be independent of age, gender and cardiovascular comorbidities (e.g. a history of hypertension). This study is among the first to report that, not only is DM a risk factor for HF, HF is also a risk factor for DM.

Since the Framingham study, it has been known that DM increases the odds of developing HF [1]. Further-

more, it has been reported that poor glycemic control is associated with a higher rate of HF admissions [6]. For example, Iribarren et al. [7], in a cohort of about 50,000 diabetic patients (none of whom had a reported history of HF), reported that each 1% increase in HbA1c correlated with an 8% increased risk of HF. Unfortunately,

Table 4. Multivariate logistic regression models of HF on worsening DM status after 3 or 4 years among nondiabetic subjects with and without adjustment for demographic, lifestyle, psychosocial, anthropometric, other diseases, medications and other factors related to HF

Predictors	Multivariate logistic regression of HF on DM status					
	Model 3 adjustment adjusting for associate factors in model 2 as well as DM medications and other biological measures (n = 3,715/3,748) ^a			Model 4 adjustment adjusting for associated factors in model 3 as well as factors related to HF (n = 3,492/3,748) ^b		
	OR	95% CI	p value	OR	95% CI	p value
HF at baseline						
No	1.00	ref.		1.00	ref.	
Yes	2.35	1.35–4.11	0.003	2.20	1.24–3.91	0.007
Gender						
Female	1.00	ref.		1.00	ref.	
Male	1.37	1.05–1.79	0.020	1.35	0.97–1.86	0.071
Low education						
No	1.00	ref.		1.00	ref.	
Yes (some high school or less)	1.26	0.97–1.63	0.084	1.29	0.98–1.70	0.069
Smoking status						
No	1.00	ref.		1.00	ref.	
Previously or currently	1.26	0.98–1.61	0.070	1.23	0.95–1.59	0.118
Impaired fasting glucose						
No, fasting glucose normal	1.00	ref.		1.00	ref.	
Yes	2.29	1.75–2.99	<0.001	2.27	1.73–2.99	<0.001
BMI	1.11	1.08–1.15	<0.001	1.10	1.06–1.14	<0.001
High-density lipoprotein, mg/dl	1.00	0.99–1.10	0.516	–	–	–
Alpha-blockers						
No	1.00	ref.		–	–	–
Yes	1.45	0.71–2.94	0.307	–	–	–
Any diuretic						
No	1.00	ref.		–	–	–
Yes	1.02	0.77–1.35	0.894	–	–	–
Fatigue in last 2 weeks						
No				1.00	ref.	
Yes				1.27	1.95–1.61	0.111
C-reactive protein (mg/l)						
1st quartile				1.00	ref.	
Interquartile (2nd–3rd)				1.27	0.90–1.78	
4th quartile				1.42	0.95–1.61	0.188
General health						
Excellent/very good				1.00	ref.	
Good				1.15	0.86–1.53	
Fair/poor				1.43	1.02–2.02	0.120
LV mass, g				1.02	0.97–1.07	0.389

^a Medications related to HF and DM (e.g. beta-blockers, alpha-blockers, angiotensin-converting enzyme inhibitors) and other biological measures (e.g. potassium, high-density lipoprotein) were determined for association ($p < 0.10$) with DM status by backward-selection criteria and added to associated ($p < 0.10$) factors in model 2.

^b Factors related to HF (e.g. LV mass, LV function, creatinine, uric acid, fatigue, trouble sleeping, minor/major ECG abnormalities) were determined for association ($p < 0.10$) with DM status by backward-selection criteria and added to associated ($p < 0.10$) factors in model 3.

Table 5. Association between HF at baseline and DM during follow-up for subjects with and without the most common treatments reported

Medications	All subjects	CHF at baseline	IGT/DM follow-up	Association between baseline CHF and DM status after 3 or 4 years		
				OR	95% CI	interaction p value
ACE inhibitor						
No	3,526 (94.2)	74 (77.9)	294 (92.5)	2.41	1.31–4.43	0.754
Yes	219 (5.8)	21 (22.1)	24 (7.5)	2.94	0.97–8.93	
Alpha-blocker						
No	3,682 (98.3)	94 (98.9)	308 (96.9)	2.69	1.59–4.57	no subject had both CHF and DM
Yes	63 (1.7)	1 (1.1)	10 (3.1)			
Beta-blocker						
No	3,295 (88.0)	85 (89.5)	268 (84.3)	3.18	1.86–5.44	no subject had both CHF and DM
Yes	450 (12.0)	10 (10.5)	50 (15.7)			
Antiarrhythmic (class 1)						
No	3,638 (97.1)	86 (90.5)	308 (96.9)	2.55	1.46–4.45	0.803
Yes	107 (2.9)	9 (9.5)	10 (3.1)	3.21	0.57–18.1	
Any calcium blocker						
No	3,314 (88.5)	72 (75.8)	276 (86.8)	2.26	1.20–4.25	0.422
Yes	431 (11.5)	23 (24.2)	42 (13.2)	3.65	1.35–9.83	
Hypertension medication						
No	2,167 (57.9)	24 (25.3)	154 (48.5)	4.49	1.75–11.5	0.110
Yes	1,578 (42.1)	71 (74.7)	164 (51.6)	1.81	0.95–3.45	
Potassium supplements						
No	3,545 (94.7)	67 (70.5)	292 (91.8)	3.04	1.67–5.55	0.128
Yes	200 (5.3)	28 (29.5)	26 (8.2)	1.14	0.36–3.58	
Nonsteroidal anti-inflammatory agents						
No	3,210 (85.7)	76 (80.0)	268 (84.3)	2.56	1.41–4.63	0.925
Yes	535 (14.3)	19 (20.0)	50 (15.7)	2.73	0.87–8.55	
Nitrates						
No	3,486 (93.1)	68 (71.6)	287 (90.3)	2.99	1.64–5.45	0.205
Yes	259 (6.9)	27 (28.4)	31 (9.7)	1.32	0.42–4.10	
HF propensity score ^a						
Lower 4 quintiles	2,972 (79.4)	35 (36.8)	237 (74.5)	2.42	1.00–5.90	0.947
Upper quintiles	773 (20.6)	60 (63.2)	81 (25.5)	2.33	1.18–4.61	

Figures are n (%) unless indicated otherwise. ACE = Angiotensin-converting enzyme; CHF = congestive heart failure; IGT = impaired glucose tolerance.

^a Propensity score for HF with all medications included as predictors in logistic regression.

tightening the control of blood glucose did not appear to result in a decreased risk of HF [8].

HF has been sometimes listed as one of the cardiovascular complications of DM [9]. However, relatively few studies have addressed the issue of HF potentially precipitating the development of DM [3, 10, 11]. We recently reviewed these studies and introduced the term ‘cardiogenic diabetes’ [12].

The CHS cohort has provided many valuable insights into the relationship of DM and HF. Gottdiener et al. [5]

confirmed that DM is a risk factor for incident HF. Barzilay et al. [13] reported that the presence of higher fasting glucose levels also increases the risk of HF. Egstrup et al. [14] found that DM was independently associated with reduced LV contractile reserve and exercise intolerance in patients with HF. Diastolic function of the left ventricle was also impaired in patients with DM [15]. However, despite these findings, we could not find any published studies from the CHS exploring the relationship between HF and the subsequent development of new-onset DM.

Several other cohort studies have identified a potential connection between HF and subsequent DM. In a large, nationwide Danish cohort of patients discharged after admission for their first myocardial infarction and with no history of either DM or HF, about 20% developed HF and 5% developed DM during the follow-up. An increasing HF severity, measured by loop diuretic requirements, was associated with increased risk of DM. Depending on whether patients were receiving angiotensin-converting enzyme inhibitors for HF, the adjusted HRs (95% CIs) for the development of DM were 1.34 (1.11–1.63), 1.63 (1.40–1.90) and 1.68 (1.25–2.25) for mild, moderate and severe HF (when compared to no HF), and 1.45 (1.13–1.88), 1.90 (1.56–2.33) and 3.02 (2.01–4.54), respectively [3]. Another study similarly found (regardless of etiology) that HF increased the risk of new-onset DM [16].

Therefore, it is logical to suggest that improvements in HF treatment may result in better glycemic control and improvement in the course of DM, in general. Indeed, a recent small study from Columbia University ($n = 15$) demonstrated, for the first time, that LV assist device implantation, which is the ultimate treatment for HF, improves glycemic control and reduces requirements for insulin and oral DM drugs [17]. This would seem to support that cause and effect may, in some circumstances, actually be reversed, and that HF could indeed influence the development of DM.

Some of the data that are traditionally interpreted as the evidence for DM being a precipitating factor of HF can, in fact, be understood in the opposite way. For instance, Suskin et al. [18] showed that, in nondiabetic patients with HF, elevated fasting glucose was associated with more severe cardiac symptoms, a worse New York Heart Association functional class and a shorter 6-min walk distance. It is possible that more severe HF accompanied by worse symptoms and poorer tolerance to exercise, resulted in elevated blood glucose in these patients without DM. Another cohort study of hospitalized nondiabetic patients with HF demonstrated a 2-fold increase in in-hospital mortality if admission blood sugar was in the upper tertile (7.2%) rather than in the lower (3%) and middle (4%) tertiles ($p = 0.02$). Furthermore, mortality risk was correlated with admission glucose levels [19]. This finding can also be interpreted equivocally. In our study, we examined the history of HF in a nondiabetic population and tested for an association with DM status after 3 or 4 years. While the CHS was not designed for/is not ideal for looking at the possibility of reverse causation, our analysis does add further credence that HF may lead to a worsening DM status and that future designs for

longitudinal studies should consider the detailed measurement of both diseases to be able to examine the underlying causal mechanisms. Without detailed biomarker information on both diseases, it will always be difficult to discriminate between the hypothesis that impaired glucose metabolism leads to a worse HF status and the alternative, i.e. that HF causes a greater impairment of glucose metabolism.

Currently, the mechanisms proposed for the association of HF with DM are unclear, but there are several possible explanations. Neurohormonal activation, in particular, increased levels of cortisol and catecholamines (typically present in HF) increase the level of blood glucose [20]. Activation of the sympathetic system stimulates gluconeogenesis as well as glycogenolysis, and therefore increases glucose production in the liver. In addition, elevated catecholamines can increase insulin resistance and this seems to reduce the release of insulin from the pancreas [21, 22]. Insulin resistance appears to progress with increasing severity of HF [23].

Another potential mechanism connecting the two conditions is a low-grade chronic inflammation with activation of multiple factors including, but not limited to, tumor necrosis factor alpha and interleukins, characteristic for HF as well as DM [24, 25].

Limitations

As the CHS was designed to look at cardiovascular outcomes and not at DM, the analysis was limited to 78.4% of subjects from the original nondiabetic cohort. A comparison of demographic and lifestyle factors between the selected and nonselected subjects shows significant differences in level of educations, exercise intensity and age at baseline. Therefore, it cannot be excluded that there was selection bias, and the magnitude of the association may be different among less-educated subjects, older subjects or those who did not exercise. In all, 47.6% subjects who were included in this study reported exercising moderately or highly while only 33.0% of the excluded subjects reported this.

The development of new-onset DM in HF is of practical importance because it is associated with increased mortality and morbidity [26]. In the CHS, the association of DM with incident HF marked an increased mortality level, independent of other cardiovascular risk factors [2].

Conclusions

In the elderly population, HF is a risk factor for new-onset DM. The presence of HF doubles the chances of developing DM within a few years. This association remains significant after adjustment for age, gender, overall health status and specific cardiovascular comorbidities such as hypertension.

Acknowledgment

The CHS was conducted and supported by the NHLBI in collaboration with the CHS Investigators.

Conflict of Interest

This report was prepared using a limited-access dataset obtained by the NHLBI and does not necessarily reflect its opinions or views or those of the CHS.

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