Diabetes and Idiopathic Cardiomyopathy

A nationwide case-control study

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OBJECTIVE — Controversy exists regarding the relation between diabetes and nonischemic idiopathic cardiomyopathy (ICM), and only limited data on the incidence of ICM in adults with diabetes are available. Therefore, we used the 1995 Nationwide Inpatient Sample (NIS) to determine discharge rates and test the hypothesis that diabetes is independently associated with ICM.

RESEARCH DESIGN AND METHODS — The 1995 NIS includes demographic and diagnostic data on all discharges from >900 representative hospitals in 19 states. ICD-9 codes were used to identify ICM, defined as discharges with a diagnosis of primary cardiomyopathy but without established risk factors for cardiomyopathy. Control subjects were selected by stratified random sampling by age to yield 10 per ICM case. The analyzed covariates included age, race, median income, diabetes, and hypertension. Multivariate logistic regression was used to conduct case-control analyses.

RESULTS — Using sampling weights, we estimated that in 1995, the rate of hospital discharge for ICM among individuals diagnosed with diabetes was 7.6 per 1,000. The prevalence of diabetes was substantially higher in the 44,837 ICM vs. 450,254 control subjects (26.6 vs. 17.2%), corresponding to a relative odds (RO) of 1.75 (95% CI 1.71–1.79). After adjusting for age, sex, race, hypertension, and median income using multiple logistic regression, diabetes remained significantly associated with ICM (RO 1.58, 95% CI 1.55–1.62).

CONCLUSIONS — We concluded that diabetes is independently associated with ICM in the general U.S. population.

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Diabetes is a well-established risk factor for congestive heart failure (CHF) (1). Much of the excess risk of heart failure among diabetic individuals is thought to come from coronary artery disease and its complications (1,2). However, data from autopsies and animal experiments, as well as clinical human cardiac studies, have tended to support the existence of a distinct "diabetic cardiomyopathy" unrelated to atherosclerosis (3). Postulated etiologic factors include hyperglycemia, hypertriglyceridemia, and hypertension, which in turn cause microvascular abnormalities, endothelial dysfunction, derangement of myocardial metabolism, glycosylation of cardiac tissues, and autonomic neuropathy (2). Although historically conceptualized as a dilated cardiomyopathy in patients without obstructive coronary atherosclerosis, most of the clinical evidence supporting the existence of a diabetic cardiomyopathy has demonstrated diastolic dysfunction in people without CHF rather than nonischemic systolic failure (2,4–6).

If diabetes leads to systolic dysfunction, then it should be a risk factor for idiopathic cardiomyopathy (ICM), a condition characterized by decreased systolic function with a dilated left and/or right ventricle. ICM is classified as "idiopathic" if it occurs in the absence of known causes of heart muscle dysfunction such as ischemia, alcoholism, or myocarditis (7). The proportion of all dilated cardiomyopathies in the idiopathic population is uncertain, but may be as high as 51% (8), corresponding to annual incidence rates of 5–8 per 100,000 in populations of European ancestry (7). Case-control studies assessing diabetes as a risk factor for ICM have reported conflicting results, perhaps because of small sample sizes or variation in criteria for selecting control subjects (9–11). However, few traditional cohort studies have systematically assessed left ventricular function in samples large enough to identify a statistically sufficient number of ICM cases. Therefore, we conducted a case-control study nested within a national hospital discharge database to determine the occurrence of ICM among individuals with diabetes and to test the hypothesis that diabetes is independently associated with ICM.

RESEARCH DESIGN AND METHODS

Data source

Data are from the Nationwide Inpatient Sample (NIS), collected under the Healthcare Cost and Utilization Project 1988–1995, a product of the Agency for Healthcare Research and Quality. The NIS is designed to approximate a 20% sample of all nonfederal, short-term general and specialty hospitals in the U.S. The sampling strategy selects hospitals within participating states according to defined strata based on ownership, bed size, teaching status, urban/rural location, and

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Abbreviations: CDC, Centers for Disease Control and Prevention; CHF, congestive heart failure; ICM, idiopathic cardiomyopathy; NIS, Nationwide Inpatient Sample.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

See accompanying editorial, p. 2949.

region. The 1995 NIS has discharge level information on primary and secondary diagnoses and procedures and demographics on all discharges from >900 hospitals in 19 states. Each discharge must be considered independently, as data elements that could directly or indirectly identify individuals are excluded (12). The NIS contains sampling weights, including strata, primary sampling unit, discharge-level probability weight, and a finite population correction factor, thereby enabling the calculation of national estimates using these data.

Table 1—*Comparison of characteristics of ICM case and control subjects*

Characteristic	Cases	Control subjects
n	44,837	450,388
Age (years)	66.3 ± 16.3	63.3 ± 22.9
Race		
White	71.7	80.6
Black	21.1	10.8
Other	7.2	8.6
Male	55.3	43.6
Zip code income		
<$20,000	13.7	11.7
$20,000–44,999	75.6	76.5
≥$45000	10.7	11.8
Hypertension	34.8	32
Diabetes	26.6	17.2

Data are percent or means ± SD. Data for race reflect 82% of discharges reporting race. Data for zip code income reflect 89% of discharges reporting median income of zip code of discharged patient.

Case selection

Cases were selected from among all discharges (alive or deceased) with a diagnosis of primary cardiomyopathy (ICD-9, code 425.4) in any diagnosis field. Based on previous experience at Johns Hopkins Hospital (8), we excluded individuals with the following comorbid conditions at discharge (insofar as they were likely indicators of an alternate cause of dilated cardiomyopathy): pregnancy, ischemic heart disease, valvular heart disease, alcoholism, thyroid disease, HIV infection or AIDS, amyloidosis, myocarditis, or chemotherapy-related diagnoses. (See APPENDIX for ICD-9 codes).

Control subject selection

Stratified random sampling was performed to select ~10 control subjects per case (13). We first divided the cases into quintiles based on age, divided the entire database into strata based on the case age quintiles, and finally selected a random sample of noncases within each age quintile by applying the appropriate sampling fraction to yield 10 control subjects per case. A sensitivity analysis was also performed using an alternate control group consisting of all control subjects without ischemic heart disease.

Covariates

Demographic covariates analyzed included age, sex, median income, and race. The median income of the discharge's residence zip code was reported in eight income categories, ranging from <$15,000 to >$45,000. We treated zip code income as a categorical variable and included an indicator for "missing" so as not to exclude the 11% missing these data. Race was systematically missing from certain hospitals and states (18% of total), thus we defined race as "black," "white," "other," or "missing." Discharges with a diabetes ICD-9 code (250.xx) among any diagnosis field were considered to have diabetes. We also identified discharges with diabetic microvascular complications (250.4, diabetes with renal manifestations; 250.5, diabetes with ophthalmic manifestations; 240.6, diabetes with neurological manifestations) and diabetic macrovascular complications (250.7, diabetes with circulatory disorders [i.e., peripheral vascular disease]); all other discharges with diabetes were considered to have uncomplicated diabetes. Hypertension was defined as the presence of ICD-9 codes 401–404 among discharge diagnoses.

Statistical analysis

Exploratory data analysis was performed using summary statistics (*t* and χ^2 tests). The unit of analysis was the hospital discharge, as we lacked data to identify individuals who had been admitted with ICM on two or more occasions. Multivariate logistic regression was used to calculate adjusted relative odds (RO) (13). All significance tests were two sided. Analyses were performed using Stata 6.0 (College Station, TX). National estimates of discharges with ICM were generated by applying the provided sampling weights using Stata survey estimation commands. Denominator data for the general U.S. population were obtained from the Centers for Disease Control and Prevention (CDC) for the 1995 population with diabetes and the U.S. Census 1995 population estimates (14,15).

Funding source and institutional review board

The funding source played no role in the interpretation of data or preparation of this study. This project was deemed exempt from review by the local institutional review board because existing publicly available data were used in a manner such that the subjects could not be identified.

RESULTS

Identification of case and control subjects

We identified 104,385 discharges with any cardiomyopathy (ICD-9 425.x) from among 6,713,935 discharges; of these, 90,097 were coded as having primary cardiomyopathy (ICD-9 425.4). There were 45,260 considered to have an alternate explanation for cardiomyopathy, with most (35,544) having a codiagnosis of ischemic heart disease. The remaining 44,837 were classified as ICM according to our definition, which represented 49.8% of discharges with primary cardiomyopathy. Among ICM cases, 63% had a codiagnosis of CHF. The mean age of cases was 66.3 years (range 0–105), whereas the mean age of all discharges in NIS was 45.5 years. Among the noncases, sampling fractions of 2.6, 12.2, 13.4, 13.4, and 12.9% were taken from among the 0–19, 20–37, 38–59, 60–74, and ≥75 age quintiles, respectively. This produced 450,254 control subjects, with a mean age of 62.8 years. A greater percentage of cases were male, were black, had

Table 2—*Relative odds of ICM by selected characteristics*

	Univariate	Multivariate
Black	2.19 (2.13–2.25)	2.38 (2.32–2.46)
Male	1.59 (1.56–1.62)	1.63 (1.60–1.66)
Median income		
<$20,000	1.29 (1.24–1.33)	1.05 (1.01–1.09)
$20,000–44,999	1.09 (1.06–1.13)	1.04 (1.01–1.08)
≥$45,000	1.0 (reference)	1.0 (reference)
Hypertension	1.15 (1.13–1.17)	0.94 (0.92–0.96)
Diabetes	1.75 (1.71–1.79)	1.58 (1.55–1.62)

Data are RO (95% CI). Multivariate odds were adjusted for age, sex, race, zip code median income, diabetes, and hypertension.

diabetes, and lived in lower median zip codes compared with control subjects (Table 1).

Discharge rates

By applying the sampling weights to generate national hospital discharge statistics, we estimated that in 1995, there were 62,405 ± 1,565 (±SE) hospital discharges for individuals with diabetes and ICM nationwide. Dividing the number of these discharges by the estimated 8.25-million diagnosed cases of diabetes in 1995 (taken from CDC surveillance statistics) (14), we estimated that the annual discharge rate for ICM is 7.6 per 1,000 persons diagnosed with diabetes in the U.S. (95% CI 7.2–7.9 per 1,000). The estimated number of all discharges with ICM was 234,250 ± 5,395 (±SE). The estimated 1995 population was 262.8 million; thus the rate of hospital discharge with ICM was 0.89 per 1,000 (95% CI 0.85–0.93 per 1,000), a rate about ninefold lower than that for diabetic patients.

Case-control analyses

ICM cases were 75% more likely to have diabetes than control subjects (RO 1.75, 95% CI 1.71–1.79). Cases were more likely to be black, male, and hypertensive and were more likely to reside in lower income zip codes (Table 2).

After adjusting for the residual age differences between case and control subjects, diabetes remained significantly associated with ICM (RO 1.67, 95% CI 1.63–1.70). Adjustment for hypertension, sex, race, and median zip code income attenuated this association only slightly (RO 1.58, 95% CI 1.55–1.62) (Table 2). This association was even stronger after excluding ischemic heart disease from control subjects, as we had previously done with cases (RO 1.89, 95% CI 1.85–1.94). Diabetes was still significantly associated with ICM after redefining cases as the subset with ICM, but without a codiagnosis of CHF (RO 1.25, 95% CI 1.20–1.30).

Although diabetes was significantly associated with ICM in all stratified analyses, the relation was slightly stronger in women than men (RO 1.68 vs. 1.51; $P < 0.001$ for interaction) and stronger in whites than in blacks (RO 1.66 vs. 1.25; $P = 0.001$ for interaction) and those without than with hypertension (RO 1.76 vs. 1.21; $P < 0.001$ for interaction).

To minimize the potential for bias related to multiple discharges of the same individuals, we performed an analysis in which we attempted to exclude hospital readmissions. We ascertained that there were at least 35,428 unique ICM discharges (based on unique combinations of age, zip code, hospital, sex, and race). When limiting analyses to these cases, the relation between diabetes and ICM did not appreciably change (adjusted RO 1.54, 95% CI 1.50–1.58).

To test the hypothesized relation between diabetic microvascular disease and ICM, we performed a subsidiary analysis, with diabetes status defined into four categories: nondiabetic, microvascular diabetes, macrovascular diabetes, or uncomplicated diabetes. Compared with discharges without diabetes, those with microvascular complications were most likely to have ICM (RO 2.47, 95% CI 2.36–2.59). A significant association remained between uncomplicated diabetes and ICM (RO 1.44, 95% CI 1.41–1.48). (Fig. 1)

Finally, to test the specificity of the relation between diabetes and ICM, we determined the association of diabetes to two other types of heart disease: cardiomyopathy attributable to valvular heart disease (7,201) and peripartum heart disease (279). In contrast to the strong relation between diabetes and ICM, there was a weak relation between diabetes and cardiomyopathy related to valvular heart disease (RO 1.06, 95% CI 1.00–1.13) and an apparent protective association with peripartum cardiomyopathy (RO 0.54, 95% CI 0.31–0.96).

CONCLUSIONS — These results support the following conclusions. First,

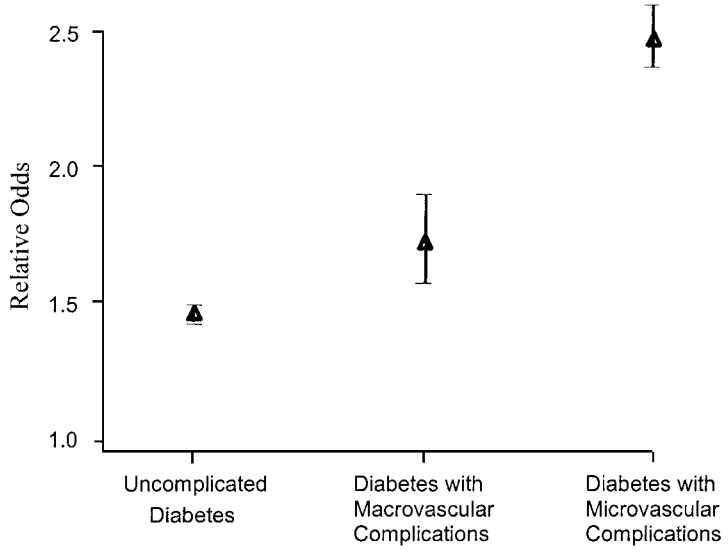

Figure 1—*Association of diabetes status with ICM in 44,837 case and 450,254 control subjects. Triangles are relative odds point estimates with vertical bars representing 95% CI.*

hospitalization for ICM occurred at a much higher rate among individuals with diabetes than in the general population. Second, diabetes was associated with ICM independently of age, race, income, or hypertension. Third, the relation between diabetes and ICM was present in men and women and in blacks and whites. Fourth, the association between diabetes and ICM was strongest among discharges with microvascular complications of diabetes, suggesting a possible link to hyperglycemia in terms of duration, severity, and/or susceptibility to myocardial injury. Finally, this relation was quite specific to ICM.

The strengths of our study included the use of a nationally representative discharge database; the selection of case and control subjects from a uniform database, making information bias unlikely; a rigorous case definition to exclude known causes of cardiomyopathy; and the selection of an age-stratified random sample of all control subjects. The main limitation was an exclusive reliance on administrative data for all aspects of the study demographic variables as well as case and covariate definition. This raises concerns about potential misclassification bias. We used the same ICD-9 codes for cardiomyopathy as a prior study for hospital case identification (11). High specificity, but lower sensitivity, has been demonstrated for such diagnoses as CHF, hyperlipidemia, angina, and diabetes when clinical and claims data were compared (16). The identification of hypertension using ICD-9 codes from hospitalization may be insensitive, as it is seldom a primary reason for hospitalization. Nondifferentially misclassified diagnoses would tend to bias our results toward the null. Sex, age, race, and zip code–derived income variables are unlikely to be misclassified in a differential manner with respect to cardiomyopathy.

There was the potential for differential misclassification based on detection bias, if cases were more likely to be diagnosed with diabetes than control subjects, given the known relation between diabetes and CHF, as well as between diabetes and heart disease, in general. This may explain the slightly attenuated association of diabetes with ICM when cases with CHF were excluded; nevertheless, a significant risk association remained for diabetes. However, control subjects were also hospitalized, and thus likely to have increased detection of diabetes compared with outpatients. Furthermore, there was little or no association between diabetes and other types of nonischemic cardiomyopathy.

Because no unique personal data were included, we could not identify multiple hospitalizations by the same individual. Therefore, our results are mainly confined to discharges rather than individuals, and we report discharge rates per population rather than incidence or prevalence per population. Nonetheless, when we limited our analysis to those discharges unique with respect to age, sex, race, zip code, and hospital, the associations did not substantially change.

Our results with regard to diabetes were consistent with those of prior studies, whether they were case-control analyses (RO 1.6–2,3) or a male-only cohort study (RO 2.97) (9,11,17,18). Likewise, our finding of an association of having ICM with being black and having lower income has been previously demonstrated (9,11). Our risk estimate for diabetes may have been conservative as we could not use community control subjects, and, in our main analysis, we did not exclude discharges with ischemic heart disease from the control subjects, who also have a high prevalence of diabetes.

Diabetes may increase the risk for ICM via the relation between metabolic abnormalities and vascular disease. Chronic hyperglycemia leads to microvascular disease, and it has been proposed that this in turn contributes to impaired circulation in the endomyocardial vasculature, causing a reduced coronary flow reserve (4,19). Elevated triglycerides, a common finding in diabetes, has also been shown to reduce coronary flow reserve (20). Insulin resistance is associated with both diabetes and impaired endothelial function, which may lead to heart muscle dysfunction as a consequence of compromised myocardial blood flow, particularly under conditions of increased demand (2). Similar pathophysiological mechanisms have been proposed to be responsible for chest pain with normal coronary arteriograms ("cardiac syndrome X") (21). Alternatively, diabetes may be associated with ICM attributable to unrecognized or subclinical ischemic heart disease, if extensive evaluations for coronary atherosclerosis are not performed and/or typical symptoms of ischemic heart disease are not present.

If diabetes causes truly nonischemic heart disease, hyperglycemia and its biochemical consequences may play an important role via either direct metabolic effects on myocytes or glycoprotein deposition leading to myocardial fibrosis (22,23). However, because ICM is rare, hyperglycemia alone is likely not sufficient to cause cardiomyopathy. Alternatively, hypertension may mediate between diabetes and ICM, as it is common among adults with diabetes (24). We could not assess history of hypertension in our cases, and our finding of a stronger relation between diabetes and ICM when hypertension-related diagnoses were absent may have been attributable to the cross-sectional nature of the data and the observation that individuals with ICM tend to have low blood pressure stemming from poor systolic function. It is also possible that diabetic cardiomyopathy is a risk state for the subsequent development of ICM. Although the term diabetic cardiomyopathy was first used to describe heart failure in diabetic patients in the absence of coronary atherosclerosis (25), it may be that the early impairment of diastolic function seen even in asymptomatic persons with diabetes (2,25–27) should be labeled "diabetic cardiomyopathy." This abnormal myocardium is then subject to further injury, leading to systolic dysfunction. For most individuals with diabetes and heart failure, the damage is mediated by atherosclerosis and ischemia (1,28). However, in some individuals, other injurious factors unrelated to coronary artery atherosclerosis predominate, leading to idiopathic cardiomyopathy.

We know of no incidence or prevalence data for ICM in individuals with diabetes. To place our estimate of 7.6 discharges of diabetes and ICM per 1,000 people with diagnosed diabetes in perspective, it is in the same range as the rate of hospital discharge for diabetes-related lower extremity amputation (9.4/1,000) (14). The rate of hospital discharge of ICM is 89/100,000; this compares with a prevalence of ICM in Minnesota of 36.5/100,000 in 1985 (29).

The main implication of our findings is that diabetes appears to be significantly associated with nonischemic systolic dysfunction and that diabetes-related ICM may occur more frequently than has been suspected. Future research should seek to

determine whether there is a directly cardiotoxic effect of hyperglycemia and to disentangle the pathways between the early diastolic dysfunction seen in diabetes and the subsequent development of systolic dysfunction attributable to either ischemic heart disease or idiopathic causes. Another implication is that future studies of diabetes treatment should consider monitoring left ventricular function.

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APPENDIX

ICM exclusions: ICD-9 codes

Pregnancy: 640–676, V22; Ischemic heart disease: 410–414; Valvular heart disease: 394–397; Alcoholism: 291, 303, 305.0–305.03, 571.0–517.3, 980, V113; Thyroid disease: 242–246; HIV/AIDS: 042; Amyloid: 277.3; Myocarditis: 422; Chemotherapy related: V073, V581, V662, V672.

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