Mortality Risk of Charcot Arthropathy Compared With That of Diabetic Foot Ulcer and Diabetes Alone

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OBJECTIVE — The purpose of this study was to compare mortality risks of patients with Charcot arthropathy with those of patients with diabetic foot ulcer and those of patients with diabetes alone (no ulcer or Charcot arthropathy).

RESEARCH DESIGN AND METHODS — A retrospective cohort of 1,050 patients with incident Charcot arthropathy in 2003 in a large health care system was compared with patients with foot ulcer and those with diabetes alone. Mortality was determined during a 5-year follow-up period. Patients with Charcot arthropathy were matched to individuals in the other two groups using propensity score matching based on patient age, sex, race, marital status, diabetes duration, and diabetes control.

RESULTS — During follow-up, 28.0% of the sample died; 18.8% with diabetes alone and 37.0% with foot ulcer died compared with 28.3% with Charcot arthropathy. Multivariable Cox regression shows that, compared with Charcot arthropathy, foot ulcer was associated with 35% higher mortality risk (hazard ratio 1.35 [95% CI 1.18–1.54]) and diabetes alone with 23% lower risk (0.77 [0.66–0.90]). Of the patients with Charcot arthropathy, 63% experienced foot ulceration before or after the onset of the Charcot arthropathy. Stratified analyses suggest that Charcot arthropathy is associated with a significantly increased mortality risk independent of foot ulcer and other comorbidities.

CONCLUSIONS — Charcot arthropathy was significantly associated with higher mortality risk than diabetes alone and with lower risk than foot ulcer. Patients with foot ulcers tended to have a higher prevalence of peripheral vascular disease and macrovascular diseases than patients with Charcot arthropathy. This finding may explain the difference in mortality risks between the two groups.

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Charcot arthropathy is a severe joint disease in the foot that can result in fracture, permanent deformity, limb loss, and other morbidities (1,2). It occurs in individuals with diabetes complicated by neuropathy and is known to have dramatic negative effects on physical function and on social, emotional, and mental health (3). However, the mortality implications associated with Charcot arthropathy are not clear.

Two previous studies reported low mortality among patients with this condition (4,5). In contrast, Gazis et al. (6) recently reported a high mortality among 47 patients treated in a specialty clinic. Forty-five percent of patients with Charcot arthropathy died after a mean follow-up of 3.7 years compared with 34.0% of those with a neuropathic foot ulcer during the same period. Because foot ulcer is a known mortality risk factor (7,8), this finding suggests that Charcot arthropathy is also associated with increased mortality risk.

The objective of this study was to examine whether Charcot arthropathy is associated with increased mortality risks. Because many patients with Charcot arthropathy experience foot ulcer sometime before or after its onset, it is not clear how much of the elevated mortality risk can be attributed to Charcot arthropathy and how much to foot ulcer or other diabetes complications. In this study, we will compare mortality risks of patients with Charcot arthropathy with those of patients with diabetes alone (e.g., without Charcot arthropathy or foot ulceration) and with those of patients with a foot ulcer to examine whether Charcot arthropathy increases mortality risk, controlling for foot ulcer, diabetes severity, other diabetes complications, and comorbidities.

RESEARCH DESIGN AND METHODS

— The institutional review board at the Edward Hines, Jr., VA Hospital approved the study including a Health Insurance Portability and Accountability Act (HIPAA) waiver of authorization.

The Department of Veterans Affairs (VA) inpatient and outpatient datasets for fiscal year 2003 (October 2002–September 2003; all years henceforth are fiscal years) were used to identify diabetic patients. A patient in this study was defined as having diabetes if he or she filled a prescription for a diabetes medication (insulin or oral hypoglycemic agent) in the current year and/or had two or more hospitalizations or outpatient visits with a diabetes code (ICD-9-CM 250.xx) over a 24-month period (9).

Identification of case patients and control subjects

We used a retrospective cohort design to compare mortality risks of patients with Charcot arthropathy with those of patients with a diabetic foot ulcer (DFU) and

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diabetes alone control subjects. The overall VA diabetic population was first divided into three mutually exclusive groups. The first included only patients in whom Charcot arthropathy was newly diagnosed in 2003. A Charcot arthropathy diagnosis was determined by an ICD-9-CM diagnostic code 713.5 in any VA inpatient and/or outpatient records.

The second group consisted of patients in whom a DFU was newly diagnosed in 2003 but who had not experienced Charcot arthropathy in 2002–2007. A DFU was identified by ICD-9-CM diagnostic codes 707.1x or 707.9 in any patient records. These are the two codes used in the VA Computerized Patient Record System for DFU: 707.1x is used when the specific site of ulceration can be determined and 707.9 is used when ulceration is found on multiple sites on the lower extremities. This method shows excellent agreement with methods used in previous studies (10,11). For example, compared with the Harrington method (11), this method had 97.2% sensitivity and 99.7% specificity with $\kappa = 0.93$.

The third group consisted of patients who have not had any diagnosis of either Charcot arthropathy or DFU in 2002–2007. For the first two groups, a condition was determined as newly diagnosed in 2003 if it was not found in any utilization records in 2002.

Using propensity score matching (12), we selected two control subjects each from the other two groups for every patient with Charcot arthropathy in the first group. One-to-two matching was used to ensure that the study sample was adequately powered. Propensity scores were obtained from a logistic regression that provided the conditional probability of a patient developing Charcot arthropathy in 2003, given the baseline covariates of age, sex, race/ethnicity, diabetes duration, and diabetes control. When multiple control subjects with the same propensity score were found, we selected one randomly.

Identification of mortality events

Mortality events were identified by death dates recorded in the VA Vital Status File. This dataset contains death dates for all VA beneficiaries and is known to have extremely high completeness (98.3% of all death dates are recorded) and accuracy (97.6% are accurate to the exact date) compared with death dates from the National Death Index (13). Currently, the VA Vital Status File contains death dates up to April 2007. For deaths that occurred between April and September of 2007, we obtained death dates from the same data sources used for constructing the VA Vital Status File and followed the same algorithms in choosing the best death date (13).

Covariates

Data for known risk factors for mortality among diabetic individuals, including age, sex, race, marital status, diabetes duration, and coexisting conditions (1), were obtained from inpatient and outpatient records in 2003. Age indicates patient's age at the time of study entry (see below). Diabetes duration was measured by the number of years a patient had had diabetes in 2003. The longest duration that can be ascertained for this study was 6 years. We obtained A1C measurements from the VA Laboratory Results National Data Extracts for 2003 for all patients in the sample. Because of the seasonal fluctuations in the A1C level (14), we computed a mean of all available A1C values for each patient for use as the baseline measure of diabetes control.

All coexisting conditions in the Elixhauser comorbidity method (15) were identified from inpatient and outpatient records. Among the 29 conditions identified, we chose only those that showed significant associations with mortality. Macrovascular complications are major mortality risk factors in diabetes (16), and ischemic heart disease and stroke were additionally identified and used in multivariable models. Supplementary Table A1 (available in an online appendix at http://care.diabetesjournals.org/cgi/content/full/dc08-1695/DC1) shows all comorbidities and their definitions in ICD-9-CM diagnostic codes.

Statistical analysis

Patients were followed from the date of study entry until 30 September 2007 for up to 5 years. Entry date was determined as the first date of diagnosis for patients in the Charcot arthropathy or DFU groups. For the diabetes alone control group, we used the first date of VA health care usage in 2003 with a diagnosis of diabetes (250.xx) as the study entry date. The time to event was measured from the study entry date to the date of death or to 30 September 2007. Cox proportional hazards models were used to test whether there were significant differences in mortality risk in the three groups after controlling for coexisting conditions. We tested the proportional hazards assumption using analysis of scaled Schoenfeld residuals (17) and goodness of fit using Cox-Snell residuals (18). Baseline diabetes control caused the models to violate the proportional hazards assumption and was not used in any Cox regression models. The full model reported in this study satisfies the assumption and shows good fit with the data.

To test whether foot ulcers experienced by patients with Charcot arthropathy can explain part of the mortality risk associated with Charcot arthropathy, we estimated two additional models. We stratified the Charcot arthropathy group by the presence of foot ulcer and compared the mortality risks among three groups for two strata separately. We first included patients without foot ulcer in the Charcot arthropathy group and their matched control subjects from the other two groups to construct a restricted sample (1,950 patients). Second, we included patients *with* foot ulcer in the Charcot arthropathy group and their matched control subjects from the other two groups to construct the second restricted sample (3,330 patients). These two restricted samples were analyzed with Cox proportional hazard models, and their results were compared with those from the full sample.

The role of peripheral neuropathy in explaining mortality risks of patients with Charcot arthropathy and DFU has been noted previously (6). Because all patients with Charcot arthropathy have neuropathy, we could not use it as a covariate in any model we estimated. To check whether neuropathy could have confounded our results, we conducted a sensitivity analysis based on a subsample that included patients with DFU and neuropathy and their matches in the other two groups.

RESULTS — Among the overall diabetic population in 2003, Charcot arthropathy was newly diagnosed in 1,050 patients, DFU was newly diagnosed in 16,260 who had never experienced Charcot arthropathy in 2002–2007, and 868,844 patients had neither Charcot arthropathy nor DFU during the same period. After 1:2 matching, there were 1,050 patients in the Charcot arthropathy group and 2,100 patients in each of the other two groups for a total of 5,250 patients in the study sample. The baseline characteristics of the sample are shown in Table 1. Three-group comparison of fac-

Table 1—*Baseline characteristics of patients in three comparison groups*

Characteristic	Comparison groups		
	Charcot arthropathy	DFU	Diabetes alone
n	1,050	2,100	2,100
Age (years)	63.0 ± 9.6	62.8 ± 9.8	62.7 ± 9.6
Race (%)			
Non-Hispanic white	72.8	73.8	72.7
Non-Hispanic black	11.1	11.8	11.2
Hispanic	3.1	1.9	3.2
Other or unknown	13.0	12.5	12.9
Male sex (%)	97.1	97.9	97.3
Married (%)	58.0	58.6	58.1
Diabetes duration ≥6 years (%)	40.9	39.8	40.9
Diabetes control (%)			
A1C <7%	31.3	31.5	31.4
A1C, 7–9%	38.2	37.6	38.2
A1C >9%	15.5	15.2	15.5
A1C, unmeasured	15.0	15.8	14.9
Comorbidities (%)			
Ischemic heart disease*	34.8	38.4	30.9
Stroke*	7.8	14.4	6.7
Peripheral vascular disease*	26.9	34.5	8.7
Congestive heart failure*	12.6	17.8	6.8
Chronic pulmonary disease*	9.8	14.6	11.1
Renal failure*	15.1	11.4	5.2
Cancer	4.0	4.5	5.6
Deficiency anemias*	17.3	13.8	5.6
Paralysis*	1.0	4.0	1.2
Other neurological disorders	3.4	3.9	2.6
Liver disease*	2.5	3.8	1.9
Coagulopathy*	1.1	2.4	1.4

Data are means ± SD or %. $n = 5,250$. *$P < 0.05$ (two-tailed χ^2 tests).

tors used in matching suggests that matching was good.

Patient age at the time of study entry was 63 years with a SD of 9.7 years. Overall, 40% of patients had diabetes for ≥6 years and 31% had an average A1C <7% in the baseline year.

Patients with a DFU tended to have coexisting conditions more frequently than those in the other two groups, including peripheral vascular disease (PVD), congestive heart failure, ischemic heart disease, stroke, and chronic pulmonary disease.

Of 5,250 patients in the sample, 1,468 (28.0%) died during follow-up, with 28.3, 37.0, and 18.8% mortality rates in the Charcot arthropathy, DFU, and diabetes alone control groups, respectively. Table 2 shows unadjusted and adjusted hazard ratios (HRs) obtained from two Cox regression models estimated from the full sample.

Compared with Charcot arthropathy, the unadjusted mortality risk was higher for the DFU group (HR 1.41 [95% CI 1.23–1.61]) but lower for the diabetes alone control group (0.61 [0.53–0.72]). HRs adjusted for comorbidities show that the differences in mortality risks between the Charcot arthropathy and the other two groups were generally smaller than the unadjusted comparisons suggest. Compared with patients with Charcot arthropathy, those with a DFU had a 35% higher mortality risk (1.35 [1.18–1.54]) and those with diabetes alone had a 23% lower mortality risk (0.77 [0.66–0.90]).

Among patients with Charcot arthropathy, 660 (63%) experienced a foot ulcer sometime between 2002 and 2007. Of these, 431 (65.3%) had ulceration concurrently with or before and 229 (34.7%) had ulceration after the onset of Charcot arthropathy. Their unadjusted mortality rates were higher if they had a foot ulcer (30.2%) than if they did not (26.9%). To estimate the contribution to mortality risk of foot ulcer among patients with Charcot arthropathy, we estimated

Table 2—*HRs of mortality for foot ulcer and diabetes only patients compared with patients with Charcot arthropathy*

Adjustment	Full sample		Restricted sample 1*		Restricted sample 2†	
	DFU	Diabetes alone	DFU	Diabetes alone	DFU	Diabetes alone
n	5,250		1,950		3,300	
Unadjusted	1.411 (1.234–1.613)	0.614 (0.529–0.715)	1.627 (1.300–2.036)	0.726 (0.566–0.931)	1.298 (1.098–1.534)	0.557 (0.461–0.674)
Adjusted†	1.348 (1.176–1.544)	0.773 (0.661–0.903)	1.409 (1.115–1.780)	0.793 (0.616–1.019)	1.319 (1.112–1.563)	0.760 (0.622–0.928)

*Restricted sample 1 includes patients with Charcot arthropathy without foot ulceration in 2002–2007 and their matched control subjects ($n = 1,950$). †Restricted sample 2 includes patients with Charcot arthropathy with foot ulceration in 2002–2007 and their matched control subjects ($n = 3,300$). ‡Adjusted for matched factors (age, sex, race, marital status, and diabetes duration) and comorbidities (ischemic heart disease, stroke, peripheral vascular disease, congestive heart failure, chronic pulmonary disease, paralysis, other neurological disorders, liver disease, renal failure, cancer, deficiency anemias, and coagulopathy).

Table 3—*Adjusted HR from the full Cox proportional hazards regression model*

Variables*	HR (95% CI)	*P*
Comparison group [Charcot arthropathy]		
Foot ulcer	1.348 (1.176–1.544)	<0.001
Diabetes alone	0.773 (0.661–0.903)	0.001
Age (years)	1.039 (1.033–1.045)	<0.001
Race [non-Hispanic white]		
Non-Hispanic black	0.978 (0.828–1.155)	0.793
Hispanic	0.921 (0.631–1.343)	0.668
Other	0.701 (0.560–0.879)	0.002
Male [female]	1.562 (1.022–2.388)	0.039
Married [not married]	0.781 (0.703–0.868)	<0.001
Diabetes ≥6 years	1.074 (0.966–1.193)	0.187
Ischemic heart disease	1.227 (1.096–1.374)	<0.001
Stroke	1.121 (0.963–1.304)	0.141
Peripheral vascular disease	1.243 (1.107–1.397)	<0.001
Congestive heart failure	1.953 (1.709–2.232)	<0.001
Chronic pulmonary disease	1.268 (1.105–1.453)	0.001
Renal failure	1.840 (1.599–2.118)	<0.001
Cancer	1.569 (1.295–1.901)	<0.001
Other neurological disorders	1.592 (1.264–2.006)	<0.001
Deficiency anemias	1.323 (1.152–1.519)	<0.001
Paralysis	1.474 (1.106–1.965)	0.008
Liver disease	2.096 (1.623–2.706)	<0.001
Coagulopathy	1.519 (1.148–2.010)	0.003

n = 5,250. *Reference categories are in brackets.

additional Cox regression models using the two restricted samples (Table 2).

Comparison of unadjusted HRs across three samples shows that the difference in mortality risks between the Charcot arthropathy and DFU groups is largest in the restricted sample 1 (Charcot arthropathy without ulcer: HR 1.63 [1.30–2.04]) and smallest in the restricted sample 2 (Charcot arthropathy with ulcer: 1.30 [1.10–1.53]). On the other hand, the difference between Charcot arthropathy and diabetes alone was larger in unadjusted rates in the restricted sample 2 (0.56 [0.46–0.67]) and smaller in the restricted sample 1 (0.73 [0.57–0.93]). When comorbidities were controlled for in the adjusted models, HRs in the three samples became considerably less variable than those from unadjusted comparisons. The adjusted HRs indicate 32–41% higher mortality risk for DFU than for Charcot arthropathy in the three samples. The adjusted comparisons between Charcot arthropathy and diabetes alone control groups show 21–24% lower mortality risk for the latter.

Table 3 shows the model estimated from the full sample. Mortality risks were significantly increased with older age, male sex, and unmarried status. Among comorbidities, liver disease, renal failure, and congestive heart failure contributed the most to the mortality risk.

We conducted sensitivity analyses. First, we examined whether the observed results might be different for the nonelderly patients (aged <65 years) with a 1:4 matched sample, and the results are shown in supplementary Table A2 (available in an online appendix). Even though none of the HRs indicated statistically significant differences in mortality risk between Charcot arthropathy and DFU groups, the overall findings are consistent with the models estimated from the full sample.

Second, we selected only patients with peripheral neuropathy in the Charcot and DFU groups and compared their mortality risks. For this comparison, we started with the patients with foot ulcers in whom neuropathy had ever been diagnosed in 2002–2007 (70%) and found their matched pairs in the Charcot arthropathy and diabetes alone control groups. The results from a Cox regression model (supplementary Table A3, available in an online appendix) suggest that DFU was associated with a significantly higher mortality risk than Charcot arthropathy among patient with neuropathy (HR 1.23 [95% CI 1.06–1.43]).

CONCLUSIONS — This study shows that patients with Charcot arthropathy or DFU have significantly increased mortality risk than otherwise comparable patients with diabetes alone. The mortality risk associated with Charcot arthropathy was confounded by the presence of a foot ulcer; however, Charcot arthropathy has significantly increased mortality risk independent of foot ulcer and other diabetes complications. When patients with Charcot arthropathy without foot ulceration were compared with their matched control subjects (restricted sample 1), the mortality risk was 63% higher in unadjusted rates for patients with foot ulcers. This difference was significantly larger than that (30%) from the comparison between patients with Charcot arthropathy with foot ulceration and patients with DFUs (restricted sample 2). This result suggests that the mortality risk in the overall Charcot arthropathy group may be in large part attributable to foot ulceration. Moreover, when the HRs were adjusted for comorbidities, they became similar for both sets of comparisons in all three models, indicating that variations in HRs across three samples were due in part also to differences in the presence of comorbidities in the three groups. However, there was still a significantly increased mortality risk associated with Charcot arthropathy, after controlling for foot ulcer or other diabetes complications such as PVD, congestive heart failure, ischemic heart disease, and renal failure.

Gazis et al. (6) reported a mortality rate of 44.7% for patients with Charcot arthropathy after a mean follow-up of 3.7 years, which is considerably higher than the 5-year mortality rate of 28.3% among our patients with Charcot arthropathy. They further reported that the mortality risk for Charcot arthropathy is not statistically different from that for neuropathic DFU, whereas our study shows a significant difference between the two groups (supplementary Table A3).

Part of these differences can be explained by the high percentage of patients with type 1 diabetes in the sample of Gazis et al. (18%) and partly by the fact that their sample consisted of patients from a large specialty foot clinic who, because of selection by referral (4), were likely to be sicker than patients in the population-based sample used in this study. They experienced onset of Charcot arthropathy 4 years earlier than patients in our sample (59 vs. 63 years), an indication that they had more severe dia-

betes than patients in our sample. Despite these differences, both studies show greatly increased mortality risks for patients with either Charcot arthropathy or DFU compared with those with diabetes alone.

These findings suggest that Charcot arthropathy and foot ulceration are markers of significant systemic pathological conditions in diabetic patients that increases their mortality risk. The pathophysiology of higher mortality risks associated with these two conditions is still largely unknown. One explanation for foot ulcer having the highest mortality risk among the three comparison groups is that the presence of ulceration increases the risk of infection, which in turn increases the potential for adverse systemic effects, multiorgan failure, and death. However, patients with Charcot arthropathy with foot ulceration did not have as high a mortality risk as those with foot ulcer alone. We conjecture that ulceration due to Charcot arthropathy (~35% of all foot ulcers experienced by patients with Charcot arthropathy) may not have as high a mortality risk as a DFU does in the absence of Charcot arthropathy. These are mostly complications arising from the mismatch between protective footwear and development of foot deformities such as protruding bones (5). The resulting secondary ulceration may be more local than systemic in etiology and hence be associated with a lower mortality risk than a typical DFU. Further, ongoing treatment of Charcot arthropathy might have led to earlier diagnosis and active treatment of both concurrent and secondary foot ulcers.

Clinically, our findings suggest that early identification and vigilant care of Charcot arthropathy and foot ulcer are important not only for treating these conditions but also for reducing mortality risks associated with them. DFU is often difficult to diagnose early because of peripheral neuropathy and lack of local and systemic signs of infection (19), making quarterly foot screening and patient education for daily foot examinations and self-care imperative for these high-risk patients.

Given that DFUs have greater mortality risks than some cancers such as prostate cancer, breast cancer, or Hodgkin's disease (20), the mortality risk needs to be communicated to the patients as early as possible so that they can assume a more active role in medical management of DFUs than they do now (21). Coexisting conditions such as cardiovascular and renal diseases need to be aggressively managed along with foot care.

This study has several limitations. The first is that it relied on inpatient and outpatient records collected for administrative purposes. Although administrative records were supplemented by extensive pharmacy data and laboratory test results, the accuracy of these records needs to be considered when the study results are interpreted. A study of Department of Veterans Affairs (VA) disease coding in the administrative databases reported that diseases were generally coded accurately but that there were also large variations in accuracy from disease to disease (22). Another study reported an extremely high accuracy of acute myocardial infarction at 96% sensitivity (23). Other conditions may not have been coded as accurately. PVD coding accuracy in the VA data is not well-known, but given the 60% sensitivity of coding for PVD in the Medicare data (24) and the fact that many patients have undiagnosed and/or asymptomatic PVD, the findings about PVD should be interpreted with caution.

Second, comorbidity measures were obtained from the baseline year and may not account for occurrences in the three groups after the baseline year. In a supplemental analysis, we assessed whether a patient in the sample had congestive heart failure in 2003–2007 and used this information in a multivariable model instead of the baseline measure. The results from this model were remarkably consistent with those from the baseline model. The reason may be that congestive heart failure is a chronic condition that persists through the patient's life span. All other comorbidities were also chronic in nature.

Third, we did not have access to data for Medicare usage by elderly veterans. A supplemental analysis showed that, compared with the number of VA users with diabetes estimated from the 2003 Behavioral Risk Factor Surveillance System national survey, almost 98% of all VA users with diabetes could be identified through VA inpatient and outpatient records alone. Nonetheless, there might have been some VA users who received diabetes care from Medicare providers where Charcot arthropathy, foot ulcer, other diabetes complications, or comorbidities were diagnosed. To the extent that these conditions were not also diagnosed by VA physicians, they might have affected our findings. However, the sensitivity analysis with patients aged <65 years (supplementary Table A2) suggests that the unobserved medical conditions listed in the Medicare data did not systematically bias the results.

In summary, to the best of our knowledge, this is the first study to compare mortality risks among patients with Charcot arthropathy, foot ulceration, and diabetes without these complications. A previous study by Pinzur and Evans (3) noted that Charcot arthropathy was associated with poor quality of life, frequent disability, and premature retirement from the workforce. Our study further suggests that it is also associated with increased mortality risk. These findings accentuate the need for early detection of Charcot arthropathy to limit the disease progression and to reduce the risk of foot ulceration and death.

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