Quantifying the Risk of Infectious Diseases for People With Diabetes

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OBJECTIVE — In vitro evidence shows that immune function is compromised in people with diabetes. Although certain rare infections are more common and infection-related mortality is higher, the risk of acquiring an infectious disease for diabetic patients has never been quantified.

RESEARCH DESIGN AND METHODS — A retrospective cohort study using administrative data compared all people with diabetes in Ontario, Canada, on 1 April 1999 to matched nondiabetic people (n = 513,749 in each group). The risk ratios of having an infectious disease and of death attributable to infectious disease between those with and without diabetes were calculated. Secondary analysis individually examined common infectious diseases. The study was repeated using a second pair of cohorts defined in 1996 to confirm stability of the estimates.

RESULTS — Nearly half of all people with diabetes had at least one hospitalization or physician claim for an infectious disease in each cohort year. The risk ratio for diabetic versus nondiabetic people was 1.21 (99% CI 1.20–1.22) in both cohort years. The risk ratio for infectious disease–related hospitalization was up to 2.17 (99% CI 2.10–2.23). The risk ratio for death attributable to infection was up to 1.92 (1.79–2.05). Many individual infections were more common in people with diabetes, especially serious bacterial infections.

CONCLUSIONS — Diabetes confers an increased risk of developing and dying from an infectious disease, corroborating both in vitro evidence and commonly held clinical belief. In addition to microvascular and macrovascular sequelae, clinicians should consider infection a complication of diabetes.

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Many clinicians believe that people with diabetes have an increased susceptibility to infection (1). In vitro evidence shows that neutrophil function is compromised (2,3) and that antioxidant systems and humoral immunity may be depressed in people with diabetes (4). Certain rare infections are more common among diabetic patients, including invasive otitis externa, rhinocerebral mucormycosis, and emphysematous infections of the gall bladder, kidney, and urinary bladder. However, many more frequently encountered infectious diseases have not been formally evaluated (1). Diabetes predisposes patients to comorbidities, such as foot ulcers, that increase susceptibility to infection, whereas some infections, such as hepatitis C, may predispose individuals to developing diabetes (5). Furthermore, diabetes influences the outcomes of specific infections, such as bacteremia and mortality following pneumococcal pneumonia (4). The risk of infection-related mortality is notably increased for diabetic adults compared with those without diabetes, but only among people with concurrent cardiovascular disease (6). Despite these observations, most previous reviews have concluded that there is no strong clinical evidence that the prevalence of infectious diseases in general is higher among diabetic patients (1,4,7).

We conducted a retrospective cohort comparison using population-based administrative data to quantify the risk of developing an infectious disease and the mortality attributable to infectious disease for people with diabetes.

RESEARCH DESIGN AND METHODS

— The universal health care system in Ontario, Canada, allows a near-complete collection of data from all hospitalizations of and physician claims for Ontario residents (population 11,410,046 in 2001). The diabetic cohort was defined as the entire population of Ontario diagnosed with diabetes before 1 April 1999, using a validated algorithm (8). The nondiabetic cohort was chosen from the remaining Ontario population alive on that date, matched 1:1 for date of birth within 30 days, sex, region, and income quintile by ecological attribution of neighborhood-level census data (9,10).

A database of hospital separation abstracts prepared by the Canadian Institute of Health Information was searched for any records between 1 April 1999 and 31 March 2000 bearing a primary or complication diagnosis code for an infectious disease. A database of all claims by Ontario physicians to the health insurance program was searched for any claims between those dates for an infectious disease. The outcome of interest was at least one hospital separation or physician claim for an infectious disease. Multiple events in the same patient were not counted. The cohorts were compared using the χ^2 test, and a risk ratio with 99% CI was calculated. The analysis was repeated evaluating only hospital separations. Mortality attributable to infectious disease was compared between the diabetic and nondiabetic cohorts. Either of two events defined attributable mortality for an individual: death during an admission with an infectious disease diagnosis code or death within 5 days of a physician claim for an infectious disease. The risk ratio with 99% CI for attributable mortality between cohorts was determined.

In a secondary analysis, all individual

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

Table 1—*Risk ratios with 99% CIs for the diabetic versus the nondiabetic population for at least one hospitalization or physician claim for an infectious disease*

Diagnosis	1999 Cohort		1996 Cohort	
	Risk ratio (99% CI)	Rate in diabetic population (per 100,000)	Risk ratio (99% CI)	Rate in diabetic population (per 100,000)
All infectious diseases	1.21 (1.20–1.22)*	46,048	1.21 (1.20–1.22)*	47,454
Infectious diseases potentially treatable on an outpatient basis				
Upper respiratory tract infections	1.18 (1.17–1.19)*	28,454	1.18 (1.17–1.19)*	29,558
Cystitis	1.39 (1.36–1.42)*	5,491	1.43 (1.39–1.46)*	5,564
Pneumonia	1.46 (1.42–1.49)*	4,919	1.48 (1.43–1.52)*	4,786
Cellulitis	1.81 (1.76–1.86)*	4,626	1.85 (1.80–1.91)*	4,671
Enteric infections	1.50 (1.46–1.54)*	4,087	1.53 (1.48–1.58)*	4,482
Otitis externa	1.14 (1.09–1.18)*	1,734	1.16 (1.11–1.21)*	1,756
Mycoses	1.38 (1.32–1.44)*	1,396	1.41 (1.34–1.48)*	1,475
Genital infections (male)	0.89 (0.86–0.89)*	1,340	0.94 (0.90–0.98)†	1,583
Otitis media	1.21 (1.15–1.28)*	1,071	1.24 (1.18–1.32)*	1,106
Chicken pox/shingles	1.16 (1.09–1.22)*	816	1.26 (1.17–1.35)*	793
Viral hepatitis	1.49 (1.39–1.60)*	682	1.49 (1.37–1.61)*	661
Pyelonephritis	1.95 (1.78–2.13)*	486	1.86 (1.69–2.05)*	505
Tuberculosis	1.12 (1.03–1.23)†	344	1.21 (1.10–1.35)*	343
Osteomyelitis	4.39 (3.80–5.06)*	340	4.15 (3.54–4.87)*	334
Herpes simplex virus	0.92 (0.84–1.02)	253	0.96 (0.86–1.07)	283
Genital infections (female)	1.16 (1.04–1.30)†	234	1.31 (1.17–1.47)*	287
Mononucleosis	1.60 (1.39–1.85)*	159	1.46 (1.24–1.73)*	148
Rectal abscess	1.97 (1.67–2.32)*	144	2.14 (1.80–2.55)*	170
Mastoiditis	1.06 (0.90–1.24)	99	1.12 (0.96–1.32)	135
Infectious arthritis	1.72 (1.42–2.08)*	98	1.88 (1.52–2.32)*	107
Human immunodeficiency virus	0.96 (0.78–1.18)	57	1.02 (0.80–1.31)	54
Infectious diseases requiring hospitalization				
Sepsis	2.45 (2.23–2.68)*	539	2.54 (2.28–2.82)*	512
Postoperative infections	2.02 (1.80–2.27)*	283	2.31 (2.02–2.64)*	308
Biliary tree infections	1.60 (1.39–1.83)*	173	1.59 (1.36–1.87)*	169
Peritonitis	1.94 (1.58–2.37)*	93	2.40 (1.93–2.99)*	116
Appendicitis	1.19 (0.96–1.47)	62	1.03 (0.80–1.32)	54

*$P < 0.0001$; †$P < 0.001$.

infectious diseases with frequencies >50 per 100,000 people were evaluated. For infections requiring in-hospital treatment, only hospital separations were counted, whereas for those that could be managed as an outpatient, both hospital separations and physician claims were counted. Risk ratios and 99% CIs were calculated for each infectious disease.

To assess the stability of any measured effects, the analyses were repeated using diabetic and nondiabetic cohorts defined on 1 April 1996, evaluating discharges and claims between 1 April 1996 and 31 March 1997.

RESULTS — There were 516,494 people with diabetes in Ontario on 1 April 1999. Because of failure to match to a nondiabetic control, 0.5% were excluded. The remaining 513,749 people with diabetes were matched to an equal number of people without diabetes. In both groups, 51.7% of people were male, with a mean ± SD age of 61.0 ± 16.0 years. From the 1996 data, 0.7% of the 404,412 people with diabetes could not be matched, so each cohort included 401,661 people, of whom 51.8% were male with a mean ± SD age of 60.9 ± 16.0 years.

In the 1999 cohort, 46.0% of diabetic people had a hospitalization or physician claim for an infectious disease in the year evaluated. Only 38.0% of people in the matched nondiabetic population had such a hospitalization or physician claim. Therefore, the risk ratio for an infectious disease hospitalization or physician claim for the diabetic cohort versus the nondiabetic cohort was 1.21 (99% CI 1.20–1.22, $P < 0.0001$) (Table 1). In the 1996 cohort, the frequencies were 47.5 and 39.2%, respectively, giving a risk ratio of 1.21 (1.20–1.22, $P < 0.0001$). The risk ratios for the primary outcome were similar between men and women and across all income quintiles. Although there were small differences by age, no consistent pattern emerged.

The majority of these events were physician claims. In the 1999 cohort, 5.2% of the diabetic population and 2.6% of the nondiabetic population had hospi-

Table 2—*Risk ratios with 99% CIs for the diabetic versus the nondiabetic population for death attributable to infectious disease*

	Risk ratio (99% CI)	
	1999 Cohort	1996 Cohort
Death attributable to infectious disease among all patients	1.84 (1.73–1.95)*	1.92 (1.79–2.05)*
Death within 5 days of a physician claim for infectious disease among patients with such claims	1.38 (1.23–1.55)*	1.39 (1.23–1.57)*
Death during hospitalization with infectious disease among patients with such hospitalizations	0.95 (0.89–1.01)	0.94 (0.87–1.01)

*$P < 0.0001$.

tal separations with infectious diseases among the discharge diagnoses. Therefore, the risk ratio for inpatient infections was 2.01 (99% CI 1.96–2.06, $P < 0.0001$). In the 1996 cohort, hospitalization rates were 5.4 and 2.5%, respectively, giving a risk ratio of 2.17 (2.10–2.23, $P < 0.0001$). There was a striking gradient by age; in 1999, the frequency of hospital separation with an infectious disease increased from 3.4% for people <30 years of age to 12.1% for those aged ≥80 years, whereas the risk ratio decreased from 4.33 (3.42–5.48, $P < 0.0001$) for people aged <30 years to 1.54 (1.47–1.62, $P < 0.0001$) for those aged ≥80 years. The risk ratio was slightly higher for women (2.12, 2.04–2.20; $P < 0.0001$) than men (1.91, 1.84–1.98; $P < 0.0001$). There was no consistent association between risk ratio and income quintile.

In 1999, 1.0% of the diabetic cohort had a death attributable to an infectious disease. The rate in the nondiabetic cohort was 0.6%, resulting in a risk ratio of 1.84 (99% CI 1.73–1.95, $P < 0.0001$) (Table 2). In 1996, the risk ratio was 1.92 (1.79–2.05, $P < 0.0001$). The risk ratio for mortality within 5 days of a physician claim for an infectious disease among those who had such claims was elevated comparing the diabetic and nondiabetic cohorts. However, the risk ratio for mortality during hospitalization with an infectious disease among those who had such hospitalizations was close to unity, occurring in ~15% of patients hospitalized for infectious diseases.

The risk ratios for the individual infectious diseases evaluated in the secondary analyses are shown in Table 1, indicating that the risk of many individual infections was increased with diabetes. These findings were also consistent in both years analyzed.

CONCLUSIONS — Nearly half of all people with diabetes had at least one hospitalization or physician claim for an infectious disease in each year studied. Furthermore, the presence of diabetes compared with matched control subjects was associated with an absolute risk increase of ~8% and a risk ratio of 1.21 for hospitalization or physician claim, confirming and quantifying a commonly held but previously unproven clinical belief. The risk was stable in both time periods studied. The risk ratio for hospitalization with an infectious disease diagnosis was even higher, up to 2.17, with a particularly high risk ratio for young people.

Confirming the findings of previous researchers who examined specific causes of death from death certificate data (6), we found that mortality attributable to infectious diseases for patients with diabetes exceeded that of those without diabetes. Death within 5 days of a physician claim for infection was elevated. However, mortality during hospitalization for infectious disease was not. Since the diabetic and nondiabetic cohorts were not matched for severity of disease or comorbidity, and since more diabetic patients than nondiabetic patients had hospitalizations with infectious diseases, these findings suggest that physicians have a lower threshold for admitting a diabetic patient with an infectious disease. However, this different hospitalization strategy appears to be appropriate, as it leads to similar in-hospital mortality rates.

The secondary analysis revealed increased risk ratios for those infections expected to be associated with diabetes, such as osteomyelitis and pyelonephritis, and did not demonstrate significant risk ratios for infections where no link with diabetes has been postulated, such as appendicitis and HIV infection. Certain infections may be more common among people with diabetes because of another factor associated with both diabetes and the infection, such as obesity with biliary tract infections or peritoneal dialysis with peritonitis. Diabetes appears to be protective against male genital infections, which may reflect the sexual dysfunction experienced by some diabetic men (11).

Some limitations of the study must be considered. Because the study was conducted using administrative data not primarily collected for research purposes, the accuracy of the coding of diagnoses is uncertain, particularly for uncommon diagnoses in the secondary analyses. However, it is unlikely that data-coding accuracy is associated with the presence or absence of diabetes in a manner that would change the true risk ratio. Furthermore, the validity of the data are supported by the consistency of the results across many different infections. Secondly, the observed differences in the risk of infection between the diabetic and nondiabetic cohorts may not be due to differences in the frequency of infectious diseases, but rather due to differences in care-seeking behavior, caregiver vigilance, or physicians' threshold for hospital admission. However, this appears unlikely by the homogeneity of the results across diagnoses and the observation that many infections for which hospitalization is not discretionary also had increased risk ratios.

These findings support in vitro evidence of impaired immune function in people with diabetes. The risk of and mortality from infectious diseases is higher in people with diabetes, and so, in addition to microvascular and macrovascular sequelae, infection must be thought of as a complication of diabetes. Clinicians must maintain vigilance for infectious diseases among diabetic patients.

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