Diabetes, Glycemic Control, and Risk of Hospitalization With Pneumonia

A population-based case-control study

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OBJECTIVE — To examine whether diabetes is a risk factor for hospitalization with pneumonia and to assess the impact of A1C level on such risk.

RESEARCH DESIGN AND METHODS — In this population-based, case-control study we identified patients with a first-time pneumonia-related hospitalization between 1997 and 2005, using health care databases in northern Denmark. For each case, 10 sex- and age-matched population control subjects were selected from Denmark's Civil Registration System. We used conditional logistic regression to compute relative risk (RR) for pneumonia-related hospitalization among subjects with and without diabetes, controlling for potential confounding factors.

RESULTS — The study included 34,239 patients with a pneumonia-related hospitalization and 342,390 population control subjects. The adjusted RR for pneumonia-related hospitalization among subjects with diabetes was 1.26 (95% CI 1.21–1.31) compared with nondiabetic individuals. The adjusted RR was 4.43 (3.40–5.77) for subjects with type 1 diabetes and 1.23 (1.19–1.28) for subjects with type 2 diabetes. Diabetes duration ≥10 years increased the risk of a pneumonia-related hospitalization (1.37 [1.28–1.47]). Compared with subjects without diabetes, the adjusted RR was 1.22 (1.14–1.30) for diabetic subjects whose A1C level was <7% and 1.60 (1.44–1.76) for diabetic subjects whose A1C level was ≥9%.

CONCLUSIONS — Type 1 and type 2 diabetes are risk factors for a pneumonia-related hospitalization. Poor long-term glycemic control among patients with diabetes clearly increases the risk of hospitalization with pneumonia.

Diabetes Care 31:1541–1545, 2008

Hospitalizations with pneumonia have increased by 20–50% in Western populations during the past 10 years (1,2). Combined with influenza, pneumonia is the seventh leading cause of death in the U.S. (3).

Diabetes is thought to be a risk factor for pneumonia, but available data are few and inconclusive (4–11). Diabetic subjects may have increased susceptibility to pneumonia for several reasons. They are at increased risk of aspiration, hyperglycemia, decreased immunity, impaired lung function, pulmonary microangiopathy, and coexisting morbidity (12). Five cohort studies (4,6,8–10) found that diabetes is a risk factor for pneumonia, with relative risks (RRs) ranging from 1.30 to 1.75, while three studies (5,7,11) failed to find an association. Existing studies have limitations: some included only patients aged >60 years (8,10,11), one did not adjust for comorbidity (9), and few were population-based (9,11). Only one study (6) of respiratory tract infections distinguished between type 1 and type 2 diabetes.

Immunologic abnormalities in diabetic subjects are related in part to the harmful effects of hyperglycemia (12). Recently, a cohort study (4) encompassing 10,063 subjects followed for 7 years found that each 1 mmol/l increase in baseline plasma glucose was associated with a 6% increase in the RR of pneumonia. However, this result was based on a single nonfasting glucose measurement. The impact of poor long-term glycemic control on risk of pneumonia-related hospitalization still remains uncertain.

Given the rising incidence of pneumonia-related hospitalizations (1,2) and the increasing prevalence of diabetes (13), it is important to clarify whether diabetes and poor long-term glycemic control is a risk factor for pneumonia. We examined whether diabetes is associated with an increased risk of pneumonia-related hospitalization and whether this risk is modulated by A1C level.

RESEARCH DESIGN AND METHODS

We conducted this population-based, case-control study in the Danish counties of North Jutland and Aarhus, with a mixed rural and urban population of ~1.15 million people. The Danish National Health service provides tax-supported health care for all residents, including free access to primary care and hospitals and reimbursement of a portion of the cost of most prescription drugs (14). Civil registration numbers, unique identifiers assigned to each Danish citizen that encode birth date and sex, allow accurate linkage among registries.

Identification of patients hospitalized with pneumonia

Hospital registries in Aarhus and North Jutland counties contain information on all hospitalizations since 1977 and on all outpatient visits since 1995. Data include dates of admission and discharge and up to 20 discharge diagnoses coded by physicians according to the ICD-10 during the study period and ICD-8 before 1994. We identified all inpatients with the following first-time discharge diagnoses recorded between 1997 and 2005: pneumonia (J12.x–J18.x), legionellosis (A481.x.), and ornithosis (A709.x) (n = 41,850) (2). We excluded 3,977 patients who lived in the counties <12 months

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Received 21 January 2008 and accepted 10 May 2008.
Published ahead of print at http://care.diabetesjournals.org on 16 May 2008. DOI: 10.2337/dc08-0138.

before the admission date and also excluded 18 patients born between 1894 and 1906, for whom we could not find control subjects, and 3,616 patients aged <15 years, leaving 34,239 adult case subjects in the final analysis set.

Selection of population control subjects

The Central Population Registry, which is updated daily, contains electronic records of all changes in vital status, including change of address, date of emigration, and date of death, for the entire Danish population since 1968. On the date of each patient's first pneumonia-related hospital admission (the index date), we randomly selected 10 control subjects from the Central Population Registry, matched by age (same year of birth), sex, and residence (the same county). We used the risk set sampling technique (i.e., eligible control subjects had to be alive and at risk of a first hospitalization with pneumonia as recorded in their hospital discharge history on the date the corresponding case was admitted) (15).

Data on diabetes

For both case and control subjects, we identified subjects with diabetes from three databases: hospital registries, prescription databases, and the Danish National Health Service Registry. We used the hospital registries to identify all subjects with a discharge or outpatient diagnosis of diabetes since 1977 based on the following ICD-codes: ICD-8 codes 249–250 (diabetes) and ICD-10 codes E10–E14 (diabetes), O24 (diabetes in pregnancy except for O24.4, which is diabetes arising in pregnancy), and H36.0 (diabetic retinopathy) (16). From the prescription database, which tracks filled prescriptions for reimbursed drugs dispensed by pharmacies in North Jutland County since 1991 and in Aarhus County since 1996, we identified all subjects with at least one recorded prescription for insulin or an oral antidiabetes drug. The Danish National Health Service Registry contains data on all citizens receiving health services, their providers, and specific health services received (17). This registry allowed us to identify subjects who had at least one visit to a chiropodist for diabetic foot care and/or who had at least five glucose-related services (blood glucose measurements performed in general practice) in 1 year and/or two glucose-related services each year during 5 subsequent years. Patients with diabetes were classified as type 1 (those with diabetes first recorded before age 30 years, using insulin monotherapy, and with no history of oral antidiabetes medications) or type 2 (the remaining diabetic patients). Duration of diabetes was computed as the time elapsed between the first record of diabetes treatment and the index date.

Data on A1C

We obtained information on A1C levels for diabetic subjects through linkage with the counties' laboratory databases. These databases contain information on all specimens submitted for analysis by hospitals and practitioners, including the exact time of blood sample collection. One or more measurements in the 12 months preceding the index hospital admission date were available for 2.731 (61%) patients. One or more measurements in the 12 months preceding the index hospital admission date for the corresponding case subject were available for 16,605 (58%) control subjects with diabetes. The most recent A1C measurement before the index hospital admission date was used in our analysis.

Data on confounding factors

Data on confounding factors were collected from the hospital registries, the prescription databases, and the Danish Civil Registration System. Based on all available hospital diagnoses except diabetes, we computed a Charlson comorbidity index score for each person (18). Three comorbidity levels were defined: low (score of 0), medium (1–2), and high (≥3). We also obtained data on several factors not included in the Charlson index, including history of alcoholism-related conditions (ICD-8 codes 291, 303, 979, 980, and 577.10; ICD-10 codes F10, K86.0, Z72.1, R78.0, T51, K29.2, G62.1, G72.1, G31.2, and I42.6), use of immunosuppressants within the year before the pneumonia-related admission (ATC codes L01, L04, and H02 AB), and use of systemic antibiotics within 90 days before the admission (ATC code J01). The Central Population Registry provided data on marital status (married, never married, divorced or widowed, or marital status unknown), subjects living with small children attending day care centers (aged <6 years, yes/no), and degree of urbanization (residence in a rural area with a population of 0–10,000, in a provincial town with a population of 10,000–100,000, or in a city with >100,000 inhabitants).

Statistical analysis

We used conditional logistic regression to compute crude and adjusted odds ratios (ORs) as a measure of RR, with associated 95% CIs, for pneumonia-related hospitalization among subjects with and without diabetes. Diabetes exposure was further categorized by type of diabetes, duration of diabetes (<5 years, ≥5 to <10 years, or ≥10 years), and A1C level (<7.0%, ≥7.0 to <8.0%, ≥8.0 to <9.0%, ≥9.0%, or unknown). We adjusted for level of comorbidity, history of alcoholism-related conditions, preadmission use of antibiotics or immunosuppressants, marital status, household presence of small children attending day care centers, and degree of urbanization. Stratified analyses were performed by sex, age-group (15–39, 40–64, 65–79, and ≥80 years), and level of comorbidity. All analyses were conducted using Stata software (version 9). The Danish Data Protection Agency approved the study (record no. 2006-41-6226).

RESULTS

Descriptive data

We identified 34,239 patients with a first-time pneumonia-related hospitalization (including 127 patients [0.37%] with legionellsis and 16 patients [0.05%] with ornithosis) and 342,390 population control subjects (Table 1). The study population was 53% male and 47% female, with a median age of 74 years. A total of 101 case subjects (0.3%) and 187 control subjects (0.1%) were diagnosed with type 1 diabetes, and 4,388 case subjects (12.8%) and 28,299 control subjects (8.3%) were diagnosed with type 2 diabetes predating the case subjects' pneumonia-related hospital admissions.

Risk estimates

The unadjusted RR for pneumonia-related hospitalization among diabetic subjects compared with nondiabetic subjects was 1.68 (95% CI 1.62–1.74) and the adjusted RR was 1.26 (95% CI 1.21–1.31) (Table 2). The adjusted RR was 4.43 (3.40–5.77) for type 1 diabetic subjects and 1.23 (1.19–1.28) for type 2 diabetic subjects. Diabetes duration ≥10 years increased the risk of pneumonia-related hospitalization (1.37 [1.28–1.47]). Exclusion of possible diabetes complications (i.e., myocardial infarction, congestive heart failure, peripheral vascu-

Table 1—*Characteristics of case subjects with a first-time hospitalization for pneumonia and population control subjects from North Jutland and Aarhus Counties, Denmark, 1997–2005*

Characteristic	Case subjects	Population control subjects
n	34,239	342,390
Diabetes		
Absent	29,750 (86.9)	313,904 (91.7)
Present	4,489 (13.1)	28,486 (8.3)
Sex		
Male	18,112 (52.9)	181,120 (52.9)
Female	16,127 (47.1)	161,270 (47.1)
Age (years) (median [interquartile range])	74 (61–82)	74 (61–82)
Comorbidity index		
Index low (0)	15,439 (45.1)	242,645 (70.9)
Index medium (1–2)	13,432 (39.2)	83,088 (24.3)
Index high (≥3)	5,368 (15.7)	16,657 (4.9)
Alcoholism-related conditions	1,732 (5.1)	4,955 (1.5)
Systemic antibiotic therapy	11,852 (34.6)	34,734 (10.1)
Immunosuppressants	5,994 (17.5)	21,681 (6.3)
Marital status		
Married	15,863 (46.3)	178,814 (52.2)
Never married	4,225 (12.3)	38,601 (11.3)
Divorced or widowed	14,064 (41.1)	124,353 (36.3)
Unknown	87 (0.3)	622 (0.2)
Living with small children	1,273 (3.7)	11,124 (3.3)
Degree of urbanization		
Rural	6,011 (17.6)	61,278 (17.9)
Provincial town	15,528 (45.4)	157,907 (46.1)
City	12,700 (37.1)	123,205 (36.0)

Data are *n* (%), unless otherwise indicated.

lar disease, cerebrovascular disease, and renal disease) from the Charlson index and adjusting for the remaining disease categories only in the model increased the effect of long-term diabetes (adjusted RR for diabetes duration ≥10 years 1.62 [1.52–1.74]). Thus, ~40% of the apparent long-term diabetes effect was caused by a higher prevalence of renal, cardiovascular, and cerebrovascular disease. A1C level also influenced the risk of pneumonia-related hospitalization among diabetic subjects. Compared with nondiabetic subjects, the RR was 1.22 (95% CI 1.14–1.30) among diabetic subjects with an A1C level <7% and 1.60 (1.44–1.76) among diabetic subjects with an A1C level ≥9% (Table 2). Using only A1C measurements within 6 instead of 12 months before admission yielded virtually identical risk estimates.

Adult diabetic subjects aged <40 years were three times more likely to be hospitalized with pneumonia than nondiabetic individuals of similar age, while the relative risk gradually decreased in elderly subjects with diabetes (Table 3). After stratifying by level of comorbidity, the association between diabetes and the risk of pneumonia-related hospitalization was highest among subjects with no coexisting morbidity (adjusted RR 1.51 [95% CI 1.41–1.61]). The same trends were observed after further stratifying by diabetes type (Table 3).

CONCLUSIONS — We found that type 1 diabetes was associated with a 4.4-fold increased risk of a pneumonia-related hospitalization, and type 2 diabetes was associated with a 1.2-fold in-

Table 2—*RRs for hospitalizations associated with pneumonia*

Exposure	Case subjects	Population control subjects	Unadjusted RR (95%CI)	Adjusted RR (95% CI)*
Diabetes				
Absent	29,750 (86.9)	313,904 (91.7)	1.0 (reference)	1.0 (reference)
Present	4,489 (13.1)	28,486 (8.3)	1.68 (1.62–1.74)	1.26 (1.21–1.31)
Diabetes type				
Diabetes absent	29,750 (86.9)	313,904 (91.7)	1.0 (reference)	1.0 (reference)
Type 1 diabetes	101 (0.3)	187 (0.1)	5.55 (4.34–7.08)	4.43 (3.40–5.77)
Type 2 diabetes	4,388 (12.8)	28,299 (8.3)	1.65 (1.59–1.71)	1.23 (1.19–1.28)
Duration of diabetes				
Diabetes absent	29,750 (86.9)	313,904 (91.7)	1.0 (reference)	1.0 (reference)
<5 years	1,941 (5.7)	12,903 (3.8)	1.60 (1.53–1.68)	1.21 (1.14–1.27)
≥5 to <10 years	1,324 (3.9)	8,817 (2.6)	1.60 (1.51–1.70)	1.24 (1.16–1.32)
≥10 years	1,224 (3.6)	6,766 (2.0)	1.93 (1.81–2.06)	1.37 (1.28–1.47)
A1C				
Diabetes absent	29,750 (86.9)	313,904 (91.7)	1.0 (reference)	1.0 (reference)
Diabetes present A1C <7%	1,149 (3.4)	7,500 (2.2)	1.64 (1.54–1.74)	1.22 (1.14–1.30)
Diabetes present A1C ≥7 to <8%	607 (1.8)	3,999 (1.2)	1.62 (1.48–1.76)	1.23 (1.12–1.36)
Diabetes present A1C ≥8-<9%	407 (1.2)	2,442 (0.7)	1.77 (1.59–1.97)	1.29 (1.15–1.44)
Diabetes present A1C ≥9%	568 (1.7)	2,664 (0.8)	2.26 (2.07–2.48)	1.60 (1.44–1.76)
Diabetes present A1C unknown	1,758 (5.1)	11,881 (3.5)	1.58 (1.50–1.66)	1.21 (1.14–1.28)

Data are *n* (%), unless otherwise indicated. *RRs adjusted for level of comorbidity, alcoholism-related conditions, use of systemic antibiotic therapy and immunosuppressants before index hospitalization, marital status, household presence of small children attending day care centers, and degree of urbanization.

Table 3—*RRs for hospitalization associated with pneumonia according to presence of diabetes (overall, type 1, and type 2), stratified by age, sex, and level of comorbidity*

	Unadjusted RR (95% CI)	Adjusted RR (95% CI)*
Diabetes (overall)		
Age (years)		
15–39	3.93 (3.16–4.87)	3.21 (2.51–4.12)
40–64	2.63 (2.43–2.84)	1.65 (1.51–1.81)
65–79	1.64 (1.56–1.73)	1.22 (1.15–1.29)
≥80	1.33 (1.25–1.41)	1.11 (1.05–1.18)
Sex		
Male	1.67 (1.60–1.75)	1.25 (1.19–1.32)
Female	1.69 (1.60–1.77)	1.26 (1.20–1.33)
Comorbidity index		
Index low (0)	1.68 (1.58–1.79)	1.51 (1.41–1.61)
Index medium (1–2)	1.22 (1.15–1.30)	1.15 (1.08–1.22)
Index high (≥3)	1.15 (0.99–1.32)	1.11 (0.95–1.28)
Type 1 diabetes		
Age (years)		
15–39	6.41 (4.69–8.74)	5.15 (3.61–7.36)
40–64	4.67 (3.12–6.98)	3.43 (2.14–5.50)
65–79	—	—
≥80	—	—
Sex		
Male	5.05 (3.68–6.94)	3.97 (2.81–5.60)
Female	6.38 (4.35–9.36)	5.28 (3.49–8.00)
Comorbidity index		
Index low (0)	4.98 (3.67–6.74)	4.76 (3.43–6.61)
Index medium (1–2)	3.35 (0.88–12.78)	3.15 (0.80–12.38)
Index high (≥3)	—	—
Type 2 diabetes		
Age (years)		
15–39	2.63 (1.94–3.58)	2.15 (1.51–3.06)
40–64	2.58 (2.39–2.79)	1.62 (1.47–1.77)
65–79	1.64 (1.56–1.73)	1.22 (1.15–1.29)
≥80	1.33 (1.25–1.41)	1.11 (1.05–1.18)
Sex		
Male	1.64 (1.57–1.72)	1.23 (1.17–1.29)
Female	1.66 (1.57–1.74)	1.24 (1.17–1.31)
Comorbidity index		
Index low (0)	1.62 (1.52–1.73)	1.45 (1.36–1.55)
Index medium (1–2)	1.22 (1.15–1.29)	1.15 (1.07–1.22)
Index high (≥3)	1.15 (0.99–1.32)	1.11 (0.95–1.28)

*RRs adjusted for level of comorbidity (except when stratified by this variable), alcoholism-related conditions, use of systemic antibiotic therapy and immunosuppressants before index hospitalization, marital status, household presence of small children attending day care centers, and degree of urbanization.

creased risk. Poor long-term glycemic control and longer diabetes duration clearly increased the risk of pneumonia-related hospitalization. Also, the relative impact of diabetes was greatest in younger adults and in subjects without coexisting morbidity.

Our data extend previous studies (4,6,8–10) suggesting that diabetes is a risk factor for pneumonia. A Dutch cohort study comparing diabetic patients with an age-matched control group of hypertensive patients, based on records from 195 general practices, showed that diabetic patients had a greater risk of lower respiratory tract infections (adjusted OR for patients with type 1 diabetes 1.42 [95% CI 0.96–2.08] and for patients with type 2 diabetes 1.32 [1.13–1.53]) (6). However, the category "lower respiratory tract infection" included milder general practitioner–diagnosed cases of acute bronchitis, influenza, pleuritis, emphysema or chronic obstructive pulmonary disease, and exacerbations of asthma in addition to pneumonia. In a Canadian cohort study, Shah et al. (9) compared all subjects with diabetes in Ontario to matched nondiabetic subjects (n = 513,749 in each group). In crude analyses, subjects with diabetes had an increased risk of pneumonia-related hospitalization or physician claims for pneumonia treatment (RR 1.46 [95% CI 1.42–1.49]). The study did not clarify whether its result was influenced by a higher level of comorbidity among subjects with diabetes compared with subjects without diabetes. Jackson et al. (8) reported that the adjusted RR for hospitalizations for community-acquired pneumonia was 1.52 (95% CI 1.29–1.78) among subjects with diabetes compared with subjects without diabetes, based on 46,237 subjects aged ≥65 years enrolled in a single HMO in Washington state. These findings may not be generalizable to subjects aged <65 years or to the general population.

The main strengths of our study include its large size, population-based design, and adjustment for important confounders made possible through access to medical databases providing a complete medical and prescription history. Furthermore, despite inevitable coding errors, the estimated predictive value of a discharge diagnosis of pneumonia in Denmark is 90% (2). The prevalence of type 2 diabetes cases identified in this study is higher than in our previous cohort study (12.8 vs. 9.8%) (19), due to improved identification of patients with untreated type 2 diabetes. Finally, by using highly valid algorithms to collect data on diabetes and possible confounding factors before the date of hospitalization for pneumonia, we were able to avoid the recall bias present in case-control studies based on interviews or questionnaires.

Limitations include the possibility that physicians are more likely to admit a diabetic patient with pneumonia to the hospital compared with a nondiabetic patient. Such bias would lead to overestimation of the RR associated with diabetes. However, an earlier study (19) showed that preadmission use of antibiotics, levels of inflammatory markers, and proportions of patients with at least one blood culture were comparable among patients with type 2 diabetes and nondiabetic patients hospitalized with pneumonia. This suggests that there was not a severe bias associated with treatment of patients with type 2 diabetes. However, the possibility remains that estimates for patients with type 1 diabetes were affected by increased surveillance. A previous cohort study (8) examining diabetes as a risk factor for pneumonia-related hospitalizations and

outpatient visits suggested that diabetic subjects who develop pneumonia are more likely to be hospitalized than nondiabetic subjects (hospitalizations for pneumonia, adjusted RR 1.52; outpatient visits for pneumonia, adjusted RR 0.90).

We also may have underestimated the duration of diabetes due to undetected type 2 diabetes. However, such misclassification is unlikely to be greater among case subjects then among control subjects. Moreover, lack of data precluded adjustment for pneumococcal and influenza vaccinations, which may reduce the risk of pneumonia. If patients with diabetes were vaccinated at higher rates than others, however, the relative risk of pneumonia-related hospitalizations would be underestimated and would not alter our conclusions.

We found a difference in risk estimates for pneumonia-related hospitalization by type of diabetes, which agrees with the study by Muller et al. (6). Patients with type 1 diabetes may be more likely to seek medical attention and to be hospitalized due to problems with glucose regulation triggered by pneumonia and risk of ketoacidosis. In addition to increased surveillance, the higher risk of pneumonia-related hospitalization in patients with type 1 diabetes compared with those with type 2 diabetes could also arise from different disease pathogenesis. Unlike type 2 diabetes, type 1 diabetes is characterized by reduced or totally absent insulin secretion. Insulin may itself have anti-inflammatory effects (20). Duration of diabetes has an impact on the risk of pneumonia-related hospitalizations, due perhaps to worsening of microangiopathic changes in the basement membranes of pulmonary blood vessels and respiratory epithelium in diabetic subjects (12).

We found that diabetes combined with an A1C level ≥9% is associated with a 60% increased risk of pneumonia-related hospitalization, while diabetes combined with an A1C level <7% was associated with a 22% increased risk, compared with subjects without diabetes. These results confirm observations from in vitro studies in which hyperglycemia was associated with abnormalities in neutrophil function, such as impaired chemotaxis, phagocytosis, and bacterial killing (21). At the same time, our results do not support the claim that "infections are no commoner in well-controlled diabetics than in nondiabetics" (22) but rather indicate that the increased susceptibility to pneumonia among diabetic subjects has a multifactorial etiology. We found that the RR of pneumonia-related hospitalization declined with age among diabetic subjects. Young adults generally have a low incidence of hospitalized pneumonia, which may explain why the relative impact of diabetes is higher.

In conclusion, our data, combined with previous results, provide strong evidence that diabetes is associated with a 25–75% increase in the RR of pneumonia-related hospitalization. Longer duration of diabetes and poor glycemic control increase the risk of pneumonia-related hospitalization. These results emphasize the value of influenza and pneumococcal immunization, particularly for patients with longer diabetes duration, and the importance of improved glycemic control to prevent pneumonia-related hospitalization among diabetic patients.

Acknowledgments— This study received financial support from the Western Danish Research Forum for Health Sciences, from "Klinisk Epidemiologisk Forskningsfond," and from "Århus Universitetshospitals Forskningsinitiativ," Denmark.

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