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ARTICLE

Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome

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Abstract
Aims/hypothesis Diabetes mellitus is believed to increase susceptibility to infectious diseases. The effects of hyperglycaemia per se on infectious disease risk are unknown and the influence of diabetes on infectious disease outcome is controversial.
Materials and methods We studied 10,063 individuals from the Danish general population, who were participants in The Copenhagen City Heart Study, over a follow-up period of 7 years. Risk of hospitalisation caused by any infectious disease, and subsequent risk of disease progression to death were estimated by Cox proportional hazards regression analysis.
Results At baseline, 353 individuals reported having diabetes. During 71,509 person-years of follow-up, a total of 1,194 individuals were hospitalised because of an infection. The risk of pneumonia (adjusted hazard ratio [aHR] 1.75, 95% CI 1.23–2.48), urinary tract infection (aHR 3.03, 95% CI 2.04–4.49) and skin infection (aHR 2.43, 95% CI 1.49–3.95) was increased in subjects with diabetes compared with subjects without. Each 1 mmol/l increase in plasma glucose at baseline was associated with a 6–10% increased relative risk of pneumonia, urinary tract infection and skin infection after adjustment for other possible confounders. Among patients hospitalised for urinary tract infection, diabetic patients were at an increased risk of death at 28 days after admission compared with non-diabetic subjects (HR 3.90, 95% CI 1.20–12.66).
Conclusions/interpretation In the Danish general population, diabetes and hyperglycaemia are strong and independent risk factors for hospitalisation as a result of pneumonia, urinary tract infection and skin infection. Further, diabetes has a negative impact on the prognosis of urinary tract infection.

Keywords Diabetes mellitus · Hospitalisation · Hyperglycaemia · Infectious diseases · Survival

Abbreviations
HR hazard ratio
ICD International Classification of Diseases

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Introduction

Diabetes mellitus is associated with an increased risk of morbidity caused by infectious diseases [1–5]. Furthermore, diabetes is associated with an increased risk of death from infectious disease in some [1, 2, 6, 7], but not all [8], studies.

Mechanistically, it is plausible that, in addition to diabetes, hyperglycaemia may itself influence the risk of infection. First, hyperglycaemia has been shown to impair important components of innate immunity in vitro, such as

chemotaxis, phagocytosis, and the bactericidal activity of neutrophils and macrophages [9–11]. Second, microangiopathy induced by diabetes can lead to ulceration and secondary infection [12]. Third, neuropathy secondary to diabetes can cause impaired bladder emptying and thereby an increased susceptibility to urinary tract infection [13]. Finally, elevated levels of urine glucose among diabetic patients may further support growth of bacteria [4].

The risk of infection among diabetic patients appears to be independent of age, sex and comorbidity, but other factors and mediators involved in the pathogenesis of diabetes have not been studied [2, 3]. In particular, a possible role of hyperglycaemia per se has yet to be investigated.

The aim of the present study was to test the hypothesis that diabetes and hyperglycaemia influence susceptibility to, and the outcome of, infectious disease hospitalisation. For this purpose, we studied a cohort of the adult Danish general population for 7 years, and associated baseline self-reported diabetes and plasma glucose measurements with subsequent risk of infections.

Subjects and methods

Study population

All subjects who were enrolled in the The Copenhagen City Heart Study between 1991 and 1994 were included in this population-based study. Details of the selection procedure, the complete examination programme and information on the subjects have previously been presented in detail [14]. Briefly, participants aged ≥20 years were selected at random following age stratification of residents of Copenhagen. Of the 17,180 individuals invited in 1991–1994, 10,127 participated. Participants who answered 'yes' to the question 'Do you have diabetes?' were classified as having diabetes. The ethics committee for the City of Copenhagen and Frederiksberg approved the study, and all participants provided written informed consent.

The Danish civil registration system contains a personal and written identification code for all individuals living in Denmark [15]. The personal identifier is used to retrieve and merge data on a particular individual from different databases. The Danish civil registration system also contains information about the vital status of each person, which means that the follow-up rate was 100%; it is therefore possible to collect data on individuals up to the exact day when they die or emigrate.

Based on the WHO International Classification of Diseases, 8th and 10th revisions (ICD-8 and ICD-10) (available at: http://www.who.int/classifications/icd/en/, last accessed in November 2006), information on morbidity causing hospitalisation was drawn from the Danish National Hospital Discharge Register (data from study inclusion to 31 December 2000 was available), whereas data on mortality was drawn from the Danish Civil Registration System National Register of Causes of Death (data from study inclusion to 31 December 2001). Infectious diseases were classified as: diarrhoeal diseases: 000–001,004–006, 008–009, A00–A01, A03–A04, A06–A09; hepatitis: 070, B15–B19; HIV/AIDS: 137, B20–B24; meningitis: 320, A39.0, G00–G03; mycoses: 110–112, 114–117, B35–B49; other viral infection: 040–061, 075, 079, B00–B09, B25–B34; parasitic infection: B50–B64; pneumonia: 480–486, A48.1, J12–J18; sepsis: 036.1, 038, A32.7, A39.2–4, A40–41, A48.3; skin infection: 680–686, A46, L00–L08; tuberculosis: 010–018, A15–A19, B90; and urinary tract infection: 590, 595, N10–12, N30.

Case validation

All infectious disease discharge records of participants admitted to Hvidovre Hospital during the study period were reviewed by one of the authors (T. Benfield). Subjects were considered to have an infection if they had relevant signs and symptoms, a positive culture from either a sterile site or relevant specimen, and/or there was documentation of treatment with an antimicrobial agent. According to records, 91 participants were admitted on 142 occasions and discharged with an infectious disease diagnosis (ICD-8 or 10) . In one case the patient file was not available. Of the remaining 141 episodes, 139 (99%) fulfilled the criteria above. The diagnosis was the primary discharge diagnosis in 100 cases (71%), whereas it was the secondary discharge diagnosis in 41 (29%).

Covariates

The following potential risk factors were considered in the analysis: age, sex, non-fasting plasma glucose, non-fasting total cholesterol, non-fasting triacylglycerol, alcohol intake, smoking, education, income, level of physical activity, lung function, BMI, self-reported diabetes, hypertension and comorbidity. Details of covariates are described elsewhere [16–20].

Statistical analysis

All participants were censored at death, emigration or on 31 December 2000, whichever came first. Separate analyses were conducted from study inclusion to a first event for each hospitalisation outcome.

All values are expressed as medians and 95% CIs, unless otherwise stated. Differences between groups were estimated by the Mann–Whitney U test and χ^2 statistics. A hazard

ratio (HR) with 95% CI for progression to infectious disease hospitalisation from inclusion in the study was estimated using Cox proportional hazards regression analysis by forced entry. Time to infectious disease hospitalisation was calculated from the date of study entry to the date of admission. Analyses of risk of death were dated according to the date of admission. Death was defined as any death that occurred within 28 days of the primary diagnosis.

Each covariate was entered separately, and covariates that were associated with disease or death at the $p<0.1$ level were included in the multivariate model. A Bonferroni-corrected p value of <0.0083 on a two-sided test (six different infectious diseases tested) was considered significant. Statistical analyses were performed using the Statistical Package for Social Sciences (version 11.0; SPSS, Chicago, IL, USA).

Results

Baseline characteristics

Among 10,063 participants, 353 (3.5%, 95% CI 3.1–3.9) had diabetes at baseline. In terms of treatment, 34 (10%, 95% CI 6–13) received insulin, 112 (32%, 95% CI 26–38) oral therapy, 52 (15%, 95% CI 11–19) diet alone, 18 (5%, 95% CI 3–8) insulin and diet, 63 (18%, 95% CI 13–22) oral therapy and diet, and 73 (21%, 95% CI 16–25) received no treatment. Participants with self-reported diabetes had higher plasma glucose (10.2 vs 5.4 mmol/l, $p=0.0001$), triacylglycerol (2.3 vs 1.5 mmol/l, $p=0.0001$) and BMI (27.8 vs 24.9 kg/m^2, $p=0.0001$), and were older (67.8 vs 60.7 years, $p=0.0001$) than non-diabetic subjects at baseline.

Infectious disease hospitalisation

During a total of 71,509 person-years of follow-up there were 90 infectious disease hospitalisations among participants with diabetes at baseline and 1,104 among participants without diabetes. This corresponds to a rate of 41.2 (95% CI 32.7–49.8) per 1,000 person-years of follow-up for participants with diabetes compared with 15.9 (95% CI 15.0–16.8) per 1,000 person-years of follow-up for participants without diabetes (HR 3.05, 95% CI 2.47–3.78).

There were 586 first-time episodes of pneumonia, 314 of urinary tract infection, 189 of skin infection, 139 of diarrhoeal disease, 99 of sepsis, 49 of other viral infections, 38 of mycoses, 27 of upper respiratory infection, 19 of tuberculosis, 15 of viral hepatitis, 14 of HIV/AIDS, 11 of meningitis and 105 of parasitic infection leading to hospitalisation. However, among the diabetic patients, there were no cases of meningitis, HIV/AIDS or upper respiratory infection, there was one case of tuberculosis and one of viral hepatitis, and two, three and six cases of mycoses, other viral infection and parasitic infection, respectively.

Pneumonia, urinary tract infection, skin infection and sepsis, but not mycosis or diarrhoeal disease, were more frequent among diabetic participants (Table 1).

Pneumonia In univariate analysis, diabetes had a hazard ratio for pneumonia hospitalisation of 2.55 (95% CI 1.86–3.49). After adjustment for age, sex, cholesterol, triacylglycerol, hypertension, income, education, smoking, physical activity and lung function, the hazard ratio was 1.75 (95% CI 1.23–2.48, $p=0.002$).

Urinary tract infection In univariate analysis, diabetes had a hazard ratio for hospitalisation caused by urinary tract infection of 3.95 (95% CI 2.75–5.66). After adjustment for age, sex, cholesterol, triacylglycerol, BMI, hypertension, income, education, alcohol use and physical activity, the hazard ratio was 3.03 (95% CI 2.04–4.49, $p=0.0001$).

Skin infection In univariate analysis, diabetes had a hazard ratio for hospitalisation for skin infection of 3.98 (95% CI 2.51–6.33). After adjustment for age, sex, cholesterol, triacylglycerol, BMI, hypertension, income, education, alcohol use and physical activity, the hazard ratio was 3.43 (95% CI 1.50–3.95, $p=0.0001$).

Sepsis

In univariate analysis, diabetes had a hazard ratio for sepsis hospitalisation of 3.78 (95% CI 1.97–7.27). After adjustment for age, sex, hypertension, income, education, alcohol use, smoking, physical activity and lung function, the hazard ratio was 3.40 (95% CI 1.08–5.30, $p=0.03$). However, after correction for multiple comparisons, the association between diabetes and risk of sepsis was not statistically significant.

Plasma glucose

At baseline, 247 (2.5%) participants had a non-fasting plasma glucose level ≥11.0 mmol/l. Of these, 152 had reported having diabetes. We used this value as a proxy for diabetes [21] and repeated the multivariate analyses as described above. The unadjusted hazard ratios were 2.00 (95% CI 1.34–2.98) for pneumonia, 2.59 (95% CI 1.58–4.24) for urinary tract infection, 2.83 (95% CI 1.67–4.78) for skin infection and 1.29 (95% CI 0.40–4.13) for sepsis. Combining plasma glucose-defined and self-reported diabetes ($n=448$) resulted in hazard ratios of 1.56 (95% CI 1.12–2.17) for pneumonia, 2.51 (95% CI 1.69–3.71) for urinary tract infection, 2.35 (95% CI 1.49–3.69) for skin infection and 2.06 (95% CI 0.98–4.36) for sepsis.

Non-fasting plasma glucose levels were higher in participants who were hospitalised as a result of an

Table 1 Incidence and risk of infectious disease leading to hospitalisation over 7 years of follow-up of 10,063 individuals from the general population, with and without diabetes

	No. of cases per 1,000 person-years of follow-up (95% CI)		HR (95% CI)		Wald p value (aHR)
	Control subjects	Diabetic subjects	Unadjusted	Adjusted	
Pneumonia	8.0 (7.3–8.6)	20.0 (14.0–26.0)	2.55 (1.86–3.49)	1.75 (1.23–2.48)[a]	0.002
Urinary tract infection	4.1 (3.6–4.6)	15.8 (10.4–21.1)	3.95 (2.75–5.66)	3.03 (2.04–4.49)[b]	0.0001
Skin infection	2.5 (2.1–2.8)	9.5 (5.4–13.7)	3.98 (2.51–6.33)	2.43 (1.50–3.95)[c]	0.0001
Sepsis	1.3 (1.0–1.6)	4.6 (1.8–7.5)	3.78 (1.97–7.27)	2.40 (1.08–5.30)[d]	0.03

[a] Adjusted for age, sex, cholesterol, triacylglycerol, hypertension, income, education, smoking, physical activity and lung function
[b] Adjusted for age, sex, cholesterol, triacylglycerol, BMI, hypertension, income, education, alcohol use and physical activity
[c] Adjusted for age, sex, triacylglycerol, BMI, income, education, alcohol use and physical activity
[d] Adjusted for age, sex, hypertension, income, education, alcohol use, smoking, physical activity and lung function
aHR, adjusted hazard ratio

infectious disease during follow-up than in participants who were not (5.6 [95% CI 5.1–6.4] mmol/l vs 5.4 [95% CI 4.9–6.1] mmol/l, p=0.0001).

Using Cox regression analysis, plasma glucose was analysed as a continuous variable. Each 1 mmol/l increment in plasma glucose at baseline was associated with an 11–16% increased unadjusted relative risk, and a 6–10% increased adjusted relative risk, of pneumonia, urinary tract infection, skin infection and sepsis (Table 2).

Mortality after hospitalisation

We further investigated hospitalisation-associated 28-day mortality rates and risk of mortality associated with self-reported diabetes at baseline. Only a hospitalisation caused by urinary tract infection was associated with an increased 28-day risk of mortality among diabetics (12.1% vs 3.2%, p=0.037), whereas mortality rates from sepsis (40% vs 39%), pneumonia (19% vs 14%), skin infection (0% vs 1%) and diarrhoeal disease (0% vs 2%) did not differ between diabetic and non-diabetic subjects.

The hazard ratio for death in relation to hospitalisation from urinary tract infection was 3.90 (95% CI 1.20–12.66). Other risk factors for death that were considered were age, sex, year of study inclusion, smoking, alcohol use, income and level of education. However, none of these were associated with outcome (p>0.1) and so were not included in the multivariate Cox regression model.

Table 2 Influence of non-fasting plasma glucose at baseline on risk of infectious disease leading to hospitalisation during 7 years of follow-up of 10,063 individuals from the general population

	HR (95% CI) per mmol/l increase in plasma glucose		Wald p value (aHR)
	Unadjusted	Adjusted	
Pneumonia	1.11 (1.08–1.14)	1.06 (1.03–1.10)[a]	0.001
Urinary tract infection	1.13 (1.10–1.17)	1.10 (1.05–1.15)[b]	0.0001
Skin infection	1.16 (1.11–1.20)	1.10 (1.04–1.15)[c]	0.0001
Sepsis	1.12 (1.05–1.19)	1.08 (0.99–1.17)[d]	0.09

[a] Adjusted for age, sex, cholesterol, triacylglycerol, hypertension, income, education, smoking, physical activity and lung function
[b] Adjusted for age, sex, cholesterol, triacylglycerol, BMI, hypertension, income, education, alcohol use and physical activity
[c] Adjusted for age, sex, triacylglycerol, BMI, income, education, alcohol use and physical activity
[d] Adjusted for age, sex, hypertension, income, education, alcohol use, smoking, physical activity and lung function
aHR, adjusted hazard ratio

Discussion

The present population-based study, with 7 years of follow-up, shows that diabetes and hyperglycaemia at baseline were both associated with an increased risk of infectious disease hospitalisation. Further, diabetes increased the risk of short-term mortality among individuals hospitalised with urinary tract infection.

It was debated for some time whether diabetes leads to an increased risk of infections [22], but recent reports have shown that a number of different infections occur at an increased frequency among individuals with diabetes [1–5].

Our observations confirm findings of previous studies and expand knowledge of the clinical utility of diabetes and infection risk to also include hyperglycaemia per se. The pathogenic effects of hyperglycaemia and diabetes that lead to an increased susceptibility to infections in different organ systems are probably multifactorial. In animal models, hyperglycaemia causes inflammation and structural changes of lung parenchyma and vasculature [23]. Glucose is detectable in airway secretions and may support the

growth of airway pathogens [24]. *Escherichia coli* adhesion to uroepithelial cells is increased in diabetic patients [25], and elevated urinary glucose levels support the growth of bacteria [26]. Lack of metabolic control, as measured by glycated haemoglobin, is a risk factor for bacteriuria [27]. In concordance, control of hyperglycaemia reduced the short-term risk of infectious complications among a population of surgical critically ill patients [28]. The benefit correlated with metabolic control rather than insulin dose [29]. Thus, prevention of hyperglycaemia and diabetes is likely to reduce the long-term risk of infectious diseases.

Diabetes increased the risk of death from urinary tract infection almost fourfold. To our knowledge, this has not previously been reported. Others have shown a two- to threefold increased risk of death among diabetic patients from infectious disease, but they did not analyse individual diseases [1, 7]. Interestingly, bacteraemia caused by enterobacteria among diabetic patients is associated with an increased risk of death [2]. Although we did not find an association between diabetes, sepsis and mortality, enterobacteria are the predominant cause of urinary tract infections. Our findings require confirmation from others, but our data indicate that diabetic patients with urinary tract infections require special attention.

Our study has several limitations. Lack of identification of all infectious events in this study could lead to an underestimation of risk. However, because all patients are treated in public hospitals in Denmark and all hospitals report to the Danish Hospital Discharge Register, underestimation of disease incidence is unlikely to seriously affect our conclusions. Subjects with known diabetes may have had a lower threshold for admission to hospital, leading to an overestimation of risk and underestimation of mortality, but this is also true for other comorbidities. Inclusion of comorbidity in the regression analysis did not alter the associations that were detected. We were unable to identify events (e.g. milder episodes of urinary tract and skin infections) that did not lead to care in a hospital because we relied on records of hospital admissions for infectious diseases. Therefore, the true risk of any infectious disease is probably higher than reported here.

In conclusion, diabetes and hyperglycaemia are strong and independent risk factors for hospitalisation because of pneumonia, urinary tract infection and skin infection. Furthermore, diabetes has a negative impact on the prognosis of urinary tract infection.

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Duality of interest The authors had no duality of interest in relation to this study.

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