Risk of Diabetes Mellitus among Patients Diagnosed with Giant Cell Arteritis or Granulomatosis with Polyangiitis: Comparison with the General Population

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ABSTRACT. ***Objective.*** Patients with organ- or life-threatening vasculitis receive high cumulative glucocorticoid (GC) doses during their disease course. GC have diabetogenic effects, but the risk of diabetes mellitus (DM) related to vasculitis therapy is not well characterized. We assessed the DM risk among patients diagnosed with giant cell arteritis (GCA) or granulomatosis with polyangiitis (GPA), i.e., patients with relatively common forms of systemic vasculitis.

Methods. We used Danish healthcare registries to identify 1682 patients diagnosed with GCA and 342 patients diagnosed with GPA from 1997 to 2015 and to obtain information regarding medication exposures. Each patient with vasculitis was matched with 9 population controls. Date of new-onset DM was defined as date of first claimed prescription for an antidiabetic drug. We used Cox regression analyses to calculate incidence rate ratios (IRR) for DM as a measure of the DM risk among patients relative to population controls. Logistic regression was used to study the association between prednisolone/prednisone (PRED) dose and DM.

Results. Median duration of followup was 6.5 years [interquartile range (IQR) 2.6–10.4] in the GCA cohort and 5.8 years (IQR 1.7–10.6) in the GPA cohort. During the first year after diagnosis of vasculitis, the IRR for DM was 7.0 (95% CI 5.2–9.3) among patients with GCA and 10.4 (95% CI 4.4–24) among patients with GPA. IRR for DM were not significantly increased in either cohort during later followup periods. Within the first year, treatment with high cumulative prednisolone/PRED doses was associated with new-onset DM among the patients with vasculitis.

Conclusion. Patients diagnosed with GCA or GPA have a markedly increased risk of new-onset DM during early treatment phases. (First Release October 15 2016; J Rheumatol 2017;44:78–83; doi:10.3899/jrheum. 160797)

Key Indexing Terms:
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The primary systemic vasculitides are inflammatory disorders of unknown etiology[1]. Glucocorticoids (GC) are core drugs in therapeutic regimens for these diseases[2]. Patients with organ- or life-threatening vasculitis are exposed to high daily doses of GC during initial treatment phases, and longterm therapy is needed to control disease activity in the majority of cases[3,4].

Treatment with GC has a multitude of adverse effects, including diabetogenic effects. Hyperglycemia and diabetes mellitus (DM) related to GC therapy arise because of a range of GC-induced metabolic changes, which encompass β cell dysfunction and insulin resistance in the liver, adipose tissue, and skeletal muscles[5].

The risk of overt DM associated with GC therapy for rheumatic diseases has previously been investigated. Among patients with rheumatoid arthritis (RA), the risk of DM was recently shown to increase with higher doses of GC and/or longer duration of therapy[6]. Treatment with high daily doses of GC has also been identified as a risk factor for DM in patients with systemic lupus erythematosus (SLE)[7,8]. These observations underscore the risk of DM associated with GC therapy, but they cannot be used to evaluate the magnitude of the DM risk among patients with vasculitis because of the substantial differences that exist between therapeutic regimens for RA, SLE, and systemic vasculitides.

In a cohort of 296 patients with antineutrophil cytoplasmic

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antibody-associated vasculitis, new-onset DM was observed in more than 10% during longterm followup[9]. To date, however, the risk of new-onset DM among patients with vasculitis has not been compared with that of age- and sex-matched population controls. Further studies are therefore needed to characterize the short- and longterm risk of DM in patients diagnosed with various systemic vasculitides.

In our present, matched cohort study, we assessed the risk of new-onset DM among patients diagnosed with giant cell arteritis (GCA) or granulomatosis with polyangiitis (GPA), i.e., patients affected by relatively common forms of systemic vasculitis. We compared the patients with matched population controls regarding incidence rates for DM, analyzed the association between GC dosing and new-onset DM among the patients with vasculitis, and described the use of anti-diabetic drugs in the cohorts during prolonged followup.

MATERIALS AND METHODS

GCA cohort. We used the Danish National Hospital Register (NHR) to identify all persons treated at Danish hospitals on an inpatient or outpatient basis under a first-time diagnosis of GCA between January 1, 1997, and June 30, 2015 [International Classification of Diseases, 8th ed (ICD-8) codes 446.30 and 446.39, and ICD-10 codes M31.5 and M31.6].

The NHR was established in 1977 and has collected information on all nonpsychiatric hospitalizations in Denmark ever since[10]. Data on outpatient hospital visits have been registered with complete coverage since 1995. Each hospital visit initiates a record, which is marked by the personal identification number of the patient (a unique number assigned to all citizens of Denmark at birth or immigration) and includes dates of admission and discharge, hospital and department codes, start and end dates of outpatient visits, a primary discharge diagnosis, and supplementary diagnoses (if appropriate). The diagnoses were coded according to a Danish version of the ICD-8 until the end of 1993 and have been coded according to the ICD-10 thereafter.

Among patients with GCA identified in the NHR, we used the Danish National Pathology Registry to select those for whom a first-time biopsy from a superficial temporal artery had been performed within 8 weeks of the clinical diagnosis and had revealed the presence of giant cell inflammation [Danish Systematic Nomenclature of Medicine codes: T45270 (superficial temporal artery) and M40160 (giant cell inflammation)]. The Danish National Pathology Registry contains detailed information on pathology specimens analyzed in Denmark with partial coverage since the 1970s and complete identification since 1997[11].

Date of study inclusion for the patients with GCA was defined as date of the first GCA diagnosis registered in the NHR or as date of the diagnostic biopsy, whichever came last.

GPA cohort. In Denmark, patients with suspected GPA are always referred to hospital-based treatment centers. The applied search strategy for patients with GPA in the NHR was previously described and demonstrated to be associated with a positive predictive value for identified cases of 0.91[12]. In brief, we selected all patients who were included in the NHR with a first-time diagnosis of GPA (ICD-8 code 446.29, and ICD-10 code M31.3) between January 1, 1997, and June 30, 2015, and who experienced at least 2 hospitalizations (both inpatient and outpatient hospital contacts were counted) under a diagnosis of GPA at any department of rheumatology in Denmark during this calendar period.

Date of study inclusion for the patients with GPA was defined as the date of the second GPA-related hospital contact with a department of rheumatology. Patients were not considered eligible if time between first-ever hospitalization for GPA and date of study inclusion exceeded 18 months.

Comparison cohorts. The Danish Civil Registration System contains data on all Danish citizens, including personal identification number, date of birth, sex, and continuously updated information on deaths and migrations[13]. By means of the Civil Registration System and the NHR, we identified 9 randomly selected, age- and sex-matched population controls for each vasculitis patient. The population controls were required to be alive, not diagnosed with GCA or GPA, and living in Denmark at the date of study inclusion of the patient.

The population controls were assigned the same date of study inclusion as the patient to whom they were matched.

Deaths and migrations. Data on deaths and migrations were obtained from the Danish Civil Registration System.

Antidiabetic medications and DM. The Danish National Prescription Registry keeps information on all prescriptions dispensed at Danish pharmacies since 1995[14]. The registry includes information on drugs prescribed by hospital-based doctors as well as general practitioners. From the registry, we obtained data on claimed prescriptions for antidiabetic drugs from January 1, 1995, until June 30, 2015. For the purposes of the present investigation, a study subject was considered to have new-onset DM if prescriptions for antidiabetic drugs were claimed during followup and no prescriptions for antidiabetic drugs had been claimed during the last 2 years preceding the date of study inclusion. Date of new-onset DM was defined as date of first claimed prescription for an antidiabetic drug after study inclusion.

Persons with claimed prescriptions for antidiabetic drugs during the last 2 years preceding the date of study inclusion were excluded from further analyses.

Prednisolone and prednisone (PRED). Information regarding claimed prescriptions for prednisolone and PRED were obtained from the Danish National Prescription Registry. Yearly, cumulative doses of these drugs were calculated on the basis of the number and strength of prescribed tablets.

Statistics. We calculated person-years of followup from date of study inclusion until date of new-onset DM, death, emigration, loss to followup, or June 30, 2015, whichever came first. We used Cox regression analyses adjusted for age at date of study inclusion and sex to calculate incidence rate ratios (IRR) with 95% CI for DM as a measure of the risk of DM among patients relative to population controls. To account for nonproportional hazard during followup, IRR were calculated separately for early and late followup periods. We used the chi-squared test to compare proportions and logistic regression analysis adjusted for age at date of study inclusion and sex to examine the association between cumulative prednisolone/PRED dose and DM.

SPSS version 22 (SPSS Inc.) was used to perform the analyses.

Ethics. The study was approved by the Danish Data Protection Agency (jr. no.: 30-0604) and by the Danish National Board of Health.

RESULTS

Cohorts. Characteristics for patients and population-controls are listed in Table 1. There were 1682 patients included in the GCA cohort, while the GPA cohort consisted of 342 patients. The comparison cohorts encompassed 15,138 persons (GCA population controls) and 3078 persons (GPA population controls), respectively.

In the GCA cohort, median time between the diagnostic biopsy and the first GCA diagnosis in the NHR was 0.1 month [interquartile range (IQR) 0.03-0.2]. In the GPA cohort, median time between first-ever hospitalization for GPA and date of study inclusion was 1.1 months (IQR 0.5–2.3).

Median duration of followup was 6.5 years (IQR 2.6–10.4) among the patients with GCA, 5.8 years (IQR 1.7–10.6) among the patients with GPA, 6.2 years (IQR

Table 1. Characteristics of patients diagnosed with GCA or GPA between 1997 and 2015 and of matched population controls[a].

Characteristics	GCA		GPA	
	Patients	Population Controls	Patients	Population Controls
No.	1682	15,138	342	3078
Men, %	498 (29.6)	4482 (29.6)	172 (50.3)	1548 (50.3)
Age at date of study inclusion[b], yrs, median (IQR)	74 (68–79)	74 (68–79)	55 (43–65)	55 (43–65)
Yrs of followup for DM, median (IQR)[c]	6.5 (2.6–10.4)	6.2 (3.0–10.6)	5.8 (1.7–10.6)	7.0 (2.7–11.1)
Person-yrs of followup	11.647	107.398	2263	23.082
Persons with new-onset DM during followup, n	148	867	28	139

[a] Each patient was matched with 9 population controls. [b] As defined in text. [c] Followup began at date of study inclusion and continued until date of new-onset DM, death, emigration, or loss to followup, or until June 30, 2015, whichever came first. GCA: giant cell arteritis; GPA: granulomatosis with polyangiitis; IQR: interquartile range; DM: diabetes mellitus.

3.0–10.6) among the GCA population controls, and 7.0 years (IQR 2.7–11.1) among the GPA population controls. The total number of persons lost to followup was 0 in the vasculitis cohorts and 3 in the comparison cohorts.

Treatment with prednisolone and PRED. There were 99% of patients with GCA and 87% of patients with GPA who claimed prescriptions for prednisolone and/or PRED within the first year of followup. During the 10th year, 37% of the patients with GCA and 46% of the patients with GPA claimed prescriptions for these drugs (Table 2). Among patients with claimed prescriptions, the median cumulative prednisolone/PRED dose was ≥ 5.6 g during the first year and ≤ 2.5 g per year during subsequent years in both vasculitis cohorts (Table 2).

During the first 10 years of observation, the proportion of individuals who claimed prescriptions for prednisolone and/or PRED did not exceed 6.5% per year among the GCA population controls and did not exceed 4.2% per year among the GPA population controls (Table 2).

Incidence of DM. In total, 148 patients with GCA and 28 patients with GPA met the predefined criteria for new-onset DM during followup. The risk of new-onset DM was 7.0× increased in the GCA cohort and 10.4× increased in the GPA cohort during the first year of observation based on 81 cases of new-onset DM in the GCA cohort and 11 cases in the GPA cohort within this time period (Table 3). Beyond the first year, incidence rates for DM were not significantly increased in either cohort compared with those in the relevant comparison cohort (Table 3).

No major differences in IRR for DM were observed between male and female patients. IRR for DM were increased across age strata during the first year of followup, with higher relative risk estimates observed for older patients than for younger patients (Table 3).

Table 2. Treatment with prednisolone and/or prednisone among 1682 patients with GCA, 342 patients with GPA, and matched population controls[a] assessed on the basis of claimed prescriptions.

Yrs from Study Inclusion[b]	Percentage of Patients with GCA Receiving Therapy/ median Yrly Dose, g[c]	Percentage of GCA Population Controls Receiving Therapy/median Yrly Dose, g	Percentage of Patients with GPA Receiving Therapy/ median Yrly Dose, g	Percentage of GPA Population Controls Receiving Therapy/median Yrly Dose, g
< 1	99.2/5.6	5.7/1.5	87.4/6.0	2.9/0.5
1	89.1/2.0	5.9/1.5	71.7/2.5	2.9/0.5
2	70.9/1.5	6.1/1.0	59.7/2.0	3.3/0.7
3	57.0/1.6	6.3/1.2	55.6/2.5	3.3/0.5
4	51.6/1.5	6.2/1.2	56.2/2.0	3.5/0.5
5	46.5/1.5	5.9/1.1	54.4/2.0	3.4/1.0
6	42.8/1.5	6.0/1.2	52.0/2.0	4.2/1.2
7	41.4/1.5	6.4/1.0	50.0/2.0	3.8/1.0
8	40.2/1.5	6.2/1.0	46.3/2.0	3.8/0.7
9	37.4/1.7	6.5/1.0	45.7/2.1	3.4/0.7

[a] Each patient was matched with 9 population controls. [b] As defined in text. [c] Cumulative yearly doses of prednisolone and/or prednisone were calculated for persons with claimed prescriptions only. GCA: giant cell arteritis; GPA: granulomatosis with polyangiitis.

Table 3. Incidence rate ratios for DM among patients diagnosed with GCA or GPA compared with age- and sex-matched population controls[a]. Values are incidence rate ratio[b] (95% CI).

Variables	< 1 Yr from Study Inclusion[c]	1–5 Yrs from Study Inclusion	> 5 Yrs from Study Inclusion
Patients with GCA, n = 1682	7.0 (5.2–9.3)	0.9 (0.6–1.3)	0.7 (0.5–1.0)
Men	6.6 (4.2–10)	0.8 (0.4–1.4)	0.5 (0.3–1.1)
Women	7.3 (5.0–10)	1.0 (0.7–1.5)	0.8 (0.5–1.2)
Age[d] 50–70 yrs	3.6 (1.7–7.5)	1.1 (0.6–2.1)	0.7 (0.4–1.2)
Age > 70 yrs	8.0 (5.9–11)	0.8 (0.5–1.3)	0.7 (0.4–1.2)
Patients with GPA, n = 342	10.4 (4.4–24)	1.6 (0.8–3.5)	1.3 (0.6–2.5)
Men	11.9 (3.2–44)	1.3 (0.5–3.9)	0.7 (0.2–2.1)
Women	9.4 (3.0–29)	2.1 (0.7–6.0)	2.1 (0.9–5.0)
Age < 50 yrs	6.1 (1.01–36)	3.2 (0.9–12)	2.1 (0.7–6.3)
Age 50–70 yrs	10.9 (3.7–32)	1.2 (0.4–3.6)	1.0 (0.4–2.6)
Age > 70 yrs	22.1 (2.0–245)	1.3 (0.2–9.9)	—[e]

[a] Each patient was matched with 9 population controls. [b] Adjusted for age and sex. [c] As defined in text. [d] Age at date of study inclusion. In the GCA cohort, no patients were < 50 years of age at date of study inclusion. [e] No cases of DM among the patients with GPA. DM: diabetes mellitus; GCA: giant cell arteritis; GPA: granulomatosis with polyangiitis.

Association between cumulative prednisolone/PRED dose and DM. Of the patients with vasculitis, 1849 patients were followed ≥ 1 year from date of study inclusion. Within the first year of followup, a cumulative prednisolone/PRED dose ≥ 5.6 g (the median cumulative dose) was associated with an adjusted OR for DM of 1.6 (95% CI 1.02–2.5) in this group. Among the same patients, the adjusted OR for DM per 10-mg increase in average daily prednisolone/PRED dose was 1.3 (95% CI 1.01–1.8) during the first year.

Use of antidiabetic drugs during followup. To assess whether the need for antidiabetic therapy during short- and longterm followup differed between patients with vasculitis and population controls with new-onset DM, we compared these cohorts regarding claimed prescriptions for glucose-lowering agents over time. As shown in Table 4, a lower proportion of diabetic patients with vasculitis than diabetic population controls claimed prescriptions for antidiabetic drugs during every year of observation from the second year onward.

DISCUSSION

Our present cohort study demonstrates a markedly increased risk of DM during initial treatment phases among patients diagnosed with GCA or GPA, whereas the risk of DM was not significantly increased in the examined vasculitis cohorts during later phases. We observed statistically significant associations between exposure to high cumulative prednisolone/PRED doses and new-onset DM among the patients with vasculitis. Thus, in agreement with observations made among patients with other diseases[6,7,8,15,16,17], our findings indicate that the increased risk of DM in GCA and GPA is related to therapy with GC in a dose-dependent manner. Moreover, our observations demonstrate that the therapeutic

Table 4. Patients with vasculitis (n = 176[a]) and population controls (n = 1006) with new-onset diabetes mellitus: claimed prescriptions for antidiabetic drugs during followup.

Yrs from First Prescription of an Antidiabetic Drug[b]	Percentage of Patients with Claimed Prescriptions	Percentage of Population Controls with Claimed Prescriptions	p Value for Difference[c]
< 1	100	100	—
1	75.0	85.4	0.002
2	67.5	84.0	< 0.001
3	58.8	82.2	< 0.001
4	59.7	82.1	< 0.001
5	55.5	81.5	< 0.001
6	48.1	84.5	< 0.001
7	48.9	80.7	< 0.001
8	59.4	79.6	0.009
9	56.7	81.0	0.005

[a] There were 148 patients with giant cell arteritis and 28 patients with granulomatosis with polyangiitis. [b] As defined in text. [c] Chi-squared test.

regimens used for remission induction in these vasculitic syndromes do not impose a substantial risk of late-onset DM on the treated patients.

The risk of DM was higher for older patients than for younger patients during the first year of observation in both vasculitis cohorts, suggesting that the relative risk of DM during high-dose GC therapy increases with age. Among individuals with new-onset DM, a lower proportion of patients with vasculitis than population controls claimed prescriptions for antidiabetic drugs during most years of followup. Because proposed risk factors for GC-induced DM include traditional risk factors for Type 2 DM in addition to dose and duration of GC treatment[5], this observation might reflect that a subgroup of predisposed patients with vasculitis progressed from latent to manifest DM during high-dose GC therapy and regained adequate glycemic control after tapering of GC. However, additional investigations are required to define predictors of DM in patients diagnosed with GCA or GPA and to analyze the interplay between treatment-related and traditional risk factors for DM.

Our study has strengths and limitations. Strengths include the large number of patients and population controls, the population-based design, the substantial number of person-years accumulated in the cohorts, the almost complete tracking of study subjects, and the high validity of available data on hospitalizations, biopsy findings, and medication exposures. Further, comparable IRR for DM were obtained in 2 cohorts consisting of patients affected by distinct forms of systemic vasculitis, a condition that strengthened our conclusions. Thus, the comparable relative risk estimates for DM observed among patients with GCA and GPA, respectively, strongly suggest that the increased risk of new-onset DM was a consequence of the provided therapy and not a phenomenon pathogenetically linked to the underlying inflammatory syndrome.

The lack of information regarding traditional risk factors for Type 2 DM is an important limitation, which prevented us from studying the DM risk associated with predisposing factors such as overweight and impaired glucose tolerance[18]. Among the patients with vasculitis, a stronger association between cumulative GC dose and new-onset DM might have emerged in analyses including other GC in addition to prednisolone and PRED. We studied only patients with GCA with at least 1 hospital contact for GCA and with biopsy-proven disease. Consequently, we were prevented from investigating whether the DM risk of GCA patients with hospital contacts and biopsy-proven vasculitis differed from that of biopsy-negative patients, nonbiopsied patients, or patients treated exclusively in private practice. Finally, a minority of study subjects might have received antidiabetic agents for polycystic ovary syndrome, but the proportion of misclassified diabetes cases is unlikely to differ between patients with vasculitis and population controls.

In the present cohorts, the likelihood of being diagnosed with DM was probably higher among the patients than among the population controls because of the clinical attention paid to persons undergoing therapy for systemic vasculitis. It must be noted, however, that we counted only cases of new-onset DM requiring glucose-lowering therapy and that Danish guidelines for detection and treatment of GC-induced DM in systemic vasculitis do not exist. It is therefore reasonable to assume that the true incidence of GC-induced DM is higher among Danish patients affected by GCA or GPA than calculated on the basis of claimed prescriptions for antidiabetic drugs, and the observed differences between patients and population controls regarding incidence rates for DM are unlikely to simply represent surveillance bias.

Our observations demonstrate that patients diagnosed with GCA or GPA have a substantially increased risk of developing DM during early followup periods. Implementation of a screening program for DM should be considered in these patient groups.

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