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Cardiovascular risk factors and diseases precede oral hypoglycaemic therapy in patients with type 2 diabetes mellitus

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Abstract

Although patients with type 2 diabetes mellitus and cardiovascular disease share common risk factors, the link between these diseases remains largely unexplained. In this case-control study, the earlier use of cardiovascular drugs (before the diagnosis of diabetes) was investigated among cases with type 2 diabetes mellitus and controls without diabetes. Using the PHARMO database, we identified 4,864 patients who were prescribed oral hypoglycaemic agent (OHA) therapy between 1985–1998 in the Netherlands. For each case, two controls matched on age, sex and pharmacy were randomly selected. Controls had not received insulins or OHA therapy. There were 2,656 (55.0%) cases compared with 2,727 (28.1%) controls who used cardiovascular drugs at the start of OHA therapy. Cases had a 3.5-fold increased risk of cardiovascular drug use ($OR_{95\%\ CI} = 3.5$ [3.2–3.8]) compared to controls. Differences in cardiovascular drug use were noted as early as 7 years before the start of OHA therapy, distinguishing cases from controls. Our finding that patients with type 2 diabetes mellitus were more likely to receive treatment for cardiovascular disease several years before they start diabetes therapy supports the hypothesis of a common underlying mechanism of these two disorders and stresses the importance of the pre-diabetic state.

Keywords: diabetes mellitus, cardiovascular drugs, case-control study, epidemiology, prevalence

Introduction

Type 2 diabetes mellitus is a complex disease associated with chronic morbidity and mortality. Patients with diabetes mellitus have an increased risk of developing cardiovascular morbidity such as atherosclerosis, coronary heart disease, cerebrovascular and peripheral arterial diseases. Although patients with type 2 diabetes mellitus and cardiovascular disease share common risk factors, the link between these diseases remains largely unexplained [1]. The occurrence of cardiovascular disease in type 2 diabetes mellitus may partly result from diabetes mellitus directly or related factors such as insulin resistance syndrome [2], or as yet unknown factors [1]. Support for an association comes from observations of an increased risk of coronary heart disease and cardiovascular risk factors in patients with newly diagnosed diabetes type 2 [3–5].

We investigated the use of cardiovascular drugs among patients suffering from type 2 diabetes mellitus and controls without diabetes mellitus before the start of oral antidiabetic treatment using pharmacy records from the Dutch PHARMO database. The aim of the study was to assess the association between early treatment of cardiovascular disease and the risk of developing type 2 diabetes mellitus.

Patients and Methods

Setting

The data used in this study were obtained from the PHARMO record-linkage system. The PHARMO database comprises drug-dispensing pharmacy records of all community-dwelling residents of eight Dutch cities, counting for more than 450,000 patient histories from 1985 onwards [6]. Virtually complete data are available for each subject, including the drug dispensed, dispensing date, duration of use, prescribed dose regimens and prescriber. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. In the Dutch health care system, residents in a community are designated to one pharmacy for receiving their prescriptions.

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Study sample

Cases were patients aged 35 years or older who received their first prescription of OHAs for the treatment of type 2 diabetes mellitus between 1985 and 1998. Cases received at least two prescriptions of hypoglycaemic agents and had not used insulin therapy before the dispensing date of their first OHA. In this approach, it is still possible that patients with slow-onset type 1 diabetes mellitus are included, although probably in small numbers. The date of the first dispensed OHA (diagnosis of type 2 diabetes mellitus) was taken as the index date. Each case was randomly matched to two controls by age (calendar year of birth), sex, and pharmacy from a pool of eligible controls in the PHARMO area. Controls were subjects who had not received any hypoglycaemic drugs (including insulin). Cases and controls with less than 6 months of drug-dispensing data before the index date were excluded from the analysis. The index date and the duration of the pharmacy record history were evened for the cases and controls. Hence, cases and controls were of the same age and gender, originated from the same area and had exactly the same length of medication history, in the same calendar period.

Cardiovascular disease indicators

The use of cardiac drugs (mainly heart glycosides, antiarrythmics and nitrates), diuretics, β-blockers, calcium-channel blockers, ACE inhibitors, lipid lowering agents, antithrombotic drugs and other antihypertensive drugs was used as a surrogate marker for cardiovascular morbidity and risk factors [7, 8]. Prevalences of cardiovascular drug use were ascertained by 6-monthly periods from seven years prior to the index date until one day before the index date.

Data analysis

Conditional logistic regression was performed to estimate matched odds ratios (OR) and 95% confidence intervals (CI) using EGRET. Data were analyzed with the Mantel-Haenszel (MH) procedure to determine whether incidence of cardiovascular drug use and type 2 diabetes mellitus were associated within each of their time points prior to the start of OHA therapy. Incidence was defined as the difference in prevalence of cardiovascular drug use between two consecutive time points [9]. For example, the prevalence for year 2 was substracted from the prevalence for year 1 to get the incidence of year 1 (number of new cardiovascular drug users) taking into account the follow-up of the study subjects. Subsequently, ORs and 95% CI between cases and controls were calculated with the incidences of cardiovascular drug use for 1-year intervals.

Results

A total of 4,864 cases were identified in the PHARMO record-linkage system for the period between 1985 and 1998 after meeting all study criteria. Table 1 shows the characteristics of cases and controls. As expected in a population of type 2 diabetes mellitus patients, the largest group (42.9%) comprised patients aged 60–74 (average 65 years), and the disease affected more women (53.5%) than men. The sample size of the study subjects increased gradually over time from 1,214 cases and 3,057 controls at seven years before the index date to 4,864 cases and 9,666 controls at the index date.

At the initiation of OHA therapy, sulphonylureas were dispensed to 94% of the cases. Tolbutamide (n = 2,714, 55.8%) was the most frequently prescribed sulphonylurea, followed by glibenclamide (n = 1,105, 22.7%) and gliclazide (n = 705, 14.5%). The remaining cases had started with biguanides (metformin) (n = 238, 4.9%) and α-glucosidase inhibitors (acarbose) (n = 53, 1.1%).

Cardiovascular drug use for both cases and controls at the start of OHA therapy is given in Table 2. Cases used cardiovascular drugs significantly more often than controls ($OR_{95\%\ CI}$ = 3.5 [3.2–3.8]). For all cardiovascular drug categories a significant increased use was observed among cases in comparison to controls (Table 2). The matched odds ratios ranged from 2.0 (95% CI: 1.6–2.6) for antihypertensive drugs to 3.1 (95% CI: 2.7–3.6) for ACE inhibitors. The major cardiovascular drug groups were diuretics (25.2% of cases versus 10.4% of controls), β-blockers (20.7% versus 10.0%), cardiac therapeutics (16.7% versus 7.1%) and antithrombotic drugs (18.2% and 9.9%). Stratification of cases into the different classes of OHAs showed similarly high use of cardiovascular drugs at start of each type of OHA therapy.

As judged by drug use [7], a higher prevalence for the cardiovascular risk factors hypertension (33.4% versus 16.6%) and dyslipidemia (4.0% versus 1.9%) was present in cases compared to controls, in accordance with previous studies [10,11]. Also, heart diseases, as indicated by the use of antithrombotics, ACE inhibitors, loop diuretics and cardiac

Table 1
Characteristics of cases and matched controls

Characteristic	Cases (n = 4,864)	Controls (n = 9,666)
Age, years		
35–44	238 (4.9)[a]	472 (4.9)
45–59	1,356 (27.9)	2,699 (27.9)
60–74	2,088 (42.9)	4,146 (42.9)
⩾75	1,182 (24.3)	2,349 (24.3)
Sex		
Female	2,603 (53.5)	5,170 (53.5)
Index year		
1985–1989	736 (15.1)	1,418 (14.7)
1990–1992	1,420 (29.2)	2,834 (29.3)
1993–1994	1,408 (29.0)	2,815 (29.1)
⩾1995	1,300 (26.7)	2,599 (26.9)
Mean duration of follow-up, years ± SEM	4.65 ± 0.04	4.68 ± 0.03

[a]Values are number of patients with percentages in parentheses unless otherwise noted.

Table 2
Cardiovascular drug use at start of oral hypoglycaemic therapy

Cardiovascular drugs	Cases (n = 4,864)	Controls (n = 9,666)	Matched odds ratio (95% CI)
Use of cardiovascular drugs			
Yes	2,676 (55.0)[a]	2,717 (28.1)	3.5 (3.2–3.8)[b]
Number of cardiovascular drugs			
None	2,188 (45.0)	6,949 (71.9)	1.0 (reference)
1	1,143 (23.5)	1,413 (14.6)	2.8 (2.6–3.1)
⩾2	1,533 (31.5)	1,304 (13.5)	4.3 (3.9–4.7)
Classified cardiovascular drugs			
Cardiac drugs	810 (16.7)	686 (7.1)	2.8 (2.5–3.2)
Diuretics	1,229 (25.3)	1,005 (10.4)	3.2 (2.9–3.5)
β-blockers	1,005 (20.7)	969 (10.0)	2.4 (2.2–2.7)
Calcium-channel blockers	549 (11.3)	485 (5.0)	2.5 (2.2–2.8)
ACE inhibitors	605 (12.4)	430 (4.4)	3.1 (2.7–3.6)
Other antihypertensive drugs	115 (2.4)	114 (1.2)	2.0 (1.6–2.6)
Lipid-lowering agents	195 (4.0)	187 (1.9)	2.1 (1.7–2.6)
Antithrombotic drugs	885 (18.2)	953 (9.9)	2.1 (1.9–2.4)

CI, confidence interval; ACE, angiotensin-converting enzyme.
[a]Number of patients with percentages in parentheses.
[b]Odds ratio with 95% CI in parentheses.

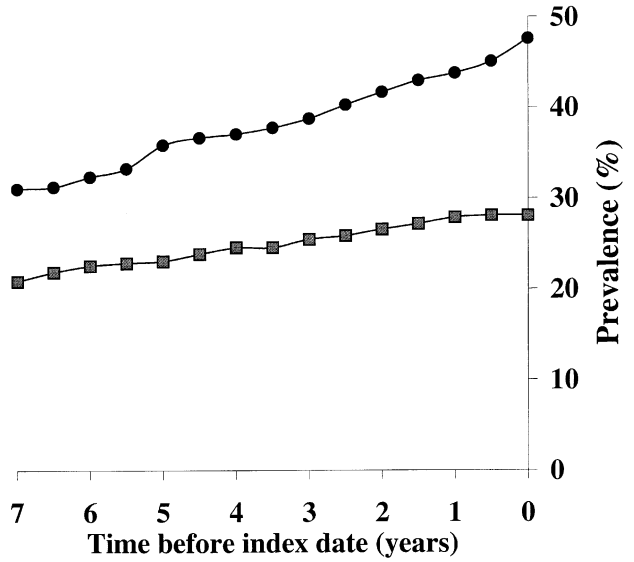

Fig. 1. Prevalence of cardiovascular drug use prior to the start of oral hypoglycaemic therapy (=index date). Legend: cases are the closed circles and controls are the squares.

drugs [7], were far more common in cases than in controls (36.3% and 17.1% respectively).

Figure 1 shows the increases in cardiovascular morbidity starting from 7 years prior to the index date. A similar pattern was found for the stratified analysis of the four index-year strata (Table 1). Type 2 diabetes mellitus and incidence of cardiovascular drug use were associated within each of the time points (χ^2 = 925.44, p < 0.001). Furthermore, increased incidence of cardiovascular drug use, as shown by increased ORs, was observed comparing cases and controls (range $OR_{95\%\ CI\ (0–7\ years)\ incidence}$ = 11.3 [8.7–14.6] −1.7 [1.5–2.0]) (Table 3).

Discussion

Our results strongly suggest an increased risk for cardiovascular drug use up to 7 years before the initiation of OHA therapy in type 2 diabetes mellitus patients compared to controls without diabetes. These results corroborate earlier findings that the occurrence of cardiovascular disorders is not only increased after subjects are diagnosed as suffering from type 2 diabetes mellitus [12–14], but already several years before the diagnosis. Several explanations for this association are possible. Type 2 diabetes mellitus and cardiovascular disease may share a common underlying mechanism, possibly insulin resistance or obesity. On the other hand, several large studies have demonstrated that mild disturbances of glucose homeostasis, impaired glucose tolerance and fasting hyperglycaemia, are also associated with excess cardiovascular risk [4,5,11,15–21]. A 20-year follow-up performed in nondiabetic, working men, age 44–45 years, in three European cohorts known as the Whitehall Study, the Paris Prospective study, and the Helsinki Policemen Study, reported age-adjusted hazard ratios for cardiovascular and coronary heart disease mortality of 1.8 [1.4–2.4] and 2.7 [1.7–4.4], respectively, for men in the upper 2.5% of the 2-h and fasting glucose distributions [21]. The observed differences in cardiovascular drug use already years before the diagnosis of diabetes could therefore, in part, be caused by undiagnosed diabetes and/or pre-diabetic states. Unfortunately, at this time it was not possible to study this with the data from the PHARMO record-linkage system.

Prognostic factors, such as body mass index (obesity), smoking history, physical activity, diet, lipids, albumin, HbA_{1c} and blood pressure, were not available in this study. These factors might also create an indication to start treatment with particular cardiovascular drugs, e.g., lipid lower-

Table 3
Incidence of cardiovascular drug use in 1-year intervals before index date

Year	Incidence cases (%)	Incidence controls (%)	OR (95% CI)
0	11.5	1.1	11.3 (8.7–14.6)
1	13.5	5.7	2.6 (2.2–3.0)
2	14.7	6.5	2.5 (2.1–2.9)
3	11.9	6.0	2.1 (1.8–2.5)
4	11.7	6.7	1.8 (1.5–2.2)
5	14.2	6.1	2.6 (2.1–3.1)
6	11.5	7.7	1.6 (1.3–2.0)
7	31.1	20.9	1.7 (1.5–2.0)

OR, odds ratio; CI, confidence interval.

ing agents. Thus, differences in cardiovascular treatment may only partially be explained by the metabolic differences between type 2 diabetes mellitus patients and controls. However, cardiovascular drug use provides an indicator of such differences [7].

Selection bias may have occurred in selecting the cases and controls. The clinical diagnosis of type 2 diabetes mellitus is usually made before the pharmacological treatment of type 2 diabetes mellitus. In the Netherlands, about 7% of type 2 diabetes mellitus patients are treated with diet only [22]. Obviously, this proportion would be much smaller 5–7 years before the start of drug treatment when already a difference in cardiovascular drug use could be observed (Figure 1). Following the diagnosis of type 2 diabetes mellitus, the Dutch guidelines recommend a change in diet for most patients for a minimum period of 3 months preceding OHA therapy [23]. Therefore, the higher prevalence of cardiovascular drug therapy prior to OHA therapy may also, in part, represent the aggressive targeting of cardiovascular risk factors in diet-controlled diabetes mellitus patients. Also, controls may have been misclassified as a result of undiagnosed or undertreated type 2 diabetes mellitus patients. These selection biases would, however, result in an underestimation of the associations. Patients who use cardiovascular drugs are more likely to be diagnosed with diabetes mellitus than those who are not using cardiovascular drugs, because of their frequent contacts with the health care system. However, the results of this study clearly demonstrated that cardiovascular diseases precede first manifestations of type 2 diabetes mellitus.

Apart from the increased cardiovascular drug use in the years preceding the diagnosis, an additional typical increase of cardiovascular drug use was noticed at start of OHA treatment compared to the preceding months (55.0% at index date). An explanation may be that patients receive an additional medical examination at the diagnosis of type 2 diabetes mellitus leading to the diagnosis and subsequent treatment of cardiovascular disease. Alternatively, patients diagnosed with cardiovascular disease get an extensive clinical examination, including blood glucose measurement. To partly remove this effect from the analyses and to have a comparable time point with the other time measurements, we used one day before the index date instead of the index date (Figure 1).

It has previously been suggested that the metabolic syndrome, including hypertension and dyslipidemia, may precede overt type 2 diabetes mellitus by several decades [11, 24]. Extrapolating our results, one might speculate those metabolic changes leading to type 2 diabetes mellitus are present as early as 15 years prior to the diagnosis at an average age of 50 years (Figure 1). The time between the clinical diagnosis and the actual start of OHA varies considerably. Because our study includes a period of 7 years before the start of OHA therapy, this does not explain our results. Moreover, the time period between the actual onset of the disease and clinical diagnosis may be as long as 4–7 years [25].

Early detection and subsequent metabolic control of type 2 diabetes mellitus might result in a reduction of microvascular complications, but only in a borderline reduction of macrovascular complications [26], and improvement of quality of life on longer term. This suggests that interventions, such as hypertension and dyslipidemia treatment, in addition to metabolic control are needed to minimize macrovascular complications [27,28]. However, as postulated by Groop *et al.* [29], it is yet unclear whether treatment of the metabolic syndrome (e.g., hypertension, lipid disorders) is able to prevent progression to manifest type 2 diabetes mellitus.

In conclusion, increased cardiovascular drug use was observed before the start of OHA therapy in type 2 diabetes mellitus patients compared to controls without diabetes. The onset of cardiovascular drug treatment several years before drug treatment of type 2 diabetes mellitus supports the hypothesis of common underlying mechanism of these two disorders and stresses the importance of the pre-diabetic state.

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