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Antidiabetic medication, statins and the risk of endometrioid endometrial cancer in patients with type 2 diabetes

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HIGHLIGHTS

- Metformin was not associated with a lowered risk of endometrioid endometrial cancer.
- EC risk was similar between metformin users and women using other forms of oral ADM.
- Statin use was found to be associated with a lower incidence of endometrioid EC.

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ABSTRACT

Objective. To gain further evidence of an association between the incidence of endometrial cancer (EC) and the use of metformin, other antidiabetic medication (ADM) and statins in women with type 2 diabetes (T2D).

Methods. A retrospective cohort of 92,366 women with newly diagnosed T2D was obtained from a diabetes register (FinDM). 590 endometrioid ECs were observed during the follow-up time. Poisson regression was utilized to estimate the hazard ratios (HRs) with 95% confidence intervals (95% CIs) of the endometrioid EC in relation to the use of metformin, other oral ADM, insulin and statins. Nested case-control analyses were performed, where up to 20 controls were matched for age and duration of DM for each EC case. The HRs were estimated by conditional logistic regression for never/ever and cumulative use of different forms of ADM and statins.

Results. In the case-control analyses the use of metformin (HR 1.24, 95% CI 1.02–1.51) and other oral ADM (HR 1.25, 95% CI 1.04–1.50) was associated with an increased incidence of endometrioid EC compared to no ADM use. No difference was observed between metformin users and those using other oral ADMs. The use of statins was inversely related to the incidence of endometrioid EC (HR 0.78, 95% CI 0.65–0.94). Results from the full cohort analysis supported this finding.

Conclusions. In our study the use of metformin or other oral forms of ADM was not associated with a lowered risk of endometrioid EC in women with T2D. Instead statins were observed to be inversely associated with endometrioid EC in this population.

1. Introduction

Endometrial cancer (EC) is the fourth most common female cancer in developed countries, with a cumulative rate up to 75 years of age of 1.8 per 100 women [1]. The incidence of EC is rising worldwide, partly due to the increasing prevalence of obesity and diabetes [2–4]. In addition, age, lack of physical activity, genetic predisposition and hormonal

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factors including low parity, late menopause and postmenopausal unopposed estrogen therapy augment the risk of EC [5,6].

Metformin is an oral form of antidiabetic medication (ADM) that has become the recommended first-line treatment in cases of type 2 diabetes [7]. In epidemiological studies use of metformin has been linked to decreased incidence and/or mortality in cases of at least some cancer types [8–12]. Metformin has shown antiproliferative and anti-invasive effects on endometrial cancer cells in preclinical studies [13,14].

The association between metformin use and endometrial cancer risk has been investigated in a few retrospective cohort studies, which have methodological challenges as a result of their observational nature [15]. Three recent studies could not find any association between metformin use and the incidence of endometrial cancer [16–18], but lowered incidence of EC in metformin users has also been reported [19].

Statins (HMG-CoA inhibitors) reduce plasma cholesterol levels and are used in primary and secondary prevention of coronary heart disease. They are among the most commonly prescribed kinds of medication worldwide. Statins have been shown to reduce levels of mevalonate and induce apoptosis of cancer cells in vitro [20]. A previous Finnish record-linkage study did not find an association between statin use and endometrial cancer incidence in the general population [21]. A meta-analysis carried out by Liu et al. also could not find an association between statin use and EC incidence, but in a subset of studies conducted in Asian populations a decrease in the risk of EC was observed among statin users [22].

We studied the associations between metformin, other forms of oral antidiabetic medication, insulin and statins with the incidence of endometrioid EC in a nationwide register-based cohort and case-control study in diabetic women.

2. Materials and methods

2.1. Data sources

This article was written following STROBE guidelines for the reporting of observational studies [23]. The data was obtained from the FinDM register, in which information about diabetic patients from several nationwide registers is combined [24]. FinDM includes precise information about the amount and the date of purchase of antidiabetic and other kinds of medication starting from 1994. Information about diagnosis set in hospital records is available from 1969 for inpatient and from 1998 for outpatient setting. Data about surgical procedures performed in hospitals are recorded from 1987. Patients with diabetes are entered in the register on the basis of diabetes diagnosis noted in hospital records or by receiving reimbursement for antidiabetic medication. A comparison of data from FinDM against a local diabetes register of the Helsinki region has demonstrated good coverage of diabetic persons in the nationwide register [25]. In some cases the duration of diabetes may be longer than indicated in the register, as FinDM does not contain information about diet-controlled diabetics treated solely in outpatient primary care setting. The classification of patients in the register to type 1 (primary insulin-dependent) and type 2 diabetes was based on the antidiabetic medication used as first-line treatment.

The records of FinDM are linked to those from the Finnish Cancer Registry, which has an excellent coverage of over 99% of all cancer cases in Finland [26], and it contains among other things the date of cancer diagnosis and the morphology of cancer. Information about the date of death from Statistics Finland is linked to FinDM. Data linkage between different registers is made based on the personal identification codes unique to each resident of Finland.

2.2. Identification of the study cohort

Details of the cohort selection process are presented in the flow chart. There were a total of 244,322 women resident in Finland with T2D in the FinDM register including patients with prevalent T2D at the beginning of 1996 and with incident diabetes diagnosed after that but no later than 31 December 2011. A total of 172,070 female patients, who were diagnosed with type 2 diabetes between the 1st of January 1996 and the 31st of December 2011 were identified from the FinDM register. The data were handled anonymously according to Finnish data protection legislation. Women with a diagnosis of EC before cohort entry were excluded. Also patients diagnosed with EC during the first year after the diagnosis of diabetes were excluded, as it is generally suggested that the increased medical surveillance following newly diagnosed diabetes leads to increased detection of occult cancers during the first year after diagnosis [27]. Women with prior hysterectomy were excluded from the cohort. Data about hysterectomies was available post-1987, leaving the possibility of some hysterectomized women remaining in the cohort. This especially concerned women in the older age categories. Patients who had used systemic hormone replacement therapy (HRT) were removed from the cohort to eliminate the effect of HRT on the incidence of EC and to exclude some of the women who had had hysterectomy before 1987. The final number of diabetic women in the cohort was 92,366.

Follow-up for the incidence of EC started at the age of 40 years whereas follow-up concerning the duration of T2D and the use of different types of ADM and statins began at the time of diagnosis of diabetes regardless of the age of the patient at that moment. Follow-up of each patient ended on the date of diagnosis of endometrioid EC, hysterectomy for other reasons, starting of systemic hormone replacement therapy, death or the end of the study period. We also performed nested case-control analyses, where up to 20 controls ($n = 11{,}792$) were matched for age and the duration of diabetes within the range of ± 182 days for each of the 590 women in the final cohort who were diagnosed with endometrioid EC during the study period. Controls were selected among those being alive and at risk of EC at the date of EC diagnosis of the case.

2.3. Classification of used medication

Exposure to anti-diabetic medication was assessed in three categories: metformin, other types of oral ADM and insulin (classification by ATC codes is shown in appendix 1). In addition the use of statins was evaluated. Exposure to any medication was defined to begin 365 days after its purchase date in order to avoid reverse causality. Both in nested case-control analyses and in the full cohort analysis patients were classified as exposed to the drug from this moment onwards throughout the follow-up time (never-/ever-exposed). In addition, cumulative use of ADM and statins was estimated in nested case-control analyses as summed amount of daily defined doses (DDD) during the follow-up period.

2.4. Statistical analysis

In the full-cohort analysis a Poisson regression model was used to estimate hazard ratios (HRs) with 95% confidence intervals (95% CIs) of the incidence of endometrioid EC in relation to metformin use and other variables [28]. A multiple Poisson regression model included in addition age, duration of diabetes and use at any time of other forms of medication (ADM and statins). Conditional logistic regression was utilized in the nested case-control analyses to estimate HRs with 95% CIs as regards the use of different forms of ADM and statins. Estimates for use at any time ("ever use") and cumulative use were obtained from separate models. The cumulative dose was categorized according to the tertiles of the total amount of daily defined doses (DDDs) used. We investigated the combined effect of metformin and statin use by including an interaction term in the conditional logistic regression model estimated in the case-control analyses. The event-based data was transformed into individual level data for statistical analysis by using SAS/STAT® software version 9.4 of the SAS System for Windows. We used

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