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Cause-specific mortality in endometrioid endometrial cancer patients with type 2 diabetes using metformin or other types of antidiabetic medication

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HIGHLIGHTS

- Our findings were inconclusive regarding the possible effect of metformin on the prognosis of endometrioid EC in women with T2D.
- Mortality from other causes was lower in metformin users compared to those with other forms of oral antidiabetic medication.
- Our results on non-EC mortality are consistent with other studies on metformin use and mortality.

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ABSTRACT

Aim. To obtain further evidence of the association between metformin or other types of antidiabetic medication (ADM) and mortality from endometrial cancer (EC) and other causes of death in patients with endometrioid EC and type 2 diabetes (T2D).

Materials and methods. A retrospective cohort of women with existing T2D and diagnosed with endometrioid EC from 1998 to 2011, obtained from a nationwide diabetes database (FinDM), were included in the study. Cumulative mortality from EC and that from other causes was described by using the Aalen-Johansen estimator. Cause-specific mortality rates were analyzed by using Cox models, and adjusted hazard ratios (HRs) with 95% confidence intervals (95% CIs) were estimated in relation to the use of different forms of ADM during the three-year period preceding EC diagnosis.

Results. From the FinDM cohort we identified 1215 women diagnosed with endometrioid EC, of whom 19% were metformin users, 12% were users of other types of oral antidiabetic medication, 25% used other types of oral antidiabetic medication plus metformin, 26% used insulin and 14% had no antidiabetic medication. Mortality from EC was not found to be different in women using metformin (HR 0.89, 95% CI 0.52–1.54) but mortality from other causes was lower (HR 0.52, 95% CI 0.31–0.88) compared with women using other types of oral ADM.

Conclusions. Our findings are inconclusive as to the possible effect of metformin on the prognosis of endometrioid EC in women with T2D. However, use of metformin may reduce mortality from other causes.

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1. Introduction

Endometrial cancer (EC) is the most common cancer of the female genital tract in Europe, the cumulative rate up to 75 years of age being 1.8 per 100 women [1]. The incidence of EC is increasing in parallel with the pandemic of obesity, physical inactivity and the increasing incidence of type 2 diabetes (T2D) [2,3]. Other known risk factors of EC include age, diabetes, low parity, late menopause, genetic predisposition and postmenopausal estrogen therapy without progestin support [4,5]. These risk factors have particularly been linked to the endometrioid type of endometrial cancer, but they also seem to be connected to non-endometrioid EC [6].

Metformin is an oral biguanide derivative that is the first-line drug in the treatment of T2D [7]. It acts by decreasing hepatic gluconeogenesis and by increasing insulin sensitivity and glucose uptake in muscle tissue. Metformin use in diabetic patients has been associated with decreased cardiovascular mortality [8] and a lower incidence and better prognosis as regards some types of cancer [9–13]. The possible anticancer mechanisms of metformin are hypothesized to be mediated both indirectly via diminished insulin levels and directly on cancer cells by its antiproliferative effects via AMPK and mTOR pathways [14–17]. Additionally, in vitro studies have shown metformin to inhibit proliferation [18] and invasion [19] of endometrial cancer cells as well as to increase their sensitivity to cytostatic chemotherapeutic agents [20–21] and progestin therapy [22].

In most retrospective studies metformin has been linked to improved prognosis in cases of endometrial cancer [23–25], but in one study, after controlling for several confounding factors, metformin was not found to be associated with overall survival (OS) or progression-free survival (PFS) in EC patients [26]. However, the numbers of diabetic patients in these studies were limited and the duration of metformin use (pre- and post-diagnostic) was unknown.

Finnish healthcare registers are among the most reliable in the world. A Finnish diabetes database (FinDM) [27] has been established for epidemiological monitoring of diabetes and its complications. In FinDM the duration of diabetes, information on antidiabetic medication used and the amount of drugs purchased is recorded. Thus, we have a solid database which gives us an excellent opportunity to evaluate the role of metformin in the survival of diabetic patients with endometrial cancer. We analyze the cause-specific mortality of these patients from EC and from other causes of death in relation to the use of antidiabetic medication during three years before the diagnosis of cancer. Our main focus is on the comparison of mortality between users of metformin and users of other types of oral ADM.

2. Materials and methods

This article was written following STROBE guidelines for the reporting of observational studies [28]. FinDM is an individual-level nationwide diabetes register which has been linked to information from the National Institute for Health and Welfare, Statistics Finland, the Social Insurance Institute and the Finnish Cancer Registry. Patients are entered into the database either through receiving reimbursement for any type of ADM or by diagnosis of diabetes in hospital records or in the Cause of Death Register. Categorization of the patients into type 1 (primarily insulin-dependent) and type 2 diabetics is made according to the types of first-line ADM purchased. A good coverage of diabetic patients by FinDM was shown when it was compared with data from a local diabetes register of the Helsinki region [29].

There were about 240,000 women with prevalent (at the beginning of 1996) or incident (from 1 January 1996 to 31 December 2011) T2D in FinDM. Women diagnosed with endometrioid-type endometrial cancer (ICD-O-3 codes C54.1/C54.9 plus M-8380/3) between the 1st of January 1998 and the 31st of December 2011, and in whom the estimated duration of T2D was at least 180 days before EC diagnosis were included in this study. Data on the histology and stage of cancer was collected from the Finnish Cancer Registry. Stage was defined as local, advanced (including growth to adjacent tissues, metastasis in regional lymph nodes and distant metastasis) or unknown. Patients with non-endometrioid EC (including serous, clear cell and mixed carcinoma) or unknown histology, leiomyosarcomas, carcinosarcomas and endometrial stromal sarcomas were excluded. Patients with prior cancer (with the exception of non-melanoma skin cancers: ICD-O-3 codes C44 plus M-8090-8095/3, M-8097-8098/3, M-8102/3, and M-8110/3) were also excluded (Fig. 1).

According to the antidiabetic medication used during the three years before EC diagnosis, the patients were categorized as follows: 1) metformin only, 2) other oral antidiabetic medication only, 3) metformin plus other oral antidiabetic medication, 4) insulin at any time and 5) no antidiabetic medication. The ATC codes for different types of ADM are listed in Appendix 1. In groups 1–3 the duration of medication use had to be 180 days or longer and thus the data on 42 patients who had used metformin and/or other oral forms of ADM 1–179 days is not shown in the Results section. One purchase of insulin was enough to locate the patients in group 4. The exposed time to all types of medication was defined during the three years preceding EC diagnosis starting from the first purchase and ending 90 days after the last purchase or on the date of EC diagnosis if it came earlier. The cumulative amount of metformin used was estimated according to daily defined doses (DDDs) purchased during the three years preceding EC diagnosis.

Follow-up started at the time of diagnosis of endometrioid EC and ended on the date of death, emigration, or 31 December 2013, whichever was first. Follow-up information was obtained from the Finnish Cancer Registry, the records of which are annually matched through computerized linkage (based on personal identity codes) with the Cause of Death Register maintained by Statistics Finland, so that the dates and causes of death (including noncancerous causes, both underlying and contributory causes of death, categorized on the basis of ICD-10 codes) are added to the records in the Registry. Personnel at the

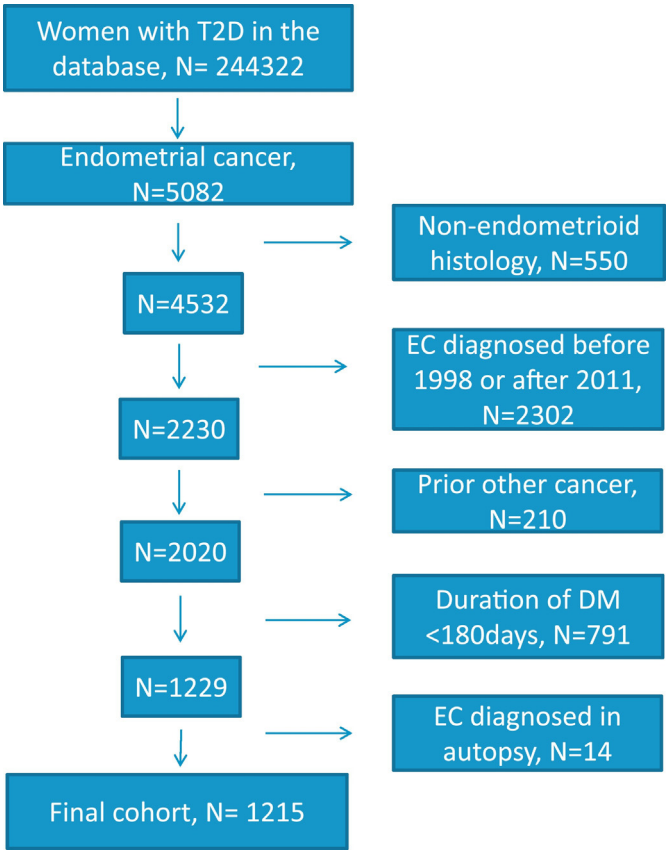

Fig. 1. Flow chart showing how the study cohort was formed.

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