Metformin use associated with lower risk of cancer in patients with diabetes mellitus type 2

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ABSTRACT

Aim In order to increase the database related to the antineoplastic potential of metformin, association between the use of metformin and risk of cancer occurrence in patients with diabetes mellitus type 2 (DM2) was investigated.

Methods In this cross-sectional study, medical records of patients with DM2 were reviewed for cancer occurrence. Data on age, body mass index (BMI), alcohol and nicotine consumption, glucose and HbA1c levels, duration of DM2, medication used in the treatment of DM2 and cancer occurrence were collected and analyzed. Unpaired Student’s t-test or Mann-Whitney U test were used for comparisons between treatment groups, and logistic regression to assess how well our set of predictor variables predicts occurrence of carcinoma. P-value less than 0.05 was considered statistically significant.

Results The mean age of 234 included patients was 66.8±11.5 years, and DM2 duration was 7±6.49 years. Mean glucose value was 8.51±4.17mmol/L, and HbA1c 7.74±1.53. Metformin therapy was prescribed in 190 (81%) patients. Cancer was diagnosed in 16 (6.8%) patients: prostate cancer in eight (3.4%), breast cancer in four (1.7%), rectal cancer in two (0.9%) and cancer of the uterus and cervix in one patient. Age, duration of DM2 and BMI did not contribute significantly to the model, while metformin use was shown to be a significant independent predictor (OR=0.049; 95% CI=0.013–0.181; p=0.001).

Conclusion Our findings support the hypothesis that the use of metformin compared to the use of other oral antidiabetic drugs is associated with a lower risk of cancer in patients with DM2.

Key words: hypoglycemic agents, type 2 diabetes, neoplasms
INTRODUCTION

The search for effective and well-tolerated antineoplastic agent is permanent. Antineoplastic activity is being investigated not only for new substances but for drugs that are already in use in the treatment of other diseases (1-5). One of them is metformin. Metformin is a drug of a biguanide group. Since the fifties of the last century, it has been used in the treatment of diabetes mellitus type 2 (DM2) (6).

In addition to glucose regulation, from 2002 epidemiological studies have shown many favourable effect of metformin. Those effects include lower mortality rate (7), protective effects against cardiovascular diseases (8) as well as reduced risk of cancer in patients with DM2 (9).

Soon after Evans et al. (2005) and Bowker et al. (2006) hypothesized metformin antineoplastic activity, its antineoplastic properties have become the focus of interest (9,10). It has been found that the main mechanism takes place primarily in the liver by decreasing hepatic glucose production through a mostly mild and transient inhibition of mitochondrial respiratory-chain complex 1 (11,12). So far adenosine monophosphate protein kinase (AMPK) has been suggested as a key target point for this action (13). Decrease in hepatic energy status activates the AMPK. Activated AMPK responds to decreased cellular energy level by changing the rate of metabolism of carbohydrate, protein and fat (13). Further research has identified liver kinase B1 (LKB-1), a well recognised tumour suppressor gene, to be the essential factor for AMPK activation by metformin (13-15). Activated AMPK reprograms cellular metabolism by acting on mammalian target of rapamycin (mTOR), fatty acid synthase and p53, the molecules which are involved in regulating cell growth and metabolism (15). Accordingly, AMPK has been suggested to affect cell growth and replication, it slows it down or, as it seems, excludes the growth of aberrant cells (13,16).

Bearing in mind that metformin treatment is inexpensive and relatively safe, its potential antineoplastic activity might be of great importance for future cancer pharmacotherapy.

However, the results of preclinical and clinical studies of antineoplastic activity of metformin are contradictory (17-20). Preclinical study results range from no effect to strong inhibition in carcinogenesis models. Because of the inconsistency of the results of different clinical trials and in order to reach the best possible evidence, more than 200 clinical trials are currently investigating the effect of metformin on tumours in both diabetic and non-diabetic patients (21).

The aim of this study was to investigate association between the risk of cancer and metformin use in patients with DM2 at the Public Health Centre of Sarajevo, Bosnia and Herzegovina.

PATIENTS AND METHODS

Patients and study design

This was a cross-sectional study. Patients with DM2 whose medical records had been available at the Public Health Centre of Sarajevo were screened for the inclusion in this study. The patients who met the inclusion criteria with the confirmed diagnosis of DM2 and a treatment with oral antidiabetic medications were included in the study. Patients treated with insulin, patients without complete medical records and patients whose cancer was diagnosed prior to DM2 were not included in the study.

The study was approved as an academic project by the Ethics Committee at School of Medicine, University of Sarajevo.

Methods

Data on age, body mass index (BMI), alcohol and nicotine consumption, last measured blood glucose and HbA1c levels, duration of DM2, medication used in the treatment of DM2 and cancer occurrence were collected.

Included patients were divided into two groups: patients with or without cancer occurrence.

Statistical analysis

Continuous numerical variables with normal distribution were expressed as mean±standard deviation, while those not normally distributed were expressed as median and interquartile range. Depending on the type of distribution of continuous numerical variables, a comparison between two treatment groups was made either by using unpaired Student’s t-test or Mann-Whitney U test as appropriate. Chi-square test (χ²) was used to
determine the relationship between categorical variables. Logistic regression was used to assess how well our set of predictor variables (type of medicine use, age, duration of DM2, BMI) predicts the occurrence of cancer. Omnibus Tests of Model Coefficients and Hosmer and Lemeshow Test were performed to assess how well the set of our predictor variables is able to predict the occurrence of cancer. The p-values less than 0.05 were considered statistically significant.

RESULTS

The final analysis was performed based on data obtained from 234 patients. The mean age was 66.8±11.5 years and DM2 duration was 7±6.49 years. Mean glucose value was 8.51±4.17mmol/L, and HbA1c was 7.74±1.53. Metformin therapy was prescribed in 190 patients, representing 81% of patients, while other oral antidiabetics were prescribed in 44 patients. Cancer was diagnosed in 16 (6.8%) patients: prostate cancer in eight (3.4%), breast cancer in four (1.7%), rectal cancer in two patients (0.9%) and cancer of the uterus and cervix in one patient. The differences in demographic and clinical characteristics of the patients with and without cancer are shown in Table 1.

Table 1. The differences in demographic and clinical characteristics of patients with and without cancer

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cancer occurrence</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Absent (n=218)</td>
<td>75 (64.5; 79.8) 0.04</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>29 (26; 32)</td>
<td>35.0 (28.3; 47.4) 0.229</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>33 (15.1%)</td>
<td>1.0 (6.25%) 0.479</td>
</tr>
<tr>
<td>Duration of DM2 (years)</td>
<td>5 (2; 10.3)</td>
<td>9.5 (4.25; 13.7) 0.05</td>
</tr>
<tr>
<td>Non regulated glucose</td>
<td>67 (30.7%)</td>
<td>5 (31.3%) 0.966</td>
</tr>
<tr>
<td>HbA1c level (%)</td>
<td>7.2 (6.7; 8.45)</td>
<td>7.42 (6.92; 8.43) 0.516</td>
</tr>
</tbody>
</table>

*Data are expressed as median (25; 75 percentile) or relative count (%)

Table 2. The logistic regression model assessing independent predictors of carcinoma in patients with DM2

<table>
<thead>
<tr>
<th>Variable</th>
<th>B coefficient</th>
<th>Exp(B)</th>
<th>95% CI for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>0.018</td>
<td>0.986</td>
<td>1.076</td>
</tr>
<tr>
<td>Duration of DM2 (years)</td>
<td>0.52</td>
<td>1.053</td>
<td>1.161</td>
</tr>
<tr>
<td>Body mass index</td>
<td>0.117</td>
<td>1.124</td>
<td>0.999 1.265</td>
</tr>
<tr>
<td>Type of medicine use</td>
<td>-3.015</td>
<td>0.049</td>
<td>0.013 0.181</td>
</tr>
<tr>
<td>Constant</td>
<td>-6.113</td>
<td>0.044</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*p=0.112, Cox-Snell (R²=0.125) and Nagelkerke (R²=0.318) supported the test model (Table 2). The overall accuracy of classification was 93.2%.

Variables age, duration of DM2 and BMI did not contribute significantly to the model, while metformin use was shown to be a significant independent predictor (OR=0.049; 95% CI 0.013–0.181; p=0.001), indicating evidence of negative association between metformin use and the diagnosis of carcinoma in the population of patients with DM2 (Table 2).

From a total of 190 participants treated with metformin, four (4/190; 2.1%) had cancer, whereas in the group treated with other oral antidiabetics 12 (12/44; 27.3%) had cancer (Figure 1). Proportion of metformin-treated patients who had a diagnosis of carcinoma was significantly lower (p<0.001). Logistic regression was used to assess how well our set of predictor variables (type of medicine use, age, duration of DM2, BMI) predicted the occurrence of carcinoma. Omnibus Tests of Model Coefficients (χ² (4)=31.188; p=0.001), Hosmer and Lemeshow Test (χ²=13.002; p=0.112), Cox-Snell (R²=0.125) and Nagelkerke (R²=0.318) supported the test model (Table 2). The overall accuracy of classification was 93.2%.

DISCUSSION

Our results showed that compared to other oral antidiabetics, metformin use was significantly associated with decreased risk of cancer disease in patients with DM2. Although well known risk factors such as patients’ age (22-24), BMI (23), nicotine and alcohol consumption (24), duration of DM2, regulation of glucose and HbA1c value were modelled, in the presented study only metformin use was found as a significant independent predictor of cancer occurrence.
Prevalence and type of cancer recorded in this study were in accordance with literature data on general cancer statistics, where the probability of developing cancer is the largest for the following five cancer types: prostate, breast, lung and bronchus, colorectal, uterine corpus and cervix (25). Extensive research has shown that DM2 itself is associated with an increased risk of cancer (26-33), as well as with increased rate of mortality in patients with cancer (34). The mechanisms of such an increased cancer risk in the patients with DM2 may be related to insulin resistance, hyperinsulinemia, proinflammatory status and increased oxidative stress (35). On the contrary but in accordance with our results, the use of metformin was proposed to be an associated protective factor against cancer (1-3).

Anticancer potential of metformin has been shown in Libby et al. (2009) observational cohort study among people with DM2. In this study metformin users had significantly lower risk of overall cancer incidence (7.3% vs. 11.6%) (2), like in our study (2.1 vs. 27.3%). In addition, our results, even in a small sample, have shown that metformin contributes significantly to the predictive ability of the model, which indicates that an increase of metformin use will result in decreased probability of the cancer occurrence (B=-3.015; OR=0.049; 95% CI 0.013−0.181). Accordingly, in systematic review and meta-analysis of 47 independent studies with 65540 cancer cases in patients with DM2, Gandini et al. (2014) reported overall cancer incidence reduction in 31% with summary relative risk (SRR) 0.69 (95% CI: 0.52–0.90) and cancer mortality in 34% patients with SRR 0.66 (95%CI: 0.54–0.81) (1). Our findings refer to the use of metformin in monotherapy, while a population-based cohort study showed the magnitude of cancer risk reduction and prolonged cancer onset time produced by metformin in patients with DM2 do not depend on whether metformin was used alone or combined with other antidiabetic drugs, but depend on a metformin dose (3). We did not investigate the association between the metformin dose and cancer risk, which is one of the limitations of our study. But in any case the doses of metformin that were used in our study were within the recommended dosage for DM2, which would mean that potential anticancer effects may not require higher doses. Additionally, limitations of this study are related to the retrospective data collection and a lack of stratification of the sample.

Presented results are related to the general occurrence of cancer, but according to other studies, metformin efficacy may be limited to just several cancer types (4,5). These results are contradictory (36,37), which indicates the necessity of further research related to this topic.

If encouraging results arise, metformin will be an attractive candidate adjuvant in the management of human neoplasias, due to its safety, tolerability and low-cost, expected to mitigate adverse effects and no-response parameters of current anti-cancer therapeutics, thus improving the quality of life and survival of cancer patients. Further long-term prospective clinical trials are needed to focus on specific types of cancer, the use in patients without DM2 as well as its use in adjuvant cancer therapy.

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**TRANSPARENCY DECLARATION**

Competing interests: None to declare.

**REFERENCES**


Primjena metformina povezana s manjim rizikom karcinoma kod pacijenata s dijabetesom melitusom tipa 2

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SAŽETAK

Cilj U cilju povećanja baze podataka vezane za antikancerski potencijal metformina, istražili smo povezanost rizika pojave karcinoma i primjene metformina u pacijenata s DM2.

Metode U prikazanoj presječnoj studiji obrađeni su medicinski kartoni pacijenata s DM2 na pojavu karcinoma. Analizirani su sljedeći parametri: starost pacijenta, indeks tjelesne mase (BMI), konzumacija alkohola i nikotina, vrijednost glukoze i HbA1c, dužina trajanja DM2, lijekovi koji se primjenjuju i pojava karcinoma. U statističkoj analizi za poređenje tretmanskih grupa korišten je nezavisni Studentov t-test ili Mann-Whitneyev U-test, a logistička regresija za analizu varijabli kao prediktora pojave karcinoma. Statistički značajna smatrana je vrijednost p< 0.05.

Rezultati U istraživanje su bila uključena 234 pacijenta, prosječne starosti 66,8±11,5 godina i prosječnim trajanjem DM2 7± 6,49 godina. Prosječna vrijednost glukoze iznosila je 8,51±4,17mmol/L i HbA1c 7,74±1,53. Metformin je primijenjen kod 190 (81%) pacijenata. Karcinom je dijagnosticiran kod 16 (6,8%) pacijenata, odnosno karcinom prostate kod osam (3,4%), karcinom dojke kod četiri (1,7%), karcinom debelog crijeva kod dva (0,9%) te karcinom uterusa i cerviksa kod po jednog pacijenta. Starost, dužina trajanja DM2 i BMI nisu značajno utjecali na model, dok se metfomin pokazao kao signifikantan neovisni prediktor smanjenog rizika pojave karcinoma (OR=0,049; 95% CI=0,013–0,181; p=0,001).

Zaključak Rezultati našeg istraživanja potvrdili su hipotezu da je primjena metformina u odnosu na druge oralne antidijabetike povezana s manjim rizikom pojave karcinoma u pacijenata s DM2.

Ključne riječi: hipoglikemici, dijabetes tipa 2, neoplazme