ORIGINAL ARTICLE

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

Jasna Kusturica[1], Aida Kulo Ćesić[1], Edis Gušić[2], Sanita Maleškić[1], Maida Rakanović-Todić[1], Damir Šečić[3]

[1]Department of Pharmacology and Toxicology, School of Medicine, University of Sarajevo, [2]Department of Health Care, Ministry of Internal Affairs of Canton Sarajevo, [3]Department of Pathophysiology, School of Medicine, University of Sarajevo; Sarajevo, Bosnia and Herzegovina

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 occurence 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 occurence. 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 occurence 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 asses how well our set of predictor variables predicts occurence 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

Corresponding author:
Jasna Kusturica
Department of Pharmacology and Toxicology, School of Medicine, University of Sarajevo
Čekaluša 90, 71000 Sarajevo,
Bosnia and Herzegovina
E-mail: jasna.kusturica@mf.unsa.ba
ORCID ID: http://www. orcid.org/: 0000-0002-4120-7230

Original submission:
07 April 2017;
Revised submission:
24 May 2017;
Accepted:
01 June 2017.
doi: 10.17392/910-17

Med Glas (Zenica) 2017; 14(2): 176-181

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 (χ^2) 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

Variable	Cancer occurrence*		p
	Absent (n=218)	Present (n=16)	
Age (years)	66 (59.8; 73)	75 (64.5; 79.8)	0.04
Body mass index (kg/m²)	29 (26; 32)	30.5 (28;34,7)	0.229
Nicotine consumption	102 (46.8%)	5 (31.3%)	0.228
Alcohol consumption	33 (15.1%)	1 (6.25%)	0.479
Duration of DM2 (years)	5 (2; 10.3)	9.5 (4.25;13.7)	0.05
Non regulated glucose	67 (30.7%)	5(31.3%)	0.966
HbA1c level (%)	7.2 (6.7;8.45)	7.42 (6.92; 8.43)	0.516

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

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 (χ^2 (4)=31.188; p<0.001), Hosmer and Lemeshow Test (χ^2=13.002; p=0.112), Cox-Snell (R^2=0.125) and Nagelkerke (R^2=0.318) supported the test model (Table 2). The overall accuracy of classification was 93.2%.

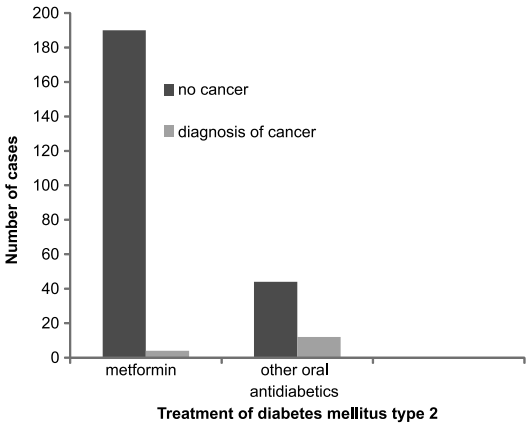

Figure 1. Prevalence of cancer in metformin-treated vs other oral antidiabetic-treated patients with DM2

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 metfomin use and the diagnosis of carcinoma in the population of patients with DM2 (Table 2).

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

	B coefficient	p	Exp(B)	95% CI for EXP(B)	
				Lower	Upper
Age (years)	0.018	0.533	1.018	0.963	1.076
Duration of DM2 (years)	0.52	0.296	1.053	0.956	1.161
Body mass index	0.117	0.052	1.124	0.999	1.265
Type of medicine use	-3.015	0.000	0.049	0.013	0.181
Constant	-6.113	0.040	0.002		

*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; Nagelkerke R2=0.318; Exp(B), odds ratio ; 95% CI, 95% confidence interval;

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 contibutes significantly to the predictive abilitiy of the model, which indicates that an increase of metfomin 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 metfomin 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 metfomin dose and cancer risk, which is one of the limitations of our study. But in any case the doses of metfomin 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.

FUNDING

No specific funding was received for this study.

TRANSPARENCY DECLARATION

Competing interests: None to declare.

REFERENCES

1. Gandini S, Puntoni M, Heckman-Stoddard BM, Dunn BK, Ford L, De Censi A, Szabo E. Metformin and cancer risk and mortality: a systematic review and meta-analysis taking into account biases and confounders. Cancer Prev Res (Phila) 2014; 7:867–85.
2. Libby G, Donnelly LA, Donnan PT. New users of metformin area at low risk of incident cancer: a cohort study among people with type 2 diabetes. Diabetes Care 2009; 32:1620–5.
3. Lin HC, Kachingwe BH, Lin HL, Cheng HW, Uang YS, Wang LH. Effects of metformin dose on cancer risk reduction in patients with type 2 diabetes mellitus: A 6-year follow-up study. Pharmacotherapy 2014; 34:36-45.
4. Donghui Li. Diabetes and pancreatic cancer. Mol Carcinog 2012; 51:64–74.
5. Li D, Yeung SJ, Hassan MM, Konopleva M, Abbruzzese JL. Anti-diabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009; 137:482–8.

6. Godarzi MO, Brier-Ash M. Metformin revisited: re-evaluation of its properties and role in the pharmacopoeia of modern antidiabetic agents. Diabetes Obes Metab 2005; 5:654–65.
7. Gosmanova EO, Canada RB, Mangold TA, Rawls WN, Wall BM. Effect of metformin-containing antidiabetic regimens on all-cause mortality in veterans with type 2 diabetes mellitus. Am J Med Sci 2008; 336:241-7.
8. Evans JM, Ogston SA, Emslie-Smith A, Morris AD. Risk of mortality and adverse cardiovascular outcomes in type 2 diabetes: a comparison of patients treated with sulfonylureas and metformin. Diabetologia 2006; 49:930-6.
9. Evans JM, Donnelly LA, Emslie-Smith AM, Alessi DR, Morris AD. Metformin and reduced risk of cancer in diabetic patients. BMJ 2005; 330:1304-5.
10. Bowker SL, Majumdar SR, Veugelers P, Johnson JA. Increased cancer-related mortality for patients with type 2 diabetes who use sulfonylureas or insulin. Diabetes Care 2006; 29:254-8.
11. Lemke TL, Williams DA, Roche VF, Zito SW. Foye's principles of medicinal chemistry. 6th ed. Philadelphia: Wolters Kluwer, Lippincott Williams & Willkins, 2008.
12. Viollet B, Guigas B, Sanz Garcia N, Leclerc J, Foretz M, Andreelli F. Cellular and molecular mechanisms of metformin: an overview. Clin Sci (Lond) 2012; 122:253-70.
13. Mičić D, Cvijović G, Trajković V, Duntas LH, Polovina S. Metformin: its emerging role in oncology. Hormones 2011; 10:5-15.
14. Sun G, Kashyap SR. Cancer risk in type 2 diabetes mellitus: metabolic Llnks and therapeutic considerations. J Nutr Metab 2011; 2011:708183.
15. Li W, Saud SM, Young MR, Chen G, Hua B: Targeting AMPK for cancer prevention and treatment. Oncotarget 2015; 6:7365-78.
16. Luo Z, Zang M, Guo W. AMPK as a metabolic tumor suppressor: control of metabolism and cell growth. Future Oncol 2010; 6:457-70.
17. Thompson MD, Grubbs CJ, Bode AM, Reid JM, McGovern R, Bernard PS, Stijleman IJ, Green JE, Bennett C, Juliana MM, Moeinpour F, SteeleVE, Lubet RA. Lack of effect of metformin on mammary carcinogenesis in nondiabetic rat and mouse models. Cancer Prev Res 2015; 8:231-9.
18. Anisimov VN, Berstein LM, Popovich IG, Zabezhinski MA, Egormin PA, Piskunova TS, Semenchenko AV, Tyndyk ML, Yurova MN, Kovalenko IG, Poroshina TE. If started early in life, metformin treatment increases life span and postpones tumors in female SHR mice. Aging (Albany NY) 2011; 3:148–57.
19. Noto H, Goto A, Tsujimoto T, Noda M. Cancer risk in diabetic patients treated with metformin: a systematic review and meta-analysis. PLoS One 2012; 7:e33411.
20. Franciosi M, Lucisano G, Lapice E, Strippoli GF, Pellegrini F, Nicolucci A. Metformin therapy and risk of cancer in patients with type 2 diabetes: systematic review. PLoS One 2013; 8:e71583.
21. Li K-L, Li L, Zhang P, Kang J, Wang Y-B, Chen H-Y, He Y. A multicenter double-blind phase II study of metformin with gefitinib as first-line therapy of locally advanced non–small-cell lung cancer. Clin Lung Cancer 2017; 18:340-3.
22. Cancer Research UK. Cancer incidence by age. December 2016. http://www.cancerresearchuk.org/health-professional/cancer-statistics/incidence/age#heading-Zero (06 January 2017).
23. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003; 348:1625–38.
24. Togashi Y, Hayashi H, Okamoto K, Fumita S, Terashima M, de Velasco MA, Sakai K, Fujita Y, Tomida S, Nakagawa K, Nishio K. Chronic nicotine exposure mediates resistance to EGFR-TKI in EGFR-mutated lung cancer via an EGFR signal. Lung Cancer 2015; 88:16-23.
25. American Cancer Society. Cancer facts and figures 2017. https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2017.html (29 May 2017)
26. Larsson SC, Mantzoros CS, Wolk A. Diabetes mellitus and risk of breast cancer: a meta-analysis. Int J Cancer 2007; 121:856-62.
27. Friberg E, Orsini N, Mantzoros CS, Wolk A. Diabetes mellitus and risk of endometrial cancer: a meta-analysis. Diabetologia 2007; 50:1365-74.
28. Wang P, Kang D, Cao W, Wang Y, Liu Z. Diabetes mellitus and risk of hepatocellular carcinoma: a systematic review and meta-analysis. Diabetes Metab Res Rev 2012; 28:109-22.
29. El-Serag HB, Hampel H, Javadi F. The association between diabetes and hepatocellular carcinoma: a systematic review of epidemiologic evidence. Clin Gastroenterol Hepatol 2006; 4:369–80.
30. Huxley R, Ansary-Moghaddam A, de González AG, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005; 92:2076–83.
31. Zhu Z, Wang X, Shen Z, Lu Y, Zhong S, Xu C. Risk of bladder cancer in patients with diabetes mellitus: an updated meta-analysis of 36 observational studies. BMC Cancer 2013; 13:310.
32. Mitri J, Castillo J. and Pittas AG. Diabetes and risk of non-Hodgkin's lymphoma: A meta-analysis of observational studies. Diabetes Care 2008; 31:2391-7.
33. Deng L, Gui Z, Zhao L, Wang J, Shen L. Diabetes mellitus and the incidence of colorectal cancer: an updated systematic review and meta-analysis. Dig Dis Sci 2012; 57:1576-85.
34. Barone BB, Yeh HC, Snyder CF, Peairs KS, Stein KB, Derr RL, Wolff AC, Brancati FL: Long-term all-cause mortality in cancer patients with preexisting diabetes mellitus: a systematic review and meta-analysis. JAMA 2008; 300:2754–64.
35. Garg SK, Maurer H, Reed K, Selagamsetty R. Diabetes and cancer: two diseases with obesity as a common risk factor. Diabetes Obes Metab 2014; 16:97-110.
36. Onitilo AA, Stankowski RV, Berg RL, Engel JM, Glurich I, Williams GM, Doi SA. Type 2 diabetes mellitus, glycemic control, and cancer risk. Eur J Cancer Prev 2014; 23:134-40.
37. Margel D, Urbach D, Lipscombe LL, Bell CM, Kulkarni G, Austin PC, Fleshner N. Association between metformin use and risk of prostate cancer and its grade. J Natl Cancer Inst 2013; 105:1123-31.

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

Jasna Kusturica[1], Aida Kulo Ćesić[1], Edis Gušić[2], Sanita Maleškić[1], Maida Rakanović-Todić[1], Damir Šečić[3]

[1]Katedra za farmakologiju i toksikologiju, Medicinski fakultet, Univerzitet u Sarajevu, [2]Zavod za zdravstvenu zaštitu, Ministarstvo unutrašnjih poslova Kantona Sarajevo, [3]Katedra za patofiziologiju, Medicinski fakultet, Univerzitet u Sarajevu; Sarajevo, Bosna i Hercegovina

SAŽETAK

Cilj U cilju povećanja baze podataka vezane za antikancerski potencijal metformina, istražili smo povezanost rizika pojave karcinoma i primjene metformina u pacijenata s dijabetesom melitusom tipa 2 (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 metfomina u odnosu na druge oralne antidijabetike povezana s manjim rizikom pojave karcinoma u pacijenata s DM2.

Ključne riječi: hipoglikemici, dijabetes tipa 2, neoplazme