Metformin Associated With Increased Survival in Type 2 Diabetes Patients With Pancreatic Cancer and Lymphoma

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ABSTRACT

Background: The biguanide drug metformin is one of the most commonly used medications for the treatment of type 2 diabetes mellitus. Diabetics are at an increased risk for cancer. Previous studies have demonstrated improved outcomes in patients taking metformin suffering from prostate, colon, lung, thyroid, and esophageal cancers. Metformin's main antineoplastic mechanism of action is thought to be mediated through inhibition of mammalian target of rapamycin, inhibition of hypoxia-inducible factor 1 (HIF-1) alpha, and activation of p53. We investigated the overall survival of type 2 diabetic patients on metformin with pancreatic cancer and lymphoma using the Computerized Patient Record System at the Veterans Affairs Medical Center, Memphis TN.

Methods: Lymphoma and pancreatic cancer patients with type 2 diabetes were sorted into an experimental (metformin) group and a control (nonmetformin) group. Patients were compared on baseline characteristics including race, body mass index, and age. Cancer outcomes including overall survival, metastasis, recurrences, and incidence of new malignancies were recorded. Hemoglobin A1C, creatinine and cancer treatment modalities were recorded and compared. Statistical analyses used included unpaired *t* tests and Chi-squared tests.

Results: There was significantly greater overall long-term survival in the metformin group compared to the nonmetformin group for lymphoma (5.89 vs 1.29 years, $P < 0.001$) and for pancreatic cancer (0.68 vs 0.22 years, $P = 0.016$). Cancer treatment modalities in both groups were comparable.

Conclusions: Metformin is associated with a significant, positive effect of increased overall survival in type 2 diabetes patients with pancreatic cancer and lymphoma. These results are encouraging, and prospective studies should be done to further investigate metformin's effects in cancer.

Key Indexing Terms: Metformin; Diabetes; Pancreatic cancer; Lymphoma; Survival. **[Am J Med Sci 2019;358(3):200–203.]**

INTRODUCTION

Many studies have demonstrated that type 2 diabetes mellitus (T2DM) patients are at an increased risk of developing many cancers.[1,2] In fact, between 8% and 18% of new cancer patients have diabetes, predominantly Type 2.[3] The link between diabetes and cancer may be related to hyperinsulinemia due to insulin resistance causing excessive activation of growth pathways in T2DM patients. A study examining the role of tumor necrosis factor (TNF)-alpha in insulin resistance demonstrated that the insulin signaling and apoptosis pathways are intimately connected through phosphatase and tensin homolog (PTEN), TNF-alpha and insulin.[4] PTEN inhibits phosphoinositide 3-kinase (PI3K) signaling of the insulin pathway producing insulin resistance. In contrast, PTEN, stimulated by TNF-alpha, promotes apoptosis through its actions on nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB).[5,6] Insulin and a related hormone, insulin-like growth factor (IGF-1), can bind to insulin receptors and stimulate the Ras/Raf/mitogen-activated protein kinase (MEK)/extracellular signal-regulated kinase (ERK) or the phosphoinositide 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathways leading to cellular proliferation.[7]

Metformin is the first-line drug for the treatment of type 2 diabetes and acts to reduce blood glucose levels

through many different mechanisms. It is thought that metformin primarily exerts its antihyperglycemic effects through the reduction of hepatic gluconeogenesis. This is accomplished by the inhibition of Complex I of the electron transport chain leading to cellular stress and increased adenosine monophosphate (AMP)/adenosine triphosphate (ATP) ratios resulting in activation of 5' AMP-activated protein kinase (AMP kinase).[8] Along with its efficacy in lowering blood sugars in type 2 diabetics, metformin also demonstrates encouraging antitumorigenic outcomes through a myriad of proposed molecular mechanisms, both mediated by AMP kinase and independent of AMP kinase activation. Metformin-activated AMP kinase inhibits a protein synthesis regulator (mTOR), suppresses angiogenesis by inhibiting hypoxia-inducible factor 1-alpha, and promotes cell cycle arrest and apoptosis.[9-12] Independent of AMP kinase, metformin has been shown to boost T cells' anticancer response, increase expression of C-myc miRNA and inhibit inflammatory cytokines needed for tumor growth via blockade of NF-KB signaling.[13-15] In addition to decreasing circulating insulin levels through increased insulin receptor sensitivity, metformin has been shown to decrease IGF-1 receptor and insulin receptor expression in endometrial cancer cell lines.[16] The lower levels of circulating insulin and IGF-1 reduce the amount of binding to the insulin receptor, especially to isoform A in cancer cells, leading to less tumor growth.[17]

We have shown in recent retrospective chart review studies improved outcomes such as increased survival in T2DM patients suffering from prostate, colon, gastroesophageal, lung and thyroid cancers.[18-20] Other studies have supported metformin's effect to bolster positive outcomes in T2DM patients suffering from pancreatic cancer and lymphoma. A recent meta-analysis of 2 randomized control studies and 9 cohort studies indicated significant survival improvement in the metformin group especially in patients with surgical resection and locally advanced tumors. However, metformin did not have a significant impact on patient survival in patients with metastatic pancreatic tumors.[21]

In patients with stage 3 and 4 diffuse B-cell lymphoma, 92% of patients on metformin experienced complete remission compared to 54% of patients not on metformin (odds ratio, 18.6 (95% confidence interval 2.15−161; $P = .0018$).[22] These results lead us to believe that metformin could play a role in generating positive outcomes for T2DM patients with these specific cancers. We hypothesize that patients with lymphoma or pancreatic cancer who are taking metformin will have greater survival than those not taking metformin.

METHODS

Using the Veterans' Affairs (VA) Hospital's Computerized Patient Record System, a retrospective chart review was conducted on 304 VA patients with pancreatic cancer and 360 patients with lymphoma from 1988 to 2018. This patient population was further narrowed to those who had been diagnosed with type 2 diabetes before their cancer diagnosis by selecting diabetic patients via ICD codes. The patients in the study could be living or deceased. The study compared the T2DM patients with cancer taking metformin (experimental group) and the T2DM patients with cancer not taking metformin (control group) on parameters such as overall survival, metastases, recurrence and rate of new malignancies. All the data for the survival outcomes were gleaned from the clinical progress notes. To qualify for the metformin group, patients must have been on metformin at least 6 months before the cancer diagnosis and stayed on metformin at least 1 year after diagnosis or were still on metformin if they passed away within 1 year of diagnosis. To qualify for the control group, the patients must have never taken metformin at any point in their treatment of diabetes. Progress notes and pharmacy records were analyzed to determine placement in the metformin or nonmetformin group. Patients in both groups were compared by race, body mass index and treatment type (surgery, radiation, chemotherapy). Hemoglobin A1C levels were recorded to be certain that both groups had similar control of their diabetes. This study has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving human subjects. This study was approved by the Institutional Review Board for Human Subjects Research, the Research and Development Committee, as well as the appropriate approving committees of the University of Tennessee Medical Student Research Fellowship (MSRF) and the University of Tennessee Health Science Center. Informed consent was waived based on the nature of the study as a retrospective chart review. Statistical analysis consisted of unpaired *t* tests and Chi-squared tests to verify the patient groups were comparable on important clinical characteristics mentioned above. Any group differences were controlled for using analysis of covariance (ANCOVA) by including the significant variable as a covariate in the model. *P* values less than or equal to 0.05 were considered significant and those between 0.05 and 0.10 were considered trends toward significance.

RESULTS

Out of the starting population of 360 lymphoma patients and 304 pancreatic cancer patients from the VA tumor registry, 77 and 74 were also T2DM patients, respectively. The number of lymphoma patients satisfying our criteria was 18 for the metformin group and 20 for the nonmetformin group. The number of pancreatic cancer patients satisfying our criteria was 18 for the metformin group and 28 for the nonmetformin group. Tables 1 and 2 demonstrate that the baseline characteristics of T2DM patients in the metformin and nonmetformin groups are mostly comparable.

There was significantly greater long-term survival in the metformin group than the nonmetformin group in lymphoma (5.89 vs 1.29 years, $P < 0.001$) (Table 3) and for pancreatic cancer (0.68 vs 0.22 years, $P = 0.016$) (Table 4).

Table 1. Baseline characteristics of patients with lymphoma.

Variable	Metformin *n* = 18 Mean ± SD or %	Nonmetformin *n* = 20 Mean ± SD or %	*P* Value
Sex, Male	94.4	100.0	0.474
Race			0.699
White	58.8	65.0	
Black	41.2	35.0	
BMI	27.51 ± 4.63	26.29 ± 5.02	0.460
Age at cancer diagnosis	64.1 ± 9.3	73.3 ± 7.5	0.002
Surgery treatment	22.2	15.0	0.682
Radiation treatment	33.3	30.0	0.825
Chemotherapy treatment	88.9	90.0	>0.999
HbA1c	7.57 ± 1.39	7.02 ± 1.58	0.273
Creatinine	1.04 ± 0.24	1.49 ± 0.55	0.003

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.

Table 2. Baseline characteristics of patients with pancreatic cancer.

Variable	Metformin *n* = 18 Mean ± SD or %	Nonmetformin *n* = 28 Mean ± SD or %	*P* Value
Sex, Male	94.4	96.4	>0.999
Race			0.227
White	61.1	42.9	
Black	38.9	57.1	
BMI	24.36 ± 5.28	25.97 ± 5.29	0.344
Age at cancer diagnosis	65.0 ± 6.45	72.3 ± 10.18	0.005
Surgery treatment	33.3	21.4	0.495
Radiation treatment	11.1	7.1	0.639
Chemotherapy treatment	44.4	28.6	0.270
HbA1c	7.63 ± 0.93	7.17 ± 1.50	0.264
Creatinine	1.06 ± 0.33	1.52 ± 0.91	0.020

Abbreviations: BMI, body mass index; HbA1c, hemoglobin A1c.

Table 3. Outcomes of patients with lymphoma.

Variable	Metformin *n* = 18 Mean ± SD or %	Nonmetformin *n* = 20 Mean ± SD or %	*P* Value
Recurrence	44.4	35.0	0.552
New malignancies	16.7	10.0	0.653
Years living after cancer diagnosis	5.89 ± 0.67	1.29 ± 0.38	<0.001*

Note: *calculated based on square root transformed data.

Table 4. Outcomes of patients with pancreatic cancer.

Variable	Metformin *n* = 18 Mean ± SD or %	Nonmetformin *n* = 28 Mean ± SD or %	*P* Value
Metastasis	77.8	82.1	0.721
Years living after cancer diagnosis	0.68 ± 0.37	0.22 ± 0.12	0.016*

Note: *calculated based on square root transformed data.

There were no significant differences in recurrence or new malignancies for lymphoma ($P = 0.552$ and $P = 0.653$). Though the metformin group had fewer metastases than the non-metformin group for pancreatic cancer, this finding was not statistically significant ($P = 0.721$). Controlling for age at diagnosis and creatinine, patients still had significantly longer survival in the metformin group vs the non-metformin group for lymphoma ($P < 0.001$ and $P < 0.001$). After controlling for age at diagnosis in pancreatic cancer, patients trend toward significantly longer survival, but they did have significantly longer survival after controlling for creatinine ($P = 0.075$ and $P = 0.042$).

DISCUSSION

Findings from this pancreatic cancer and lymphoma sample suggest that metformin may increase the survival of patients with these cancers. This study yielded meaningful findings supporting our hypothesis that cancer patients on metformin live significantly longer than patients not on metformin. Metformin achieves its anti-cancer effects through various mechanisms of action. One possible mechanism specific to pancreatic cancer is its role as a mitochondrial stressor. Around 90% of pancreatic cancers express the KRAS oncogene, and rely more upon oxidative phosphorylation than aerobic glycolysis. Metformin could more efficiently disrupt this type of energy metabolism.[23]

There are a few limitations to our study. Sample sizes were small ranging from 18 to 28 patients after applying inclusion criteria despite starting with a large group of cancer patients. The patient population was almost completely male, and the study was carried out at one VA medical center (Memphis). Our small sample size impacted the significance of survival time in pancreatic cancer after controlling for age at cancer diagnosis. Another limitation is the significant difference for both lymphoma and pancreatic cancer in the baseline renal function. This was expected since metformin is contraindicated if renal function is severely decreased.

In conclusion, this retrospective chart review study demonstrates that metformin, as an adjuvant to traditional cancer therapy, is associated with overall increased years of survival in patients with lymphoma or pancreatic cancer. We would like to see a prospective study in T2DM patients taking metformin to confirm these results. As more research is conducted with metformin, we anticipate that metformin or a derivative drug may someday be used as an anti-cancer drug independent of diabetic status.

REFERENCES

1. **Smith U, Gale EM.** Cancer and diabetes: are we ready for prime time? *Diabetologia*. 2010;53:1541–1544.
2. **Vigneri P, Frasca F, Sciacca L, et al.** Diabetes and cancer. *Endocr Relat Cancer*. 2009;16:1103–1123.
3. **Coughlin SS, Calle EE, Teras LR, et al.** Diabetes mellitus as a predictor of cancer mortality in a large cohort of US adults. *Am J Epidemiol*. 2004;159:1160–1167.
4. **Solomon SS, Odunusi O, Carrigan D, et al.** TNF-alpha inhibits insulin action in liver and adipose tissue: a model of metabolic syndrome. *Horm Metab Res*. 2010;42:115–121.
5. **Taniguchi CM, Tran TT, Kondo T, et al.** Phosphoinositide 3-kinase regulatory subunit p85alpha suppresses insulin action via positive regulation of PTEN. *Proc Natl Acad Sci U S A*. 2006;103:12093–12097.
6. **Gustin JA, Machama T, Dixon TE, et al.** The PTEN suppressor protein inhibits TNF-induced NFKB activity. *J Biol Chem*. 2001;276:27740–27744.
7. **Gong J, Kelekar G, Shen J, et al.** The expanding role of metformin in cancer: an update on antitumor mechanisms and clinical development. *Target Oncol*. 2016;11:447–467.
8. **Luengo A, Sullivan LB, Vander Heiden MG.** Understanding the comlexity of metformin action; limiting mitochondrial respiration to improve cancer therapy. *BMC Biol*. 2014;12:82.
9. **Morita M, Gravel SP, Hulea L, et al.** MTOR coordinates protein synthesis, mitochondrial activity and proliferation. *Cell Cycle*. 2015;14:473–480.
10. **Faubert B, Boily G, Izreig S, et al.** AMPK is a negative regulator of the Warburg effect and suppresses tumor growth in vivo. *Cell Metab*. 2012;17:113–124.
11. **Alao JP.** The regulation of cyclin D1 degradation: roles in cancer development and the potential for therapeutic invention. *Mol Cancer*. 2007;6:24.
12. **Sahra IB, Laurent K, Loubat A, et al.** The antidiabetic drug metformin exerts an antitumoral effect in vitro and in vivo through a decrease of cyclin D1 level. *Oncogene*. 2008;27:3576–3586.
13. **Eikawa S, Nishida M, Mizukami S, et al.** Immune-mediated antitumor effect by Type 2 diabetes drug, metformin. *Proc Natl Acad Sci U S A*. 2015;112:1809–1814.
14. **Moiseeva O, Deschenes-Simard X, St-Germain E, et al.** Metformin inhibits the senescence associated secretory phenotype by interfering with IKK/NF-κB activation. *Aging Cell*. 2013;12:489–498.
15. **Blandino G, Valerio M, Cioce M, et al.** Metformin elicits anticancer effects through the sequential modulation of DICER and c-MYC. *Nat Commun*. 2012;3:865.
16. **Memmott RM, Dennis PA.** LKB1 and mammalian target of rapamycin as predictive factors for the anticancer efficacy of metformin. *J Clin Oncol*. 2009;27:e226.
17. **Oliveras-Ferraros C, Vazquez-Martin A, Menendez JA.** Genome-wide inhibitory impact of the AMPK activator metformin on [kinesins, tubulins, histones, auroras and polo-like kinases] M-phase cell cycle genes in human breast cancer cells. *Cell Cycle*. 2009;8:1633–1636.
18. **Solomon SS, Chong RW, Vasudevan V, et al.** Metformin has positive therapeutic effect on prostate cancer in patients with Type 2 diabetes mellitus. *Am J Med Sci*. 2016;351:416–419.
19. **Solomon SS, Branch P, Brannick B, et al.** Metformin improves outcomes in T2DM patients with thyroid and gastroesophageal cancers. *Ann Clin Exp Metab*. 2017;2:1019.
20. **Henderson D, Frieson D, Zuber J, et al.** Metformin has positive therapeutic effects in colon cancer and lung cancer. *Am J Med Sci*. 2017;354:246–251.
21. **Li X, Li T, Liu Z, et al.** The effect of metformin on survival of patients with pancreatic cancer: a meta-analysis. *Sci Rep*. 2017;7:5825.
22. **Yaser A, Rahman Z, Kuriakose P.** Clinical impact of metformin in diabetic diffuse large B-cell lymphoma patients: a case-control study. *Leuk Lymphoma*. 2017;58(5):1130–1134.
23. **Viale A, Pettazzoni P, Lyssiotis CA, et al.** Oncogene ablation-resistant pancreatic cancer cells depend on mitochondrial function. *Nature*. 2014;514:628–632.

Submitted March 13, 2019; accepted June 6, 2019.

Conflict of interest and funding statement: There are no conflicts of interest. Supported in part by NIH grant award number: DK-113964-02, extension funds.

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