Metformin exposure is associated with improved progression-free survival in diabetic patients after resection for early-stage non-small cell lung cancer

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ABSTRACT

Objective: There are little clinical data assessing the antineoplastic effect of metformin in patients with non-small cell lung cancer. We hypothesized that in diabetic patients undergoing pulmonary resection for early-stage non-small cell lung cancer, metformin exposure is associated with improved survival.

Methods: An institutional database was used to identify patients with stage I or II non-small cell lung cancer who underwent pulmonary resection between 2004 and 2013. Patients were divided into 3 cohorts: type II diabetic patients with metformin exposure (cohort A, n = 81), type II diabetic patients without metformin exposure (cohort B, n = 57), and nondiabetic individuals (cohort C, n = 77). Univariate, multivariate, and propensity-matched analyses were performed to assess progression-free and overall survivals between groups.

Results: A total of 215 patients with stage I and II non-small cell lung cancer treated with surgical resection were identified for analysis with a median follow-up of 19.5 months. Patients in cohort A had lower T- and N-stage tumors than those in cohorts B or C. However, on multivariate analysis adjusting for age, gender, and T and N stage, progression-free survival was greater for cohort A than cohort B (hazard ratio [HR], 0.410; 95% confidence interval, 0.199-0.874; $P = .022$) or cohort C (HR, 0.415; 95% confidence interval, 0.201-0.887; $P = .017$). Likewise, when propensity-matched analyses were performed, cohort A demonstrated a trend toward improved progression-free survival compared with cohort B ($P = .057$; HR, 0.44; c-statistic = 0.832) and improved progression-free survival compared with cohort C ($P = .02$; HR, 0.41; c-statistic = 0.843). No differences were observed in overall survival.

Conclusions: Metformin exposure in diabetic patients with early-stage non-small cell lung cancer may be associated with improved progression-free survival, but no effect was seen on overall survival. Further studies are warranted to evaluate if there is a therapeutic role for metformin in the treatment of non-small cell lung cancer. (J Thorac Cardiovasc Surg 2016;152:55-61)

PFS: metformin-exposed versus nonmetformin-exposed patients.

Central Message

Metformin exposure in type 2 diabetic patients with NSCLC is associated with improved PFS.

Perspective

Metformin exposure in patients who underwent pulmonary resection for early-stage NSCLC may be associated with improved PFS. Further prospective studies assessing metformin as an adjuvant agent in lung cancer are needed to determine whether there is a role for metformin in the treatment of early-stage lung cancer.

See Editorial Commentary page 62.

Lung cancer is the leading cause of cancer death, with more than 220,000 patients being diagnosed in the United States in 2014, resulting in approximately 160,000 deaths during this period.¹ Unfortunately, the 5-year survival for patients with lung cancer remains

poor at approximately 15%, because most patients are diagnosed with late-stage disease when curative therapy is no longer available.² Therefore, novel therapies aimed at improving survival in lung cancer are of utmost importance.

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Abbreviations and Acronyms

AMPK	= AMP-activated protein kinase
BMI	= body mass index
ECOG	= Eastern Cooperative Oncology Group
HR	= hazard ratio
IGF-1	= insulin-like growth factor 1
NSCLC	= non-small cell lung cancer
OS	= overall survival
PFS	= progression-free survival

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Emerging evidence suggests that metformin, a biguanide commonly used to treat type 2 diabetes, may serve as an adjuvant agent to reduce cancer risk and improve survival in certain cancers, including breast and colorectal.^{3,4} In addition, *in vitro* and *in vivo* studies have suggested metformin has an antineoplastic effect.^{5,6} Studies of human non-small cell lung cancer (NSCLC) cells in a murine model have demonstrated that metformin inhibits tumor cell proliferation via activation of the ataxia telangiectasia-mutated AMP-activated protein kinase (AMPK) pathway, inducing p53- and p21-mediated G1 cycle arrest and apoptosis.⁷ Recent studies examining the association between metformin use and survival among diabetic patients with advanced-stage NSCLC have demonstrated conflicting results.⁸⁻¹¹ Furthermore, the effect of metformin on progression-free survival (PFS) and overall survival (OS) in patients with early-stage NSCLC has yet to be determined. We hypothesized that preoperative metformin exposure is associated with improved survival in diabetic patients with early-stage lung cancer who underwent pulmonary resection.

PATIENTS AND METHODS

After Institutional Review Board approval, all patients who underwent pulmonary resection for stage I or II NSCLC between 2004 and 2013 at Rush University Medical Center were identified. Inclusion criteria were age more than 18 years, type 2 diabetes, and histologically confirmed stage I or II NSCLC. A control group of nondiabetic patients was identified by querying our departmental database for all patients who underwent pulmonary resection for stage I or II NSCLC during the study period. Exclusion criteria included only patients who did not consent to clinical data collection for research purposes. All stage classifications are reported according to the American Joint Committee on Cancer seventh edition criteria and confirmed by pathological evaluation.^{12,13} The following demographic data were abstracted from each patient record: age, sex, gender, race, calculated body mass index (BMI), preoperative Eastern Cooperative Oncology Group (ECOG) score, and tobacco smoking history.

Additional data extracted from the records included pathologic TNM stage, tumor histology, adjuvant chemotherapy, preoperative renal function and fasting serum glucose, diabetic medication regimen, metformin dosage, surgical procedure, prior malignancy of any type, and comorbidities. Patients were classified as having metformin exposure if they had documented use of metformin within 6 months before the surgical resection, in accordance with previously published studies.^{6,14} For every patient, charts were reviewed through the most recent follow-up date for metformin exposure.

Patients were divided into 3 groups for comparison: cohort A (type 2 diabetic patients with metformin exposure), cohort B (type 2 diabetic patients without metformin exposure), and cohort C (nondiabetic patients). Patient demographics, treatment strategies, and survival were compared between groups. All patients were followed with a history, physical, and a noncontrast chest computed tomography scan every 6 months for the first 2 years and then yearly for life. OS was calculated as the time from date of surgery to death or last documented follow-up. PFS was calculated from the date of surgery to the date of first recurrence, defined as the last date of negative radiographic imaging and clinical examination. If there was no recurrence, and the patient died, the PFS was based on the date of death. PFS and OS curves were estimated by Kaplan-Meier method and compared across groups by log-rank tests. Hazard ratios (HRs) and association of PFS or OS with multiple covariates were assessed using the Cox proportional hazards model. To reduce confounding effects, adjusted Kaplan-Meier estimates and log-rank tests based on inverse propensity score of treatment weighting were calculated, as previously described.¹⁵⁻¹⁷

RESULTS

A total of 215 patients with stage I or II NSCLC who underwent pulmonary resection were examined. Median follow-up was 19.5 months. Cohort A ($n = 81$) consisted of type II diabetic patients exposed to metformin, cohort B ($n = 57$) consisted of type II diabetic patients without metformin exposure, and cohort C ($n = 77$) consisted of nondiabetic individuals without metformin exposure. One patient in cohort B was placed on metformin 2 years after surgical resection. There were no differences in age, gender, BMI, race, comorbidities, preoperative ECOG score, pathologic stage, procedure, or adjuvant chemotherapy use observed between cohorts. Cohort A had a lower T stage than cohort C, and there was a trend toward fewer patients with N1 cancer in cohort A than cohorts B or C. In addition, cohort C had more current smokers and lower creatinine and serum glucose levels than cohorts A or B (Tables 1 and 2).

During the study period, 21 patients died, 47.6% (10/21) with evidence of recurrence and 52.4% (11/21) without recurrence (Figure 1, A). By examining patients with recurrence ($n = 46$), 54.3% (25/46) had local recurrence and 45.7% (21/46) had recurrence in distant locations (Figure 1, B). There were 37 of 106 diabetic patients (cohorts A and B) and 32 of 52 nondiabetic patients (cohort C) who were lost to follow-up (defined as alive without recurrence with >1 year between the date of last follow-up and data collection).

Among type II diabetic patients, PFS was greater for patients in group A (metformin exposure, median PFS not reached) than in group B (nonmetformin, median = 37.4 months), (HR, 0.406; 95% confidence interval [CI], 0.194-0.848;

TABLE 1. Patient demographics*

	Cohort A DM II metformin (n = 81)	Cohort B DM II nonmetformin (n = 57)	Cohort C Nonmetformin (n = 77)	P value
Age (y ± SD)	69.0 ± 8.9	70.4 ± 9.67	68.0 ± 10.2	.396
Gender (male)	42 (51.9)	32 (56.1)	38 (49.4)	.738
Smoking history				
Pack-years (±SD)	34.7 ± 32.2	35.9 ± 34.4	38.2 ± 33	.809
Current smoker	14 (17.3)	14 (24.6)	28 (36.4)	.023
Never smoker	15 (18.5)	11 (19.3)	11 (14.3)	.693
BMI (kg/m ² ± SD)	31.4 ± 7.2	29.4 ± 6.2	26.3 ± 4.5	.085
Preoperative FSG (mg/dL ± SD)	132.5 ± 48.9	142.34 ± 63.9	100 ± 18.5	<.001
Preoperative creatinine	1.0 ± 1.4	1.7 ± 1.4	1.0 ± 0.3	<.001
Preoperative ECOG score				.528
0	19 (23.5)	15 (26.3)	27 (35.1)	
1	42 (51.9)	31 (54.4)	37 (48.1)	
2	18 (22.2)	8 (14)	11 (14.3)	
3	2 (2.5)	3 (5.3)	2 (2.6)	
Race				.950
Caucasian, non-Hispanic	57 (70.4)	40 (70.2)	61 (79.2)	
African American/Black	15 (18.5)	12 (21.1)	11 (14.3)	
Hispanic	2 (2.5)	1 (1.7)	1 (1.3)	
Asian	3 (3.7)	1 (1.7)	2 (2.6)	
Other	4 (4.9)	3 (5.3)	1 (1.3)	
Diabetic medication				<.001
Insulin	10 (12.3)	23 (40.4)	0	
Nonmetformin/noninsulin	0	18 (31.6)	0	
Diet controlled	0	16 (28.1)	0	
Comorbidities				
HTN	61 (75.3)	44 (77.2)	49 (63.6)	.147
Hyperlipidemia	41 (50.6)	28 (49.1)	25 (32.9)	.054
Dialysis	0	1 (1.7)	0	.999
Prior malignancy of any type	32 (39.5)	16 (28.1)	26 (33.8)	.379
COPD	21 (25.9)	14 (24.6)	21 (27.3)	.939

Boldface indicates $P < .05$. DM, Diabetes mellitus; SD, standard deviation; BMI, body mass index; FSG, fasting serum glucose; ECOG, Eastern Cooperative Oncology Group; HTN, hypertension; COPD, chronic obstructive pulmonary disease. *All data presented as n (%) unless otherwise specified.

$P = .016$) (Figure 2, A). On multivariate analysis, after adjusting for age, gender, and T and N stage, metformin use in type II diabetic patients was significantly associated with PFS (HR, 0.410; 95% CI, 0.199-0.874; $P = .022$). In an inverse propensity-weighted analysis, with propensity score based on age, gender, histology, and T and N stage (group A, $n = 81$; group B, $n = 57$), the difference in PFS between the metformin and nonmetformin groups remained significant ($P = .043$; HR, 0.46; c-statistic = 0.658). With a propensity score based on age, gender, histology, T and N stage, serum creatinine, and fasting serum glucose (group A, $n = 71$; group B, $n = 49$), the difference in PFS between the metformin and nonmetformin groups trended toward significance ($P = .057$; HR, 0.44; c-statistic = 0.832; standardized differences in Table E1).

Similar results were observed when comparing PFS between group A (metformin exposure, median PFS not reached) and group C (nondiabetic, median 42.3 months) (HR, 0.446; 95% CI, 0.223-0.891; $P = .022$) (Figure 2, B). On multivariate analysis, after adjusting for age, gender, and T and N stage, metformin use in diabetic patients was

significantly associated with PFS compared with PFS in nondiabetic patients (HR, 0.415; 95% CI, 0.201-0.887; $P = .017$). In an inverse propensity-weighted analysis based on age, gender, histology, and T and N stage (group A, $n = 81$; group C, $n = 77$), the difference in PFS between groups A and C remained significant ($P = .007$; HR, 0.37; c-statistic = 0.744). With a propensity score based on age, gender, histology, T and N stage, BMI, ECOG score, and chronic obstructive pulmonary disease (group A, $n = 71$; group C, $n = 49$), the difference in PFS between the metformin and nondiabetic groups remained significant ($P = .02$; HR, 0.41; c-statistic = 0.843) (standardized differences in Table E2).

Among patients exposed to metformin (cohort A), most received 500 mg ($n = 43$) or 1000 mg daily ($n = 34$), whereas 1 patient received 750 mg and 3 patients received 850 mg daily. When divided into “low-dose” (500-750 mg/d) or “high-dose” (850-1000 mg/d) metformin exposure, the association between dose and PFS was not significant ($P = .703$) (Figure 3). OS did not differ

TABLE 2. Staging, treatment, and histologic characteristics*

	Cohort A DM II metformin (n = 81)	Cohort B DM II nonmetformin (n = 57)	Cohort C Non-DM (n = 77)	P value
Pathologic stage				.222
IA	52 (64.2)	30 (52.6)	41 (53.2)	
IB	17 (21.0)	12 (21.1)	25 (32.5)	
IIA	6 (7.4)	8 (14.0)	8 (10.4)	
IIB	6 (7.4)	7 (12.3)	3 (3.9)	
T-stage				.028
T1a	40 (49.4)	24 (42.1)	27 (35.1)	
T1b	14 (17.3)	10 (17.5)	16 (20.8)	
T2a	16 (19.7)	13 (22.8)	31 (40.3)	
T2b	6 (7.4)	4 (7.0)	3 (3.9)	
T3	5 (6.2)	6 (10.5)	0	
N-stage				.062
N0	78 (96.3)	50 (87.7)	66 (85.7)	
N1	3 (3.7)	7 (12.3)	11 (14.3)	
Procedure				.440
Lobectomy	48 (59.3)	43 (75.4)	50 (64.9)	
Wedge resection	24 (29.6)	10 (17.5)	21 (27.2)	
Segmentectomy	2 (2.5)	1 (1.7)	3 (3.9)	
Pneumectomy	5 (6.2)	1 (1.7)	3 (3.9)	
Bilobectomy	2 (2.5)	2 (3.5)	0	
Chemotherapy				
Adjuvant	6 (7.4)	8 (14.0)	5 (6.5)	.267
Platinum based	5 (6.2)	5 (8.8)	3 (4.9)	.503
Histology				.002
Adenocarcinoma	44 (54.3)	29 (50.9)	56 (72.7)	
Squamous cell carcinoma	20 (24.7)	23 (40.3)	16 (20.8)	
Neuroendocrine	12 (14.8)	5 (8.8)	0	
Carcinoma, NOS	5 (6.2)	0 (0.0)	5 (6.5)	

Boldface indicates $P < .05$. DM, Diabetes mellitus; NOS, not otherwise specified. *All data presented as n (%).

significantly between group A and group B (HR, 0.778; 95% CI, 0.225-2.691; $P = .69$) (Figure 4, A) or group A and group C (HR, 0.47; 95% CI, 0.163-1.362; $P = .16$) (Figure 4, B). The point estimates of the HR for OS suggest that there may be a signal here that is worth pursuing. A post hoc power calculation suggests that a sample size of 285 patients would be required in each group to have 80% power in detecting an HR of 0.47 for an OS with a $P = .05$.

DISCUSSION

Studies have reported a survival benefit in patients with metformin-treated type 2 diabetes and advanced-stage NSCLC.⁸⁻¹⁰ The current study suggests an association between metformin exposure and improved PFS in diabetic patients with early-stage lung cancer treated with pulmonary resection. Although an OS difference was not proven, our results suggest a potential signal that might be better demonstrated with a larger sample size than we had in our study. These data contribute to a growing body of literature supporting the antineoplastic effect of metformin.

Although controversial, emerging evidence supports the use of metformin as an adjuvant agent in cancer therapy.¹⁸

A recent meta-analysis associated the use of metformin in type 2 diabetic patients with a 31% reduction in lifetime cancer risk and a 35% reduction in the risk of cancer mortality.¹⁸ Observational studies have suggested that metformin use in diabetic patients plays a protective role in breast and colorectal cancer, reducing incidence and mortality.^{3,4,11,18-20} However, other reports have found no association between duration or dose of metformin use and cancer risk.^{21,22} A recent study failed to demonstrate a survival benefit from metformin use among type 2 diabetic patients with NSCLC treated with definitive chemoradiation.²³ However, the small sample size, short duration of follow-up, and increased BMI, age, and associated hypertension in the metformin group may have prevented the detection of any survival benefit.²³

Metformin primarily reduces circulating glucose levels in patients through AMPK activation mediated by liver kinase B1, a tumor suppressor protein that responds during metabolic stress.²⁴ Proposed anticarcinogenic effects of metformin occur through the liver kinase B1/AMPK pathway by inhibition of the mammalian target of rapamycin pathway, causing inhibition of protein synthesis, cell

FIGURE 1. Death with and without recurrence (A) and local versus distant recurrence (B). *DM*, Diabetes mellitus.

cycle arrest, and apoptosis.²⁵ Although a recent study has suggested that the activation of AMPK may fuel cell growth,²⁶ metformin also can inhibit the mammalian target of rapamycin pathway via the rag GTPase-dependent pathway, an AMPK-independent mechanism.²⁷ Because elevated insulin-like growth factor 1 (IGF-1) can be protumorigenic, studies have explored the utility of metformin in reducing IGF-1-mediated tumorigenesis, demonstrating that metformin inhibited tobacco carcinogen-induced lung tumorigenesis in nondiabetic mice via decreased IGF-I levels independent of AMPK pathways.²⁸ A significant decrease in tumorigenesis via rag GTPase-dependent pathway and modulating receptor-tyrosine kinase activity, independent of the IGF-1 level reduction, has been demonstrated in mice treated with metformin.²⁸ Furthermore,

clinically achievable metformin doses have been reported to enhance the response of NSCLC cells to ionizing radiation via the AMPK-dependent pathway.²⁹

Although promising evidence from population-based, in vitro, and animal models exist, few studies have assessed the direct influence of metformin on survival.^{8-10,30} Mazzone and colleagues³⁰ reported a reduced risk of developing lung cancer in diabetic patients receiving metformin; however, metformin therapy was associated with more aggressive histologic subtypes and metastatic disease. It has been suggested that lung cancers that develop in the presence of metformin may bypass key energy regulatory mechanisms, presenting with more aggressive phenotypes. Another retrospective study reported reduced lung cancer mortality in patients with type 2 diabetes treated with

FIGURE 2. A, PFS curves, metformin-exposed diabetic versus nonmetformin-exposed diabetic patients (HR, 0.406; 95% CI, 0.194-0.848; $P = .016$). B, PFS curves, metformin-exposed diabetic versus nondiabetic patients (HR, 0.446; 95% CI, 0.223-0.891; $P = .022$). *Solid lines* indicate PFS estimates, and *dashed lines* indicate confidence limits. *DM*, Diabetes mellitus.

FIGURE 3. PFS curves, low-dose (500-750 mg/d) versus high-dose (850-1000 mg/d) metformin exposure. *Solid lines* indicate PFS estimates, and *dashed lines* indicate confidence limits.

metformin monotherapy therapy versus nonmetformin therapy.⁸

Metformin use has been associated with improved PFS and OS compared with insulin use and other oral antidiabetic drugs in patients with advanced NSCLC.⁹ A large population-based study examined the effect of metformin in patients with stage IV NSCLC, showing a significantly longer survival in patients with type 2 diabetes receiving metformin compared with those without metformin treatment.¹⁰ A recent study also demonstrated improved median PFS and OS among patients with small cell lung cancer treated with metformin.³¹ The current study supports these findings, demonstrating an association between metformin exposure and PFS in those with early-stage lung cancer.

The similar OS with or without metformin exposure may be a reflection of the modest sample size in the current

study. However, improved PFS without a difference in OS has been reported with metformin use in ovarian and colorectal cancer.^{32,33} Longer duration of follow-up may be required to demonstrate an association between metformin exposure and OS in early-stage NSCLC.

Study Limitations

The current study has several limitations. The small sample size and relatively short follow-up duration have the potential to make clinically important differences appear statistically insignificant. Although no difference was reported in pathologic staging between groups, patients in cohort A had higher T- and N-stage tumors than patients in cohorts B and C, potentially introducing bias. However, multivariate and propensity-adjusted analyses demonstrated associations between metformin exposure and PFS. The large number of patients lost to follow-up likely represents the tertiary nature of our medical center; many patients prefer to follow-up with their local oncologist for cancer surveillance. Although this loss to follow-up is a potential confounder, it seems unlikely that those lost to follow-up would preferentially recur. Furthermore, it is plausible that insulin-dependent patients use more health care resources, potentially resulting in more frequent or earlier imaging than noninsulin-dependent patients, confounding the results. However, analysis of their ECOG scores do not reflect a difference in functional status between groups to support this theory. In addition, because of the retrospective nature of the study, the severity of diabetes and effect of chronic hyperglycemia could not be accurately assessed. Although hemoglobin A1C would have been the ideal surrogate for long-term diabetic control, these data were inconsistently documented in the medical record. Likewise, although metformin dosing is reported, the duration of use was not analyzed because of limited

FIGURE 4. A, OS curves, metformin-exposed diabetic patients versus non-metformin-exposed diabetic patients (HR, 0.778; 95% CI, 0.225-2.691; $P = .69$). B, OS curves, metformin-exposed diabetic versus nondiabetic individuals (HR, 0.47; 95% CI, 0.163-1.362; $P = .16$). *Solid lines* indicate OS estimates, and *dashed lines* indicate confidence limits. DM, Diabetes mellitus.

data availability, despite having the potential to affect the metformin-related tumor response. We acknowledge that our definition of PFS resulted in interval-censored data but was analyzed as usual time-to-event data, which is an additional potential limitation of the analysis. Finally, data on cancer-specific survival were not analyzed, which would give the best assessment of metformin–tumor interaction.

CONCLUSIONS

These data suggest that metformin exposure in diabetic patients who underwent pulmonary resection for early-stage NSCLC is associated with improved PFS. The difference in OS between groups was not statistically significant but was suggestive of a possible effect worthy of additional study. Conflicting evidence continues to emerge surrounding the antineoplastic effects of metformin. Further prospective studies assessing metformin as an adjuvant agent in lung cancer are needed to determine whether there is a role for metformin in the treatment of early-stage lung cancer.

Conflict of Interest Statement

Gary Chmielewski, Michael Liptay, and Christopher Seder report consulting fees from Covidien. All other authors have nothing to disclose with regard to commercial support.

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Key Words: lung cancer, diabetes, survival, Metformin, outcomes

TABLE E1. Unweighted and inverse probability-weighted standardized differences for patients with metformin exposure (cohort A) and without metformin exposure (cohort B)

	Unweighted SD	Inverse probability-weighted SD
Age	0.146763556	-0.177048851
Creatinine	0.739891213	0.303401416
FSG	0.173441594	0.047828304
Gender	0.086124972	0.053719813
N1	0.320324194	0.076358695
T1a	-0.146470441	0.002894285
T1b	0.006853657	-0.025393409
T2a	0.074667730	0.050060961
T2b	-0.015070858	-0.018886240
Adenocarcinoma	-0.069010183	0.050839344
Squamous cell	0.339050439	0.048520095
Path, other	-0.188186636	-0.038673132

SD, Standardized difference; FSG, fasting serum glucose.

TABLE E2. Unweighted and inverse probability-weighted standardized differences for patients with metformin exposure (cohort A) and nondiabetic patients (cohort C)

	Unweighted SD	Inverse probability-weighted SD
Age	-0.09625344	0.108979874
BMI	-0.84320241	-0.266300683
Gender	-0.05004333	-0.034413224
N1	0.37635496	0.108717658
COPD	0.03048377	0.130645450
T1a	-0.29297662	-0.068507259
T1b	0.08912843	0.094038237
T2a	0.45910250	0.096789232
T2b	-0.15249957	-0.068341815
ECOG 0	0.25724830	0.086352262
ECOG 1	-0.07605304	-0.054173536
ECOG 2	-0.20654810	-0.023982023
Adenocarcinoma	0.38956518	0.156832618
Squamous cell	-0.09344299	0.002765884
Path, other	-0.58976782	-0.410587724

SD, Standardized difference; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group.