Developments and Experiments in Health and Medicine

Year: 2026
Volume: 40
Issue: 2

RESEARCH ARTICLE

Pages:158-164

Impact of metformin on recurrence and progression in nonmuscle invasive bladder cancer

Kas invazyonu olmayan mesane kanserinde metforminin nüks ve progresyon üzerine etkisi

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Effect of Metformin on Bladder Cancer
Received: 07.05.2025
Accepted: 19.01.2026
DOI: 10.18614/dehm.1687924

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Year: 2026
Volume: 40
Issue: 2

RESEARCH ARTICLE

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ABSTRACT

BACKGROUND

This study investigated the effect of metformin use on recurrence and progression in patients with non-muscle-invasive bladder cancer (NMIBC).

METHODS

Patients who underwent primary transurethral resection of bladder tumors between 2016 and 2020 were retrospectively screened. Only patients diagnosed with NMIBC were included. These patients were divided into two groups according to metformin use, and recurrence and progression rates were compared between the groups.

RESULTS

A total of 176 NMIBC patients met the inclusion criteria, 37 of whom were metformin users. Demographic characteristics and follow-up durations were comparable between metformin users and non-users. Recurrence was observed in 8.1% of patients in the metformin group, whereas the recurrence rate was 32.4% among non-users ($p = 0.003$). No progression was observed in the metformin group. In contrast, the progression rate among non-users was 8.6% ($p = 0.064$).

CONCLUSION

Metformin use was associated with lower recurrence and progression rates in patients with NMIBC. Prospective randomized controlled trials are warranted to further clarify the potential protective role of metformin in bladder cancer.

KEYWORDS

Metformin, recurrence, urinary bladder neoplasms

ÖZ

AMAÇ

Bu çalışmada, kas invazyonu olmayan mesane kanseri (KİOMK) tanısı alan hastalarda metformin kullanımının nüks ve progresyon üzerine etkisinin araştırılması amaçlanmıştır.

GEREÇ YÖNTEM

2016–2020 yılları arasında primer transüretral mesane tümörü rezeksiyonu yapılan hastalar retrospektif olarak tarandı. Yalnızca NMIBC tanısı alan hastalar çalışmaya dahil edildi. Hastalar metformin kullanım durumuna göre iki gruba ayrıldı ve gruplar arasında nüks ve progresyon oranları karşılaştırıldı.

BULGULAR

Toplam 176 NMIBC hastası dahil edilmiştir ve bunların 37'si metformin kullanıcısıdır. Metformin kullanan ve kullanmayan gruplar arasında demografik özellikler ve takip süreleri açısından anlamlı fark saptanmamıştır. Metformin kullanan grupta hastaların %8.1'inde nüks izlenirken, bu oran metformin kullanmayan grupta %32.4 olarak bulunmuştur ($p = 0.003$). Metformin kullanan grupta progresyon gözlenmezken, metformin kullanmayan grupta progresyon oranı %8.6 olarak saptanmıştır ($p = 0.064$).

SONUÇ

Metformin kullanımı, KİOMK hastalarında daha düşük nüks ve progresyon oranları ile ilişkili bulunmuştur. Metforminin mesane kanserindeki potansiyel koruyucu rolünü daha net ortaya koymak için prospektif, randomize kontrollü çalışmalara ihtiyaç vardır.

ANAHTAR KELİMELER

Mesane tümörleri, metformin, nüks

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Bladder cancer is the tenth most common type of cancer when both sexes are evaluated (1). Nearly 75% of all newly diagnosed bladder cancer cases are non-muscle-invasive bladder cancer (NMIBC) (1). However, 50% of all NMIBC cases become muscle-invasive during follow-up, with metastasis occurring within short periods of time (1). Close follow-up, correct treatment, and accurate prediction of recurrence and progression are required to prevent disease recurrence and progression (1). Even with intravesical Bacillus Calmette–Guérin (BCG) immunotherapy and intravesical chemotherapeutic agents, progression is observed with a probability of 0.12%-20% in the first year of follow-up and 0.6%-40% in the fifth-year follow-up (2). On the other hand, recurrence is observed in 15%-60% of cases in the first year of follow-up and 31%-78% in the fifth year (2). Therefore, it is essential to investigate new treatment modalities to prevent progression and recurrence.

Diabetes mellitus is associated with an increased incidence of bladder cancer and poor prognosis in cancer patients (3). However, it has been found that the use of metformin in diabetic patients can reduce the incidence of some cancer types and may also be associated with good prognosis (4-8). Metformin may increase survival in prostate cancer, lung cancer, and breast cancer via different mechanisms (9,10). It inhibits the ubiquinone oxidoreductase enzyme and impairs adenosine triphosphate (ATP) synthesis, thus increasing the amount of adenosine monophosphate (AMP) in the cell (7,9,11). Increased AMP triggers the activation of the AMP kinase (AMPK) pathway, which subsequently causes inhibition of the mammalian target pathway of the rapamycin protein complex (mTOR), resulting in inhibition of the protein synthesis required for cell growth and proliferation (7,9,11). In addition, metformin inhibits the cyclooxygenase 2 (COX2) pathway and reduces prostaglandin E2 (PGE2) synthesis, thus inhibiting Janus kinase 2 (JAK2)/signal transducer and activator of transcription 3 (STAT3), allowing cells to be caught in the G1/S phase during proliferation (4). All of these pathways are involved in bladder cancer recurrence and progression. Therefore, in the present study, we hypothesize that metformin use may reduce recurrence and progression in patients with NMIBC.

Materials and Methods

Study population

Patients who underwent primary transurethral resection of a bladder tumor for a bladder mass between January 2016 and December 2020 were retrospectively screened. After pathological evaluation, 176 patients diagnosed with NMIBC were included in the study. Patients with a previous history of bladder cancer or a history of pelvic radiotherapy were excluded. Clinical and medical records were retrospectively reviewed. Patients were divided into two groups according to metformin use. Clinical demographic characteristics, laboratory findings, pathological features, and recurrence and progression status during follow-up were compared between the two groups.

Handling of missing data

Patients with missing data for any of the key variables, including metformin use, pathological findings, and follow-up outcomes, were excluded from the analysis. No data imputation methods were applied and all analyses were performed using complete-case data only.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics 24.0 (IBM Corp., Armonk, NY, USA). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to assess the normality of continuous variables. The chi-square test was used for comparisons of categorical variables and the Mann–Whitney U test was applied for continuous variables that were not normally distributed. Results were expressed as median (minimum-maximum), number, and percentage (%). Values of $p < 0.05$ were considered statistically significant.

Results

The median primary tumor size was 3.0 cm (range: 0.5-15.0 cm). Solitary tumors were detected in 98 patients (55.7%), while 78 patients (44.3%) had multiple tumors. Pathological staging revealed pTa disease in 111 patients (63.1%) and pT1 disease in 65 patients (36.9%). High-grade urothelial carcinoma was identified in 70 patients (39.8%), whereas 106 patients (60.2%) had low-grade tumors. Concomitant carcinoma in situ (CIS) was present in 16 patients (9.1%). Histological patterns were papillary in 162 cases (92.0%), solid in 8 cases (4.5%), micropapillary in 4 cases (2.3%),

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and squamous differentiation in 2 cases (1.1%). The median follow-up duration was 26.7 months (range: 2.3-59.1 months). During follow-up, 74 patients (42.0%) received intravesical BCG therapy, 5 patients (2.8%) received intravesical mitomycin C, and 2 patients (1.1%) received intravesical epirubicin. Overall, recurrence was observed in 48 cases (27.3%) and progression occurred in 12 cases (6.8%). The median time to recurrence was 15 weeks (range: 4-116 weeks), while the median time to progression was 26 weeks (range: min: 6-68 weeks). Fifty-four patients (30.7%) had a history of diabetes mellitus, and 37 of these patients were treated with metformin. There were no statistically significant differences according to metformin use regarding age, sex, presence of concomitant CIS, pathological stage, or tumor grade ($p > 0.05$ for all comparisons) (Table 1). Recurrence was experienced by 3 of 37 patients (8.1%) in the metformin group compared to 45 of 139 patients (32.4%) in the non-user group, indicating a significantly lower recurrence rate among metformin users ($p = 0.003$) (Table 1).

Table 1. Comparison of demographic characteristics, pathological results, recurrence, and progression status of patients between groups according to usage of metformin.

	Metformin non-users	Metformin users	p
Age, years			
Median (min-max)	69 (24-88)	66 (52-90)	0.820*
Sex			
Male	120 (86.3%)	32 (86.5%)	0.980**
Female	19 (13.7%)	5 (13.5%)	
Stage			
pTa	85 (61.2%)	26 (70.3%)	0.307**
pT1	54 (38.8%)	11 (29.7%)	
Grade			
Low	81 (58.3%)	25 (67.6%)	0.305**
High	58 (41.7%)	12 (32.4%)	
Concomitant carcinoma in situ			
Yes	14 (10.1%)	2 (5.4%)	0.380**
No	125 (89.9%)	35 (94.6%)	
Recurrence in total cohort (n = 176)			
Yes	45 (32.4%)	3 (8.1%)	0.003**
No	94 (67.6%)	34 (91.9%)	
Recurrence without intravesical treatment (n = 97)			
Yes	22 (28.2%)	2 (10.5%)	
No	56 (71.8%)	17 (89.5%)	0.091**
Recurrence with intravesical treatment (n = 79)			
Yes	28 (42.2%)	1 (7.6%)	
No	38 (57.8%)	12 (82.4%)	0.015**
Progression in total cohort (n = 176)			
Yes	12 (8.6%)	0 (0%)	0.064**
No	127 (91.4%)	37 (100%)	
Progression without intravesical treatment (n = 97)			
Yes	5 (6.8%)	0 (0%)	
No	68 (73.2%)	24 (100%)	0.233**
Progression with intravesical treatment (n = 79)			
Yes	7 (10.6%)	0 (0%)	
No	59 (89.4%)	13 (100%)	0.269**
Follow-up time, months			
Median (min-max)	26.8 (12.1-59.1)	23 (13.2-55)	0.964*

*: Mann–Whitney U test was used. **: Chi-square test was used.

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Patients were stratified according to the administration of intravesical therapy. Among those who did not undergo intravesical treatment, metformin users demonstrated numerically and proportionally lower recurrence rates; however, this difference did not reach the level of statistical significance (p = 0.091) (Table 1). In contrast, for patients receiving intravesical therapy, the recurrence rate was markedly reduced in patients treated with metformin (7.6%) compared to those who did not use metformin (42.2%), and this difference was statistically significant (p = 0.015) (Table 1).

Progression occurred in 0 of 37 patients (0%) in the metformin group and in 12 of 139 patients (8.6%) in the non-user group; however, this difference did not reach the level of statistical significance (p = 0.064) (Table 1). In subgroup analysis of progression, no progression was observed among patients using metformin regardless of their intravesical therapy status. Conversely, in patients not using metformin, progression was detected in 10.6% of those who underwent intravesical therapy and in 6.8% of those who did not. These differences did not reach statistical significance (p = 0.269 and p = 0.233, respectively) (Table 1). The time to recurrence was similar between the two groups (p = 0.481) (Table 1).

Discussion

In this study, we have demonstrated that metformin use was associated with a significantly lower recurrence rate in patients with NMIBC. A trend toward reduced progression was also observed, although it did not reach the level of statistical significance. These findings support the potential protective role of metformin in NMIBC, particularly in reducing tumor recurrence.

The risk of bladder cancer is 35% higher in patients with diabetes mellitus (1,12), but it has been found that the use of metformin in this patient group increases cancer-related and recurrence-free survival (6,7,10,13,14). In the review study conducted by El-Arabey, it was concluded that metformin can prevent the recurrence and progression of bladder cancer through seven different pathways including the disruption of cell proliferation by AMPK activation, suppression of IGF-1 by regulated plasma glucose levels, inhibition of the synthesis of antiapoptotic proteins such as BCL2 and MCL1, increased cytotoxicity of chemotherapeutic agents, oxidative stress and DNA damage, immunomodulatory effects, and autophagic mechanisms (7). It has been shown in both in vivo and in vitro studies that the use of metformin can inhibit the proliferation of cancer cells (4,9). Wu et al. reported that metformin exerts anticarcinogenic effects via AMPK activation and that inhibition of the STAT3 pathway can prevent the transformation of precancerous lesions into invasive cancer (9). Cyclin E is a poor prognostic marker in bladder cancer and plays a critical role in the G1/S phase of cell-cycle progression (15). Wu et al. found that metformin use led to a relative reduction in cyclin E expression in both in vivo and in vitro models (9). Although metformin has been shown to suppress cancer cell proliferation, its direct effect on apoptosis has not been clearly demonstrated (9).

Liu et al. reported that metformin induced COX-2/PGE2/STAT3 inhibition, resulting in cell-cycle arrest of proliferating cancer cells in the G1/S phase (4). Furthermore, they showed that metformin may prevent the progression of dysplastic lesions to invasive disease. Based on these findings, it was suggested that while metformin may not prevent the initial development of bladder cancer, it may play a role in reducing tumor recurrence and progression (4). In a study by Wang et al. including 122 NMIBC patients, disease-specific and overall survival rates were found to be higher in the group using metformin (11). In contrast to our findings, however, no significant differences were observed between the groups in terms of recurrence rates or pathological features, even in subgroup analyses. This discrepancy may be explained by differences in patient selection, as the study by Wang et al. (11) included only patients with a high risk of recurrence. Hu et al. reviewed nine studies evaluating the association between metformin use and bladder cancer and reported that metformin did not affect cancer incidence overall (10). However, their subgroup analyses revealed that metformin use in non-Asian populations and in patients with a primary diagnosis of NMIBC was associated with reduced recurrence rates, a finding consistent with our results.

Despite these promising findings, our study has several limitations. The most important limitation is the study's retrospective design, which may have introduced selection bias and limits the feasibility of causal interpretation. Furthermore, the exact duration and dosage of metformin use

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could not be determined, and the study population consisted predominantly of male patients, which may have limited the generalizability of the results.

Conclusion

This study has shown that the use of metformin reduces NMIBC recurrence. Metformin use was also associated with a lower progression rate, although this difference did not reach the level of statistical significance. These findings suggest that metformin may have a potential adjunctive role in the management of NMIBC. Prospective randomized studies are warranted to confirm the clinical benefit of metformin and clarify its role as an adjunct treatment in patients with NMIBC.

Acknowledgments
The authors thank all the patients and their families and caregivers for their participation in this study. This study was presented as an abstract at the 15th Urooncology Congress held by the Urooncology Association of Türkiye.

Statement of ethics
The protocol for this research project was approved by a suitably constituted ethics committee of the relevant institution and it conformed to the provisions of the Declaration of Helsinki (Dokuz Eylül University Committee for Interventional Research, Approval No. 2022/40-12). Informed consent was obtained from all patients.

Informed consent
Written informed consent was obtained from all patients before the study began. The study was conducted ethically following the principles of the World Medical Association's Declaration of Helsinki.

Data availability statement
All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

Authorship contribution
M.S. Özer: Project development, data collection, data analysis, manuscript writing, and editing. V. Şen (corresponding author): Data analysis, manuscript editing. S. Terzi: Data collection, data analysis. O. Bozkurt: Manuscript editing. Ö. Demir: Manuscript editing. G. Aslan: Manuscript editing. M.U. Mungan: Manuscript editing. İ. Çelebi: Manuscript editing. A.A. Esen: Manuscript editing.

Conflict of interest statement
The authors declare that there was no conflict of interest in this study.

Source of funding
No funding.

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