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Dimethyl Fumarate Improves Detrusor Contractility in Streptozotocin-Induced Diabetic Rats

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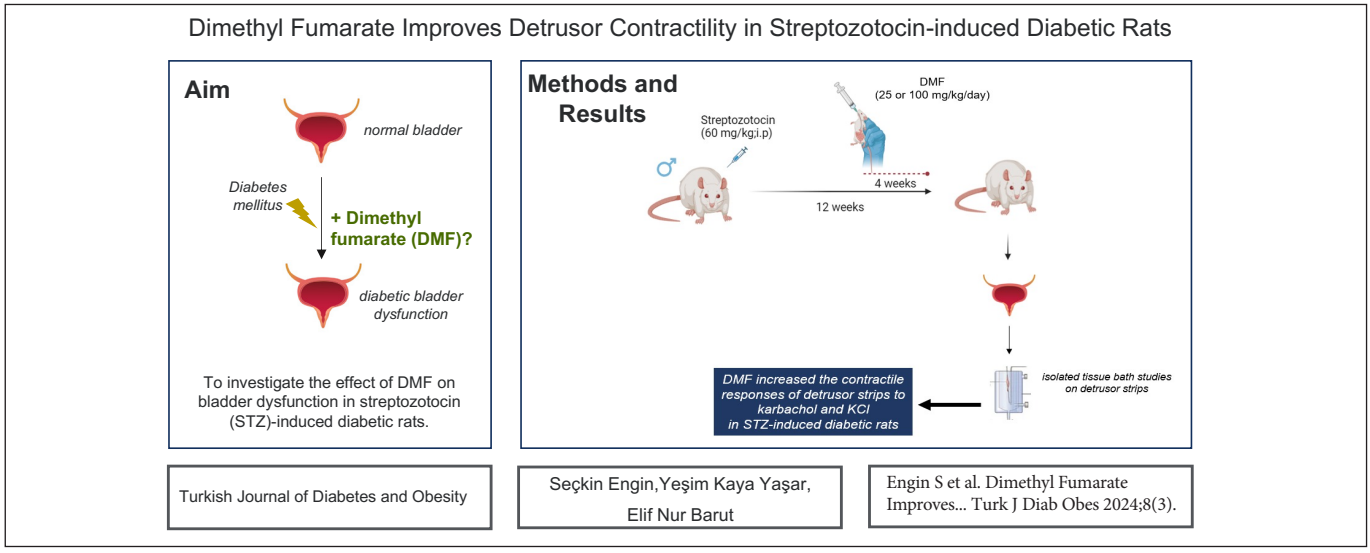
GRAPHICAL ABSTRACT



ABSTRACT

Aim: The present study aimed to investigate potential effect of dimethyl fumarate (DMF) on bladder dysfunction in streptozotocin (STZ)-induced diabetic rats.

Material and Methods: Adult male Sprague Dawley rats were given a single intraperitoneal dose of streptozotocin (60 mg/kg) to induce diabetes. After eight weeks, diabetic and nondiabetic rats were orally treated with DMF (25 or 100 mg/kg/day) or vehicle for four weeks orally. At 12 week after diabetes induction, in vitro organ bath studies were performed on detrusor strips of each rat and the contractile responses to KCl and carbachol (CCh) of the strips were evaluated.

Results: The maximal KCl (80 mM)- and CCh-induced contractile responses of detrusor strips significantly ($p<0.05$) reduced in diabetic group (84.35±13.56 and 178.80±29.66 mg tension/mg tissue, respectively) compared to the control group (175.10±13.42 and 399.40±77.63 mg tension/mg tissue, respectively). Moreover, DMF (100 mg/kg/day for 4 weeks) restored the impaired maximal contractile responses to KCl (158.20±25.82 mg tension/mg tissue) and CCh (342.50±42.86 mg tension/mg tissue) in diabetic rats, but DMF at 25 mg/kg had no effect.

Conclusion: The results of our preclinical study suggest that DMF has the potential to be repurposed as a promising therapeutic for the treatment of diabetes-associated bladder dysfunction.

Keywords: *Bladder, Carbachol, Contraction, Detrusor muscle, Diabetic complication, Dimethyl fumarate, Streptozotocin*

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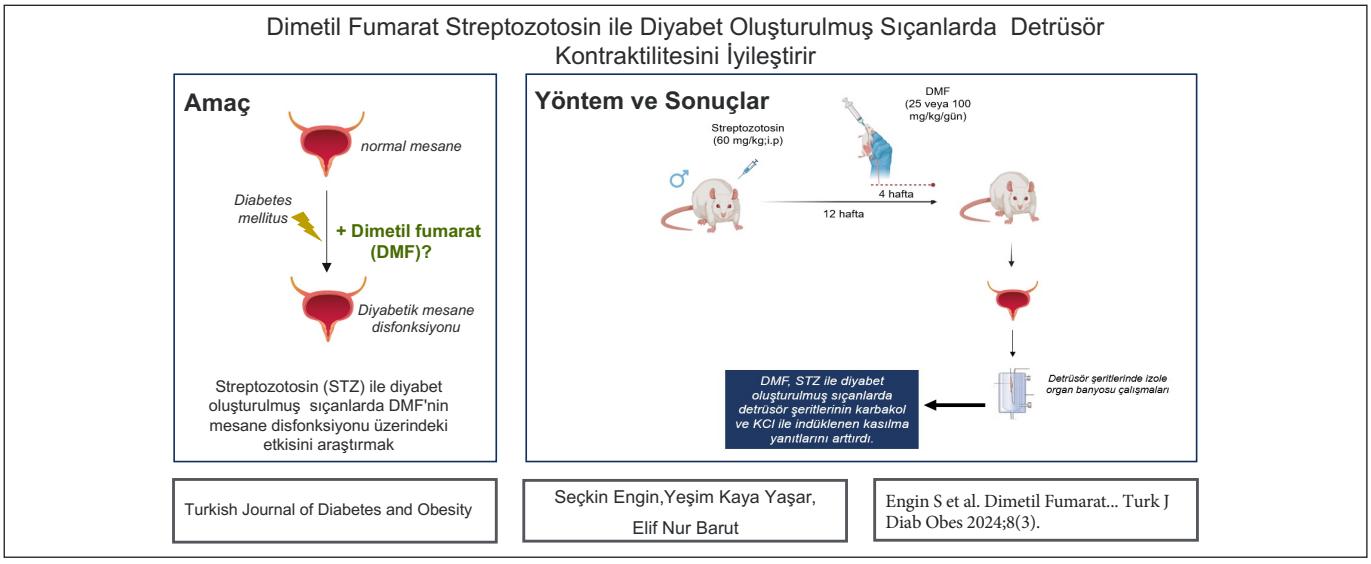
Dimetil Fumarat Streptozotosin ile Diyabet Oluşturulmuş Sıçanlarda Detrüsör Kontraktilitesini İyileştirir

GRAFİKSEL ÖZET



ÖZ

Amaç: Bu çalışmada streptozotosin ile diyabet oluşturulmuş sıçanlarda, dimetil fumaratın (DMF) mesane disfonksiyonu üzerindeki potansiyel etkisi araştırıldı.

Gereç ve Yöntemler: Yetişkin erkek Sprague Dawley sıçanlara diyabet indüksiyonu için tek doz intraperitoneal streptozotosin (60 mg/kg) verildi. Sekiz hafta sonra, diyabetik ve diyabetik olmayan sıçanlara dört hafta boyunca oral DMF (25 veya 100 mg/kg/gün) veya taşıyıcı tedavileri uygulandı. Diyabet indüksiyonundan 12 hafta sonra, her bir sıçanın detrüsör şeritleri üzerinde in vitro organ banyosu çalışmaları yapıldı ve şeritlerin KCl ve karbakol (CCh) ile indüklenen kasılma yanıtları değerlendirildi.

Bulgular: Detrüsör şeritlerinin KCl (80 mM) ve CCh ile indüklenen maksimum kasılma yanıtları, diyabetik grupta (sırasıyla 84,35±13,56 ve 178,80±29,66 mg gerim/mg doku) kontrol grubuna (sırasıyla 175,10±13,42 ve 399,40±77,63 mg gerim/mg doku) göre önemli ölçüde azaldı ($p<0,05$). Ayrıca, DMF (4 hafta boyunca, 100 mg/kg/gün) tedavisi, diyabetik sıçanlarda KCl (158,20±25,82 mg gerim/mg doku) ve CCh (342,50±42,86 mg gerim/mg doku) ile indüklenen bozulmuş maksimum kasılma yanıtlarını düzeltti; ancak 25 mg/kg dozda DMF tedavisi hiçbir etki göstermedi.

Sonuç: Preklinik çalışmamızın sonuçları, DMF'nin diyabetle ilişkili mesane fonksiyon bozukluğunun tedavisinde umut verici bir terapötik olarak yeniden konumlandırma potansiyeline sahip olduğunu göstermektedir.

Anahtar Sözcükler: *Detrüsör kası, Dimetil fumarat, Diyabetik komplikasyon, Karbakol, Kasılma, Mesane, Streptozotosin*

INTRODUCTION

Diabetic bladder dysfunction (DBD) is one of the leading complications of diabetes mellitus, characterized by symptoms of both overactive and underactive bladder, leading to impaired quality of life in diabetic patients (1,2). DBD is thought to have multifactorial pathogenesis including hyperglycemia-induced myogenic, urothelial and neuronal alterations, resulting in bothersome lower urinary tract symptoms such as urgency, urinary incontinence, urinary retention or dysuria (3,4). Current therapy for DBD is mainly based on good glycemic control and symptomatic treatments, which are not completely effective in eliminating the symptoms. Thus, disease-modifying therapeutic approaches targeting to pathological mechanisms of DBD have recently gained attention (5). Growing evidence indicates that increased oxidative stress plays an essential role in the development of DBD, occurring due to the imbalance of free radicals production and antioxidant regulation in hyperglycemic condition (4,6). To date, several antioxidants have been reported to be beneficial in DBD and the efficacy of various antioxidants is still under investigation (6).

Dimethyl fumarate (DMF) is a fumaric acid ester that has been used to treat psoriasis and relapsing forms of multiple sclerosis (7). Although DMF exerts pleitropic effects

via multiple mechanisms, the therapeutic effects of DMF is mainly based on its antioxidant effect via induction of the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway (8). Nrf2 is a crucial transcription factor that coordinates redox homeostasis by promoting the upregulation of antioxidant genes such as catalase, glutathione peroxidase, heme oxygenase-1 and superoxide dismutase, thus enabling to supress oxidative stress (9). Recent studies have demonstrated that disturbed Nrf2 pathway contributes to oxidative stress-associated cellular injury and, Nrf2 activation might be an emerging strategy for diabetic complications (10-13). Until now, DMF, a potent activator of Nrf2, has been reported to improve diabetes-associated wound, fatty liver, cardiomyopathy and vascular complications (15-17). Also, a recent research by Wang et al. reported that Nrf2 deletion contributes to bladder dysfunction in diabetic mice (18). Nevertheless, the effect of DMF on DBD is completely unknown. Thus, the present study aimed to determine whether DMF treatment could improve bladder function in streptozotocin (STZ)-induced diabetic rats.

MATERIALS and METHODS

Animals

A total of 34 age-matched male Sprague-Dawley rats (weighing 234-340 g) obtained from Surgical Application and Research Center of Karadeniz Technical University were used. All animals were housed in standard cages under controlled environmental conditions with a 12/12 h light/dark cycle and allowed to free access to standard diet and tap water. All experimental procedures were approved by Institutional Animal Care and Use Committee (approval number: 2021/55) and performed in accordance with the Guide for the Care and Use of Laboratory Animals and the ARRIVE guidelines 2.0.

Induction of Diabetes and Treatment Protocol

22 of rats were intraperitoneally injected with STZ (60 mg/kg) to induce type-1 diabetes, and the remaining 12 rats only received injections of citrate phosphate buffer to create nondiabetic groups. All STZ-injected rats were allowed overnight to drink 5% glucose solution in order to prevent sudden death due to severe hypoglycemia. Three days later (week 0), fasting blood glucose level of rats was measured with a handheld glucometer (Accu-Chek®, Germany) from a drop of tail-vein blood. Rats with fasting blood glucose level ≥ 250 mg/dL were deemed diabetic (19). Four of STZ-injected diabetic rats died before DMF or vehicle administration. Eight weeks after STZ injection (week 8), rats were randomly divided into five groups; control (nondiabetic rats receiving vehicle of DMF, n=6), DMF100 (nondiabetic rats receiving DMF at 100 mg/kg, n=6), Diabetic (diabetic rats receiving vehicle), Diabetic+DMF25 (diabetic rats receiving DMF at 25 mg/kg, n=6) and Diabetic+DMF100 (diabetic rats receiving DMF at 100 mg/kg, n=6). All rats were treated orally via gavage needle once daily for four weeks. 12 weeks after diabetes induction (week 12), bladder function was evaluated by isometric contraction measurements performed on the detrusor smooth muscle strips of rats. DMF was freshly dispersed in a vehicle containing 2.5% sodium carboxymethyl cellulose before administration. Body weight and fasting blood glucose level were measured and recorded weekly. The doses and experimental design were chosen based on previous studies (20,21).

Ex Vivo Contractility Studies

At the end of week 12, urinary bladder was quickly removed from each rat under anaesthesia with ketamine/xylazine (80/10 mg/kg). Then, one detrusor smooth muscle strip was prepared from each bladder described previously (22,23). Longitudinal detrusor strips were suspended between hooks on an isometric force transducer (MAY FDT-10A Force Displacement Transducer, Commat, Ankara, Türkiye) connected to an MP35 data acquisition system (Biopac Systems, Goleta, CA, USA) in 30 mL organ baths filled with Krebs-Henseleit buffer and aerated with 95% O2 and 5% CO2 at 37°C. Strips were allowed to equilibrate at a resting tension of 1 g for 60 min with replacement of bath solution every 20 min. Then, the strips were first contracted by KCl (80 mM). After relaxation to baseline, contractile responses to muscarinic agonist carbachol (CCh, 10^{-8}-10^{-4} M) were evaluated in the strips. Contractile responses were normalized to the wet weight of the respective urinary bladder strips (24).

Statistical Analysis

Data were presented as mean ± standard error of the mean (SEM) and statistically analyzed by unpaired t-test or ANOVA with Bonferroni multiple comparison when appropriate. For Statistical analysis and graph generation, GraphPad Prism 5.01 (GraphPad Software, USA) was used. $P<0.05$ was considered significant.

RESULTS

Effect of DMF Treatment on Metabolic Parameters of Rats

The body weights and fasting glucose levels of each group are presented in Figure 1A,B. Initial body weight of rats were similar among all of the groups ($p>0.05$), whereas the mean body weight of diabetic group (254.13±13.69 g and 249.70±9.10 g, respectively) were significantly ($p<0.001$) lower than that of control group (342.50±4.82 g and 364.30±11.46 g, respectively) at the end of 8th and 12th week after diabetes induction. Three days after STZ administration (week 0), fasting blood glucose level of diabetic group

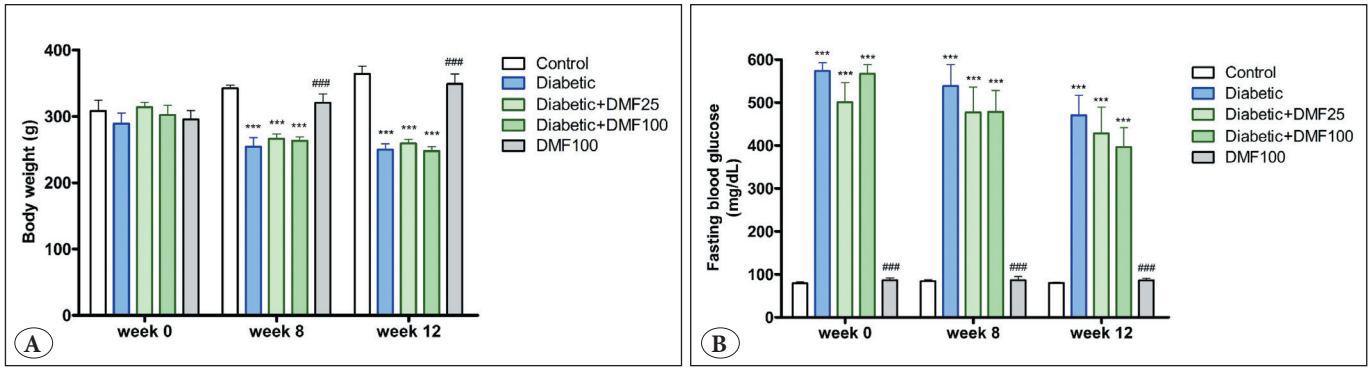


Figure 1: Time-course assessment of **(A)** body weight and **(B)** fasting blood glucose level in all groups. Data were expressed as mean±SEM (n=6/group). ***p<0.001 compared with control group, ###p<0.001 compared with diabetic group. DMF, dimethyl fumarate. SEM; standard error of the mean.

(573.30±19.78 mg/dL) significantly increased compared to that of control group (79.00±3.75 mg/dL, p<0.001). At weeks of 8 and 12, fasting blood glucose level still remained higher in diabetic group compared to control group (p<0.001). Both the marked increase in fasting blood glucose level and the decrease in the body weights of diabetic rats indicated the induction of diabetes model following STZ injection. Moreover, the 4-week DMF treatment (25 or 100 mg/kg) did not alter the body weight as well as fasting blood glucose level of diabetic rats (p>0.05).

Effect of DMF Treatment on KCl-Induced Contraction of Detrusor Strips in Diabetic Rats

A significant decrease (p<0.001) in the KCl-induced maximum contraction of detrusor strips was observed in the diabetic group (84.35±13.56 mg tension/ mg tissue) compared to the control group (175.10±13.42 mg tension/mg tissue). Moreover, decreased KCl-induced contractile responses of detrusor strips in diabetic group (84.35±13.56 mg tension/ mg tissue) were restored in DMF (100 mg/kg)-treated rats (p<0.05, 158.20±25.82 mg tension/mg tissue; Figure 2A,B).

Effect of DMF Treatment on CCh-Induced Contraction of Detrusor Strips in Diabetic Rats

CCh (10^{-8}-10^{-4} M) evoked concentration-dependent contraction in the detrusor strips of all groups (Figure 3A,B); however, the CCh-induced maximum contraction was significantly reduced in the diabetic group (178.80±29.66 mg tension/mg tissue) compared to control group (p<0.05, 399.40±77.63 mg tension/mg tissue; Figure 3B and 3C). Whereas treatment with DMF at 25 mg/kg did not induce any alterations, DMF-treated diabetic rats at 100 mg/kg showed a marked increase in the contractile response to CCh compared with the diabetic group (p<0.05, 342.50±42.86 and 178.80±29.66 mg tension/mg tissue, respectively; Figure 3B,C).

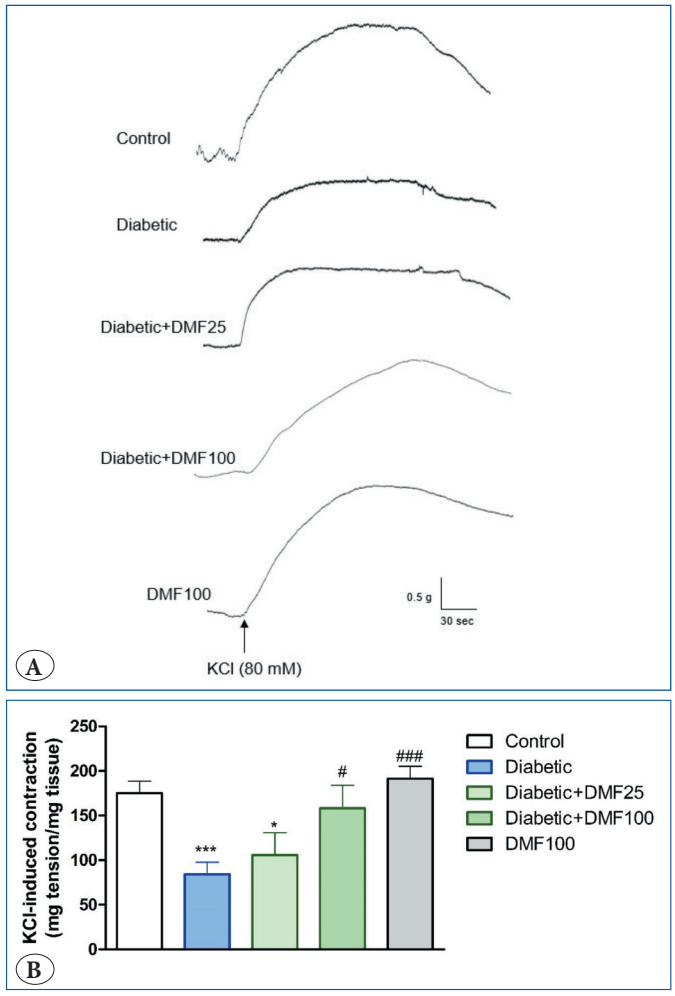


Figure 2: DMF (100 mg/kg) treatment restored the KCl (80 mM)-induced maximum contraction of detrusor strips in STZ-induced diabetic rats. **(A)** Representative original traces of KCl-induced contractions. **(B)** The maximal contractile response to KCl in the detrusor strips of all groups. Data were expressed as mean±SEM (n=6/group). *p<0.05, ***p<0.001 compared with control group. #p<0.05, ###p<0.001 compared with diabetic group.
DMF: *Dimethyl fumarate.* ***SEM:*** *Standard error of the mean.*

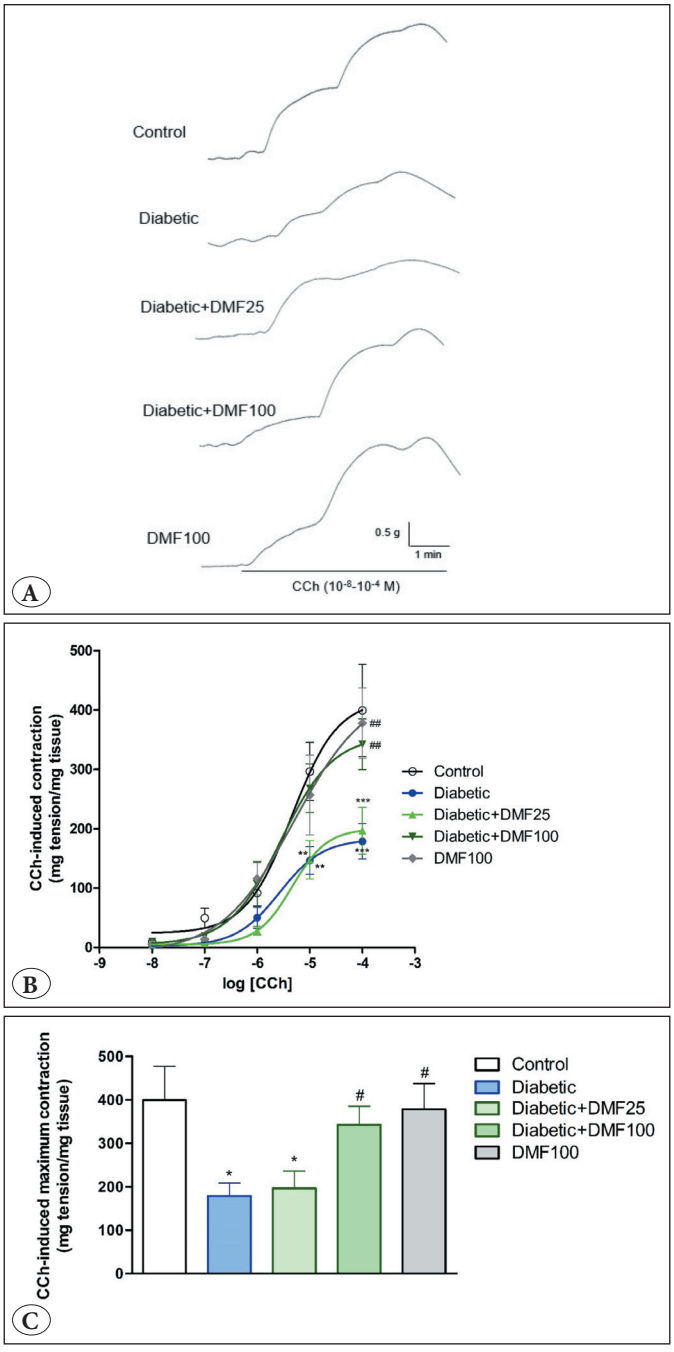


Figure 3: DMF (100 mg/kg) treatment restored the CCh (10-8-10-4 M)-induced contraction of detrusor strips in STZ-induced diabetic rats. **(A)** Representative original traces of CCh-induced contractions. **(B)** Cumulative concentration-response curves for CCh (10-8–10-4 M). **(C)** The maximal contractile response to CCh in the detrusor strips of all groups. Data were expressed as mean±SEM (n=6/group). *p<0.05, **p<0.01, ***p<0.001 compared with control group. #p<0.05, ##p<0.01 compared with diabetic group.

DMF: *Dimethyl fumarate,* ***SEM:*** *Standard error of the mean.*

DISCUSSION

Diabetes mellitus is now regarded as global epidemic affecting nearly 537 million individuals according to the International Diabetes Federation and it is widely accompanied by deleterious complications including DBD leading to bothersome lower urinary tract symptoms (2,25). Although DBD is one of the most common diabetic complications with an estimated prevalence up to 80%, it is usually underrecognized (1). It is typically not life threatening, however, DBD is associated with debilitating clinical symptoms such as overactive bladder, urinary urgency, frequency or incontinence, resulting in poor quality of life and high economic burden on the healthcare system (2,5). Although the physiopathology of DBD is yet to be fully understood, mounting evidence suggests the multifactorial impact of hyperglycemia on smooth muscle, neurons or urothelium of the bladder, leading to varied clinical presentations of DBD (3,4). It is well known that the bladder undergoes temporal changes resulting from initial compensatory phase and later decompensated phase under diabetic conditions in a time-dependent manner. The compensated state develops after the onset of diabetes, characterized by increased contractility and followed by a decompensated state occurs in the late stage of diabetes, along with impaired bladder sensation, detrusor underactivity and urinary retention (26,27). Current treatment of DBD consists of behavioral therapy, pharmacological agents or surgery, which is usually associated with limited efficacy and various complications. Pharmacological treatment of DBD is completely based on alleviating the symptoms of DBD, therefore, there is an unmet need for the development of novel therapeutics to delay disease progression (3,5).

Oxidative stress is crucial for the development of DBD as it contributes to cellular damage driving the disturbed neuronal, myogenic and urothelial function (28). Many studies have demonstrated that reactive oxygen species are markedly increased while the activities of antioxidant scavenging enzymes including catalase, superoxide dismutase, heme oxygenase-1 and glutathione peroxidase are hampered in the bladder tissues of diabetic rodents. Moreover, a number of antioxidants have been shown to be effective in restoring histological and functional disturbances in DBD (6,29). Therefore, hyperglycemia-induced oxidative stress is thought to be an important underlying cause of DBD and, consequently, inhibiting oxidative stress is considered a promising strategy for treating DBD. Nrf2 is a master transcription factor that regulates the cellular response to the redox state binding to the enhancer regions called antioxidant response element, promoting the up-regulation of antioxidant enzymes (9). Recent studies have shown the disrupted

Nrf2 signaling in diabetic conditions. Additionally, compounds that activate Nrf2 have shown beneficial effects in animal models of diabetic complications (10). Among Nrf2 activators, DMF is currently indicated for the treatment of psoriasis and relapsing forms of multiple sclerosis due to its antioxidant and antiinflammatory properties (7). DMF has been previously proven to be also effective in diabetes-associated complications via the activation of Nrf2 (14-17). Hu et al. showed that DMF (10 mg/kg/day for 12 weeks) improved cardiac dysfunction in diabetic mice by activating myocardial Nrf2 (14). Moreover, DMF (20, 40 and 80 mg/kg) has been reported to be effective in wound healing in STZ-induced diabetic mice via the stimulation of Nrf2 signaling (15). Amin et al. also showed that DMF (25 mg/kg/day for 8 weeks) restored the contractile response and the relaxation of aortic rings in STZ-induced diabetic rats through the downregulation of oxidative stress via Nrf2 activation (16). A recent study has shown that DMF (25 mg/kg/day for 12 weeks) significantly ameliorated fatty liver in type 2 diabetic rats by the upregulation of Nrf2 signaling (17). These studies demonstrate the dose-dependent therapeutic effect of DMF in different animal models of diabetic complications. However, the effect of DMF on DBD has not yet been clarified. Thus, we investigated the effect of DMF on bladder function in STZ-induced diabetic rats.

Our study revealed that diabetic rats exhibited a significant reduction in the KCl- and muscarinic agonist CCh-induced contractile responses of detrusor strips, indicating a decompensated state of DBD at 12 weeks of diabetes. Similar to our results, the decompensated phase of DBD has been reported to occur 9-12 weeks after the induction of diabetes in animal models (26,30). Moreover, we found that treatment with DMF (100 mg/kg/day for 4 weeks) restored the decreased contractile responses to KCl and CCh in the detrusor strips of diabetic rats without affecting hyperglycemia.

Herein, we provided the first evidence that DMF improved detrusor contractility in STZ-induced diabetic rats. Additional research is required to determine whether the antioxidant effect of DMF in the bladder tissues of diabetic rats contributes to its beneficial effects on DBD via Nrf2 activation. Our results suggest the repurposing potential of DMF as a pharmacological approach for the treatment of DBD.

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None.

Author Contributions
Conceptualization: **Seçkin Engin,** Methodology: **Seçkin Engin, Yeşim Kaya-Yaşar, Elif Nur Barut,** Formal analysis and investigation: **Seçkin Engin, Yeşim Kaya-Yaşar, Elif Nur Barut,** Writing - original draft preparation: **Seçkin Engin,** Writing - review and editing: **Seçkin Engin, Yeşim Kaya-Yaşar, Elif Nur Barut.**

Conflict of Interest
No conflicts of interest, financial or otherwise, are declared by the authors.

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Ethical Approval
All animal protocols were approved by the Institutional Animal Care and Use Committee of Karadeniz Technical University (approval number: 2021/55) .

Peer Review Process
Extremely and externally peer-reviewed.

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