評価で93％が改善を認め，ある程度の有効性が示されている[25]．また最近では，カプサイシンやレジニフェラトキシンといった神経毒を用いて求心線維を脱感作させることで，間質性膀胱炎の疼痛を緩和する治療の試みも報告されている[26,27]．

4　生活指導

間質性膀胱炎の症状は，食事や周囲の環境，ストレスなどの要因によっても左右される．症状のコントロールには，上に挙げた各種治療法はもちろんであるが，それと並んで症状を左右する要因をうまく調整することが重要である[28-30]．

間質性膀胱炎の病態のひとつに，膀胱粘膜の機能障害で尿が膀胱粘膜に浸透し，そのために慢性炎症が引き起こされていることが考えられる．したがって，障害された膀胱粘膜を浸透してくる尿が濃縮尿であったり，膀胱粘膜に発現しているTRP（transient receptor potential）チャンネルを刺激するような物質が尿中に多く含まれれば当然，症状の増悪を来す．

経過が長いほど，患者は濃縮尿が症状を悪化させたり，特定の食品が症状の悪化をもたらすことを自覚し，こまめに飲水を行ったり，刺激になる食品を回避することである程度の症状のコントロールを得ているが，自覚していない場合もあり，排尿日誌やこまめな問診を行うことで患者にフィードバックし，今後の生活で注意してもらうようにアドバイスしている．刺激となる食品は症例によって若干の差異はあるようであるが，よく聴取されるのは膀胱粘膜の透過性を亢進させるカリウムを多く含む食品（生野菜や果物）や唐辛子などの香辛料，オレンジなどのかんきつ類などTRPチャンネルのagonistを含む食品が多いようである[31]．他に，コーヒーなどカフェインを多く含む飲料，酢の物なども刺激物としてよく聴取される[32]．

他の症状を悪化させる環境因子としては，低温環境が最もよく聴取される．多くの場合，四肢の冷えで膀胱症状の悪化を自覚しており，患者は適宜冷えを防ぐために着重ねや懐炉を用いるなどしているが，中には飲料・生薬（生姜や香辛料を含むもの）で体を温めようとして，かえって症状の悪化を来している場合もあり，注意が必要である．

最後に，生活指導で欠かせないものとしては患者のストレスコントロールが挙げられる．間質性膀胱炎はストレスで症状が悪化することが報告されており[33]，ストレスの軽減を図ることが症状のコントロールのうえで重要であることが示唆されている[29]．

5　外科治療（膀胱部分切除術，膀胱全摘・尿路変更術）

種々の保存的治療で症状のコントロールがつかない症例は，特に明確な適応基準や定められた術式はないが，膀胱摘除術・尿路変更術もしくは膀胱部分切除術・回腸利用膀胱拡大術の適応となる．ただし，膀胱拡大術に関しては膀胱三角部を残すことから賛否が分かれており，術式の選択においては症状遺残の可能性などを含めて勘案し，慎重に検討を進める必要がある．なお，アメリカでは膀胱摘除術・回腸導管造設術が最も選択されている術式となっている[34]．治療効果は，Rossbergerらによると潰瘍を有する間質性膀胱炎患者では82％で症状の寛解が得られたのに対して，潰瘍を有さない間質性膀胱炎ではわずか23％であった[35]．他にもPeekerらも同様の報告をしており[36]，治療効果は潰瘍の有無によって規定されており，この点においても間質性膀胱炎は潰瘍の有無で病態が異なる可能性が示唆されている．

Ⅲ　間質性膀胱炎の治療の問題点と課題

このように，現在間質性膀胱炎に行われている治療は対症療法がほとんどであり，わが国ではガイドラインに基づいて診断を兼ねた膀胱水圧拡張術を中心に，内服治療や膀胱内注入治療を組み合わせて行うことで症状のコントロールを図っているのが現状である．

これですべての症例で完全に症状がコントロールできているわけではない．1回の膀胱水圧拡張術であたかも完治したかのように症状が改善するケースもあれば，さまざまな治療を行っても症状のコントロールがつかず，最終的に膀胱全摘・尿路変更に至るケースもある．さらにいえば，現在間質性膀胱炎の症状と相関することが示されている客観的な指標（尿中マーカーなど）が存在しないため，治療効果自体の評価が患者の主観によって左右されている現状がある．これらを勘案すると個々の症例にとって，どの治療についても受けるに当たって効果があるのかないのか予測できないことがほとんどで，それが間質性膀胱炎の治療における限界といえる．

「間質性膀胱炎」の疾患名で，あたかも単一の病因病態を有する疾患と錯覚しがちだが，潰瘍の有無をはじめ，さまざまな病因病態の帰結として間質性膀胱炎となっているのが間質性膀胱炎患者を多く診てきたものなら抱く実感である．治療に対する反応性の違いもすなわち，実は異なる病態の証左なのかもしれない．

将来的には，病因病態に応じて病型が分類され，それぞれの病型にカスタマイズされた治療法でエビデンスが確立され，より多くの間質性膀胱炎患者にスムーズな治療効果をもたらすことが期待される．

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Characteristics of Lower Urinary Tract Dysfunction and Bladder Afferent Nerve Properties in Type 2 Diabetic Goto-Kakizaki Rats

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Abbreviations and Acronyms

CCh = carbachol

CMG = cystometry

CV = conduction velocity

DM = diabetes mellitus

DSM = detrusor smooth muscle

EFS = electrical field stimulation

FV = frequency-volume

GK = Goto-Kakizaki

STZ = streptozotocin

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Purpose: We investigated longitudinal changes in lower urinary tract function, especially sensory function, in the type 2 diabetes mellitus model of Goto-Kakizaki rats.

Materials and Methods: We used 16 Wistar and 16 Goto-Kakizaki rats. Body weight, blood glucose, 24-hour voiding frequency-volume data and cardiovascular system data were measured every 3 weeks starting at age 5 weeks until age 14 weeks and then every 6 weeks until age 44 weeks. At ages 10 and 46 weeks conscious cystometry was done, pelvic afferent nerve fiber conduction velocity was measured using urethane anesthesia and isolated detrusor smooth muscle function was determined.

Results: Goto-Kakizaki rats showed lower body weight, higher blood glucose and mean voided volume, and less voiding frequency than Wistar rats throughout the observation period. In 46-week-old Goto-Kakizaki rats lower peak micturition pressure, larger bladder capacity and higher bladder compliance were noted on cystometry, while slower conduction velocity and a lesser proportion of Aδ fibers were observed on conduction velocity measurement. Goto-Kakizaki rats showed a lower contractile response to carbachol but not to electrical field stimulation or high K^+ in isolated detrusor smooth muscle. These differences between the 2 groups of rats at age 46 weeks were not noted at age 10 weeks. Cardiovascular system results did not differ between the 2 groups.

Conclusions: The results of this longitudinal study in Goto-Kakizaki rats indicate that type 2 diabetes induces bladder sensory dysfunction, manifesting as slower bladder afferent conduction velocity, larger bladder capacity and greater hypocontractility to acetylcholine.

Key Words: urinary bladder; diabetes mellitus; neurons, afferent; diabetic neuropathies; rats

Diabetic uropathy is found in more than 80% of individuals with diabetes, more often than widely recognized complications such as neuropathy and nephropathy, which affect fewer than 60% and 50% of patients, respectively.[1,2] However, little is known about the natural history of these common, troublesome complications. Animal models have the potential to reveal mechanisms and aid in the development of treatment strategies for diabetic uropathy.[3]

The STZ induced DM rat model is the most commonly used experimental model for type 1 DM. STZ induced DM results in bladder hypertrophy[4–6] and decreased CV.[7] However, the exact mechanisms involved in the pathophysiology of lower urinary tract dysfunction related to changes in bladder afferent fi-

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bers have not been clarified in patients with type 2 DM. The GK rat is a widely accepted, genetically determined rodent model for human type 2 DM.[8–10] This rat is characterized by nonobesity, early and mild insulin resistance, later abnormalities in insulin secretion and modest hyperglycemia.[11]

Previous studies in GK rat bladders revealed that contractile responses to CCh, adenosine-5′-triphosphate and EFS changed significantly under age dependent conditions.[12,13] Another study was done of functional, structural and molecular changes in the peripheral (sciatic) nerve and dorsal root ganglion in GK rats.[11] However, to our knowledge no investigation has focused on bladder afferent nerve function in this type 2 DM rat model. Therefore, we investigated longitudinal changes in lower urinary tract function, especially sensory function, using GK rats as the type 2 DM model.

METHODS

Experimental Animals and Design

We used adult male rats, including 16 Wistar rats as controls and 16 GK rats. The rats were maintained under standard laboratory conditions with a 12:12-hour light-dark cycle, and free access to food pellets and tap water. The protocol was approved by the University of Tokyo Graduate School of Medicine animal ethics committees.

Eight rats per group (CLEA Japan, Tokyo, Japan) were obtained at 4 weeks old. Every 3 weeks until age 14 weeks and every 6 weeks from ages 14 to 44 weeks body weight and 24-hour FV data were measured. In addition, at around 1:00 p.m. the rat was placed in a warm (38C) restraint cage, and heart rate and blood pressure were measured while conscious by tail cuff plethysmography using a BP-98A-L device (Softron, Tokyo, Japan). Subsequently, the blood glucose level was determined in blood obtained from the tail vein using the Glu-Test Every dis-

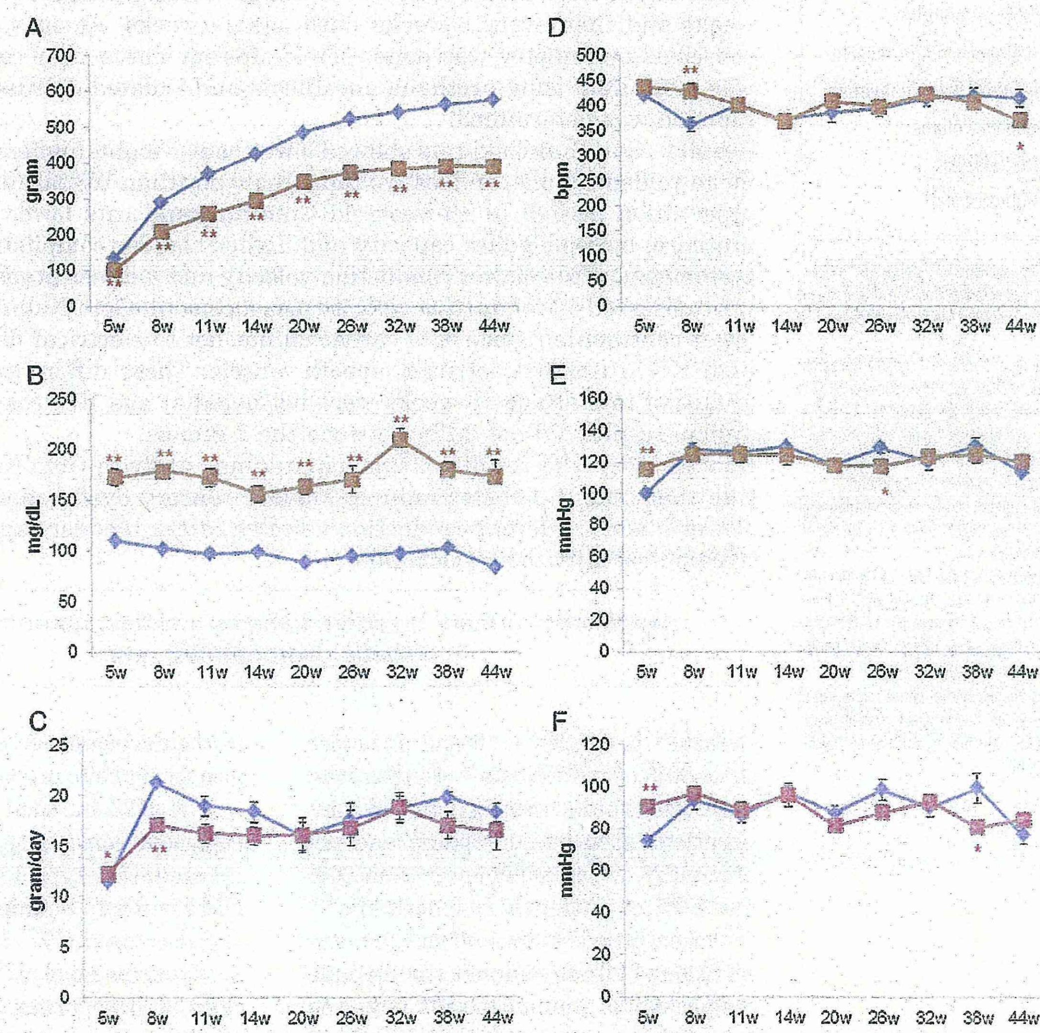


Figure 1. Changes in body weight (*A*), blood glucose (*B*), *24-hour food intake* (*C*), heart rate (*D*), and systolic (*E*) and diastolic (*F*) blood pressure during development from ages 5 to 44 weeks (*w*). Blue curves indicates 8 Wistar rats. Red curves indicates 8 GK rats. Single asterisk indicates significantly different vs Wistar rats (unpaired Student t test $p < 0.05$). Double asterisks indicate significantly different vs Wistar rats (unpaired Student t test $p < 0.01$). *bpm*, beats per minute.

posable glucose test sensor (Sanwa Kagaku Kenkyusho, Tokyo, Japan). At age 46 weeks CMG was done and CV was measured.

After the rats were sacrificed by an overdose of anesthesia, the bladder was isolated and bladder weight was measured. Isolated DSM contractile function was evaluated.

Another 8 rats per group were obtained at age 8 weeks. At age 10 weeks all mentioned experiments were performed in these animals.

Measurement

Frequency-volume. The rat was placed without any restraint in an MCM/TOA-UF001-006 metabolic cage (Mitsubishi Chemical Medience, Tokyo, Japan) for 24 hours to adapt to the environment. Due to a specially designed net, this metabolic cage can pass urine separately from feces, enabling precise measurement of voided urine volume. After 24-hour adaptation voided volume, voiding frequency and water intake volume were recorded using a PowerLab® data acquisition system continuously for 24 hours starting at 9:00 a.m. The rat had free access to water and food during recording.

Cystometry. The rat was anesthetized with 30 mg/kg pentobarbital sodium intraperitoneally. A PE-50 catheter (Clay-Adams, Parsippany, New Jersey) was inserted in the bladder through the dome and secured. Continuous CMG was performed in conscious rats 4 days after surgery. Each rat was placed in an MCM/TOA-UF001-006 metabolic cage for at least 2 hours to adapt to the environment. The bladder catheter was connected to a DX-100 pressure transducer (Nihon Kohden, Tokyo, Japan) and a KDS100 microinjection syringe pump (Muromachi, Tokyo, Japan) via a 3-way tap. Room temperature saline was continuously instilled in the bladder at 0.08 ml per minute. Intravesical pressure and voided volume were recorded continuously using PowerLab. All cystometric parameters were averaged for 60 minutes after pressure curves stabilized.

Conduction velocity. After CMG, the rat was anesthetized with urethane (1.2 gm/kg intraperitoneally). The left pelvic nerve was dissected from surrounding tissue proximal to the major pelvic ganglion and placed on a pair of silver electrodes. Fine filaments were dissected from the left L6 and S1 dorsal roots, and placed across shielded bipolar silver electrodes after laminectomy. Clearly different unitary action potentials of afferent fiber originating from the bladder after pelvic nerve electrical stimulation were recorded. They were identified by the Spike2 impulse shape recognition program (Cambridge Electronic Design,

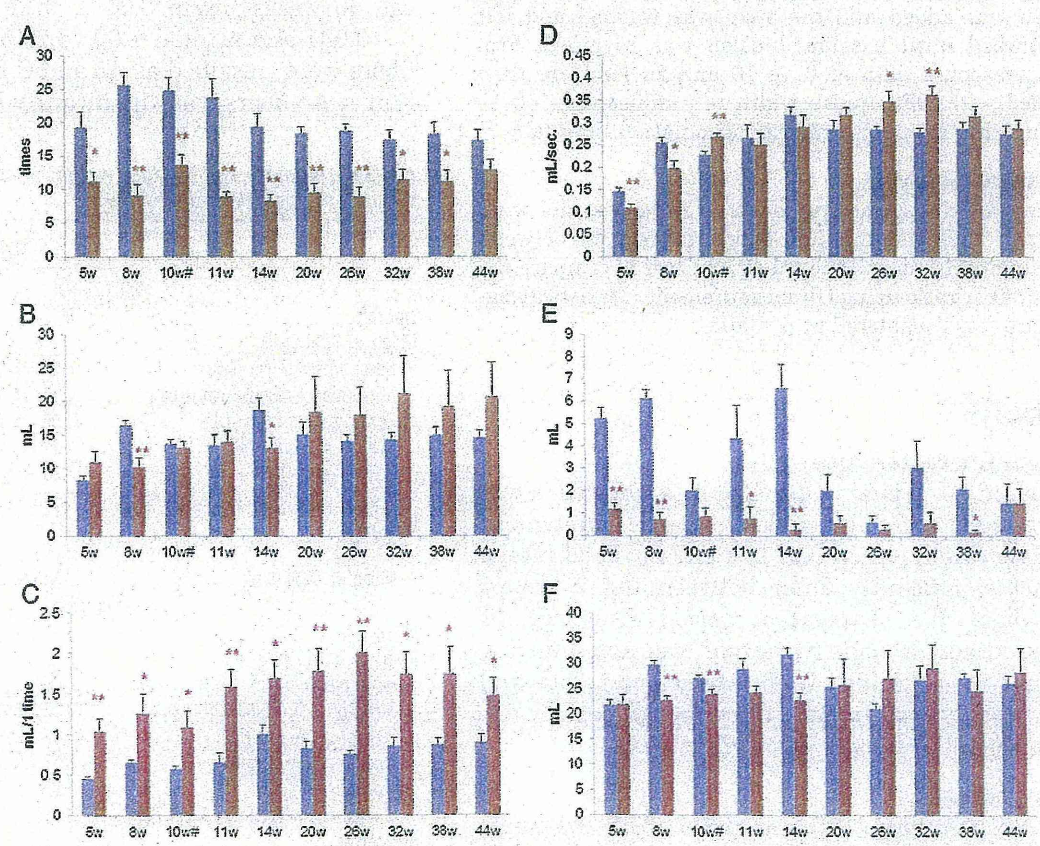


Figure 2. Changes in 24-hour voiding frequency (*A*), 24-hour total voided volume (*B*), 24-hour mean voided volume (*C*), 24-hour mean urinary flow rate (*D*), water intake volume during 9:00 a.m. to 9:00 p.m. light cycle (*E*) and 24-hour water intake (*F*) during development from ages 5 to 44 weeks (*w*). Blue bars indicate 8 Wistar rats. Red bars indicate 8 GK rats. Pound sign indicates additional 8 Wistar and 7 GK rats. Single asterisk indicates significantly different vs Wistar rats (unpaired Student t test p <0.05). Double asterisks indicate significantly different vs Wistar rats (unpaired Student t test p <0.01).

Cambridge, United Kingdom). CV was calculated from the response latency to electrical stimulation and the conduction distance between the stimulation and recording sites. Fibers with a CV of more than 2.5 m per second were designated Aδ fibers and those with a CV of less than 2.5 m per second were designated C fibers.[14]

Isolated DSM contractile function. The rat was sacrificed and the bladder was removed. After measuring bladder weight, bladder strips was separated equally (approximately 1 × 1 × 5 mm) from the bladder body longitudinally. Isolated DSM strips were transferred to 5 ml organ baths containing Krebs solution, composed of 118 mM NaCl, 4.7 mM KCl, 2.5 mM $CaCl_2$, 12.5 mM $NaHCO_3$, 1.2 mM KH_2PO_4, 1.2 mM $MgSO_4$, and 5.55 mM glucose. This was maintained at 37C, and bubbled with a mixture of 95% oxygen and 5% CO_2 to achieve pH 7.4. The strip was attached at one end to a tissue holder and at the other end to a Type 7923 force displacement transducer (NEC San-Ei Instruments, Tokyo, Japan). Data were recorded and analyzed by PowerLab. The strip was stretched until 1 gm stable tension was achieved. After the 2-hour equilibration period, the experiment was started by exposing the strips to high K^+ (62 mM) Krebs solution. The K^+ Krebs solution was washed out and contraction was evoked using the muscarinic agonist CCh (10^{-8} to 10^{-3} M) (Wako Chemical, Tokyo, Japan). The final concentration of CCh was added and the strip was washed and left undisturbed until baseline tension was regained. Frequency-response data at 2, 5, 10 and 20 Hz were then recorded with EFS (pulse width 0.8 millisecond, 50 V, 5-second duration and 1-minute stimulation interval).

Statistical Analysis

All data are shown as the mean ± SEM. Results were analyzed using the unpaired Student t test for between group comparisons and the chi-square test to compare the Aδ-to-C fiber ratio using CV measurement. Statistical significance was considered at $p < 0.05$.

RESULTS

General Characteristics

Compared to Wistar rats, GK rats showed lower body weight and higher blood glucose throughout the observation period (fig. 1, *A* and *B*). Food intake did not significantly differ between the 2 groups throughout the observation period after age 11 weeks, although slight variation was noted during the first 8 weeks (fig. 1, *C*). Mean heart rate and blood pressure parameters did not significantly differ between the groups (fig. 1, *D* to *F*).

Measurement

Frequency-volume. Upon analysis of FV measurement during the total of 24 hours, voiding frequency was significantly lower in GK than in Wistar rats. In contrast, mean voided volume was significantly greater in GK rats throughout the whole observation period. Total voided volume, mean urinary flow rate and water intake volume during the total of 24 hours did not significantly differ between the groups, although in each these values tended to increase with age (fig. 2). Similar tendencies were observed when the corresponding values were divided by light and dark cycles, except water intake volume during the light cycle, which was significantly less in GK rats (fig. 2, *E* and data not shown).

Cystometry. No cystometric parameter analyzed showed a significant difference between the 2 groups at age 10 weeks. At age 46 weeks peak pressure in GK rats was significantly lower than in Wistar rats, while GK rats had significantly larger bladder capacity and voided volume, and greater bladder compliance than Wistar rats (see table). Post-void residual volume was minimal in each group at ages 10 and 46 weeks.

Conduction velocity. A total of 3,877 single unit afferent fibers were isolated in a total of 28 rats, including 3,028 units from the L6 and 849 from the S1 dorsal root. CV did not differ between GK and Wistar rats at age 10 weeks (mean 4.48 ± 0.16 vs 4.47 ± 0.20 and median 2.20 vs 2.10). However, it was significantly slower in GK than in Wistar rats at age 46 weeks (mean 3.64 ± 0.17 vs 7.13 ± 0.37, $p < 0.001$ and median 1.62 vs 2.15, fig. 3, *A*). When fibers were classified as Aδ and C fibers, the proportion of Aδ fibers was significantly lower in GK than

CMG parameters and bladder weight in conscious Wistar and GK rats at ages 10 and 46 weeks

	Wistar	GK
Age 10 wks		
No. rats	8	7
Mean ± SEM CMG:*		
Basal pressure (cm H_2O)	5.84 ± 0.61	5.10 ± 0.57
Micturition threshold (cm H_2O)	12.58 ± 0.77	10.72 ± 0.60
Peak pressure (cm H_2O)	47.06 ± 2.93	41.57 ± 3.56
Bladder capacity (ml)	1.27 ± 0.10	1.15 ± 0.07
Voided vol (ml)	1.29 ± 0.07	1.28 ± 0.08
Bladder compliance (ml/Δ cm H_2O)	0.108 ± 0.008	0.115 ± 0.010
Bladder wt:		
No. rats	8	8
Mean ± SEM (gm)	0.146 ± 0.005	0.192 ± 0.026
Age 46 wks		
No. rats	7	8
Mean ± SEM CMG:*		
Basal pressure (cm H_2O)	6.00 ± 0.47	5.39 ± 0.43
Micturition threshold (cm H_2O)	13.13 ± 0.44	11.14 ± 0.56†
Peak pressure (cm H_2O)	47.62 ± 2.50	36.66 ± 1.83‡
Bladder capacity (ml)	1.67 ± 0.11	2.47 ± 0.17‡
Voided vol (ml)	1.77 ± 0.12	2.63 ± 0.27†
Bladder compliance (ml/Δ cm H_2O)	0.131 ± 0.011	0.226 ± 0.015‡
Bladder wt:		
No. rats	8	8
Mean ± SEM (gm)	0.245 ± 0.017	0.220 ± 0.015

* Bladder capacity = intercontraction interval × saline instillation rate and bladder compliance = bladder capacity/(micturition threshold − basal pressure).
† Significantly different vs Wistar (unpaired Student t test $p < 0.05$).
‡ Significantly different vs Wistar (unpaired Student t test $p < 0.01$).

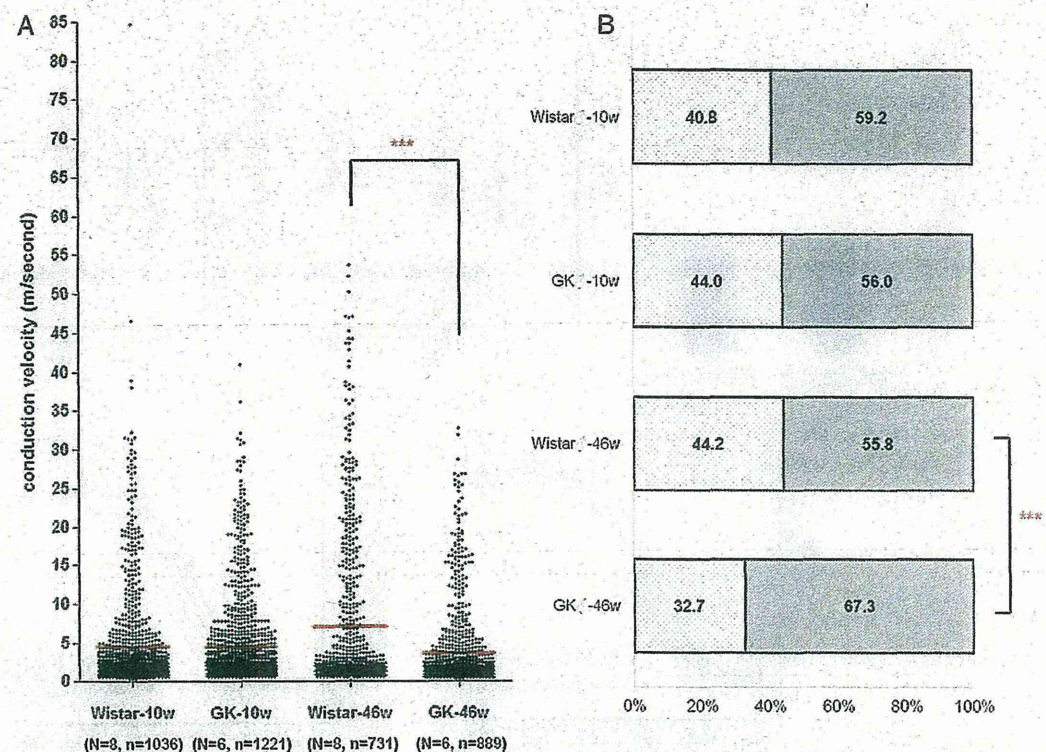


Figure 3. CV results (*A*), and ratio of Aδ (light gray bars) and C (dark gray bars) fibers (*B*) in each group. *w*, weeks. Asterisks indicate significantly different vs age matched Wistar rats (unpaired Student t test p <0.001).

in Wistar rats at age 46 weeks (32.7% vs 44.2%, p <0.001) but not at 10 weeks (44.0% vs 40.8%, fig. 3, *B*).

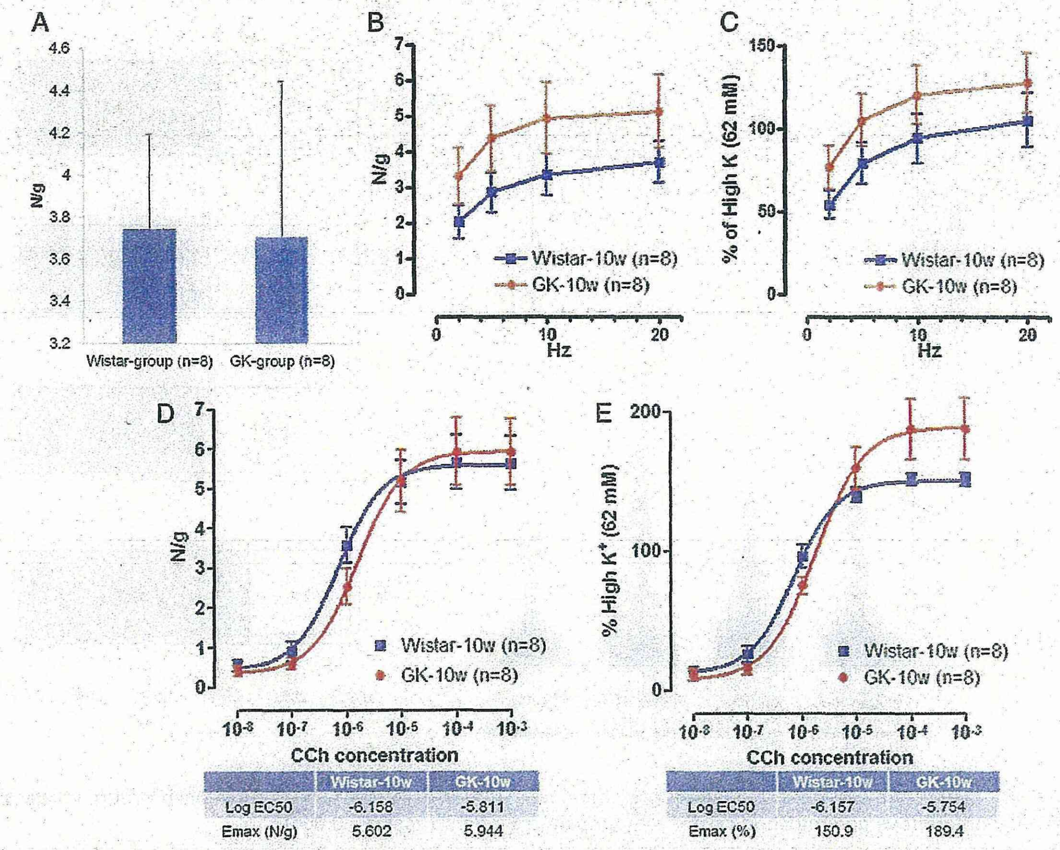
Isolated DSM contractile function and bladder weight. The contractile response to high K^+ or EFS did not significantly differ between the 2 groups at age 10 or 46 weeks. The response to CCh in GK rat bladders was significantly weaker than in Wistar rat bladders at age 46 weeks but not at age 10 weeks (figs. 4 and 5). No significant difference in bladder weight was found between Wistar and GK rats at ages 10 and 46 weeks (see table).

DISCUSSION

GK rats had higher blood glucose and smaller body weight than age matched Wistar control rats throughout the observation period, although food intake did not differ significantly between the groups after age 11 weeks. These findings are consistent with previous observations.[11–13] The groups did not significantly differ in cardiovascular function. Previous studies revealed mild cardiomyopathy in GK rats,[15–17] which is generally in line with our data.

We investigated lower urinary tract function in GK rats. For FV measurements the most remarkable differences between the groups were larger voided volume per micturition and less voiding frequency in GK rats. Voiding frequency in the Wistar group was more than that reported previously.[12,18] This contradictory result may have occurred due to the different experimental setup. We used a metabolic cage with a special net that allows urine to pass separately from feces, thus, enabling more precise measurement of voided urine volume. On the other hand, neither total voided volume nor water intake volume significantly differed. These results suggest that bladder sensation in response to bladder distention may be impaired in GK rats.

To clarify this speculation, further experiments were performed using CMG and CV measurements. Although we found no significant differences in any CMG parameters analyzed between the groups at age 10 weeks, at age 46 weeks GK rats had larger bladder capacity and voided volume, and greater bladder compliance than age matched controls. In accordance with these CMG findings, GK rats showed significantly slower CV of pelvic afferent nerve fibers at age 46 weeks but not at age 10 weeks. There were large variations in CV data but such variations were also observed in our previous reports.[19–23] These CMG and CV measurements in GK rats further indicate the progression of sensory dysfunction associated with type 2 DM.



	Wistar-10w	GK-10w
Log EC50	-6.158	-5.811
Emax (N/g)	5.602	5.944

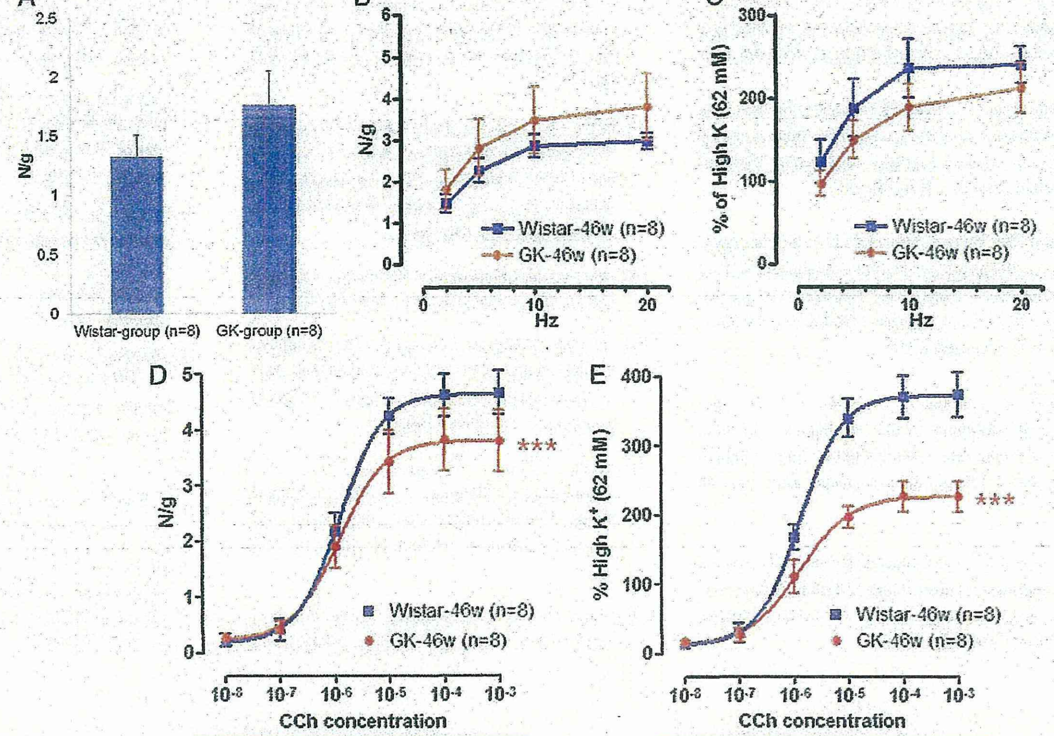
	Wistar-10w	GK-10w
Log EC50	-6.157	-5.754
Emax (%)	150.9	189.4

Figure 4. Contractile response to high 62 mM K^+ (*A*), 2, 5, 10 and 20 Hz EFS (*B* and *C*), and 10^{-8} to 10^{-3} M CCh (*D* and *E*) at age 10 weeks (*w*). *N/g*, N, gm. *Emax*, maximum relaxation. *EC50*, concentration needed to produce 50% response. No significant difference was found between 2 groups (unpaired Student t test).

There was a discrepancy between FV measurements, and CMG and CV results in 10-week-old rats, ie we found a significant difference in FV but not in CMG or CV. Possibly the artificial conditions during CMG and CV measurements, such as inserted catheters, intravesical saline instillation and urethane anesthesia, affected the results and obscured the difference detected by FV measurements, which was done under more natural conditions.

Previous studies in STZ induced DM rats showed increased bladder capacity, voided volume, contraction duration and post-void residual volume, suggesting bladder sensory impairment and detrusor underactivity.[24,25] We found similar findings suggestive of bladder sensory impairment in GK type 2 diabetic rats, as mentioned. However, we also found significantly lower peak pressure during voiding in 46-week-old GK rats. This may represent detrusor underactivity, although no significant increase in mean post-void residual volume or decrease in mean urinary flow rate was detected. Murakawa et al reported that 2-month-old GK rats showed normal nerve CV and no morphometric abnormalities in the sciatic motor nerve, while in 18-month-old GK rats CV was decreased to 76% of control values and there were loss of small myelinated fibers, atrophy and loss of unmyelinated axons, and an increased frequency of regenerating fibers.[11] In agreement with this previous report, our CV measurements revealed that bladder afferent nerve CV was decreased and the proportion of myelinated fibers was decreased in aged GK rats.

In in vitro functional studies contractility in response to a high K^+ concentration or to EFS showed no significant difference between the 2 rat bladder groups at ages 10 and 46 weeks. On the other hand, the response to CCh was significantly lower in GK than in Wistar rats at age 46 weeks but not at age 10 weeks. Yono et al observed that the maximum contractile response to CCh was similar in GK and Wistar rat bladders until age 8 weeks, while at age 16 weeks the contractile response to CCh was increased in GK rats.[13] Saito et al reported that CCh induced detrusor contractility was significantly increased in GK rats at ages 12 and 70 weeks.[12] We could not determine the reasons for such contradictory results between our and previous studies. To speculate, differences in experimental procedures between the previous and current series, such as rat age, vendor and experimental setup, may have influenced this discrepancy. In the current CMG measurement



	Wistar-46w	GK-46w
Log EC50	-5.914	-5.932
Emax (N/g)	4.667	3.827

	Wistar-46w	GK-46w
Log EC50	-5.891	-5.896
Emax (%)	373.2	227.8

Figure 5. Contractile responses to high 62 mM K^+ (*A*), 2, 5, 10 and 20 Hz EFS (*B* and *C*), and 10^{-8} to 10^{-3} M CCh (*D* and *E*) at age 46 weeks (w). *N/g*, N, gm. *Emax*, maximum relaxation. *EC50*, concentration needed to produce 50% response. Asterisks indicate significantly different vs age matched Wistar rats (unpaired Student t test $p < 0.001$).

decreased peak pressure was noted in GK rats at age 46 weeks. This may be linked to the decreased contractile response to CCh, suggesting that acetylcholine mediated bladder contractile mechanisms during voiding may be impaired in GK rats at age 46 weeks.

Together, these findings suggest that type 2 DM may induce impaired bladder sensation and bladder contractility during voiding in rats. Further investigation is needed to determine the natural history of lower urinary tract dysfunction in this experimental rat model of type 2 DM.

CONCLUSIONS

The results of our longitudinal study in GK rats indicate that type 2 DM induces bladder sensory dysfunction, represented as slower conduction velocity of bladder afferents, and greater bladder capacity and bladder hypocontractility to acetylcholine. To our knowledge this is the first direct demonstration of bladder afferent dysfunction in type 2 diabetic GK rats. GK rats can serve as a model for investigating the sensory dysfunction and detrusor underactivity associated with type 2 DM.

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