Title:

Type 2 diabetes mellitus patients manifest characteristic spatial EMG potential distribution pattern during sustained isometric contraction

Authors:

Kohei Watanabe, Ph.D.[1, 2], Toshiaki Miyamoto, M.S. [1], Yoji Tanaka, B.S. [1], Kazuhito Fukuda, M.D. [3], Toshio Moritani, Ph.D. [1]

Affiliations:

[1] Laboratory of Applied Physiology, Graduate School of Human and Environmental Studies, Kyoto University, Kyoto, Japan

[2] Japan Society for the Promotion of Science (JSPS), Kyoto, Japan

[3] First Department of Internal Medicine, University of Toyama, Toyama, Japan

Acknowledgements

This research was supported in part by a Grant-Aid for Japan Society for the Promotion of Science (No. 22-1944). The authors are sincerely grateful to Prof. Roberto Merletti and the Researchers of LISiN (Politecnico di Torino, Italy) for helpful suggestions and the support in the use of multi-channel surface electromyography system (electrode and amplifier).

Correspondence:

Kohei Watanabe, Ph.D.

Laboratory of Applied Physiology, Graduate School of Human and Environmental Studies, Kyoto University

Yoshida Nihonmatsucho, Sakyo-ku, Kyoto, Kyoto 606-8501, Japan

Phone: +81 75 753 2878, Fax: +81 75 753 2878

e-mail: watanabe.kohei@aw7.ecs.kyoto-u.ac.jp

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Abstract:

Aim The purpose of the present study is to investigate spatial surface electromyography (SEMG) potential distribution pattern in type 2 diabetes mellitus (T2DM) patients. *Methods* Nine T2DM patients and nine age-matched healthy men (CON) performed a sustained isometric knee extension at 10% of maximal voluntary contraction for 120 s. Multi-channel SEMG was recorded from the vastus lateralis muscle by means of 64 electrodes. To characterize spatial SEMG potential distribution pattern, modified entropy and correlation coefficients between same electrode locations were calculated at 15, 60 and 120s for the root mean square values. *Results* At 60 and 120s, modified entropy in T2DM was significantly lower than those in CON ($p < 0.05$). Correlation coefficients for T2DM were significantly higher than those for CON at 60 and 120s ($p < 0.05$). *Conclusion* From these results, we suggested that T2DM patients continue to recruit limited and same motor units during the sustained contraction at low force level.

Abbreviations:

CON: control, MF: median frequency, MU: motor unit, MVC: maximal voluntary contractions, RMS: root mean square, SEMG: surface electromyography, T2DM: type 2 diabetes mellitus, VL: vastus lateralis.

Keywords:

type 2 diabetes mellitus, multichannel surface electromyography, knee extensor, vastus lateralis muscle, muscle fatigue

Conflict of interest statement

There was no conflict interest in this study.

Introduction

Recent estimates indicate there were 171 million people in the world with diabetes in the year 2000 and this is projected to increase to 366 million by 2030 [1]. In diabetes patients, 90%-95% of cases were categorized as type 2 diabetes mellitus (T2DM), previously referred as non-insulin dependent diabetes. This type of diabetes encompasses individuals who have insulin resistance and usually have relative insulin deficiency. More importantly, T2DM is a significant cause of premature mortality and morbidity related to cardiovascular disease, blindness, kidney and nerve disease, and amputation [2].

For the prevention and management of T2DM, exercise has been strongly recommended along with diet and medication [3]. The previous studies have collected physiological responses to exercise in T2DM patients in order to understand physiological characteristics during exercise and design effective exercise program for this type of patients [3]. Since T2DM is caused by dysfunction in metabolic system, most of previous studies had focused on metabolic and cardiovascular responses to exercise in T2DM patients [4-8]. These studies also demonstrated the premature muscular fatigue and the reduced exercise tolerance in T2DM patient during treadmill exercise, cycling, and planter flexion exercise [4-7].

On the other hand, functional impairments in neuromuscular system had also been observed. Hyperglycemia in T2DM patients induces oxidative stress in diabetic neurons and

78 results in diabetic neuropathy, i.e. diabetic distal symmetrical sensorimotor polyneuropathy and
79 diabetic automatic neuropathy [9-11]. Effect of diabetic neuropathy on motor control during quiet
80 standing and gait had been reported [12-15]. Central nervous system is regulated by afferent input
81 from the receptors connected with peripheral nervous in even simple muscle contraction at a joint as
82 well as in other complex human movement [16]. We, thus, suspect that some degree of
83 neuromuscular impairments might be present in those patients with T2DM during sustained muscle
84 contraction in which both neural and metabolic adjustments would be required. In addition to
85 metabolic dysfunction, neuromuscular system also may be one of the factors of the premature
86 muscular fatigue and the reduced exercise tolerance in T2DM patient [4-6].

87 Recently, neuromuscular functions such as motor unit (MU) recruitment strategy or
88 functional compartmentalization within a muscle have been assessed from spatial distribution pattern
89 of muscle activation by using multi-channel surface electromyography (SEMG) technique [17-22].
90 The previous studies demonstrated that spatial EMG potential distribution pattern within a muscle is
91 altered by contraction levels or fatigue [17,21-24]. This phenomenon has been explained by a
92 spatial inhomogeneity in the location of different types of muscle fibers [25] and a clustering of
93 muscle fiber innervated by one MU in limited territory [26]. Recruitment and rate coding for these
94 different types of muscle fibers for increasing torque or fatigue would induce changes in spatial
95 distribution of SEMG potential. For sustained contraction, nociceptive afferent input from

96 contracted muscle to central nervous system was suggested as one of the major mechanisms of
97 alteration in spatial distribution (redistribution) of muscle activation [18,19,27]. Assessment of
98 spatial distribution pattern of muscle activation would be an efficient tool to investigate
99 neuromuscular function related with the responses in peripheral nervous system.

100 The purpose of the present study is to investigate spatial distribution pattern of muscle
101 activation during sustained contraction in T2DM patients. We hypothesized that redistribution of
102 spatial EMG potential distribution pattern is attenuated in T2DM patients as some degree of
103 neuromuscular impairments might be present in those patients during sustained muscle contraction
104 in which both neural and metabolic adjustments would be required.

105

106 **Materials and Methods**

107 ***Subjects***

108 Nine elderly men with type 2 diabetes mellitus (T2DM) and nine age-matched healthy
109 men (CON) participated in this study. All subjects in T2DM group have been diagnosed as T2DM
110 and treated in the hospital for 7- 38 years (Table 1). The subjects of both groups gave written
111 informed consent for the study after receiving a detailed explanation of the purposes, potential
112 benefits, and risks associated with participation in the study. Age, body mass, BMI, maximal
113 voluntary contraction (MVC) torque during isometric knee extension and MVC torque relative to

114 body mass were matched between the groups (Table 1). All subjects in both groups had no history
115 of any locomotor disorders. Blood sample was collected to determine the concentration of
116 glycosylated hemoglobin (HbA1C) levels, which is used as an index of average blood glucose levels
117 over the preceding 2-3 months and as a diagnostic criteria for diabetes mellitus [28]. All
118 procedures used in this study were in accordance with the Declaration of Helsinki and were
119 approved by the Committee for Human Experimentation at the Graduate School of Human and
120 Environmental Studies, Kyoto University and for Kyoto Teishin Hospital.

121 ***Experimental design***

122 The subjects were tested for maximal voluntary contractions (MVC) during isometric knee
123 extension according to our previous procedures [21,22]. After sufficient rest period, each subject
124 performed a sustained contraction at 10% of MVC for 120 s during isometric knee extension.
125 During sustained contraction, multi-channel SEMG was recorded from the vastus lateralis (VL)
126 muscle.

127 Isometric knee extensions were performed on a custom dynamometer mounting a force
128 transducer (LU-100KSE; Kyowa Electronic Instruments, Tokyo, Japan). During contraction, both
129 hip and knee joint angles were flexed at 90° (180° is fully extended), respectively. The MVC
130 involved a gradual increase in knee extension force exerted by the knee extensor muscles from
131 baseline to maximum in 2-3 s and then sustained at maximum for 2 s. The timing of the task was

based on a verbal count given at a 1-s interval, with vigorous encouragement from the investigators when the force began to plateau. The subjects performed at least two MVC trials with ≥ 2 min rest between trials. The highest MVC force was used to calculate the MVC torque and target torque for sustained contraction. Knee extension torque was calculated as the product of the knee extension force and length between the estimated knee joint center and the distal portion of the shank linked to force transducer. After MVC, the sustained contraction at 10% of MVC force was performed for 120 s. The produced and target torques were shown to the subjects on a personal computer monitor. Subjects practiced MVC and sustained contraction ≥ 10 min before test session.

EMG recording

Multi-channel SEMG signals were detected from the VL muscle with a semi-disposable adhesive grid of 64 electrodes (ELSCH064R3S, OT Bioelectronica, Torino, Italy) using the same procedure as that used in our previous study [21,22]. This muscle is one of the knee extensor muscles which play important roles during human movements and most previous studies have focused on this muscle to investigate disease related changes in metabolism or histochemistry of a skeletal muscle [7,8,29]. Thus, we selected the VL muscle to detect SEMG in the present study. The grid is made of 13 rows and 5 columns of electrodes (1 mm diameter, 8 mm inter-electrode distance in both directions) with one missing electrode at the upper left corner. Prior to attaching the electrode grid, the skin was cleaned with alcohol. Conductive gels were inserted into the

150 cavities of the grid electrode to assure proper electrode skin contact. The center of electrode grid
151 was placed at mid-point of the line between the head of great trochanter and inferior lateral edge of
152 patella. The rows of electrodes were placed along the longitudinal axis of VL muscle such as the
153 line between the head of great trochanter and inferior lateral edge of patella. The position of
154 missing electrode was located at proximal side of longitudinal axis of VL muscle. The grid
155 electrode was connected to the amplifier through 4 connectors which were fixed at the subject skin
156 by elastic tape. A reference electrode was placed at the iliac crest. At the center of electrode
157 location, longitudinal ultrasonographic image (SSD-900, ALOKA, Tokyo, Japan) were taken to
158 determine the thickness of the subcutaneous tissue and VL muscle.

159 Monopolar SEMG signals were amplified by a factor of 1000, sampled at 2048 Hz and
160 converted to digital form by a 12-bit analog-to-digital converter (EMG-USB, OT Bioelectronica,
161 Torino, Italy) with the signal of force transducer. Recorded monopolar SEMG signals were off-line
162 band-pass filtered (10 - 500 Hz) and transferred into analysis software (MATLAB R2009b,
163 MathWorks GK, Tokyo, Japan). Fifty-nine bipolar SEMG signals along the rows were made from
164 64 electrodes. To calculate root mean square (RMS) and median frequency (MF), SEMG signals
165 were sampled over 1 s from 1 s before the given time to the given time at 15 s, 60 s, and 120 s.
166 From 59 RMS and MF values normalized by the value at 15 s, mean normalized RMS and MF
167 values were calculated at 60 s and 120 s.

Modified entropy was calculated for 59 absolute RMS values (in space) at each time as done by Farina in a previous work [17]. Decrease in modified entropy means that increase of heterogeneity in spatial EMG potential distribution within an electrode grid.

In each time point, 59 absolute RMS values were categorized into three activation level by the percentage of peak RMS value at each time, i.e. low (0~33% of peak RMS), middle (33~66% of peak RMS), and high (66~100% of peak RMS) activation. Number of channel was counted in individual activation levels.

To characterize changes in spatial SEMG potential distribution with time course, correlation coefficients were calculated from the 59 pairs of absolute RMS values (RMS map) at same locations at between 15 s and other two sampled time.

Statistics

All data are provided as mean and SD. Before the analysis, the normal distribution of the data was confirmed using Shapiro-Wilk test. The parametric analysis was used for normally distributed data and the non-parametric analysis was used for non-normally distributed data. Age, body mass, BMI, MVC torque, MVC torque relative to body mass, HbA1C, and VL muscle thickness were compared between groups using *t*-test. Thickness of subcutaneous tissue was compared between groups using Mann-Whitney *U*-test. Friedman test and Mann-Whitney *U*-test was performed for mean normalized RMS and MF values, number of channel with three activation

levels, modified entropy, correlation coefficient of RMS map, and performed force to investigate changes with time course and to compare between the groups at the given times, respectively. The level of statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS software (version 15.0; SPSS, Tokyo, Japan).

Results

There were no significant differences between the groups in anthropometric parameters, MVC torque, MVC torque relative to body mass, and thickness of subcutaneous tissue and VL muscle ($p > 0.05$) (Table 1). A significant difference between the groups was observed in HbA1C as expected ($p < 0.05$) (Table 1).

For mean normalized RMS and MF values, there were no significant changes with time course in both groups and no significant difference between the groups ($p > 0.05$). There were also no significant differences in the performed forces at the given times ($p > 0.05$), indicating that the targeted torque was well controlled by the subjects of both groups.

Fig. 1 illustrated representative multi-channel SEMG amplitude shown as color map at the given times for T2DM and CON groups. In T2DM, large areas with low RMS value were demonstrated at all times. Changes in spatial SEMG potential distribution with time course were seen in both groups. However, changes in spatial SEMG potential distribution in CON group was

greater than that in T2DM group in these representative data.

No significant change with time was found in modified entropy for both groups ($p > 0.05$) (Fig. 3). Modified entropy in T2DM group was significantly lower at 60 and 120s than those in CON group ($p < 0.05$) (Fig. 2), indicating that heterogeneity in spatial EMG potential distribution was greater in T2DM group.

There were no significant changes with time in number of channel with all activation level for both groups ($p > 0.05$). Thus, numbers of channel with three activation levels were shown only at 120s in Fig. 3. Number of channel with low activation was significantly greater in T2DM group than CON group ($p < 0.05$). In T2DM group, numbers of channel with low and middle activation were significantly greater than high activation level ($p < 0.05$). On the other hand, in CON group, numbers of channel with middle activation level were significantly greater than low and high activation level ($p < 0.05$).

Significant changes were found in correlation coefficients of RMS map with time course in both groups ($p < 0.05$). At 60 s and 120 s, correlation coefficients of RMS map in T2DM were significantly higher than those in CON ($p < 0.05$) (Fig. 4). This means that the time course change in spatial SEMG potential distribution was smaller in T2DM group.

Discussion

In the present study, mean normalized RMS and MF values did not change with time for both groups. During relative low-level sustained contraction (< 10% of MVC), blood flow through the muscle is sufficient to prevent fatigue [30]. Thus, fatigue-induced progressive MU recruitment, increased firing frequency and decrement in conduction velocity of action potential, which are causes of increase in RMS and decrease in MF during sustained contraction [31-33], could not be occurred in both groups. Also, there were no significant differences in these global SEMG variables between the groups at the given times, although the previous reports demonstrated premature muscular fatigue in T2DM patient [4-6]. These findings would indicate that the given task in the present study does not induce muscular fatigue even in T2DM patients. On the other hand, the fatigability during isometric contraction depends on absolute force [34]. In the present study, absolute target force during sustained contraction was matched between the groups owing to matched absolute MVC torque. We thus assumed that the burden for working muscle was controlled between the groups.

Heterogeneity in spatial EMG potential distribution within an electrode grid was greater in T2DM group in the present study (Fig. 2). This would be due to greater number of electrode with low RMS values in T2DM group as compared with CON group (Fig. 3). From these findings, it was suggested that limited area was activated within a muscle during a sustained contraction in T2DM patients. Heterogeneity in spatial EMG potential distribution can be explained by spatial

240 inhomogeneity in the location of different types of muscle fibers [25] and a clustering of muscle
241 fiber innervated by one MU in limited territory [26]. We thus supposed that in T2DM patients
242 limited MUs were recruited during sustained contraction at low force level. Since the previous
243 studies demonstrated that a reduction in slow oxidative muscle fibers or lower percentage of type 1
244 muscle fiber in VL muscle of T2DM patients [7,8,29], muscle fibers or MUs contributing to low
245 level contraction may be smaller in T2DM patients. Moreover, denervation of muscle fibers and/or
246 increase of intramuscular fat tissue caused by diabetic amyotrophy have been demonstrated in
247 diabetes mellitus patients including T2DM patients [11]. These morphological changes may also
248 induce heterogeneity spatial EMG potential distribution within a muscle in T2DM group.
249 While RMS and MF values calculated from all electrode pairs were unchanged with time,
250 spatial distribution pattern of SEMG changed with time for both groups. Also, change in spatial
251 distribution pattern of SEMG was smaller in T2DM group in the present study (Fig. 4). Under the
252 assumption that the observed changes in spatial EMG potential distribution pattern might reflects
253 recruitment of heterogeneously located MUs with limited territory within a muscle [25,26], our data
254 suggests that limited number of the same MUs might have been activated continuously during
255 sustained contraction in T2DM patients. Since chemical responses such as blood lactate
256 concentration arise even in low-level sustained contraction (10% of MVC) [30], chemical stimuli
257 may be one of the causes of change in spatial distribution pattern. It is well known that central

nervous system is regulated by afferent input from the receptors within a muscle during contraction [16]. Madeleine et al. (2006) and Falla et al. (2008) demonstrated that nociceptive afferent input elicited by experimental muscle pain changes spatial distribution pattern of SEMG during sustained contraction in the upper trapezius muscle [18,27]. These results indicate nociceptive afferent input contributes to recruitment and/or derecruitment of MU during a sustained contraction. Diabetic peripheral neuropathy is one of the severe complications in T2DM patients [9-11]. In particular, dysfunction in small diameter nerves, i.e. pain, thermal perception, and pressure, named as diabetic distal symmetrical sensorimotor polyneuropathy, is early and often occurs in T2DM patients [9-11]. We thus infer that diabetic peripheral neuropathy decreases afferent input to central nervous system during muscle contraction. Due to this reduction in afferent input, recruitment and/or derecruitment could be not progressed during a sustained contraction and thereby attenuates change in spatial distribution of muscle activation in T2DM patients. However, degree of diabetic peripheral neuropathy for T2DM patients was not assessed in the present study. More detailed work is necessary to investigate the relationship between spatial EMG potential distribution pattern and diabetic peripheral neuropathy.

Farina et al. (2006) showed that changes in spatial distribution of SEMG potential correlates with exhaustion time during low level isometric contraction for the upper trapezius muscle [17]. This suggests that redistribution of muscle activation

276 plays a key role of prolonging muscular fatigue during sustained contraction [17]. The premature
277 muscular fatigue and the reduced exercise tolerance in T2DM patient are well known [4-6] and it has
278 been recognized that dysfunction in metabolic and cardiovascular systems are main causes of that
279 [4-8]. From the result of present study, it was assumed that in addition to dysfunction
280 in metabolic and cardiovascular systems specific activation pattern in neuromuscular
281 system could also contribute to premature muscular fatigue and the reduced exercise
282 tolerance in T2DM patients.

283 In conclusion, we compared spatial distribution pattern of muscle activation during
284 sustained contraction between T2DM patients and age-matched healthy men using multi-channel
285 SEMG for the knee extensor muscle. Limited area was activated within a muscle and the
286 attenuation of redistribution in spatial EMG potential pattern was seen in T2DM patients. From
287 these results, we suggested that T2DM patients might activate limited numbers of the same MUs
288 continuously during the sustained contraction at low force level.

289

290 **Acknowledgement**

291 This research was supported in part by a Grant-Aid for Japan Society for the Promotion of Science
292 (No. 22-1944). The authors are sincerely grateful to Prof. Roberto Merletti and the Researchers of
293 LISiN (Politecnico di Torino, Italy) for helpful suggestions and the support in the use of

multi-channel surface electromyography system (electrode and amplifier).

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Figure legends

Fig. 1 Representative root mean square value for all channels shown as color map at selected times during sustained contraction for the subjects from type 2 diabetic mellitus patient (T2DM) group and age-matched healthy control group (CON).

Fig. 2 Mean (± SE) modified entropy during sustained contraction. T2DM, type 2 diabetes mellitus patients group; CON, age-matched healthy control group. * $p < 0.05$ vs. CON group.

Fig. 3 Mean (± SE) number of channel with three different root mean square levels during sustained contraction at 120s. T2DM, type 2 diabetes mellitus patients group; CON, age-matched healthy control group. * $p < 0.05$ vs. CON group. # $p < 0.05$ vs. high level. + $p < 0.05$ vs. low level.

Fig. 4 Mean (± SE) correlation coefficient values in root mean square map between at 15s and 120s during sustained contraction. T2DM, type 2 diabetes mellitus patients group; CON, age-matched healthy control group. * $p < 0.05$ vs. CON group.

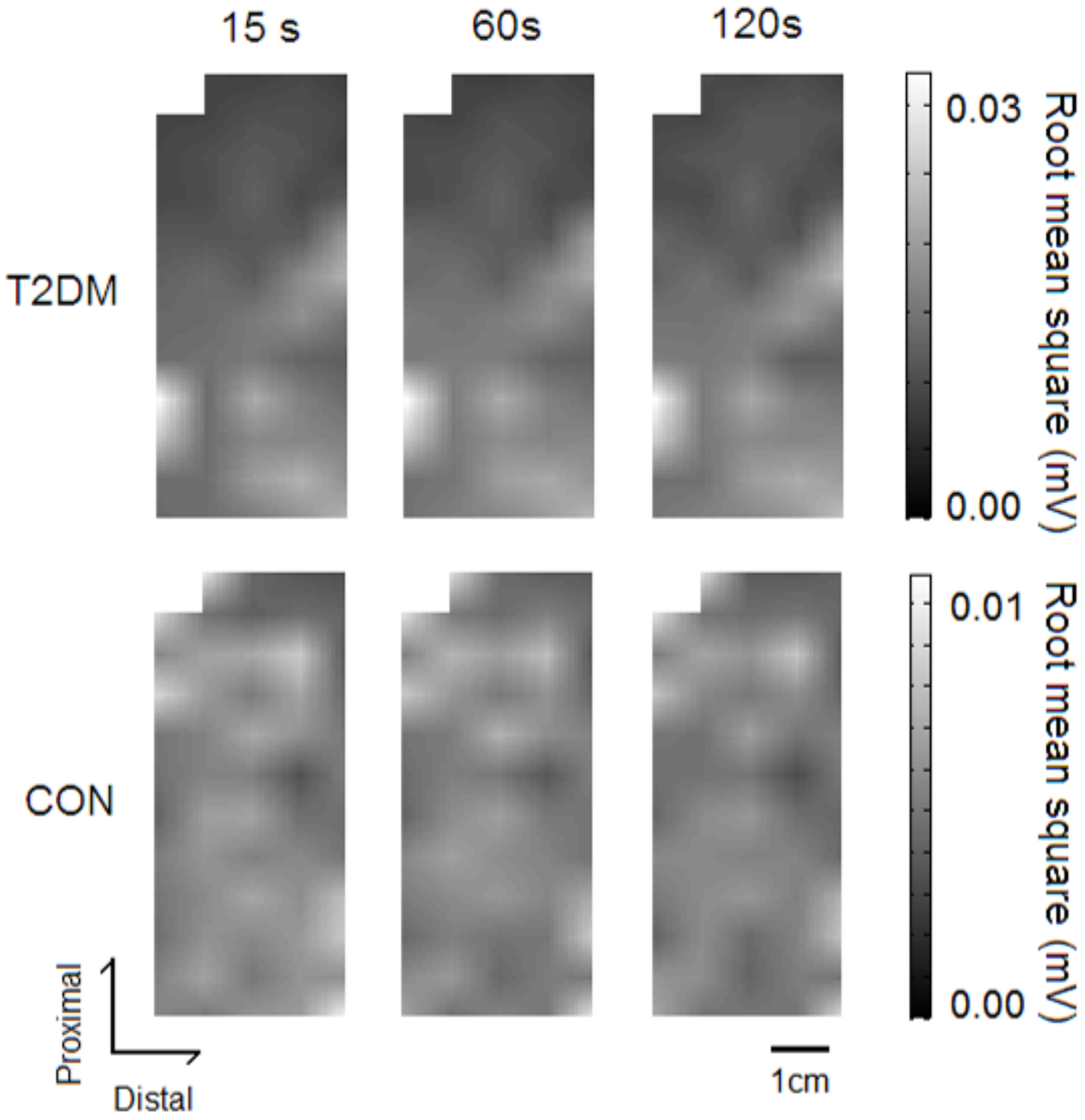
15 s
60s
120s
T2DM
CON
0.03
0.00
Root mean square (mV)
0.01
0.00
Root mean square (mV)
Proximal
Distal
1cm

Fig. 1

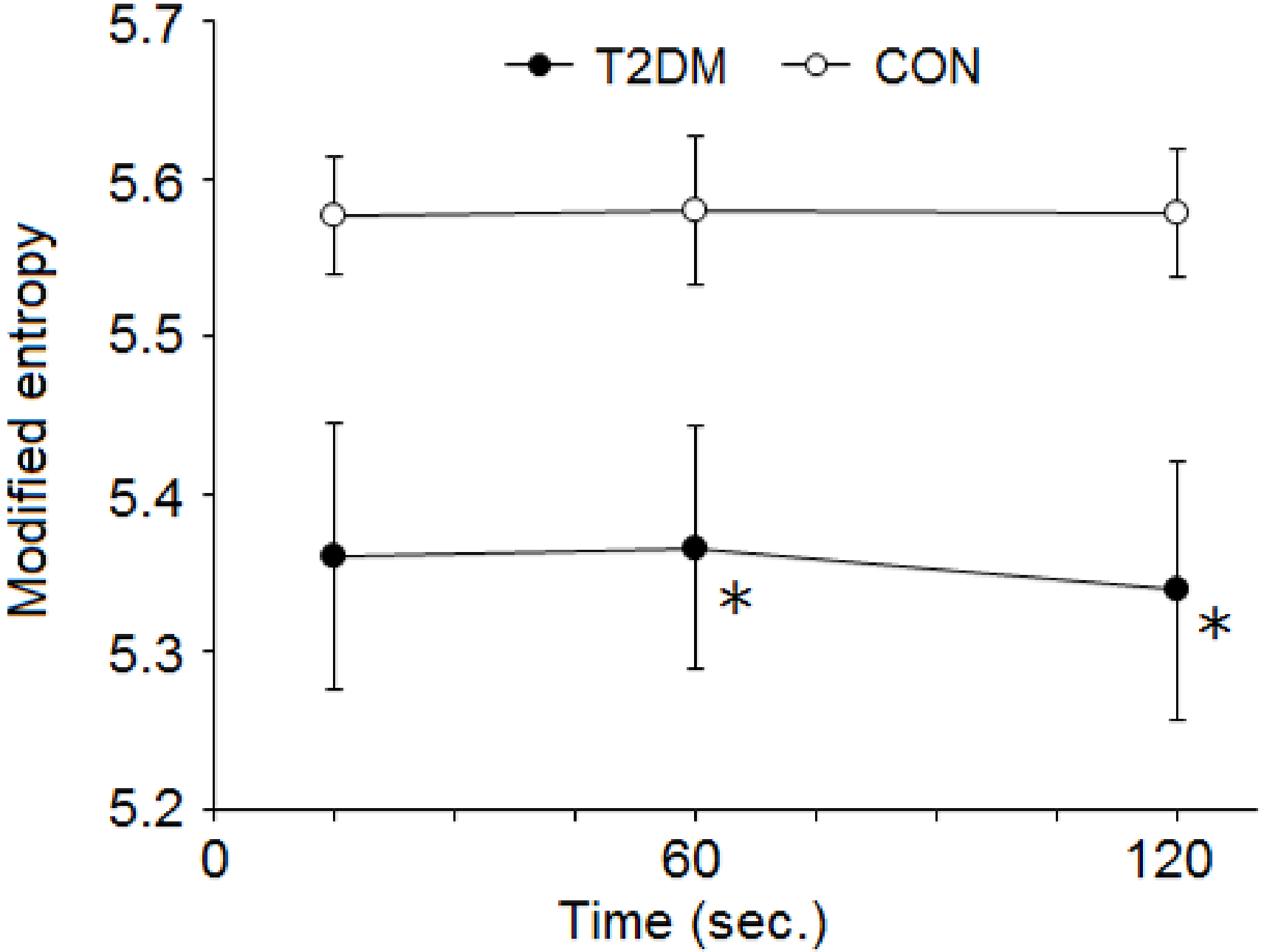

Fig. 2

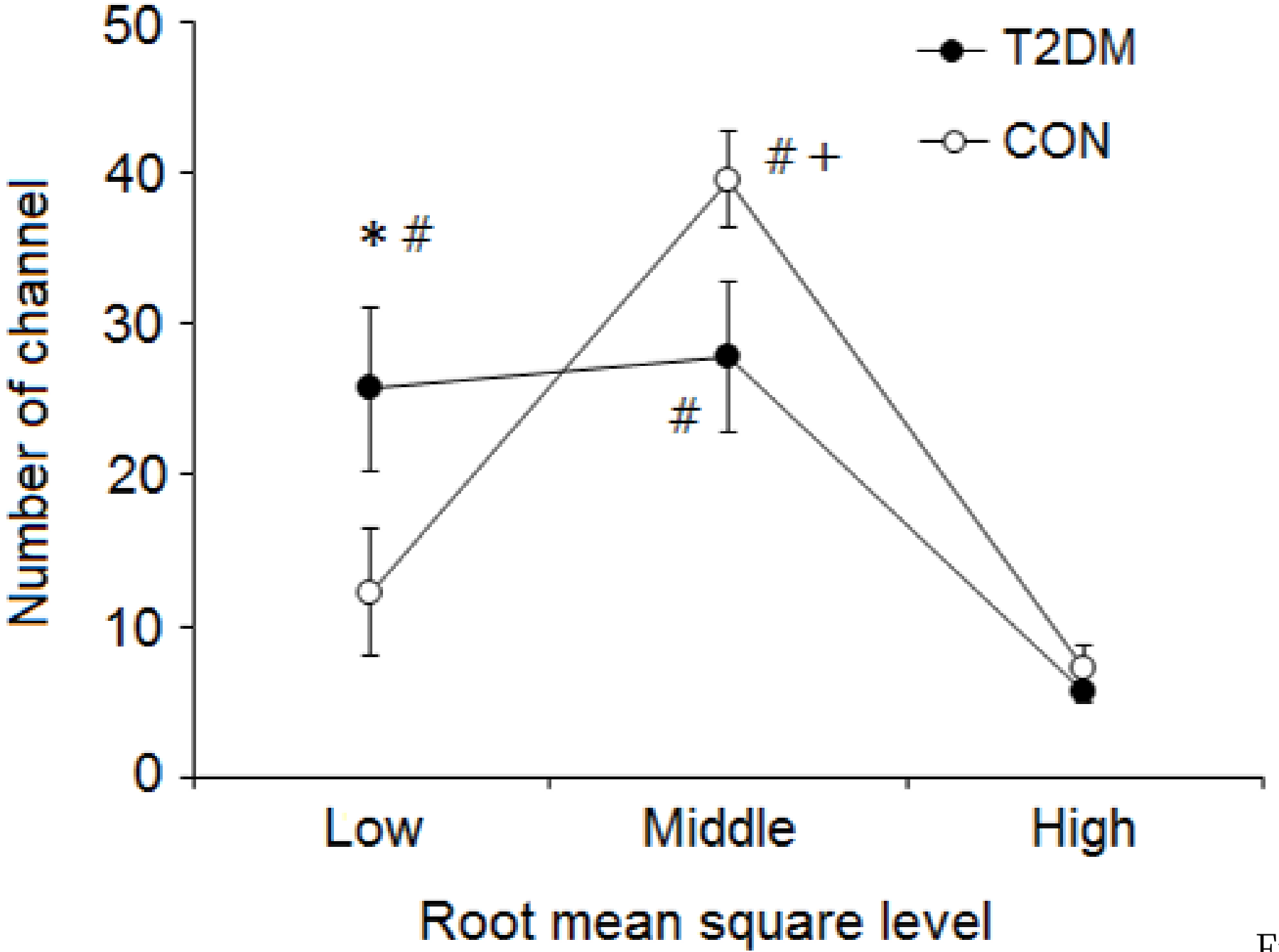
50
40
30
20
10
0
Number of channel
T2DM
CON
* #
# +
#
Low
Middle
High
Root mean square level

Fig. 3

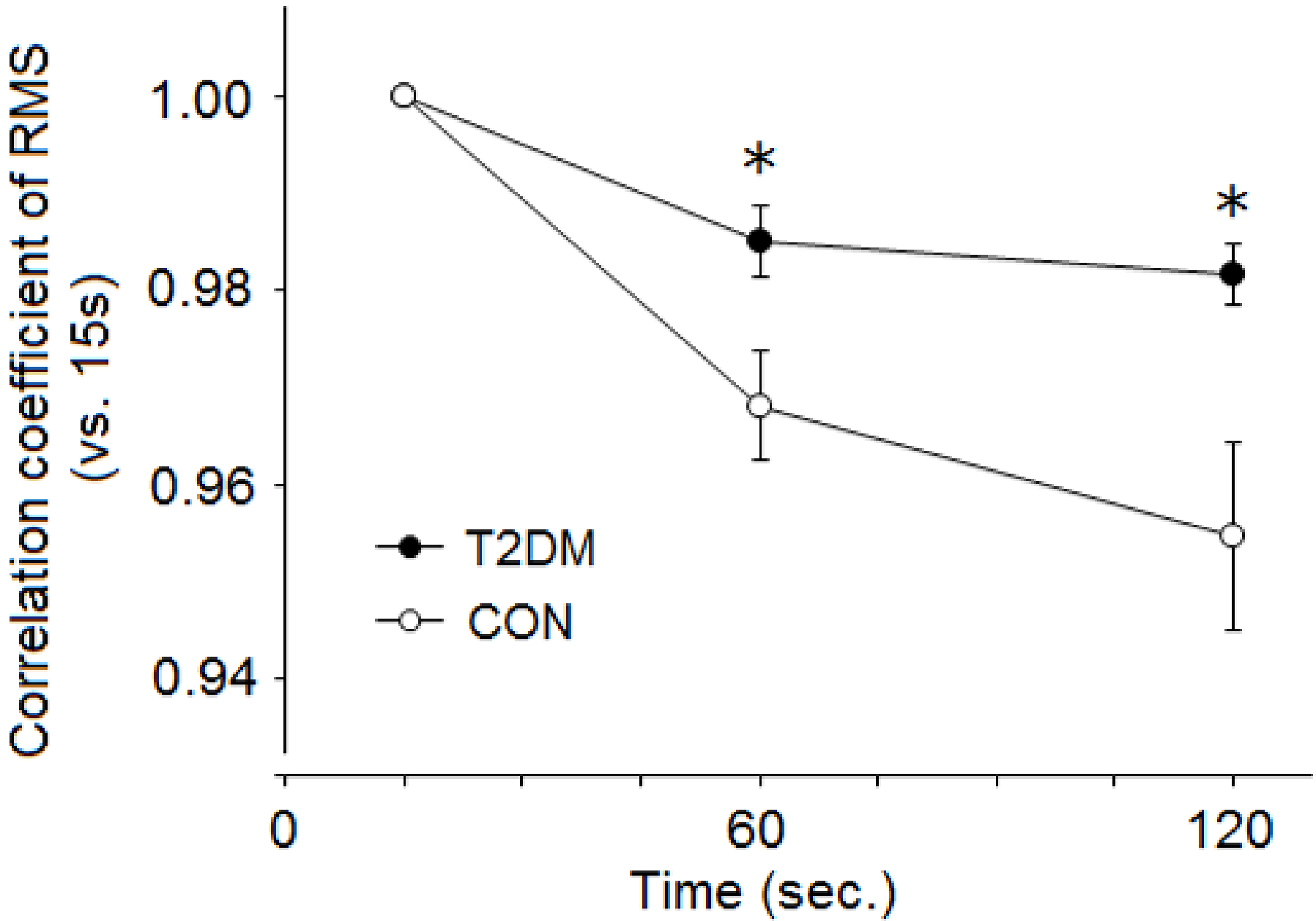
Correlation coefficient of RMS
(vs. 15s)
1.00
0.98
0.96
0.94
T2DM
CON
*
*
0
60
120
Time (sec.)

Fig. 4

Table 1 Characteristics of the subjects for type 2 diabetes mellitus patients (T2DM) and age-matched healthy control (CON)

	T2DM	CON
Age (year)	70.6 ± 6.7	72.6 ± 3.8
Height (cm)	166.0 ± 7.0	163.8 ± 3.2
Body mass (kg)	61.9 ± 7.3	62.9 ± 3.6
BMI	22.5 ± 2.3	23.4 ± 1.5
MVC (Nm)	116.7 ± 19.8	124.0 ± 29.6
MVC / Body mass (Nm/kg)	1.9 ± 0.3	2.0 ± 0.5
HbA1C (%)	7.9 ± 0.9	5.3 ± 1.7 *
Duration of T2DM (year)	18.9 ± 11.9	
Subcutaneous tissue thickness (cm)	0.36 ± 0.18	0.40 ± 0.07
Muscle thickness (cm)	2.03 ± 0.31	2.21 ± 0.33

Data are mean ± SD. * $p < 0.05$ vs. T2DM.