ORIGINAL ARTICLE

Magnesium-responsive genes are downregulated in diabetic patients after a three-month exercise program on a bicycle ergometer

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Abstract

Background: Exercise is an effective therapy for the management of diabetes because it helps regulate glucose and magnesium homeostasis. Nevertheless, the mechanisms by which exercise exerts effects on magnesium transport remain unclear. This study investigated the expression of genes encoding magnesium transporters (GMTs) after a three-month exercise program in diabetic patients.

Methods: This study was conducted with a within-subject pre-post design. A total of 15 adult patients with type 2 diabetes mellitus (T2DM) were recruited and underwent a three-month indoor bicycle exercise program. The expression of five GMTs (*CNNM2*, *TRPM6*, *TRPM7*, *SLC41A1*, and *SLC41A3*) was determined in blood samples. Relevant anthropometric values and biochemical parameters were also determined.

Results: Although the body weight and body mass index decreased after three months exercise, there were no significant differences. Fasting blood glucose, glycated hemoglobin (HbA1c), waist circumference, and magnesium levels decreased after the exercise program ($p < 0.05$). The expression of *SLC41A1* and *SLC41A3* were downregulated after exercise, but only *CNNM2*, *TRPM6*, and *TRPM7* showed significantly decreased expression levels compared with those before the exercise program ($p < 0.05$).

Conclusion: The three-month exercise program ameliorated blood glucose levels and downregulated the expression of magnesium-responsive genes in patients with T2DM.

Keywords: Blood glucose; Exercise; Magnesium; Magnesium transporter; Type 2 diabetes mellitus

1. INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a widespread health problem with a dramatically increasing prevalence worldwide, and it is associated with increased cardiovascular risk.[1] Three key aspects of diabetes management include suitable medications, healthy diet, and appropriate exercise.[2] Appropriate exercise improves blood pressure and glucose management, attenuates lipids, aids weight loss, enhances anti-inflammation, and plays a key role in the prevention and management of diabetes.[3] Several studies have revealed that regular exercise reduces glycated hemoglobin (HbA1c), waist circumference, triglycerides (TG), and systolic blood pressure in patients with T2DM.[3,4]

Over the past few decades, researchers have investigated the ability of exercise to alter or regulate magnesium homeostasis, including enzyme activation, nucleotide binding, and transmembrane electrolyte flux.[5] Nielsen and Lukaski suggested that exercise may induce magnesium redistribution in the body to compensate for metabolic demand.[6] Additionally, exercise is suggested to impact magnesium transport, which may result in depleted blood magnesium levels and increased demand for magnesium intake because of metabolic requirements.[7]

Magnesium homeostasis plays an essential role in the regulation of cellular physiology and biochemical functions.[8] Altered blood magnesium levels may in turn shift the balance

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of other ions, resulting in metabolic or pathological changes.[8–11] Magnesium homeostasis is maintained by regulation via hormones and specific transporters, such as cyclin and CBS domain divalent metal cation transport mediator 2 (*CNNM2*), transient receptor potential melastatin 6 and 7 (*TRPM6* and *TRPM7*), solute carrier family 41 members 1–3 (*SLC41A1, SLC41A2,* and *SLC41A3*), and by regulatory means such as hormones.[8,12] Previous studies have shown that exercise regulates magnesium and glucose transport by the interactions of cation channels (eg, Ca^{2+}, K^+, and Na^+) and ion exchangers and/or pumps (eg, Na^+/K^+ and Na^+/Mg^{2+}).[8,13]

Despite the evidence that magnesium is associated with blood glucose regulation and is influenced by exercise, there is limited knowledge regarding the molecular mechanisms by which exercise modulates the molecular manipulation of magnesium homeostasis.

In our previous study, the downregulation of *SLC41A1* (encoding for the Na^+/Mg^{2+} exchanger) following acute exercise was observed, and the level of *SLC41A1* returned to basal status 24 hours after the acute exercise.[14] However, the effects of exercise on the expression of genes encoding magnesium transporters (GMTs) and on the regulation of blood magnesium and glucose levels remain unclear. In the present study, we investigated the status of magnesium (blood magnesium levels and the expression of GMTs) in T2DM patients. The exercise protocol consisted of a three-month indoor bicycle exercise program. Additionally, anthropometric values and biochemical parameters of blood samples were determined. The aims of this study were to investigate changes in blood glucose and magnesium levels and the expression of GMTs after a three-month exercise in T2DM patients. The results of this study may contribute to an improved understanding of the role of magnesium in glucose regulation in T2DM patients following a three-month exercise program.

2. METHODS

This prospective open-label study was approved by the ethical review board of the Taichung Veterans General Hospital (IRB TCVGH No: SG12147). Adult participants with T2DM were recruited, and informed consent was obtained. In this study, the diagnosis of diabetes was based on the criteria of the American Diabetes Association.[15] Subjects were excluded if they had the following: (1) a hyperglycemic crisis or HbA1c > 12%, (2) acute or chronic renal diseases with serum creatinine levels > 200 mmol/L, (3) acute or chronic infectious diseases, (4) changes in medications for diabetes, hypertension, hyperlipidemia, or had antiplatelet or anti-inflammation therapy within the past month, or (5) a limited ability to perform the regular exercise program, which was assessed according to the physician's clinical judgment.

2.1. Indoor bicycle exercise program and exercise intensity

A cardiopulmonary exercise test (CPET) was performed, and exercise intensity was determined according to our previous report.[16] Briefly, the cardiopulmonary fitness of the patients (maximum oxygen consumption, VO_2 max) was obtained using a MasterScreen CPX system (CareFusion Respiratory Care, CA, USA) with a cycle ergometer. All recruited patients underwent a three-month scheduled exercise program. In addition, the in-home training modality consisted of a commercially available bicycle (Giant CS800, Taichung, Taiwan) with an indoor bicycle trainer (Giant Cyclotron Mag, Taichung, Taiwan) for at least 3 days per week. For in-home exercise, an initial 5 minute warm-up period at an intensity according to the Borg rating of perceived exertion scale of 9 was suggested. The recommended training intensity was 60% VO_2 max determined from the CPET, and the home bicycle exercise duration was 40 minutes, with a subsequent 5 minute cool-down period.[17] During the study, diets and medications were not changed.

2.2. Biochemical and anthropometric measurements

Blood samples were collected for measurements of fasting blood glucose (FBG), HbA1c, lipoprotein profiles, and the expression of GMTs at fasting and resting statuses before and after the exercise program. Plasma magnesium levels were measured using a Spotchem EZ sp-4430 automatic analyzer (ARKRAY, Inc., Kyoto, Japan). Blood glucose, TG, and cholesterol concentrations were measured by using commercially available kits (Beckman Coulter, Fullerton, USA). High-density lipoprotein (HDL) and low-density lipoprotein (LDL) levels were measured by using commercially available kits (Roche Diagnostics GmbH, Mannheim, Germany). In addition, the anthropometric data, including height, body weight, BMI, blood pressure, and waist circumference, were measured.

2.3. GMT expression

The expression of five GMTs (*CNNM2*, *TRPM6*, *TRPM7*, *SLC41A1*, and *SLC41A3*) was determined. Total RNA extractions, RNA reverse transcription, quantitative real-time PCR (qRT-PCR), and data analysis were performed as previously described by Lin et al.[18] Briefly, peripheral blood was collected and centrifuged, total RNA was extracted from buffy coat layer using RNAzol RT (Molecular Research Center, Inc., USA). An RNA 6000 Nano LabChip analyzer (Agilent 2100 bioanalyzer; Agilent, Santa Clara, CA, USA) was used to assess the RNA integrity. A volume of 1 μg of total RNA was reverse transcribed to cDNA using SuperScript III First-Strand Synthesis SuperMix for qRT-PCR (Invitrogen by Life Technologies, Carlsbad, CA, USA). The expression levels of the five GMTs were determined by SYBR Green-based qRT-PCR (Life Technologies, USA). The ΔΔCt method was used for the relative quantification of GMT expression.[18]

2.4. Statistical analysis

Categorical variables were analyzed according to the frequency distribution and were expressed as numbers and percentages (n [%]). Continuous variables of a skewed distribution were expressed as the median and range (25th percentile to 75th percentile). In addition, a paired *t*-test was used to evaluate the difference between the means before and after the three-month exercise protocol, and the data are presented as the mean values and SD. Pearson's correlation (r) analysis was used to determine the correlation between two continuous variables. A p-value < 0.05 was considered statistically significant.

3. RESULTS

3.1. Baseline characteristics

A total of 15 adult patients (eight males and seven females) with T2DM and a median age of 53 years were recruited from Taichung Veteran's General Hospital. The characteristics of the 15 T2DM patients are shown in Table 1.

3.2. Clinical data, metabolic parameters, and plasma magnesium before and after exercise

The body weight, BMI, metabolic parameters, and plasma magnesium levels that were collected before and after the three-month exercise program are shown in Table 2. Although the body weight and body mass index (BMI) decreased after three-month exercise, there was no significant difference. The FBG, HbA1c, and waist circumference levels significantly decreased

Table 1

The characteristics of 15 patients with T2DM

Variables	n, %	Median (25th percentile–75th percentile)
Age, y		53 (48–59)
Sex		
Male	8 (53.3)	
Female	7 (46.7)	
Duration of diabetes, y		5.0 (2.0–12.0)
Diabetes medication		
No medication	2 (13.3)	
Oral hypoglycemic drug	8 (53.3)	
Insulin and oral hypoglycemic drug	5 (33.3)	
Lipid-lowering medication		
No medication	8 (53.3)	
Oral medication	7 (46.7)	

The categorical variables were analyzed according to the frequency distribution and expressed as numbers and percentages (n [%]). The continuous variables are presented as the median and range (25th percentile–75th percentile).
T2DM = Type 2 diabetes mellitus.

by 16%, 4.9%, and 2.0%, respectively, after the exercise program ($p < 0.05$). None of the patients had hypomagnesemia ($[Mg^{2+}]_p < 0.75$ mmol/L) before the exercise program. The plasma magnesium levels decreased by 4.7%, and two patients had hypomagnesemia after the exercise program ($p = 0.023$). However, the total cholesterol, HDL, LDL, and TG levels in the blood were not significantly different before and after the exercise program.

3.3. The expression of magnesium transporter genes after exercise

The expression of *CNNM2*, *TRPM6*, and *TRPM7* was significantly downregulated after the exercise program ($p < 0.05$). Although the expression levels of *SLC41A1* and *SLC41A3* decreased after the exercise program, there were no significant differences compared to the expression levels before the exercise program (Fig. 1.).

Table 2

Clinical data, metabolic parameters, plasma magnesium levels, and magnesium transporter gene expression before and after the exercise training program

Variables	Exercise training program		p^a
	Before	After	
Body weight, kg	83.0 ± 11.6	81.6 ± 11.2	0.079
BMI, kg/m^2	31.3 ± 4.6	30.8 ± 4.1	0.082
Waist circumference, cm	103.9 ± 14.5	101.8 ± 14.8	0.033*
Metabolic parameters			
FBG, mg/dL	187.5 ± 15.2	159.0 ± 17.0	0.009*
HbA1c, %	8.6 ± 0.4	8.3 ± 0.7	0.034*
Total cholesterol, mg/dL	174.3 ± 6.8	178.7 ± 18.5	0.543
HDL, mg/dL	53.5 ± 3.2	51.2 ± 5.5	0.532
Triglyceride, mg/dL	120.5 ± 12.0	137.0 ± 19.1	0.123
LDL, mg/dL	106.1 ± 7.1	119.0 ± 14.0	0.199
Plasma magnesium, mg/dL[b]	2.07 ± 0.14	1.97 ± 0.18	0.023*

*$p < 0.05$.
BMI = body mass index; FBG = fasting blood glucose; HbA1c = glycated hemoglobin; HDL-C = high-density lipoprotein; LDL = low-density lipoprotein.
[a]A paired *t*-test was used to analyze the difference in the means before and after the exercise training program. The data are reported as means ± SD.
[b]Plasma magnesium levels were measured in 12 of the 15 patients.

4. DISCUSSION

The results of this study provide evidence that a three-month in-home bike exercise program significantly downregulated the expression of *CNNM2*, *TRPM6*, and *TRPM7*, improved FBG and HbA1c, and reduced the waist circumference. Exercise is an essential factor in the prevention and management of diabetes.

In this study, improved control of FBG and HbA1c levels and a reduced waist circumference were observed. Several studies have reported that exercise ameliorates hyperglycemia in T2DM patients.[19,20] Boule et al observed decreases in HbA1c but no substantial changes in the BMI after an exercise program that lasted 8 weeks or more in patients with T2DM.[19] Jorge et al reported that the postprandial plasma glucose, FBG, and HbA1c levels decreased by 25.0%, 13.5%, and 2.8%, respectively, after aerobic exercise (three times per week and 60 minutes per session) in T2DM patients.[20] The results from the present study agreed with these previous reports and confirmed that exercise intensity and duration were properly performed in this study. In this study, although the body weight and BMI decreased after this three-month exercise intervention, there was no significant difference. The duration of exercise, type of exercise, and diet control together play a role in weight reduction.[21] Further study may be necessary to disclose the association between BMI reduction and magnesium gene expression after exercise training.

The downregulation of the expression of *CNNM2*, *TRPM6*, and *TRPM7* was observed in this study. Studies have shown that exercise not only affects glucose availability and the action of insulin but also manipulates blood magnesium levels in T2DM patients.[22,23] Magnesium transporters in different parts of the body may play different functional roles. *TRPM7*, *SLC41A1*, and *SLC41A3* are ubiquitously expressed. *TRPM6* and *CNNM2* are significantly expressed in the kidney and intestine.[8,24] *CNNM2* is predominantly expressed in the basolateral membrane of distal tubular segments; therefore, *CNNM2* has been speculated to regulate magnesium in the blood by manipulating renal magnesium reabsorption.[25] To the best of our knowledge, this is the first study to demonstrate the downregulation of *CNNM2* expression in the blood after a three-month exercise program in T2DM patients. Exercise-induced hormones and metabolite activities may cause urinary magnesium loss by reducing renal tubular magnesium reabsorption.[26] Huang et al reported that high amounts of daily physical activity is related to low serum magnesium in diabetic patients.[23] Indeed, our data also revealed that blood magnesium levels slightly decreased while downregulating CNNM2 expression after the exercise program. Therefore, it was hypothesized that long-term exercise may deplete magnesium in the blood and increase the demand for magnesium due to metabolic requirements and could therefore downregulate *CNNM2* expression. Further research is necessary to clarify this issue.

Both *TRPM6* and *TRPM7* transporters preferentially transport magnesium and calcium into cells.[8] The *TRPM6* transporter has been shown to be specifically expressed in the colon, lung, and kidney and manipulates the reabsorption of magnesium via an active and transcellular process in the distal convoluted tubule.[24] *TRPM7* is ubiquitous and may play significant roles in the regulation of magnesium homeostasis in the body. In this study, *TRPM6* and *TRPM7* expression was significantly downregulated after a three-month exercise program in T2DM patients. This implies that the three-month exercise likely triggers the effective metabolic response. Downregulated *TRPM6* and *TRPM7* expression may establish blood calcium and magnesium levels and then maintain the effectiveness of glucose utilization after exercise.

Although the SLC41 family includes three members (A1, A2, and A3), studies have primarily focused on the *SLC41*, *A1*, and *A2*

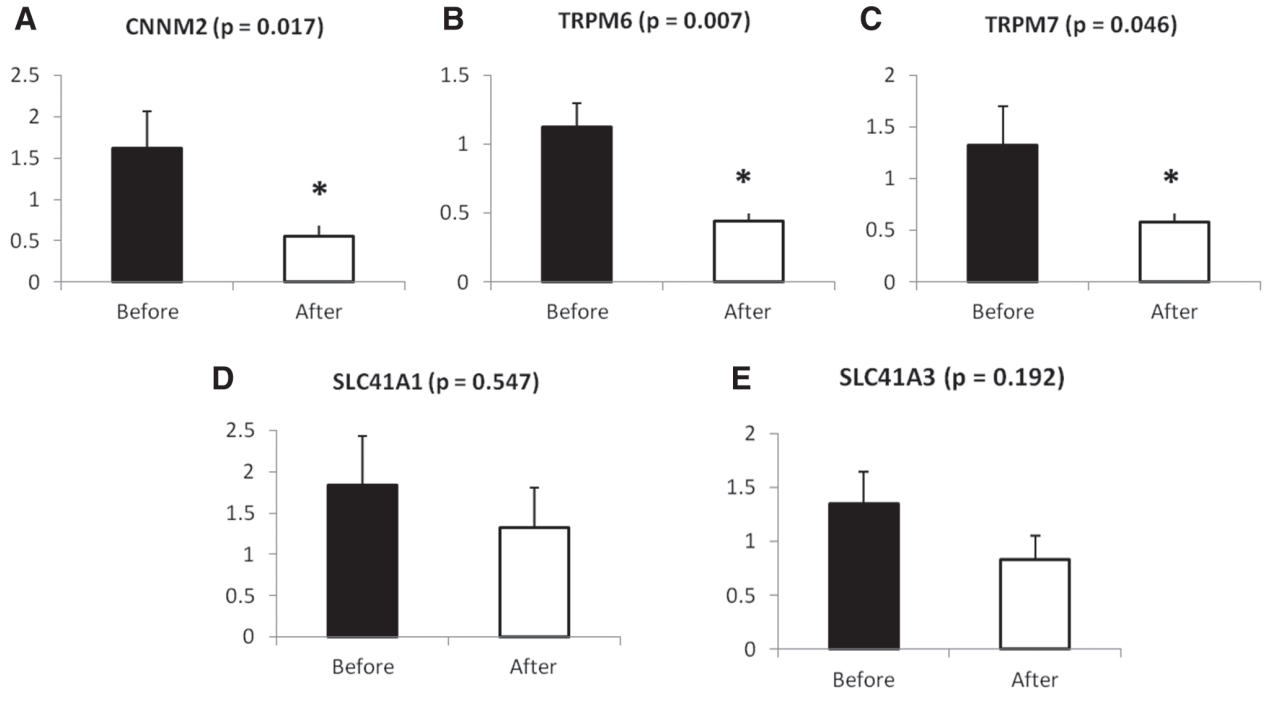

Fig. 1 The expression levels of magnesium transporters before and after a 3-month bike exercise program: A, *CNNM2*; B, *TRPM6*; C *TRPM7*; D, *SLC41A1*; and E, *SLC41A3*.

isoforms.[27] *SLC41A1*, a Na^+/Mg^{2+} exchanger defined by Kolisek et al,[27,28] regulates magnesium efflux. In this study, although the expression levels of *SLC41A1* and *SLC41A3* decreased, there were no statistically significant differences. Previous studies have demonstrated that acute exercise increases glucose availability and induces *SLC41A1* downregulation.[22] In our previous study,[14] the expression of *SLC41A1* was significantly downregulated by 23.6% and led to temporarily increased plasma magnesium levels during acute exercise. However, *SLC41A1* expression and plasma magnesium levels all returned to basal levels within 24 hours after exercise. Therefore, *SCL41A1* may be a fast-acting gene, which is highly responsive to acute exercise but not to long-term exercise.

One limitation of this study is that the expression of GMTs may vary in different tissues or organs of the body. Our data demonstrated that the expression of *TRPM6*, *TRPM7*, and *CNNM2* in the blood (or leukocytes) was downregulated after the three-month exercise program, but the expression levels in other parts of the body were not examined. Therefore, the results may have variations and may not represent the expression levels throughout the whole body in T2DM patients. Second, the underlying mechanism of GMT downregulation is not clear. Both *SLC41A1* and *SLC41A2* expression has been shown to be involved in the regulation of magnesium efflux, while the function of *TRPM6*, *TRPM7*, and *CNNM2* have been found to play a role in regulating magnesium influx.[8,12] The downregulation of *TRPM6*, *TRPM7*, and *CNNM2* in this study may imply that long-term exercise has an effect on reducing magnesium influx into cells. In addition, nondiabetic control subjects were not enrolled in this study; therefore, it is not clear whether the downregulation of GMTs occurs in nondiabetic subjects. Further research is necessary to elucidate the underlying mechanism of the exercise-induced downregulation of GMTs.

In conclusion, this study demonstrated that a three-month in-home exercise program decreased FBG and HbA1C levels and the waist circumference in T2DM patients. The expression of all investigated GMTs was downregulated, especially *CNNM2*, *TRPM6*, and *TRPM7*, which showed significant downregulation after the exercise program. Future studies that are designed to investigate the underlying mechanism of these downregulated *GMT* genes and the effects of varied exercise programs may be beneficial for T2DM patients.

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