## Effect of Tai Chi Exercise on Type 2 Diabetes: A Feasibility Study

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Abstract: This feasibility study investigated the effects of Tai Chi, a mind-body exercise, on management of Type 2 diabetes mellitus. A total of 25 subjects (20-70 years) were recruited to participate in two 60-minute instructed Tai Chi exercise sessions each week for 12 weeks. The primary outcome measures (physiological variables) were hemoglobin  $A_1C$  (HbA1c) taken at baseline and after 12 weeks of intervention, and self-reported fasting blood glucose level measured at baseline, 3, 6, 9, and 12 weeks of intervention. The secondary outcome measures (psychosocial variables) were Diabetes Quality of Life Questionnaire (Diabetes-39) and Exercise Self-Efficacy administered at baseline and 12 weeks. A semi-structured interview was conducted at the end of the study (week 12). Paired *t*-tests was employed to determine all pre- and post-intervention measurement changes, while individual growth curves were generated to show changes in fasting blood glucose levels during the study period. A rather high attrition rate of 48% was observed among the participants. The data showed no significant effect of Tai Chi on HbA1c and self-reported fasting blood glucose, although there seemed to be a trend of lowered HbA1c. Analysis of subjects' response suggested a positive experience for those who completed the intervention.

**Keywords:** Mind-body exercise, hemoglobin A<sub>1</sub>C, fasting blood glucose.

Abbreviations: T2DM: type 2 diabetes mellitus; HbA1c: hemoglobin A1C; BMI body mass index.

#### Introduction

Exercise has been well known to benefit patients with type 2 diabetes mellitus (T2DM), and is a cornerstone of diabetes management (ADA, 2004). Several long-term studies have demonstrated a consistent beneficial effect of regular physical activity training on carbohydrate metabolism and insulin sensitivity, which can be maintained for at least 5 years (ADA, 2004). Improvements in glycosylated hemoglobin (HbA1c) were generally 10–20% of baseline and were most marked in patients with mild T2DM and in those who are likely to be the most insulin resistant. A recent meta-analysis suggested that exercise training (i.e. aerobic exercise, resistance training) reduced HbA1c level in T2DM by approximately 0.66%, an amount that would be expected to significantly reduce the risk of diabetic complications (Boulé et al. 2006). However, research suggested that adherence to exercise training is low among DM patients (Shultz et al. 2001; Banzer et al. 2004). The low adherence may be due to factors such as time, venue, transportation, weather, equipment, cost, physical capability, priority, and interest.

For individuals with diabetes, aerobic physical activity of moderate intensity has been recommended by American Diabetes Association (ADA, 2004), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK, 2004), American Obesity Association (AOA, 2005), and other organizations. As an alternative exercise that may be suitable for T2DM patients, Tai Chi is a moderateintensity exercise of aerobic nature with approximately 60–70% of heart rate maximum and 55% of oxygen uptake peak (Lai et al. 1993; Lan et al. 2001). Compared to other types of exercise, Tai Chi is an easy, low-cost exercise that is practiced barehanded without the need of any equipment, at anytime, anywhere, with a minimal requirement of space (as small as a living room), and at a very low risk of injury. Tai Chi features gentle, smooth, graceful, coordinated and flowing movements of

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different body parts accompanied with deep breathing and mental concentration to achieve not only improved fitness, health, and relaxation, but also mind-body harmony and a balanced personal sense of well being.

Stress adversely affects glycemic control in patients with T2DM, and stress reduction with relaxation techniques has been recommended in the management of hyperglycemia (Jaber et al. 1993; McGrady and Horner, 1999). Van Rooijen et al. (2004) reported that relaxation reduced HbA1c in T2DM patients to a greater extent than aerobic exercise intervention. In another study, significantly lower fasting plasma glucose in subjects with hyperglycemia was observed after an 8-day lifestyle modification program featuring yoga postures, breathing, and relaxation exercise (Bijlani et al. 2005). To achieve relaxation, the American Diabetes Association (ADA, 2006) recommends the following techniques: (i) deep breathing, (ii) progressive relaxation therapy featuring alternative tensing and relaxing muscles, (iii) exercise involving circling movements, and (iv) replacement of negative thoughts with positive ones. Among different types of exercise, Tai Chi is a unique mind-body exercise that includes all of the above relaxation techniques, and may offer benefits of combined physical exercise and stress reduction that no other exercise can. However, no study has been reported on the possible beneficial effects of Tai Chi on T2DM management. There is only one published clinical study on Tai Chi and glycemic control (Thomas et al. 2005). However, this study used healthy (non-diabetic) elderly, and showed that Tai Chi had no significant effect on glycemic and insulin sensitivity indices. The significance of such a result is questionable since in non-diabetic individuals, there was no room for improvement of glycemic and insulin sensitivity indices (ceiling effect). Such a result does not address whether or not Tai Chi can benefit glycemic control in T2DM patients. The present study is the first clinical feasibility study investigating the effects of Tai Chi on T2DM patients. Such effects were investigated through physiological glycemic measures including HbA1c and fasting blood glucose level. In addition, in order to evaluate the effect of Tai Chi on stress reduction and relaxation (psychosocial variables), the Diabetes-39 Quality of Life questionnaires, Exercise Self-Efficacy, and semi-structured interview were implemented in this study.

## **Patients and Methods**

## Experimental design

This feasibility study was designed to evaluate accrual rate, retention and compliance, adverse events, delivery of the Tai Chi intervention, and appropriateness of inclusion/exclusion criteria. It was a pretest-posttest clinical trial involving a total of 25 T2DM subjects, 20-70 years of age, diagnosed with T2DM for less than 10 years, to receive group Tai Chi exercise training for 12 weeks. The primary outcome measures (physiological variables) were HbA1c and fasting blood glucose levels, and the secondary outcome measures (psychosocial variables) were Diabetes-39 Quality of Life, and Exercise Self-Efficacy. In addition, a semi-structured qualitative evaluation was also implemented. HbA1c, Diabetes-39 Quality of Life, and Exercise Self-Efficacy outcome measures were obtained at baseline and after 12 weeks of intervention. Fasting blood glucose levels were obtained at baseline, 3, 6, 9, and 12 weeks. In addition, a semi-structured qualitative evaluation was conducted after 12 weeks.

### Subject recruitment

Subjects 20 to 70 years of age were recruited through local TV and radio announcements, and flyers. All potential subjects signed the Informed Consent Form approved by the local Institutional Review Board before the inception of any study procedure. To be included, a subject was required to have a documented duration of T2DM diagnosis for less than 10 years, a baseline HbA1c between 7.1 and 12.0%, ambulatory capability, and ability to stand for at least 15 minutes. Subjects with type 1 DM, documented history of significant diabetic neuropathy, performing Tai Chi regularly during the past 2 months, regularly performing exercise for more than 2 hours weekly, currently taking medications that may alter glycemic control (betablockers, oral corticosteroids, hydrochlorothiazide, niacin or nicotinic acid derivative) were excluded. Before the exercise program, in order to minimize risk, each subject underwent a detailed medical evaluation to carefully screen for the presence of macro- and microvascular complications that may be worsened by the exercise program. A careful medical history and physical examination was also performed focusing on the symptoms and signs of disease affecting the heart and blood vessels, eyes,

kidneys, feet, and nervous system. All individuals were screened thoroughly for any underlying complications of muscles, ligaments, bones, and joints before beginning the exercise program, as recommended by American Diabetes Association (ADA, 2004).

### Tai Chi intervention

Subjects attended two 60-minute instructed Tai Chi practice sessions each week for 12 weeks. Each session consisted of 10 minutes of warm-up exercise, 40 minutes of Tai Chi, and 10 minutes of cool-down exercise. The warm-up featured exercise of major joints and muscle groups at a low-intensity level to prepare the skeletal muscles, heart, and lungs for a progressive increase in exercise intensity, following the recommendation of American Diabetes Association (ADA, 2004). After warm-up, subjects were taught by an experienced instructor to practice the 24-form simplified Yang-style Tai Chi (Liang et al. 1996; Drewe, 2002), the most popular Tai Chi routine among dozens practiced worldwide, during each session. In addition to the gentle, coordinated and flowing movements of different body parts, relaxation and deep breathing were emphasized during the exercise practice. The Tai Chi training was followed by a cool-down exercise structured similar to the warm-up, to gradually bring the heart rate down to its pre-exercise level (ADA, 2004).

Since Tai Chi exercise involves significant footwork, participants were advised to take precautionary measures to prevent blisters and keep the feet dry in order to minimize trauma to the feet, as recommended by American Diabetes Association (ADA, 2004). Participants were also reminded to drink enough water before, during, and after exercise, as dehydration can affect blood glucose levels and heart function adversely. The gym was air-conditioned to avoid dehydration due to excess heat. Precautionary measures were also taken, such as eating a snack before exercise, to prevent hypoglycemia due to exercise. Participants were instructed to notice and report symptoms such as hunger, nervousness, shakiness, or sweating. Glucose tablets, fruit juice, regular soft drink were prepared to raise blood glucose if needed.

Attendance was recorded for each participant, and compliance was defined as the number of sessions completed divided by the total number of sessions prescribed. Subjects were asked to maintain their regular diet, medication, normal daily activities and lifestyle throughout the study.

## Primary outcome measures (physiological variables)

HbA1c analysis was performed using a fingerstick blood sample and was calculated by the DCA 2000 Analyzer (DCA 2000 Plus, Bayer Corp., U.S.A.). HbA1c is an index of metabolic control for the preceding 10–12 weeks secondary to the slow irreversible reaction between haemoglobin molecules of red blood cells and glucose. Fasting blood glucose level was measured by subjects at home using glucometer (Ascensia Elite XL, Bayer Corp.), after subjects received training from a Certified Diabetes Educator on the appropriate use of glucometers provided by the study. Subjects were asked to take and log fasting (no less than 8 hours) blood glucose readings at home for three consecutive days, and the average data of the three readings were used.

# Secondary outcome measures (psychosocial variables)

Diabetes Quality of Life Questionnaire (Diabetes-39), a 39-item self-report instrument, covers 5 domains including energy and mobility (15 items), diabetes control (12 items), anxiety and worry (4 items), social and peer burden (5 items), and sexual functioning (3 items) (Boyer and Earp, 1997). Each item had 7-point visual analogue scale (from 1 =not affected, to 7 = extremely affected). Each domain was derived from the items under the same domain and linearly transformed to 0-100 scales from least [0] to maximum [100] negative impact on quality of life. A higher score of each domain hence reflects worse quality of life. The scales relate well to general quality of life and distinguish well among individuals on the basis of disease severity, type and age. High internal consistency (alpha range 0.8–0.9), demonstration of construct validity and good reliability of Diabetes-39 have been reported (Boyer and Earp, 1997).

Self efficacy is a phenomenon that has been identified as a strong determinant of health behaviors, and numerous studies have been undertaken to positively determine its role as potent mediating variable in shaping behavioral outcomes

#### Table 1. Physical exercise self-efficacy scale.

Please answer the following question regarding your ability to participate in the Tai Chi exercise program by checking the response that best applies to you:

1 very unsure	2 rather unsure	3 rather sure	4 very sure
"How sure are you that you could ov the Tai-Chi exercises?"	ercome the following barriers	in performing	
I can manage to perform my Tai Chi	exercises		
aeven when I have worries and 1 very unsure;	problems. 2 rather unsure;	3 rather sure;	4 very sure
<ul> <li>beven if I feel depressed.</li> <li>1 very unsure;</li> </ul>	2 rather unsure;	3 rather sure;	4 very sure
<ul><li>c even when I feel tense.</li><li>1 very unsure;</li></ul>	2 rather unsure;	3 rather sure;	4 very sure
<ul> <li>deven when I am tired.</li> <li>1 very unsure;</li> </ul>	2 rather unsure;	3 rather sure;	4 very sure
<ul> <li>eeven when I am busy.</li> <li>1 very unsure;</li> </ul>	2 rather unsure;	3 rather sure;	4 very sure

(Maibach et al. 1991; Schwarzer, 1995). It has been posited that self efficacy exerts the single most significant effect on health behavior, influencing the appraisal of one's personal resources and contributing to the formation of the intention to act. In this study, the role of self-efficacy in determining the ability of subjects with diabetes to perform Tai Chi exercises successfully, and to maintain a Tai Chi exercise regimen during the study period was investigated via a modified Exercise Self-Efficacy Questionnaires (see Table 1) (Bandura, 1977; Schwarzer, 1992; Bandura, 2001). Exercise Self-Efficacy Ouestionnaires were administered at baseline and 12 weeks. This 5-item instrument included questions about how sure the subject could practice exercise when they were busy, tired, feeling tense, depressed, or having worries and problems. With score ranging from 1 (very unsure) to 4 (very sure), a higher score reflects more self-efficacy.

### Semi-structured interview

A semi-structured interview was also conducted with every participant at the end of the study concerning the present Tai Chi program. Such interview consisted of only open-ended questions as listed in Table 2, and was conducted to gather in-depth response regarding participants' experience related to Tai Chi and the effectiveness of the intervention program.

## **Statistical Methods**

### Sample size calculation

Assuming a mean group baseline HbA1c of 8.5% with SD of 1.0%, a 0.7% reduction in HbA1c, and a within-subject correlation (r) of 0.5, a sample of n = 18 would yield a power of 0.8 for a paired t-test at  $\alpha = 0.05$ , two-tailed. Based on an estimated attrition rate of 30%, 25 participants were required at the inception of the study.

### Data analysis

A series of paired *t*-test was conducted to compare pre- and post-test measures of HbA1c, Diabetes-39 Quality of Life, and Exercise Self-Efficacy. Individual growth curves were generated to examine possible systematic patterns of change in fasting blood glucose levels during the study period. Content analysis was performed on the qualitative data obtained from the semi-structured interviews.

## Results

### **Baseline characteristics**

Table 3 listed baseline characteristics of subjects. Twenty-five subjects participated in the study (8 males, 17 females), with a mean age of 53.3 years

Qualitative Responses	Frequency	%
Best experience related to Tai Chi?		
Relaxing/stress release	9	69
Energy increase	9	69
Lowered blood sugar level	7	54
Feeling better in general	3 3	23
Easy form of exercise	3	23
Sleep better	1	8
Worst experience related to Tai Chi?		
Discomfort/back pain/feet hurt	4	31
Blood sugar went up	1	8
Boring	1	8
Things that made it easy for continuous participation i	n the exercise program?	?
Instructor's modeling and verbal persuasion	5	39
Class time	4	31
Class location	4	31
Difficulties in continuous participation in the exercise	program?	
Class time	7	54
Class location	3	24
Transportation	1	8
Intention to exercise Tai Chi regularly from now on?		
Will continue on my own	7	54
Will continue with a tape	3	24
Not plan to exercise Tai Chi any more	1	8

Table 2. Results of qualitative analysis based on semi-structured interview (n = 13).

(SD = 9.5 years), an average BMI of 35.7 (SD = 7.7), and an average of 8.4 years of diagnosis of T2DM (SD = 7.2 years). Most participants were under more than one medication treatment during the current study [no medication (n = 3), 1 medication (n = 3), 2 medications (n = 7), 3 medications (n = 6), 4 medications (n = 5), 5 medications (n = 1)], for the control of glucose, insulin, cholesterol, blood pressure, depression, thyroid, or stomach acid (Table 3). Subjects reported no change in medications during the study period.

#### Attrition and Compliance

Only 13 of the 25 subjects completed the study (48% attrition rate). Reported reasons of dropout included loss of interest, time conflict, lack of transportation, and sicknesses unrelated to intervention. The average compliance rate of subjects who completed the study was 87%, ranging from 78 to 96%. There was no significant difference in baseline HbA1c level, blood glucose level, diabetes history, or age between subjects who dropped out and those who completed the study. Sporadic complaints of minor muscle soreness and foot and knee pain were made mainly during the first few

days of the intervention. No other adverse effect associated with the practice of Tai Chi was reported by the participants.

## Primary outcome measures (physiological variables)

The current results showed no significant change in HbA1c level in subjects who completed the study, although there seemed to be a trend of lowered HbA1c from a pre-test mean of 9.1% (SD = 1.4%) to a post-test mean of 8.1% (SD = 2.0%), a 1.0% net decrease, or 11% relative decrease of baseline (P = 0.104). Figure 1 shows the HbA1c data for each subject at baseline and 12 weeks. The individual growth curves of fasting blood glucose level shown in Figure 2 also revealed no systematic patterns of change.

## Secondary outcome measures (psychosocial variables)

Results of Diabetes-39 Questionnaires in Table 4 suggested that Tai Chi exercise did not significantly affect quality of life on any scale including energy and mobility, diabetes control, anxiety and worry,

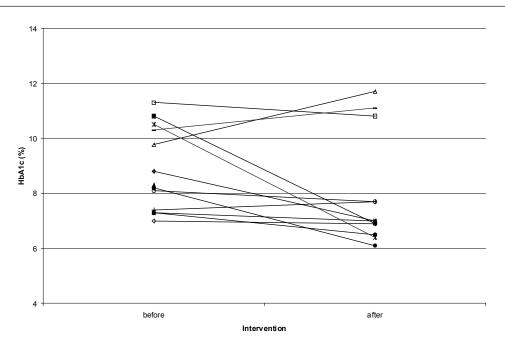


Figure 1. Effect of Tai Chi on HbA1c. Data of each subject at baseline (before) and 12 weeks (after) the Tai Chi intervention (n = 13).

social and peer burden, and sexual functioning. Similarly, no significant change in Exercise Self-Efficacy was observed (Table 4).

#### Semi-structured interview outcomes

Analysis of subjects' qualitative response is exhibited in Table 2 which summarizes the proportion of each theme being mentioned by the 13 subjects interviewed. The qualitative analysis revealed best experience about Tai Chi exercise, including relaxing and stress release, energy increase, lowered blood sugar level based on daily glucose log at home, feeling better, easy form of exercise, and better sleep. The worst experience included

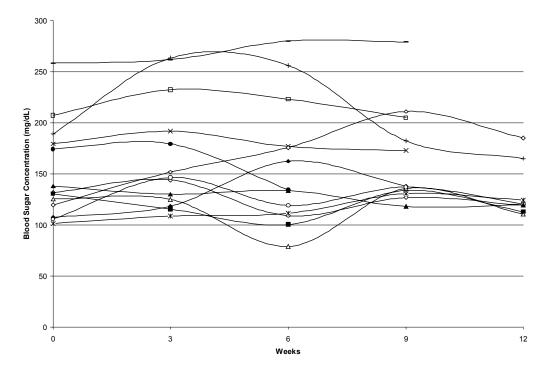


Figure 2. Effect of Tai Chi on fasting blood glucose. Data of individual subject at baseline (Wk 0), 3, 6, 9, and 12 weeks (n = 13).

Table 3. Baseline characteristics.

Characteristic	n = 25
Age, years, mean ± SD	53.3 ± 9.5
<b>Sex</b> , n (%)	
Male	8 (32%)
Female	17 (68%)
Weight, kg, mean ± SD	94.9 ± 22.3
Height, m, mean ± SD	1.6 ± 0.1
Body Mass Index (BMI), kg/m2, mean ± SD	35.7 ± 7.7
Years diagnosed with Type 2 DM, yr, mean ± SD	8.4 ± 7.2
HbA1c, %, mean ± SD	8.13 ± 1.91
General health condition (self response)	
Satisfactory, n (%)	15 (60%)
Good, n (%)	6 (24%)
Not good, n (%)	3 (12%)
Don't know, n (%)	1 (4%)
Other medical history	
Smoking	4 (16%)
Hypertension	3 (12%)
Coronary artery disease	2 (8%)
Heart value surgery	1 (4%)
Stroke	2 (8%)
Heart bypass surgery	1 (4%)
Allergies	8 (32%)
Significant nerve damage or loss of feeling in feet	3 (12%)
Medication, (n/total n) (%)	
Glucose	22/25 (88%)
Insulin	7/25 (28%)
Cholesterol	10/25 (40%)
Blood pressure	9/25 (36%)
Depression	6/25 (24%)
Thyroid	2/25 (8%)
Stomach acid	3/25 (12%)

SD = standard deviation.

feeling discomfort, back pain and feet hurt, increased blood sugar level, and boring. The factors that made it easy for the subjects to continuously participate in Tai Chi exercise included instructor's modeling and verbal persuasion, class time, and class location, while the factors such as class time, class location, and transportation made it difficult. More than 80% of the subjects expressed willing to continue Tai Chi exercise regularly, either on their own or following a tape.

#### Discussion

The present study showed that after 12 weeks of Tai Chi exercise, most (70%) subjects experienced

a decrease in HbA1c level, ranging from 0.3% to 4.1%. Only 30% subjects exhibited an increase in HbA1c level, ranging from 0.2 to 1.9%. Although we did not observe a statistically significant difference, due to a small sample size and a large standard deviation, the average decrease of 1.0% in HbA1c level or 11% decrease relative to baseline was comparable with decreases 10–20% of baseline reported in the literature using different physical activity regimens (ADA, 2004). Such decrease was also considered clinically significant as 0.66% of reduction in HbA1c level as a result of exercise training would be expected to significantly reduce the risk of diabetic complication in

	Before Tai Chi	After Tai Chi	<i>P</i> -value <sup>†</sup>
Energy and mobility	30.6 ± 15.5	30.8 ± 15.9	0.97
Diabetes control	44.0 ± 25.3	40.3 ± 17.2	0.56
Anxiety and worry	46.3 ± 25.7	40.1 ± 26.3	0.53
Social and peer burden	33.2 ± 27.2	24.0 ± 16.8	0.27
Sexual function	20.0 ± 18.0	24.8 ± 17.9	0.45

\*Values are expressed as the mean  $\pm$  standard deviation (SD), n = 13. Score from 0 (least negative on quality of life) to 100 (maximum negative impact on quality of life).

<sup>†</sup>Data was analyzed by paired *t* test.

T2DM patients (Boulé et al. 2006). Future study with a large sample size is needed to confirm Tai Chi's effect on lowering HbA1c in T2DM with clinical significance.

During the course of the intervention, a number of subjects reported lower glucometer readings taken at home within two or three days immediately after each Tai Chi session, followed by a regression back to the original higher value before the next Tai Chi session. In the present study, subjects performed Tai Chi exercise twice a week, and there was a break of 3 or 4 days between exercise sessions. Such a long break of no exercise may reduce the response of insulin sensitivity owing to Tai Chi, and resulting in no change in blood sugar level. This is supported by Sato et al. (2003) that improved insulin sensitivity due to exercise decreased within 3 days after exercise and was no longer apparent after one week. Deen (2004) also reported that the impact of exercise on insulin sensitivity was evident for 24 to 48 hours and disappeared within three to five days. In the present study, the short-term change of blood sugar level right after Tai Chi training was apparently not reflected by the HbA1c or fasting blood glucose outcome measure. Beneficial effect of Tai Chi exercise might be better manifested through practice at a higher frequency (every other day or even everyday), so that the benefits could be maintained until the next exercise, and this is worthy of investigating in a future study.

There are some limitations in this feasibility study. This study involved a small sample size and no control for comparison. The study was powered to detect a clinically meaningful decrease in HbA1c assuming an attrition rate of 30% over the 12-week study period. However, a 48% attrition rate significantly limited the potential to identify any possible effect of Tai Chi on glycemic control. The current results showed no significant change in HbA1c level of those completed study, although there seemed to be a trend of lowered HbA1c from pre-intervention mean to post-intervention mean. Drop-outs were not included in the above analysis. Cohen's d (effect size) of the test was 0.56. With this effect size, N of 13 yields a power of 0.44 for the paired t-test performed at  $\alpha = 0.05$ , two-tailed. The rather high attrition rate observed in this study might be due to the following reasons: (1) As part of the recruitment strategy, we advertised and offered each participant a free glucometer and test strips once they passed screening. Glucometer was in fact necessary for a subject to measure fasting blood glucose at home as an outcome measure. Some of the subjects might

	Before Tai Chi	After Tai Chi	<i>P</i> -value <sup>†</sup>
I can manage to perform my Tai Chi exercise			
a even when I have worries and problems	$3.2 \pm 0.6$	$3.4 \pm 0.5$	0.48
b even if I feel depressed	$3.3 \pm 0.6$	$3.4 \pm 0.5$	0.73
c even when I feel tense	$3.4 \pm 0.5$	$3.5 \pm 0.5$	0.70
d even when I am tired	$3.2 \pm 0.5$	$3.3 \pm 0.5$	0.45
e even when I am busy	$3.2 \pm 0.6$	$3.2 \pm 0.6$	1.00

 Table 5. Results of self-efficacy evaluation.\*

\*Values are expressed as the mean ± standard deviation (SD), n = 13. Score from 1 (very unsure) to 4 (very sure). <sup>†</sup>Data was analyzed by paired *t* test. be more interested in such a free gift than Tai Chi itself, and quitted soon after screening. (2) During the current study, we had to change the Tai Chi exercise venue once because the original venue had to go through remodeling. The new venue we could find was the gym of an elementary school located in a district of different social economic level and crime rate in the city. This unexpected transition might have negatively affected subjects' adherence to the intervention program. (3) We lost more subjects after the transition from Central Daylight Time to Central Standard Time in October, as it became dark earlier (our exercise session was from 5:30 to 6:30 p.m.). The adherence could have been better had we been able to avoid these incidents. Based on the current qualitative analysis, subjects reported class time, class location, and transportation as difficulties in continuous participation in Tai Chi program. Relevant strategies should be developed to improve adherence in future studies. To further improve adherence, future studies may consider using combined group and home exercise program. Studies using an initial period of supervision, followed by relatively informal home physical activity programs with regular, frequent follow-up assessments, had the best adherence in this population (ADA, 2004).

In conclusion, the current results showed no significant effect of Tai Chi on HbA1c, fasting blood glucose, Diabetes-39 Quality of Life, or Exercise Self-Efficacy, although there seemed to be a trend of lowered HbA1c. Analysis of subjects' qualitative response suggested a positive experience for those who completed the intervention. Future studies should use a larger number of subjects with improved retention to verify Tai Chi's possible effect on HbA1c and those advantages reported in the present qualitative analysis.

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