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Impact of modified glucose target and exercise interventions on vascular risk factors

Kaberi Dasgupta *, Steven A. Grover, Deborah Da Costa, Ilka Lowensteyn, Jean-François Yale, Elham Rahme

McGill University, Montreal, Canada

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Abstract

Potent glucose-lowering medications other than metformin may impede weight loss in type 2 diabetes (T2D). Supervised exercise programs improve glycemic control without significantly enhancing weight loss; their impact on fitness and blood pressure in T2D remains unclear. In this pilot study, 42 type 2 diabetes patients were randomized to (i) liberalized (10 mmol/l) OR strict (7 mol/l) preprandial glucose thresholds for adjustment of medication other than metformin and (ii) dietary counseling with OR without supervised exercise (2 × 2 factorial design). Weight (−1.2% versus −0.3%, $p = 0.38$) and hemoglobin A1C changes (−0.8% versus 0%, $p = 0.37$) were similar for glucose threshold-defined groups. Dietary counseling with supervised exercise participants had greater improvement in mean arterial pressure than those not randomized to an exercise program (−3.3% versus 1.1%, $p = 0.02$). Overall weight (−1.5% versus 0%, $p = 0.06$) and fitness changes (5.4% versus 1.5%, $p = 0.18$) were not significantly different between these groups, but weight (−1.6% versus 0%, $p = 0.03$) and fitness changes (21.3% versus 1.5%, $p = 0.03$) were significantly greater among those who attended ≥75% of exercise classes. Liberalizing preprandial thresholds neither enhances weight loss nor compromises hemoglobin A1C. T2D patients who consistently participate in supervised exercise programs may experience modest weight loss and significant improvements in fitness and blood pressure.

Keywords: Supervised exercise; Type 2 diabetes; Weight; Fitness; Blood pressure

1. Introduction

Among type 2 diabetes (T2D) patients, those who intentionally lose weight have a 28% lower cardiovascular mortality at 12 years follow-up than those who do not lose weight [1]. However, achieving weight loss is particularly challenging for T2D patients. In a meta-analysis of supervised exercise trials in T2D, dietary counseling ± exercise resulted in net weight loss of less than 4% [2], compared to an 11% weight loss reported in a meta-analysis of weight loss studies among overweight patients without T2D [3]. T2D patients experienced less weight loss than their overweight spouses in a trial assessing an identical weight control program in both groups [4].

Tight glycemic control reduces rates of diabetes-associated complications [5], but is associated with additional weight gain. During the United Kingdom Prospective Diabetes Study (UKPDS), tight control with insulin/secretagogues (preprandial glucose target 6 mmol/l versus 15 mmol/l) was associated with a 3–

Abbreviations: BMI, body mass index; EST, exercise stress test; HDL, high-density lipoprotein; IQR, interquartile range; MAP, mean arterial blood pressure; METS, metabolic equivalents; T2D, type 2 diabetes

* Corresponding author at: Clinical Epidemiology; Montreal General Hospital, 1650 Cedar Avenue, L10-425, Montreal, Que., Canada H3G 1A4. Tel.: +1 514 934 1934x44715; fax: +1 514 934 8293.
E-mail address: Kaberi.Dasgupta@mcgill.ca (K. Dasgupta).

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4 kg additional weight gain. Only metformin-treated patients avoided such a weight increase [5]. T2D patients may limit physical activity because of concerns about exercise-associated risks such as hypoglycemia and ischemia. Exercise initiation in a supervised setting may simultaneously optimize intensity and safety, and significantly improve glycemic control [2]. Less well defined is the impact of supervised exercise on fitness and blood pressure, both important in the development of cardiovascular disease [5–9].

To facilitate weight loss, improve glycemic control, enhance fitness, and lower blood pressure, we formulated the following three-point intervention: (i) dietary counseling with supervised exercise, (ii) metformin at maximum tolerated doses and (iii) liberalized preprandial glucose threshold for adjustment of other medications to permit reduced use of these medications. This pilot study was conducted to assess the feasibility of such an approach. We report on (i) the impact of a liberalized threshold on hemoglobin A1C levels and (ii) the relationship between changes in fitness to changes in weight and blood pressure. We also provide estimates of the magnitude of change in weight, fitness, and blood pressure levels associated with study interventions.

2. Patients and methods

2.1. Study design

This pilot trial (2×2 factorial design) was conducted in Montreal, Que., Canada. Following completion of recruitment, participants were randomized to (i) dietary counseling with OR without supervised exercise and (ii) liberalized OR strict preprandial glucose thresholds for adjustment of glucose-lowering medication other than metformin. Procedures were approved by the Institutional Review Board of McGill University. Written informed consent was obtained.

2.2. Participants

Eligibility requirements included age 30–70 years, physician T2D diagnosis, body mass index (BMI) $\geq$28 kg/m^2, and $\geq$5 metabolic equivalents (METS) during a symptom-limited maximal baseline exercise stress test. Exclusion criteria included insulin use, foot ulcers, pregnancy, lactation, untreated diabetic retinopathy, or conditions/medications that could affect weight (e.g. cirrhosis, corticosteroids). Pre-menopausal women were asked to use a reliable method of contraception. Recruitment was conducted between May and September 2003 largely through out-patient clinics (diabetes, internal, family medicine) affiliated with McGill University.

2.3. Interventions

Between September 2003 and March 2004, interventions were conducted through the Cardiovascular Health Improvement Program (CHIP), McGill University's cardiac rehabilitation centre.

2.3.1. Dietary counseling

A registered dietitian provided individualized dietary counseling based on Canadian Diabetes Association guidelines [10] (six sessions over 24 weeks, 145 min total counseling time).

2.3.2. Supervised exercise

Group sessions (6–10 per group) supervised by an exercise physiologist involved 45 min of cardiovascular exercise (treadmill, cycling, cross-trainer) and 15 min of stretching. Heart rate was monitored (polar heart rate monitors) and maintained at 65–85% of the maximum rate achieved during baseline exercise stress testing (see Section 2.2). Supervised sessions commenced at a frequency of three times per week, with one supervised session discontinued at 8-week intervals. Participants were encouraged to continue to exercise at least 135 min per week for the entire 24-week intervention, and were asked to exercise without supervision as the supervised sessions were discontinued. The rationale for this strategy was to gradually accustom participants to exercise independently, using the training that they had acquired from the exercise physiologists. Those randomized to dietary counseling alone were offered an identical supervised exercise program following outcome assessments at 24 weeks.

2.3.3. Adjustment of glucose-lowering agents

Participants performed two preprandial glucose measures daily. Medications were adjusted at 2–4-week intervals (frequency of follow-up visits). Metformin was increased as tolerated to a maximum total daily dose of 2550 mg [11]. Other agents were adjusted at average preprandial glucose values of $\geq$7 or $\geq$10 mmol/l, dictated by randomization. The 10 mmol/l value, the mean renal threshold for glucose excretion in T2D [12], was selected in order to limit medication use without inducing osmotic diuresis. Medications were added according to the following sequence and discontinued in the reverse order: sulfonylurea, thiazolodinedione, and insulin. At each visit, a urine dipstick chemical analysis was performed to assess for glycosuria.

2.4. Study measures

Anthropomorphic assessments were conducted by a nurse blinded to treatment assignment. Weight in light clothes was determined using a standing beam balance scale (Detecto, Dufort and Lavigne). Waist circumference was measured in the standing position, midway between the lower ribs and the iliac crest [13]. Blood pressure was determined in the seated position with a mercury sphygmomanometer, following a 5 min rest period. Mean arterial blood pressure was calculated as follows: [(2/3) × systolic blood pressure + (1/3) × diastolic blood pressure] [14]. Hemoglobin A1C was assessed using a Hitachi 717 analyzer (Roche Diagnostics, Canada) on a venous blood sample. A maximal exercise stress test (EST) was performed using the Bruce protocol [15]. Study physicians could employ modified Bruce and Ramp protocols at their discretion, provided that the same protocol was employed at both baseline and 24-week assessments.

3. Statistical analyses

3.1. Between-group comparisons

Parameters compared included changes from baseline levels of weight (primary outcome), waist circumference, and hemoglobin A1C. Absolute change was divided by corresponding baseline value and multiplied by 100%. Additional comparisons for the dietary counseling with versus without supervised exercise groups were changes in fitness and mean arterial blood pressure. Exercise stress test duration was the measure of fitness employed. Additional comparisons for groups defined by preprandial glucose thresholds were 90-day average preprandial glucose levels (latter 90 days of intervention period), frequency of glycosuria, and proportion with a low-recorded glucose value (<4 mmol/l at least once).

Missing values were replaced by most recent values (12 weeks/baseline). Because of the small number of participants in each arm [16], nonparametric methods (median, interquartile range, median test) were employed. The median test examines the null hypothesis that there is no difference in median values between the populations from which two samples are drawn. Within each sample, the numbers of values above and below the combined sample median are determined and a 2 × 2 table is created. Pearson's χ^2-test is used to determine whether the observed and expected frequencies in each group differ [16]. In a post hoc analysis, baseline characteristics and outcomes of high (≥75%) and low frequency (<75%) exercise class attendees were compared with the dietary counseling alone group.

3.2. Linear regression analyses

Parametric methods were permitted by the larger sample size achieved by combining outcomes from intervention arms. Through linear regression models, we assessed the relationships between 90-day preprandial glucose value and hemoglobin A1C and between change in fitness and changes in each of the following: weight, mean arterial pressure, and hemoglobin A1C.

3.3. Sample size considerations

Using a t-test with a 0.025 two-sided significance level, we determined that a sample size of 21 per group

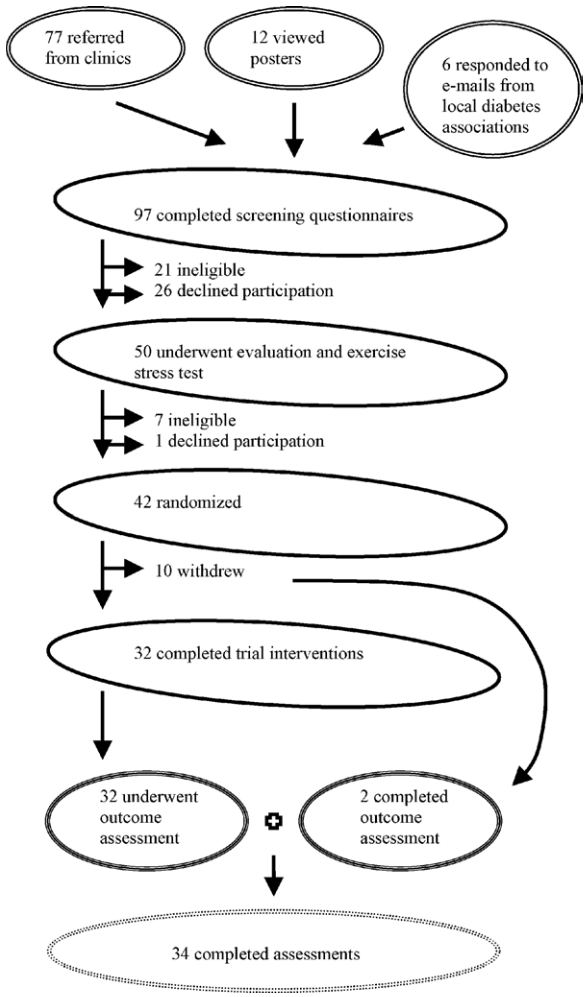

Fig. 1. Participant flow.

for each two-group comparison would have 80% power to detect a difference in weight change of 4.5%, assuming a common standard deviation of 4.5% [17].

4. Results

4.1. Participant flow

As indicated in Fig. 1, 97 individuals completed a screening questionnaire. The most frequent reason for nonparticipation was lack of time/interest (16 individuals). Fifty participants underwent a complete medical evaluation. Reasons for ineligibility identified included angina (one candidate) or ≤5 METS (three candidates) during stress testing, knee pain (osteoarthritis) (one candidate), and BMI <28 kg/m^2 (one candidate).

A total of 42 individuals were randomized (21 men and 21 women). A total of 10 individuals discontinued interventions, but among these, 2 returned for final assessment. One of these 2 had a previous history of cardiovascular disease (7 mmol/l threshold; diet with supervised exercise) and was hospitalized for an acute coronary syndrome. The event was not attributed to study procedures. Rates of discontinuation of interventions were equally distributed between the dietary counseling with versus without supervised exercise intervention arms and did not differ significantly between 10 and 7 mmol/l arms (13%, 3/22 versus 25%, 5/20, $p = 0.7$). The primary reason reported for discontinuing study interventions was time constraint because of work or family responsibilities.

4.2. Baseline characteristics

There were no significant differences between groups (Tables 1 and 2). None of the participants had a history of diabetic retinopathy or neuropathy.

4.3. Exercise class attendance

Nine attended ≥75% of scheduled exercise sessions (85–100%) and 12 attended ≤75% (4–71%). Average

Table 1
Baseline characteristics: dietary counseling alone vs. dietary counseling with supervised exercise

	Dietary counseling alone, $N = 21$ [median (IQR[a]) or number (%)]	Dietary counseling with supervised exercise, $N = 21$ [median (IQR[a]) or number (%)]
Demographic characteristics		
Age (years)	49 (46, 55)	54 (47, 58)
Women	12 (57)	9 (43)
Professional	8 (38)	6 (29)
Technician	5 (23)	7 (33)
Other	8 (38)	8 (38)
Body mass and fitness		
BMI[b] (kg/m^2)	36.6 (31.6, 39.8)	36.4 (32.8, 41.8)
Waist circumference (cm)	114 (104, 121)	116 (111, 130)
Stress test duration (min)	7.3 (6.4, 9.3)	6.8 (6.3, 8.0)
Glycemic control		
Hemoglobin A1C	0.071 (0.063, 0.074)	0.072 (0.061, 0.077)
Metformin	16 (76)	17 (81)
Sulfonylurea	10 (48)	8 (38)
Thiazolodinedione	4 (19)	3 (14)
Diabetes duration (years)	3 (1, 5)	2 (1, 3.5)
Blood pressure		
Mean arterial (mmHg)	113 (106, 117)	118 (107, 123)
Systolic (mmHg)	130 (120, 130)	130 (120, 140)
Diastolic (mmHg)	80 (74, 90)	80 (80, 90)
Number of medications	1 (0, 1)	1 (0, 1)
Previous history of cardiovascular disease	2 (10)	2 (10)
Habits		
Current smokers	2 (10)	0 (0)
Alcohol use	11 (52)	12 (57)

[a] Interquartile range.
[b] Body mass index.

Table 2
Baseline characteristics by preprandial glucose threshold for adjustment of glucose-lowering medications other than metformin

	Preprandial capillary plasma glucose threshold	
	7 mmol/l, $N = 20$ [median (IQR[a]) or number (%)]	10 mmol/l, $N = 22$ [median (IQR[a]) or number (%)]
Demographic characteristics		
Age (years)	49 (46, 56.5)	53.5 (47, 59)
Women	11 (55)	10 (45)
Professional	4 (20)	10 (45)
Technician	8 (40)	4 (18)
Other	8 (40)	8 (36)
Body mass and fitness		
BMI[b] (kg/m^2)	35.6 (32.4, 41.4)	37.4 (31.0, 40.8)
Waist circumference (cm)	115 (107, 121)	115 (105, 128)
Stress test duration (min)	7.2 (6.4, 9.2)	7.3 (6.3, 8.5)
Glycemic control		
Hemoglobin A1C	7.0 (6.3, 7.4)	6.9 (6.1, 7.6)
Metformin	14 (70)	19 (86)
Sulfonylurea	7 (35)	11 (50)
Thiazolodinedione	3 (15)	4 (18)
Diabetes duration (years)	2 (1, 4)	3 (1.8, 5)
Previous history of cardiovascular disease	1 (5)	3 (14)
Habits		
Current smokers	1 (5)	1 (5)
Alcohol use	13 (65)	10 (45)

[a] Interquartile range.
[b] Body mass index.

attendance of exercise classes (48 sessions offered) was 64% overall and 72% after exclusion of 3 those who discontinued study interventions. Compared to the dietary counseling alone group, those with a high exercise session attendance were older (56 years versus 49 years, $p = 0.03$). Those with lower attendance tended to be more overweight (BMI 39.5 versus 36.6, $p = 0.06$).

4.4. Between-group comparisons

4.4.1. Dietary counseling alone versus with supervised exercise-overall

The dietary counseling with supervised exercise group lost somewhat more weight [−1.5% (IQR −2.0 to 1.5%) versus 0% (IQR −3.7 to 0.6%), $p = 0.06$], but waist circumference changes were similar between groups [−1.5% (IQR −2.5 to 0%) versus −1.2% (IQR −2.6 to 0%), $p = 0.38$]. Fitness change did not significantly differ between groups [5.4% (IQR 0–23.2%) versus 1.5% (IQR −1.7 to 10.4%), $p = 0.18$]. The dietary counseling with supervised exercise group had significantly greater improvement in blood pressure control [−3.3% (IQR −8.4 to 5.5%) versus 1.1% (IQR −9.1 to 6.5%), $p = 0.02$]. Change in hemoglobin A1C did not differ significantly between groups [−3.0% (IQR −9.2 to 1.7%) versus 0% (IQR −3.1 to 5.6%), $p = 0.22$]. The proportion of participants with at least one recorded low glucose level was somewhat higher in the diet and supervised exercise group [65%, 13/20 versus 35%, 7/20, $p = 0.06$].

4.4.2. Dietary counseling alone versus with supervised exercise-subgroup analyses

The magnitude of difference in blood pressure between diet and exercise versus diet alone groups was similar when the analysis was restricted to those without a change in number of antihypertensive agents, although both sample size ($n = 32$) and level of significance decreased ($p = 0.06$). High exercise class attendance was associated with significantly greater weight change [−1.6% (IQR −3.7 to −1.0%) versus 0%, $p = 0.03$] and improvements in fitness [21.3% (IQR 5.4–25.2%) versus 1.5%, $p = 0.03$] and mean arterial blood pressure [−3.3% (IQR −10.5 to −1.9%) versus 1.1%, $p = 0.02$] compared to dietary counseling alone. Change in hemoglobin A1C did not differ significantly between groups even when exercise class attendance

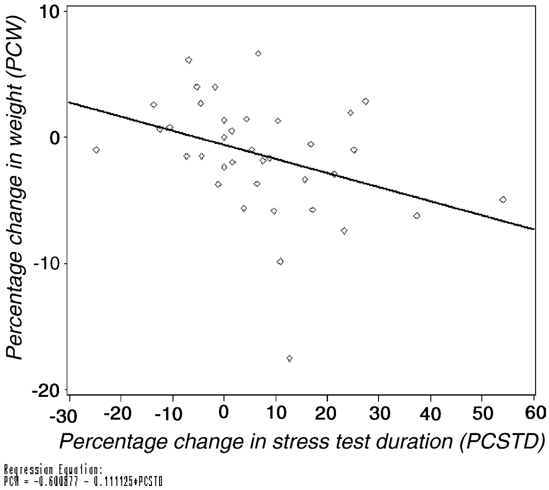

Fig. 2. Relationship between changes in fitness and weight.

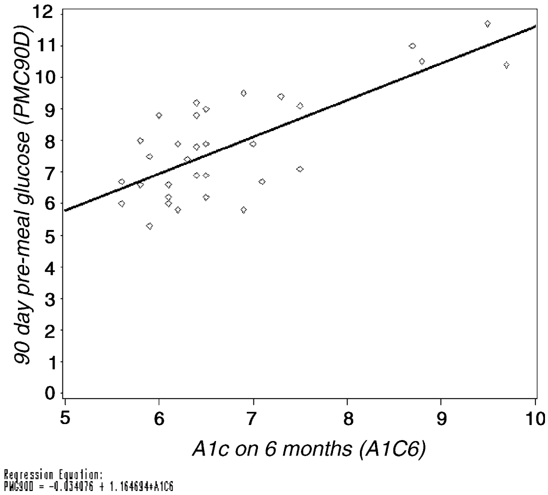

Fig. 4. Relationship between 90-day average preprandial capillary plasma glucose level and hemoglobin A1C at 24 weeks.

was considered [−8.6% (IQR −19 to 1.7%) versus 0%, $p = 0.12$].

4.4.3. Preprandial glucose thresholds for medication change

Median 90-day average preprandial glucose was significantly higher ($p = 0.01$) in the 10 mmol/l threshold arm (8.4 mmol/l, IQR 6.6–9.4 mmol/l) than the 7 mmol/l arm (6.9 mmol/l, IQR 6.6–7.5 mmol/l). Rates of glycosuria did not differ significantly [0% (IQR 0–14%) versus 6.2% (IQR 0–24%), $p = 0.28$]. Two participants in each group commenced metformin treatment. In the 10 mmol/l threshold group, two participants discontinued sulfonylurea and three discontinued thiazolodinedione medication. The proportion of participants with a low-recorded glucose value did not differ between groups [45% (10/22) versus 50% (10/20), $p = 0.50$]. There were no significant between-group differences in terms of changes in weight [−1.2% (IQR −3.7 to 2.0%) versus −0.3% (IQR −2.7 to 7.3%), $p = 0.38$], hemoglobin A1C [−0.8% (IQR −8.6 to 5.6%) versus 0% (IQR −11.7% to 3.7%), $p = 0.37$], or waist circumference [−1.3% (IQR −2.5 to 0%) versus −1.4% (IQR −3.1 to 0%), $p = 0.62$].

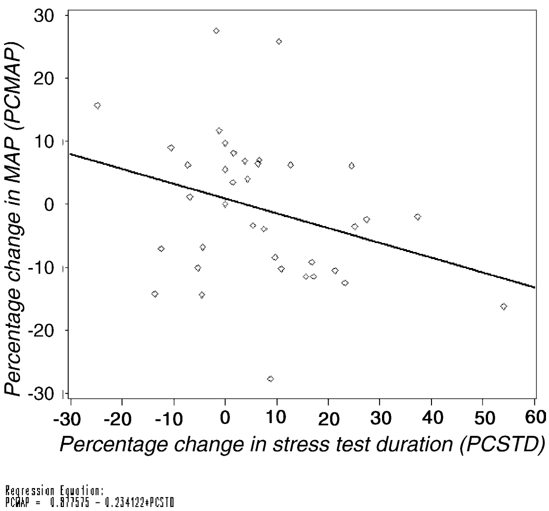

Fig. 3. Relationship between changes in fitness and mean arterial blood pressure.

4.5. Linear regression analyses

In separate linear regression models, a 10% increase in fitness was significantly associated with a 1% reduction in weight ($p = 0.05$) (Fig. 2) and a 2.3% reduction in mean arterial pressure ($p = 0.04$) (Fig. 3). There was no significant association between changes in fitness and hemoglobin A1C. There was a positive linear relationship between average 90-day preprandial capillary blood glucose and hemoglobin A1C level (Fig. 4). Each unit increment hemoglobin A1C corresponded to a 1.16 mmol/l increment in the average 90-day preprandial capillary blood glucose value ($p < 0.001$).

5. Discussion

Overall weight change was small during our 24-week pilot trial (<2%), but similar in magnitude to that experienced by T2D patients in other weight loss interventional studies [2]. The difference in weight change between dietary counseling with and without supervised exercise groups approached statistical significance but was small in magnitude (1.5%) [2]. The small weight change in all patients may have partly been attributable to the fact that the intervention period included the holiday season, a time of weight gain [19]. The weight change difference between differing preprandial threshold arms was smaller (0.9%) and nonsignificant. The low rate of hypoglycemia reported in our patients – and likely the consequent absence of any associated appetite stimulation – may have accounted for the absence of a significant difference in weight change between the two preprandial threshold arms. Most of our patients were receiving metformin only at baseline and would therefore be less likely to experience large excursions in blood glucose levels.

Change in hemoglobin A1C did not differ significantly between the dietary counseling with and without supervised exercise arms. This may be attributable to the high level of glycemic control at baseline (Table 1). There was no linear relationship between changes in fitness and hemoglobin A1C. A T2D supervised exercise trial meta-analysis similarly found neither exercise intensity nor volume to be associated with post-intervention hemoglobin A1C, although supervised exercise was associated with improvement in hemoglobin A1C levels [2].

In our study, the 10 mmol/l arm had significantly higher 90-day preprandial glucose levels and some reduction in glucose-lowering medication compared to the 7 mmol/l arm. Nonetheless, these groups did not differ significantly in terms of hemoglobin A1C change. This is consistent with the results of a single previous trial that examined the issue of preprandial glucose thresholds/targets. van der does et al. randomized T2D patients ($n = 176$) to targets of <6.5 mmol/l versus <8.5 mmol/l [18]. The <6.5 mmol/l group experienced more medication intensification but no greater improvement in hemoglobin A1C levels 1 year later. Preprandial glucose levels of <6 mmol/l are recommended by the International Diabetes Federation and levels of 5–7.2 mmol/l are supported by the American Diabetes Association. Our results suggest that a hemoglobin A1C level of 7% may be achieved with a 90-day preprandial glucose level of 8.1 mmol/l (Fig. 4). Further study examining this issue is warranted.

We found consistent attendance of a supervised exercise program to be associated with a statistically and clinically significant fitness improvement. Median improvement was 1.5% in the dietary counseling alone group, 5.4% overall in the dietary counseling with supervised exercise group, and 21.3% among those who participated in $\geq$75% supervised exercise sessions. Among men with T2D, Church and colleagues demonstrated a steep inverse gradient between fitness and mortality that was independent of BMI, glucose level, blood pressure, total cholesterol level, and history of smoking or cardiovascular disease [9].

In our pilot study, the dietary counseling with supervised exercise arm experienced significantly greater blood pressure improvement compared to the dietary counseling alone arm. This difference was likely driven by the fitness change among those with a high exercise class attendance. Improvements in fitness and blood pressure were linearly related (Fig. 3). One previous trial involving a structured exercise program (treadmills, stationery bicycles, rowing machines) also found exercise to be associated with a significant blood pressure lowering effect among T2D patients [8]. Two other trials did not find walking programs to be associated with a statistically significant blood pressure lowering effect in this population [6,7]. Exercising at a more intense level than walking may be necessary to lower blood pressure.

The occurrence of the holiday period (December/January) during our trial may have attenuated weight change. This period has been associated with weight increases in nondiabetic populations [19]. One previous study that achieved 7% weight loss among T2D patients incorporated cognitive behavioural therapy and incentive-based strategies (e.g. return of a deposit with consistent attendance) [4]. Budgetary constraints precluded use of such approaches during our pilot study. Our ability to identify significant between-group differences was clearly limited by sample size. It is important to note, however, that our study was designed to provide feasibility data. Nonetheless, some significant differences did emerge. Budgetary factors did not permit monitoring of activity/diet. However, self-report of food intake and physical activity is subject to inaccuracies [20]. Weight and fitness measures may be more reliable outcome measures [21].

In conclusion, results from this pilot study suggest that neither supervised exercise programs nor liberalization of preprandial glucose targets offer clinically significant reduction in weight among T2D patients. However, consistent participation in a program of supervised exercise offers clinically and statistically significant improvements in fitness and blood pressure control. Future research should focus on the identification of strategies to maximize exercise class attendance in order to realize these benefits. Our results also suggest that, in conjunction with maximal metformin dosing and dietary counseling, allowing higher capillary blood glucose thresholds may reduce the need for other medications without compromising glycemic control. A larger study is needed to further examine this possibility.

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