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The effect of a 6-month walking program on biochemical parameters in sedentary adults with type 2 diabetes mellitus

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ABSTRACT

This study assessed the effect of a 6-month walking program on biochemical parameters in patients with type-2 diabetes mellitus. A group of 40 sedentary patients with type-2 diabetes volunteered to participate in this study. Plasma glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, urea, creatinine, uric acid, C-reactive protein (CRP), and erythrocyte sedimentation rate were measured. Differences in outcome measures between pre- and post-intervention were assessed using paired t-test or Wilcoxon signed-rank test, with effect sizes interpreted separately for normally (μ^2: *small* 0.01–0.06, *moderate* 0.061–0.14, and *large* >0.14) and non-normally distributed data (r: *small* = 0.1–0.3, *moderate* = 0.3–0.5, and *large* >0.5). Significant ($p < 0.001$) *large* decrease between the initial and final measurements was observed for glucose (r = 0.62), total cholesterol ($\mu^2 = 0.88$), triglycerides (r = 0.62), LDL (r = 0.61), AST ($\mu^2 = 0.82$), ALT ($\mu^2 = 0.79$), gamma-glutamyl transferase ($\mu^2 = 0.79$), urea ($\mu^2 = 0.92$), creatinine (r = 0.62), uric acid (r = 0.62), CRP ($\mu^2 = 0.80$), and erythrocyte sedimentation rate ($\mu^2 = 0.58$). On the other hand, significant ($p < 0.001$) *large* increase between the initial and final measurements was observed for HDL (r = 0.62). Supervised 6-month aerobic walking program is an effective strategy in (1) reducing hyperglycemia; (2) increasing HDL and reducing LDL, and triglycerides; (3) reducing plasma biomarkers of liver dysfunction, kidney dysfunction, and inflammation in type-2 diabetic patients.

Keywords: exercise, glucose, lipid profile, biochemical parameters, type-2 diabetes mellitus, patients

Abbreviations:
ALT: alanine aminotransferase
AMPK: AMP-activated protein kinase
AST: aspartate aminotransferase
BMI: body mass index

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CRP: C-reactive protein
HbA1c: glycosylated haemoglobin A1c
HDL: high-density lipoprotein cholesterol
IL-10: interleukin-10
LDL: low-density lipoprotein cholesterol
TNF-a: tumor necrosis factor alpha

INTRODUCTION

Type-2 diabetes mellitus is a growing worldwide chronic disease characterized by chronic hyperglycemia with disturbance of carbohydrates, protein, and fat metabolism.[1] Specifically, the number of people with diabetes has risen from 108 million in 1980 to the current 463 million.[2] On a global scale, diabetes hits mainly middle-aged people between 40 and 59, which causes enormous economic and social implications, including direct medical costs, indirect costs associated with productivity loss or earnings, and premature mortality.[3] Parallel to an emerging epidemic and significant economic burden, much progress has been made in understanding the risk factors for diabetes mellitus over the past few decades. While diabetes might have a genetic background, the main etiological risk factors are overweight, obesity, and physical inactivity.[4]

Physical activity is widely recommended as an essential non-pharmacological therapeutic strategy for type-2 diabetes prevention and metabolic control.[1] Week doses of low- to moderate-intensity activity for 150 min has been recommended by the American College of Sports Medicine as the minimum amount of aerobic exercise required for good health in individuals with type-2 diabetes.[5] Considering the familiar pattern, walking is the most common, most accessible, safe, and convenient exercise type for individuals with type-2 diabetes. Recent clinical trials provide strong evidence for the value of aerobic exercise in reducing body weight[6] and abdominal visceral fat accumulation[7] with subsequent improvements in insulin sensitivity,[6] blood pressure,[6] lipid profile,[6,8] and glycemic control.[7,9]

In addition to abnormalities in lipid profile and glycemic control, type-2 diabetes mellitus patients are highly prone to abnormal liver biomarkers,[10,11] renal disease, and low-grade inflammation with increased C-reactive protein (CRP).[12,13] To date, inconsistent evidence has been reported regarding the effect of aerobic exercise on serum liver enzymes (alanine aminotransferase,[14-16] aspartate aminotransferase,[14-16] and gamma-glutamyl transferase[14-16]), renal function (creatinine[17] and uric acid[12,17]), and CRP[12] in patients with type-2 diabetes mellitus. Considering the collective evidence and the key role of lifestyle interventions in managing diabetes, there is a need for solid and detailed evidence of the effects of exercise on biochemical parameters, including glycemic control, lipid profile, renal function, liver function, and inflammation. Therefore, this study aimed to quantify the effects on biochemical parameters in subjects with type-2 diabetes after a 6-month period of low to moderate-intensity walking exercise.

METHODS

An observational study with a pre-post design was adopted, wherein each participant completed a 6-month supervised walking program.

Participants

A group of 40 (20 male and 20 female) sedentary patients (<3 days/week of physical exercise

lasting 30 minutes or longer)[18] with type-2 diabetes mellitus [age: 45 ± 14.4 yr, pre-intervention and post-intervention body mass index (BMI): 35.1 ±1.2 kg/m^2 and 29.6 ±1.4 kg/m^2] volunteered to participate in 6-month supervised progressive aerobic exercise program conducted outdoors on forest paths. All of them were Caucasian on combined oral antidiabetic and insulin therapy. The following inclusion criteria were applied: (1) patients with type-2 diabetes mellitus who meet one of the following criteria[19]: glycosylated hemoglobin (HbA1C) ≧6.5%, or fasting plasma glucose ≥7.0 mmol/L, or 2-h plasma glucose ≥11.1 mmol/L during an oral glucose tolerance test, or random plasma glucose ≥11.1 mmol/L; (2) 30–60 years of age; (3) not engaged in any exercise in the last five years. In addition, all participants were free from diabetic nephropathy, diabetic retinopathy, severe diabetic neuropathy, and severe cardiovascular and cerebrovascular diseases. After receiving a full explanation of the testing protocol, all participants provided informed consent and medical history forms before partaking in the study. Study procedures were approved by the Research Ethics Committee of the Faculty of Medical Sciences in accordance with the Helsinki Declaration.

Biochemical analysis

Blood samples (10 mL) were drawn from the antecubital vein with seated participants in the morning (7:00–9:00 h) after overnight fasting. Plasma glucose, triglyceride, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma-glutamyl transferase, urea, creatinine, uric acid, CRP, and erythrocyte sedimentation rate were analyzed using a biochemistry analyzer (Targa BT 2000 Biotecnica instruments S.p.A, Rome, Italy).

Intervention

All patients received standard diabetes care, including pharmacological treatment and dietary prescriptions individually planned to produce a mild hypocaloric diet (30 kcal per kg of ideal body weight per day), with the following energy distribution[14]: 35% protein, 25% lipids, and 40% carbohydrates. Exercise sessions were supervised by the investigator and performed four times per week with a gap of no more than two consecutive days. The exercise session consisted of a 5-minute warm-up protocol followed by the main walking phase (40–55 min) and ended with a 5-minute cool-down (final stretching for the quadriceps, hamstrings, ankle plantar flexors, chest, and elbow flexors and extensors muscles). During weeks 0–4, weeks 5–14, and weeks 15–24, the exercise volume and intensity was progressively increased (Table 1). Each participant self-

Table 1 Details of exercise program

Order	Content	Period	Duration	Intensity	Frequency
Warm-up	Stretching	1st–24th week	5 min		
Walking	Low intensity (Normal walking)	1st week	40 min	11–13 RPE or 55–64% HR_{max}	4 times/week
		2nd week	45 min		
		3rd week	50 min		
		4th week	55 min		
	Moderate intensity (Brisk walking)	5th–14th week	40 min	14–15 RPE or 65–75% HR_{max}	
		15th–24th week	50 min		
Cool down	Stretching	1st–24th week	5 min		

RPE: Rating of perceived exertion

controlled exercise intensity using Borg's 20-point Likert scale [light 11–13 AU (corresponding to 55–64% HR_{max}), moderate 14–15 AU (corresponding to 65–75% HR_{max})].[20] Exercise program was always conducted at a fixed intensity throughout the session. Borg's Category-Ratio scale was established as a reliable and valid indicator of exercise intensity.[21,22]

Statistical analysis

Using G*Power software (with a 2-tailed alpha value of 0.05, an effect size of 0.5, and power of 0.80), a sample size of 27 was estimated, supporting the present analyses (n = 40). Shapiro-Wilk tests revealed that glucose, creatinine, uric acid, HDL, triglycerides, and LDL were not normally distributed, while all remaining parameters were normally distributed. Differences in outcome measures between pre- and post-intervention were assessed using the Wilcoxon signed-rank test for non-normally distributed data and paired t-test for normally distributed data. All data are presented as means ± SD, and statistical significance was set at $p \leq 0.05$. Effect sizes were calculated and interpreted separately for normally (μ^2: *small* 0.01–0.06, *moderate* 0.061–0.14, and *large* >0.14) and non-normally distributed data (r: *small* = 0.1–0.3, *moderate* = 0.3–0.5, and *large* >0.5) as[23]:

$\mu^2 = \frac{t^2}{t^2+(n-1)}$, where t-value is the output of paired t-test,

$r = \frac{z}{\sqrt{n*2}}$, where z is standardized values for the U-value, and n is total number of observations.

RESULTS

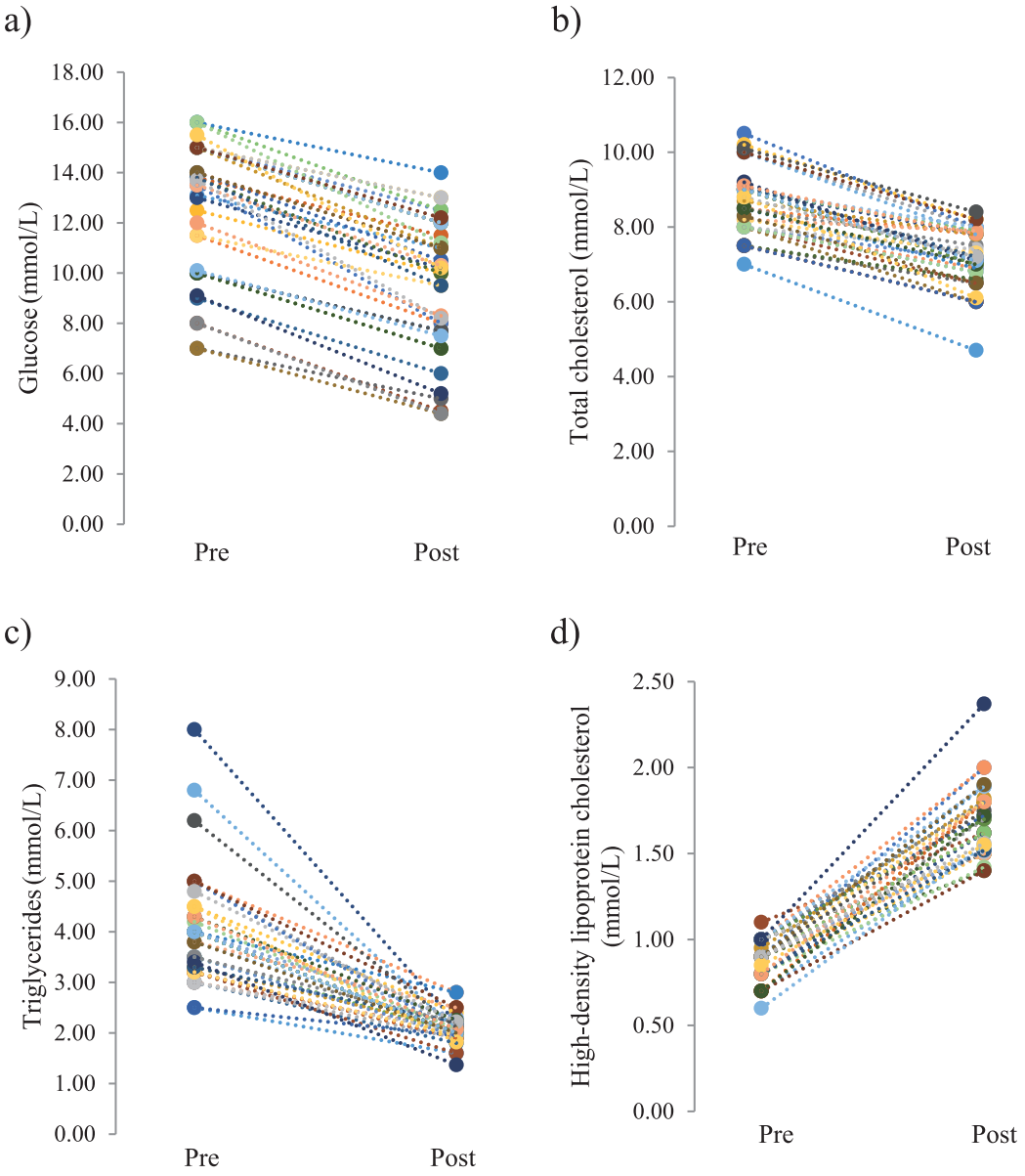
The mean ± SD, absolute mean difference, and effect sizes are presented in Table 2. Individual differences in glucose, total cholesterol, triglycerides, HDL, LDL, AST, ALT, and gamma-glutamyl transferase between pre- and post-intervention are presented in Figure 1. Individual differences in urea, creatinine, uric acid, CRP, and sedimentation between pre- and post-intervention are presented in Figure 2.

Significant ($p < 0.001$) *large* decrease between the initial and final measurement was observed for BMI ($\mu^2 = 0.87$), glucose ($r = 0.62$), total cholesterol ($\mu^2 = 0.88$), triglycerides ($r = 0.62$), LDL ($r = 0.61$), AST ($\mu^2 = 0.82$), ALT ($\mu^2 = 0.79$), gamma-glutamyl transferase ($\mu^2 = 0.79$), urea ($\mu^2 = 0.92$), creatinine ($r = 0.62$), uric acid ($r = 0.62$), CRP ($\mu^2 = 0.80$), and erythrocyte sedimentation rate ($\mu^2 = 0.58$). On the other hand, significant ($p < 0.001$) *large* increase between the initial and final measurement was observed for HDL ($r = 0.62$).

Table 2 Differences in outcome measures between pre- and post-intervention

Variables	Intervention		Mean difference (95% CI)	Magnitude	*P* values
	Pre	Post			
Metabolic control					
Glucose[#] (mmol/L)	12.61 ± 2.69	9.47 ± 2.66	–3.14 (–3.45, –2.84)	r = 0.62	< 0.001
Lipid profile					
Total cholesterol (mmol/L)	8.64 ± 0.85	7.1 ± 0.78	–1.54 (–1.18, 1.90)	μ^2 = 0.88	< 0.001
Triglycerides[#] (mmol/L)	4.03 ± 1.10	2.07 ± 0.27	–1.96 (–2.29, –1.63)	r = 0.62	< 0.001
HDL[#] (mmol/L)	0.89 ± 0.11	1.68 ± 0.20	0.79 (0.73, 0.86)	r = 0.62	< 0.001
LDL[#] (mmol/L)	5.98 ± 0.99	4.74 ± 0.63	–1.30 (–1.50, –1.10)	r = 0.61	< 0.001
Liver function					
AST (U/L)	39.30 ± 9.62	22.87 ± 5.62	–16.43 (–18.91, –13.93)	μ^2 = 0.82	< 0.001
ALT (U/L)	42.73 ± 11.71	24.05 ± 6.80	–18.67 (–21.77, –15.58)	μ^2 = 0.79	< 0.001
Gamma-GT (U/L)	37.70 ± 11.37	20.07 ± 6.71	–17.62 (–20.58, –14.67)	μ^2 = 0.79	< 0.001
Renal function					
Urea (mmol/L)	8.52 ±1.25	6.26 ± 1.17	–2.25 (–2.47, –2.03)	μ^2 = 0.92	< 0.001
Creatinine[#] (μmol/L)	101.15 ± 7.06	84.55 ± 10.77	–16.60 (–18.64, –14.59)	r = 0.62	< 0.001
Uric acid[#] (μmol/L)	348.36 ± 48.54	292.21 ± 50.58	–56.15 (–66.18, –46.12)	r = 0.62	< 0.001
Inflammation					
C-reactive protein	5.52 ± 1.77	3.46 ± 1.51	–2.06 (–2.40, –1.73)	μ^2 = 0.80	< 0.001
Sedimentation (mm/h)	15.23 ± 4.31	10.43 ± 3.79	–4.80 (–6.14, –3.45)	μ^2 = 0.58	< 0.001

[#] Data analyzed using Wilcoxon signed-rank test.
HDL: High-density lipoprotein cholesterol
LDL: Low-density lipoprotein cholesterol
ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
Gamma-GT: Gamma-glutamyl transferase


a)
Glucose (mmol/L)
18.00
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Pre
Post
b)
Total cholesterol (mmol/L)
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Pre
Post
c)
Triglycerides (mmol/L)
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Pre
Post
d)
High-density lipoprotein cholesterol (mmol/L)
2.50
2.00
1.50
1.00
0.50
0.00
Pre
Post

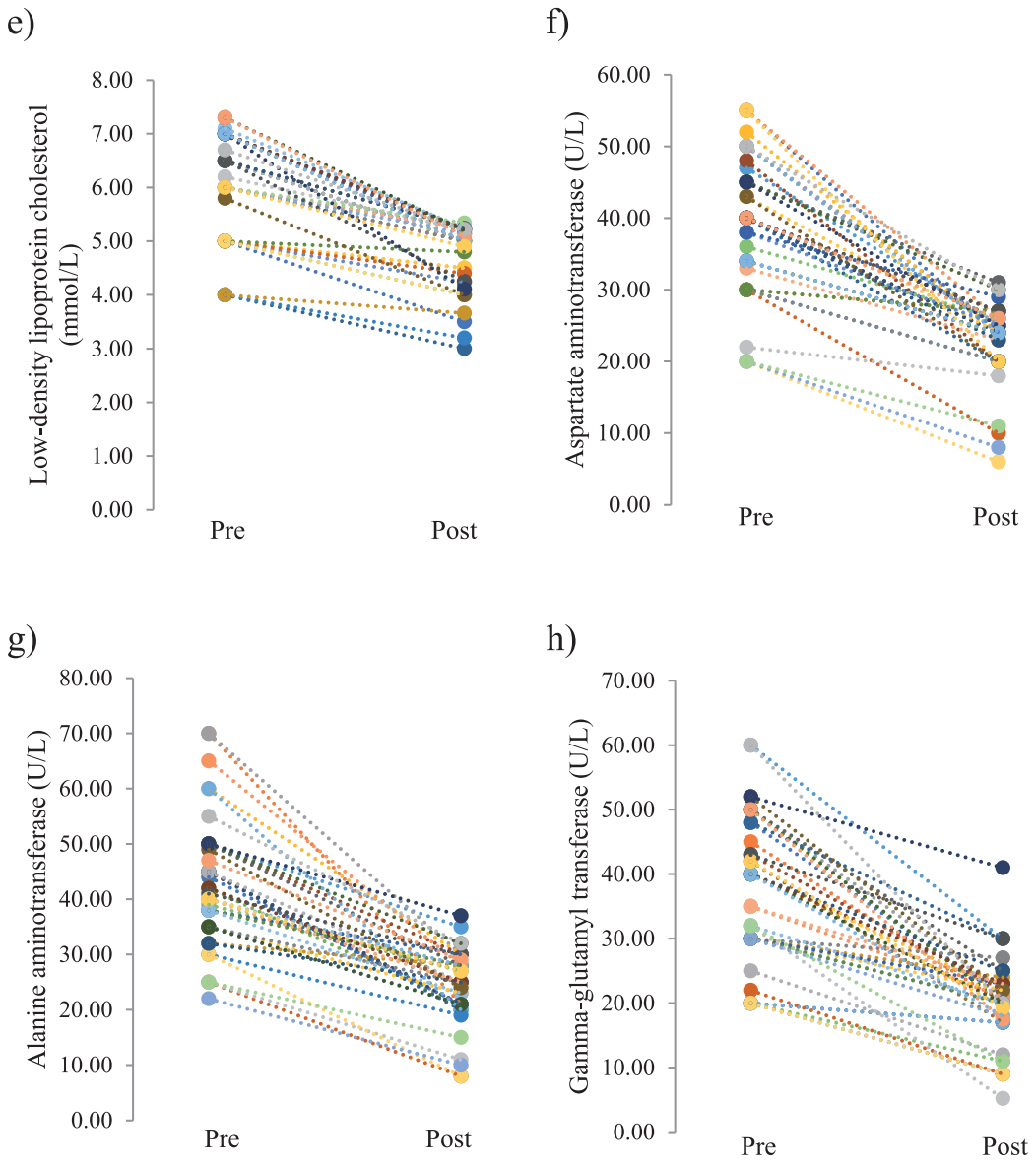
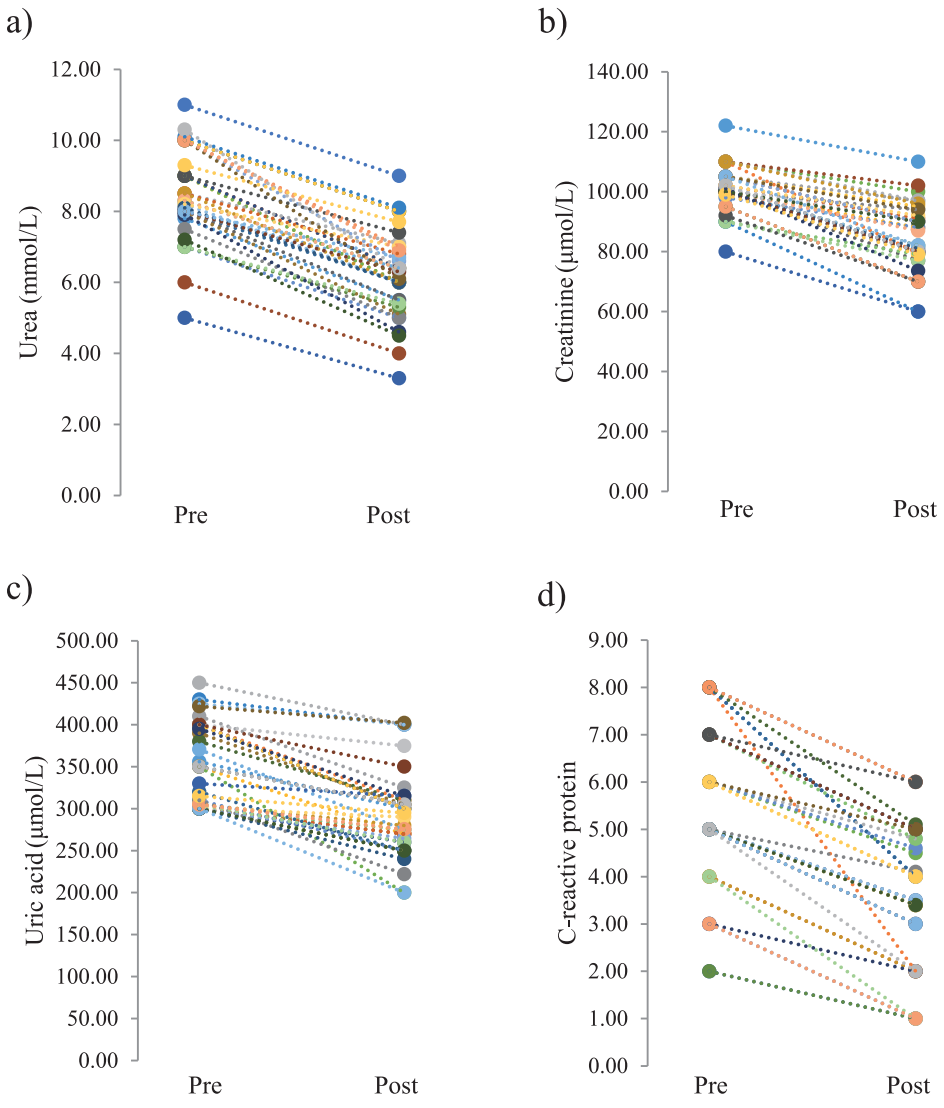


Fig. 1 Individual differences in metabolic control, lipid profile, and serum liver enzymes between pre- and post-intervention

Fig. 1a: Differences in blood glucose between pre- and post-intervention.
Fig. 1b: Differences in total cholesterol between pre- and post-intervention.
Fig. 1c: Differences in triglycerides between pre- and post-intervention.
Fig. 1d: Differences in high-density lipoprotein cholesterol between pre- and post-intervention.
Fig. 1e: Differences in low-density lipoprotein cholesterol between pre- and post-intervention.
Fig. 1f: Differences in aspartate aminotransferase between pre- and post-intervention.
Fig. 1g: Differences in alanine aminotransferase between pre- and post-intervention.
Fig. 1h: Differences in gamma-glutamyl transferase between pre- and post-intervention.


a)
Urea (mmol/L)
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Pre
Post
b)
Creatinine (μmol/L)
140.00
120.00
100.00
80.00
60.00
40.00
20.00
0.00
Pre
Post
c)
Uric acid (μmol/L)
500.00
450.00
400.00
350.00
300.00
250.00
200.00
150.00
100.00
50.00
0.00
Pre
Post
d)
C-reactive protein
9.00
8.00
7.00
6.00
5.00
4.00
3.00
2.00
1.00
0.00
Pre
Post

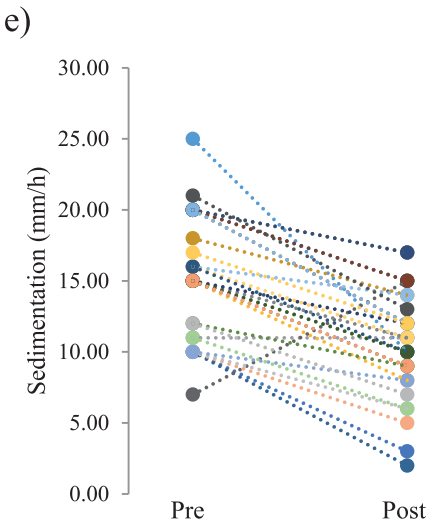


Fig. 2 Individual differences in renal function and inflammation between pre- and post-intervention
Fig. 2a: Differences in urea between pre- and post-intervention.
Fig. 2b: Differences in creatinine between pre- and post-intervention.
Fig. 2c: Differences in uric acid between pre- and post-intervention.
Fig. 2d: Differences in C-reactive protein between pre- and post-intervention.
Fig. 2e: Differences in sedimentation between pre- and post-intervention.

DISCUSSION

Our study investigated the effect of a 6-month walking program on biochemical parameters in patients with type-2 diabetes mellitus. A supervised 6-month aerobic walking program is an effective strategy in (1) improving glycemic control; (2) increasing HDL and reducing LDL and triglycerides; (3) reducing plasma biomarkers of liver dysfunction (AST, ALT, and gamma-glutamyl transferase), kidney dysfunction (urea, creatinine, and uric acid) and inflammation (CRP and erythrocyte sedimentation rate) in type-2 diabetic patients.

The walking program effectively reduced fasting plasma glucose concentration in patients with type-2 diabetes mellitus. The reduction in plasma glucose observed in our study (–24.9%) was greater than those observed previously.[24-27] For instance, supervised walking performed for 3 months (3 days/wk, 30–40 min/day[24]; 3 days/wk, 60 min/day[25]), 4 months (3 days/wk, 45 min/day[26]) and 6 months (4 days/wk, 45–60 min/day[27]) significantly reduced fasting plasma glucose concentration by 13%,[24] 10.2%,[25] 9.1%,[26] and 10.8%[27] in patients with type-2 diabetes mellitus. Percentage variations between our results and those observed previously may be due to differences in baseline plasma glucose concentration. Specifically, the higher plasma glucose concentration at baseline of the patients investigated in our study (12.6 ± 2.7 mmol/L) might underpin the greater effect of exercise we observed compared with patients examined previously (7.7 ± 2.8 mmol/L,[24] 10.3 ± 5.7 mmol/L,[25] 8.6 ± 2.2 mmol/L,[26] 9.6 ± 1.3 mmol/L[27]). Upregulation of mitochondrial proteins involved in respiration (citrate synthase), increased glycogen synthase activity, and increased glucose transporter type 4 protein content may improve glycemic control.[28] Collectively, these findings suggest that walking for 3 days/wk, 45–60 min/day may benefit glycemic control in patients with type-2 diabetes.

The six-month walking program also improved the lipid profile (HDL, LDL, triglycerides) in

patients with type-2 diabetes mellitus. On the other hand, findings from randomized trials of short-term aerobic exercise (2–4 months, 3 days/wk, 20–60 min/day, supervised walking program) in patients with type-2 diabetes mellitus revealed no significant differences in HDL,[25,26,29,30] LDL,[25,26,29] and triglycerides [25,26,29,30] between exercise and control groups. While findings from our study should be interpreted cautiously due to the absence of a control group, discrepancies between our results and those found in previous studies might be related to the longer intervention protocol we adopted. It is plausible that clinical benefits may become more pronounced with increased duration of intervention. In support of this assertion, the 6-month aerobic program (4 days/wk, 45–60 min/day, supervised walking and running) has been found to be effective in increasing HDL, as well as reducing LDL and triglycerides in patients with type-2 diabetes mellitus compared to sedentary control subjects.[27] Several studies have suggested that the HDL-raising effect of endurance exercise could be underpinned by the concomitant loss of body mass or fat.[31,32]

Our study also showed a decrease in ALT, AST, and gamma-glutamyl transferase after 6 months of the walking program. The fat accretion in the liver is typically accompanied by elevated serum liver enzymes and is frequently observed in people with diabetes.[33] Exercise appears to inhibit the synthesis of fats in the liver and activate the AMP-activated protein kinase (AMPK) pathway by increasing fat oxidation.[34] In contrast to our data, a recent study of pre-diabetic patients demonstrated non-significant changes in ALT, AST, and gamma-glutamyl transferase after undertaking long-term aerobic exercise (8.6 months, 2–3 days/wk, 30–60 min/day).[16] Damaged liver function (at baseline) in patients with diabetes type-2 examined in our study (AST: 39.3 ± 9.6 U/L; ALT: 42.7 ± 11.7 U/L; gamma-glutamyl transferase: 37.7 ± 11.4 U/L) likely promoted higher response to exercise than pre-diabetic patients examined recently (AST: 28.1 ± 12.8 U/L; ALT: 21.1 ± 10.1 U/L; gamma-glutamyl transferase: 26.2 ± 8.9 U/L). On the other hand, the significant improvement in serum liver enzymes we observed align with data from large cohort studies,[15,35] showing that 2-month (3 days/wk, 20–45 min, walking) and 3-month aerobic exercise (3 days/wk, 40 min/day, walking and diet regime – 1200 kcal) produced a significant reduction in ALT, AST, and gamma-glutamyl transferase in patients with type-2 diabetes mellitus. Altogether, the existing evidence suggests that aerobic exercise benefits liver function in patients with type-2 diabetes mellitus.

The kidneys are the main route for the excretion of metabolic wastes, such as creatinine, urea, and uric acid. Increased serum levels of these three indicators imply a decrease in clearance and the inability of the kidneys to excrete them from the blood.[36] Type-2 diabetes mellitus- induced changes in the kidney functionality we observed were diminished by 6-month aerobic exercise, resulting in decreased creatinine, urea, and uric acid levels. Our findings align with data reported by Youseff et al,[37] demonstrating a beneficial effect of exercise (3 months, 3 days/wk, 15 min/day) in reducing creatinine and urea in patients with diabetic kidney disease. Increased creatinine clearance might be associated with the exercise-induced decrease in BMI.[38] Indeed, the participants examined in our study experienced a significant decrease in BMI following the 6-month exercise program. In addition, Zoppini et al[12] also reported that 6 months of aerobic exercise (2 days/wk, 60 min/day) resulted in a significant reduction of uric acid in patients with type-2 diabetes mellitus. The beneficial effects of exercise on glycemic control, lipid metabolism, and inflammation could strongly contribute to improving renal function.[39]

The six-month walking program favorably affects inflammatory responses (CRP and erythrocyte sedimentation rate) in patients with type-2 diabetes mellitus. While no evidence is available regarding the effect of exercise on erythrocyte sedimentation rate in type-2 diabetic patients, Kadoglou et al[27] also confirmed 6-month aerobic exercise (4 days/wk, 45–60 min/day) was beneficial in reducing CRP. Although the underlying mechanism for the direct effect of exercise on CRP and erythrocyte sedimentation rate is not completely clear, it has been suggested

that exercise may regulate the synthesis of interleukins and cytokines by increasing levels of interleukin-4, interleukin-10 (IL-10) and suppressing tumor necrosis factor alpha (TNF-*a*).[40,41] In addition, the anti-inflammatory effect of exercise seems to be mediated by a downregulation of visceral fat mass with a subsequent decreased release of adipokines from adipose tissue.[42] This led us to speculate that the absence of weight loss may explain the non-significant change in CRP following 6 months of aerobic exercise (2 days/wk, 60 min/day) in patients with type-2 diabetes mellitus.[12] Further studies are needed to identify the molecular mechanisms underlying the anti-inflammatory effect of exercise and the site(s) where this action is predominantly exerted (IL-10, TNF-*a*, leptin, adiponectin, and resistin).

Some limitations of our investigation should be acknowledged. First, the current study did not include a control condition which might be considered in future research. Second, although participants received dietary prescriptions that were individually planned to produce a mild hypocaloric diet, future research should strictly measure participants' dietary intake to better account for the potential confounding influence of diet on study results. Third, future work should examine the effect of exercise on HbA1c to precisely monitor long-term glycemic control.

CONCLUSION

A supervised 6-month aerobic walking program is an effective strategy in (1) improving glycemic control; (2) increasing HDL and reducing LDL and triglycerides; (3) reducing plasma biomarkers of liver dysfunction (AST, ALT, and gamma-glutamyl transferase), kidney dysfunction (urea, creatinine, and uric acid) and inflammation (CRP and erythrocyte sedimentation rate) in type-2 diabetic patients.

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DISCLOSURE STATEMENT

The authors declare that there is no conflict of interest.

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