https://doi.org/10.46389/rjd-2024-1059
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2024; volume 31, issue 1, pages 65–69

Original Article

Effect of exercise on TNF-α levels in patients with type 2 diabetes in Bengkulu, Indonesia

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Received: 29 October 2023 / Accepted: 15 February 2024

Abstract

Along with diet and medication, exercise is now recommended as the first approach for type 2 diabetes (T2DM) patients. Previous studies indicate that regular exercise has an anti-inflammatory effect. TNF-α is one of the prominent pro-inflammatory mediators involved in the pathophysiology of T2DM; however, the effect is inconclusive. Therefore, this study aimed to determine the effect of diabetes exercise on the TNF-α level in patients with T2DM. A pre-test and post-test one-group design research was conducted at the Community Health Centre Sentinel Bengkulu, Indonesia, from November to December 2019. Patients with type 2 diabetes received diabetes exercise training for eight weeks (one time per week). Our study involved fifteen T2DM patients: 55.53±3.16 years old; male/female ratio, 2/13; and duration of diabetes was 13.87±2.94 years. Exercise training reduced TNF-α level (from 78.60±14.38 to 61.47±11.56 pg/mL; p<0.0001). Fasting blood glucose decreased after diabetes exercise (190±50.43 *vs.* 221.53±39.02 mg/dL; p=0.0065). Performing diabetes exercise exerts anti-inflammatory effects in T2DM patients. This observation should encourage patients with T2DM to increase their physical activity levels to prevent diabetes complications.

Keywords: type 2 diabetes, exercise training, TNF-alpha.

Introduction

Diabetes has developed into a global epidemic, affecting an estimated 415 million people globally in 2015, and is anticipated to reach 486.1 million by 2045 [1, 2]. In 2018, Indonesia Basic Health Research (RISKESDAS) reported that diabetes prevalence had reached 10.9 percent. In Bengkulu, the diabetes case was 19.353 [3].

In addition to diet and medication, exercise is now recommended as the first approach for newly diagnosed type 2 diabetes (T2DM) patients [4]. The possible benefits of exercise in the T2DM treatment regimen are substantial [5]. Diabetes exercise is a low-impact and rhythmic aerobic activity. The movements are enjoyable and not monotonous and can be performed by people of all ages. Diabetes exercise involves rhythmic muscle, joint, vascular, and nerve motions through stretching and relaxation [6, 7]. According to PERSADIA (Indonesian Diabetic Association), diabetes exercise is a physical activity customized to a patient's age and physical condition. The latest Indonesia diabetes exercise series 7 focuses on the regular movement of muscles, joints, and nerves via body stretching and relaxation [8, 9].

In diabetes, hyperglycemia-induced oxidative stress promotes inflammation by releasing pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1 [10]. Inflammation has previously been recognized as a significant risk factor for diabetes and is associated with the onset and progression of complications [11]. TNF-α (tumor necrosis factor-alpha) is one of the most prominent pro-inflammatory mediators involved in developing insulin resistance and the pathophysiology of T2DM. Chronic inflammation significantly contributes to non-communicable diseases such as T2DM [12]. Plomgaard *et al.* showed that plasma TNF-α is associated with insulin resistance even after adjusting

for various confounding variables (obesity and other inflammatory markers). The TNF-α protein levels are higher in type 2 diabetes muscle fibers [13]. Additional research supports the hypothesis that TNF-α may have a role in developing insulin resistance in type 2 diabetes mellitus [14].

Several studies indicate that regular exercise has an anti-inflammatory effect [15–21]. However, exercise has no decisive impact on circulating TNF-α; prior research has shown that its levels remain constant or increase/decrease following physical exercise. Therefore, this study aimed to determine the effect of diabetes exercise on the TNF-α level in patients with T2DM in the Bengkulu population in Indonesia.

Material and methods

Study design and patients

This pre-test and post-test one-group design research was conducted at the Community Health Centre (PUSKESMAS) Sentinel Bengkulu between November and December 2019. The inclusion criteria for choosing and participating patients were: (1) patients aged 50–60 diagnosed with T2DM; (2) fasting plasma glucose (FPG) level ≥126 mg/dL; and (3) agree to participate in this research program. All eligible participants with T2DM were invited to enroll in this supervised diabetes aerobic exercise that included one session (every Friday) per week, 30–60 minutes per session for eight weeks (total of eight sessions).

Laboratory, anthropometric measures, and clinical data collection

Before the first diabetes exercise session, demographic and clinical parameters, including gender, age, blood pressure (BP), height, and body weight, were recorded. Systolic and diastolic BP were determined using a standard aneroid sphygmomanometer. A basic aneroid sphygmomanometer was used to measure systolic and diastolic blood pressure. An anthropometric scale was used to measure body weights and heights to calculate the Body Mass Index (BMI).

Blood samples were collected before and after eight weeks of exercise. Capillary blood glucose testing was performed before the first exercise as baseline values and at the end of the exercise session. Fasting plasma glucose (FPG) was measured using a Point of Care Testing Method using the reliable and well-valid glucometer (EasyTouch® GCU Monitoring System). The blood glucose measuring range was 20–600 mg/dL. TNF-α levels were determined using the TNF-α ELISA assay kit (CLOUD-CLONE CORP (CCC, USA; minimum detectable limit <6.5 pg/mL).

Statistical analysis

Results are presented as mean±standard deviation (S.D). Data were recorded in Excel Office 365 (Microsoft Corp., Redmond, Washington, USA), and Graph Pad Prism 9 was used to perform statistical analysis (Graph Pad Software Inc., San Diego, CA). The Shapiro–Wilk test was used to see whether data followed a normal distribution. Data distribution was normal; therefore, a paired t-test was used to statistically compare TNF-α levels before and after exercise. When p-value<0.05, the results were interpreted as statistically significant.

Ethics statement

This study was approved by the Health Research Ethics Committee of Poltekkes Kemenkes Bengkulu (Approval number: DM.01.04/053/10/2019 dated 31-10-2019). All participants signed consent for participation.

Results

Our study involved fifteen T2DM patients who met the inclusion criteria: 55.53±3.16 years old; male/female ratio, 2/13; the mean duration of diabetes was 13.87±2.94 years, and the mean SBP and DBP were 156.93±27.59 and 83.13±15.0 mmHg, respectively (Table 1).

Four patients (26.67%) were overweight, and 11 (73.33%) patients were of normal weight. There was a statistical difference regarding mean TNF-α level post-diabetes exercise (61.47±11.56 *vs.* 78.60±14.38 pg/mL, p<0.0001) (Figure 1). A significant difference was observed in mean fasting blood glucose level post-diabetes exercise (190±50.43 *vs.* 221.53±39.02 mg/dL; p=0.0065).

Discussion

Following the eight-week diabetes exercise program, our results demonstrate that in patients with T2DM, diabetes exercise training is associated with a TNF-α decline of –17.31%. These results suggest that an aerobic diabetes exercise program is beneficial for type 2 diabetic patients.

https://doi.org/10.46389/rjd-2024-1059

Table 1: Subject Characteristics and clinical data (N=15).

Characteristics	Values
Gender (M/F)	3/12
Age, years (range)	55.53±3.16 (50–60)
SBP (mmHg)	156.93±27.59
DBP (mmHg)	83.13±15.0
Height (m)	1.61±0.07
Weight (kg)	60.33±6.37
BMI (kg/m²)	23.24±1.92
Diabetes duration (years)	13.87±2.94
FPG before exercise (mg/dL)	221.53±39.02
FPG after exercise (mg/dL)	190.00±50.43

Note: Values are presented as frequency (n) or mean±S.D.; SBP – systolic blood pressure; DBP – diastolic blood pressure; BMI – body mass index; FPG – fasting plasma glucose.

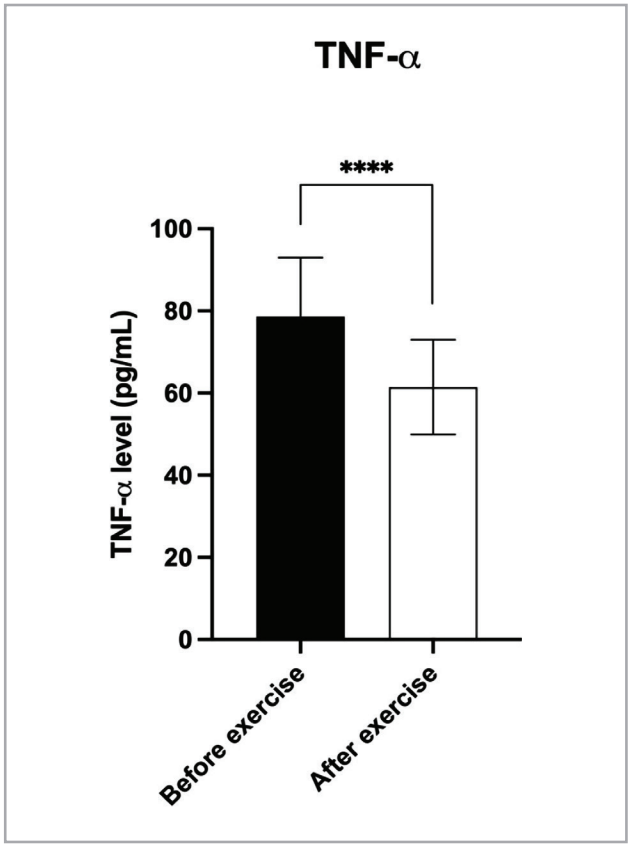

Figure 1: TNF-α levels baseline and after diabetes exercise (N=15). Data are presented as mean±SD. **** – Result of paired t-test (P<0.0001).

Exercise has been shown to reduce acute and chronic inflammation [22, 23]. Low-grade systemic inflammation is common in T2DM patients since these individuals had considerably higher levels of circulating inflammatory markers [24]. TNF-α is a primary pro-inflammatory mediator that contributes substantially to the development of insulin resistance and the pathogenesis of T2DM by inducing low-grade tissue-specific inflammation. TNF-α inhibits the expression of GLUT4 and the serine phosphorylation of IRS-1, two critical enzymes involved in insulin synthesis. Increased TNF-α promotes insulin resistance in adipocytes and peripheral tissues via insulin signaling [14, 25, 26].

In this present study, the levels of TNF-α changed after diabetes exercise. In accordance with our findings, Abd El-kader *et al.* reported a significant decrease in TNF-α in T2DM patients following three months of aerobic exercise. They discovered that moderate aerobic exercise had a stronger impact on inflammatory cytokines than mild aerobic exercise in obese type 2 diabetes individuals [27]. One study also showed TNF-α levels reduced by 20% in the diabetes group after twelve weeks of the aerobic training program [21]. On the other hand, Arslan *et al.* studied the effects of 12 weeks of aerobic exercise on TNF-α in 64 diabetic individuals. They found that TNF-α levels were unaffected by physical training, and these findings conflicted with our results [17]. Similarly, after 12 weeks of aerobic activity, Jorge *et al.* showed no changes in TNF-α levels [20].

The following are possible mechanisms of the anti-inflammatory effect of exercise: (1) Regular exercise might reduce visceral fat accumulation and pro-inflammatory cytokine production and inhibit inflammatory cell aggregation and infiltration, thereby reducing systemic inflammation and maintaining normal insulin signaling [28]; (2) Several anti-inflammatory factors produced by contracting skeletal muscle fibers might be released into the bloodstream during exercise. Interleukin-6, which increases rapidly in response to exercise, requires specific changes in cytokine levels (decreases TNF-α production) to exert its anti-inflammatory effect directly. Exercise may increase insulin sensitivity by suppressing TNF-α, which is linked to insulin resistance. Long-term metabolic changes, including body composition, fitness, lipid, and glucose metabolism, may also be involved indirectly in exercise's anti-inflammatory effects [23].

Physical activity is a natural, potent anti-inflammatory and metabolism-improving approach with few adverse effects that should be incorporated into the therapy of individuals with chronic diseases such as T2DM [29]. Along with diabetic medication, diet and behavior modification are central components of all T2DM programs [30]. The consensus of diabetes management in Indonesia recommended exercise as first-line therapy for type 2 diabetes [31]. Exercise also stimulates

metabolism, increases glucose uptake, improves insulin sensitivity, and facilitates glucose control [32].

The data on the anti-inflammatory effects of exercise and diabetes are inconsistent. Thus, exercise has a varied impact on TNF-α. As a result, there is a discrepancy between physical exercise and changes in TNF-α levels. The main explanation for this discrepancy may be related to the differences in research demographics, methodologies, type and duration of exercise, detection methods, and sample sizes.

Limitations of this study warrant mention. The primary limitation was that this study had a small sample size (N=15) and did not include a control group. The small number of participants may have underpowered the study. As a result, these data should be interpreted cautiously and may not be generalized to other populations. Despite the limitations, there are several strengths, such as the participants' high rate of study completion and the availability of regular and supervised diabetes exercise in the Community Health Centre (PUSKESMAS). Further studies with different populations, another inflammatory biomarker, and type of exercise are recommended.

Conclusion

Our results demonstrated that a diabetes exercise program affects the level of TNF-α in T2DM patients. Patients with T2DM should be encouraged to increase their physical activity to prevent the early onset of diabetes complications.

Acknowledgments

The authors thank Poltekkes Kemenkes Bengkulu for the financial support (Budget Implementation List/ DIPA 2019).

Conflict of interest

The authors declare no conflict of interest.

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