# EFFECT OF MODERATE-INTENSITY TREADMILL EXERCISE ON INCREASED ADIPONECTIN LEVELS IN TYPE 2 DIABETES MELLITUS PATIENTS

ORIGINAL ARTICLE
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ARTÍCULO ORIGINAL

*EFEITO DO EXERCÍCIO EM ESTEIRA DE INTENSIDADE MODERADA NO AUMENTO DOS NÍVEIS DE ADIPONECTINA EM PACIENTES COM DIABETES MELLITUS TIPO 2*

*EFECTO DEL EJERCICIO EN CINTA DE CORRER DE INTENSIDAD MODERADA SOBRE EL AUMENTO DE LOS NIVELES DE ADIPONECTINA EN PACIENTES CON DIABETES MELLITUS TIPO 2 PSİCOLÓGİCA*

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## ABSTRACT

Introduction: Adiponectin plays a significant role in the metabolic system in proinflammatory cytokine inhibition and glucose uptake utilization. The treadmill is an aerobic walking device that stimulates natural walking features. Exercises increase adiponectin levels leading to improvement in insulin sensitivity. Objectives: To analyze the effect of aerobic exercise using a moderate-intensity treadmill with a gradual increase in speed and inclination on adiponectin levels in men with type 2 diabetes mellitus (T2DM). Method: Twenty-two participants with T2DM were randomized into treadmill exercise and control groups. The experimental group underwent 30-minute sessions of moderate-intensity treadmill exercise with increasing speed and gradual inclination three times a week for four weeks. The control group underwent individual exercise for 150 minutes per week. Participants were assessed for clinical and laboratory parameters before and after the four-week program. Results: There was a significant increase in the adiponectin level from 456.3 ± 42 pg/ml to 586.3 ± 87.8 pg/ml (p=0.04, p<0.05) in the treadmill exercise group. In the control group, adiponectin only increased from 466.7 ± 85 pg/ml to 471.8 ± 59 pg/ml (p=0.646). Conclusion: Moderate-intensity treadmill with increasing speed and gradual inclination was found to lead to a significantly better outcome in improving adiponectin levels than standard individual physical exercise in managing T2DM. ***Level of evidence II; Therapeutic studies – Investigation of the treatment results.***

**Keywords:** Adiponectin; Exercise; Treadmill test; Type 2 Diabetes Mellitus.

## *RESUMO*

*Introdução: A adiponectina desempenha um papel significativo no sistema metabólico na inibição da citocina pró-inflamatória e na utilização da captação de glicose. A esteira é um aparelho de caminhada aeróbica que estimula as características da caminhada natural. Os exercícios aumentam o nível de adiponectina, resultando na melhora da sensibilidade à insulina. Objetivos: Analisar o efeito de exercícios aeróbicos em uma esteira de intensidade moderada com um aumento gradual de velocidade e inclinação sobre os níveis de adiponectina em homens com diabetes mellitus tipo 2 (DMT2). Método: Vinte e dois participantes com DMT2 foram randomizados para grupos de exercício em esteira e controle. O grupo experimental realizou sessões de 30 minutos de exercício em esteira de intensidade moderada com velocidade crescente e inclinação gradual três vezes por semana durante quatro semanas. O grupo de controle se submeteu a exercício individual durante 150 minutos por semana. Os participantes foram avaliados em relação aos parâmetros clínicos e laboratoriais antes e após o programa de quatro semanas. Resultados: Houve um aumento significativo no nível de adiponectina de 456,3 ± 42 pg/ml para 586,3 ± 87,8 pg/ml (p=0,04, p<0,05) no grupo de exercício em esteira. No grupo de controle, a adiponectina apresentou um pequeno aumento de 466,7 ± 85 pg/ml para 471,8 ± 59 pg/ml (p=0,646). Conclusão: Descobriu-se que exercícios na esteira de intensidade moderada com velocidade crescente e inclinação gradual conduzem a um resultado significativamente superior na melhora dos níveis de adiponectina em relação a exercícios físicos individuais padrão ao tratar o DMT2.* ***Nível de evidência II; Estudos terapêuticos – Investigação de resultados do tratamento.***

***Descritores:*** *Adiponectina; Exercício; Teste de esteira rolante; Diabetes mellitus tipo 2.*

## *RESUMEN*

*Introducción: La adiponectina desempeña un papel importante en el sistema metabólico al inhibir las citoquinas proinflamatorias y al utilizar la captación de glucosa. La cinta de correr es un dispositivo de caminata aeróbica que estimula las características de la marcha natural. Los ejercicios aumentan el nivel de adiponectina, lo que se traduce en una mayor sensibilidad a la insulina. Objetivos: Analizar el efecto de los ejercicios aeróbicos en una cinta de correr de intensidad moderada con un aumento gradual de la velocidad y la inclinación sobre los niveles de adiponectina en hombres con diabetes mellitus tipo 2 (DMT2). Método: Veintidós participantes con DMT2 fueron asignados*

*aleatoriamente a grupos de ejercicio en cinta de correr y de control. El grupo experimental realizó sesiones de ejercicio en cinta de correr de 30 minutos de intensidad moderada con velocidad creciente e inclinación gradual tres veces por semana durante cuatro semanas. El grupo de control se sometió a ejercicios individuales durante 150 minutos a la semana. Se evaluaron los parámetros clínicos y de laboratorio de los participantes antes y después del programa de cuatro semanas. Resultados: Hubo un aumento significativo del nivel de adiponectina de 456,3 ± 42 pg/ml a 586,3 ± 87,8 pg/ml (p=0,04, p<0,05) en el grupo de ejercicio en cinta de correr. En el grupo de control, la adiponectina presentó un pequeño aumento de 466,7 ± 85 pg/ml a 471,8 ± 59 pg/ml (p=0,646). Conclusión: Se descubrió que los ejercicios en cinta de correr de intensidad moderada con velocidad creciente e inclinación gradual conducen a un resultado significativamente superior en la mejora de los niveles de adiponectina en comparación con los ejercicios individuales estándar en el tratamiento de la DMT2.* ***Nivel de evidencia II; Estudios terapéuticos – Investigación de resultados del tratamiento.***

***Descriptores:*** *Adiponectina; Ejercicio; Prueba ergométrica de bicicleta; Diabetes mellitus tipo 2.*

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## INTRODUCTION

Diabetes mellitus is a metabolic disease on a spectrum of hyperglycemia due to abnormalities in insulin secretion, insulin action, or both. Most diabetes cases are caused by type 2 diabetes mellitus (T2DM) by 90-95%, where lack of physical activity plays a significant role.[1]

The current recommendation for T2DM management suggests that physical activity improves glycemic control, insulin sensitivity, lipid profile, blood pressure, and related cardiovascular risk. Thus, as a nonpharmacological therapeutic strategy, physical activity plays a fundamental role in T2DM.[2] Aerobic exercise is a generally accepted therapeutic strategy for T2DM since it has beneficial effects for glycemic control and reduces metabolic risk factors for cardiovascular diseases, including insulin resistance.[3] Guidelines suggested a weekly accumulation of (minimum) 150 minutes of moderate-intensity aerobic exercise by 40–59% of heart rate reserve (HRR) or oxygen uptake reserve ($VO_2R$) for at least three days per week, with no more than two consecutive days without exercise.[4]

Adiponectin, another term for AdipoQ or ACRP30, is a hormone secreted by adipose tissue into the body's circulation. Adiponectin has a significant role in the metabolic system and is a factor in many metabolic diseases such as obesity, type 2 diabetes mellitus, coronary heart disease, and metabolic syndrome.[5] Adiponectin is found in the plasma at relatively high levels (2-10 µg/ml).[6]

Elevated proinflammatory cytokines in chronic conditions might cause a decrease in insulin sensitivity. Several studies have reported that proinflammatory cytokine levels are elevated in T2DM patients, which is associated with disease progression in T2DM. Adiponectin plays a role in inflammatory mediator inhibition, insulin sensitivity improvement, glucose utilization, and fatty acid oxidation in muscle cells. However, in T2DM patients or obesity, adiponectin levels tend to become low.[7] A few studies in obese mice reported that adiponectin improves glucose transporter-4 (GLUT-4) translocation and glucose uptake in skeletal muscle cells. Adiponectin improves insulin sensitivity by decreasing muscular lipid content.[8]

Exercise alone or in combination with diet-induced weight loss significantly increases plasma adiponectin levels in both obese and insulin-resistant subjects, leading to improved insulin sensitivity and reduction in proinflammatory cytokines.[9] Treadmill aerobic walking stimulates natural walking features. Exercises facilitate glucose uptake since the working muscle is more sensitive to insulin than the muscle at rest. With endurance exercise, muscle's sensitivity to insulin also increases. The number of insulin receptors in working muscle is more than the muscle at rest.[10]

The purpose of this study was to analyze the effect of aerobic exercise using moderate-intensity treadmill exercise method with increasing speed and gradual inclination for 90 minutes, three times per week for a four weeks program on adiponectin levels compared to advisory individual physical exercise at home for 150 minutes every week in T2DM patients.

## MATERIAL AND METHODS

### Design and inclusion criteria

The design of this study was a quasi-experimental design of a randomized pre-and-post experimental group. A total of twenty-two subjects with type 2 diabetes mellitus participated in this study. Inclusion criteria were male patients, aged 35-55 years old, with systolic blood pressure within 110-130 mmHg, who underwent medicational treatment of T2DM. Subjects with chronic conditions such as restrictive/obstructive pulmonary disease, history of either cardiac, kidney, thyroid, liver disease or cancer, history of erythema, ulcers or gangrene, peripheral diabetic neuropathy, history of long-term steroid use or taking vitamin D supplements, vestibular and proprioceptive disturbance, and neuromusculoskeletal disease were excluded from the study. Drop-out criteria include hypoglycemia, cardiac disease or ischemia, or chest pain during or after exercise.

Participants were assessed for clinical and laboratory parameters such as body mass index, blood pressure, fasting plasma glucose, random plasma glucose, HbA1c, and serum adiponectin level. The Dr. Soetomo General Hospital Ethical Committee approved this investigation, and a signed informed consent form was obtained from all participants.

### Protocols

Participants were randomized into two groups, intervention and control groups. The intervention group conducted an aerobic treadmill exercise program for four weeks, including 3 sessions per week with a moderate-intensity training program. The treadmill exercise went for 30 minutes. A-5 minute warm-up using treadmill was initiated before exercise, then continued with 20 minutes of moderate intensity exercise using motor driven treadmill (BTL) with standard protocol increasing speed and inclination every three minutes to reach the target heart rate of 60-75% of the maximum heart rate (according to age), then the session ended with a 5 minute cool down. Participants in the control group received advisory individual physical exercise at the home of 150 minutes per week, participants in control group underwent standard exercise according to Indonesian Diabetes Guidelines from PERKENI which the same as American Diabetic Association (ADA) guidelines with the sum of 150 minutes every week of any aerobic exercise. Both groups were followed up for four weeks.

The intervention group's training protocol was taken from the Modified Bruce test with increasing speed and inclination every three minutes to reach the target heart rate of 60-75% of the maximum heart rate (according to age). Before and after exercise, vital signs were examined.

Plasma glucose levels were also measured using a glucometer (easy touch). Participants were declared fit to exercise if blood glucose levels were within 100-250 mg/dL. Treadmill EN-Mill® 2007 was used as a walking exercise device. Polar H10 heartbeat sensors were used for heart rate monitoring, installed on the participant's chest, and connected through Bluetooth to smartphones.

Blood samples were taken from participants in both groups 30 minutes before exercise and at the last training program. Blood was drawn and put in a plain tube (without any activator) and was kept in a -80ºC refrigerator. Measurement of adiponectin levels was carried out on all participants using the Enzyme-Linked Immunosorbent Assay (ELISA) kit from Elabscience, USA.[11]

### Statistical Analysis

Values were reported as mean ± SD (standard deviation) except for categorical variables such as frequency and percentages. Shapiro-Wilk test was used to determine the distribution of continuous variables ($p>0.05$). A comparison between the two groups was performed using the Independent Sample T-test for normally distributed data. When the variables were not normally distributed, the comparison was performed using the Mann-Whitney U test. For categorical data such as the history of insulin use, dyslipidemia, and hypertension, Pearson Chi-Square ($\chi^2$) test was performed to determine the difference between the two groups. p-Values < 0.05 were considered statistically significant. Relationships between variables were analyzed using Pearson's or Spearman's rank correlation coefficients. Statistical analysis was conducted using Statistical Package of Social Science (SPSS), ver 25.0 (SPSS Inc., Chicago, IL). A p-value of <0.05 was considered statistically significant.

## RESULTS

A sum of twenty participants, all males, were included in the analysis after two participants dropped out due to hypoglycemia during exercise. Participants who were diabetic patients from outpatient clinic in Dr Soetomo General Hospital, Surabaya, East Java, Indonesia underwent simple random sampling and were randomized equally to both groups. Clinical and laboratory values such as body mass index (BMI), systolic pressure, HbA1c, fasting plasma glucose (FPG) level, random glucose level, and adiponectin level at baseline measurement are shown in Table 1. Both groups' characteristics did not differ at the baseline, but there was a significant difference in age in both groups (p=0.017) (Table 1).

After four weeks of the exercise program, both groups completed follow-up. Table 2 showed that there was a significant increase in adiponectin level before and after the program in the treadmill exercise group (456.3 ± 42 to 586.3 ± 87.8) (p=0.04). There was also an increase in adiponectin level in the control group (466.7 ± 85 to 471.8 ± 59), but the change was not statistically significant. The change (delta) in adiponectin level between the two groups was also found to be increased drastically in the intervention group by 129.9 ± 108.5. The change of adiponectin level in the control group was also found (5.08 ± 104.6) but was way less than the intervention group. The difference in adiponectin levels between both groups was found statistically significant (p=0.017) (Figure 1, Figure 2).

Body mass index (BMI) and fasting plasma glucose (FPG) levels at baseline and after exercise were also measured to evaluate the difference in both groups. At baseline, no significant difference was found in both groups. After four weeks, BMI was found to be slightly increased in both groups, but the change was not statistically significant. Both groups had a reduction in fasting plasma glucose levels. In the intervention group, the reduction in fasting glucose level was from 123 ± 71.8 to 99.5 ± 41, but the change was not significant. In the control group, meanwhile, the decrease in fasting glucose level (110.6 ± 20.7 to 77.3 ± 19.5) was found statistically significant (p=0.022) (Table 3).

**Table 1.** Baseline characteristics of moderate-intensity treadmill exercise and control group.

| | Treadmill Exercise Group (n= 10) | Control Group (n=10) | P value |
|---|---|---|---|
| Age, years (Mean ± SD) | 50.7 ± 4.5 | 46.1 ± 3.8 | 0.017 X* |
| Duration of DM, years (Mean ± SD) | 5.5 ± 4.7 | 4.5 ± 4.7 | 0.361 X |
| Body Mass Index (kg/m$^2$) | 23.9 ± 3.6 | 26.7 ± 4.4 | 0.141 Y |
| HbA1c (%) | 6.5 ± 1.2 | 7.9 ± 2.1 | 0.09 Y |
| Random Glucose (mg/dL) | 180.7 ± 50.4 | 159.3 ± 3 | 0.272 Y |
| Systolic pressure (mmHg) | 116 ± 7 | 114 ± 7 | 0.435 X |
| Fasting Glucose (mg/dL) | 123 ± 71.8 | 110.6 ± 20.7 | 0.226 X |
| Adiponectin (pg/ml) | 456.3 ± 42 | 466.7 ± 85 | 0.597 X |
| Clinical Characteristic | | | |
| Insulin Use, n (%) | 4 (40) | 2 (20) | 0.628 Z |
| Dyslipidemia, n (%) | 2 (20) | 2 (20) | 1.000 Z |
| Hypertension, n (%) | 4 (40) | 2 (20) | 0.628 Z |

*p-value of <0.05 was found significant; X Mann-Whitney U test was used to determine the differences between groups for age, duration of DM, systolic pressure, fasting glucose, and adiponectin level; Y Independent Sample T-Test was used to determine the differences between groups for BMI, HbA1c, and random glucose; Z Pearson Chi-Square ($\chi^2$) test was used to determine the differences between groups for the history of insulin use, dyslipidemia, and hypertension.

**Table 2.** Changes in adiponectin level before and after exercise.

| Adiponectin level (pg/ml) | Treadmill Exercise Group (n= 10) | Control Group (n=10) | p-value |
|---|---|---|---|
| Before exercise | 456.3 ± 42 | 466.7 ± 85 | 0.597 X |
| After exercise | 586.3 ± 87.8 | 471.8 ± 59 | 0.03 Y |
| Mean difference before and after exercise (p-value) | 0.004 A* | 0.646 B | - |
| ΔAdiponectin | 129.9 ± 108.5 | 5.08 ± 104.6 | 0.017 Y |

*p-value of <0.05 was found significant; A Paired T-Test, B Wilcoxon-signed Rank Test, X Mann-Whitney U test, Y Independent Sample T-Test

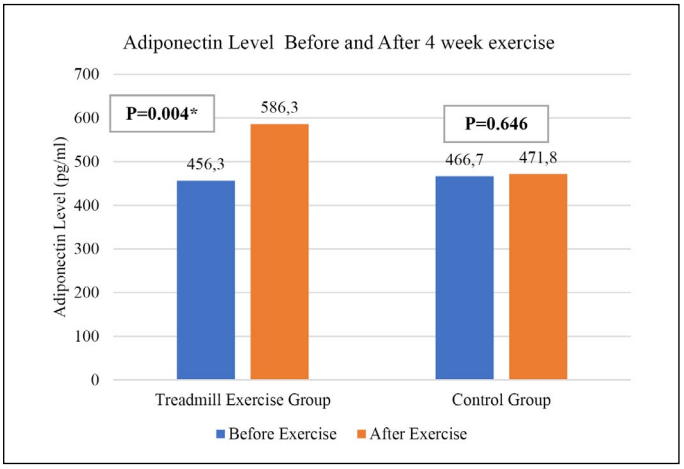


**Figure 1.** Adiponectin level at baseline and at the end of 4 weeks exercise program.

## DISCUSSION

In this study with twenty participants of T2DM patients, an increase in adiponectin levels was found in both supervised treadmill exercise and individual advisory home exercise after four weeks. Nevertheless, adiponectin levels were found to be significantly increased in the treadmill exercise group from 456.3 ± 42 pg/ml to 586.3 ± 87.8 pg/ml (p=0.04, p<0.05). However, after the exercise program, this change in adiponectin levels was not accompanied by the change in body mass index or fasting plasma glucose level. There was no reduction in weight or BMI, but moderate-intensity aerobic treadmill exercise has already been effective in increasing adiponectin levels. The tendency of adiponectin levels in

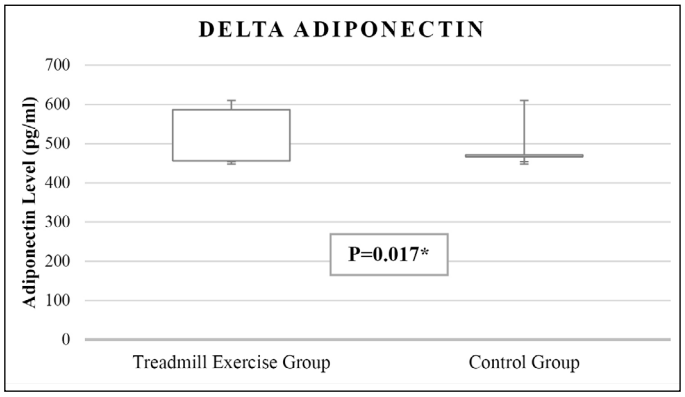


**Figure 2.** Change in adiponectin level (delta) between treadmill exercise and control group..

**Table 3.** Comparison of characteristics between baseline and after four weeks program.

| | | Treadmill Exercise Group (n= 10) | Control Group (n=10) | p value |
|---|---|---|---|---|
| BMI (kg/m$^2$) | Before exercise | 23,9 ± 3,6 | 26,7 ± 4,4 | 0,141 $^Y$ |
| | After exercise | 24,9 ± 4 | 27,4 ± 5,3 | 0,25 $^Y$ |
| | Mean Difference (p value) | 0,21 $^A$ | 0,128 $^A$ | - |
| FPG (mg/dL) | Before exercise | 123 ± 71,8 | 110,6 ± 20,7 | 0,226 $^X$ |
| | After exercise | 99,5 ± 41 | 77,3 ± 19,5 | 0,18 $^Y$ |
| | Mean Difference (p value) | 0,386 $^B$ | 0,022 $^A$ | - |

*p-value of <0.05 was found significant; $^A$ Paired T-Test, $^B$ Wilcoxon-signed Rank Test, $^X$ Mann-Whitney U test, $^Y$ Independent Sample T-Test .

the treadmill group to be higher than the control group at the end of the exercise program could be influenced by several factors, including better glucose control and a BMI level close to normal at baseline. Although initially, adiponectin levels were lower in the treadmill exercise group before the program, those factors could play a role in improving adiponectin levels in the treadmill exercise group.

Several prior studies also investigated the relationship between adiponectin and aerobic exercise in T2DM patients. Some studies found consistent results with ours. Balducci et al[12] compared aerobic with aerobic combined with resistance exercise in T2DM patients. For aerobic exercises, a treadmill and/or cycloergometer were used. The aerobic-only group had twice a week supervised 60-minutes sessions at 70-80% VO2max; aerobic combined with resistance training had 40 min aerobic exercise at 70-80% VO2max + 20 min resistance exercise at 80% one-repetition maximum. The exercise program was carried out for 12 months. It was reported that adiponectin levels increased by 36% (from 16 µg/ml to 21,76 µg/ml) in the aerobic exercise program and 38% (from 14.5 µg/ml to 20.01 µg/ml) in the aerobic combined with resistance program. This study also found a significant reduction in hs-CRP and several inflammatory biomarkers after exercise, indicating that exercise has a full anti-inflammatory and insulin-sensitizing effect. Thus, physical exercises were also found to stimulate the anti-inflammatory pathway and benefit cardiovascular risk factors.[12]

A similar result was reported from the study by Thompson et al[13] that compared the group of usual care, the group of diet, and a group of intensive diet and physical activity. Physical activity was carried out with at least 30 minutes of brisk walking for a minimum of five days a week over the subject's prior usual physical activity. Each patient was given a pedometer, and the activity was gradually increased over five weeks and maintained until a 12 months program. The results reported that in the intervention group of exercise and intensive diet, inflammatory markers (IL-6, sICAM-1, CRP) and adiponectin levels were improved after six months. Adiponectin levels increased from 4.8 µg/ml to 5.68 µg/ml by six months and 5.76 µg/ml by 12 months. Thus, the results indicated that intensive diet accompanied by physical activity was more effective compared to usual or conventional treatment at targeting inflammatory markers in T2DM patients.[13]

A study conducted by Ku et al[14] compared three groups: aerobic training, resistance training, and control group. The aerobic exercise was carried out by walking for 60 minutes at moderate intensity (3.6-5.2 metabolic equivalents) five times a week for 12 weeks. This study reported that adiponectin levels increased significantly by 75.1% from 3.86 ± 2 µg/ml to 6.76 ± 1.24 µg/ml in the aerobic exercise group. There was also a significant increase of adiponectin by 46.2% in the resistance exercise group. The results of several kinds of exercise suggested that aerobic exercise was found to be more effective in reducing adipose tissue than resistance exercise. However, aerobic exercise was not always statistically superior to resistance exercise.[14]

Several studies also found contrasting results. Some found no exercise-induced variation in adiponectin levels or even a decrease in adiponectin levels instead. A study conducted by Dede et al[15] found that the aerobic exercise training program induced a significant decrease in adiponectin levels from 6.6 ± 0.8 µg/ml to 6.0 ± 0.8 µg/ml after 12 weeks aerobic exercise period. The exercise was carried on using a treadmill three times per week, with training length and intensity gradually progressing until the target heart rate was achieved. Participants progressed from 15-20 minutes per session at 60% of the maximum heart rate to 45 minutes per session at 75% of the measured heart rate. The study stated that the decrease in adiponectin levels might be caused by the increase in proinflammatory cytokines and different adiponectin isoforms or the expression of adiponectin receptors. It stated that there was a lack of multi-isoforms and adiponectin receptors might have caused the limitation in this study.[15]

Boudou et al[16] reported that a supervised intensive training program did not induce significant changes in adiponectin levels despite a tremendous decrease in abdominal fat. It was reported that the level of adiponectin went from 6.3 ± 2.75 µg/ml to 6.0 ± 3.5 µg/ml after eight weeks of supervised endurance exercise (75% VO2peak, 45 min) twice a week. The result might be happened because of different adiponectin variations. However, the study found an inverse relationship between body weight changes and adiponectin levels in the trained group.[16]

A study conducted by Jorge et al[17] also found a decrease in adiponectin levels after training. The study compared four training groups: aerobic training, resistance training, aerobic combined with resistance, and control group. Aerobic training was carried out by cycling at the heart rate corresponding to the lactate threshold, three days per week of 60 minutes supervised sessions for 12 weeks. In the aerobic training group, adiponectin levels were found to be decreased from 5.58 ± 5.73 µg/ml to 3.38 ± 2.22 µg/ml.[17]

Treadmill exercise method with increasing speed and inclination gradually increases body metabolism with more muscles involved rhythmically. This method requires great energy; hence the oxygen consumption is also greater. Increasing the speed will also gradually increase the heart rate.[18]

Our research also found that the control group with simple advisory lifestyle intervention of physical activity for a total of 150 minutes every week also induced a slight increase in adiponectin levels. Although the result was not found statistically significant compared to moderate-intensity aerobic treadmill exercise, it still showed that physical exercise in routine could generate beneficial changes in adiponectin levels.

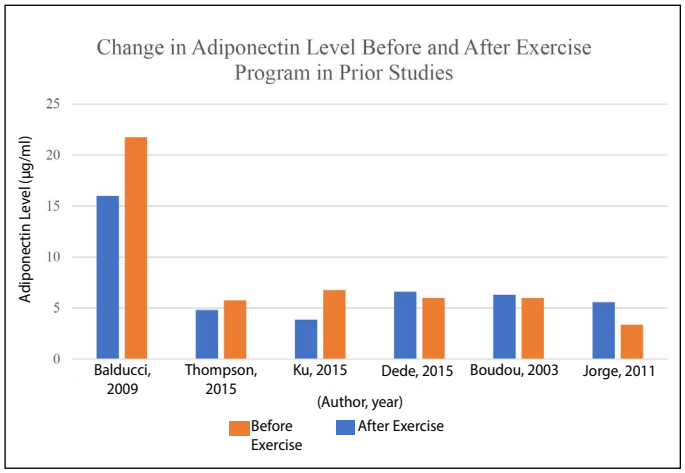


**Figure 3.** Change in adiponectin level before and after exercise program in several prior studies.

## CONCLUSION

In conclusion, our findings were in line with the view that any kind of routine physical exercise has beneficial effects on adiponectin levels and anti-inflammatory markers. However, aerobic exercises with moderate intensity treadmill with increasing speed and gradual inclination three times per week for four weeks were significantly better in improving adiponectin levels than standard individual physical exercise in managing T2DM. Our exercise could be a suggestion for better management and therapy of T2DM. since this study suggested shorter time of exercise from the standard aerobic exercise of diabetics.

Further studies are needed to evaluate different aerobic exercise modalities or even modify the length of the treadmill exercise program from only four weeks to six months to evaluate better efficacy in increasing adiponectin levels.

All authors declare no potential conflict of interest related to this article

**AUTHORS' CONTRIBUTIONS:** Each author made significant individual contributions to this manuscript. SWM: conceptualization, formal analysis, funding acquisition, investigation, project administration, supervision, final approval. AI: conceptualization, data curation, investigation, resources, preparation of the entire research project. DT: writing and revision, intellectual concept, supervision, final approval. TNS: writing and revision, statistical analysis, analysis of the data.

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