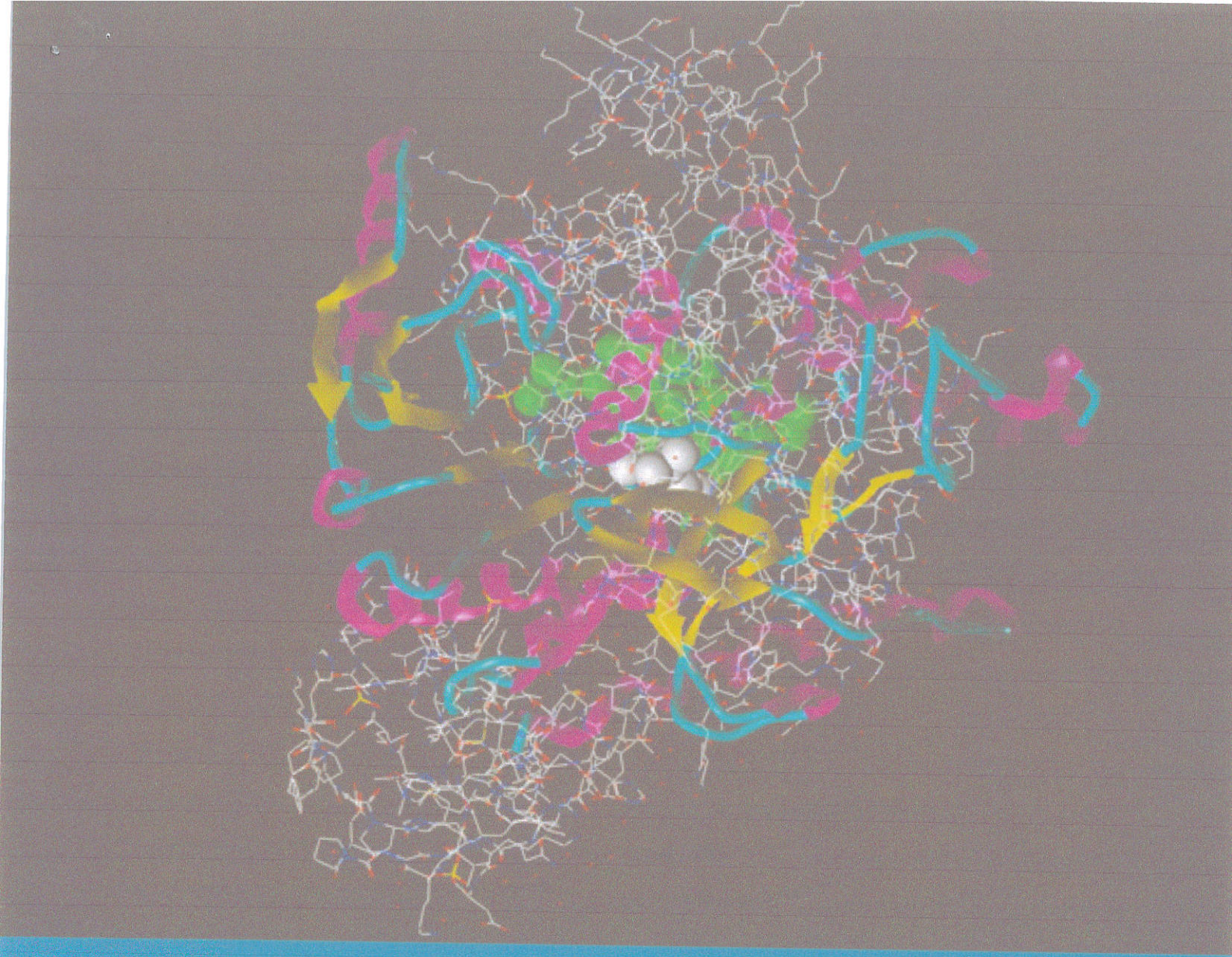

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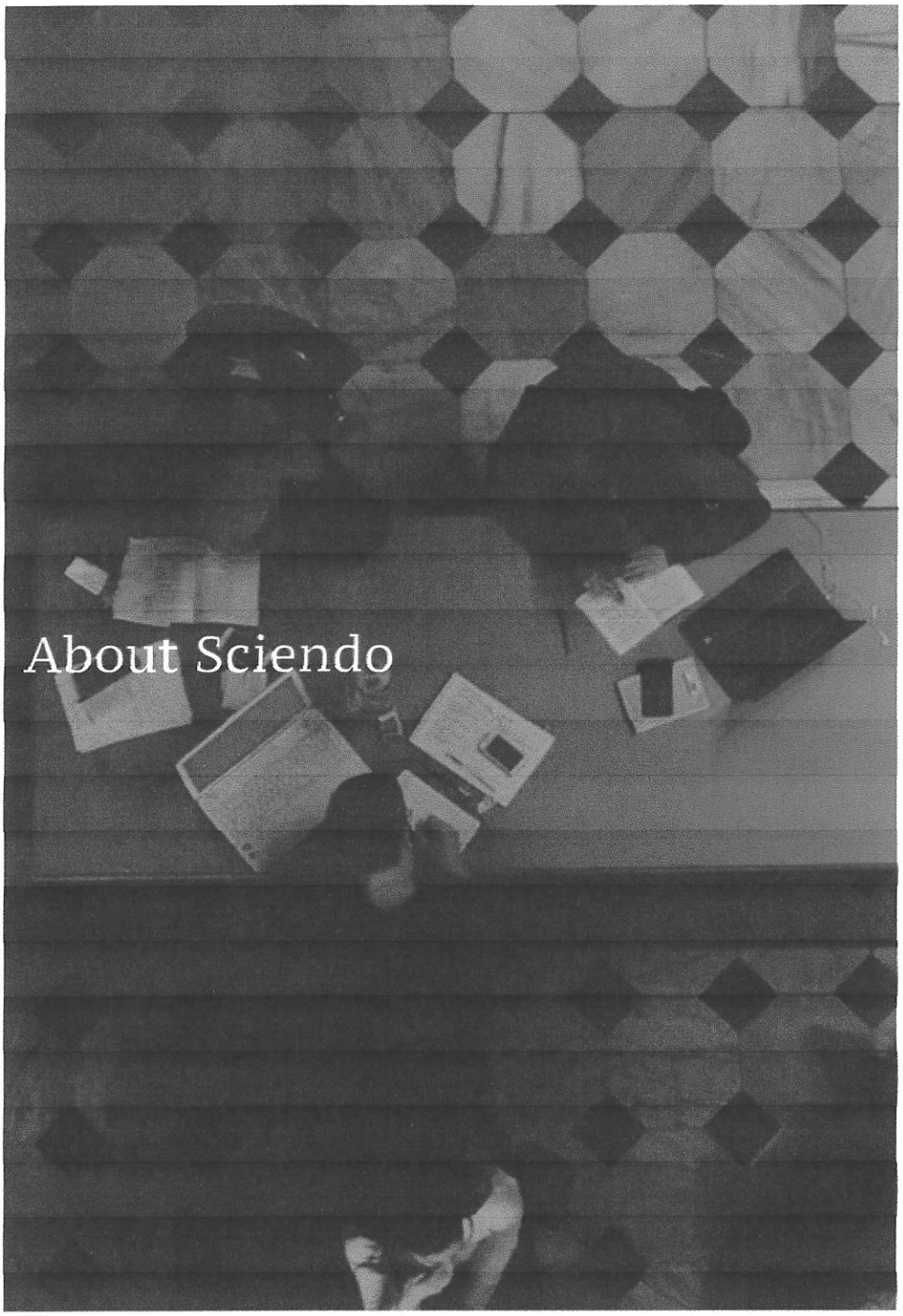

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Effects of aerobic exercise on adiponectin levels potentially mediated by vitamin D in type 2 diabetic patients

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Objective. The positive effects of exercise on adiponectin and vitamin D have independently been reported. Recent studies have suggested that vitamin D increases adiponectin synthesis through inhibition of the rennin-angiotensin system in adipose tissue. However, studies evaluating the effects of an aerobic exercise on adiponectin and vitamin D simultaneously investigating the potential mechanism of vitamin D-dependent adiponectin pathways in patients with type 2 diabetes mellitus (T2DM) are still limited. This study was undertaken to examine the effects of aerobic exercise on adiponectin and its association with vitamin D in patients with T2DM.

Methods. Total twenty-two patients with T2DM were randomly divided into intervention and control group. The intervention group underwent a moderate intensity of a walking mode treadmill aerobic exercise for four weeks. The exercise protocol was adapted from modified Bruce test with a periodic speed and inclination increase. In both groups, body mass index (BMI), vitamin D, and adiponectin levels, were measured before and after four weeks of the lasting program.

Results. The mean of the increased adiponectin and vitamin D levels after exercise was significantly higher in the intervened than the control group, but statistically significant difference was only found in the adiponectin effect (p=0.017). There was a significant association found between vitamin D and adiponectin in the intervention group after data adjustments to age and BMI (p=0.005).

Conclusion. Moderate intensity of treadmill exercise with increased speed and inclination periodically increased adiponectin level in patients with T2DM. The increased adiponectin might potentially be mediated by increased vitamin D, but the level of their association impact was dependent on the age and BMI.

Key words: adiponectin, aerobic exercise, vitamin D, type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a metabolic disease characterized by chronic hyperglycemia resulting from insulin resistance with relative insulin deficiency or insulin secretory defect with insulin resistance American Diabetes Association (ADA 2013). This type is the most prevalent form which accounts for 90–95% of all diabetic patients. The number of people with diabetes has quadrupled from 108 million in 1980 to 422 million in 2014 World Health Organization (WHO 2016). Diabetes can lead to complications in many organs and increase the mortality risk. WHO has reported that diabetes was the ninth leading cause of death worldwide in 2019 with estimation about 1.5 million deaths directly

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caused by diabetes (WHO 2021). T2DM became one of the major health problems in the world due to the high morbidity and mortality rates.

Previous studies have reported an association between low adiponectin level with increased risk of T2DM (Duncan et al. 2004; Li et al. 2009). Adiponectin is one of peptides secreted by adipocytes known to exert insulin sensitizer, anti-hyperglycemic, anti-inflammatory, and anti-atherogenic effects (Achari and Jain 2017). Adiponectin is known to have a protective effect on the diabetes progression through sensitizing insulin by the glucose uptake increase in the muscle cell (up regulate GLUT 4 translocation), reduction of the gluconeogenesis in the liver, and stimulation of glucose and fatty acid metabolism (Polito et al. 2020). Some researchers have been conducted to evaluate potential factors that increase circulating adiponectin as a promising therapeutic strategy in T2DM, one of which is physical exercise (Simpson and Singh 2008). Several studies have documented that exercise is positively associated with increased adiponectin level, but the results were inconsistent depending to age, gender, body mass index, health status, types, duration, and intensity of the exercise (Simpson and Singh 2008). Cnop et al. (2003) have suggested that the effect of exercise on the adiponectin levels was probably mediated by body composition change. However, other mechanisms may possibly link exercise to adiponectin level.

The US National Health and Nutrition Examination Survey (NHANES III 1997) report has suggested that physical exercise is positively correlated with increased serum vitamin D, which is an essential steroid metabolite with multiple metabolic effects including regulation of insulin secretion. Positive effects of exercise on serum vitamin D have been suggested to be directly related to enhanced of vitamin D mobilization from adipose tissue (Hengist et al. 2019). Vitamin D is also indicated to have a direct association with adiponectin varies with race, gender, and body mass index (BMI) (Bidulescu et al. 2014). Recent study has shown that serum vitamin D has a positive correlation with serum adiponectin in prediabetic and type 2 diabetic groups (Banerjee et al. 2016). The mechanisms proposed is negative regulation of rennin-angiotensin system in adipose tissue by vitamin D that conquers the inhibition of adiponectin secretion (Vaidya et al. 2011). However, it is not yet clear, whether exercise induced change in the adiponectin levels may directly or indirectly be mediated by vitamin D. To our knowledge, none of the studies carried out was centered to perform a simultaneous evaluation of the effects of aerobic exercise on adiponectin and vitamin D with aim to reveal the potential mechanism of vitamin D-dependent adiponectin pathways in the patients with T2DM. This present study was aimed to examine the effects of aerobic exercise training on adiponectin level and its association with the serum vitamin D in patients with T2DM.

Materials and methods

Study design and subjects. The current study was pretest-posttest control group design which subjects randomly assigned to intervention and control group with same assessment measures obtained before and after the treatment. The inclusion criteria included male T2DM patients who have been treated by standard medication, age between 35–55 years old, and systolic blood pressure within 110–130 mmHg. We excluded subjects with restrictive or obstructive respiratory tract disease, neuromusculoskeletal disease, peripheral diabetic neuropathy, had sign of inflammations, ulcer or gangrene on either one or both legs, history of heart, kidney, thyroid, and liver disease, vestibular or proprioceptive disturbance, use of long-term steroids and vitamin D supplements, and had routine aerobic exercise at least two times per week. Subjects with symptoms of chest pain, chest tightness, hypoglycemia or sign of ischemia identified by electrocardiogram during or after exercise was dropped out from the study. Twenty-two subjects were participating in the study, then divided into intervention and control group by randomized ballot. Written informed consent was obtained from all the subjects before their participation in the study. This study has been approved by Health Research Ethics Committee of Dr. Soetomo General Hospital Surabaya Indonesia with recommendation number 1266/KEPK/VI/2019.

Experimental protocols. The intervention group was given aerobic exercise with moderate intensity and frequency three sessions per week for four weeks. The training protocol was taken from a modified Bruce test with total seven stages with increasing speed and inclination periodically every 3 min to reach target heart rate (60–75% of maximum heart rate). Aerobic exercise was performed by walking exercise in Treadmill EN-Mill 2007. The heart rate of the subjects was monitored using a portable heart rate monitor throughout the entire session of exercise to maintain the exercise intensity. Treadmill exercise was lasted for about 30 min, included each 5 min for warm-up and cool-down. Vital signs (blood pressure, heart rate, oxygen saturation) and capillary

blood glucose were assessed before training program. Subjects with normal vital sign and blood glucose level within 100–250 mg/dL were allowed to conduct the exercise. Borg scale was also assessed during treadmill to monitor perceived exertion. The subjects in the control group were instructed to maintain their lifestyle based on standards of medical care in diabetic patients, including medical nutrition therapy and exercise with duration min 150 min per week.

Anthropometric data and biochemical analysis. Clinical data (age, history of T2DM, the presences of comorbid, blood pressure) were obtained from all study subjects. Anthropometric data were measured in both groups before and after four-week program. Height and weight were examined to calculate body mass index [BMI=weight (kg)/height^2 (m^2)]. Peripheral blood samples were collected in plain tube without any activator from all study subjects before and after four-week program. Blood samples, then stored at –80°C refrigerator until analysis done. Glycemic parameters (random plasma glucose, fasting plasma glucose, fasting insulin, HbA1C), serum vitamin D, and adiponectin were measured in both groups before the start of the intervention. Vitamin D and adiponectin were measured again after four-weeks program in both groups. Vitamin D levels were measured using Siemens ADVIA Centaur Vitamin D with chemiluminescent immunoassay (CLIA). Adiponectin concentration was measured as total adiponectin by ELISA kit (E-EL-H5811, Elabscience, USA). Change of BMI, vitamin D, and adiponectin after four-week program in both groups were determined by subtracting those variables post to pre intervention.

Statistical analysis. SPSS version 16.0 was used for statistical analysis. The results of the study were presented in tabular forms. Continuous variables were presented as mean and standard deviation for normally distributed data. Continuous variables with skewed distributed data were presented as median and interquartile range. Categorical variables were presented as frequency and percentage. Comparison of clinical characteristics and biochemical parameters between intervention and control group were examined using independent sample t test for normally distributed data, Mann Whitney U test for skewed distributed data, and Chi square test for categorical variables. Bivariate correlation analysis using Pearson (for normally distributed data) or Spearman (for skewed distributed data) was also performed between the change of adiponectin level and the other studied parameters. Linear regression models were employed to investigate the relationship between change of vitamin D level and change of adiponectin level after four-week program in both groups with adjustment for their potentially confounding variables (age and BMI). A p-value <0.05 was considered statistically significant.

Results

Among 22 subjects, one subject in the intervention group was dropped out from the study due to suffered from hypoglycemia during exercise program and one subject in the control group also could not participate until completion of the study. Total 20 subjects completed the study at the end. Table 1 showed that there were no significant statistical difference of baseline clinical characteristics and laboratory parameters between each group, except for median of age (p=0.017). All study subjects had low levels of serum vitamin D (below 30 ng/ml). There was no difference of BMI and change of BMI after four-week program in both groups. Adiponectin levels post four-week program were significantly higher in the intervention than control group (p=0.003). Adiponectin increased in both groups as shown in Table 2, but statistically significant difference was only found in the intervention group (p=0.017). Median of increased vitamin D level was higher in the intervention group, but statistically insignificant (p=0.821).

Bivariate correlation analysis showed that age, BMI, and change of vitamin D level independently were not predictor of change in adiponectin level after exercise as shown in Table 3. Linear regression model was employed to investigate the relationship among the change of adiponectin level with change of vitamin D level and other confounding variables. Age and BMI were included in the model to adjust for their potentially confounding effects. The results from multiple linear regression analysis are presented in Table 4 below. Increased of vitamin D level in exercise group was significantly associated with increased adiponectin level (β=1.027, p=0.005) after adjusting for age and BMI after exercise (fitted model: F=6.79, p=0.023, adjusted R^2 =0.659). In this model, age (β=0.852, p=0.018) and BMI after exercise (β=0.769, p=0.032) were also found to be significant predictors for change of adiponectin level after exercise in the intervention group.

Discussion

This study demonstrates the effects of aerobic exercise on adiponectin levels in patients with T2DM and its correlation with change of vitamin D levels

Table 1
Baseline characteristics of the study subjects in each group.

Parameters	Intervention group (n=10)	Control group (n=10)	p-value
Age (years)	51(49–55)	47 (43–49)	0.017[a]
Diabetes duration (years)	3 (2–10)	2 (1–7)	0.361[a]
Presence of dyslipidemia (%)	20	20	1.000[c]
Presence of hypertension (%)	40	20	0.628[c]
Insulin use (%)	40	20	0.628[c]
BMI (kg/m^2)	23.9±3.5	26.7±4.4	0.141[b]
Systolic pressure (mmHg)	115 (110–120)	110 (110–120)	0.435[a]
Laboratory parameters:			
Random plasma glucose (mg/dL)	180±50	159±32	0.272[b]
Fasting plasma glucose (mg/dL)	123 (102–179)	106 (98–132)	0.226[a]
Fasting insulin (µ/ml)	10.2 (7.3–12.0)	8.5 (5.3–17.1)	0.545[a]
HbA1C (%)	6.5±1.2	7.9±2.1	0.090[b]
Vitamin D (ng/ml)	18.3 (16.2–23.1)	20.2 (18.8–25.4)	0.226[a]
Insufficiency vitamin D (%)	40	60	
Deficiency vitamin D (%)	60	40	
Adiponectin (pg/mL)	456 (420–473)	448 (418–482)	0.597[a]

Abbreviations: BMI – body mass index; HbA1C – hemoglobin A1c. [a]Mann Whitney U test was performed; [b]Independent sample t test was performed; [c]Chi-square test was performed.

Table 2
Comparison of clinical and laboratory parameters after four-week program between groups.

Variables	Intervention group (n=10)	Control group (n=10)	p-value
BMI (kg/m^2)			
Baseline	23.9±3.5	26.7±4.4	
After 4 weeks	24.9±4.0	27.4±5.3	0.250[b]
Change of BMI	0.28 (–0.45–1.88)	0.35 (–0.002–1.8)	1.000[a]
Vitamin D (ng/ml)			
Baseline	18.3 (16.2–23.1)	20.16 (18.82–25.39)	
After 4 weeks	21.7±4.5	23.26±5.47	0.510[b]
Change of vitamin D level	1.98 (–0.10–3.23)	1.2 (–1.35–4.18)	0.821[a]
Adiponectin (pg/mL)			
Baseline	456 (420–473)	448 (418–482)	
After 4 weeks	586±88	472±59	0.003[b]
Change of adiponectin level	130±108	5±105	0.017[b]

Abbreviations: BMI – body mass index. [a]Mann Whitney U test was performed; [b]Independent sample t test was performed.

to investigate the potential mechanism of vitamin D-dependent adiponectin pathways. Our study suggests that aerobic exercise with moderate intensity for four weeks increased adiponectin levels in patients with T2DM with mean difference 130±108 pg/ml. These findings complement the current knowledge regarding the effects of exercise on adiponectin level in diabetic patients. The results are in line with the previous systematic review and meta-analysis of 19 randomized controlled trials in prediabetic and diabetic adults that reported increased levels of adiponectin with mean difference 0.42 µg/ml

Table 3
Correlation between clinical and metabolic parameters to adiponectin before adjustment

Variables	Change of adiponectin level			
	Intervention group		Control group	
	p-value	r	p-value	r
Age	0.510	0.237	0.342	–0.337
Change of BMI	0.187	–0.455	0.595	0.192
Change of vitamin D level	0.603	0.188	0.450	0.270

Abbreviations: BMI – body mass index.

Table 4
Correlation between vitamin D and adiponectin with adjustment to age and BMI.

Predictors	Change of adiponectin level			
	Intervention group		Control group	
	β	p-value	β	p-value
Age	0.852	0.018	–0.478	0.240
BMI after 4 weeks	–0.769	0.032	–0.129	0.726
Change of vitamin D level	1.027	0.005	0.422	0.292

Abbreviations: BMI – body mass index.

(95% CI 0.23–0.60, p<0.00001) after physical exercise, especially aerobic but neither resistance nor concurrent exercise (Becic et al. 2018). Exercise duration of the present study was shorter than recent study performed by Aly et al. (2014) that have shown an increased adiponectin in type 2 diabetic patients after moderate intensity of supervised aerobic training for 12 weeks. The benefits of exercise in our study may be resulted from increasing speed and inclination periodically on a walking mode treadmill that thought to have greater stimulation on the musculoskeletal system and energy metabolism compared with walking on a flat surface (Kim et al. 2020). Both BMI in each group of this study was increased after four-week program, but lower in the intervention group. The effects of exercise on adiponectin were suggested to determine by body composition change, especially reduction of intraabdominal fat mass (Cnop et al. 2003; Simpson and Singh 2008). Unfortunately, several indexes to estimate body fat (e.g., waist circumference, waist-hip ratio, or skin fold thickness) were not measured in the study though could affect on adiponectin. Correlation of increased adiponectin level with change of BMI after exercise in this study showed insignificant result. However, BMI is an index of lean body mass and cannot precisely measure body composition (muscle mass or body fat percentage). Other mechanisms could also possibly mediate the effects of exercise on adiponectin, e.g., via vitamin D pathways.

All study subjects in both groups had lower levels of baseline serum vitamin D (below 30 ng/ml). This data supports the results of previous research about the higher incidence of vitamin D deficiency or insufficiency in the diabetic population (Bayani et al. 2014). Deficient of vitamin D linked to abruption of insulin secretion and sensitivity that suggested to have a connection with the incidence or progression of T2DM (Mathieu and Gysemans 2005). Baseline serum vitamin D in the intervention group were lower than a control group that may be affected by an older median of age or diabetes duration. However, increased vitamin D levels in the intervention group after aerobic exercise were higher than the control group but statistically insignificant. Adipose tissue was known to act as a reservoir for vitamin D due to lipophilicity and exercise was suggested to strongly stimulate vitamin D mobilization from adipose tissue (Hengist et al. 2019). Previous studies reported that exercise caused the rise of glucagon, adrenaline, and atrial natriuretic peptide as stimulatory lipolytic hormones and suggested as a key mechanism of vitamin D release from adipose tissue (Moro et al. 2007; Hengist et al. 2019). The lipolytic response of adipose tissue to exercise in obesity was reported reduced compared with lean controls (Mittendorfer et al. 2004). This condition may explain the lower increased vitamin D levels in control group due to higher mean of baseline BMI. However, little is known

about the effect of exercise on serum vitamin D in type 2 diabetic patients. Previous research conducted in rat experimentally-induced T2DM showed significant increase of serum vitamin D in diabetic group after moderate swimming exercise with duration 60 min a day and frequency five times a week for 4 weeks (Aly et al. 2016). These exercise protocols may suggest that higher frequency or duration of exercise is needed to increase vitamin D level significantly in patients with T2DM. This analysis supports the results from previous studies that reported higher vitamin D level in person with more intense physical activity (Chin et al. 2017).

We hypothesized that increased adiponectin level in type 2 diabetic patients might be potentially mediated by increased vitamin D level after aerobic exercise. However, the association between vitamin D and adiponectin in previous studies showed various results. Study in healthy non-diabetic adults indicating direct relationship between vitamin D and adiponectin but the association disappeared after adjustment to BMI (Gannage-Yared et al. 2009; Liu et al. 2009). Study in biracial population-based samples conducted by Bidulescu et al. (2014) reported that the association of vitamin D and adiponectin is dependent on race, gender, and BMI category. However, these studies were carried out on a heterogeneous population that numerous confounding might affect adiponectin concentration, e.g., age, gender, race, BMI, diabetes and hypertension status, anti-hypertensive drug use, dietary electrolyte intake, dietary patterns, physical activity, alcohol intake, and menopausal status (Vaidya et al. 2012).

We found a significant association between vitamin D and adiponectin in the intervention group after adjusting to age and BMI ($p=0.005$). Recent studies have suggested that vitamin D affects adiponectin synthesis by adiponectin expression gene upregulation in visceral fat and down-regulation of TNF-α gene that inflicts the adiponectin synthesis (Gannage-Yared et al. 2009). Another study also proposed that vitamin D conquers the inhibition of adiponectin synthesis through negative regulation of rennin-angiotensin system in adipose tissue (Vaidya et al. 2011). In our linear regression model, age and BMI were also found to be significant predictors of increased adiponectin level after exercise in the intervention group. These results may indicate that the association of vitamin D and adiponectin after aerobic exercise is dependent on age and BMI. Age is positively correlated with increased adiponectin level after exercise ($p=0.018$). This result builds on existing evidence of higher adiponectin concentration on older age (Isobe et al. 2005). Decreased of adiponectin clearance by kidney was suggested as a possible cause for adiponectin increase with age (Isobe et al. 2005). Hence, BMI after exercise is inversely associated with increased adiponectin level in the intervention group ($p=0.032$). This result also similar with previous study in large samples revealed lower adiponectin level in subjects with higher BMI (Nielsen et al. 2020). This finding indicates that adipose tissue may exert a negative effect on adiponectin secretion as suggested in previous studies (Foula et al. 2020).

This study has certain limitations. First, the sample size was relatively small, but it was sufficient to reproduce the association of interest. Potential confounding variables that might affect vitamin D and adiponectin concentration (e.g., dietary intake of calcium, use of thiazolidinediones medication or insulin) were not controlled in the present study. Although our study suggested that the increased adiponectin levels after aerobic exercise might be affected by vitamin D, an association was examined using the observational analysis. Thus, the direct causal-effect relationship cannot be proven. Therefore, further research with longitudinal design is needed to establish the directionality of vitamin D on adiponectin level. Since our study indicated that vitamin D might have a potential mechanism to mediate the increased adiponectin, which known to exert many benefits in patients with T2DM, future research to evaluate the effect of vitamin D supplementation on adiponectin level in type 2 diabetic patients is warranted.

Conclusion

Moderate intensity of the treadmill exercise with increased speed and inclination periodically increased adiponectin levels in patients with T2DM. The increased adiponectin levels might potentially be mediated by increased vitamin D after aerobic exercise, but the association is dependent on the age and BMI.

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Conflict of interest: *The authors declare no conflict of interest.*

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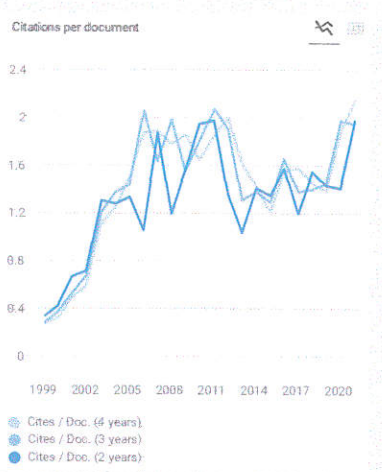

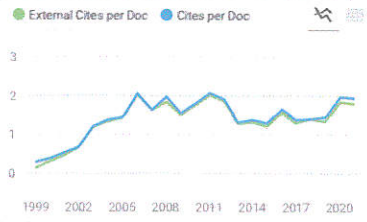

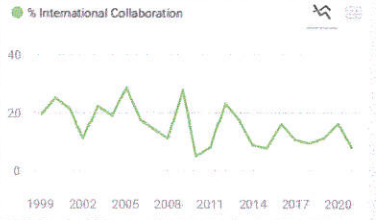

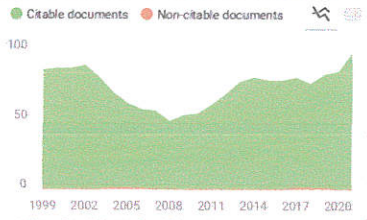

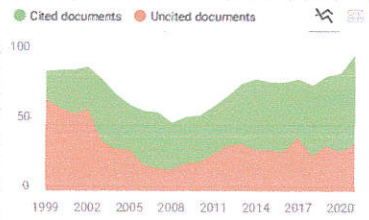

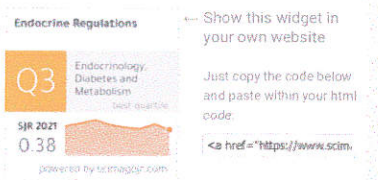

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