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Effects of treadmill exercises on pancreatic β cell function through the role of vitamin D in patients with type 2 diabetes mellitus

Efectos de los ejercicios de la cinta de correr sobre la función de las células β pancreáticas a través del papel de la vitamina D en pacientes con diabetes mellitus tipo 2

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SUMMARY

Background: *Vitamin D is a lipophilic compound that can be trapped in adipose tissue that is often obtained in metabolic syndrome. This study aims to compare 25(OH)D levels and pancreatic β cell function before and after moderate-intensity treadmill with increased speed and gradual inclination in type 2 diabetic patients.*
Method: *In this quasi-experimental trial with a pretest-posttest design, 22 patients with T2DM were divided into 2 groups: the exercise group and the control group. Participants were assessed for clinical and biochemistry. Serum insulin, fasting blood glucose, 25(OH)D, and HOMA B were calculated. All measurements were performed at the beginning and after 4 weeks of training.*
Results: *Vitamin D levels before and after the treadmill in the exercise group were 19.22 ± 4.06 ng/mL and 21.74 ± 4.53 ng/mL, respectively. While vitamin D levels before and after the treadmill in the control group were 21.71 ± 4.22 ng/mL and 23.25 ± 5.46 ng/mL, respectively. Vitamin D levels before and after the treadmill in the exercise group were significantly increased (p= 0.041) but not in the control group (p= 0.355). A significant improvement that was observed in the homeostatic model assessment of β cell function (HOMA B) was both significantly ameliorated (p= 0.013 and p= 0.032, respectively).*

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Conclusion: *Moderate intensity treadmill exercises with increased speed and gradual inclination can increase vitamin D levels and pancreatic β cell function.*

Keywords: *HOMA B, treadmill, type 2 diabetes mellitus, 25(OH)D*

RESUMEN

Antecedentes: *La vitamina D es un compuesto lipofílico que puede quedar atrapado en el tejido adiposo que se obtiene a menudo en el síndrome metabólico. Este estudio tiene como objetivo comparar los niveles de 25 (OH) D y la función de las células β pancreáticas antes y después de la cinta de correr de intensidad moderada con mayor velocidad e inclinación gradual, en pacientes diabéticos Tipo 2.*
Método: *En este ensayo cuasiexperimental con un diseño pretest-postest, 22 pacientes con DM2 se dividieron en 2 grupos: el grupo de ejercicio y el grupo de control. Los participantes fueron evaluados en términos clínicos y bioquímicos. Se calculó la insulina sérica, la glucemia en ayunas, la 25 (OH) D y el HOMA B. Todas las mediciones se realizaron al inicio y después de 4 semanas de entrenamiento.*
Resultados: *Los niveles de vitamina D antes y después de la cinta de correr en el grupo de ejercicio fueron 19,22 ± 4,06 ng/mL y 21,74 ± 4,53 ng/mL, respectivamente. Mientras que los niveles de vitamina D antes y después de la cinta en el grupo de control fueron 21,71 ± 4,22 ng /mL y 23,25 ± 5,46 ng/mL, respectivamente. Los niveles de vitamina D antes y después de la cinta de correr en el grupo de ejercicio aumentaron significativamente (p = 0,041) pero no en el grupo de control (p= 0,355). Una mejora significativa que se observó en la evaluación del modelo homeostático de la función de las células β (HOMA B) mejoró significativamente (p= 0,013 y p= 0,032, respectivamente).*
Conclusión: *Los ejercicios en cinta de correr de intensidad moderada con mayor velocidad e inclinación gradual pueden aumentar los niveles de vitamina D y la función de las células β pancreáticas.*

Palabras clave: *HOMA B, cinta rodante, diabetes mellitus tipo 2, 25 (OH) D*

INTRODUCTION

Diabetes mellitus (DM) is a global health burden affecting 285 million (6.4 %) people over the world, costing $367 billion annually. Type 2 diabetes mellitus (T2DM) is one of the leading causes of morbidity and mortality in 90 % to 95 % of all diabetic cases. The number of T2DM patients is expected to rise to 300 million by 2025 (1). Vitamin D seems to act to maintain many of the sequential events that enable the β-cells located in the pancreatic islets of Langerhans to release the insulin necessary to control blood levels of glucose (2). Vitamin D has both direct and indirect effects, the latter via regulation of calcium effects on various mechanisms related to the pathophysiology of type 2 diabetes, including pancreatic beta-cell dysfunction, impaired insulin action, and systemic inflammation. Recently, vitamin D receptor (VDR) and vitamin D-metabolizing enzymes were detected in various cell types, including pancreatic β-cells and insulin-responsive cells such as adipocytes. Adipose tissue is a major site of vitamin D storage and an important source of adipokines and cytokines participating in the formation of systemic inflammation. It is well known that obesity, especially visceral, is one of the major risk factors for T2DM (3). Vitamin D, a lipophilic compound, may be trapped in adipose tissue, resulting in serum deficiency (4). Vitamin D deficiency contributes to decreased insulin secretion in pancreatic β cells so that it can be associated with the onset of diabetes (3,5,6). Physical exercise is a strong stimulus for lipid mobilization from adipose tissue so that it can increase circulating vitamin D serum (7-9).

Treadmill is a type of aerobic exercise that has many advantages. This form of exercise resembles a natural walking feature driven by a motor or manual equipment involving a large group of lower leg muscles along with a rhythmic upper body muscle (10,11). On a treadmill workout, the speed component relates to the fast-twitch muscle fibers recruited where the fast-twitch muscle produces a higher and stronger contraction force than the slow-twitch muscle fibers, whereas the gradual inclination will also involve more muscles being recruited and works to maintain balance (11). Muscles that work will be more sensitive to insulin response than muscles that are resting. The more muscles involved, the greater the assimilation of glucose per unit of insulin during exercise. The binding of insulin to the increased receptor sites further allows for greater insulin-mediated glucose uptake (10).

This study aims to compare 25(OH)D levels and pancreatic β cell function before and after moderate-intensity treadmill with increased speed and gradual inclination in type 2 diabetic patients. We hypothesized that there would be a significant rise of 25(OH)D levels and HOMA B value after 4 weeks of training and also there were significant differences in 25(OH)D levels and HOMA B value between the two groups.

METHODS

Study design and inclusion criteria

The design of this study was a randomized pre- and post-test group. Twenty-two patients were recruited in the study. The subjects were divided into two groups: the exercise group and the control group. Inclusion criteria were male patients who have been treated with medication standard T2DM, age within 35–55 years old, and systolic blood pressure within 110-130 mmHg and also signed the informed consent form. Subjects with chronic conditions such as restrictive/obstructive respiratory tract disease, history of cardiac, kidney, thyroid, liver disease or cancer, had erythema, ulcers or gangrene in one or both legs, peripheral diabetic neuropathy, use of medications such as long-term steroids or those taking vitamin D supplements, neuromusculoskeletal disease, vestibular and proprioceptive disturbance, and a patient had a routine aerobic exercise at least two times per week were excluded from the study. Dropout criteria included changes of ischemia or cardiac disease during an exercise identified by electrocardiogram or if there were complaints of hypoglycemia, chest pain, or tightness during or after exercise. The study was approved by the Ethics committee of Dr. Soetomo General Academic Hospital Surabaya, Indonesia with ethical clearance no.1266/KEPK/VI/2019. All participants received written and verbal information regarding the nature and potential risks of the study and they were required to provide signed informed consent.

Protocols

Twenty patients took part in the study for four weeks. Participants were assessed for clinical and biochemistry. Subjects were examined in detail for recording weight, height, and body mass index (BMI). Serum insulin, fasting blood glucose, 25(OH)D, and HOMA B were calculated. All measurements were performed at the beginning and after 4 weeks of training. All the subjects in both groups were recommended to continue their previous routine medications. The subjects in the control group were also instructed to maintain their modification lifestyle until the end of the study.

An aerobic exercise program was conducted for 4 weeks (3 sessions/week, moderate intensity). The training protocol was taken from the Modified Bruce test with a total of 7 stages with increasing speed and inclination periodically every 3 minutes to reach the target heart rate (60 %-75 % maximum heart rate). Before and after exercises, we examined vital signs for blood pressure, heart rate, and oxygen saturation. We also had checked blood sugar using a glucometer (easy touch) and explained about the Borg scale. Subjects in the exercise group were allowed to exercise if blood glucose level 100-250 mg/dL. Treadmill EN-Mill® 2007 were used as walking exercise devices. We utilized Polar H10 heartbeat sensors for the heart rate, installed them to the participant's chest, and connected them through Bluetooth to smartphones (Figure 1). The treadmill exercise was about 30 min long. A 5-min warm-up was initiated before the exercise then we had core exercises which lasted for 20 min and a 5-min cool-down.

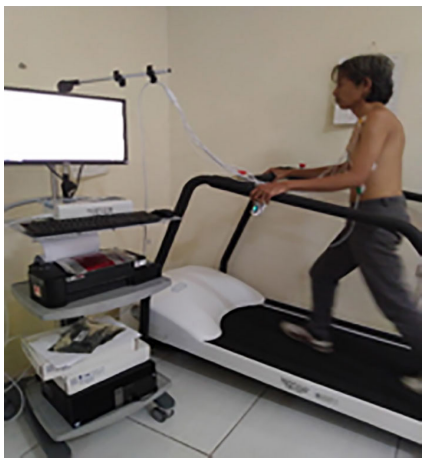

Figure 1. Participant in exercise group.

Blood samples were taken from all groups 30 min before the exercise and the last training program. Blood was drawn and put in a plain tube (without any activator) and kept in a -80 ºC refrigerator. 25(OH)D were measured using Siemens ADVIA Centaur Vitamin D with chemiluminescent immunoassay (CLIA). The function of pancreatic β cells was determined by homeostatic model assessment (HOMA) using fasting insulin and glucose concentrations. Homeostatic model assessment of β cell function (HOMA-B) was calculated through the formula: [(20 x fasting insulin (μU / mL)] / [(fasting blood sugar (mmol / L) -3.5)].

Data Analysis

We observe the average value of 25(OH)D and HOMA B. Statistical analysis was performed using SPSS for Windows version 26. The data were analyzed by descriptive tests such as mean, median, and SD (standard deviation). Shapiro-Wilk tests were performed to assess the normality of the variables before further statistical analysis. Delta 25(OH)D and HOMA B show the different values of pre-and post-exercise in each group. We used Independent samples test (for normally distributed) or Mann-Whitney U-Test (for non-normally distributed) to measure the significance of each group. The effects of treadmill exercise on the variables between the two groups were analyzed by Paired T-test (for normally distributed) or Wilcoxon test (for non-normally distributed). Statistical significance was set at $p<0.05$.

RESULTS

Twenty participants completed the 4-week intervention after two participants dropped out of the supported exercise due to hypoglycemia observed during the exercise tolerance test. All the participants were divided into two groups by randomized ballot. Table 1 demonstrates the descriptive statistics of the basic and clinical characteristics of the exercise and control groups. Patient characteristics at baseline were balanced between the two groups, especially for ages (p= 0.017). There were also no significant baseline differences between exercise and control groups for mean serum 25(OH) and HOMA-B levels.

Figure 2 shows the comparison of vitamin D status before and after treadmill exercise in the two groups. Before the program, the vitamin D status of the exercise group was 40 % for Vitamin D Insufficiency (VDI) and 60 % for Vitamin D Deficiency (VDD) while in the control group, they were 60 % for VDI and 40 % VDD. After the program, we got in the exercise group 10 % normal (Vitamin D sufficient), 60 % VDI, and 30 % VDD while in the control group, they were 20 % VDS, 50 % VDI, and 30 % VDD.

Figure 3 shows the change (delta) of vitamin D in the two groups. The mean delta 25(OH)D levels increase in the exercise group was 2.52 ± 4.65 ng/ml, while in the control group it also increased 1.53 ± 4.98 ng/mL. Comparison of delta 25(OH)D levels between two groups was calculated using the Mann Whitney test with the results of no statistically significant difference (P= 0.821).

Table 2 shows the comparison of vitamin D before and after the 4-week treadmill program in the two groups. Based on the Wilcoxon test, there was a significant difference in vitamin D levels before and after the treadmill exercise program in the exercise group (p= 0.041). Whereas in the control group, the paired T-test was used and there was no significant difference (p= 0.355) (Figure 4).

Figure 5 shows the change (delta) of HOMA-B in the two groups. The mean HOMA-B levels increase in the exercise group was 93.98±159.34 % and 227.7±284.08 % in the control group. Comparison of delta HOMA-B levels between two groups was calculated using the Mann Whitney test with the results of no statistically significant difference (p= 0.226). Table 3 shows baseline values and changes after 4 weeks in the two groups. HOMA-B level increased significantly in both groups as 197.77±245.6 % in exercise group (p = 0.013) and 343.38±349.86 % in control group (p = 0.032). There was a significant difference in the change of HOMA-B after 4-weeks in the exercise and control groups (Figure 6).

Table I

Descriptive characteristics

Basicp Characteristics	Exercise group (n=10)		Control groups (n=10)		p
	Mean ± SD	Median (Min-Max)	Mean ± SD	Median (Min-Max)	
Age (years)	50.7±4.52	51(40-55) **	46.10±3.84	47(40-52) **	0.017[b]
Duration of diabetes (years)	5.55±4.69	3(1.5-15) **	4.55±4.65	2(1-15) **	0.361[b]
BMI (kg/m^2)	23.89±3.56*	24.52(17.1-29.7)	26.66±4.44*	26.17(20.9-34.89)	0.141[a]
SBP (mmHg)	116±6.99	115(110-130)**	114±6.99	110(110-130) **	0.435[b]
HbA1C (%)	6.55±1.18*	6.35(4.5-9.0)	7.93±2.13*	7.7(5.2-11.8)	0.090[a]
Random blood glucose (mg/dL)	180.7±50.35*	178.5(103-280)	159.3±32.0*	152(117-228)	0.272[a]
25(OH)D (ng/mL)	19.22±4.06	18.3 (12.87-25.17) **	21.71±4.22	20.1 (17.38-29.59) **	0.226[b]
HOMA-B (%)	103.79±137.4	56.77 (13.3-456.8) **	115.68±127.8	63.00 (26.95-442.6) **	0.450[b]
Fasting Insulin (μU/mL)	11.28+6.17	10.22 (6.62-27.87) **	18.35+17.31	8.51 (5-24.85) **	0.545[b]
Clinical Characteristics	Σ	n (%)	Σ	n (%)	p
Insulin exogenous (%)	10	100	10	100	0.628[c]
Yes	4	40	2	20	
No	6	60	8	80	
Hypertension (%)	10	100	10	100	0.628[c]
Yes	4	40	2	20	
No	6	60	8	80	
Dyslipidemia (%)	10	100	10	100	1.000[c]
Yes	2	20	2	20	
No	8	80	8	80	

[a] = Independent T-test; [b] = Mann-Whitney test; [c] = Chi-Square test
Significant if p<0.05
Note. BMI: Body Mass Index; HOMA-B: Homeostatic model assessment of β cell function; SBP: Systolic Blood Pressure

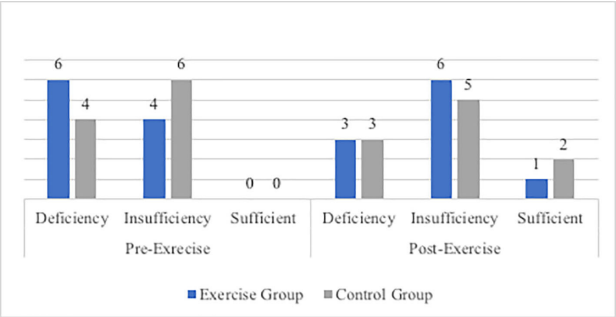

Figure 2. Clinical characteristics of vitamin D status in the two groups.

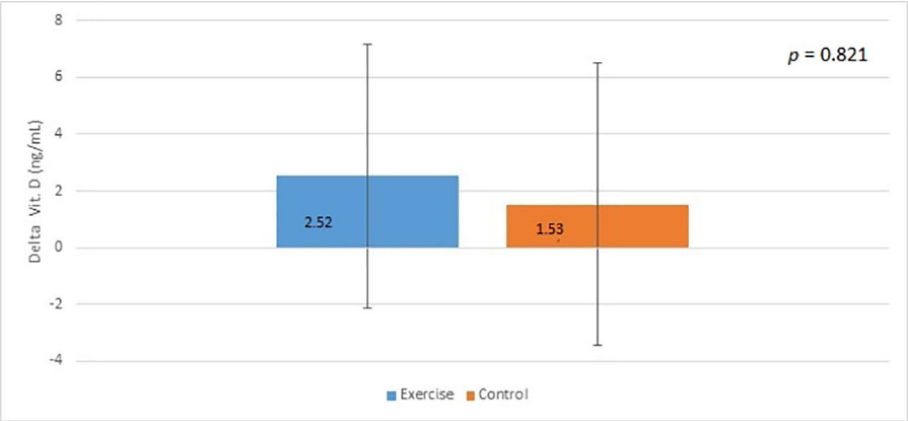

Figure 3. The change (Delta) of vitamin D in the two groups.

Table 2

Vitamin D levels before and after treadmill in both groups

Vitamin D	N	Mean ± SD (ng/mL)		p-value
		Pre	Post	
Exercise Group	10	19.22 ± 4.06	21.74 ± 4.53	0.041*
Control Group	10	21.71 ± 4.22	23.25 ± 5.46	0.355

* Significant if P <0.05

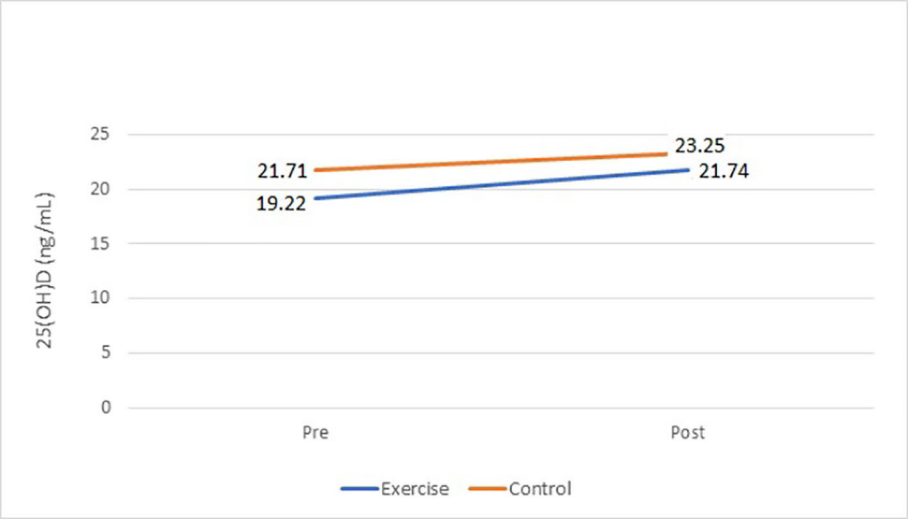

Figure 4. Changes in mean of 25(OH)D from baseline to week-4 in the two groups.

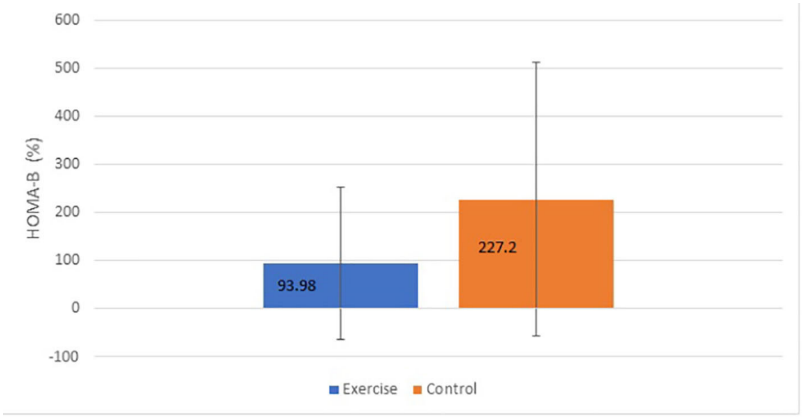

Figure 5. The change (Delta) of HOMA-B levels in the two groups.

Table 3

HOMA-B levels Before and After Treadmill in Both Groups

HOMA-B	N	Mean ± SD (%)		p-value
		Pre	Post	
Exercise Group	10	103.79 ± 137.49	197.77 ± 245.60	0.013*
Control Group	10	115.68 ± 127.89	343.38 ± 349.86	0.032*

* Significant if p <0.05

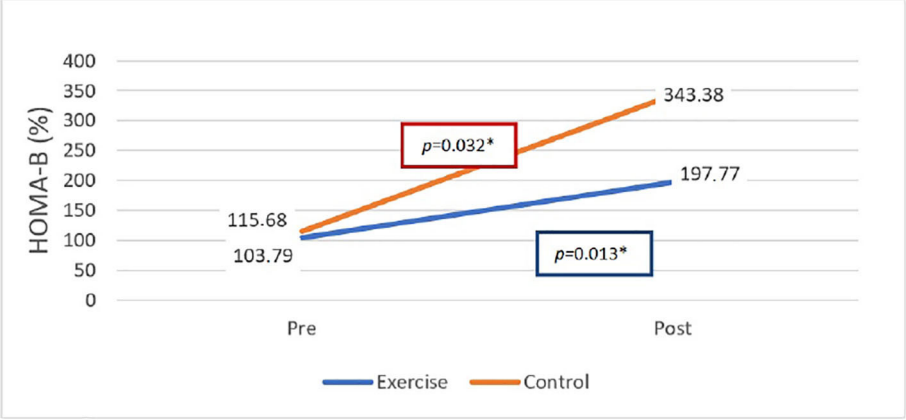

Figure 6. Changes in mean of HOMA-B from baseline to week-4 in the two groups.

DISCUSSION

Changes in vitamin D levels can occur in both groups because the intervention given to both groups, supervised and independent physical exercise, so that affected increasing vitamin D levels. The results of this study are in accordance with several previous studies which reported a positive relationship between physical exercise and vitamin D levels. In this study, there were a significant difference in the mean 25(OH)D levels before and after the treadmill exercise program in the exercise group. Meanwhile, in the

control group, there was no significant difference in 25(OH)D before and after the 4-week program. Previous research has also shown a positive relationship between physical activity and vitamin D levels. According to the studies analyzed, the increased plasma concentration of vitamin D occurs with physical activity both indoors and outdoors (12). A randomized trial study using a parallel-group design method conducted by Aoki et al. (2018) in Japan reported the change (delta) of vitamin D in the exercise group was 1.4 ± 2.33 ng/mL (p= 0.385) compared to the vitamin D group was 20.5 ± 2.42 ng/mL (p= 0.001). An intervention study on 22 subjects conducted by Sun et al. (2017) in Japan also proved that there was a direct effect of physical exercise on serum 25(OH)D concentrations, both acute and chronic exercise (9). Several other studies also reported the same thing that exercise could be a therapeutic target of adipose tissue dysfunction. Chronic increase in physical activity can increase adipocyte function so that regular physical exercise can increase sensitivity to various mediators such as insulin and adrenaline in adipose tissue in individuals with metabolic syndrome.

Several previous studies have been conducted to determine vitamin D status and its relationship with glycemic control in type 2 diabetes mellitus. In this study the subjects were given the intervention of physical activity, treadmill exercise, then analysis was carried out regarding changes in vitamin D levels before and after exercise. The level of vitamin D was serum 25(OH)D (calcidiol). Differences in vitamin D status were influenced by many other confounding factors such as age, race/ethnicity, ultraviolet exposure, gender, BMI, physical activity, use of drugs that affect vitamin D metabolism, and various comorbid diseases (12,13). Vitamin D status was also associated with cardiometabolic diseases such as metabolic syndrome, obesity, hypertension, and diabetes (3,6).

Vitamin D is lipophilic and accumulates substantially in adipose tissue. Treadmill exercise is a powerful stimulus for lipid mobilization from adipose tissue. It is therefore conceivable that vitamin D 'trapped' in adipocytes is mobilized (along with stored lipid) by physical activity. During exercise, there is a rise in plasma glucagon, adrenaline, and atrial natriuretic peptide (ANP) and a decrease in plasma insulin concomitant with increased adipose tissue blood flow. Glucagon, adrenaline, and ANP are stimulatory lipolytic hormones, and suppression of insulin leads to a potent increase in lipolysis. This leads to hydrolysis of triacylglycerol from the lipid droplet of adipocytes by the action of adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL). Exercise in the fasted or the fed state leads to an approximate twofold to threefold increase in adipose tissue lipolysis and, when stored triacylglycerol is hydrolyzed, vitamin D metabolites may also be released from the lipid droplet (7,8).

Insulin resistance and impaired β cell function are important pathological bases for impaired glucose metabolism and the occurrence of type 2 diabetes. According to a population-based study conducted by Cai et al., (2019) in China, insulin resistance is a major determinant of the development of prediabetes while cell function β is the main determinant of the development of type 2 diabetes (13). The subject population in this study were patients with type 2 diabetes, so changes in pancreatic β cell function after being given treadmill exercise intervention are important to evaluate. In this study, the mean value of HOMA-B in the exercise group was 103.79 ± 137.49 % and in the control group was 115.68 ± 127.89 %. This value indicates that the function of pancreatic β cells in both groups was still in the normal range (N: 70-150 %) and there was no significant difference between the two groups (p= 0.450). In this study, the mean value of HOMA B in the exercise group was lower than that of the control group possibly due to several associated risk factors present in the study subjects. In the exercise group, initial data were obtained that the duration of suffering from disease was longer than in the control group (5.5 years) compared to the control group, which was only 4.5 years (p= 0.361), so the possibility of a decrease in beta-cell function was greater in the exercise group. In addition, in the majority of subjects in the exercise group, comorbid hypertension was greater (40 %) compared to the control group (20 %) with mean systolic blood pressure in the exercise group which was also higher (116 ± 6.99 mmHg) compared with the control group (114 ± 6.99 mmHg).

The results of this study indicate that the

pancreatic beta-cell compensation appears heavier in the control group. HOMA-B which has exceeded 150 % means that there was excess activity of beta cells which leads to loss of beta-cell function. In this study, the results showed that there were significant differences in HOMA-B before and after the exercise program in the two groups, the exercise group, and the control group. This happens because of the effect of exercise on the body's metabolism, both acute and chronic. Treadmill with an increasing speed and gradual inclination will increase the body's metabolism, involve more muscles working rhythmically, increasing energy requirements so that the required oxygen consumption is also greater. Increasing the speed will gradually increase the heart rate along with the load speed. The higher the speed, the muscles will work harder so that oxygen demand also increases. This increase in oxygen demand as a source of energy to maintain performance in completing exercise duration (14). The gradual increase in inclination will also increase the work activity of the lower limb muscle groups. This increase in activity is due to increased muscle function in addition to moving as well as maintaining balance (15). Furthermore, the action of insulin on the muscles and liver can be modified by both the acute effect of exercise and regular physical activity so that a supervised exercise program can better improve glycemic control through increased β cell function (16).

CONCLUSION

Moderate intensity treadmill exercises with increased speed and gradual inclination can increase vitamin D levels and pancreatic β cell function.

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Disclosure

The authors declare no conflicts of interest.

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