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Morning Exercise is More Effective in Ameliorating Oxidative Stress in Patients with Type 2 Diabetes Mellitus

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Abstract

BACKGROUND: Exercise has been believed to be an important step in treating and preventing Type 2 diabetes mellitus complications. The circadian rhythm influences systems in the body, including antioxidants in the human body. By synchronizing exercise with exercise time, it will maximize the benefits of exercise for health.

AIM: This study aims to examining the effect of morning and afternoon exercise on increasing glutathione peroxidase-1 and improving oxidative stress in patients with T2DM.

METHODS: Twenty-two T2DM patients were randomly assigned to morning and afternoon exercise groups. The exercise treatment in this study was as diabetes Persadia gymnastic for 10 weeks. All participants were taken venous blood before exercise and after the 10th week. The data examined comprised GPx-1 (glutathione peroxidase-1) and MDA (malondialdehyde). The pre- and post-data were statistically processed using a comparative test.

RESULTS: After 10 weeks of exercise, GPx-1 levels increased significantly in both groups ($p = 0.00$). The increase in this enzyme was considerably greater ($p = 0.00$) in the morning group than in the afternoon group (130.37 ± 2.4 ηg/ml vs. 72.38 ± 3.93 ηg/ml). MDA levels decreased significantly in morning and afternoon groups ($p = 0.00$). The decrease in MDA was significantly greater ($p = 0.00$) in the morning than in the afternoon exercise group (8.22 ± 0.36 μmol/L vs. 5.2 ± 0.86 μmol/L).

CONCLUSIONS: Exercise in the morning was more effective in improving oxidative stress by increasing glutathione peroxidase-1 enzyme and reducing malondialdehyde in patients with type 2 diabetes mellitus.

Introduction

Diabetes mellitus is a multisystem disease with micro- and macro-vascular complications [1]. The imbalance between oxidative stress and antioxidant defense is one mechanism underlying these cardiovascular complications [2]. Oxidative stress is a condition in which there is an imbalance between antioxidant defenses and free radicals [3], [4]. Increased levels of free radicals will oxidize proteins, lipids, and nucleic acids. Oxidation of lipids produces lipid peroxides, which can be measured from levels of malondialdehyde (MDA) [5].

Patients with diabetes mellitus experience oxidative stress decreased levels of antioxidants in the body (including GPx) and increased plasma MDA levels. Decreased antioxidant capacity will cause oxidative stress, which predisposes to cardiovascular disease complications [6], [7]. Under oxidative stress, reactive oxygen species (ROS) trigger endothelial dysfunction through impaired signaling of nitric oxide (NO), a vasoprotective agent. Superoxide reacts with NO to form peroxynitrite, a potent vasoconstrictor. ROS are also associated with structural changes in vascular wall thickening and lumen narrowing [3].

GPx is an intracellular enzyme important in the body's antioxidant defense. This enzyme converts hydrogen peroxide (H_2O_2) into the water and lipid peroxide into alcohol, especially in the mitochondria and cytosol. This enzyme has an important role in inhibiting the oxidation process of lipids, protecting cells from oxidative stress [5]. GPx-1 is present in all cell types, and this enzyme deficiency is associated with atherosclerosis [3].

Exercise is one of the non-pharmacological treatments for T2DM patients [8]. Exercise is a lifestyle intervention that has been shown to increase the body's antioxidants and improve oxidative stress [9]. Shear stress due to increased blood flow during exercise can increase the antioxidant enzymes of superoxide dismutase (SOD) and glutathione peroxidase (GPx), which are responsible for ROS scavenging [10], [11], [12]. Several studies have found that exercise reduces the incidence of diabetes and serves as the foundation for T2DM management [7].

The redox system experiences a circadian rhythm, in which antioxidants are more efficient in the early morning and higher levels of lipid peroxidation in the afternoon [13]. Oxidative stress was higher in the early evening, with peak concentrations of MDA occurring at 18:00 (lower value at 06:00). The parameters of antioxidant status (total antioxidant status (TAS), total bilirubin (TBIL), uric acid (UA), CAT, and GPx activity) were higher in the early morning, with peak concentrations at 06:00 [13], [14].

By synchronizing exercise with exercise time, it is expected to get better benefits for health, especially in the body's antioxidant system. Current exercise protocols do not specify which time to exercise is better, in the morning or afternoon. However, research on this subject is still very limited. The purposes of this study were to analyze and prove the effectiveness of exercise in the morning and afternoon on GPx-1 enzyme levels and plasma MDA levels in patients with T2DM.

Methods

This research has received ethical approval from the Health Research Ethics Commission of Dr. Moewardi Hospital Surakarta, Central Java, Indonesia, No: 85/II/HREC/2021.

Research subjects were recruited from diabetes Persadia gymnastic participants in Palur, Karanganyar, Central Java, Indonesia. All members of the Persadia gymnastics association here are 90 people. Inclusion criteria were included in the study: Female gender, age 55−65 years, and BMI 23−25 kg/m^2. Exclusion criteria were excluded from the study: Receiving insulin therapy and suffering from severe complications. The participants' diet was carried out according to the doctor's recommendations, and oral antidiabetic drugs were still allowed to be consumed. Twenty-eight people who met the selection criteria were then randomly divided into the same number of morning and afternoon exercise groups. This study was intended for a research trial on a larger scale and took place during the COVID-19 pandemic at the end of 2021. Gymnastics was carried out by implementing strict health protocols. This protocol is to prevent the transmission of COVID-19 through physical distancing, washing hands with soap or hand sanitizer, and wearing masks. Six people were dropped out during the 10-week exercise treatment due to illness.

The exercise treatment was in the form of Persadia diabetes gymnastics, a moderate-intensity exercise. Moderate-intensity exercise has been shown to not cause oxidative stress. This exercise was created by the Ministry of Health of the Republic of Indonesia specifically for DM patients (https://youtu.be/Sb-dyG_V8G4). The exercise consists of a 5−10 min warm-up and stretching session, 20−30 min of core movement, and 5−10 min of cooling down. This Persadia gymnastics was carried out 3 times/week for 10 weeks, and its implementation was under the supervision of a certified trainer. The morning group exercise was done from 07.00 to 08.00, and the afternoon group was carried out from 16.00 to 17.00 (Figure 1).

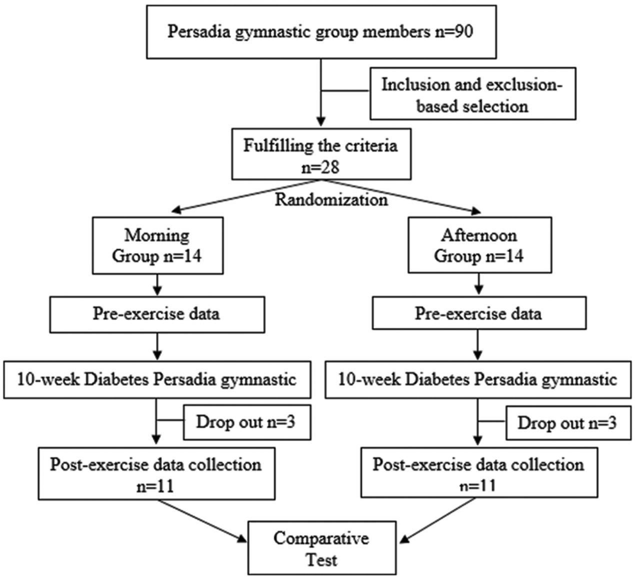

Figure 1. Research flowchart

Participants were given an explanation of the research aims and procedures according to informed consent. The explanation includes what activities could and could not be done and what foods/drinks could and could not be eaten/drank during the treatment. Participants were prohibited from participating in other sports other than Persadia gymnastics. They were not allowed to take antioxidant supplements. Blood was taken from the median cubital vein before exercise, and after the 10th week, according to the blood draw protocol.

Biochemical assessment

Random plasma glucose was measured using the hexokinase method. Random plasma glucose levels were measured in mg/dl. MDA was estimated using a spectrophotometric method focusing on the reaction of MDA and thiobarbituric acid (TBA). The MDA concentration (measured at 532 nm) was expressed in µmole/L. Plasma levels of GPx-1 were analyzed using the Abbexa ELISA kit. To reduce variability, duplicate samples were run on each plate with the ELISA kit using standard 96-well plates, and the two aliquots mean was used to measure GPx-1 concentration.

Statistical analysis

Data were presented in the form of mean ± SD. The Shapiro–Wilk test was used to analyze the data normality, while the Levene's test was used the analyze variance. The GPx-1 data were normally shared and homogeneous. A dependent t-test was used for the pre- and post-exercise. To ascertain the difference data of morning and afternoon groups, an independent t-test was used. The MDA data for the morning and afternoon groups were normally distributed and homogeneous. To determine the difference between pre- and post-exercise data, the dependent t-test was used. Meanwhile, the MDA difference data were normally distributed but not homogeneous, so Mann–Whitney U-test was implemented. SPSS program (version 25) was used to measure data, and the significant difference was set up at the level of $p < 0.05$.

Results

The subjects' characteristics included age, BMI (WHO criteria), and random plasma glucose levels that were normally distributed and homogeneous (Table 1).

Table 1: Characteristics of morning and afternoon groups (mean ± SD)

Variable	Mean ± SD		p
	Morning group (*n* = 11)	Afternoon group (*n* = 11)	
Age (year)	61.09 ± 3.59	60.64 ± 3.64	0.77*
BMI (kg/m^2)	23.99 ± 0.58	24.35 ± 0.55	0.15*
Random plasma glucose (mg/dl)	226.98 ± 40.15	230.98 ± 45.75	0.72#
The duration of suffering from T2DM illness (year)	13.91 ± 3.02	14.92 ± 4.18	0.74#

*Independent t-test, #Mann–Whitney U-test. BMI: Body mass index, T2DM: Type 2 diabetes mellitus, SD: Standard deviation.

GPx-1 is one of the first-line antioxidant enzymes important for protecting the body from oxidative stress. The level of this enzyme will decrease in conditions of oxidation accentuate. Figure 2 shows an increase in GPx-1 enzyme levels after 10 weeks of exercise. Tests using t-test showed a significant increase in levels of GPx-1 pre- and post-exercises (p = 0.00) in both the morning and afternoon exercise groups. This shows that regular exercise in the morning and afternoon could increase levels of the antioxidant enzyme GPx-1. The increase in GPx-1 levels was significantly different (p = 0.00) between the morning and afternoon exercise groups, where the increase was greater in the morning group.

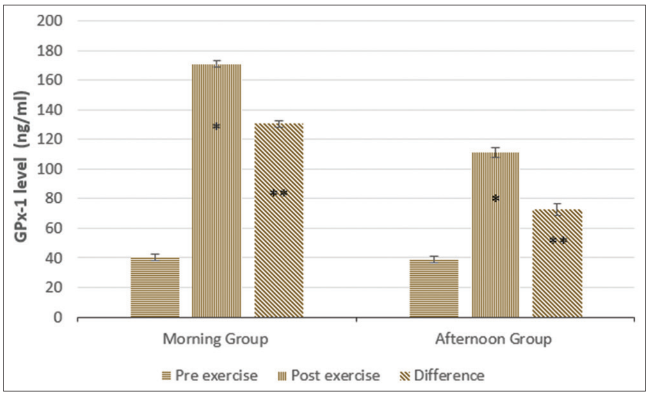

*Figure 2. Effects of morning and afternoon exercise for 10 weeks on plasma GPx-1 levels. Data are presented in Mean ± SD (n = 11 people/group). GPx-1 was examined using the ELISA method. *p < 0.05 compared to the pre-exercise group (dependent t-test). **p < 0.05 difference between the morning and afternoon groups (independent t-test).*

MDA is a dialdehyde compound that is the end product of lipid peroxidation. A high concentration of MDA indicates an oxidation process in the cell membrane. The results of pre-exercise and post-exercise measurements indicated a significant decrease in MDA (p = 0.00) both in the morning exercise group and the afternoon exercise group (t-test). This shows that regular Persadia gymnastics could reduce MDA levels. The decrease in MDA levels was different between the morning and afternoon exercise groups, where the decrease in MDA was significantly greater (p = 0.00) in the morning exercise group (Figure 3).

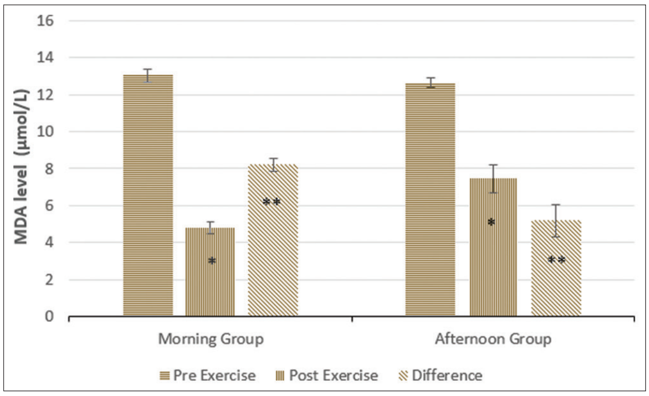

*Figure 3. Effects of the morning and afternoon exercise for 10 weeks on plasma MDA levels. Data are presented in Mean ± SD (n = 11 people/group). MDA was checked by the TBARS method. *p < 0.05 compared to the pre-exercise group (dependent t-test). **p < 0.05 difference between the morning and afternoon groups Mann–Whitney U-test.*

Discussion

Regular exercise is the main non-pharmacological management in patients with T2DM. Exercise can increase antioxidant capacity and reduce oxidative stress in this disease [15]. Diabetes Persadia gymnastic is recommended for people with diabetes mellitus because this exercise includes moderate-intensity exercise that is suitable for people with diabetes and the elderly [16]. Moderate-intensity exercise does not increase lipid peroxidation. The previous research has indicated that moderate- and long-term exercise activates the production of endogenous antioxidants [14]. Besides being influenced by intensity, duration, and frequency, exercise is also influenced by the time of exercise (time of day). Thus, it is necessary to determine the right time so that exercise provides greater benefits to the prevention of cardiovascular complications in T2DM.

This study's findings revealed a significant increase in GPx-1 after diabetes exercise in both the morning and afternoon groups. The previous research on experimental animal models of DM showed a significant increase of the antioxidant enzyme GPx-1 after treadmill and swimming exercise compared to the sedentary DM control group [17], [18], [19]. Twelve weeks chronic exercise of moderate-intensity exercise significantly increased GPx levels (41.75%) in healthy elderly women [12]. Yoga and conventional exercise for 6 months increased SOD levels in T2DM patients significantly [20]. Sixteen weeks of exercise significantly increased GPx activity (15%) in healthy elderly subjects [18].

Several studies have shown that regular, moderate-intensity exercise induces the endogenous antioxidant system (EAS) and protects the body from damage caused by oxidative stress, therefore reducing the risk of cardiovascular disease [19]. The aging process causes an increase in protein breakdown through oxidative damage and selective protein degradation, accompanied by a decrease in protein synthesis. This gradually leads to a decrease in antioxidant enzyme levels in aging tissue, especially in skeletal muscle. Endurance training can reverse age-related reductions in muscle protein content, as well as mitochondrial oxidative capacity [18].

Increased blood flow during exercise causes shear stress able to increase the antioxidant enzymes of superoxide dismutase (SOD) and glutathione peroxidase (GPx), which are responsible for scavenging reactive oxygen species (ROS) [10]. Exercise can upregulate the expression of heat shock protein to increase antioxidant capacity in patients with T2DM. Another mechanism, exercise will activate nuclear factor erythroid 2-related factor 2 (Nrf2). Nrf2 is a nuclear transcription factor that coordinates a complex antioxidant cytoprotection system, stimulated by increased oxidative stress during exercise. Activation of Nrf2 by physical activity binds to the antioxidant response element (ARE) and activates the antioxidant response. Nrf2 regulates the synthesis and metabolism of glutathione [19], [20].

Measurement of GPx-1 in this study showed that the increase in GPx-1 levels was greater after exercise in the morning compared to the afternoon. The results of this study are in line with the results of research by Hammouda *et al*. They concluded that antioxidant status was more efficient in morning exercise than in the afternoon in young football players [13]. Circadian rhythms regulate all activities in the body, including the antioxidant system, where the activity of the antioxidant system is higher in the morning [14], [13]. High GPx levels in the morning will increase even higher by doing moderate-intensity exercise regularly. The mechanism for the greater increase in GPx-1 in the morning group may be related to higher levels of melatonin in the morning than in the afternoon [14]. Melatonin secretion was still ongoing at 08.00 and was not secreted again at 16.00. Melatonin has been shown to increase higher after exercise in the morning than in the afternoon [21]. Afternoon exercise blunted/reduced melatonin secretion compared to morning exercise [22]. Melatonin is an antioxidant hormone that can stimulate other antioxidant enzymes (SOD and GPx) [23]. Melatonin contributes to an increase in the body's total antioxidant capability [24]. The antioxidant ability of melatonin is 10 times more efficient than other antioxidants [25]. Meanwhile, Mc. Mullan *et al*.'s study found an independent relationship between decreased melatonin secretion and an increased risk of T2DM [26]. However, in this study, melatonin levels were not measured.

Another factor contributing to the greater increase in GPx-1 in the morning exercise group was that during exercise in the morning a person would be exposed to UVB-rich sunlight (290–315 nm), which would increase the body's production of Vitamin D. In most people, UVB rays are the main source of Vitamin D [27]. Vitamin D levels in T2DM patients were lower than in controls [28]. Vitamin D has been shown to have antioxidant activity. Vitamin D can fight the activity of NADPH oxidase in producing ROS, so it will increase antioxidant enzymes [28], [29].

Meanwhile, in this study, plasma MDA levels decreased significantly after regular exercise ($p < 0.05$), both for the morning exercise group and the afternoon exercise group. The results of the previous studies in Turkey in patients with T2DM, and experimental animal models of DM, showed that regular aerobic exercise could significantly reduce MDA levels compared to controls [6], [17]. Regular aerobic exercise for 12 weeks in patients with T2DM significantly reduced MDA levels [6]. Research on experimental animal models of DM showed that swimming for 2 months could significantly reduce MDA levels [17]. Hatha yoga and conventional exercise for 6 months could significantly reduce MDA levels in patients with T2DM [30]. Regular moderate-intensity exercise would improve redox homeostasis by increasing antioxidant levels (SOD and TAS) and reducing MDA levels [7], [31]. Chronic exercise with strenuous intensity would significantly increase MDA levels, but moderate-intensity exercise tended to decrease MDA levels, which means lower levels of oxidative stress [32]. Research on the Wistar rat model DM also showed that regular exercise for 6 weeks increased levels of the antioxidant enzyme GPx and decreased plasma and cardiac MDA levels [33].

This study indicated that the decrease in MDA levels after regular exercise in the morning was significantly greater than after exercise in the afternoon. This decrease was associated with an increase in the antioxidant enzyme GPx-1 in the morning group which was greater than in the afternoon group. The previous research involving healthy respondents showed that there was a significant increase in MDA levels after the afternoon Yo-Yo intermittent recovery test (YYIRT) exercise [34].

Research by Kim *et al*., 2015, showed that there was a higher increase in plasma adrenaline after exercise in the afternoon, compared to the morning. This increase in adrenaline affected the increase in interleukin-6, which, in turn, IL-6 would increase lipolysis and plasma free fatty acid levels [35]. Meanwhile, patients with T2DM experienced a 30% decrease in the number and size of mitochondria, and dysfunctional mitochondrial proteins in skeletal muscle cells (skeletal myocyte). Therefore, the increase in post-exercise FFA in the afternoon accompanied by a decrease in the oxidation ability in DM patients was at risk for the accumulation of intermediate FFA compounds such as ceramide, and diacylglyceride, long-chain fatty acyl-CoA. This will lead to increased oxidative stress, impaired insulin signaling, and insulin resistance [3], [8]. Meanwhile, patients with T2DM have chronically elevated plasma FFA levels, which cause insulin resistance in the muscles and liver and interfere with insulin secretion in the pancreas. This phenomenon is termed lipotoxicity, which causes pancreatic β-cell dysfunction [36]. However, adrenaline and free fatty acid levels were not measured in this study.

The small research sample and unanalyzed intake of food and energy are the limitation of this study, so it requires careful interpretation of the results. However, these research data have confirmed previous studies, which state that exercise is beneficial for improving oxidative stress by increasing plasma GPx-1 levels and decreasing plasma MDA levels. Moreover, it turned out to be the fact that the improvement was more significant in the morning exercise group.

Conclusions

This study proved that exercise could improve oxidative stress by increasing levels of the GPx-1 antioxidant enzyme and lowering MDA levels. Exercise in the morning has a greater effect on improving oxidative stress, so it is hoped that it will be able to prevent cardiovascular complications in patients with DMT-2.

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References

1. Decroli E. In: Kam A, Effendi YP, Decroli GP, Rahmadi A, editors. Diabetes Melitus Tipe 2. 1st ed. Padang: Bagian IPD FK Universitas Andalas Padang; 2019.
2. Hwang M, Kim S. Type 2 diabetes : Endothelial dysfunction and exercise. J Exerc Nutr Biochem. 2014;18(3):239-47. https://doi.org/10.5717/jenb.2014.18.3.239
PMid:25566460
3. Akhigbe R, Ajayi A. The impact of reactive oxygen species in the development of cardiometabolic disorders: A review. Lipids Health Dis. 2021;20(1):23. https://doi.org/10.1186/s12944-021-01435-7
PMid:33639960
4. Kayama Y, Raaz U, Jagger A, Adam M, Schellinger IN, Sakamoto M, *et al*. Diabetic cardiovascular disease induced by oxidative stress. Int J Mol Sci. 2015;16(10):25234-63. https://doi.org/10.3390/ijms161025234
PMid:26512646
5. Ighodaro OM, Akinloye OA. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): Their fundamental role in the entire antioxidant defence grid. Alexandria J Med. 2018;54(4):287-93. https://doi.org/10.1016/j.ajme.2017.09.001
6. Arslan M, Ipekci SH, Kebapcilar L, Dede ND, Kurban S, Erbay E, *et al*. Effect of aerobic exercise training on MDA and TNF-α levels in patients with Type 2 diabetes mellitus. Int Sch Res Notices. 2014;2014(4):820387. https://doi.org/10.1155/2014/820387
PMid:27437465
7. Teixeira-Lemos E, Nunes S, Teixeira F, Reis F. Regular physical exercise training assists in preventing Type 2 diabetes development : Focus on its antioxidant and anti-inflammatory properties. Cardiovasc Diabetol. 2011;10(1):12. https://doi.org/10.1186/1475-2840-10-12
PMid:21276212
8. Dipla K. The FITT principle in individuals with Type 2 diabetes : From cellular adaptations to individualized exercise prescription. J Adv Med Med Res. 2017;22(11):1-18. https://doi.org/10.9734/JAMMR/2017/34927
9. Möbius-Winkler S, Linke A, Adams V, Schuler G, Erbs S. How to improve endothelial repair mechanisms : The lifestyle approach. Expert Rev Cardiovasc Ther. 2010;8(4):573-80. https://doi.org/10.1586/erc.10.7
PMid:20397830
10. Di Francescomarino S, Sciartilli A, Di Valerio V, Di Baldassarre A, Gallina S. The effect of physical exercise on endothelial function. Sport Med. 2009;39(10):797-812. https://doi.org/10.2165/11317750-000000000-00000
PMid:19757859
11. Ghisi GL, Durieux A, Pinho R, Benetti M. Physical exercise and endothelial dysfunction. Arq Bras Cardiol. 2010;95(5):e130-7. https://doi.org/10.1590/s0066-782x2010001500025
PMid:21225112
12. Rusip G, Suhartini SM. Effects of moderate intensity exercise on glutathione peroxidase activity and vo2 max in elderly women. Open Access Maced J Med Sci. 2020;8(A):230-3. https://doi.org/10.3889/oamjms.2020.3837

13. Hammouda O, Chahed H, Chtourou H, Ferchichi S, Miled A, Souissi N. Morning-to-evening difference of biomarkers of muscle injury and antioxidant status in young trained soccer players. Biol Rhythm Res. 2012;43(4):431-8. https://doi.org/10.1080/09291016.2011.599638
14. Ammar A, Chtourou H, Souissi N. Effect of time-of-day on biochemical markers in response to physical exercise. J Strength Cond Res. 2017;31(1):272-82. https://doi.org/10.1519/JSC.0000000000001481

    PMid:27191691
15. Atalay M, Laaksonen DE. Diabetes, oxidative stress and physical exercise. J Sport Sci Med. 2002;1(1):1-14.

    PMid:24672266
16. Kholid A. Prosedur Senam Diabetes Melitus; 2007. Available from: https://www.academia.edu/35646071/PROSEDUR_SENAM_DIABETES_MELLITUS.
17. Karimi SA, Salehi I, Taheri M, Faraji N, Komaki A. Effects of regular exercise on diabetes-induced memory deficits and biochemical parameters in male rats. J Mol Neurosci. 2021;71(5):1023-30. https://doi.org/10.1007/s12031-020-01724-3

    PMid:33000398
18. Fatouros IG, Jamurtas AZ, Villiotou V, Pouliopoulou S, Fotinakis P, Taxildaris K, *et al*. Oxidative stress responses in older men during endurance training and detraining. Med Sci Sports Exerc. 2004;36(12):2065-72. https://doi.org/10.1249/01.mss.0000147632.17450.ff

    PMid:15570141
19. Vargas-Mendoza N, Morales-González Á, Madrigal-Santillán EO, Madrigal-Bujaidar E, Álvarez-González I, García-Melo LF, *et al*. Antioxidant and adaptative response mediated by Nrf2 during physical exercise. Antioxidants (Basel). 2019;8(6):196. https://doi.org/10.3390/antiox8060196

    PMid:31242588
20. Lew JK, Pearson JT, Schwenke DO, Katare R. Exercise mediated protection of diabetic heart through modulation of microRNA mediated molecular pathways. Cardiovasc Diabetol. 2017;16(1):10. https://doi.org/10.1186/s12933-016-0484-4

    PMid:28086863
21. Marrin K, Drust B, Gregson W, Morris CJ, Chester N, Atkinson G. Diurnal variation in the salivary melatonin responses to exercise : Relation to exercise-mediated tachycardia. Eur J Appl Physiol. 2011;111(11):2707-14. https://doi.org/10.1007/s00421-011-1890-7

    PMid:21399961
22. Carlson LA, Koch AJ, Pobocik KM, Lawrence MA, Brazeau DA. Influence of exercise time of day on salivary melatonin responses. Int J Sports Physiol Perform. 2018;14(3):351-3. https://doi.org/10.1123/ijspp.2018-0073
23. Tarocco A, Caroccia N, Morciano G, Wieckowski MR, Ancora G, Garani G, *et al*. Melatonin as a master regulator of cell death and inflammation : Molecular mechanisms and clinical implications for newborn care. Cell Death Dis. 2019;10(4):317. https://doi.org/10.1038/s41419-019-1556-7

    PMid:30962427
24. Benot S, Goberna R, Reiter RJ, Garcia-Mauriño S, Osuna C, Guerrero JM. Physiological levels of melatonin contribute to the antioxidant capacity of human serum. J Pineal Res. 1999;27(1):59-64. https://doi.org/10.1111/j.1600-079x.1999.tb00597.x

    PMid:10451025
25. Tan DX, Manchester LC, Esteban-Zubero E, Zhou Z, Reiter RJ. Melatonin as a potent and inducible endogenous antioxidant: Synthesis and metabolism. Molecules. 2015;20(10):18886-906. https://doi.org/10.3390/molecules201018886

    PMid:26501252
26. McMullan CJ, Schernhammer ES, Rimm EB, Hu FB, Forman JP. Melatonin secretion and the incidence of type 2 diabetes. JAMA. 2013;309(13):1388-96. https://doi.org/10.1001/jama.2013.2710

    PMid:23549584
27. Nimitphong H, Holick MF. Prevalence of Vitamin D deficiency in Asia Vitamin D status and sun exposure in Southeast Asia. Dermatoendocrinol. 2013;5(1):34-7. https://doi.org/10.4161/derm.24054

    PMid:24494040
28. Elnasr MS, Ibrahim IM, Alkady MM. Role of Vitamin D on glycemic control and oxidative stress in Type 2 diabetes mellitus. J Res Med Sci. 2017;22:22. https://doi.org/10.4103/1735-1995.200278

    PMid:28413419
29. Kim DH, Meza CA, Clarke H, Kim JS, Hickner RC. Vitamin D and endothelial function. Nutrients. 2020;12(2):575. https://doi.org/10.3390/nu12020575
30. Gordon LA, Morrison EY, McGrowder DA, Young R, Fraser YT, Zamora EM, *et al*. Effect of exercise therapy on lipid profile and oxidative stress indicators in patients with Type 2 diabetes. BMC Complement Altern Med. 2008;8:21. https://doi.org/10.1186/1472-6882-8-21

    PMid:18477407
31. Anam SC, Sulistiawati S, Purwanto B. Acute response moderate intensity treadmill training on decrease malondialdehyde in obesity women. Str J Ilm Kesehat. 2020;9(2):358-67. https://doi.org/10.30994/sjik.v9i2.301
32. Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, *et al*. Effect of different intensities of exercise on endothelium-dependent vasodilation in humans role of endothelium-dependent nitric oxide and oxidative stress Circulation. 2003;108:530-5. https://doi.org/10.1161/01.CIR.0000080893.55729.28

    PMid:12874192
33. Naderi R, Mohaddes G, Mohammadi M, Ghaznavi R, Ghyasi R, Vatankhah AM. Voluntary exercise protects heart from oxidative stress in diabetic rats. Adv Pharm Bull. 2015;5(2):231-6. https://doi.org/10.15171/apb.2015.032

    PMid:26236662
34. Aloui K, Abedelmalek S, Chtourou H, Wong DP, Boussetta N, Souissi N. Effects of time-of-day on oxidative stress, cardiovascular parameters, biochemical markers, and hormonal response following level-1 Yo-Yo intermittent recovery test. Physiol Int. 2017;104(1):77-90. https://doi.org/10.1556/2060.104.2017.1.6

    PMid:28361573
35. Kim H, Konishi M, Takahashi M, Tabata H, Endo N, Numao S, *et al*. Effects of acute endurance exercise performed in the morning and evening on inflammatory cytokine and metabolic hormone responses. PLoS One. 2015;10(9):e013767. https://doi.org/10.1371/journal.pone.0137567

    PMid:26352938
36. Kuryłowicz A, Kózniewski K. Anti-inflammatory strategies targeting metaflammation in Type 2 diabetes. Molecules. 2020;25(9):2224. https://doi.org/10.3390/molecules25092224

    PMid:32397353