Exercise Moderate Interval as an Alternative Exercise Model to Improve Insulin Sensitivity in Type 2 Diabetes Mellitus

Yetty Machrina^{1,*}, Ambrosius Purba², Dwi Rita Anggraini³

¹Department of Physiology, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

²Department of Physiology, Faculty of Medicine, Universitas Padjajaran, Indonesia

³Department of Anatomy, Faculty of Medicine, Universitas Sumatera Utara, Indonesia

Received October 15, 2021; Revised January 17, 2022; Accepted January 25, 2022

Cite This Paper in the following Citation Styles

(a): [1] Yetty Machrina, Ambrosius Purba, Dwi Rita Anggraini, "Exercise Moderate Interval as an Alternative Exercise Model to Improve Insulin Sensitivity in Type 2 Diabetes Mellitus," *Universal Journal of Public Health*, Vol. 10, No. 1, pp. 138 - 144, 2022. DOI: 10.13189/ujph.2022.100115.

(b): Yetty Machrina, Ambrosius Purba, Dwi Rita Anggraini (2022). *Exercise Moderate Interval as an Alternative Exercise Model to Improve Insulin Sensitivity in Type 2 Diabetes Mellitus*. *Universal Journal of Public Health*, 10(1), 138 - 144. DOI: 10.13189/ujph.2022.100115.

Copyright©2022 by authors, all rights reserved. Authors agree that this article remains permanently open access under the terms of the Creative Commons Attribution License 4.0 International License

Abstract Background: Previous study had found that adherence of patient Diabetes type-2 in moderate to vigorous continuous exercise was poor. Meanwhile regularly exercise needs to control fasting plasma glucose in T2DM. Exercise moderate interval (EMI) shows a significant effect to reduce insulin resistance in metabolic syndrome patients. But, studies to find the effect of EMI or EMC to muscle insulin receptor distribution are still limited. So, the purpose of this study is to compare the effects of EMI vs EMC in increasing insulin receptors and reducing insulin resistance in T2DM rat models. **Methods:** An experimental study was conducted in T2DM rat models. According to the treatments, rats were randomly assigned into the following 3 groups: sedentary group (SG), exercise moderate continuous (EMC) and exercise moderate interval (EMI). Each training session was performed on treadmill for eight weeks, three times weekly. Insulin receptor was assessed by immunohistochemistry. Meanwhile, insulin resistance was determined by Homeostatic Model Assessment for Insulin (HOMA-IR) score measured before and after completing the training session. **Results:** This study found that the insulin receptors in EMI = 184% and EMC= 158%. Both insulin receptors in the treatment groups had a significant difference to the sedentary group ($p=0.002$), but there was no significant difference in insulin receptors between EMI and EMC group ($p=0.222$). HOMA-IR in EMI group was

16.6 $\pm$ 4.0 significantly different with HOMA-IR in EMC group such as 43.3 $\pm$ 8.6 ($p=0.000$). There was a negative correlation between insulin receptor and insulin resistance ($p=0.047$, $r=-0.520$). **Conclusion:** Both exercise moderate interval and exercise moderate continuous could increase insulin receptors on skeletal muscle, but exercise moderate interval showed better improve insulin sensitivity after eight weeks' exercise. We suggested exercise moderate interval as an alternative exercise for Type 2 Diabetes Mellitus.

Keywords Insulin Receptor, Insulin Resistance, Exercise Moderate Interval, Exercise Moderate Continuous

1. Introduction

Nowadays, exercise in T2DM has been popular due to its potential to improve insulin sensitivity [1,2,3]. Increasing insulin sensitivity is characterised by decreasing insulin resistance and lowering fasting plasma glucose [4]. American Diabetes Care has declared that aerobic exercise that spares 150 minutes/week with moderate to vigorous intensity is recommended for the management of T2DM [5]. Birkinshaw et al (2018) found that T2DM patient did

not follow exercise guidance nor aerobic and resistance training with moderate and vigorous intensity. The adherence was poor [6]. Age category and type of medication were influence factors of adherence [7]. Machrina et al found that both continuous training and interval training had glycemic control effect on T2DM rat models [8].

Insulin receptors where ligand binds, mostly found in skeletal muscle, liver and adipose tissue, play an important role in maintaining glucose homeostasis. They are known to be down-regulated in T2DM [9,10]. These receptors also play an important role for insulin signalling to reduce blood glucose [11]. Decreased in receptor density affects insulin signalling downstream, resulting in disruption of glucose transporter-4 (GLUT-4) translocation to the cell surface [12, 13, 14] which promotes hyperglycemia. Exercise is known to activate AMP- kinase and stimulate insulin signaling, regulate GLUT-4 translocation that facilitates glucose to enter the cell. [15] Meanwhile, cortisol from adrenal cortex is released as the stressor effect of exercise, promotes gluconeogenesis at cellular metabolism that up-regulates insulin receptor gene expression [16].

Many studies proved that both continuous training and interval training had a positive effect to insulin resistance and fasting blood glucose [17]. These trainings, although performed in the same intensity, are different in metabolic energy usage, because there is an active rest phase in interval training. A study found that exercise carried out continuously even in moderate intensity could not have a high level of adherence for patients without supervision [18]. This condition was probably related to saturation that arose during exercise. People, then, tried to apply interval training model to maintain glycemic control in diabetic patient [19,20,21] and studies found that exercise carried by intervals gave a better reduction in insulin resistance rather than exercise carried out continuously in patients with metabolic syndromes and type 2 DM [22,23].

This study was conducted to find out the effect of EMC and EMI increasing insulin receptors. The comparison impact between these exercises to insulin receptor is still limited. Accordingly, the purpose of this study was to compare level of insulin receptors and insulin resistance in skeletal muscles of type 2 DM rat models with interference of that two models of training.

2. Material and Methods

2.1. Animal Model

This was an experimental study using male Wistar (*rattus novergicus,sp*) which was obtained from Bogor Agricultural Institute. Eighteen rats were placed in a room that is regulated a 12/12 hours dark/light cycle. All the experimental procedures involving animals were performed in accordance with the ethics of experimental

animals. Making rats become T2DM model, they were given high fed diet (HFD) for five weeks. Then, the rats were injected low dose of Streptozotocin (30 mg/kg and 45 mg/kg body weight, dissolved in 0.1 cc citrate buffer pH 4.5) twice by 1-week intervals intraperitoneally. Rats were defined as T2DM model if fasting blood glucose > 200 mg/dl and HOMA-IR > 6.5. We divided groups into a sedentary group (SG), exercise slow interval (EMI) and exercise moderate continuous (EMC).

2.2. Exercise Protocol

The intervened groups, such as EMI and EMC were given exercise every two days, 30 minutes for each session, with a speed of 25 m/min continuously for EMC, 2 x 10 min with a-minute active rest for EMI group. Interventions were given throughout 8 weeks for both groups. Meanwhile SG left without physical activity.

2.3. HOMA-IR Assessment

We assessed HOMA-IR and fasting blood glucose before and after exercise intervention. About 3 ml blood was taken from tail vein and put into a non-EDTA tube, then it was centrifuged in 6000 rpm for 3 minutes to get blood serum. Ten µl of blood serum was used to assess insulin hormone using ELISA method. This examination procedure is performed in accordance with Elisa Kit instruction (Qayee-Bio, Shanghai). Insulin level then was read by Elisa reader. Fasting blood glucose was assessed by spectrophotometer. Fasting blood glucose and fasting insulin were calculated to determine HOMA-IR, which is an indicator for insulin resistance.

2.4. Immunohistochemistry for Insulin Receptor

After all protocol was done, all rats were executed with sedation and *musculus gastrocnemius* was excised and kept in paraffin block for immunohistochemical examination. Paraffin block was deparaffinized with xylol, sliced with microtome, and the slice was put on the object glass. Slides was dehydrated with ethanol 90% and 70% for 5 minutes each. It soaked into buffer saline and buffer citrate pH 6. The primary antibody (Insulin receptor antibody from GeneTex) and secondary antibody (Dako) were dripped on the slide after washed with PBS. Antibodies bound to fluorescent receptors are calculated manually on four medium fields of view. Insulin receptors were determined by assessing the receptor distribution and staining intensity. Insulin receptor density was expressed as a percentage. Calculations are made by anatomical pathologists and validated by two observers.

2.5. Expression of GLUT-4

About 30 mg of skeletal muscle tissue was extracted with RNA isolation kit from Tiangen (Tiangen, Beijing,

China). Working solution was prepared 2x qPCR B SensiFast SYBR, Primer 0,8µl, Primer R 0,8µl, template RNA 2µl and NF water 6,4µl. Beta actin was chosen as reference gene. Primer for GLUT-4 (F) 5'-GCCGGGACACTATACCCTATT -3', (R) 5'-GAATACAGCAAGGACCAGTGT-3'. Beta actin (F) 5'-GTGTGGATTGGTGGCTCTAT-3' (R) 5'-GAAAGGGTGTAACACGCAGC-3'. The amplification process was performed using RotorGene (Qiagen, Germany), which was programmed to perform the following steps; 2 min hold at 95°C, and then 40 cycles at 95°C for 5 s and 60°C for 20 s.

2.6. Statistic Analysis

All data were analysed using SPSS. Data normality was tested with *Shapiro wilk* ($p > 0.05$). Kruskal Wallis and Mann U Whitney test were used to compare insulin receptors and insulin resistance among groups. Besides, Wilcoxon test was used to compare Insulin receptor between EMI group and EMC group and the correlation between insulin receptor and insulin resistance in this study was analysed with Spearman rank correlation. Data was significant if the p -value < 0.05 .

2.7. Ethics

Selection, calculation of sample number, method of administering treatment and way of animal execution were according to the ethics of animal experiment, i.e. reduction and refinement. This study had been approved by the medical faculty of Universitas Sumatera Utara and Adam Malik general hospital committee ethic No. 263/KOMET/FK USU/2016.

3. Result

The Average of fasting blood glucose and HOMA-IR before intervention in the three groups can be seen in table.1 From the data we can see that fasting blood glucose before intervention of all groups was > 200 mg/dl and HOMA-IR $> 6,5$. These meant that all subjects had become T2DM.

Insulin receptors in both treatment groups were increased compared to that in the sedentary group. Statistical analysis found that there was a difference in distribution percentage of insulin receptor between sedentary group and treatment groups ($p=0,002$). Percentage of insulin receptors distribution in EMI was higher than that in EMC but post host LSD analysis result shows that it was not significant. ($p=0,093$). (figure.1a)

HOMA-IR in EMI decreased significantly ($p=0.001$) compared to that in SG.(figure.1b) Unlike EMI, in EMC eight weeks of exercise did not improve HOMA-IR significantly compared to that in SG ($p=0.066$) (figure. 1b) Insulin receptors upregulation on skeletal muscle is followed by insulin resistance reduction. There was a negative correlation between insulin receptors and insulin resistance in this study ($p=0,047$, $r = -0,520$). Insulin resistance decreased because insulin receptors on skeletal muscle and mRNA GLUT-4 gene expression increased in the treatment groups followed by lowering plasma glucose between groups. The magnitude of decrease in fasting blood glucose in EMI is in line with increase in insulin receptors while mRNA GLUT-4 gene expressed 3,75 fold in EMI than control, and 2,39 fold in EMC (figure.2 and figure.3)

Table 1. The Average of fasting blood sugar and HOMA-IR before intervention

Groups	Blood Glucose (mg/dl)		HOMA-IR	
	Mean	SD	Mean	SD
SG	474.80	55.68	107.1	14.4
EMI	452.60	31.28	94.0	21.1
EMC	339.00	13.71	90.5	40.5

Notes: SD = standar deviation, SG=sedentary group, EMI = exercise moderate interval , EMC = exercise moderate continuous

Figure 1. Insulin receptor and insulin resistance difference between sedentary and treatment groups after 8 weeks exercise.

IR=insulin receptor (%), HOMA-IR= Homeostatic Model Assessment for Insulin Resistance, ΔFBG= FBG post test-pre test. (mg/dL)

Figure 2. The comparison of insulin Receptor, HOMA-IR and FBG decreased between EMI and EMC

Figure 3. Relative expression of GLUT-4 mRNA EMI vs EMC

Immunohistochemical findings of insulin receptor expression from T2DM rat model gastrocnemius. IR expression was sign by brown staining. Scored was according to area and intensity of membranous staining. (A) exercise moderate interval, score 2; (B) exercise moderate continuous, score 2; and (C) sedentary, score 1. (Magnification, x400)

Figure 4. Immunohistochemical finding of the skeletal muscle insulin receptor in control and treatment groups

4. Discussion

Performing exercise three times a week for eight weeks can improve insulin sensitivity by increasing insulin receptors and reducing insulin resistance. The results showed that insulin receptors in both EMC and EMI increased significantly compared to that in the sedentary group. In this study, the percentage distribution of insulin receptors in EMI was more than that in EMC, even though

it was not statistically different. This result was linear with Tjonna et.al. In that study, aerobic interval training induced insulin receptors phosphorylation enhancement in skeletal muscle [23].

During exercise, sympathetic activity suppressed pancreatic beta cells and increased cortisol and glucagon secretion to meet glucose demand to the cells. It is known that cortisol influences gene transcription, and high blood glucose is a sensor for insulin receptors to increase their

density. During the intermittent phase of slow interval training, decreased sympathetic activity promotes insulin release from the pancreatic beta cells. If this happens for several times, this stimulation certainly increases the number of insulin receptors [24,25]. Meanwhile, in moderate continuous training, insulin secretion was suppressed throughout the exercise.

The increase of insulin receptors in the treatment group was linear with reduction of insulin resistance and glucose levels in both groups. These results were more significant than that from the continuous group. Mitranun et al. found that patients with type-2 diabetes mellitus who trained on the treadmill 30-40 min/day, three times a week for 12 weeks showed that interval training was effective in maintaining glycemic control as well as continuous training, even gave more significant improvements [26]. Along with Mitranun, Villages JM also found muscle adaptation remodelling was faster in aerobic interval training especially in high intensity, thus increasing mitochondrial capacity that decreases insulin resistance faster than that in moderate continuous training [27]. Likewise, the activity of AMPK and PGC-1 α in the liver that have importance roles in gluconeogenesis and mitochondrial biogenesis, the gene expression decreased similar with higher intensity after being given exercise for 8 weeks, in DMT2 rats. [28]

Exercise intensity in moderate continuous training and slow interval training were the same. The difference is in the type of exercise, one continuously and the other intervally. Exercise carried out continuously means someone does the exercise consistently for 30 minutes without any rest, while interval training means there is an intermittent resting phase for a minute. Intermittently conducted exercises give benefits to the patient regarding eliminating boredom and fatigue so that their adherence to exercise becomes greater [13]. Moreover, sympathetic suppression during exercise will disappear for a moment so that the insulin hormone release at intervals without having to wait up to 30 minutes [29,30]. Insulin hormone is a ligand where its augmentation promotes more insulin receptor synthesis. Upregulation of the insulin receptors on the skeletal muscle, liver and adipose tissue leads to improve insulin signalling. Thus, insulin receptor sensitivity became better [31,32].

5. Conclusion

Exercise for eight weeks could increase the level of insulin receptors in skeletal muscle both in EMI and EMC. Insulin receptors distribution enhancement was higher in EMI compared to EMC and so in case with GLUT-4 mRNA gene expression. This enhancement was parallel with reduction in insulin resistance and fasting blood glucose. EMI was recommended as an alternative exercise model for patients with type 2 diabetes mellitus rather than EMC.

Acknowledgment

This study was supported by the grants Number 183/UN5.2.3.1/PPM/SP/2016 from Indonesian Higher Education. The author is also very grateful to the laboratory staff for experimental animals.

Conflict of Interest

There was no conflict of interest in the study.

REFERENCES

- [1] Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, ... & Braun B. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. *Diabetes care*. 2010;33(12): e147-e167. URL: <https://doi.org/10.2337/dc10-9990>
- [2] Van Dijk JW, Manders RJ, Tummers K, Bonomi AG, Stehouwer CD, Hartgens F, & Van Loon LJ. Both resistance and endurance-type exercise reduce the prevalence of hyperglycaemia in individuals with impaired glucose tolerance and in insulin-treated and non-insulin-treated type 2 diabetic patients. *Diabetologia*. 2012;55(5):1273-1282. URL: <https://doi.org/10.1007/s00125-011-2380-5>
- [3] Van Dijk JW, Tummers K, Stehouwer CD, Hartgens F, & Van Loon LJ. Exercise therapy in type 2 diabetes: is daily exercise required to optimize glycemic control?. *Diabetes care*, 2012. DC_112112. URL: <https://doi.org/10.2337/dc11-2112>
- [4] Dugan, JA. Exercise recommendations for patients with type 2 diabetes. *Journal of the American Academy of Pas*. 2016; 29(1): 13-18. URL: <https://doi.org/10.1097/01.jaa.0000475460.77476.f6>
- [5] American Diabetes Association. *Standards of medical care in diabetes—2015 abridged for primary care providers. Clinical diabetes: a publication of the American Diabetes Association*. 2015;33(2): 97 . URL: <https://doi.org/10.2337/diaclin.33.2.97>
- [6] Amy Birkinshaw, Riette Nel & Corinna Walsh (2018) Adherence of patients with type 2 diabetes mellitus with the SEMDSA lifestyle guidelines, *Journal of Endocrinology, Metabolism and Diabetes of South Africa*, 23:2, 39- 45, DOI: 10.1080/16089677.2018.1433110
- [7] ALhariri I A, Daud F , Almainan A and Sultan Saghir SAM. Factors associated with adherence to diet and exercise among type 2 diabetes patients in Hodeidah city, Yemen. *Diabetes Manag* (2017) 7(3) , 264–271
- [8] Machrina Y, Purba A, Lindarto D, & Daulay M. Chronic Effect Various Type of Exercises to Fasting Blood Glucose and Insulin Resistance. *Sumatera Medical Journal*, 2019: 2(2); 61-66. URL: <https://doi.org/10.32734/sumej.v2i2.1063>
- [9] Okabayashi Y, Maddux BA, McDonald AR, Logsdon CD,

- Williams JA and Goldfine ID. Mechanisms of Insulin-Induced Insulin-Receptor Downregulation: Decrease of Receptor Biosynthesis and mRNA Levels. *Diabetes* 1989 Feb; 38(2): 182-187. URL : <https://doi.org/10.2337/diab.38.2.182>
- [10] Greenstein B. *Endocrinology at a Glance*. Arizona Arthritis Center. College Medicine University of Arizona. Blackwell Science. 2006; p 75-76 .
- [11] Sherwood L. *Human physiology: from cells to systems*. 2015
- [12] Bhattacharya S, Dey D, & Roy SS. Molecular mechanism of insulin resistance. *Journal of biosciences*. 2007; 32(2): 405-413. URL : <https://doi.org/10.1007/s12038-007-0038-8>
- [13] Dey D, Basu D, Roy SS, Bandyopadhyay A, & Bhattacharya S. Involvement of novel PKC isoforms in FFA induced defects in insulin signaling. *Molecular and cellular endocrinology*. 2006;246(1-2): 60-64. URL : <https://doi.org/10.1016/j.mce.2005.12.014>
- [14] Choi K and Kim. Molecular Mechanism of Insulin Resistance in Obese and Type 2 Diabetes. *Korean J Intern Med* 2010;25:119-129. URL: <https://dx.doi.org/10.3904/jkim.2010.25.2.119>
- [15] Sarvas, JL, Otis JS, Khaper N, & Lees SJ. Voluntary physical activity prevents insulin resistance in a tissue specific manner. *Physiological reports*. 2015;3(2). URL : <https://dx.doi.org/10.14814%2Fphys2.12277>
- [16] Machrina Y, Purba A, Lindarto D, Maskoen AM. Exercise Intensity Alter Insulin Receptor Gene Expression in Diabetic Type - 2 Rat Model. *Open Access Maced J Med Sci*. 2019;7(20):3370-5. URL : <https://doi.org/10.3889/oamjms.2019.425>
- [17] Soewondo P. *Current Practice in the Management of Type 2 Diabetes in Indonesia*. 2011.
- [18] Bartlett JD, Hwa Joo C, Jeong TS, Louhelaine J, Cochran AJ, Gibala MJ, ... & Morton JP. Matched work high-intensity interval and continuous running induce similar increases in PGC-1 α mRNA, AMPK, p38, and p53 phosphorylation in human skeletal muscle. *Journal of applied physiology*. 2012;112(7): 1135-1143. URL : <https://doi.org/10.1152/japplphysiol.01040.2011>
- [19] Jakobsen I, Solomon TPJ, Karstoft K. The Acute Effects of Interval-Type Exercise on Glycemic Control in Type 2 Diabetes Subjects: Importance of Interval Length. A Controlled, Counterbalanced, Crossover Study. *PLoS ONE* .2016;11 (10); e0163562. URL : <https://doi.org/10.1371/journal.pone.0163562>
- [20] Gallo-Villegas, J., Aristizabal, J.C., Estrada, M. *et al*. Efficacy of high-intensity, low-volume interval training compared to continuous aerobic training on insulin resistance, skeletal muscle structure and function in adults with metabolic syndrome: study protocol for a randomized controlled clinical trial (Intraining-MET). *Trials* . 2018;**19**, 144 URL : <https://doi.org/10.1186/s13063-018-2541-7>
- [21] Alizadeh Z, Kordi R, & Mansournia MA. Adherence to intermittent and continuous aerobic exercise prescription in overweight and obese women, a randomized clinical trial. *Archives of Exercise in Health & Disease*. 2014;4(3). DOI: 10.5628/aehd.v4i3.146
- [22] Motiani KK, Savolainen AM, Eskelinen JJ, Toivanen J, Ishizu T, Yli-Karjanmaa M, et al. Two weeks of moderate-intensity continuous training, but not high-intensity interval training, increases insulin-stimulated intestinal glucose uptake. *Journal of Applied Physiology*. 2017;122(5): 1188-1197. URL: <https://dx.doi.org/10.1152%2Fjappphysiol.00431.2016>
- [23] Tjønnå AE, Lee SJ, Rognmo O, Stølen TO, Bye A , Haram PM, et.al. 2008. Aerobic interval training versus continuous moderate exercise as a treatment for the metabolic syndrome. A pilot study circulation,118:346-354. URL : <https://doi.org/10.1161/CIRCULATIONAHA.108.772822>
- [24] Hill EE, Zack E, Battaglini C, Viru M, Viru A, Hackney AC. Exercise and circulating cortisol levels: the intensity threshold effect. *Journal of endocrinological investigation*.2008. Vol. 31(7):587-91. URL : <https://doi.org/10.1007/bf03345606>
- [25] Geer EB, Islam J, Buettner C. Mechanisms of glucocorticoid-induced insulin resistance: focus on adipose tissue function and lipid metabolism. *Endocrinology and Metabolism Clinics*. 2014;43(1);75-102. URL: <https://doi.org/10.1016/j.ecl.2013.10.005>
- [26] Mitranun W, Deerochanawong C, Tanaka H, & Suksom D. Continuous vs interval training on glycemic control and macro - and microvascular reactivity in type 2 diabetic patients. *Scandinavian journal of medicine & science in sports*. 2014;24(2); e69-e76. URL : <https://doi.org/10.1111/sms.12112>
- [27] Gallo-Villegas J, Aristizabal JC, Estrada M, Valbuena LH, Narvaez-Sanchez R, Osorio J, et al Efficacy of high-intensity, low-volume interval training compared to continuous aerobic training on insulin resistance, skeletal muscle structure and function in adults with metabolic syndrome: study protocol for a randomized controlled clinical trial (Intraining-MET). *Trials*. 2018; 19(1): 144. URL: <https://doi.org/10.1186/s13063-018-2541-7>
- [28] Machrina Y, Pane YS, Lindarto D. The Expression of Liver Metabolic Enzymes AMPK α 1, AMPK α 2, and PGC-1 α due to Exercise in Type-2 Diabetes Mellitus Rat Model. *Open Access Maced J Med Sci*. 2020; 8(A):629-632. URL : <https://doi.org/10.3889/oamjms.2020.4550>
- [29] Wilcox G. Insulin and insulin resistance. *Clinical Biochemist Reviews*. 2010;26(2), 19
- [30] Raven PB, Wasserman DH, Squires WG, Murray TD. *Exercise Physiology An Integral Approach*. International Edition. Wadsworth, Cengage Learning. 2013; p149, 192-194.
- [31] Motallebi F, Shakerian S, Ranjbar R. Effect of 8 Weeks Aerobic Interval Training on Glycosylated Hemoglobin and Insulin Resistance Index in Diabetic Mellitus Type 2 Women. *Quarterly of the Horizon of Medical Sciences*. 2016;22(2):137-143
- [32] Karstoft K, Winding K, Knudsen SH, James NG, Scheel MM, Olesen J (2014). Mechanisms behind the superior effects of interval vs continuous training on glycaemic control in individuals with type 2 diabetes: a randomised controlled trial. *Diabetologia*. 2014;57(10): 2081-2093. URL: <https://doi.org/10.1007/s00125-014-3334-5>