Combination of Aerobic and Resistance Exercise in Lowering Blood Glucose Levels Compared to Aerobic or Resistance Exercises in a Male Wistar Rat Model with Diabetes Mellitus

Sahrul Latif[1], Dwikora Novembri Utomo[2], Purwo Sri Rejeki[3]

[1]*Student of Magister Program of Sport and Health Science, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia*

[2]*Department of Orthopedics and Traumatology, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia*

[3]*Department of Physiology, Faculty of Medicine, University of Airlangga, Surabaya, Indonesia,*

{kosambi_bante, dwikora_utomo, purwo_faal}@yahoo.com, purwo-s-r@fk.unair.ac.id

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Abstract: Diabetes mellitus (DM) is one of the biggest global health emergencies in the 21st century. Exercise plays an important role in the prevention and management of type 2 diabetes because of its function in controlling blood glucose levels. This study aimed to compare the decrease of glucose levels as a result of aerobic, resistance and combination exercise in a male Wistar mice DM model. It was an experimental study with a pretest-posttest group design. A total of 33 male Wistar rats were divided into three groups; K1 (aerobic exercise), K2 (resistance training) and K3 (aerobic and resistance combination exercises). Glucose level data were collected before and after the *treatment*. The data of each group were processed using a paired t-test. Differences between groups were tested using One-Way ANOVA followed by Post Hoc with LSD. Mean glucose levels of K1 pre-test was 322.18±26.430 mg/dL, post-test 117/36±19.946 mg/dL ($p < 0.001$), K2 pre-test 365.27±67.406 mg/dL, post-test 121.36±20.461 mg/dL ($p<0.001$), K3 pre-test 394.64±73.992 mg/dL, post-test 114.27±17.124 mg/dL ($p = 0.001$). Mean Δ blood glucose level in group K1 (204.82 ± 29.842) mg/dL, K2 (243.91±60.907) mg/dL and K3 (280.36±29.924) mg/dL. One-Way ANOVA test results showed $p = 0.013$ and the LSD test compared between K1 and K2 ($p = 0.111$), K1 compared to K3 ($p = 0.003$), K2 compared to K3 ($p = 0.136$). The three types of exercises (aerobic, resistance and combination) lowered the blood glucose levels. Comparison between the three types of exercises showed that combination exercise has better ability in lowering blood glucose levels compared to other exercises.

1 INTRODUCTION

Medical discovery and innovations against diabetes mellitus (DM) continue to grow and the number of adult patients is expected to increase faster than before (Danaei et al., 2011). Based on data from the International Diabetes Federation in 2015, the prevalence of diabetes mellitus is 1 in 11 adults and is expected to increase in 2040 to 1 in 10 adults. Riskesdas (Basic Health Research) results of the Ministry of Health of the Republic of Indonesia in 2013 showed that the proportion of diabetes mellitus in Indonesia is 6.9% with an estimated absolute number of 12 million people, while undiagnosed patients is estimated to be more than 8 million people. Personal health costs and public costs due to diabetes mellitus are quite high and are expected to double in the next 25 years, leading to an increase in the economic burden for patients and the healthcare system (Scobie, 2007; Huang et al., 2009). Lack of understanding of social and economic impacts is the biggest barrier to blood glucose control. Thus, the combination of diet, physical activity and formulating a prevention policy that suppresses the increase of type 2 diabetes mellitus is needed.

Exercise has an important role in the prevention and management of type 2 diabetes mellitus because of its ability to control blood glucose (Colberg et al., 2010). This type of combination exercise can improve the control of blood glucose greater than isolated exercise (Oliveira et al., 2012). Research combining aerobic exercise and resistance training (combination exercise) has proven to be more

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advantageous and better than the type of exercise modality (Colberg et al., 2010; Snowling and Hopkins, 2006). Simultaneous exercise between resistance and aerobic exercise resulted in disrupted adaptation. The genetic and molecular adaptation mechanisms induced by resistance and aerobic exercise are different, and each mode of activation of the exercise can suppress certain gene parts and cellular signaling pathways (Hawley, 2009). To this extent the effect of combination exercises performed separately when compared with aerobic exercise and resistance to control of blood glucose levels has not been elucidated.

Aerobic exercise activates the signal pathway of adenosine-monophosphate-activated protein kinase (AMPK)-p38, mitogen-activated protein kinase (MAPK), and the peroxisome proliferator-activated receptor-gamma co-activator (PGC)-1 axis. Activation of AMPK from aerobic exercise may inhibit the mTOR signal through the tuberous sclerosis complex (TSC) and suppress the induction of muscle protein synthesis in resistance exercise. While resistance exercise activates phosphatidylinositol 3-kinase (PI3-k), the target activation of rapamycin (mTOR) signifies a cascade to modulate protein synthesis levels or long-term (weeks to months) damage and muscle hypertrophy; thus, it is estimated that combination exercise which is done separately between aerobics and its combination will result in a decrease in glucose levels better than either aerobic or resistance exercise only (Snowling and Hopkins, 2006). This study aimed to prove that aerobic, resistance and combination exercises have the ability to lower blood glucose levels in a male Wistar rat model with diabetes mellitus, as well as compare the result of combination exercises and aerobic exercise as well as resistance training in lowering blood glucose levels.

2 MATERIAL AND METHODS

2.1 Research design

It was a laboratory experimental study with a pretest-posttest group design (Zainuddin, 2014). The subjects of this study were male Wistar rats, aged 8-10 weeks, weighing 100-200 grams and agile physical condition. The 33 rats were divided into three groups. K1 group was given aerobic exercise, K2 was given resistance training and K3 was given combination exercises. The study protocol was approved by the ethics committee of Dr. Soetomo Teaching Hospital Surabaya, Indonesia on July 27, 2007 with the number 748-KE.

2.2 Diabetes Mellitus Model

Diabetes mellitus condition was induced through the provision of a high-fat diet and STZ injection. A high-fat diet with 29% fat content, 35% carbohydrate and 17% protein was given for 28 days. STZ injections of 27.5 mg/kg in a citrate buffer (pH 4.3-4.5) were given as a single dose with a concentration of 22.4 mg/ml on day 29 (Rimbun., 2015). Hyperglycemic rats are rats with blood sugar levels of 180-500 mg/dL (Etuk, 2010).

2.3 Aerobic Exercise

Aerobic exercise was carried out with 3% weight-bearing swimming of fasting weight, tied 5 cm from the tip of the tail. Exercise was given once a day and 3 times/week. The swimming time was 80% of the maximum swimming time.

2.4 Resistance Exercise

Resistance exercises were carried out with 9% weight-bearing swimming of fasting weight, tied 5 cm from the tip of the tail; exercises were performed in 3 sets with 3 repetitions of each set with the time for each set being 60 seconds. Exercise was given 1 times/day with the frequency of 3 times/week and done for 4 weeks. The swimming time was 80% of the maximum swimming time.

2.5 Combination Exercise

Combination exercise was done by combining aerobic exercise and resistance training in separate sessions. The aerobic exercise was given twice/week, while resistance training was given once/week for 4 weeks. The length of swimming time was 80% of the maximum swimming time (McArdle and Montoye, 1966).

2.6 Blood Glucose Level

Blood glucose measurements were taken from the rats' tails using an on-Call device plus blood glucose meter. Measurements were made one day pre-treatment and one day post-treatment.

2.7 Data Analysis

Data were analyzed using descriptive distribution, analyzed by a normality test, homogeneity test, and paired t-test to see the effect of treatment in the same group and the One-Way ANOVA test to ascertain the difference between the groups. It was then followed by Post Hoc Test using LSD. The data were analyzed using SPSS 20.0 *for Windows*.

3 RESULT

3.1 Body Weight

The smallest pretreatment weight was 105 grams and the largest was 181 grams. The smallest post-admission weight was 107 grams and the largest was 202 grams. The result details are shown in Table 1.

3.2 Blood Glucose Level

The lowest blood glucose levels after the high-fat diet and induced STZ (pre-exercise) was 292 mg/dL and the highest was 562 mg/dL. The lowest post-exercise blood glucose level was 71 mg/dL and the highest was 155 mg/dL. The results are shown in Table 2.

Based on the paired t-test, there were differences in pre-test and post-test glucose levels between groups K1 ($p = 0.006$), K2 ($p = 0.000$) and K3 ($p = 0.001$) with all groups showing $p < 0.05$.

3.3 Pre-test and post-test

The delta of pretest and post-test glucose level data exhibited the lowest level of 157 mg/dL and the highest one of 426 mg/dL. See Table 3 for details.

4 DISCUSSION

4.1 The Effect of Aerobic Exercise on Blood Glucose Level

K1 group shows that aerobic exercise can lower blood glucose levels in a male Wistar mice model with diabetes mellitus. The decrease in blood glucose levels due to aerobic exercise is similar to that of the research showing that aerobic exercise improves blood glucose control and decreases oxidative stress in type-2 diabetes mellitus (Nojima et al., 2008). Other studies revealed that aerobic exercise is beneficial for blood glucose control and blood glucose absorption as well as increased muscle insulin sensitivity (Colberg et al., 2010).

Several studies conducted based on different durations of aerobic exercise showed that short-term aerobic exercise decreases arterial stiffness in the carotid and femoral arteries by using ultrasound examination. This flexibility improvement is associated with amelioration of insulin resistance that affects the relationship between exercise and insulin resistance in skeletal muscle and arterial wall stiffness in type-2 DM (Yokoyama, 2003). Meanwhile moderate intensity aerobic exercise plays an important role in disrupting the normal development of diabetic peripheral neuropathy (DPN) in type-2 DM (Dixit et al., 2014).

The active mechanism of aerobic exercise in lowering blood glucose levels through activation of signaling pathways is involved in metabolic homeostasis, namely adenosine monophosphate-activated protein kinase (AMPK)-p38, mitogen-activated protein kinase (MAPK), and the peroxisome proliferator-activated receptor-gamma co-activator (PGC-1) axis. Aerobic exercise promotes muscle protein expression that can increase muscle capacity to increase glucose uptake in two ways. The first way is to inhibit the elements that interfere with the stimulus of insulin by increasing the capacity of beta-oxidation of fatty acids through increased mitochondrial density. The second way is by increasing the expression of GLUT4 and the insulin path component (Dos Santos et al., 2015).

4.2 Effects of Resistance Exercises on Blood Glucose Level

K2 group shows that resistance training can lower blood glucose levels in a male Wistar mice model with diabetes mellitus. The results of this study are similar to research where resistance training increased insulin sensitivity and glucose tolerance; therefore, it is very effective to improve overall metabolic health and reduce metabolic risk factors in DM patients (Strasser, 2013). Recent research suggests that resistance training is considered a future prescription for improving type 2 diabetes. This type of exercise is a promising strategy for promoting overall metabolic health in individuals with type 2 DM, through improved mitochondrial muscle performance and increased muscle mass that positively impacts the response to insulin and glucose control (Pesta, 2017).

The glucose clearance mechanism as a beneficial effect is due to stimulation of glycogen synthesis resistance training by inhibition of glycogen synthase kinase 3β (GSK3) by AKT. GSK3β regulates the storage of glucose in the form of glycogen. AKT inhibits GSK3 by phosphorylating serine residues (Ser9 in GSK3). GSK3 inhibition increases the activation of glycogen synthase that contributes to glycogen stimulation. Glycogen synthase is an enzyme responsible for catalyzing the α (1→4) relationship in glycogen formation in non-oxidative glucose removal. The increased activity of AKT-mediated glycogen synthase is a form of adaptation of glucose control in response to resistance training (Case et al., 2011).

Table 1: Mean and delta of pre-test and post-test weight gain

Group	n	Weight (gram)		Δ weight (gram)
		Pretest Mean ± SD	Post-test Mean ± SD	Mean ± SD
K1	11	153.00 ± 20.746	162.64 ± 23.775	- 9.636 ± 9.287
K2	11	144.00 ± 22.974	150.55± 22.518	- 6.545 ± 3.857
K3	11	147.55 ± 13.772	150.55 ± 22.518	- 5.455 ± 4.156

Table 2: Mean and delta of pre-test and post-test weight gain

Group	n	Blood glucose level (mg/dl)						Sig.
		Pretest			Post test			
		Mean ± SD	Min	Max	Mean ± SD	Min	max	
K1	11	322.18 ± 26.430	292	379	117.36 ± 19.946	71	142	0.000*
K2	11	365.27 ± 67.406	310	541	121.36 ± 20.461	104	155	0.000*
K3	11	394.64 ± 73.992	311	562	114.27 ± 17.124	90	142	0.000*

*Superscripts show results that have significant differences in pretest and post-test ($p < 0.05$)

Table 3. Mean and delta of pre-test and post-test weight gain

Group	n	Mean Δ Blood Glucose Level (mg/dL) Mean ± SD	Minimum	Maximum
K1	11	(204.82 ± 29.842)^{a}	157	244
K2	11	(243.91 ± 60.907)^{a,b}	167	399
K3	11	(280.36 ± 29.924)^{b,c}	180	426

*Superscripts show result that have significant differences in pretest and post-test ($p < 0.05$)

4.3 The Effect of Combination Exercises on Blood Glucose Levels

K3 group shows that combination exercises can lower blood glucose levels in a male mice Wistar model with diabetes mellitus. These results are similar to those stating that combined exercise is an effective exercise method for improving functional capacity, body fat mass, strength and blood glucose control in people with type 2 DM (Maiorana et al., 2002).

A Randomized Controlled Trial conducted a combination of aerobic exercise and resistance training compared with the control group without exercise resulted in improved HbA1c levels in type 2 DM patients. However, this cannot be achieved by either aerobic or resistance exercise only (Church et al., 2010). This is in line with the opinion that a combination of resistance and aerobic exercise regimens increases the control of glucose greater than aerobic exercise or resistance training intervention alone (Oliveira et al., 2012).

Combination exercises in this study were conducted at different times because the research conducted showed that simultaneous exercise comprising resistance and aerobic exercise resulted in disrupted adaptation, compared to one exercise mode only. The genetic and molecular adaptation mechanisms induced by resistance and aerobic exercise are different with each activation mode of the exercise suppressing certain gene parts and cellular signaling pathways. Resistance training induces increased activity of the phosphatidylinositol 3-kinase (PI3-k)-Akt-activation target of rapamycin (mTOR) which signifies a cascade to modulate the rate of protein synthesis or long-term damage and muscle hypertrophy. Aerobic exercise activates signaling pathways involved in metabolic homeostasis, consisting of adenosine monophosphate-activated protein kinase (AMPK)-p38, mitogen-activated protein kinase (MAPK), and the peroxisome proliferator-activated receptor-gamma co-activator (PGC)-1 axis. Activation of AMPK from aerobic exercise can inhibit the mTOR signal through the tuberous sclerosis complex (TSC) and suppress the induction of muscle protein synthesis in resistance exercise (Hawley, 2009).

4.4 Comparison of Glucose Levels In Aerobic, Resistance and Combination Exercises

After the training period, all types of exercise (aerobic, resistance and combination) can lower the blood glucose levels in animal models with diabetes mellitus. The lowering in blood glucose levels was greatest due to the combination exercises, whereas the lowest blood glucose levels resulted from aerobic exercise. The aerobic exercise and resistance training exercises did not differ, and nor did the resistance exercise and combination exercise. Different results were obtained in aerobic exercise and combination exercises. This suggests that combination exercises are better than aerobic exercise in lowering blood glucose levels.

Aerobic exercise causes GLUT4 translocation to the cell surface and increased glucose transport (Zierath and Hawley, 2004; Sakamoto, 2002). Resistance exercise induces the response of hypertrophy and a shift in the type of muscle fibers in muscle exercises, which leads to increased utilization of whole-body glucose (Marcus et al., 2008).

Combination exercises performed in separate sessions are very advantageous because they induce two pathways that do not cause disrupted adaptation. Adaptation of chronic aerobic exercise improves the performance capacity, while mitochondrial biogenesis is a result of activation of specific gene transcription during and after a single exercise. The adaptation form chronic resistance of induced exercise from is muscle hypertrophy occurrence in response to the coordination of genes and molecules that promote the enlargement of pre-existing muscle cells through the incorporation and addition of myonuclei (Fluck and Hoppeler, 2003).

The short study period (four weeks) in this study may be one of the causes of no significant difference found between the treatment of K1 and K2, treatment of K2 and K3. Aerobic exercise can increase steady-state mitochondrial protein content by 50-100% within 6 weeks. The mean half-life of protein turnover ~ 5-7 days indicates that stimulation by repetitive exercise is necessary to maintain increased mitochondrial content (Zierath and Hawley, 2004). While acute resistance training increases the turnover of skeletal muscle protein up to 48 hours after completion of exercise, either involving concentric or eccentric contractions, both are effective in increasing the turnover of these muscle proteins (Phillips et al., 1997).

5 CONCLUSION

Aerobic, resistance and combination exercises can lower blood glucose levels. Comparison of the three types of exercise shows that combination exercises give a better result than aerobic exercise in lowering blood glucose levels. In the future, combination exercises can be used as a procedure for regulating glucose levels in type 2 diabetes mellitus.

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