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Effects of Continuous Moderate Intensity Training (MICT) and Intermittent Calorie Restriction on Changes in Blood Sugar Levels and The Number of Pancreatic Beta Cells of Female Mice Pancreas (*Mus Musculus*) on A High Glycemic Index Diet

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ABSTRACT
A diet with a high glycemic index can cause metabolic disease and requires prevention through exercise, diet, or both. This study examined the effect of a combination of Moderate Intensity Continuous Training (MICT) and Intermittent Calorie Restriction (CR) on blood glucose levels and pancreatic beta cells in female mice (Mus musculus) fed with a high glycemic index diet. Using a randomized control trial, four groups were studied: control group (KN), intermittent CR (KI), MICT (KL), and combination group (KK), with interventions including diet reduction and swimming training. KI had the highest change in blood glucose levels after and before intervention, followed by KN, KK, and KL with fasting blood glucose levels and two-hour postprandial glucose levels respectively, KN (26.50 ± 32.42) and (31.25 ± 26.17), KI (44.00 ± 19.84) and (49.40 ± 20.84), KL (-2.67 ± 32.87) and (4.83 ± 15.33), KK (15.67 ± 44.12) and (13.50 ± 32.02), with not significantly different. The number of beta cells in each group was KN (74.43 ± 27.45), KI (63.68 ± 34.23), KL (71.08 ± 31.69), and KK (82.22 ± 83, 92), not significantly different. There were no significant changes or effects on blood sugar levels and beta cell numbers in female mice (Mus musculus) fed a high glycemic index diet combined with MICT and intermittent CR.

Keywords: MICT; Calorie restriction; blood glucose; number of pancreatic beta cells.

INTRODUCTION
A high glycemic index diet is a type of diet that consumes carbohydrates that are quickly broken down by the body and cause a rapid increase in blood glucose [1]. Foods with a high glycemic index are widely consumed by people all over the world, one of which is in Africa where 44% of traditional foods are types of foods with a high glycemic index, while in India-Asia this value reaches 37% [2]. In addition, based on data from the 2018 Indonesian Basic Health Research, the level of consumption of foods and drinks with a high glycemic index in Indonesia is also very high, reaching 87.9% for sweet foods and 91.49% for sweet drinks [3].

A diet with a high glycemic index is closely related to various metabolic diseases such as obesity, diabetes mellitus, and cardiovascular disease. Foods with a high glycemic index will cause hyperglycemia which underlies the pathophysiology of diabetes mellitus where beta cell dysfunction and insulin resistance will occur and then lead to a decrease in the number of pancreatic beta cells [4]. In addition, foods with a high glycemic index have been shown to have a positive correlation with increased hunger and appetite so they can cause obesity [5]. Insulin resistance experienced by diabetics and high body weight in obese people can then increase the risk of cardiovascular disease [6]. Therefore, it is very important to seek prevention of various metabolic diseases for someone with a high glycemic index diet.

Lifestyle, especially physical exercise, and diet, are very influential factors in preventing various metabolic diseases for someone with a high glycemic index diet.

Research shows that there is a remission of diabetes mellitus of up to 80% in patients who carry out an intensive program that includes diet and physical exercise [7]. A calorie-restricted diet is one method that is often used for people with obesity and diabetes mellitus. The calorie restriction carried out must be adjusted to energy needs, the severity of obesity, and the accompanying diseases and treatments [8].

Moderate-intensity continuous physical training is a type of continuous physical exercise that is done at moderate intensity (peak heart rate reaches 64-76% of maximum heart rate. A study conducted by Cao, *et al*. [9] explained that moderate-intensity continuous training can increase glycolipid metabolism levels. In addition, research on other types of physical exercise for people with Diabetes Mellitus has also been widely conducted, such as aerobic exercise and weight lifting which are effective in reducing HbA1c levels [10]. This indicates a positive signal for further research on the various types of exercise and diet methods that can be done by someone with a high glycemic index diet. However, research related to the combination of physical exercise and diet is currently not very much done and the existing research so far has been carried out in the long term. So this long period of time cannot accurately indicate when the combination of physical exercise and diet will have an effect on subjects with a high glycemic index diet. This certainly does not rule out the possibility that there will be a significant effect that has been shown from the combination of physical exercise and diet on subjects with a high glycemic index in a shorter period of time so that a review can be carried out in providing a time period for combining diet and physical exercise on someone with a high glycemic index diet. Therefore, research is needed by combining physical exercise and diet in a shorter period of time to see exactly when there is an effect on subjects with a high glycemic index diet. This study is expected to provide knowledge about the effect of a combination of moderate-intensity continuous training and intermittent calorie restriction on the number of pancreatic beta cells on a high glycemic index diet for 4 weeks. Furthermore, this study can be applied to prevent various metabolic diseases such as obesity, diabetes mellitus, and cardiovascular disease for someone with a high glycemic index diet.

MATERIALS AND METHODS

This study is an experimental study that compares changes in blood glucose levels with a randomized pre-posttest control group design and a posttest-only control group design for the evaluation of pancreatic beta cell counts in female mice (*Mus musculus*) after four weeks of intervention. The four groups were: the control group (KN); intermittent caloric restriction group (KI); moderate-intensity continuous training group (KL); combined treatment of intermittent caloric restriction and moderate-intensity continuous training group (KK).

Mices were allowed to acclimatize to the laboratory environment for one week before any treatments. Mices in all groups were orally gavaged at a volume of 0.0325 ml/g body weight three times a week of 40% dextrose as a high-calorie diet [11]. Intermittent caloric restriction involved a diet at 50% of the standard volume, while the exercise group animals swam for 30 minutes three times a week, and the combination group alternated between both [12]. After a 4-week intervention, fasting blood glucose levels and postprandial glucose were assessed. The beta cell count in the mouse pancreas was determined by extracting the pancreas and counting the cells under a microscope. The mices population used consisted of 24 healthy female mice, approximately eight weeks of age, weighing between 20-30 grams, each of which was divided into 6 mice per group.

Data processing and analysis were carried out with the help of SPSS software with the analysis stages of descriptive analysis test, normality test, homogeneity test, and difference test. The difference test uses the ANOVA test if the data is normally distributed. If the data is not normally distributed, use the Kruskal-Wallis test. The results of the significant difference test will then be followed by a Post-Hoc test to find out which groups have significant differences

RESULTS AND DISCUSSION

Analysis of Changes in Blood Sugar Levels of Female Mice (*Mus musculus*)

TABLE 1: Changes in blood sugar levels post-intervention compared to pre-intervention.

Variable	Changes in blood sugar levels (mg/dl)		
	Group	Mean	*p-value*
Fasting Blood Glucose	KN	26.5 ± 32.4	0.189
	KI	44.0 ± 19.8	
	KL	-2.7 ± 32.9	
	KK	15.7 ± 44.1	
Two-Hour Postprandial Glucose	KN	31.2 ± 26.2	0.037*
	KI	49.4 ± 20.8	
	KL	4.8 ± 15.3	
	KK	13.5 ± 32.0	

Changes in blood sugar levels before and after intervention in this study showed a variety of average differences in blood sugar levels but had the same pattern, both fasting blood glucose and two-hour post prandial glucose. This pattern is that the average change in blood sugar levels was the largest in sequence in the group with intermittent calorie restriction diet (KI), followed by the control group (KN), the group with a combination of diet and exercise (KK), and the group with moderate intensity continuous training (KL). However, the difference test of the average difference in blood sugar levels in each group showed insignificant results, except for the two-hour post prandial glucose levels.

This significant result was then tested by a Post Hoc test and a significant difference was found between the moderate-intensity continuous training group (KL) and the intermittent calorie restriction group (KI).

TABLE 2: Post Hoc Test on Changes in Two-Hour Postprandial Glucose.

Group		*p-value*
KL	KN	0.055
KI	KI	0.011*
KL	KK	0.522
KN	KI	0.283
KN	KK	0.386
KI	KK	0.060

- *Effect of Intermittent Calorie Restriction on Blood Sugar Levels of Female Mice (Mus musculus)*

In this study, the group with intermittent calorie restriction experienced the highest increase in blood sugar levels compared to the group with moderate intensity continuous exercise, as well as the combination and control groups. Research conducted by Hutchinson [13] in 2011 showed that calorie restriction for three weeks in mice will increase the sensitivity of the hypothalamic-pituitary-adrenal axis which can trigger stress. This can cause an increase in basal corticosterone levels and an increase in corticosterone secretion in response to stress in mice with calorie restriction compared to control mice. Increased corticosterone levels are directly correlated with increased cortisol levels [13].

Furthermore, research conducted by Duregon, *et al.* [14] showed a decrease in fasting blood glucose levels in groups of female mice on a calorie restriction diet or an intermittent diet after 20 weeks. This study divided female mice into three groups, namely a group with a calorie restriction diet in the form of a reduction in calories consumed by 20%, an intermittent diet group in the form of limiting meal times to 4 to 8 hours per day, and a control group. In addition, mice on a calorie-restricted diet showed significantly faster results than the control group in managing glucose in the bloodstream in a glucose tolerance test [14].

The stress experienced by mice on a short-term calorie restriction diet can explain the increase in blood sugar levels that occurred in the group with an intermittent calorie restriction diet. Cortisol is an insulin antagonist hormone that can inhibit insulin secretion, stimulate glucagon secretion, and interfere with insulin signaling [15]. In addition, cortisol can also stimulate gluconeogenesis in the liver and potentiate the effects of epinephrine, which increases glycogenolysis and can ultimately lead to increased blood sugar levels [16]. Meanwhile, in the long term, the body may have shown adaptation to an intermittent calorie restriction diet. Thus, a low glycemic load and regular time in managing glucose in the body due to an intermittent calorie restriction diet will cause an increase in the glucose tolerance test and positive results in changes in blood sugar levels.

- *Effect of MICT on Blood Sugar Levels of Female Mice (Mus musculus)*

This study showed that the group with moderate-intensity continuous training had the best results in blood sugar changes, even experiencing a decrease in the average GDP level, although not significant. Similar insignificant results related to blood sugar levels and exercise were shown by a study by Shakoor, *et al.* [17] in 2023 which showed no significant changes in serum glucose in mice that did physical exercise for 4 weeks using a treadmill. The mice in this study did moderate-intensity continuous training using a treadmill with a normal diet consumption. However, there was a significant increase in glucose tolerance test results in mice after 4 weeks of exercise compared to before starting exercise. This value increased when the exercise was continued until week eight [17].

In contrast, a study conducted by O'Neill, *et al.* [18] on female mice (*Mus musculus*) with 4 weeks of physical exercise showed no increase in glucose tolerance test results. The mice in this study were modeled with type 1 diabetes and experienced insulin resistance using streptozotocin (STZ) injections. The mice were then given physical exercise using a treadmill for 4 weeks and a glucose tolerance test was performed at the end of the intervention by injecting 1g/kgBW glucose solution to the mice and then measuring their blood sugar levels after 15, 30, 60, 90, and 120 minutes. The results of this study indicate that the exercise performed by the mice could not increase the glucose tolerance of the mice, but it is known that there is an increase in insulin sensitivity in the mice as seen through the insulin sensitivity test. The lack of increase in glucose tolerance in this study may be due to the duration of the study which was not long enough to prevent downregulation of genes involved in glucose transport in the skeletal muscles of mice with STZ administration [18].

The results of another study conducted by Chang, *et al.* [19] showed a significant decrease in fasting blood glucose levels in mice with a high-fat diet that did treadmill exercise for 12 weeks. This study also found an increase in insulin sensitivity and pancreatic beta cell function in mice that did the exercise [19]. Research conducted by Bronczek, *et al.* [20] showed an increase in glucose tolerance test results in mice after 8 weeks of physical exercise [20]. Physical exercise can lower blood sugar levels by increasing glucose utilization. During exercise, muscles use more glucose for energy and increase blood glucose uptake by a mechanism known as exercise-stimulated glucose uptake [21]. In addition, glucose absorption will continue to increase for up to 120 minutes after physical activity, due to increased expression of GLUT4 (Glucose Transporter type 4) in the plasma membrane and T tubules. Insulin sensitivity will also increase for at least 16 hours after exercise [20].

This suggests that in the short-term significant results may not be obtained because the body has not adapted enough to counteract the adverse effects of a high glycemic index diet. One adaptation that the body may make is to prevent the downregulation of genes involved in glucose transport in skeletal muscle. However, in the long term such as 8 weeks or 12 weeks, the body may have been able to adapt well so that significant results in decreasing blood sugar levels and increasing glucose tolerance test results can be found. In addition, the direct effects of exercise can also be seen because exercise will directly increase the body's glucose needs so a decrease in blood sugar levels can also be seen directly. Therefore, this can explain the best results shown by the group with moderate-intensity continuous training on changes in blood sugar levels compared to other groups.

- *Effect of Intermittent Calorie Restriction and MICT Combination on Blood Sugar Levels of Female Mice (Mus musculus)*

In this study, the combination of an intermittent calorie restriction diet and moderate-intensity continuous training did not show significant changes in blood sugar levels. However, the average blood sugar level in this combination group had the second-best results after the group that only did moderate-intensity continuous training. This may be because in this group there is also the influence of stress that can be experienced by mice at the beginning of the intermittent calorie restriction diet so the blood sugar levels of this group of mice still show higher levels than the group that only did moderate-intensity continuous training.

Research conducted by Beals, et al. [22] combines a combination of diet and exercise in humans to determine its effect on someone with obesity and prediabetes. This study shows that the combination of exercise and a calorie-restriction diet can increase whole-body insulin sensitivity 2 times greater than just doing calorie restriction alone. The increase in insulin sensitivity in the group on a calorie-restriction diet and exercise was also accompanied by an increase in muscle gene expression involved in mitochondrial biogenesis, energy metabolism, and angiogenesis. This suggests that the combination of exercise and calorie restriction diet has significant metabolic benefits, especially in obese and prediabetic patients. Thus, although there have been no significant results from the combination of exercise and diet in this study, it is important to know the long-term effects of the combination of the two.

Analysis of the Number of Beta Cells in the Pancreas of Female Mice (*Mus musculus*)

TABLE 3: Number of Beta Cells Post intervention.

Number of Beta Cells (/5 visual fields)		
Group	**Mean**	***p-value***
KN	74.4 ± 27.4	0.554
KI	63.7 ± 34.2	
KL	71.1 ± 31.7	
KK	82.2 ± 83.9	

The average number of beta cells in this study showed no significant difference between groups. However, there was a difference in the average number of beta cells where the group with a combination of calorie restriction and moderate-intensity continuous training had the highest value. This value was then followed by the average value of the control group, the moderate intensity continuous training group, and the intermittent calorie restriction group.

- *Effect of Intermittent Calorie Restriction on the Number of Pancreatic Beta Cells in Female Mice (Mus musculus)*

In this study, the number of beta cells in the intermittent calorie restriction group showed the lowest results. These results are similar to the study conducted by Gao, *et al*. [23] on model mice with a 40% calorie restriction diet for 3 weeks. This study used DIO C57BL/6 mice which are type 2 prediabetes and obesity model mice. Before the intervention, the mice were exposed to a high-fat diet for 8 weeks and then changed to a normal diet during the intervention. After 3 weeks of treatment, the pancreatic islets of Langerhans were stained with HE staining and immunohistochemistry, and then their morphology was observed. The results obtained were beta cell hypertrophy in the control group with a high-fat diet without calorie restriction. Meanwhile, the group with calorie restriction showed a smaller beta cell size compared to the control group [23].

The smaller number of beta cells in the calorie restriction group may be because in this group the body can prevent hypertrophy due to the high glycemic index diet carried out by the subjects. Beta cell hypertrophy, which is a beta cell size that is larger than normal beta cells, can be caused by increased insulin requirements such as in obesity or insulin resistance. Hypertrophy that occurs in beta cells can initially help compensate for increased insulin requirements, but can ultimately lead to beta cell dysfunction and death in the long term [24]. However, it should be noted that in this study the difference in the number of beta cells shown did not show significant results, so further research is needed to determine the exact effect of an intermittent calorie restriction diet on the number of beta cells in the islets of Langerhans.

- *Effect of MICT on the Number of Pancreatic Beta Cells in Female Mice (Mus musculus)*

In this study, the number of beta cells owned by the group with moderate-intensity continuous training did not have a significant difference compared to the other groups. Although not directly using the number of beta cells as a variable, similar results can be seen from the study conducted by Bittencourt, *et al.* [25]. In this study, mice with a high-fat diet were given an intervention in the form of moderate-intensity continuous training for 8 weeks. This study was conducted by comparing the treatment of mice that were chronically exposed to a high-fat diet with control mice with a normal diet. These mice were then given moderate-intensity continuous training by swimming for 30 minutes 5 times a week for 8 weeks. The results of this study showed no significant difference in results related to the protection of the islets of Langerhans from pro-inflammatory cytokines between mice exposed to a high-fat diet compared to control mice. In the group with a high-fat diet, there was no significant increase in HSP70 even though they had been exercising for 8 weeks. HSP70 is a cytoprotective and anti-inflammatory protein whose expression is regulated by the Heat Shock Response (HSR) [25].

Research conducted by Bronczek, *et al.* [20] on healthy mice that did physical exercise for 10 weeks showed a positive effect on increasing the viability and function of the islets of Langerhans. This is indicated by a decrease in genes related to endoplasmic reticulum stress and an increase in the expression of the Ins2 gene which is responsible for coding preproinsulin in the islets of Langerhans of mice [20]. Another study by Calegari, *et al.* [26] showed that animal models that did endurance training for 8 weeks experienced an increase in the proliferation ability and resistance of pancreatic beta cells compared to controls that did not exercise. This increase occurs through activation of the AKT and ERK 1/2 pathways, increased antioxidant capacity, decreased ROS production, and proteins that cause apoptosis [26]. Similar results were also obtained from research conducted by Paula, *et al.* [27]. This study was conducted by exercising type 1 diabetes model mice using a treadmill for 8 weeks. The pancreas of mice was then surgically isolated and exposed to inflammatory mediators (IL-1β and IFNγ). The pancreas of mice that exercised showed lower levels of apoptosis markers such as iNOS protein, NO production, and cleaved caspase-3 levels compared to non-exercise controls [27]. This indicates that longer-term exercise for approximately 8 weeks may be able to show significant results on the number of beta cells by providing proliferative effects and protection from apoptosis in beta cells of the islets of Langerhans mice.

- *Effect of Intermittent Calorie Restriction and MICT Combination on the Number of Pancreatic Beta Cells in Female Mice (Mus musculus)*

Research that combines exercise and diet has been previously conducted by Huang, *et a*l. [28]. In this study, male mice were randomly divided into 6 different treatment groups that were conducted for 8 weeks. The 6 treatment groups consisted of a low-fat diet group, a low-fat diet group and 30% calorie restriction, a high-fat diet group, a high-fat diet group and 30% calorie restriction, a high-fat diet and physical exercise group, and a combination group of high-fat diet with 30% calorie restriction and physical exercise. Physical exercise was done by running. The results obtained in this study showed that physical exercise significantly reduced obesity caused by a high-fat diet, while calorie restriction effectively prevented metabolic disorders that could be caused by a high-fat diet. The combination of both can reduce insulin resistance and suppress pro-inflammatory cytokines in white fat cells [28].

In this study, the combination of intermittent calorie restriction diet and moderate-intensity continuous training did not show a significantly different number of beta cells compared to the control group or the group that did not do the combination of both. However, the highest number of beta cells in this combination group may be due to a better protective effect in the form of proliferative effects and prevention of apoptosis compared to the control group, or the group that only did intermittent calorie restriction or moderate-intensity continuous training.

CONCLUSION

There was no significant difference in blood sugar levels of female mice (*Mus musculus*) between all groups (KN, KI, KL, and KK), except for the two-hour post-prandial glucose levels between the KI and KL groups. From the largest average, changes in fasting blood glucose levels and two-hour post-prandial glucose levels occurred in groups KI, KN, KK, and KL, respectively. Meanwhile, there was also no significant difference in the number of beta cells in the pancreatic islets of Langerhans of female mice (*Mus musculus*) between all groups (KN, KI, KL, and KK). From the largest average number of beta cells in order, there were groups KK, KN, KL, and KI.

For future research, observations can be made on the effects of intermittent calorie restriction and moderate-intensity continuous training on changes in blood sugar levels and the number of beta cells in mice in the longer term and with a larger number of subjects so that the results obtained are more numerous with more accurate results in describing the effects of the intervention on the dependent variables studied. Further research using Immunohistochemical staining can also be done to increase the accuracy in calculating the number of beta cells.

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