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Effect of Moderate-Intensity Continuous Training (MICT) on Pancreatic Islet of Langerhans' Morphology and Cell Count of Female Rats (*Rattus norvegicus*) Exposed to High-Calorie Diet

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ABSTRACT

Introduction: Calorie consumption that exceeds normal limits each year can be a risk factor in causing diabetes mellitus (DM). This condition causes the body to be in a state of hyperglycemia, which will trigger changes in the diameter and number of Langerhans islet cells. Moderate-intensity continuous training (MICT) is recommended as a physical exercise method to help prevent DM.

Methods: This true experimental study used a randomized post-test-only control group design. Wistar female rats were randomly divided into three large groups: (A) the control group without a high-calorie diet and exercise, (B) the group with a high-calorie diet without exercise, and (C) the group with both a high-calorie diet and exercise (MICT). This experiment lasted for four weeks with an exercise frequency of five times a week. One-way analysis of variance (ANOVA) revealed that group differences in diameter had results of p=0.130 (p>0.05), whilst the number of islets of Langerhans had results of p=0.068 (p>0.05).

Results: There was no significant difference in the islets of Langerhans' diameter between the three groups (p=0.116). The number of islets of Langerhans also had no significant differences (p=0.068).

Conclusion: There was no significant effect of a high-calorie diet and MICT physical exercise on the diameter and number of pancreatic islets of Langerhans cells in female rats (*Rattus norvegicus*).

Highlights:
1. Moderate-intensity continuous training exercise did not affect the diameter of pancreatic islets of Langerhans in a high-calorie diet subject.
2. Moderate-intensity continuous training exercise did not affect the number of pancreatic islets of Langerhans in a high-calorie diet subject.

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Introduction

According to the latest annual statistics report from the United Nations (UN) Food and Agriculture Organization (FAO), global per capita calorie intake increased by an average of 9% last year, reaching 2,960 calories per day.[1] Indonesians consume approximately 3.2 million tons of sugar annually.[2] The World Health Organization (WHO) strongly advises limiting daily sugar consumption to below 10% of total energy intake for both adults and children.[3] There is also a conditional recommendation for even further reduction, aiming for below 5% or approximately 25 grams (equivalent to six teaspoons) per day.[3] This reduction could yield additional benefits, including a decreased risk of type 2 diabetes mellitus (DM).[4] Diabetes mellitus is among the top 10 diseases that cause the most deaths worldwide.[5] It is a collective term to describe heterogeneous metabolic disorders characterized by chronically high blood sugar levels.[6] In 2021, the Southeast Asia region reported that there were 90 million adults (20-79 years old) living with diabetes.[7] This is expected to increase to 113 million by 2030 and 152 million by 2045.[7] In Indonesia, the data of Basic Health Research (RISKESDAS) in 2013 and 2018 showed that the prevalence trend of DM increased from 6.9% to 8.5%.[8]

Diabetes mellitus is characterized by inadequate insulin production, resulting in prolonged high blood glucose levels, a condition known as hyperglycemia. Insulin is a hormone consisting of a series of amino acids produced by beta (β) cells in the islets of Langerhans within the pancreas. In humans, the islets of Langerhans are a collection of ovoid-shaped cells, measuring 76x175 µm. These islets are scattered throughout the pancreas, although they are more commonly found in the cauda (tail) compared to the caput (head) and corpus (body) of the pancreas.[9] The islets of Langerhans form in irregular shapes, predominantly circular to oval. Additionally, dispersed individual endocrine cells, which are not confined within an islet, can also be found throughout the pancreatic acinar and ductal tissues. The beta-to-alpha cell ratio is higher in mice than in humans, with beta cells constituting the majority of endocrine cells within an islet (approximately 50-70% in humans and 60-80% in rats).[10] Alpha cells account for 20-40% and 10-20% of endocrine cells in human and rat islets, respectively.[10] Each islet receives 1-5 arterioles, which then branch into a dense, fenestrated capillary network, the extent of which depends on the islet size.[10]

Insulin secretion is controlled by a negative feedback system directly between β cells of the islets of Langerhans of the pancreas and the concentration of glucose in the blood. Increased blood glucose levels at the time of food absorption directly stimulate β cells to produce and secrete insulin. It is this simple negative feedback system that serves to maintain relatively constant glucose regulation without requiring neural input or other hormones.[11]

Overweight and obesity result from various factors, including behavioral influences such as dietary habits, insufficient sleep or physical activity, certain medications, and genetic predisposition or family background. Obesity, a persistent health condition, heightens the susceptibility to heart disease, the primary cause of mortality in the United States (US), and is associated with numerous other health issues, including type 2 DM and cancer.[12] Therefore, it is necessary to develop a method for managing and preventing these issues. Physical exercise may play a role in reducing the risk of diabetes.[13] Moderate-intensity continuous training (MICT) is the most widely used moderate-intensity physical exercise in type 2 DM.[14]

A recent study on Streptozotocin-induced diabetic rats suggests that continuous moderate-intensity swimming exercises, performed four times a week for four weeks, increase the number of β cells in the islets of Langerhans.[15] The function of β cells is to synthesize, store, and release insulin, an anti-hyperglycaemic hormone that helps maintain circulating glucose concentrations within a narrow physiological range.[11]

Further research is needed to determine the optimal intensity, time, and frequency for stimulating the proper exercise to increase the number and diameter of pancreatic islets of Langerhans. Existing studies show the effect of continuous moderate-intensity physical exercise on the increase in β cells within the islets of Langerhans in Streptozotocin-induced diabetic male rats. However, the impact of this diet on the diameter and number of pancreatic islets of Langerhans in female rats (*Rattus norvegicus*) remains unknown. Therefore, this study aimed to determine the effect of MICT on the diameter and number of pancreatic islets of Langerhans from female rats (*Rattus norvegicus*) exposed to a high-calorie diet.

Methods

Study Design and Setting

This experimental study used a randomized controlled method with a post-test control group design, based on the study conducted by Herawati, *et al*. (2020).[16] The study stated that the design was chosen under the assumption that within a particular population, each unit shared similar characteristics, eliminating the need for initial measurements and allowing measurements to be performed only at the end.[16] Data collection was conducted only at the end of the experiment. This study received ethical clearance from the Ethics Committee for Health Research, Universitas Airlangga, Surabaya (No. 217/EC/KEPK/FKUA/2022).

Experimental Model

This study utilized white female rats (*Rattus norvegicus*) as experimental animals. The inclusion criteria used in this study were female rats with an age range of 8-12 weeks and an average normal body mass index (BMI) of 0.4504-0.5044 g/cm^2. The sample size was determined based on Federer's formula: (r-1) (t-1)≥15, where r represents the number of replications or sample size, and t denotes the number of treatment groups. Additionally, the likelihood of dropping out was 10%. A total of 27 rats were used in this study, distributed across three groups. Before the initiation of treatments, a one-week adaptation period was provided for the rats to acclimate to the experimental conditions. The

groups were categorized as follows: control groups (Group A), positive and negative controls (Group B), and treatment groups (Group C).

In the negative control group (Group A), rats received only a standard diet without any additional treatment. In the positive control group (Group B), rats were administered a high-calorie diet consisting of 40% dextrose solution at a rate of 0.0325 mL/g body weight, starting at 6:00 AM, followed by standard feeding. For the treatment group (Group C), rats were exposed to a high-calorie diet in addition to the standard diet. Concurrently, they underwent MICT in the form of swimming. In the initial week, rats swam without any added load for 1 minute. Subsequently, for the following weeks, the rats swam with a load equivalent to 6% of their body weight. This swimming regimen commenced during the estrous phase, with exercise durations increasing from 10 minutes in the second week to 20 minutes in the third week and 30 minutes in the fourth week. This comprehensive treatment protocol was implemented over a duration of 28 days.

Measurement of Diameter and Number of Islet Langerhans Cells

After 28 days of intervention, surgical procedures were performed on rats. Before dissection, the rats were euthanized using pure chloroform. Pancreatic tissue samples were then collected and put into an organ collection container and fixed in a 10% neutral-buffered formalin solution to prevent organ degradation. Pancreatic samples are processed into preparations using formalin-fixed, paraffin-embedded (FFPE) techniques, and then prepared for hematoxylin and eosin (H&E) staining. The diameter and number of cells in the islets of Langerhans were then evaluated under a light microscope at 400x magnification, with the average number of cells calculated across five islets.[16]

Data Analysis

The data in this study underwent analysis using a normality test and a homogeneity test, which were performed with the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) for Windows version 25, maintaining a 95% confidence level.[17] The analysis of data using one-way Analysis of Variance (ANOVA) was performed to determine significant effects of this experiment.[17]

Results

The study lasted for 35 days, including the adaptation phase for the experimental animals. The study was conducted at the Experimental Animal Laboratory, Faculty of Medicine, Universitas Airlangga, Surabaya.

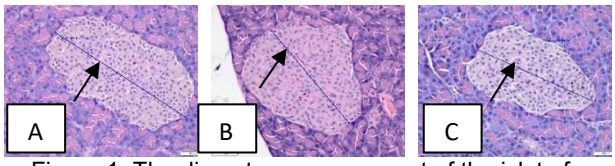

Figure 1. The diameter measurement of the islet of Langerhans (black arrow) on: A) Group A, B) Group B, C) Group C (hematoxylin and eosin staining on light microscopic with 400x magnification)

A total of 27 white female rats were utilized, with three rats assigned to each experimental group.

Table 1. The average diameter of the islets of Langerhans after treatment in every group

Group	Diameter of the Islet of Langerhans (m)	SD
A	247.7216	92.45860
B	288.6200	17.13189
C	312.8297	59.43694

m: meter; SD: standard deviation
Source: Research data, processed

Data analysis using one-way ANOVA resulted in a p-value of 0.130 (p>0.05), indicating that MICT had no significant effect on the diameter of pancreatic islets of Langerhans in female rats (*Rattus norvegicus*) subjected to a high-calorie diet.

Table 2. Result analysis of one-way analysis of variance (ANOVA)

Indicator	Signification	Conclusion
Diameter of the islet of Langerhans	0.130	Not significant

Source: Research data, processed

Additionally, the average diameter of the pancreatic islets of Langerhans revealed that Group C exhibited the largest average diameter, followed by Group B and then Group A.

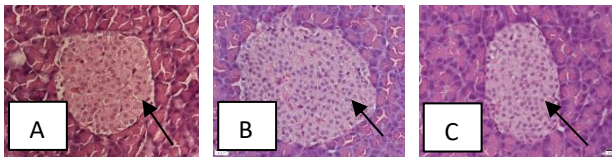

Figure 2. The microscopic of the beta cell islet of Langerhans (black arrow) on A) Group A, B) Group B, C) Group C (hematoxylin and eosin staining on light microscopic with 400x magnification)

The analysis of data using one-way ANOVA yielded a p-value of 0.068 (p>0.05), indicating that MICT did not have

a significant impact on the number of cells in the Langerhans pancreatic islets of female rats (*Rattus norvegicus*) subjected to a high-calorie diet.

Table 3. The average number of islet cells of Langerhans after treatment in every group

Group	Number of Islet Cells of Langerhans	SD
A	228.289	70.6906
B	273.622	44.6769
C	203.933	64.9738

SD: standard deviation
Source: Research data, processed

Moreover, the average number of cells in the pancreatic islets of Langerhans revealed that Group B exhibited the highest average number of cells, followed by Group A and then Group C.

Table 4. Result analysis of one-way analysis of variance (ANOVA)

Indicator	Signification	Conclusion
Number of islet cells of Langerhans	0.068	Not significant

Source: Research data, processed

Discussion

This study showed that there was no effect of MICT on the diameter and number of cells inside Langerhans islets of female rats (*Rattus norvegicus*) pancreas when exposed to a high-calorie diet. This can occur due to many factors, such as lack of duration and dose of dietary exposure, differences in the type of subjects and calories used from previous studies that showed significant results, the adaptation reaction of the pancreas of the rat to maintain normal blood glucose levels, and the type of exercise intensity used. Consumption of a high-calorie diet can be a trigger factor for DM. Foods that are high in calories and energy density will also increase the risk of DM, especially type 2.[4]

Rats given a high intake of glucose showed a reduction in the number of cells inside Langerhans islets, possibly due to the apoptosis mechanism of pancreatic β cells.[16] The duration and the number of high-calorie diets used in this study may be factors that cause insignificant differences in this study. In another study, the use of high-calorie diets with an addition of 7.4% of calories, conducted for 8 weeks, showed significant results in changes to the pancreatic islets of Langerhans.[18] In contrast, this study used a 3% calorie addition conducted for 4 weeks. Therefore, the insufficient dosage and duration of treatment in this study prevented full development of hyperglycemia, resulting in an insignificant impact. The type of subject can also affect changes in the diameter of the Langerhans islets within the pancreas. There is a noticeable difference between the number of β and α cells present in type 2 DM mice and normal mice. Based on histopathological features found in normal mice, its cells consist of 65% β cells and 35% α cells, with 50% of its Langerhans islets being more than 150 μm in diameter. On the other hand, 67% of Langerhans islets found in moderately diabetic mice were less than 150 μm in diameter.[10]

Female rats undergo various phases that influence their hormonal condition. Evaluating the estrous cycle in experimental animals proves valuable in determining reproductive status. This assessment of the estrous phase can also serve to examine the impact of drugs and chemicals on reproductive function, often manifested through typical morphological, cytological, and histological alterations in reproductive organs, along with changes in the duration of specific phases of the estrous cycle.[19] A study using 4-week-old albino male rat subjects showed significant results in shrinking the diameter of pancreatic Langerhans islets.[20] Meanwhile, in this study, the subjects used were female rats aged 8-12 weeks to represent the female gender, who are more easily obese due to the secretion of hormones such as estrogens. Estrogen in women is associated with adiposity and increased subcutaneous fat mass in the gluteofemoral region. However, other sources found that estrogen can also decrease central mass in women of reproductive age, leading to protective cardiometabolic effects.[21] Disruptions in reproductive function and hormonal secretion may arise when calorie intake falls short of meeting energy requirements and fails to supply adequate carbohydrates for the brain, consequently affecting the pulsation of gonadotropin-releasing hormone (GnRH).[22] Therefore, female rats are more protected from metabolic diseases such as DM.[22]

The type of calories used in the study can also affect the change in diameter that occurs in the pancreatic islets of Langerhans in mice. The use of a high-fat diet, accounting for as much as 45% of the total diet intake, compared to a high-calorie diet that relies on carbohydrates and protein, is also considered more likely to contribute to obesity. This is because metabolic changes during consumption of a high-fat diet can create conditions of glucose intolerance and trigger the development of type 2 DM.[20] Conditions where excessive fat accumulation adversely affects health are generally described as obesity and overweight.[23] Abnormalities in glucose intolerance conditions cause a decrease in glucose intake into cells and an increase in glucose levels in the blood, resulting in a hyperglycemic state. Changes in the histological structure of pancreatic islets of Langerhans are one of the distinctive features often found in patients and animal models of DM.[10]

Other factors that may promote weight gain include a lack of physical activity.[24] Therefore, a high-calorie diet based on fat was more effective in inducing obesity in rats than one based on carbohydrates, specifically dextrose 40%. Additionally, the administration of glucose at a dose of 0.013 gr/gr mouse body weight resulted in an insignificant change in the number of pancreatic Langerhans islet cells.[16] Within the Langerhans islets of the pancreas, there are two main subclasses of endocrine cells, the insulin-producing β cells and glucagon-secreting α cells, both of which play an active role in the secretion of insulin.[11] Insulin is a hormone consisting of a series of

amino acids produced by β cells within the pancreatic Langerhans islets.[9] Insulin secretion is controlled by a negative feedback system directly between β cells inside the Langerhans islets and blood glucose concentrations. Increased blood glucose levels at the time of food absorption directly stimulate β cells to produce and secrete insulin. It is this simple negative feedback system that serves to maintain relatively constant glucose regulation without the need for nerve work or other hormones. In addition to these mechanisms, cooperation between β and α cells also plays a crucial role in regulating their hormone secretion in response to changes in glucose levels. Without a balance between insulin and glucagon, glucose levels would become disrupted.[11]

The existence of pancreatic adaptive reactions allows β cells to proliferate, ensuring blood glucose levels remain within the normal range.[11] Rats have an adaptive response that enables them to maintain homeostasis within 18 hours, preventing hyperglycemia caused by the downregulation of specific genes. This gene pool, known as the 'regulome', comprises 334 genes related to β-cell functions, according to an analysis by the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway.[25] This adaptive reaction causes rats to avoid chronic hyperglycemia and prevent glucotoxicity to β-cell Langerhans islets within the pancreas. Glucotoxicity causes dysfunction and changes in β-cell mass, which in turn impact insulin secretion. Abnormalities in glucose intolerance conditions cause a decrease in glucose intake into cells and an increase in glucose levels in the blood, resulting in a hyperglycemic state. Changes in the histological structure of pancreatic islets of Langerhans are one of the distinctive features often observed in patients and animal models of DM.[10] Therefore, the presence of adaptation reactions makes changes in the diameter and number of islets of Langerhans preventable.[10]

Epidemiological studies indicate that physical exercise is associated with a relative reduction in diabetes risk of approximately 30%.[13] Controlled trials in non-diabetic individuals have also demonstrated the beneficial effects of physical exercise on insulin sensitivity and glycemic control, observed through continuous glucose measurements.[13] Consistent physical activity provides cardiovascular health advantages, enhances glycemic control, insulin signalling, and blood lipid levels. It also contributes to decreasing low-grade inflammation, improving blood vessel function, and weight loss. The heightened insulin sensitivity throughout the entire body after exercise can last up to 96 hours. Additionally, sustained control of glucose levels is optimized through physiological adaptations that occur over weeks, months, and years of exercise training. These adaptations are influenced by exercise intensity, duration, and frequency, and they contribute to the reduction of HbA1c, a marker associated with DM.[26]

Moderate-intensity continuous training is the most widely used exercise in type 2 DM.[14] In a study conducted by Groussard, *et al*. (2019), a comparison was made between groups that did not exercise, MICT groups, and high-intensity interval training (HIIT) groups.[27] The MICT group and the HIIT group had a similar beneficial effect on increasing the activity of superoxide dismutase (SOD), an enzyme that helps combat free radicals in the body. However, the HIIT group was also shown to be better at increasing antioxidants in muscles during exercise.[27] Antioxidants are essential for counteracting the production of reactive oxygen species (ROS) triggered by a high-calorie diet. Long-term exposure to ROS due to high glucose levels causes an increase in protein and lipid glycation, thereby increasing advanced glycation end products (AGEs).[28] The presence of AGEs induces the formation of ROS, which can lead to increased oxidative stress. Existing ROS will interfere with the processing of pancreatic and duodenal homeobox 1 (PDX-1) messenger ribonucleic acid (mRNA), which functions as a transcription factor to regulate cell life.[29]

Glucotoxicity causes dysfunction and changes in β-cell mass, leading to decreased insulin secretion. Increased free fatty acid (FFA) levels in the body, resulting from prolonged exposure to high blood glucose, will also induce apoptosis. Inhibited FFA oxidation will trigger the formation of long-chain acyl-CoA esters that have the potential to be toxic to the body. High FFA levels can also suppress the anti-apoptotic factor Bcl-2.[30] Therefore, β cells will be more prone to apoptosis. The presence of high glucose levels increases the release of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), a cellular signal that induces pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ). These components can directly affect the expression of pro-apoptotic genes in pancreatic β cells.[28] This mechanism ultimately affects the function of pancreatic β cells, causing dysfunctional β cells to trigger apoptosis. Apoptosis occurring in the pancreatic islets of Langerhans causes a reduction in diameter. Therefore, compared to using MICT, the use of HIIT can further prevent the shrinkage of the pancreatic islets of Langerhans. A study conducted over 9 weeks, with swimming exercise performed as frequently as 6 times per week, also yielded insignificant results in the difference between groups of rats that exercised and those that did not, regardless of whether they received vitamin C supplements or not.[18]

The existence of apoptosis can be prevented by physical exercise. Regular and measurable physical exercise promotes glucose uptake, helping to maintain blood glucose levels within the normal range. Increased glucose intake occurs through the translocation of glucose transporter type 4 (GLUT4) to the cell surface, which is stimulated by calmodulin-dependent protein kinase (CaMK) and adenosine monophosphate (AMP)-activated protein kinase (AMPK), thereby facilitating glucose entry across cell membranes. The CaMK enzyme is activated by muscle contraction, leading to an increase in cytosolic Ca^{2+}.[31] Moderate-intensity continuous training significantly decreases blood glucose levels in the morning and evening due to an increase in GLUT4 expression in contracting muscles.[32] However, excessive physical exercise can also trigger an increase in appetite, which will also increase apoptosis in cells due to insulin resistance.[33] Moreover,

physical exercise also affects the circulation of neurons, allowing more oxygen and nutrients to enter the brain.[34]

Strengths and Limitations

The strength of this study lies in the precise measurement of the variables, specifically the diameter of pancreatic Langerhans islets. This accuracy was achieved through the use of highly reliable software. However, certain limitations should be acknowledged. This study was unable to control stress factors among individual experimental animals, and genetic variations in the experimental animals remained uncontrollable. Additionally, the staining method employed failed to provide precise results for each cell type within the pancreatic Langerhans islets.

Conclusion

There was no significant effect of MICT physical exercise on the diameter and number of Langerhans cell islets within the pancreas of female rats (*Rattus norvegicus*) with a high-calorie diet on a 4-week trial period. Within 4 weeks, the effect of physical exercise was proven to be insignificant. The average number of pancreatic Langerhans islet cells was determined, with Group B having the most significant average number of cells, followed by Group A and then Group C. The average diameter of the pancreatic Langerhans islet was also obtained, with Group C having the largest average diameter, followed by Group B and then Group A. In conclusion, a longer duration is required to achieve the desired preventive effect. This study employed histochemical examinations to stain and color the islets of Langerhans. Further research is needed using immunohistochemical examination to distinguish more specific types of cells within the islets of Langerhans.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Ethical Clearance

This study had received ethical clearance from the Ethics Committee for Health Research, Universitas Airlangga, Surabaya (No. 217/EC/KEPK/FKUA/2022) on 21-11-2022.

Authors' Contributions

Designed the study and drafted the manuscript: EWS. Collected data and performed background literature review: EWS. Performed statistical analysis: EWS. Supervised results and discussion: HKS, AR and LH. All authors reviewed and approved the final version of the manuscript.

Data Availability

Available.

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