High Calorie Diet with A Combination of Intermittent Restriction Affects The Reproductive Cycle and The Uterine Weight of Mice (Mus Musculus)

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Original Research

HIGH CALORIE DIET WITH A COMBINATION OF INTERMITTENT RESTRICTION AFFECTS THE REPRODUCTIVE CYCLE AND THE UTERINE WEIGHT OF MICE *(Mus musculus)*

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ABSTRACT

Balanced calories affected for body health and daily activities. Lose of energy can disturb the health and daily activities, while over calorie for diets also causes disorders such as metabolic. When there are excess calories in the body will be involved. It can be an obesity risk, diabetes mellitus, fertility disorder, cancer, and cardiovascular disease. Furthermore, in women there can be an increase in menstrual disorders and fertility disorder risk (Silvestris et al., 2018). This study aims to analyze high-calorie diet influence with interval restrictions combination on the reproductive cycle and weight of the uterus in mice. Experimental laboratory is a mouse (mus musculus) female's balb/c as object population. Sampling techniques using probability sampling with simple random sampling type. The study results on fisher's exact test gave a result of $p > 0.05$ so there was no significant difference between control group, high calorie diet group, and high calorie diet with interval restrictions group on the results of vaginal swabs /post-treatment reproductive cycle. The study outcome on robust tests between control, high calorie diet, and high calorie diet with interval restrictions groups. Obtained results ($p < 0.05$) that mean there are some significant discrepancies in the weight of uterine organ between groups. Calories balance in the body can impact female reproductive health.

***Keywords**: High-calorie diet; restriction; health risk; reproductive health; dextrose*

ABSTRAK

Asupan kalori yang seimbang mempengaruhi kesehatan tubuh dan aktivitas sehari-hari. Kehilangan energi dapat mengganggu kesehatan dan aktivitas sehari-hari, sedangkan kelebihan kalori untuk diet juga dapat menyebabkan gangguan seperti metabolisme. Ketika ada kelebihan kalori dalam tubuh maka akan mengakibatkan kelebihan berat badan. Hal ini dapat menjadi risiko obesitas, diabetes mellitus, gangguan kesuburan, kanker, dan penyakit kardiovaskular. Lebih lanjut, pada wanita dapat meningkatkan risiko gangguan menstruasi dan gangguan kesuburan (Silvestris et al., 2018). Penelitian ini bertujuan untuk menganalisis pengaruh diet tinggi kalori dengan kombinasi pembatasan interval terhadap siklus reproduksi dan berat uterus pada mencit. Laboratorium eksperimental dengan populasi mencit (mus musculus) balb/c betina. Teknik pengambilan sampel menggunakan probability sampling dengan tipe simple random sampling. Hasil penelitian Fisher's Exact Test didapatkan hasil $p > 0,05$ sehingga tidak terdapat perbedaan bermakna antara kelompok kontrol, kelompok diet tinggi kalori, dan kelompok diet tinggi kalori dengan pembatasan interval terhadap hasil swab vagina./siklus reproduksi pasca perawatan. Hasil penelitian uji robust antara kelompok kontrol, diet tinggi kalori, dan diet tinggi kalori dengan batasan interval kelompok, diperoleh hasil ($p < 0,05$) yang berarti terdapat perbedaan yang bermakna pada berat uterus antar kelompok. Keseimbangan kalori dalam tubuh dapat berdampak pada kesehatan reproduksi wanita.

***Kata Kunci:** Diet tinggi kalori; pembatasan; risiko kesehatan; kesehatan reproduksi; dekstrosa*

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INTRODUCTION

Balanced calories intake affects body health and daily activities. Less and over of calorie affected in the body so it requires a healthy diet with balanced calorie to keep good physical health. According to the Department of Public Health, Ministry of Health of the Republic of Indonesia in 2018, a healthy and balanced diet is a pattern of consumption of foods containing nutrients in the type and amount that suits the needs of the body. Energy and nutrients were depending on age, gender, weight and high, climate, and physical activity. Less of energy can disturb physical health and daily activity, the opposite over of diet calorie could be infected disorder in the body like metabolic disorders. If there is overload calorie in the body, it will cause over weight. When there were excess calories in the body, it will involve overweight. It can be obesity risk, diabetes mellitus, fertility disorder, cancer, and cardiovascular disease. Furthermore, in women, a risk of menstrual disorders and fertility disorder can increase (Silvestris et al. 2018).

The prevalence of obesity in Indonesia is 15,4% until the last 2019. Based on the Ministry of Health in the East Java province in 2018, there was 16% or 1,163,118 people less than 5 years old were obese. Obesity can cause many disorders, so that the morbidity and morality of the obese people were quite high. Therefore, obesity can impact on direct and indirect health cost. It was estimated in developed countries that the obesity cost is 2-10% of the national health cost in each country every year. Therefore, a daily calorie reduction was needed under mortgage without malnutrition and other important nutrients called restrictions. In 2012, the American College of Obstetricians and Gynecologists reported that the obesity women will have hyperplasia endometrium premenopausal risk, where estrogen levels are higher than progesterone hormones are low until none. Restriction is calorie limitation with a consistent pattern to reduce the average daily caloric intake.

Some previous studies showed that calorie limitation has health benefits. Energy intake and obesity incidence in health inspectors on Pidie sub-district in Aceh indicated significant correlation (Ramadhaniah et al. 2014). The study on hormonal estrogen effects in estradiol and the histology of mice's uterus (*mus musculus*) concludes that estrus cycle age seen in the phases of diestrus and estrus mice, the treatment was six times longer than control. It could happen, because estrogen induced in treated mice affects the pituitary's performance in secreting LH and FSH, so that there is chaos in the estrus cycle age and in the estrus cycle constituent phase on the thickness of the control endometrium and the estrogen treatment has a significant effect that is equal to 0.04 ($p<0$ 0.05) (Narulita et al. 2017). A full nutrition macro-Nutritional status and stress can affect a normal menstrual cycle in teenagers (Sitoayu et al. 2017).

A study concluded that low carbohydrate diets can reduce insulin levels in the blood, correct hormone imbalance, and produce a normal ovulation return to pregnancy (McGrice & Porter, 2017). However, the research of a high-calorie diet combined with a sequential restriction to prevent excess calories from healthy female reproduction, where one of which was seen in the weight of the uterus and the reproductive cycle, was unknown clearly. Therefore, it is recommended to analyze the high-caloric diet impact with a three-time a week combination of restriction on the reproductive and weight of the uterus.

The study aimed at seeing high-calorie effect diet without a regular combination of restriction cycles on the inverse cycle of reproduction and the weight of the uterus in mice, knowing high-calorie diet effect with an interval of the reproductive and weight of the uterus in inducing, the difference between a high-calorie diet and the thinning weight mice, the difference between a high-calorie diet with and without the interval of reproductive cycle and uterus mice weights.

MATERIALS AND METHODS

We had carried out an experimental laboratory to investigate and search for the influence of certain treatments under controlled conditions. The research design used was the randomized post-test only control design. The samples given treatment, as well as a control group, were taken randomly from the population (Sugiono 2012). The studied period in April 2021. The research population was mice (*Mus musculus*) female balb/c. The sample technique used was probability sampling involved with random sampling (Herawati et al. 2016). The independent variables were restriction calories interval and a high-calorie diet, while the dependent variables were reproduction cycle and the weight of the uterus.

The study was initiated with research ethics and declared worthy of ethics by the Ethics Commission of

the Faculty of Medicine, Universitas Airlangga, under a decree no.83/ ec/kepk/fkua/2021. Before given treatment, the mice were acclimatized (adjusted to the environment) for a week in experimental animal cages at the Faculty of Veterinary Medicine, Universitas Airlangga. During acclimatization, they were fed and watered according to the standard amount and nutrition. Then, the mice swam and cooled to introduce the mice to the water. The mice were weighed at the beginning before treatment and every week to determine the weight and dose of 40% dextrose sonde in each mouse. After acclimatization, a vaginal swab was performed on the mice to determine the reproductive cycle, with the estrus mice phase could be treated for 4 weeks.

The mice were randomly divided into three treatment groups, namely K1 (control) was mice group that were not treated, K2 was mice group treated with a high-calorie diet with 40% dextrose sonde as much as 0.0325 ml/1 gBW mice (Herawati et al. 2016) (± 10.00 am), and K3 was mice group treated with a high-calorie diet with 40% dextrose sonde as much as 0.0325 ml/1 gBW mice (Herawati et al. 2016) (±10.00 pm) and Calorie restriction (-50% feed) (Pósa et al. 2015) from standard feed is 20g/mice every three times per-week (Tuesday, Thursday, Saturday at ±10.00 am) (Herawati et al. 2016).

After treatment for 4 weeks, a vaginal swab was undertaken to determine the reproductive cycle experienced by mice (not waiting for a certain phase in mice) for surgery, then taking blood and organs from the uterus, liver, ovaries, brain, heart, visceral fat of mice at the Embryology Laboratory of the Faculty of Veterinary Medicine, Universitas Airlangga. The surgery was performed by anesthetizing the mice using 70% ether which was placed in a closed container. Surgery was performed on the abdomen to take the uterine organs in the mice and weighed to determine uterus weights. After surgery, the mice organs that could still be used were stored and preserved for further research, while unused organs of mice were destroyed or cremated by the laboratory as part of the research waste treatment.

The processing and data analysis used descriptive statistic test, the normality test using kolmogorov-smirnov, the homogeneity test using levene's test, acquired variant of a homogeneous nature if p> 0.05, the different was that if normal distribution data used anova one way analysis, and data were not normally distributed, so that kruskal Wallis could be used.

RESULTS

Characteristics of the mice

Statistical tests of descriptive, normality, and comparative homogeneity were conducted on uterine weight data in the control group (K1, with n=12), high-caloric diets group (K2, with n=9), high-calorie dieters with restriction intervals (K3, with n=11), and the significance of the average difference in body weight between groups (α=0,05). The results of the body weight statistics test were displayed (Table 1).

The previous table indicated that there was no significant difference in average weight before and after treatment between groups, indicated by a p-value >0.05. In the control group (K1), the p-value was < 0.05 which indicated a significant difference between the weight before and after the treatment, the high-calorie diet group (K2) with a p-value of >0.05 indicated no significant difference between weight before and after the treatment, while the high-calorie diet group with interval restriction (K3) with p-value <0.05 indicated a significant difference between weight before and after treatment. The vaginal swab calculations of mice in the control group, high-calorie diet, and high-calorie diet with interval restriction were using Fisher's exact test analysis, because the samples were less than twenty.

Table 1. Weight distribution, differences between groups, and statistical test results

	K1(n=12) Avarage±SD	K2(n=9) Avarage ± SD	K3(n=11) Avarage± SD	Comparation test (p value)
BB(pre)	20.25±3.251	21.89 ± 5.159	22.18 ±3.311	0.266(Kruskal wallis)
BB(post)	24.75±3.166	25.22±3.801	24.73±1.902	0.920 (anova)
(p value)	0,002	0,084	0.001	[redacted]
	Wilcoxon	Pair t test	Pair t test	
Delta	4.50±2.195	3.33±5.074	2.55±1.809	0.416 (Robust Tests)

Table 2. Vaginal swab in mice

Group	n	(%) Swab Vagina Percentage				Comparison test (p value)
		Proestrus	Estrus	Metestrus	Diestrus	
K1	7	42,9%	0%	0%	57,1%	0,38
K2	5	0%	20%	20%	60%	
K3	7	14,3%	28,6%	0%	57,1%	

According to Table 2, it declared that there were discrepancies in reproductive cycles based on treatment. At the most encountered by proestrus in negative control groups (K1) with a value of 42.9%, diestrus is most likely to be in high-caloric diets (K2) with a value of 60%, estrus was most likely to be in high-calorie dieters with restriction intervals (K3) with a value of 28.6%, and metestrus was most encountered in high-calorie diets (K2) with a value of 20%.The fisher's exact test results, p>0.05 made no significant difference between negative control groups with a high-calorie diet and a high-calorie diet with a restriction interval against the vaginal swab results.

Descriptive statistic tests, normality, and homogeneity of comparison were carried out on uterine weight data obtained in the control group (K1, n=12), the high-calorie diet group (K2, n= 9), and the high-calorie diet group with interval restriction (K3, n). = 11) to look at the significant difference in the mean between groups (α = 0.05). The post-treatment uterine weight statistic tests results were described in Table 2.

Table 3. Statistic data test for mice uterus weight post-treatment

Group	n	Uterus weight (g)(avarage ± SD)	Comparative test (p value)
K1	12	0,11 ± 0,445	0.032
K2	9	0,19 ± 0,101	
K3	11	0.12±0.053	

The results from the pre, can be seen that the high-calorie diet group (K2) has a higher average uterine weight than the other groups, they had an average value 0.19. Normality test with Shapiro-Wilk test and homogeneity test with Levene's test showed that uterine weight data were normally distributed (p>0.05) and were not homogeneous (p<0.05), so that the Robust test was carried out to see the differences between groups. The results obtained (p<0.05) indicated that there was a significant difference in the weight of uterine organs between groups.

DISCUSSION

The effect of a high-calorie diet without restriction on the cycle of reproduction and the weight of the uterus in mice

A study on the effect of feeding a high-fat diet of caloric intake function of diet resulted in that 5 mice were kept on a standard diet of animal pellets to serve as a control group (a) and 15 are fed a high-fat diet of 9 weeks to induce obesity (Hussain et al. 2016). Animals fed a high diet of fat are divided into four groups, namely (a) the high-fat diet of *ad libitum*, (b) the isokal, (c) high-fat diet groups, and (d) the hypoglycaemic diet. These could conclude that *ad libitum* high-fat diet dominated the normal estrus cycle and increased the luteal cell apoptosis in fat mice.

High-fat dietary restraint disrupts normal estrus cycles and causes functional deficiency of corpuscles in fat females. A result of a study suggested that dietary high fat definitely affected women's reproductive function regardless of their caloric intake. In addition, a study by Cheng et al. (2018) concluded that transgenic profile changes that were affected by e2 and/or HFD could interfere with the homeostasis endometrium and contribute to hyperplasia endometrium development. The uterus tissue changed its dynamic histology structure according to the hormone estrogen changing levels (Weihua et al. 2000). Solon-Biet et al. (2015) conducted a study on macronutrient balance, reproductive function, and lifespan in human mice, leads the largest uterus mass on a high-protein and low-carbohydrate diet, whereas the biggest ovarian follicles number on a high-protein and low-carbohydrate diet. Otherwise, the estrus cycle was more likely in mice with lower protein and carbohydrates, and corpora luteal numbers, which showed the most recent ovulation on high-protein and low-carbohydrate diets similar to those favoring the greatest longevity. The study noted that a high-fat diet could cause hyper cholesterol that could increase oxidative stress, and resulted in apoptosis of the nuclear arkuata neuron. This arcuate nucleus neuron apoptosis could affect the hypothalamus in producing

GnRh, and reduce its production of anterior pituitary in producing FSH and HHLS.

Hormones played a role in affecting corpus luteum secretes progesterone and estrogen. FSH worked on granulosa cells to increase the androgen conversion into estrogen. Production of estrogen for endometrial proliferation and progesterone to prepare for implantation of the embryo in the endometrium (Young 2013). Therefore, if FSH and LH levels decreased, it could cause a decrease in the hormones estrogen and progesterone, so that the uterine tissue underwent dynamic histological changes in accordance with changes in estrogen hormone levels (Weihua et al. 2000). Lenert et al. (2021) study on homeostatic regulation of estrus cycle of young female mice on western diet, concluded that there was no effect on the cycle of diet, measured by the percentage of mice that complete one full cycle of estrus during each sample study period.

Based on the results of this study, the uterine weight analyses used 12 samples in the control group (K1), 9 samples in the high-calorie diet group without interval restriction (K2), and 11 samples in the high-calorie diet group with interval restriction (K3). There was a significant difference in the uterine weight of mice in the control group (K1) with the effect of a high-calorie diet without a combination of interval restriction group (K2), with the largest uterine weight in the high-calorie diet without restriction (K2) group. In vaginal swab analysis or reproductive cycle with a total of 7 samples in the control group (K1), 5 samples in the high-calorie diet group without interval restriction (K2), and 7 samples in the high-calorie diet group with interval restriction (K3), found no significant difference. Between negative control group (K1) and high-calorie diet group (K2) on the results of the vaginal swab or reproductive cycle with the most reproductive cycles were the diestrus phase among all groups. This would not coincide with the calculation for four weeks that the proestrus or estrus cycle would correspond to the 5-day cycle. The circumstances were due to external factors, environmental and internal, physical, and addict psychological abuse.

Effect of high calorie diet with interval restriction combination on reproductive cycle and uterine weight in mice

Xie et al. (2020) concluded that restriction saves female mice from weight gain, glucose intolerance, ovarian follicle loss, and estrous cycle dysfunction caused by a high-fat diet. A study by Markowiak and Slizewska (2017) on caloric restriction increases ratio of estrogen to androgen receptors expression in murine ovaries - potential therapeutic implications, concluded that prolonged calorie restriction (9 months) in female rats led to increased expression of estrogen receptors, while at the same time not affecting the expression of androgen receptor on ovarian cells. Calorie restriction resulted in estrogen lower levels in the blood circulation, leading to a higher sensitivity of cells to this hormone.

In the proliferative phase, the main hormone during this phase was estrogen, particularly 17-beta estradiol. The phase goal was to grow the uterus endometrial lining. 17-beta-estradiol achieved this by increasing the growth of the uterus endometrial lining, stimulating an increase in the number of stroma and glands, and increasing the depth of the artery supplying the endometrium, the spiral arteries (Thiyagarajan et al. 2019). Uterine tissue experienced dynamic changes in histologic structure according to changes in estrogen hormone levels (Weihua et al. 2000), so that if the estrogen level was low, it could reduce the uterus weight and the reproductive cycle affects. For example, calorie restriction was a “stressor” processed in the brain and could modify the release of sex hormones through the hypothalamic-pituitary-gonadal axis. Reproduction and fertility were regulated through the hypothalamic-pituitary-gonadal axis hormones.

With regard to intermittent fasting, it was possible that individuals who did not get sufficient caloric intake to support the hypotamater-pituitary-gonadal axis might experience irregular periods. The result of this study also resulted that the uterine weights analyzed were 12 samples in the control group (K1), 9 samples in the high-calorie diet without interval restriction group (K2), and 11 samples in the high-calorie diet with interval restriction group (K3). There were significant differences in uterine weight mice in the control group (K1) with the high-calorie diet effect with an interval restriction group (K3) combination.

In vaginal swab analysis or reproductive cycle with a total of 7 samples in the control group (K1), 5 samples in the high-calorie diet without interval restriction group (K2), and 7 samples in the high-calorie diet with interval restriction group (K3), there were no significant differences between the control group (K1) and the high-calorie diet with interval restriction group (K3) on the results of the vaginal swab or reproductive cycle with the most estrus phase compared to other groups, but the most diestrus phase occurred in the high-calorie diet with interval restriction group (K3). This situation occurred, because it was influenced by external factors,

namely the environment and internal (physical and psychological) in mice that could not be avoided.

The difference between the effect of high calorie diet with and without a combination of interval restriction on the reproductive cycle and uterine weight in mice

Previous studies conducted on the effect of a high-calorie diet without a combination of interval restriction on the reproductive cycle and uterine weight in mice, on the effect of a high-calorie diet with a combination of interval restriction on the reproductive cycle and uterine weight in mice, had resulted in different results. This was reinforced by a significant study on the effect of a high-calorie diet without a combination of interval restrictions on the reproductive cycle and uterine weight in mice, which showed feeding a high-fat diet definitely affects female reproductive function regardless of caloric intake (Hussain et al. 2016).

A study by Cheng et al. (2018) on estrogen and a high-fat diet causing changes in the endometrial transcriptome profile of C57BL/6 mice, concluded that changes in the endometrial transcriptome profile influenced by E2 and/or HFD could disrupt endometrial homeostasis and contribute to endometrial hyperplasia development. Uterine tissue experienced dynamic histological structural changes in accordance with changes in estrogen hormone levels (Weihua et al. 2000). A study on the effect of a high-calorie diet with a combination of interval restriction on the reproductive cycle and uterine weight mice, concluded that restriction saved female rats from weight gain, glucose intolerance, ovarian follicle loss and estrus cycle dysfunction caused by a high-fat diet (Hua et al. 2020).

A study by Słuczanowska-Głąbowska et al. (2015) on caloric restriction increases the ratio of estrogen to androgen receptors expression in murine ovaries - potential therapeutic implications, concluded that prolonged calorie restriction (9 months) in female rats causes increasing estrogen receptor expression, while at the same time not affecting the expression of androgen receptors on ovarian cells. Calorie restriction resulted in lower levels of estrogen in the blood circulation leading to a higher sensitivity of cell to this hormone. Uterine tissue experienced dynamic histological structural changes in accordance with changes in estrogen hormone levels (Weihua et al. 2000), so that if the level of estrogen was low, it could reduce the weight of the uterus and affect the reproductive cycle.

Based on uterine weight analysis, the high-calorie diet group (K2) had a higher average uterine weight than the other groups, there is 0.19 ± 0.101. Robust test was conducted to see differences between groups. The results were obtained ($p < 0.05$), which meant that there was a significant difference in the weight of the uterine organ between the control group (K1), high-calorie diet without interval restriction group (K2), and high-calorie diet with interval restriction group (K3). In the post-treatment vaginal swab analysis or the reproductive cycle of mice with a total of 7 samples in the control group (K1), 5 samples in the high-calorie diet without interval restriction group (K2), and 7 samples in the high-calorie diet with interval restriction group (K3), in the comparison between groups, the proestrus phase was most commonly found in the negative control group (K1), the diestrus and metestrus phases were most common in the high-calorie diet group (K2). The estrus phase was most commonly found in the high-calorie diet with interval restriction group (K3). The fisher's exact test gave the results $p > 0.05$, so that there was no significant difference between the control group (K1) and the high-calorie diet without interval restriction group (K2), and the high-calorie diet with interval restriction group (K3) on the results of the vaginal swab. This situation occurred, because it was influenced by external factors, namely environmental and internal (physical and psychological) in mice that could not be avoided.

CONCLUSION

A high-calorie diet with interval restriction combination did not impact the reproductive cycle, but had an effect on the uterine weight of mice, compared to subjects who did not do interval restriction combination. To determine the underlying mechanism, further research was needed to determine the thickness of the endometrium and the influence of hormones, such as FSH, LH, estrogen, and progesterone.

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PAGE 1

PAGE 2

PAGE 3

PAGE 4

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