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Recovery of vitamin d levels by cholecalciferol supplementation on obese rats

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ABSTRAK

Latar Belakang: *Obesitas disebabkan oleh penumpukan lemak dalam tubuh karena faktor biologis, psikososial, dan perilaku. Prevalensi obesitas mencapai 42,24% di Amerika Serikat, sementara overweight dan obesitas mencapai 59% di Eropa. Obesitas dapat menyebabkan defisiensi vitamin D melalui berbagai mekanisme.*
Tujuan: *Untuk mengatahui pengaruh pemberian suplementasi cholecalciferol terhadap kadar 25(OH)D pada tikus obesitas.*
Metode: *Dalam penelitian ini, kami melakukan penelitian true experiment with. pre-post test control group design. Penelitian ini menganalisis 3 kelompok tikus galur Sprague Dawley jantan yang diinduksi dengan diet tinggi lemak tinggi fruktosa (HFHF) menjadi tikus obesitas. Masing-masing kelompok mendapatkan cholecalciferol sebanyak 2,500 IU/200gr/hari pada kelompok P1, 5,000IU/200gr/hari pada kelompok P2, dan 10,000 IU/200gr/hari pada kelompok P3 selama 8 minggu. Tikus kemudian dianalisis kadar serum 25(OH)D sebelum dan sesudah perlakuan.*
Hasil: *Suplementasi cholecalciferol secara signifikan meningkatkan kadar vitamin D pada setiap kelompok intervensi yang diberikan cholecalciferol. Rerata kadar 25(OH)D kelompok P1,P2, dan P3 sebelum perlakuan berturut-turut adalah 29,43±0,83 ng/mL, 28,61±1,57 ng/mL, dan 28,86±1,46 ng/mL. Rerata kadar 25(OH)D setelah suplementasi cholecalciferol untuk kelompok P1,P2, dan P3 berturut-turut adalah 74,27±0,77 ng/mL, 100,30±1,48 ng/mL, dan 126,73±2,30 ng/mL. Ada perbedaan yang signifikan antara nilai 25(OH)D sebelum dan sesudah perlakuan pada ketiga kelompok intervensi dengan nilai (p<0,05).*
Kesimpulan: *Pemberian cholecalciferol mampu meningkatkan kadar 25(OH)D pada tikus jantan yang diinduksi obesitas.*

KATA KUNCI*: cholecalciferol; obesitas; vitamin D*

ABSTRACT

Background: *Obesity is caused by the accumulation of fat in the body due to biological, psychosocial and behavioral factors. The prevalence of obesity reaches 42.24% in the United States, while overweight and obesity reaches 59% in Europe. Obesity can cause vitamin D deficiency through various mechanisms.has an impact on poor diet quality, in the long term, it can affect the nutritional status.*
Objectives: *To determine the effect of cholecalciferol supplementation on 25(OH)D levels in obese mice.*
Methods: *: In this research, we conducted a true experiment research with pre-post test control group design. This study analyzed 3 groups of male Sprague Dawley rats that were induced by a high-fat, high-fructose (HFHF) diet to become obese rats. Each group received 2,500 IU/200gr/day of cholecalciferol in group P1, 5,000IU/200gr/day in group P2, and 10,000 IU/200gr/day in group P3 for 8 weeks. The mice were then analyzed for serum 25(OH)D levels before and after treatment.*
Results: *Cholecalciferol supplementation significantly increased vitamin D levels in each intervention group given cholecalciferol. The mean 25(OH)D levels in groups P1, P2, and P3 before treatment were 29.43 ± 0.83 ng/mL, 28.61 ± 1.57 ng/mL, and 28.86 ± 1.46, respectively. ng/mL. The mean 25(OH)D levels after cholecalciferol supplementation for groups P1, P2, and P3 were 74.27±0.77 ng/mL, 100.30±1.48 ng/mL, and 126.73±2 respectively. .30 ng/mL. There was a significant difference between the 25(OH)D values before and after treatment in the three intervention groups with values (p<0.05).*
Conclusions: *Administration of cholecalciferol can increase 25(OH)D levels in male mice that are induced by obesity.*

KEYWORD*:* *Premarital women of reproductive age; body image; skipping meals behavior*

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INTRODUCTION

Obesity occurs when there's excess fat accumulation which increases risk for adverse health outcomes. According to WHO, obesity is defined as an increase in body mass index of more than 30 kg/m². There are various factors that causes obesity including an individual's genetic predisposition and environmental influences (1). The condition of obesity may cause risk of various noncommunicable disease, such as metabolic syndromes, type-2 diabetes mellitus, cardiovascular diseases, non-alcoholic fatty liver disease, cancer, sleep apnea, and various abnormalities of the reproduction organ (2).

The problem of obesity is present in multiple age groups, starting from toddlers, school-aged children, teenagers, adults, and the elderly (3). In the year 2018, the prevalence of obesity reached 42,24% of the total population in USA, while in 2022 in Europe the obesity or overweight prevalence reached 59% (4). In 2019, almost half of Asian children suffers from obesity or overweight, while in China over 2,15% to 13,99% of the total population suffers from obesity (5). According to 2018 Basic Health Research of Indonesia, the prevalence of obesity in Indonesia at the age of 18 and over is 21.8%. The highest prevalence was in North Sulawesi (30.2%), DKI Jakarta (29.8%), East Kalimantan (28.7%), West

Papua (26.4%), Riau Islands (26.2%), and followed by other provinces. This data increased from 2007, which was 10.5% to 11.5% in 2013 and 21.8% in 2018 (6).

The causes of obesity are multifactorial, involving biologic, psychosocial, and behavioral factors (7). One such factors is the condition of vitamin D deficiency. The prevalence of vitamin D deficiency has been reported to rise simultaneously with obesity prevalence in the World (8). The Evidence from National Health and Nutrition Examination Survey (NHANES) and Framingham study also found that the risk of obesity increases by vitamin D deficiency (9). The condition of vitamin D can also rise to abnormalities in lipid profiles marked by lower HDL and increases in tryglicerides. Conversely, obesity can also cause vitamin D deficiency which may be caused by volumetric dilution, low UV light exposure, and faster metabolism clearance (10,11). It is estimated that 20-100% of elderly in the US, Canada, and Europe suffers from vitamin D deficiency and about 1 billion people in the world suffers from vitamin D deficiency or insufficiency (12).

There is a consensus that severe vitamin D deficiency should be corrected (13). Increasing vitamin D levels has been reported to produce positive effects on BMI reduction, where a study found that vitamin D supplementation can significantly reduce body weight, BMI, waist circumference, and hip circumference (14). Deficiency of vitamin D and excessive accumulation of fat have negative effects resulting excessive metabolic processes and disruption of enzymes, resulting in accumulation of inactive forms and reduced bioavailability of vitamins D. In obesity, vitamin D affects insulin secretion, tissue sensitivity to insulin, and systemic inflammation. The direct and paracrine effects of vitamin D lead to VDR activation in pancreatic beta cells, CYP27B1 expression, and local synthesis of 1,25(OH)2D (15). Vitamin D correction was reported to also be able to provide beneficial effects on metabolic disturbances (16). In this study, the author is interested in finding the correlation between cholecalciferol supplementation on vitamin D (25(OH)D) levels on obesity model rats.

MATERIALS AND METHODS

Animal Preparation

We analyzed the effect of cholecalciferol supplementation on vitamin D levels of thirty male Sprague-Dawley rats aged 6-8 weeks. Rats were obtained from the Laboratory of the Center for Food and Nutrition Studies, Gadjah Mada University. Rats were divided into 5 treatment groups, each group consisted of 6 rats. The groups were normal control (KN), negative control (K-), and intervention groups which are P1, P2, and P3 groups. The rats were adapted for 7 days in laboratory environment before given intervention. Every rat was given standard feeding and free access to water during the study. The cages were made of hygienic polypropylene, had a 12-hour light and dark cycle, and houses 6 rats each. To achieve obesity status, the rats were given High fat high fructose (HFHF) which were comprised of B2-2 food (32 grams), duck egg yolk (28 grams), chicken liver (12 grams), and butter (4 grams) for 30 days. Fructose content of 10% is also given by dissolving 20 ml of 55% high fructose syrup on 100 ml aquadest until achieved homogeneity. Rats were declared obese if the Lee obesity index value was > 300 The Lee Obesity index is determined by the equation Lee Obesity Index=$\sqrt[3]{}$(Body weight (g))/(Nasoanal length (mm))

Vitamin D Supplementation And Intervention Evaluation

Cholecalciferol is given in the form of a soft gel, the dose of which has been converted to an animal dose given via gastric probe once every 08.00 WIB. Rats in the KN group only received BR-2 pellet and PAM ad libitum throughout the study. The rats on K- group were given HFHF diet for 28 days. Rats in the P1 group received HFHF for the first 28 days then receive 2500 IU cholecalciferol, while P2 groups received 5000 IU of cholecalciferol, and P3 received 10000 IU of cholecalciferol. The HFHF were given on day 8-36, then the cholecalciferol was given on day 38-87.

Measurement of 25(OH)D Levels

The free form of 25(OH)D was measured using the ABclonal ELISA kit. On day 37 and day 88, blood samples were taken through the retro-orbitalis vein. The rats were conditioned as comfortable as possible by being held and clamped at the nape. Rats were injected intramuscularly with ketamine. Medial canthus, the part under the eyeball, then scratched using a microhematocrit tube until it hits the retro orbital vein. The blood sample that comes out is collected in a microtube as much as 10-15% of the total blood volume. Using the blood sample, 25(OH)D levels are measured using ABclonal ELISA kit.

Statistical Analysis

Results of the research data were processed using SPSS version 16. The normality test used the Shapiro-Wilk test. Meanwhile, for homogeneity of variance between groups, the Levens test is used. Data is said to be normally distributed if $p > 0.05$ and is said to be homogeneous if $p > 0.05$. Statistical analysis was used to determine the differences between 25 (OH)D before and after using the parametric paired t-test. Test to see the differences between each group for normally distributed and homogeneous data using the One Way ANOVA par-ametric test. If the data is significant $p < 0.05$, continue with the Post Hoc LSD test

This research has obtained an ethical clearance letter number 17/ UN27.06.11/KEP/EC/2023 from the Ethics Commission of Faculty of Medicine of Sebelas Maret University.

RESULTS AND DISCUSSIONS

Animal Characteristics

The average body weight of the rats after adaptation (before the mice were induced by obesity) did not differ between groups. This indicated that the weight of the mice was the same or homogeneous, both in the control mice and in the treatment mice. All rats fed by HFHF has acquired obesity state. The highest increase in body weight occurred in the P3 groups, namely 32.66 ± 1.21 and the lowest occurred in the normal control group, namely 14.00 ± 0.63. There was a significant increase in body weight ($p < 0.001$) in both the control group and the treatment group after being given the HFHF diet for 28 days.

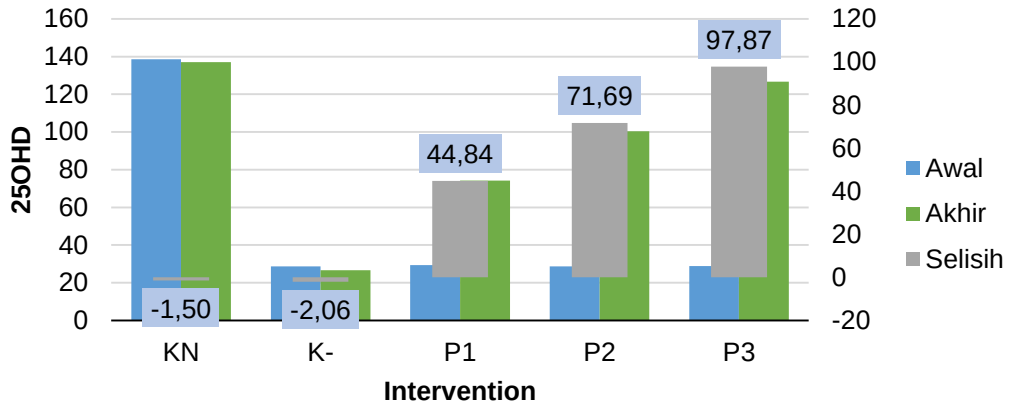
Table 1. Mean difference in 25(OH)D with of rats before and after administration of cholecalciferol with ELISA

Group	25 (OH)D (ng/dL)			p^a
	Before Intervention	After Intervention	Δ 25 (OH)D	
KN	138.57±3.97	137.07±4.04	-1.50±0.23	<0.001*
K-	28.68 ±1.06	26.67±0.86	-2.00±0.63	0.001*
P1	29.43±0.83	74.27±0.77	44.84±0.26	<0.001*
P2	28.61±1.57	100.30±1.48	71.68±0.27	<0.001*
P3	28.86±1.46	126.50±2.42	97.86±2.87	<0.001*
P^b	0.007*	< 0.001*	< 0.001*	

Description: KN: Normal male rats; K(-): Obese male rats ; P1: Obese male rats + cholecalciferol 2,500 IU/200 g/day; P2: Obese male rats + cholecalciferol 5,000 IU/200 g/day; P3: Obese mice + cholecalciferol 10,000 IU/200 g/day; Δ 25 (OH)D : Average increase before and after treatment; *: There is a significant difference ($p<0.05$); pa: Statistical results of paired t-test (difference before and after treatment); pb: Statistical results of comparison between groups using the One Way ANOVA test

25(OH)D Levels After Administration of Supplements

Free 25(OH)D levels analysed using ELISA in obesity-induced rats on the K(-) group were found to be worse than non-obesity rats in the KN group. Mean values of 25(OH)D on the cholecalciferol intervention groups were found to be significantly higher than rats that were not supplemented by cholecalciferol. The mean values of 25(OH)D on the KN group were 137.06 ng/ml, while in the K(-) group were 26.67 ng/ml. Mean values of 25(OH)D levels on P1,P2,P3 groups before supplementation were 29.43±0.84 ng/mL, 28.61±1.57 ng/mL, and 28.87±1.46 ng/mL respectively. The mean 25(OH)D values on the P1,P2,P3 intervention groups after cholecalciferol supplementation were 74.27 ng/ml, 100.30 ng/ml, 126.73 ng/ml respectively. There were significant difference between mean values of 25(OH)D before cholecalciferol supplementation and after cholecalciferol supplementation in the P1,P2,P3 groups ($p<0.05$). Analysis of Variance (ANOVA) showed a significant difference between mean 25(OH)D values of the 5 study groups ($p<0.05$).



Levels in the different experimental groups, p = 0.000; (KN: Normal Control group; K(-): Negative control group; P1: Intervention group using 2500 IU Cholecalciferol; P2: Intervention group using 5000 IU cholecalciferol; P3: Intervention group using 10000 IU cholecalciferol)

Figure 1. Mean values of 25(OH)D

Vitamin D is an unique vitamin made from skin exposure to sunlight in the form of vitamin D3 when the skin is exposed to UVB light. Vitamin D in its active form exerts various actions in the human body, such as to inhibit angiogenesis, inhibits renin production, induces terminal differentiation, and stimulates macrophage cathelicidin production (17). Vitamin D has been also reported to assist on prevent or treat obesity. Obesity was found to be associated with low vitamin D status, but weight loss has little effect on improving vitamin D levels (18). The serum 25-hydroxyvitamin D (25(OH)D) concentration has long been used as a parameter of choice for the assessment of vitamin D status. Vitamin D deficiency was reported in another study to be elevated in obese subjects, in which prevalence of vitamin D deficiency was 35% higher in obese subjects (19). Although the presence of vitamin D deficiency on obese subjects is a well-documented finding, there are still yet a definitive answer whether vitamin D causes or the consequence of obesity (10). Vitamin D can inhibit adipogenesis from anti-adipogenic and pro-lipolytic hormone interaction. Vitamin D increase lipolysis with adrenergic stimulus that result in increasing hormone sensitive lipase and lipoprotein lipase, thus leads to suppression of the vitamin D receptor of PPARγ, regulation of adipogenesis and lipogenesis in 3T3-L1 adipocytes. The supplementation of vitamin D were also reported to provide beneficial effects on obese subjects experiencing weight loss such as decrease of weight, fat mass, and MCP-1, thus suggesting the synergistic effect of weight loss and vitamin D supplementation (18).

Supplementation of vitamin D, together with exercise or mild caloric restriction, had been shown to improve markers of inflammation (20). Hanafy and Elkatawy stated that vitamin D acts through an intracellular increase in ionized calcium, thus stimulate the apoptosis of adipocytes through sympathetic nervous system activation to augment diet-induced thermogenesis and fat oxidation. As the results, vitamin D increase the energy expenditure. Vitamin D effect to weight loss also come from their act in gastrointestinal tract, which enhance fecal fat excretion and control the appetite hormone (16).

In our study, we have analyzed the effect of cholecalciferol supplementation on 25(OH)D levels, which we have found a significant increase of 25(OH)D levels on all three intervention groups given cholecalciferol either in 2500 IU, 5000 IU, or 10000 IU. ($p<0.05$). The highest increase occurred in obese rats that received 10,000 IU of cholecalciferol, with an average change of 97.86 ± 2.87 ng/ml. The lowest increase occurred in rats that received 2,500 IU of cholecalciferol with a mean change of 44.84 ± 0.26 ng/ml. This result is in accordance with several other studies, such as a report from Sekel et al which found which found that daily dosage of 10,000 IU vitamin D3 supplementation for 5 months mitigated the high prevalence of vitamin D deficiency (21). Zmitek et al also reported a significant increase in 25-OH-VitD levels of vitamin D deficient subjects supplemented with 1000 IU cholecalciferol for 2 months (25 µg daily) (22). Quraishi et al also found similar result where high-dose cholecalciferol supplementation (200,000 IU and 400,000 IU) rapidly and safely improves 25-hydroxyvitamin D levels in severe sepsis or septic shock patients (23). A higher dose of cholecalciferol appears to give a higher increase in 25(OH)D as well, according to the results of this study (24).

Literature characterising the dose-response curve to vitamin D shows varied results. Clinical studies investigating these relationships vary in dosing regimen, administrative routes, assay methods for 25(OH)D and demographics as well as control of endogenous vitamin D production. There is no agreement on the dose that will bring individual patients to that level. The pharmacokinetics of vitamin D distribution must take into account absorption, distribution, metabolism, and excretion, as well as varied methods of delivery (25).

Vitamin D deficiency may be treated with supplementation of cholecalciferol or calcifediol. Cholecalciferol was found to be more likely to achieve normal serum levels of 25(OH)D (25-hydroxy-vitamin D). Calcifediol is reserved for patients with liver failure or severe intestinal malabsorption syndrome (26). The mechanism of how obesity causes vitamin D deficiency may be caused by volumetric dilution of fat volumes into the serum liver, and muscle (10). Obesity may also cause the state of vitamin D deficiency from lifestyle factors such as reduced sun exposure of obese people which causes the reduction of vitamin D synthesis in the skin (11). A study by Carelli et al have reported that obese people have a higher vitamin D as reserves, which may explain the reduction amount of circulating serum 25(OH)D (27). Vitamin D supplementation may provide various benefits for the obese population, such as correcting lipid profiles and reduce inflammation markers (28,29).

CONCLUSIONS AND RECOMMENDATIONS

Cholecalciferol supplementation can improve 25(OH)D levels. Restoring vitamin D levels in vitamin D deficiency population can provide various benefits such as improving metabolic parameters and reducing inflammation markers. There are still paucity of studies analysing the causality of vitamin D and obesity. Future studies should analyse whether vitamin D is the causative factor of obesity or the consequence of obesity.

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