JKKI: Jurnal Kedokteran dan Kesehatan Indonesia
Indonesian Journal of Medicine and Health
Journal homepage: https://journal.uii.ac.id/JKKI
P-ISSN 2085-4145 | E-ISSN 2527-2950 || JKKI 2025;16(2): 170-179

Vitamin D supplementation and moderate intensity continuous training: Impact on leptin and anthropometric measures in obese individual

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Article Info:

Keywords: obesity; leptin; anthropometry; exercise; vitamin D

Article History:

Received: July 24, 2024
Accepted: May 15, 2025
Online: August 22, 2025

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DOI: 10.20885/JKKI.Vol16.Iss2.art3

Original Article

ABSTRACT

Background: Vitamin D may potentially have a significant influence in managing obesity-related risk factors. The current evidence suggests that observational studies have found a negative correlation between leptin levels and serum vitamin D, but heterogeneous intervention studies have not shown a significant effect.
Objectives: This study aims to examine the effect of the combination of moderate-intensity continuous training (MICT) and vitamin D3 on leptin and anthropometry.
Methods: A true experimental, randomized pre and post-test control group design were performed on 36 subject (18 male and female each) for 12 weeks. A treatment group received MICT and vitamin D3, control group only received MICT and placebo. Both groups received moderate-intensity exercise (64-75% HR Max) with a frequency of 3x/week and a time of 60 minutes, carried out. In the treatment group, 5000 IU vitamin D3 was administered daily for 12 weeks, while the control group only received a placebo. In this study, hypothesis testing was conducted to compare the means of two independent groups using an independent t-test or Mann-Whitney test. For comparisons between two related groups, a paired t-test or the Wilcoxon Signed Rank Test was used.
Results: After conducting a test to compare two sample means from unrelated groups, statistically significant differences were observed between the treatment and control groups in this study. For the variables of BMI ($p=0.025$), waist circumference ($p=0.042$), body weight ($p=0.008$), leptin ($p=0.015$) and vitamin D3 ($p<0.001$).
Conclusion: Combination of vitamin D3 supplementation and MICT significantly lowered leptin and anthropometry in obese individuals.

INTRODUCTION

The number of obesity is increasing all the time.[1] Regional variations in the prevalence of overweight were observed, with the African and South-East Asian WHO areas having 31% and the Americas region having 67%.[2] According to Riskesdas 2018, the obesity prevalence in Indonesia was 21.8%, up from 14.8% in 2013 and 10.5% in 2007. By 2023, it increased to 23.4%. In Bali, obesity rise from 23.3% to 23.9% in 2023, showing a significant rise in obesity over time.[3]

Obesity is frequently linked to insufficient levels of vitamin D3 in the serum in both children and adults across many races and geographic regions.[4] Vitamin D (D3 or cholecalciferol) is first converted in the liver to 25(OH)D. It is then converted in the kidneys to $1,25(OH)_2D_3$, also known as calcitriol, the active form of vitamin D. There's a correlation between serum concentrations of

hydroxyvitamin D or calcidiol/ 25(OH)D and insulin resistance and metabolic syndrome.[5,6] In a study conducted on the American population, it was shown that vitamin D deficiency's occurrence was 3.09 times more in obese individuals compared to a control group. Similarly, in those who were physically inactive, the occurrence of vitamin D deficiency was 2 times higher than in the control group.[7] In a population in Bali of 50 obese and normal subjects, it was found that 56% had vitamin D deficiency, 30% had insufficiency, and only 14% vitamin D sufficiency.[8] In addition to low serum vitamin D levels, obesity also has an increase in leptin (called hyperleptinemia) caused by leptin resistance. This increase in leptin causes insulin resistance, dyslipidemia and atherosclerosis.[9,10] Study on obese female subjects in Bali, Indonesia found that, in obese patients there was an increase in leptin, and could increase the risk of metabolic syndrome 256 times compared to those who had normal leptin levels.[5]

Obesity treatment can be in the form of pharmacotherapy, behavior modification, diet, exercise and surgery.[11,12] Exercise is one of the therapeutics for obesity management by lowering adipose tissue and improving cardiorespiratory function.[13–15] One of the exercises that is safe for obesity is moderate intensity continuous training (MICT). MICT is usually recommended in obese patients who are going to lose weight.[16] When compared to high intensity interval training (HIIT), MICT is a safer exercise to be done in the elderly, heart diseases, obesity, and metabolic syndrome.[17]

Research suggest that vitamin D can also be utilized as an intervention therapy for obesity control. This is because vitamin D has the potential to decrease the risk factors associated with obesity, including cardiometabolic risk. Individuals with low serum 25(OH)D are more likely experience weight gain, an rise in body mass index (BMI), and waist circumference (WC).[1] A rise of 25 nmol/L in serum vitamin D levels is linked to a 10% decrease in the likelihood of developing abdominal obesity, including conditions like diabetes and cardiovascular disease.[18] A study conducted by Buscemi et al. revealed that obese individuals generally have decreased levels of vitamin D in their bloodstream, which subsequently increase following weight loss.[19] The efficacy of vitamin D administration in reducing BMI and waist circumference was demonstrated in a meta-analysis, while it did not yield statistically significant results for weight loss.[20] The efficacy of vitamin D on anthropometry is also not consistent. The combination of endurance training and vitamin D 2000 IU/day did not significantly reduce waist circumference (WC).[21] Meanwhile different systematic reviews and meta-analysis show that vitamin D supplementation has no significant effect on BMI and WC. However, after conducting a subgroup analysis, there was a decrease in BMI and WC in obese Asian female subjects after treatment for ≥ 6 months. [22]

Vitamin D can suppress the release of leptin in adipose tissue.[23] In animal subjects, calcitriol (1,25(OH)2D3) enhanced leptin production in adipose tissue (in vivo and ex vivo).[24] Nevertheless, in systematic reviews and meta-analyses, no significant correlation observed between vitamin D and leptin.[9] Levels of leptin were decreased in rats that were given 2400 IU of vitamin D.[25] Similarly, administering daily dose 2000 IU vitamin D had no impact on leptin levels.[26]

Several research demonstrate inconclusive findings regarding the effects of vitamin D on leptin levels and anthropometry. However, a study found that when resistance exercise and vitamin D (1000 IU/day) were combined (8 weeks), reduction in leptin levels in obese women were observed.[13] In contrast, In contrast, Lithgow presented contradictory findings (4000 IU/day Vitamin D, 8 weeks, high intensity training).[27]

MICT is widely recognized for its benefits in obesity management, yet the potential synergistic effect of combining this with vitamin D supplementation has not been fully explored. The purpose of this study was to determine whether the effects of MICT in conjunction with vitamin D supplementation through leptin levels, body weight, body mass index, and waist circumference. This research is expected to providing further insights into the potential therapeutic strategies for obesity management.

METHODS

Participants

The subject of this study is obese people in Buleleng, Bali, Indonesia. In this research, the sample size calculation for the difference between two independent group means is based on Poccock's formula. According to research by Nikniaz et al. (σ=1.37, μ=6.31, μ2=4.98) [31] and also Najafi and Fatolahi (σ=4.5, μ1=18.8, μ2=11,2)[13], the sample size per group is 16.63. Considering a 10% drop out, the sample size is adjusted to 18 participants per group. A multi-stage random sampling and a single-blind design were used in this study.

Inclusion criteria: (1) Obese patients with waist circumference (WC) (≥ 90 cm in male and ≥ 80 in female) or BMI≥25 kg/m^2, (2) Subjects aged 20-45 years, (3) For female who are not pregnant, (4) do not have ascites, (5) not allergic with vitamin D, (6) not suffering from diabetes, heart disease, hypertension, kidney, autoimmune and lung diseases, (7) not doing routine aerobic exercise in the last 6 months, (8) not doing a weight loss program, (9) serum vitamin D levels≤30 ng/ml. Exclusion criteria: (1) smoker, (2) routinely consume vitamin D in the last 6 months, (3) take drugs for obesity, (4) menopause. Drop out criteria: (1) Not participating in a complete exercise intervention (not attending>3 times), (2) The sample was injured or sick while undergoing exercise. (3) The sample resigned as the subject of the study. At the beginning of the study, 40 sample subjects were obtained, but 4 subjects were dropped out for not regularly participating in the intervention and resigned as research subjects. At the end, the number of subjects of this study are 36 people, consisting of 18 male and 18 female.

Procedure

The study was conducted for 12 weeks and consisted of two groups: the treatment group (MICT+vitamin D 5000 IU), and the control group (MICT+placebo). It is recommended to take it after breakfast and follow up through the whats app or phone to ensure sample compliance in consuming vitamin D. MICT is carried out at 64-75% HR Max, frequency 3x/week with a time of 60 minutes for 12 weeks. It consists of 3 phases, the first is a warm-up (light intensity) with a time of 5-10 minutes (50-60% HR max), the second is the active phase (40 minutes, 64-75 HR Max), and the third is cooling down (50-60% HR Max) until a resting heart rate is reached. The exercise was carried out using the Ergocycle Technogym Excite 700 Upright Exercise Bike, Treadmill Technogym Run 700 Visioweb, Total TL 22 AC Treadmill.

Measure

In this study, serum levels of 25(OH)D and leptin were measured using ELISA (ng/mL) with the ichroma™ Vitamin D Neo kit and the DBC Human Leptin ELISA kit, respectively. Waist circumference was measured using the Onemed OD 235 measuring tape. Body weight and body fat composition were assessed using the Omron HBF-375 digital scale and body fat analyzer, while height was measured with the GEA HT721 stadiometer.

Analysis:

Descriptive statistics were used to summarize subject characteristics and study variables, expressed as means ± standard deviations or relative frequencies (for categorical data). Hypothesis testing for independent groups was conducted using the independent t-test (parametric) or Mann-Whitney U test (non-parametric). For paired data, the paired t-test or Wilcoxon Signed Rank Test was applied, depending on the data distribution. A p-value<0.05 was considered statistically significant. Effect sizes were calculated using Cohen's d**,** with interpretation as follows: d = 0.2: small effect, d = 0.5: moderate effect, d = 0.8*:* large effect

Ethical statement

This study was approved by the Health Research Ethics Committee of STIKES Bina Usada Bali (Approval No: 075/EA/KEPK-BUB-2023).

RESULTS

Baseline characteristics showed no significant differences between the treatment and control groups in terms of age, body weight, leptin levels, and waist circumference (p>0.05). However, significant differences were observed in serum 25(OH)D levels and sex distribution (p<0.05, Table 1). Within-group analysis revealed that the treatment group experienced a significant reduction in body weight, waist circumference, and BMI (p<0.05). In contrast, the control group showed a significant reduction only in BMI (p<0.05), with no significant changes in waist circumference or body weight (p>0.05). Leptin levels significantly decreased in the treatment group (p<0.05), while the control group exhibited a non-significant increase (p>0.05).

Quantitatively, the treatment group showed reductions in weight (-2.76±2.78 kg), waist circumference (-5.58±5.76 cm), and BMI (-1.05±1.1 kg/m^2). In comparison, the control group had smaller changes in weight (-0.63±2.33 kg), waist circumference (-2.61±5.27 cm), and BMI (-0.47±0.75 kg/m^2). Leptin decreased by -3.59±4.62 ng/mL in the treatment group, while the control group saw an increase of 0.36±4.63 ng/mL. Vitamin D levels increased by 14.57±8.98 ng/mL in the treatment group and 2.31±8.18 ng/mL in the control group, with significant differences only found in the treatment group (p<0.05). Between-group comparisons showed statistically significant differences in body weight (p=0.008), waist circumference (p=0.042), BMI (p=0.025), leptin (p=0.015), and vitamin D levels (p<0.0001). Effect size analysis using Cohen's d revealed a moderate effect for waist circumference (d=0.70) and BMI (d=0.61), and a strong effect for body weight (d=0.83), vitamin D (d=0.93), and leptin (d=0.85, Table 2).

Table 1. Subject Characteristics

Characteristic	Treatment (Mean±SD)	Control (Mean±SD)	p-value
Age (Years)	39.94±8.24	33.50±8.36	0.605
Body Weight (kg)	88.31±17.01	91.59±23.84	0.638
Waist circumference (cm)	104.38±9.69	106.83±11.52	0.496
25(OH)D (ng/ml)	16.11±3.68	20.21±5.38	0.012*[a]
BMI (kg/m2)	32.66±4.90	34.37±8.91	0.481
Leptin (ng/ml)	17.73±2.79	16.61±4.93	0.408
Gender			
- Male (%)	6 (33%)	12 (67%)	0.046*[b]
- Female (%)	12 (67%)	6 (33%)	

*p<0.05, [a]Independent t-test, n=18, [b]Chi square,

DISCUSSION

The effect of vitamin D on leptin involves the inhibition of tumor necrosis factor-alpha (TNF-α) and its effects on adipocytes.[28] Calcitriol reduced nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) phosphorylation by 36% when combined with exercise.[29] This effect is likely attributable to enhanced lipolysis mediated by increased expression of the vitamin D receptor (VDR).[30]

In this study, leptin levels were found exceed normal. This is consistent with a study conducted by Al-sultan & Al-e Elq, which concluded that serum leptin was significantly larger in obese subjects compared to normal subjects.[32] In accordance with a study conducted by Sundari et al. using obese subjects, the average leptin level in the subject was 26.9 ng/ml.[5] Study on 94 subjects consisting of 55 obese subjects and 39 non-obese subjects, concluded that the increase in leptin in obesity was in line with an increase in BMI.[33] This aligns with research conducted by Kumar et al., on 92 subjects with a BMI>25 kg/m2, concluding that more than 50% of obese subjects and 13.1% of non-obese subjects had leptin levels of more than 21.8 ng/ml. In this study it was also found that increased leptin levels were associated with insulin resistance.[34]

Table 2. The results of the test for 2 samples related and unrelated groups for each variable

Variable	Treatment (Mean±SD)	Control (Mean±SD)	p-value	Effect Size
Body Weight (kg)				
- Pretest	88.31±17.01	91.59±23.84		
- Postest	85.55±17.89	90.95±23.78	0.008[D]	0.83
- Δ	-2.76±2.78	-0.63±2.33		
p-value	0.003[E*]	0.296[E]		
sWaist circumference (cm)				
- Pretest	104.38±9.69	106.83±11.52		
- Posttest	98.8±11.44	104.61±13.15	0.042[B*]	0.70
- Δ	-5.58±5.76	-2.21±3.52		
p-value	0.001[C*]	0.262[C]		
BMI (kg/m2)				
- Pretest	32.66±4.90	34.37±8.91		
- Posttest	31.61±5.17	33.89±8.88	0.025[D*]	0.61
- Δ	-1.05±1.1	-0.47±0.75		
p-value	0.004[E*]	0.020[E*]		
Vit D (ng/ml)				
- Pretest	16.11±3.68	20.21±5.38		
- Posttest	30.68±9.35	22.52±6.95	0.000[B*]	0.93
- Δ	14.57±8.98	2.31±8.18		
p-value	0.000[C*]	0.247[C]		
Leptin (ng/ml)				
- Pretest	17.73±2.79	16.61±4.93		
- Posttest	14.14±3.84	16.98±4.30	0.015[B*]	0.85
- Δ	-3.59±4.62	0.36±4.63		
p value	0.004[C*]	0.740[C]		

[B]Independent t-test, [C]Paired t-test, [D]Mann-whitney u test, [E]Wilcoxon sign rank test

In obese patients, leptin resistance is characterized by an abnormal increase in serum leptin with a decrease in leptin function to decrease appetite, increased energy expenditure and decreased blood glucose.[35] Leptin stimulates lipolysis and inhibits lipogenesis. However, obesity causes leptin resistance, resulting in an increase in leptin in the blood.[36] An increase in leptin increases the oxidation of fatty acids and lowers blood sugar, but in obese subjects, leptin resistance occurs which causes an increase in appetite and weight.[37] This increase in leptin causes insulin resistance, dyslipidemia and arterosclerosis.[9,10] Leptin resistance occurs as a result of consuming an excessive amount of energy and having a sedentary lifestyle, leading to elevated levels of leptin in the bloodstream.[38] Reduced expression of the leptin receptor, disruption of LEP-R signaling, or the inability of leptin to reach target cells are the causes of leptin resistance. Leptin expression is modulated by eating habits and the circadian rhythm, which may be relevant. Leptin resistance can result from reduced leptin transport across the blood brain barrier (BBB), as evidenced by studies.[39] Leptin resistance is primarily attributed to genetic abnormalities, specifically in the OB and DBU genes. These mutations lead to an abnormal increase in appetite, known as hyperphagia, which is a rather uncommon occurrence.[40]

In this study, significant decreases and differences were found from anthropometric variables such as body weight, BMI and waist circumference. Significant differences were found in anthropometric variables compared to control after MICT intervention and vitamin D supplementation. In accordance with a study conducted by Alamdari et al. which examined the effects of aerobic exercise with a frequency of 3 times/week, duration of 30 minutes with an intensity of 60%-70% heart rate reserve (HRR) effective in weight loss, but not significantly reduce BMI.[41] The administration of vitamin D 50.000 IU/week for 6 weeks resulted in a

significant decrease in weight, BMI and waist circumference.[42] Another retrospective study in obese men aged 18-50 years who underwent a weight loss program, also found that vitamin D supplementation of 2000 IU/day and 4000 IU/day significantly reduced weight, BMI and waist circumference compared to no vitamin D administration.[43]

Different results were found in study on children aged 6-14 years, vitamin D supplementation 1200 IU for 26 weeks, could not reduce BMI. In this study, the increase in vitamin D levels after intervention was only up to 24.99 ng/ml.[44] However, other studies that combined resistance training and vitamin D 1000 IU did not find a significant decrease in weight and BMI.[13] This is likely because resistance training increases muscle mass. High intensity interval training and vitamin D 4000 IU for 6 weeks did not significantly reduce weight, BMI, waist circumference and leptin, only increased aerobic capacity.[27] It is likely due to the intervention being given in just 6 weeks, so it is not enough to improve the vitamin D status which can affect leptin and anthropometry. The decrease in leptin only occurs when the vitamin D status >30 ng/ml.[45] Circuit training combined with vitamin D supplementation 1200 IU per day for 12 weeks in type 2 diabetes patients, significantly reduces BMI and body weight.[46]

According to the findings of this research, the treatment group had a considerable reduction in leptin levels when compared to the control group. In obesity, dysfunction of adipose tissue occurs which causes an increase in leptin.[47] In vitro studies in humans stated that $1,25(OH)_2D$ and 25(OH)D3 inhibit the secretion of leptin in adipose tissue in both subcutaneous and omentum.[29] In line with a study which examined the combination of resistance training and vitamin D supplementation of 1000 IU for 8 weeks, leptin levels decreased significantly in obese female subjects.[13] A prospective ttudy on subjects with nonalcoholic steatohepatitis in Egypt, who were given vitamin D 4000 IU for 12 weeks, significantly reduced serum leptin.[46] Also in line with study on diabetic subjects who were given 50.000 IU of vitamin D every week for 8 weeks, significantly reducing leptin by 13.29% (pre 22.42 ng/ml and post 19.44 ng/ml).[48] Studies in mice also concluded that administration of vitamin D reduced leptin by reducing visceral adipose tissue.[25,49]

Vitamin D supplementation decreases visceral adipose resulting in a decrease in leptin.[25,49] Leptin has the ability to activate c-Jun N-terminal kinase (JNK) and NF-kB which play an important role in regulating the transcription of pro-inflammatory cytokines such as TNF-α and IL-1β.[50,51] $1.25(OH)_2D3$ in adipose tissue decreases NF-kB phosphorylation by 36% and Extracellular signal-Regulated Kinase (ERK) 1/2 by 35%.[29] In this study, the observed decrease in leptin levels following the combination of moderate-intensity continuous training (MICT) and vitamin D supplementation may be attributed to the ability of vitamin D to inhibit leptin secretion by reducing NF-κB phosphorylation. Additionally, the reduction in leptin is likely related to decreased visceral adipose tissue, as reflected by significant reductions in waist circumference and body weight.[13,49] Furthermore, the combined intervention may enhance vitamin D receptor (VDR) regulation in adipose tissue by promoting lipolysis.[30] Improving leptin sensitivity through multimodal strategies such as diet, exercise, and supplementation tends to be more effective in promoting weight loss than single interventions.[38] This effect may be more pronounced when accompanied by reductions in free fat mass.

One limitation of this study is the absence of direct body fat measurement. In fact, changes in visceral adipose tissue are best reflected by changes in body fat percentage. An increase in body fat percentage has been associated with lower vitamin D levels and higher leptin levels.[10] Another limitation is the study design, which only included two groups: a treatment group receiving both MICT and vitamin D, and a control group receiving MICT and a placebo. Future studies should consider including four distinct groups—MICT plus vitamin D, MICT only, vitamin D only, and a true control group—to better assess the independent and combined effects of these interventions. While this research contributes to the understanding of obesity management, it also holds potential for further exploration in the context of other chronic diseases such as diabetes, cardiovascular disease, and hypertension, which could be addressed in future investigations.

CONCLUSION

This study demonstrated that a combination of moderate-intensity continuous training (MICT), performed for 180 minutes per week, and daily vitamin D supplementation of 5000 IU over a 12-week period significantly reduced leptin levels and improved anthropometric parameters in obese subjects. These findings suggest that MICT, when combined with high-dose vitamin D supplementation, plays a contributory role in reducing leptin concentrations and improving body composition in individuals with obesity.

The proposed mechanisms include inhibition of the NF-κB pathway, suppression of leptin secretion, and reduction of visceral adipose tissue. This study suggests that combining moderate-intensity continuous training (MICT) with vitamin D supplementation may enhance leptin sensitivity and potentially yield greater weight loss effects compared to single interventions. Further research is warranted to explore the combined effects of other exercise modalities and vitamin D on pro-inflammatory cytokines, adiponectin levels, body fat, and additional obesity-related biomarkers. Studies with larger sample sizes are also necessary to determine the broader applicability of MICT and vitamin D combination therapy in the general population.

CONFLICT OF INTEREST

No conflict of interest.

ACKNOWLEDGEMENT

The author expresses gratitude to the Faculty of Medicine, Universitas Pendidikan Ganesha.

DATA AVAILABILITY

The authors confirm that the data supporting the findings of this study are available within the article.

SUPPLEMENTAL DATA

All relevant data has been presented in this manuscript, and there is no additional data provided separately.

AUTHOR CONTRIBUTION

PAS: ideas, design, literature search, data acquisition, data analysis, statistical analysis, manuscript preparation; NLKAA: ideas, design, literature search, manuscript preparation; IMKW: literature search, data acquisition, data analysis, manuscript preparation; NMSDL: literature search, data acquisition, data analysis, manuscript preparation; IMYP: ideas, design, manuscript review, manuscript editing.

DECLARATION OF USING AI IN THE WRITING PROCESS

The authors declare the use of AI to assist in citation searching.

LIST OF ABBREVIATIONS

MICT: moderate-intensity continuous training; HR-max: heart rate maximum; BMI: body mass index; WHO: world health organization; NHANES: National Health and Nutrition National Survey; Riskesdas: Riset Kesehatan Dasar; HIIT: high-intensity interval training; WC: waist circumference; BW: body weight; LEP-R: leptin receptor; BBB: blood brain barrier; HRR: heart rate reserve; JNK: Jun N-terminal kinase; NF-kB: nuclear factor kappa B; TNF-α: tumor necrosis factor alpha; IL-1β: interleukin 1 beta; ERK1/2: Extracellular signal-regulated protein kinase ; VDR: vitamin D receptor.

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