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Effect of Vitamin D Supplements on the Body Weight and Glycaemia in Wistar Rats

Claudia R. P. Detregiachi[1], Patrícia Cincotto dos Santos Bueno[1], Sandra Maria Barbalho[1,2*], Karina R. Quesada[1], Cora L. Brandão[1], Izabella B. V. Pedroso[1] and Mariane M. Alves[1]

[1]University of Marilia (UNIMAR), Marılia – Av. Higino Muzzi Filho, 1001 Marília - São Paulo, Brazil.
[2]School of Food Technology (FATEC), Av. Castro Alves, 62 - Marılia – São Paulo, Brazil.

Authors' contributions

This work was carried out in collaboration between all authors. Authors CRPD and PCDSB designed the study and wrote the protocol. Authors SMB, KRQ and CLB managed the literature search process and wrote the manuscript. Authors MMA and PCDSB performed statistical analysis. All authors read and approved the final version of the manuscript.

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Original Research Article

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ABSTRACT

Aims: The objective of this study was to evaluate the effects of vitamin D supplementation on the body weight and glycaemia on Wistar rats.

Study Design: Thirty female rats were divided in 3 groups (n=10) according to: G1 - control group, G2 - group treated with vitamin D (6 mg/kg); G3 - group treated with vitamin D (12 g/kg). The experiment lasted for 14 days and during this period the animals were weighed every two days.

Methodology: On the 15th day the animals were anesthetized and euthanized with overdose of intraperitoneal thiopental and blood samples were collected for determination of glycaemia. To the evaluation of variables, we used the one way ANOVA and Tukey tests. The probability of significance considered was 5% ($p < 0.05$). The correlation analysis between variables was

**Corresponding author: E-mail: smbarbalho@gmail.com;*

performed using the Pearson coefficient. The probability of significance considered was 5% ($p < 0.05$) for the operations performed.
Results: Our results show that animals receiving vitamin D supplementation had significantly higher blood glucose levels (G2: 152.2±14.23 md/dL and G3: 212.6±53.23 mg/dL) compared to the control group (144.1±32.02 mg/dL) ($p < 0.0007$). No significant differences were found between the three groups regarding the average of weight gain ($p = 0.1466$).
Conclusion: Our results show negative effects on the glycaemia and body weight especially with higher doses of vitamin D. We suggest that further studies are necessary to outline the actual effects of the supplementation. Besides, the optimal doses also need to be established.

Keywords: Vitamin D; glycaemia; body weight; Wistar rats.

1. INTRODUCTION

Vitamin D is a fat soluble steroid hormone, and may be found in two forms, as ergocalciferol (vitamin D2) produced by plants and fungi and as cholecalciferol (vitamin D3: 1,25-Dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) produced by the animal tissue and the cutaneous synthesis under the action of ultraviolet light at 7-dehydrocholesterol present in the skin [1].

Although vitamin D is synthesized in the skin from 7-dehydrocholesterol exposed to UVB radiation, it also may be obtained from the diet what is particularly important to people who have limited exposure to the sunlight. The main dietary sources of this vitamin include oily fish, egg yolk and supplemented milk [2].

The need for vitamin D from the birth to 50 years of age is 5 ug/day. This need increases 10 ug/day in individuals between 50 and 70 and 15 ug/day in those over 70 years old [3]. In most individuals, skin synthesis is the major source of vitamin D obtained from sunlight exposure and to a lesser extent from dietary and supplemental sources [4].

Vitamin D is widely known for its role in the development and maintenance of bone tissue, as well as in the maintenance of homeostasis of calcium and phosphorous. Recent evidences suggest this vitamin is also involved in many vital cellular processes such as cell differentiation and proliferation, hormone secretion (for example insulin), role in the immune system and several chronic diseases such as obesity [5,6].

Authors have shown that the Vitamin D3 act as a potent modifier of the risk of developing type 2 diabetes (T2DM) [7,8]. Studies in humans have confirmed these findings showing that individuals with reduced concentration of Vitamin D3 were at a higher risk of developing DM2 [9,10].

The development of T2DM involves modifications in the function of pancreas β cells and peripheral resistance to insulin. The Vitamin D3 may influence these mechanisms due to the presence of the vitamin D receptor in these cells as well as in adipose and muscular tissues [11]. Findings in animal models have suggested that vitamin D is involved in the synthesis and secretion of insulin, which may indicate that insufficient Vitamin D3 could have an impact on the DM2 development [12,13].

Many clinical studies have evaluated the deficiency of this vitamin in the pathogenesis of T2DM, but with controversial results [14-19]. Davidson et al. [20] conducted a double-blind, randomized and controlled study with individuals diagnosed as possessing pre-diabetes and demonstrated that vitamin D deficiency and vitamin D supplementation had no effect on insulin secretion, insulin sensitivity or development of diabetes compared to placebo. However, another representative study using adult population in the United States found a positive association between the serum levels of Vitamin D3 and pre-diabetes, regardless of the presence of other risk factors [21]. Population-based studies have demonstrated a negative correlation between total body fat with serum Vitamin D3, which remained negative even after adjusting for age, season, vitamin D intake and breed [22-23].

The deficiency of Vitamin D3 frequently observed in obese individuals may be associated to decreased sunlight exposure and also related to factors that trigger the accumulation of body fat corporal [24]. Studies have shown that one possibility to the deficiency of Vitamin D3 in obese patients may be related to its accumulation in adipocytes reducing its bioavailability and triggering the hypothalamus to develop a cascade of reactions that result in increased sensation of hunger and reducing energy expenditure [25].

In view of these controversial findings, this study aimed to identify the effects of vitamin D supplementation on the body weight and glycaemia on Wistar rats.

2. MATERIALS AND METHODS

This is an experimental, interventional, longitudinal and prospective study using female Wistar albino rats weighing approximately 230 g to 250 g, which were kept in the vivarium at UNIMAR. The rats were housed in collective cages under a dark/light cycle of 12 hours, room temperature of 22 ± 2℃, and relative air humidity of 60±5%. Throughout the experiment, the animals were fed and watered ad libitum.

After seven days of acclimation to the vivarium conditions, the rats were divided randomly in the following groups (n=10 per group).

- G1 – Control group that was fed water and rat food ad libitum and daily treated with 0.3 mL of olive oil (gavage route).
- G2 – Control that was fed water and rat food ad libitum and daily treated with 6 µg/kg of vitamin D3 mixed in 0.3 mL of olive oil (gavage route).
- G3 – Control that was fed water and rat food ad libitum and daily treated with 12 µg/kg of vitamin D3 mixed in 0.3 mL of olive oil (gavage route).

The weight gain was evaluated every two days and the consumption of water and rat food was recorded 3 times a week.

After 14 days of treatment and a 10-hour fast, the animals of G1, G2 and G3 were euthanized with a lethal intraperitoneal injection of thiopental (200 mg/Kg) until complete sedation. After that blood samples were drawn from the vena cava to determine glycaemia.

Statistical analysis of quantitative data was carried out with support from BioEstat 5.0. The descriptive analysis of the data is presented in tables. To the evaluation of variables, we used the one way ANOVA and Tukey tests. The probability of significance considered was 5% ($p < 0.05$).

This research was approved by the Animal Research Ethics Committee of the University of Marília (UNIMAR/ Marília, SP, Brazil) with protocol number 18/2015.

3. RESULTS AND DISCUSSION

The animals in the three experimental groups had similar mean weight at baseline ($p = 0.5199$) and at the end of the experimental period ($p = 0.6425$). There was no significant difference between groups regarding to weight gain ($p = 0.1466$). Also no significant differences were found in food ($p = 0.8773$) and liquid ($p = 0.7261$) consumption between the groups, although the groups of animals supplemented with vitamin D (G2 and G3) consumed a larger amount of rat food when comparing to the control group (Table 1).

Animals from G2 and G3 groups, which received vitamin D supplementation in the different doses had average blood glucose levels of 152.2±14.23 mg /dL and 212.6±53.23 mg/dL, respectively, which were significantly higher than the glucose of the control group (G1) which was 144.1±32.02 mg /dL (Fig. 1).

Considering the difference in the mean of blood glucose among the three experimental groups we have performed Tukey test supplementary to the ANOVA in order to evaluate the contrast between peer groups. There was no significant difference in mean blood glucose among animals of G1 and G2, but significant differences were found when comparing G1 and G3; G2 and G3 ($p < 0.01$) (Table 2).

Table 1. Initial and final weight, weight gain, feed and water intake during the trial period

Parameters	G1 (n=10)	G2 (n=10)	G3 (n=10)	p-value*
	Mean ± standart deviation			
Body weigh at baseline (g)	126.0±26.00	122.8±10.97	117.4±9.61	0.5199
Body weigh at the end of experimental period(g)	153.0±18.27	162.8±33.26	158.5±11.77	0.6425
Body weight gain (g)	26.3±11.37	40.0±28.68	41.1±6.53	0.1466
Food intake (g)	344.4±103.37	371.8±91.50	371.2±104.71	0.8773
Water intake (mL)	655.0±150.41	737.0±168.35	663.0±208.07	0.7261

**Anova one way test. G1= Control group. G2= Group treated with vitamin D (6 µg/kg). G3= Group treated with vitamin D (12 µg/kg). P = .05*

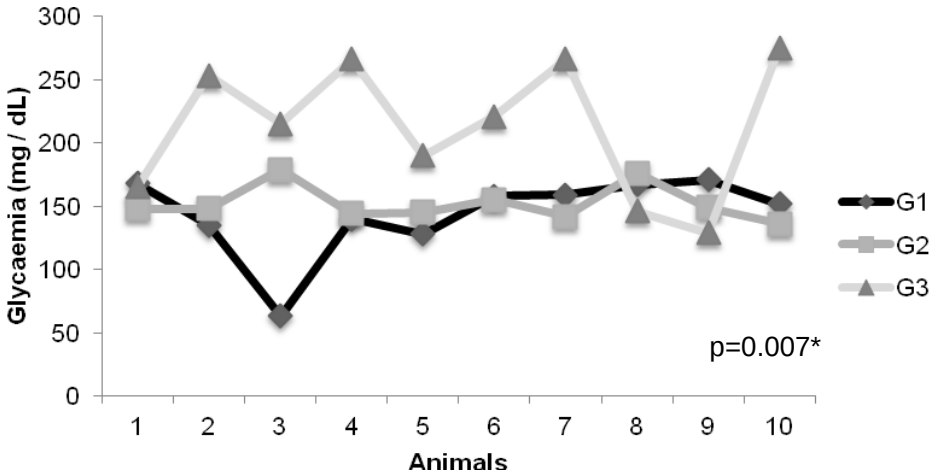

Fig. 1. Glycaemia measured at the 15th day of the experimental period
** Anova one way test*

Table 2. Comparison of the glycaemia between experimental groups using Tukey test

Comparison	p-valor
G1 x G2	ns
G1 x G3	p<0,01
G2 x G3	p<0,01

G1= Control group. G2= Group treated with vitamin D (6 μg/kg). G3= Group treated with vitamin D (12 μg/kg), ns = Not significant, P = .05

Data from this study show no significant interference of vitamin D3 supplementation on the amount of food intake however the animals from the supplemented groups showed higher values in the weight gain when compared to the control group.

Bland et al. [12] showed that pancreatic islets are able to produce $1\alpha,25(OH)_2D_3$ and able to respond rapidly to treatment with $1\alpha,25(OH)_2D_3$ and authors postulate that local production of vitamin D may be an autocrine link between Vitamin D status and pancreatic function.

Beaulieu et al. [13] showed that the glucose-stimulated insulin release is found to be lower in vitamin D-deficient rats.

Ortega et al. [26] showed different results on the body weight of overweight and obese women. They found that women with higher levels of vitamin D responded more positively to low-calorie diets and lost more body fat during the experimental period.

Caan et al. [27] demonstrated that postmenopausal women who received vitamin D and calcium supplementation had a lower weight gain compared to placebo. In addition, Zhu et al. [28] also supplemented patients with vitamin D and calcium in a low calorie diet and found that the body weight reduction was significantly higher than control group. Vimaleswaran et al. [29] studied the causality and the relationship between body mass index (BMI) and vitamin D in a very large number of individuals (up to 42,000 participants) and concluded that obesity leads to a low status of this vitamin but it is unlikely that the deficiency predisposes to a higher BMI.

In the other hand, Major et al. [30] studied overweight and obese women and concluded that the use of vitamin D and calcium did not interfere significantly in the weight loss.

In their review, Pathack et al. [31] intended to assess the association between vitamin D intake and obesity. They analyzed eighteen studies in humans and the authors concluded that there is a possible and small effect of vitamin D supplementation in reducing BMI, but significant results are only obtained when combined with caloric restriction.

Our study did not show significant difference in food intake among the groups, but animals supplemented with vitamin D3 had higher food intake compared to the control group. This may be associated with vitamin D storage in adipocytes, which decreases its bioavailability resulting in increased hunger and reduced

exergy expenditure [32] due to hypothalamus responses, which could also explain the increased weight gain in supplemented animals when they are compared to the control group.

We also did not find significant differences in the glycaemia among control group and the group supplemented with low dose of the vitamin (G2). However, when comparing the control group and the group that received high doses (G3) and comparing G2 with G3, differences were significant. G3 presented significantly higher blood glucose values compared to the other two groups.

In contrast to our results, Liu et al. [33] found a decrease in fasting glucose levels after supplementation with vitamin D in adults, and concluded that there is an inverse relationship between blood concentration vitamin D3, fasting glucose and insulin resistance.

Von Hurst et al. [34] showed that women supplemented with vitamin D improved significantly insulin resistance over six months without presenting any effect on the body weight. However, in a systematic review conducted by George et al. [35], authors suggested no significant improvement in fasting glucose, glycated hemoglobin or insulin resistance in individuals treated with Vitamin D when compared to placebo. In patients with diabetes or glucose intolerance, this meta- analysis showed a small positive effect on fasting glucose and insulin resistance.

Other studies have found a positive relationship between vitamin D intake and insulin sensitivity, which is independent of age, total body fat and energy intake [33,36,37], although Hidayat et al. [38] and Giorelli et al. [39] did not found an association between vitamin D deficiency and type 2 diabetes mellitus. Davidson et al. [20] did not found effects on the insulin levels in glucose intolerant individuals that received high levels of vitamin D.

Sergeev [40] postulate that an increase in the intake of vitamin D_3 in an induced obesity mouse model is associated with decrease in the weight of white adipose tissue and may help insulin secretion from pancreatic β-cells, thus contributing to the prevention of obesity and type 2 diabetes. Sepehrmanesh et al. [41] studied supplementation in a group of patients with depression and found positive effects on the maintenance of the glycaemia. Loy et al. [42] studied a very large group of women regarding to maternal Vitamin D3 status and plasma glucose concentrations and found positive associations. Jamka et al. [43] performed a systematic review to assess the effect of vitamin D supplementation on the glucose and insulin metabolism in overweight and obese subjects and concluded that this study does not provide evidence that vitamin D supplementation has significant effect on glucose and insulin metabolism in this group of patients. Similarly, in their review, Pilz et al. [44] pointed that there are no enough data available to recommend vitamin D supplementation to help the glycemic control.

It is important to say that Wistar rats are good animal models to study the effect of different pharmacological compounds and then draw a parallel with humans. However, our study does not have enough data to show that the doses used were sufficient to interfere with the insulin release.

4. CONCLUSION

There are controversial studies in the literature on the effects of vitamin D supplementation on the body weight and glycaemia. Our results show negative effects on these parameters especially with the higher dose of this vitamin. We suggest that further studies are necessary to outline the actual effects of the supplementation. Besides, the optimal doses also need to be established.

CONSENT

It is not applicable.

ETHICAL APPROVAL

Approval by the Animal Research Ethics Committee of the University of Marília (UNIMAR/ Marília, SP, Brazil) with protocol number 18/2015.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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