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Original Research

Consequences of Hypervitaminosis D in NZW Rabbit Model

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ABSTRACT

Background: This study examines the effect of hypervitaminosis D on serum lipids and on kidney functions in New Zealand White (NZW) rabbit. It aims to study whether renal insufficiency or failure, due to hypervitaminosis D, is calcium-related or not. As well, it also discusses a possible link between hypervitaminosis D and hypercholesterolemia. **Methods:** Four Groups of six animals each, were divided into: Group I, received regular diet, Group II received regular diet +10,000/day vitamin D2; Group III, received 0.25% cholesterol diet; as well as Groups IV received 0.25% cholesterol diet plus 10,000 IU. Blood samples were taken at the end of the study and examined for Total Cholesterol (TC), Triglycerides (TG), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Blood Urea Nitrogen (BUN), Creatinine, Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (ALP), Calcium and Phosphate. As well, 25- hydroxyvitamin D (25 (OH) D) was measured using tandem LC-MS/MS. **Results:** The initial (0 time) serum TC, TG, LDL, HDL, Creatinine, Calcium, Phosphate and 25 (OH) D levels were not significantly different among different groups including control. At 1- and 2-month time, values from serum TC, TG, LDL, HDL and TC/HDL-C ration of Groups III and IV were significantly different from controls (p<0.05). As well, values from serum 25 (OH) D of Group II and IV were significantly different from controls (p<0.05) at 1- and 2-month time. However, values from serum Creatinine and Calcium of Group II were significantly different from controls (p<0.05) at 1- and 2-month time. **Conclusion:** Hypervitaminosis D may aggravate hypercholesterolemia, and it also induces renal insufficiency and/ or failure through a calcium-dependent mechanism.

Highlights:

1. Excessive vitamin D supplementation, particularly when combined with a hypercholesterolemic diet, aggravated hyperlipidemia and elevated serum calcium levels in NZW rabbits.
2. Hypervitaminosis D was associated with increased serum creatinine and hypercalcemia, suggesting potential renal impairment secondary to excessive vitamin D intake.

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Introduction

Unlike the water-soluble vitamins, vitamin D causes disease due to excess as well as deficiency[1]. Excessive vitamin D supplementation in human food and in diets of animals intended for human consumption may be harmful since vitamin D3, is fat soluble and accumulates in all body tissues[2]. Among the factors that may predispose individuals to vitamin D intoxication are increased calcium intake, decreased renal function, diminished estrogen levels, the existence of sarcoidosis [3] or other vitamin D-hypersensitivity syndromes associated with over-production of 1, 25 (OH) 2D [4]. Linden [5] conducted an epidemiological study in humans finding a correlation between moderately high intakes of vitamin D with increased incidence of myocardial infarction. He also suggested that patients with hypercalcemia because of vitamin D intoxication are likely to develop renal calculi [5]. In the same essence, Moon et al [6] proposed that the 'epidemic' of ischemic heart disease in North America paralleled an increase in consumption of vitamin D accompanied by a decrease in that of magnesium. A Finish Study has been conducted at 1997 [7] on postmenopausal women who were on hormone replacement therapy (HRT) and receiving a long-term vitamin D supplementation. This study found that the serum concentrations of LDL-Cholesterol increased and those of HDL-Cholesterol and the HDL/LDL ratio decreased in the vitamin D3 group even more than those in the placebo group, although the differences between the groups were not statistically significant. They concluded that vitamin D3 supplementation may have unfavourable effects on lipids in postmenopausal women such as increased serum levels of LDL-Cholesterol.[7]

Misselwitz et al [8] identified 10 children with the combination of bilateral nephrocalcinosis and hypercalciuria with normal serum calcium and phosphate. These children were receiving intermittent high dose of vitamin D prophylaxis during infancy.[8]

In this study we are addressing the consequences of taking high doses of vitamin D. Until now, defining optimal dose of vitamin D still a troublesome as many factors are involved such as serum level 25 (OH)D, habitat (tropical, north, etc.), nutritional status, sex, age, and race. One of the themes of this study is attempting to define an optimal dose of vitamin D administration.

Material and Methods

Animals: Following the methods described previously (9- 15), twenty four female New Zealand White rabbits weighed 1.8 to 2 kg and aged 6- 8 weeks were assigned in five study groups (6 animals per group): 1) controls receiving regular diet + 1 ml olive oil on lettuce leaves (Group I) ; 2) animals fed on regular diet plus 10,000 IU/day vitamin D2 (Sigma; Markham, Ontario, Canada) dissolved in

olive oil*; 3) animals fed on 0.25% cholesterol-enriched diet (Purina (St Louis, MO, USA) and did not contain any antioxidants (Groups II and III). 4) animals fed on 0.25% cholesterol-enriched diet plus 10,000 IU/day vitamin D2 dissolved in olive oil (Group IV). Each animal was receiving 1 ml vitamin D2 solution (vehicle was olive oil) individually on lettuce leaves. The rabbits were housed in individual cages at room temperature of 22–24°C and a relative humidity of 40–60% under a 12-h light/12-h dark cycle.

The experimental protocols were approved by the Ethics Committee of the University of Saskatchewan and the animal care was performed according to the approved standards for Laboratory Animal Care. Following 18 h of fasting, blood samples (from the ear marginal artery) were collected before (0 time) and after 4 and 8 weeks on the respective diets for measurement of total cholesterol (TC), triglycerides (TG), low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), TC/HDL-C, Blood Urea Nitrogen (BUN), Creatinine, ALT, AST, ALP, calcium and phosphate. At the end of the protocol (8 weeks) rabbits were anesthetized with ethanol, pentobarbital sodium (50 mg kg^{-1} IV) (Bimedia-MTC Animal Health Inc., Cambridge, ON, Canada) in the marginal ear prior to euthanasia.

Olive oil was chosen to dissolve vitamin D2 over drinking water. As vitamin D2 is insoluble in water, olive oil was chosen to ensure the maximum solubility of vitamin D2. According to some reports released from Sigma Aldrich, the maximum possible solubility of vitamin D2 in water is 0.23 mg in 1 ml of water.

Blood Chemistry: Total cholesterol, triglycerides, HDL, BUN, creatinine, calcium and phosphorus, ALT, AST and ALP were measured on an automated Beckman Synchron LX20 Clinical System Analyzer. LDL-C was calculated. Cholesterol risk ratio was estimated using the TC/HDL-C ratio. However, 25 (OH) D was measured using Tandem MS/MS.

Statistics: The data are expressed as mean ± standard error mean (SEM). Then groups of data were compared with an analysis of variance (One way ANOVA) followed by Tukey's multiple comparison tests.

Results

Serum Lipids

Serum Cholesterol

The basal levels of Serum Total Cholesterol in Groups I, II, III, and IV were averaged as 1.5±0.2, 1.6±0.3, 1.9±0.8, and 1.6±0.5 respectively. The basal serum levels were not significantly different among different groups including control. Figure 1 shows that the initial (0 time) serum levels were not significantly different among different groups including control. At 1 month time, groups I and II showed slight alteration with no significant difference

(p value > 0.05). As well, values of Groups III and IV were significantly different from Groups I and II at 1 month time (p<0.05). At 2-month time, groups I and II showed slight alteration with no significant difference. Values of Groups III and IV were significantly different from Groups I and II (p < 0.05). Serum cholesterol of Group III slightly decreased when compared with the corresponding value at 1 month time. However, values of serum cholesterol from Group IV slightly increased when compared with the corresponding value at time 1 month. Group III was not significantly different from Group IV at 2-month time (p>0.05).

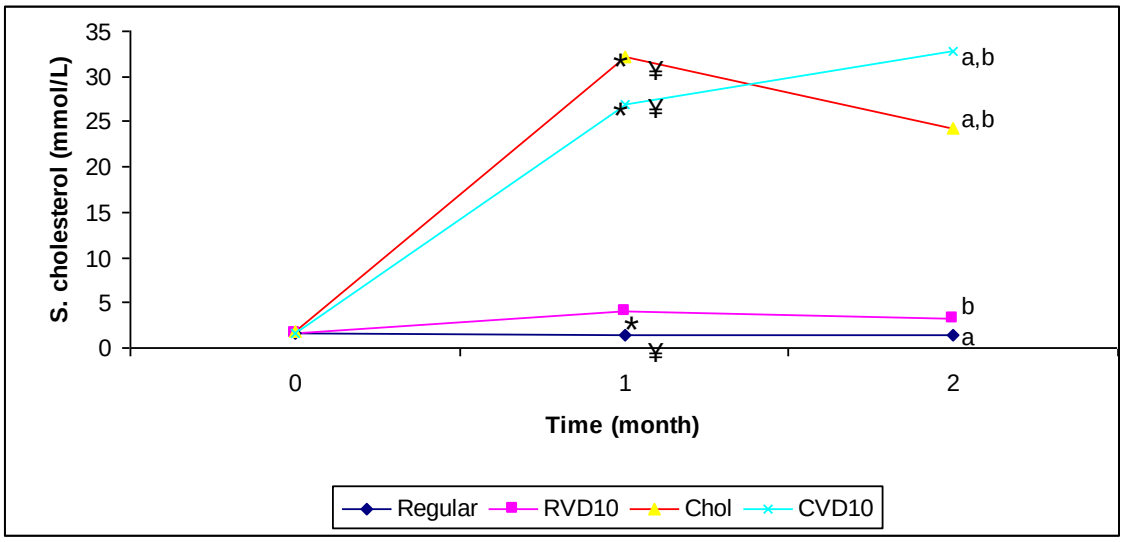

Figure 1. Sequential changes in the levels of serum cholesterol (mmol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. [¥]p< 0.05, comparison of values from Group I against Group III and IV at 1 month time. *p<0.05, comparison of values from Group II against values from Group III and IV at 1 month time. At 2-month time, [a]p<0.05, comparison of values from Group I against values from Group III and Group IV. [b]p<0.05, comparison of values from Group II against values from Group III and Group IV.

Serum Triglycerides

The basal levels of serum triglycerides in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were averaged as 0.96±0.4, 0.96±0.4, 0.79±0.3, and 0.77±0.3, respectively. As shown in Figure 2, the basal levels of serum triglycerides in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were not significantly different among different groups including control. At 1 month time, groups I and II showed slight alteration with no significant difference. Values of Groups III and IV were significantly different from values of Groups I and II at 1 month time (p<0.05). At 2-month time, values from Groups I and II were similar. Values of Groups III and IV were significantly different from Groups I and II (p < 0.05) at 2-month time. Serum triglycerides

of Group III decreased when compared with the corresponding value at 1 month time. However, values of serum triglycerides from Group IV slightly increased when compared with the corresponding value at time 1 month. Group III was not significantly different from Group IV at 2-month time (p>0.05).

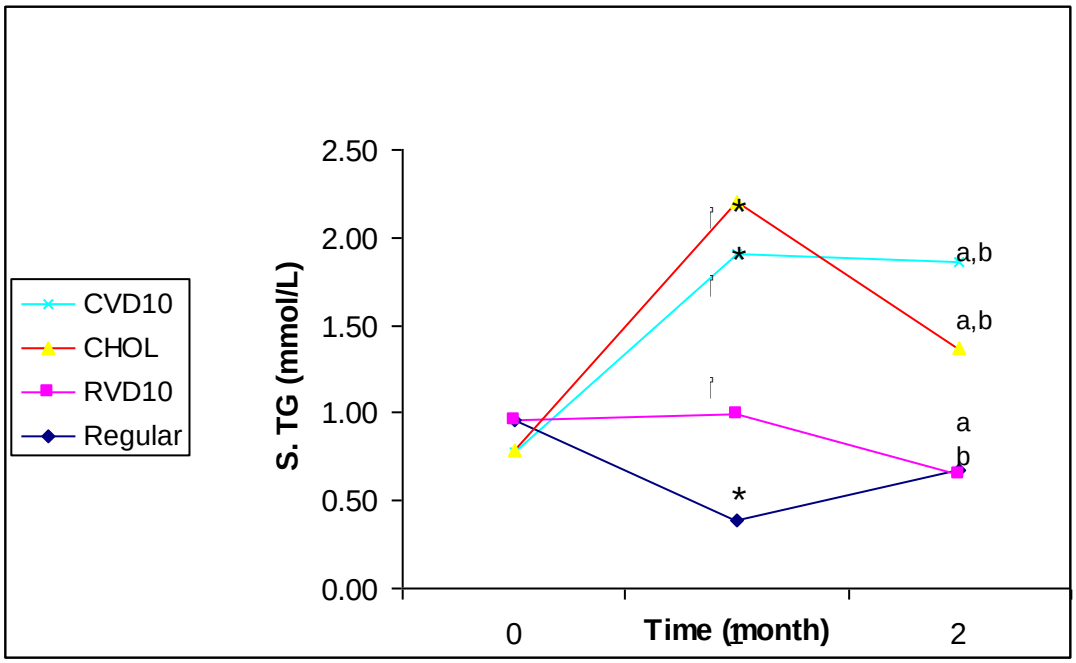

Figure 2. Sequential changes in the levels of serum triglycerides (mmol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. *p<0.05, comparison of values from Group I against values from Group III and IV. ǂ p< 0.05, comparison of values from Group II against Group III and IV at 1 month time. [a]p<0.05, comparison of values from Group I against Group III and IV and [b]p<0.05, Group II vs. Group III and IV at 2-month time

Serum Lipoproteins

Serum Low Density Lipoprotein (LDL)

The basal levels of serum LDL in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were averaged as 1.16±0.2, 1.71±0.2, 2.3±0.7 and 1.92±0.4, respectively. Figure 3 shows that the basal levels of Serum LDL in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were not significantly different among different groups including control. At 1 month time, groups I and II showed slight alteration with no significant difference. Values of Groups III and IV were significantly different from values of Groups I and II at 1 month time (p<0.05). At 2-month time, values from Groups I and II showed a slight alteration with no significant difference. Values of Groups III and IV were significantly different from Groups I and II ($p < 0.05$) at 2-month time. Serum LDL of Group III decreased when compared with the corresponding value at 1 month time. However, values of serum

LDL from Group IV slightly increased when compared with the corresponding value at time 1 month. Group III was not significantly different from Group IV at 2-month time (p>0.05).

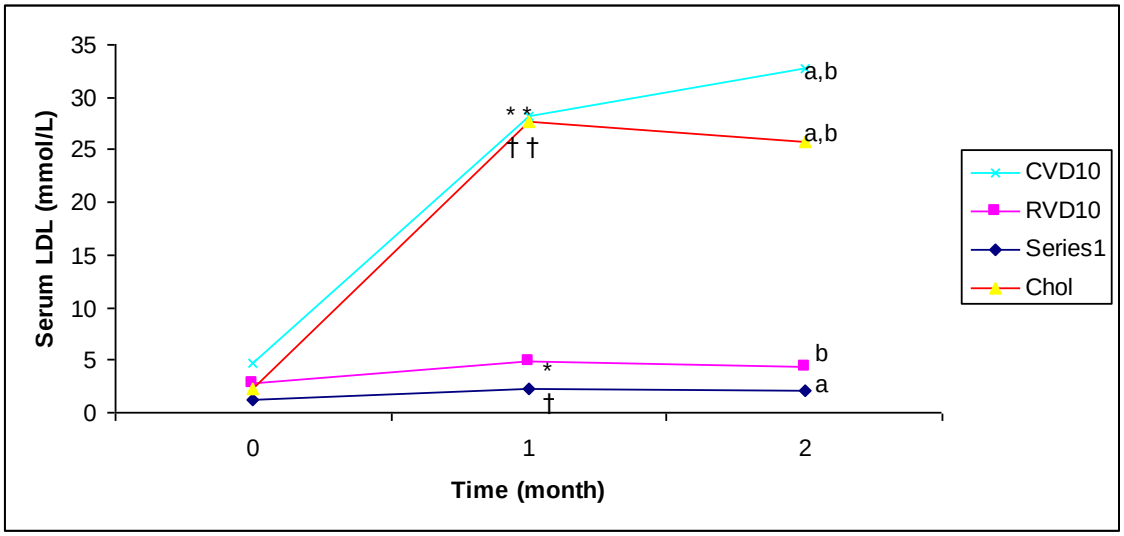

Figure 3**.** Sequential changes in the levels of serum LDL (mmol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. No significant difference among the four groups at 0 time. At 1 month time, † p< 0.05, comparison of values of group I against values from Group III and IV. *p<0.05, comparison of values from group II against values from Group III and IV. At time 2 months, [a]p< 0.05, comparison of values from group I against values from Group III and IV. [b]p<0.05, comparison of values from group II against values from Group III and IV.

Serum High Density Lipoprotein (HDL)

The basal levels of serum HDL in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were averaged as 0.57±0.1, 0.58±0.1, 0.72±0.2 and 0.64±0.1 respectively. As shown in Figure 4, the basal levels of Serum HDL in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were not significantly different among different groups including control. At 1 month time, groups I and II showed slight alteration with no significant difference. Values of Groups III and IV were significantly different from values of Groups I and II at 1 month time (p<0.05). At 2-month time, values from Groups I and II showed a slight alteration with no significant difference. As well, values of Group I increased when compared with the corresponding values at 1 month time while values from Group II showed slight decrease. Values of Groups III and IV were significantly different from Groups I and II (p < 0.05) at 2-month time. Group III was not significantly different from Group IV at 2-month time (p>0.05).

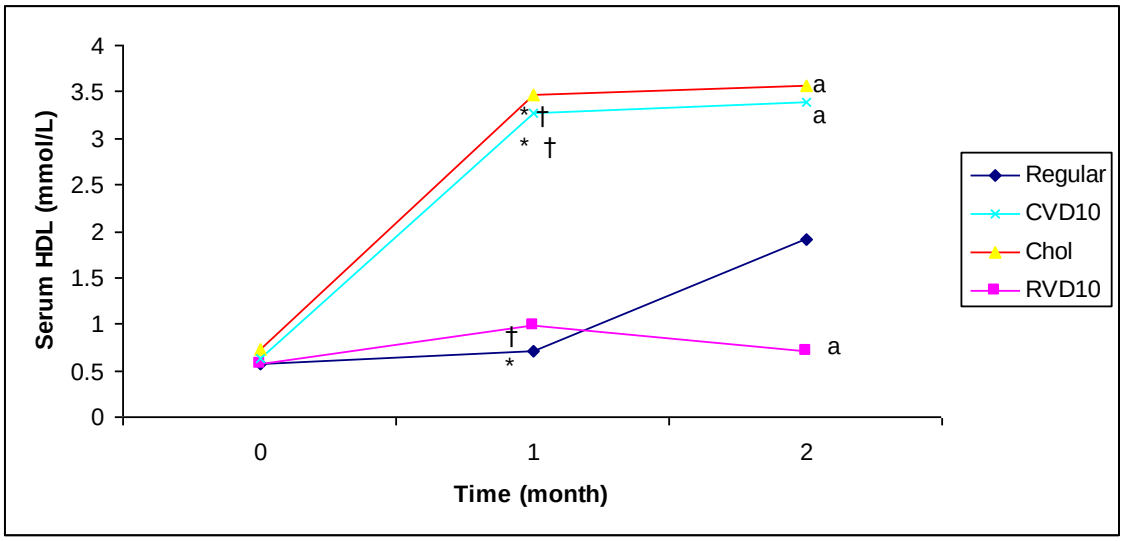

Figure 4. Sequential changes in the levels of serum HDL (mmol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. No significant difference among the four groups at 0 time. At 1 month time, *p<0.05, comparison of values from group I against values from Group III and IV. As well, † p< 0.05, comparison of values of group II against values from Group III and IV. At time 2 months, [a]p< 0.05, comparison of values from group II against values from Group III and IV.

T/HDL-C ratio

The basal levels of serum T/HDL-C ratio in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were averaged as 2.8±0.5, 2.8±0.5, 2.5±0.7and 2.6±0.3 respectively. As shown in Figure 5, the basal levels of Serum T/HDL-C ratio in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were not significantly different among different groups including control. At 1 month time, groups I and II showed slight alteration with no significant difference. Values of Groups III and IV were significantly different from values of Groups I and II at 1 month time (p<0.05). At 2-month time, values from Groups I and II showed a slight alteration with no significant difference. Values of Groups III and IV were significantly different from Groups I and II ($p < 0.05$) at 2-month time. Group III was not significantly different from Group IV at 2-month time (p>0.05).

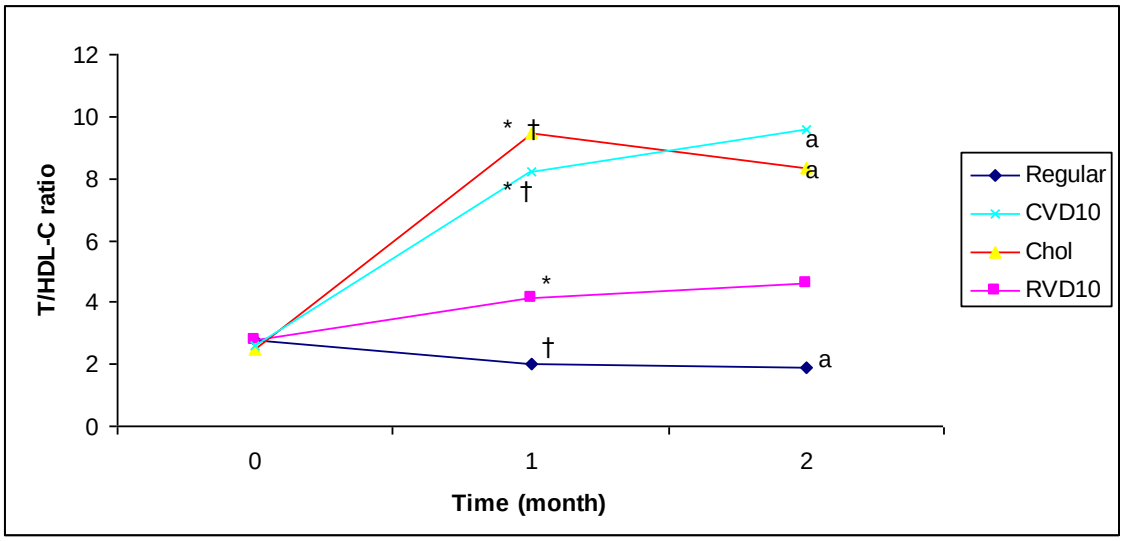

Figure 5. Sequential changes in the levels of serum T/HDL-C ratio in Groups I, II, III and IV. Results were expressed as mean ± SEM. No significant difference among the four groups at 0 time. At 1 month time, $^{\dagger}p< 0.05$, comparison of values of group I against values from Group III and IV. As well, $^{*}p<0.05$, comparison of values from group II against values from Group III and IV, $^{a}p< 0.05$, comparison of values from group II against values from Group III and IV.

Serum Total 25 (OH) D

Serum 25 (OH) D3 and 25 (OH) D2 were measured by using MS/MS and the total 25 (OH) D was calculated from the sum of the two fractions. Table 1 shows the differences from means (nmol/L) in respect to Time (0, 1 and 2 month) and diet. The basal levels of serum total 25 (OH) D in Groups I (Regular), II (RVD10), III (Chol), IV and (CVD10) were averaged as 123.3±29.7, 151.7±70.7, 106.7±24.1 and 102.0±13.3 respectively. Figure 6 shows that the initial (0 time) serum levels were not significantly different among different groups including control. At 1 month time, groups I and II showed slight alteration with no significant difference (p value > 0.05). Values of Groups II and IV were significantly different from values from Groups I and III at 1 month time ($p<0.05$). At 2-month time, groups I and III were similar. Values of Groups II and IV were significantly different from Groups I and II ($p < 0.05$) at 2-month time. Serum 25 (OH) D of Groups II and IV sharply increased when compared with the corresponding values at 1 month time. Group II was significantly different from Group IV at 2-month time ($p>0.05$).

Table 1: A comparison between values from means of serum 25 (OH) D2, 25 (OH) D3 and total 25 (OH) D (nmol/L) in respect to Time and Diet from Groups I, II, III and IV.

Time	Diet	25OHD2	25OHD3	T25OHD
0	Regular	89.67	33.67	123.33
1	Regular	83.50	59.50	142.83
2	Regular	68.83	19.67	88.33
0	RVD10	80.50	71.17	151.67
1	RVD10	32.33	693.33	725.67
2	RVD10	23.83	969.33	993.17
0	Chol	90.50	16.00	106.67
1	Chol	57.17	39.50	96.5
2	Chol	52.67	28.33	80.67
0	CVD10	84.17	17.83	102.00
1	CVD10	24.83	357.50	382.33
2	CVD10	29.00	680.00	709.00

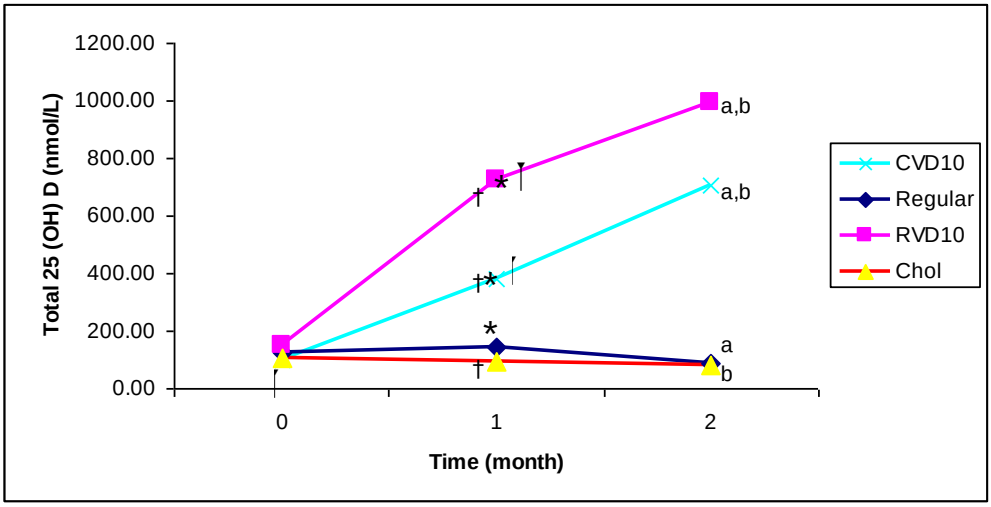

Figure 6. Sequential changes in the levels of serum total 25 (OH) D (mmol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. †p< 0.05, comparison of values of group I and II at 0 time against values from Group III and IV at 1 vs. 2-month times. *p<0.05, Group II vs. Group III and IV and ᵀp< 0.05 Group I vs. Group III and IV at 1 month time. [a]p<0.05, Group I vs. Group III and IV and [b]p<0.05, Group II vs. Group III and IV at 2-month time.

Serum Creatinine

The basal levels of Serum Creatinine in Groups I, II, III, IV and V were averaged as 62.3±12.0, 70.5±9.7, 75.0±8.0, 73.8±5.0 and 65.3±6.4 µmol/l respectively. The basal serum levels were not significantly different among different groups including control. **Fig. 7** indicated that the basal serum levels were not significantly different among different groups including control. At 1 month time, Group II was significantly different Groups I and III (p<0.05). However, Group II showed slight alteration when compared with Group IV with no significant difference (p>0.05). Values of Groups II were significantly different from Groups I, III and IV (p < 0.05) at 2-month time. However, Groups I, III and IV were not significantly different (p>0.05).

S. Calcium

The basal levels of Serum Calcium in Groups I, II, III, and IV were averaged as 3.1±0.09, 3.3±0.15, 3.1±0.11, and 3.2±0.22 respectively. At 1 month time, values from Groups I, III and IV showed slight alteration with no significant differences (p>0.05). However, value from Group II was significantly different from those of Groups I, III and IV (p<0.05) (**Fig. 8**). As well, value from Group II was significantly different from the corresponding at 0 time (p<0.05) (Fig.8). At 2-month time, values from Groups II were significantly different from those from Groups I, III and IV (p<0.05) (Fig.3). However, values from Group II were significantly different from the corresponding at initial time (p<0.05) (Fig.3).

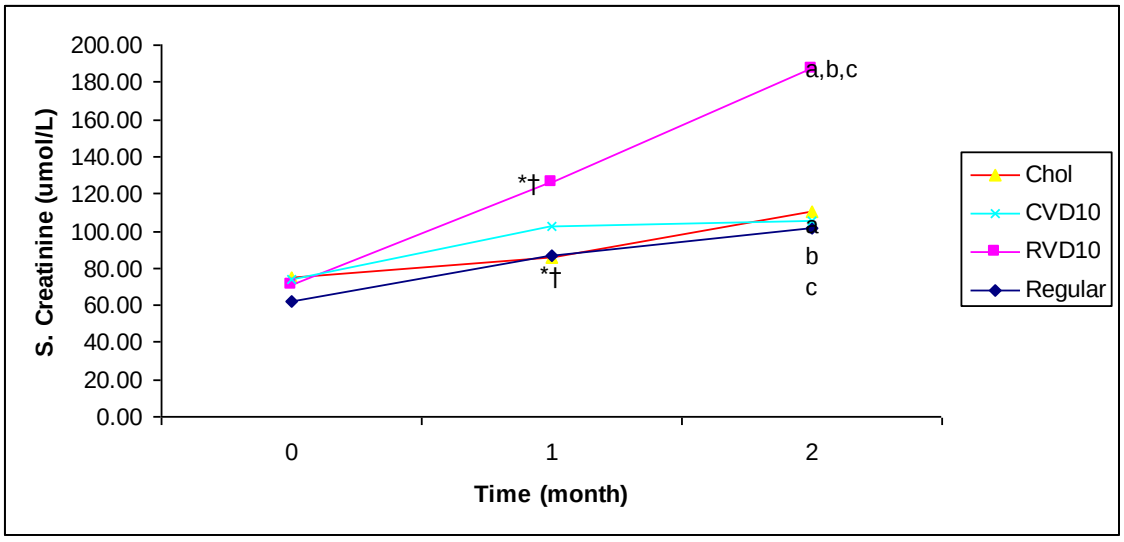

Figure 7. Sequential changes in the levels of serum Creatinine (umol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. †p< 0.05, comparison of values of group I vs. values from Group II at 1 month time. *p<0.05, Group III vs. values from Group II. [a]p<0.05, Group I vs. Group II, [b]p<0.05, Group III vs. Group II and [c]p<0.05, Group IV vs. Group II at 2-month time.

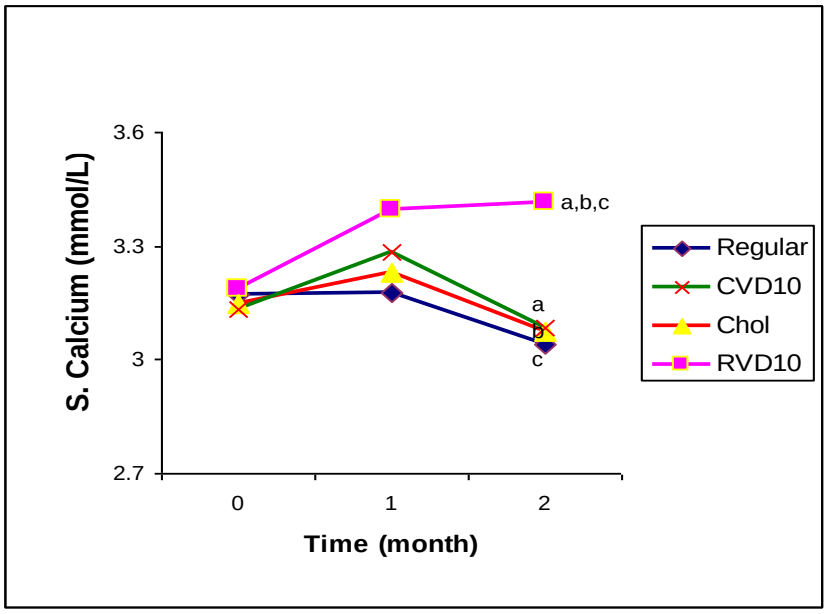

Figure 8. Sequential changes in the levels of serum Calcium (mmol/L) in Groups I, II, III and IV. Results were expressed as mean ± SEM. †p< 0.05, comparison of values of group I vs. values from Group II at 1 month time. *p<0.05, Group III vs. values from Group II. [a]p<0.05, Group I vs. Group II, [b]p<0.05, Group III vs. Group II and [c]p<0.05, Group IV vs. Group II at 2-month time.

Discussion

Vitamin D supplementation in combination with a hypercholesterolemic diet have been extensively used for decades by investigators studying hypercholesterolemic rabbit models of atherosclerosis. In terms of the necessity of having vitamin D dissolved in organic solvents, corn oil or olive oil, we chose olive oil as a vehicle to ensure that the proper dose reaches every individual animal. This causes that group V (GV) did not last for more than 2 weeks. The same procedure was used by Toda et al[23] with exception of using corn oil instead of olive oil and having the dose administered/kg body weight (not fixed dose). Due to that, they lost most of their animals early in the study. In our procedure, we fixed the dose to 1 ml of vitamin D solution. In contrary to Toda's and our procedure, other investigators used drinking water to dissolve vitamin D[9,11] which, we thought, did not ensure the appropriate dose as vitamin D is water insoluble.

In this study, we reported that vitamin D supplementation enhances hypercholesterolemia even in the group II (GII) that did not include cholesterol in the diet. However, hypercholesterolemia was even aggravated when vitamin D was combined with cholesterol in diet in comparison to cholesterol diet alone. This finding was totally correlated with others on Male Sprague-

Dawley rat and NZW rabbit [10, 11]. Both research teams did not validate a scientific explanation for this observation. Huang et al[16] suggested a synergistic effect of vitamin D with dietary fat in a similar study conducted on swine. On the other hand, Hines et al[17] have conducted a study on the effects of dietary calcium and vitamin D on young goats. They found no direct effect of vitamin D on hypercholesterolemia.

In clinical setting, as indicated in the introduction, Heikkinem et al[7] found that LDL-C increased while HDL-C and HDL/LDL ratio decreased in women on long-term vitamin D3 supplement who were also receiving HRT. They also found that pure vitamin D3 medication (HRT not included), led to a 4.1% increase in LDL-C and a 10.5 % decrease in the HDL/LDL ratio [8]. Some reports stated that 8 cases were vitamin D intoxicated due to drinking excessively fortified cow milk [18]. On the other hand, some other reports did not confirm that high vitamin D status is associated with high risk of hypercholesterolemia or myocardial infarction[19– 22]. Taking together, there is a controversy in terms of optimal vitamin D dosing in experimental animals and in human subjects.

Hypercalcemia and/or hypercalciuria are the consequence of increases in intestinal absorption and bone resorption as well as renal impairment [24]. One of the important criteria of renal impairment is elevated serum creatinine that we indicated in our results. This finding was also correlated with the findings of Rezzoli et al[24]. Rezzoli et al and we reported that hypervitaminosis D may develop renal impairment by causing the elevation of serum creatinine with normo- or hypercalcemia. Misselwitz et al[8] reported a combination of bilateral nephrocalcinosis and hypercalciuria in 10 children due to vitamin D overdose[8]. Seelig et al[1] blamed hypervitaminosis D or infantile hypercalcemia in causing renal acidosis.

Conclusion

Our finding that hypercalcemia was developed due to excess vitamin D supplementation whether in a combination with regular chow or 0.25% cholesterol diet was also partially correlated with Tang's et al findings (10). They reported that administration of excessive vitamin D to rats could enhance intestinal calcium absorption and bone resorption, leading to hypercalcemia.

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