Lipid profile of childhood cancer survivors and the effects of vitamin D supplementation: a prospective study

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Abstract

Background: Childhood cancer survivors (CCS) have high prevalence of obesity vitamin D (VD) deficiency together with dyslipidemia. We aimed to evaluate lipid profile and the effect of VD supplementation in CCS.

Results: VD deficiency was more frequent among obese CCS and their lipid profiles, TC, and LDL-C levels were significantly higher compared to non-obese patients. After VD supplementation trials, VD levels increased among obese and non-obese children albeit it was significantly higher in non-obese subjects while the lipid profile of obese patients significantly decreased. Also, parathyroid hormone levels were persistently elevated among VD-deficient obese patients. Yet, the weight of obese patients remained unchanged.

Conclusion: VD deficiency was more prevalent among obese CCS. VD supplementation helped in normalization of the lipid profile of obese CCS. Regular measurement of PTH and 25OH-VD is recommended for CCS especially obese ones who may need VD supplementation.

Keywords: Childhood cancer survivor, Body mass index, Obesity, Vitamin D supplementation

Background

One of the complications of cancer therapy for children and adolescents is obesity, which is a risk factor for the development of adulthood dyslipidemia [1]. This is explained by positive energy balance because of overconsumption of food calories and decreased physical activity [2]. In addition, a unique risk factor for obesity and dyslipidemia among those children, that is, the cancer treatment received at a very young age including corticosteroids which are known to be critically involved in regulating energy intake, storage, and mobilization, and their prolonged use has shown effects on body composition with increased body fat [3]. Previous researches found that VD status index serum 25-hydroxy vitamin D (25OH-VD) tends to be lower among obese adults [4, 5] and obese children [6]. This is explained by many mechanisms including dilutional effect of distribution of vitamin D (VD) in larger fat content, sedentary life with decreased sun exposure, food imbalance favoring energy-dense foods, and compensatory hyperparathyroidism found in obese adults [4, 5]. In addition, VD status, lower 25OH-VD combined with specific unfavorable lipid markers (dyslipidemia) has been associated with increasing risk of cardiovascular diseases during childhood/adulthood [5–11]. The aim of this study is to measure lipid profile in CCS and evaluate the effect of VD supplementation, on their lipid profile and body weight.

Methods

This is a prospective, Institutional Review Board (IRB) approved study. It was conducted throughout a period of 2 years (from 2017 to 2019). Childhood cancer survivors’ long-term follow-up medical record data and charts were gathered from the outpatient clinics of King...
Abdullah Medical City’s (KAMC) Oncology Center, Jeddah, Saudi Arabia. All research work steps were conducted in accordance with the Declaration of Helsinki [7]. The subjects included were children and adolescents diagnosed with different types of malignancy (leukemia, lymphoma, solid tumors) and who had completed their treatment for more than 12 months before enrollment. Children who were still on chemotherapy treatment, experienced a relapse, or who were already on VD supplementation were excluded.

**Weight status assessment**

The patients’ height and weight were assessed to the nearest 0.1 cm and 0.1 kg, respectively, utilizing the Health-O-meter Professional (Austin, IL, USA) (https://pdf.medicalxpo.com/pdf/health-o-meter-professional/160lb/79708-185156.html). Body mass index (BMI) was calculated from the formula, weight (kilograms)/height² (meters). BMI and standard deviation scores (Z-scores) for the anthropometric data were calculated from the WHO (2007) standard BMI and BMI-for-age (5-19 years) Z-score 13. The WHO BMI-for-age reference data was utilized, and obesity was defined conventionally, as obese ≥ 95th percentile, overweight as 85th to 94th percentiles, and underweight as < 5th percentile. We included only 2 categories of patients: non-obese patients with normal weight (BMI, 5th-85th percentiles) and obese patients (BMI ≥ 95th percentile).

The 25-OH-VD levels were evaluated using vitamin D total assay (The ADVIA Centaur (Siemens Healthcare Diagnostics Inc., Tarrytown, NY)), a competitive one-pass antibody immunoassay 14. VD status was classified as VD sufficient (VDS) (serum 25OH-VD ≥ 30 ng/ml), VD insufficient (VDI) (serum 25OH-VD 20-30 ng/ml), and VD deficient (VDD) (serum 25OH-VD < 20 ng/ml) 15-17. VDD survivors were treated with oral VD 50,000 units weekly, for 8 weeks 18 followed by oral monthly vitamin-D3 tablets 50,000 IU over a period of 6 months. VD levels were measured after completing 6 months of VD treatment to detect the response to supplementation.

Laboratory evaluations and investigations were conducted to establish the baseline before and after VD supplementation levels for serum calcium, serum phosphorus, serum magnesium, and parathyroid hormone (PTH), lipid profile (total cholesterol (TC)), low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), and triglycerides (TG).

The two patients’ categories (obese and non-obese) were followed regarding their compliance and response to oral monthly administered vitamin D3 tablet for 6 months.

**Statistical methods**

The Statistical Package for Social Sciences (SPSS) version 18.0 for Windows (SPSS, Inc., Chicago, IL, USA) was utilized for statistical analysis. Categorical data was expressed as numbers and percentage (%), while quantitative data was presented as mean ± standard deviation (SD) or median and IQR. Depending on the nature of the data, comparisons were made by utilizing the Student’s t test and Chi-square test. Pearson correlation was used to detect the linear relationship between two continuous variables. P value less than 0.05 was considered statistically significant.

**Results**

Out of the 95 long-term follow-up patients who survived childhood cancers, 57 (24 male: 33 female) were enrolled in the study. Patients were divided according to BMI into 2 groups: 17 obese (BMI > 95th percentile) and 40 non-obese patients (BMI: 5th-85th percentile). According to initial 25OH-VD levels, 35 patients (61.4%) were VDD (25OH-VD < 20 ng/ml) and 15 patients (26.3%) were VDI (25OH-VD 20-30 ng/ml), while the remainder 7 patients (12.3%) had VDS levels (25OH-VD > 30 ng/ml) (Fig. 1).

Table 1 shows patients BMI differences and comparisons. Obese patients were found to be significantly older in age with higher percentages being female (76.5%) of which 70% were of post-pubescent age (Tanner 3-5). Obese patients had initially significant lower 25OH-VD in comparison to non-obese patients. Obese patients were significantly represented in the VDD group at 88.2% (15/17 patients) as compared to 50% of non-obese patients (20/40 patients). Obese patient’s lipid profiles, TC, and LDL-C levels were significantly higher compared to non-obese patients. No difference between the 2 groups was found with regards to serum calcium, phosphorus, magnesium, or parathyroid hormone.

VD treatment/supplementation was administrated to obese and non-obese VDD patients over 6 months which successfully raised their 25OH-VD levels, though more significantly (P = 0.02) in non-obese subjects (25OH-VD, 26.74 ± 4.48 ng/ml) compared to their obese counterparts (25OH-VD, 18.73 ± 6.61 ng/ml), while 55% (11/20) of non-obese patients were VDS compared to 26.6% (4/15) of obese patients. A significant negative correlation was found between 25OH-VD levels and BMI, body weight and age of the patients but did not correlate with PTH or lipid profile laboratory tests as shown in Table 2.

Table 3 shows significant decreases in PTH levels among non-obese compared to obese patients after VD supplementation. VD levels significantly increased while lipid markers (TC, LDL-C) decreased after VD supplementation in obese patients. No changes were found with regards to weight or BMI in obese patients compared to their own initial values before supplementation. No complications or adverse effects were detected in any of the VD treated/supplemented patients. Compliance of patients was found to be ~93% with only 4
patients were not compliant and subsequently, they were excluded from the results in the next phase of the study.

**Discussion**

We evaluated in this study the lipid profile, prevalence of VD deficiency and the effect of VD supplementation among CCS, and the overall effects of the 6-month VD supplementation on their VD levels, weight status, and lipid profiles.

**Lipid profile and VD effect**

This study found significantly higher levels of TC and LDL-C among obese patients which reduced significantly after VD treatment/supplementation. Other studies on obese children, reported associations between low 25OH-VD levels and unfavorable lipid profiles [8]. Censani et al. [8] reported that VDD patients (25OH-VD < 20 ng/mL) had significantly higher TC, TG, and LDL-C levels compared with patients with higher VD (25OH-VD = 20 ng/mL). Sriram et al. [9] and Rusconi et al. [10] showed an inverse correlation between 25OH-VD levels and TC/LDL-C levels. Aypak et al. [11] found a higher LDL-C and TG, and lower HDL-C in obese children compared to lean children. Conversely, Rajakumar et al. [12] and Delvin et al. [13] found no differences in most lipid parameters (TC, LDL-C, TG) between subjects with sufficient/deficient 25OH-VD. Although they did not give an explanation for this, however, Rajakumar et al. [12] reported a positive correlation between plasma 25(OH)D and HDL cholesterol (a favorable lipid biomarker) in both black and white children. Furthermore, they found that vitamin D deficiency was associated with higher adiposity measures (visceral adipose tissue in whites and greater subcutaneous adipose tissue in blacks and explained this finding by ethnic differences between African–American and Caucasian races).

**VD status**

Obese patients had a significantly lower 25OH-VD and higher VDD percentage (88.2%) compared to (50%) in non-obese patients. Few studies have reported low VD in obese children. Olson et al. [14] evaluated 6-16 years olds of which 411 were obese and 87 non-overweight (control group), and reported VDD as being significantly more prevalent in obese children. Another study, Rajakumar et al. [6] studied VD status in African-American children finding VDD being detected in 57% (12/21) obese patients versus 40% (8/20) non-obese patients as a baseline. After a trial run of VD treatment for 1 month: VDD was still persistent in 24% (5/21) obese patients and 11% (2/18) non-obese patients.

Low VD levels among obese subjects were explained with reduced bioavailability because of storage of VD (fat-soluble vitamin) in larger fat compartment tissues.
Also, sedentary lifestyles of obese individuals and reduced outdoor activities with less sunlight exposure which is essential for VD production [14, 15]. It may also be because food imbalance favoring energy-dense foods by obese children at the expense of foods rich in vitamins and minerals (vegetables, fruits) as well as meat or fish, which decreases availability of VD intake [16]. It may also be as a result of compensatory hyperparathyroidism has been observed in obese adults with low 25OH-VD levels [4, 5].

VD and PTH effects on adiposity

This study reports no change to body weight and BMI after VD treatment/supplementation of obese patients. As weight reduction requires integrated strategies such as implementing strict dietary controls, involvement in fitness, and physical exercise. This is consistent with previous researches confirming no reduction of body weight or BMI in obese adolescent children or adults after VD treatment for 3 up to 12 months [17, 18]. High levels of PTH, which persisted among obese VDD groups even after VD supplementation, may be an indication of more

| Table 1 Baseline characteristics, anthropometric, and laboratory data of the studied patients |
|-----------------------------------------------|-------------------------------|-------------------------------|-------------------------------|-------------------|
| **All studied patients (57 patients)** | **Obese patients (17 patients)** | **Non-obese patients (40 patients)** | **P value** |
| Age on study (years) | Median (IQR) | 14.9 (11.15, 17.0) | 16.6 (15.4, 17.0) | 12.8 (9.8, 16.8) | 0.001* |
| | [Minimum-maximum] | [5.1-18] | [11.7-18] | [5.1-18] | |
| Sex | Male:female | 24 (40.4%):33 (59.6) | 5 (23.5%):12 (76.5%) | 19 (47.5%):21 (52.5%) | 0.15 |
| Type of malignancy | | | | |
| Leukemia/lymphoma | 41 (71.9%) | 12 (70.6%) | 29 (72.5%) | 0.88 |
| Solid tumor | 16 (28.1%) | 5 (29.4%) | 11 (27.5%) | |
| Weight (kg) | 44.97 ± 19.1 | 68.9 ± 12.9 | 33.8 ± 10.8 | < 0.001* |
| BMI (kg/m²) | 21.11 ± 5.97 | 29.4 ± 3.27 | 17.0 ± 1.96 | < 0.001* |
| Initial VD status | | | | |
| VDD (25OH-VD < 20 ng/ml) | 35 (61.4%) | 15 (88.2%) | 20 (50%) | 0.020* |
| VDI (25OH-VD, 20-30 ng/ml) | 15 (26.3%) | 1 (5.9%) | 14 (35%) | |
| VDS (25OH-VD ≥ 30 ng/ml) | 7 (12.3%) | 1 (5.9%) | 6 (15%) | |
| Calcium (mg/dl) | 9.8 ± 0.7 | 9.9 ± 0.5 | 9.7 ± 0.6 | 0.27 |
| Phosphorus (mg/dl) | 5.2 ± 1.5 | 5.2 ± 1.3 | 5.3 ± 1.8 | 0.33 |
| Magnesium (mg/dl) | 2.43 ± 0.32 | 2.31 ± 0.25 | 2.45 ± 0.30 | 0.09 |
| PTH (pgm/ml) | 44.5 ± 9.0 | 44.7 ± 10.7 | 45.4 ± 9.2 | 0.53 |
| TC (mg/dl) | 175.51 ± 49.73 | 182.6 ± 22.3 | 171.4 ± 24.2 | 0.014* |
| TG (mg/dl) | 85.35 ± 31.89 | 88.7 ± 45.2 | 83.0 ± 24.3 | 0.64 |
| HDL-C (mg/dl) | 41.67 ± 12.24 | 42.5 ± 12.6 | 41.5 ± 11.3 | 0.966 |
| LDL-C (mg/dl) | 104.86 ± 20.39 | 109.8 ± 26.8 | 90.5 ± 25.3 | 0.039* |

BMI: body mass index, PTH: parathyroid hormone, 25OH-VD: 25-hydroxyvitamin D, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol, VDD: vitamin D deficient, VDI: vitamin D insufficient, VDS: vitamin D sufficient

*P < 0.05 is of significance

| Table 2 Spearman’s correlation coefficient of 25-OH VD with different anthropometric and laboratory variables |
|-----------------------------------------------|-------------------------------|-------------------------------|-------------------|
| **R** | **B co-efficient** | **P value** |
| Age on study | 0.390 | −0.70 | 0.005* |
| Weight | −0.353 | −0.145 | 0.007* |
| Height | −0.236 | 0.035 | 0.053 |
| BMI | −0.370 | −0.40 | 0.005* |
| PTH | 0.196 | 0.030 | 0.35 |
| TC | −0.299 | −0.021 | 0.08 |
| TG | −0.163 | −0.023 | 0.34 |
| HDL-C | 0.172 | 0.010 | 0.39 |
| LDL-C | −0.152 | −0.022 | 0.12 |

BMI: body mass index, PTH: parathyroid hormone, 25OH-VD: 25-hydroxyvitamin D, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol

*P < 0.05 is of significance
Table 3 Before and after VD supplementation anthropometric and laboratory data of the supplemented patients (obese/non-obese) (results presented as mean ± SD)

|                      | Obese patients | Non-obese patients |
|----------------------|----------------|--------------------|
|                      | Before VD supplementation (N = 17) | After VD supplementation (N = 15) | Before VD supplementation (N = 20) | After VD supplementation (N = 20) |
| BMI                  | 29.4 ± 3.27  | 27.35 ± 1.5        | 18.2 ± 1.1                        | 18.6 ± 2.4                        |
| BMI-Z score          | 2.24 ± 0.42  | 2.11 ± 0.22        | 0.42 ± 0.74                       | 0.43 ± 0.62                       |
| Calcium (mg/dl)      | 9.9 ± 0.5    | 9.6 ± 0.5          | 9.7 ± 0.5                         | 9.6 ± 0.3                         |
| Phosphorus (mg/dl)   | 5.2 ± 1.3    | 5.4 ± 0.5          | 5.4 ± 0.1                         | 5.3 ± 0.4                         |
| Magnesium (mg/dl)    | 2.31 ± 0.25  | 2.32 ± 0.35        | 2.32 ± 0.31                       | 2.38 ± 0.22                       |
| PTH (pg/ml)          | 44.7 ± 10.7  | 43.2 ± 9.9         | 44.2 ± 8.0                        | 34.3 ± 14.2** (P = 0.0119)        |
| 25OH-VD (ng/ml)      | 13.30 ± 5.67 | 18.73 ± 6.61* (P = 0.018) | 15.36 ± 5.73                      | 26.74 ± 4.48** (P < 0.0001)      |
| TC (mg/dl)           | 182.6 ± 22.3 | 162.3 ± 21.1* (P = 0.013) | 172.4 ± 20.2                      | 161.4 ± 24.2                      |
| TG (mg/dl)           | 88.7 ± 45.2  | 86.6 ± 34.1        | 86.0 ± 25.7                       | 83.0 ± 29.3                       |
| HDL-C (mg/dl)        | 42.5 ± 12.6  | 43.4 ± 10.7        | 44.5 ± 17.2                       | 42.5 ± 11.3                       |
| LDL-C (mg/dl)        | 109.8 ± 26.8 | 94.8 ± 20.6* (P = 0.049) | 92.3 ± 21.7                       | 90.5 ± 25.3                       |

BMI: body mass index, PTH: parathyroid hormone, 25OH-VD: 25-hydroxyvitamin D, TC: total cholesterol, TG: triglycerides, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol.

*p ≤ 0.05 of significance (obese before and after VD supplementation)

**p ≤ 0.05 of significance (obese after VD supplementation versus non-obese patients after VD supplementation)

need for VD to be given to those patients. Similar to our study, Amini et al. [19] and Rusconi et al. [10] reported that 25OH-VD deficiency in obese children was also associated with higher levels of PTH.

VD treatment for obese children

In our study, VD supplementation trials were less successful in increasing 25OH-VD in all obese patients, possibly suggesting the requirement for higher doses or more frequent courses of VD treatment/supplementation in obese children. Previous studies support and suggest the need for higher doses to be administered to obese children as their bioavailability evaluations, after oral VD at 50,000 units, were found to be less effective [4]. Harel et al. [17] in their study, evaluated a high dose VD treatment trial administered to VDD obese adolescents (25OH-VD < 20 ng/ml) at 50,000 units per week for 6-8 weeks, and for VDI (25OH-VD, 20-30 ng/mL) at 800 units per day for 3 months, and reported a significant increase in 25OH-VD after the initial course of VD treatment in only 28% of the participants.

Limitation of the study

The small sample sizes of the study, being conducted in a single-center, retrospective nature of the study, non-randomization of patients, were some limitations of this study. There was also a difficulty in evaluating the exact food consumption and physical activity of patients (which certainly would affect VD and weight status of our studied patient) because of recall bias and non-cooperation of many parents/patients.

Conclusion

We found a higher prevalence of VDD and higher lipid profile levels, TC and LDL-C levels, among obese CCS patients compared to non-obese subjects. VD supplementation administered to VD deficient patients successfully raised 25OH-VD levels more significantly in non-obese patients. This may suggest the higher requirements of VD for obese CCS patients. Additional large-scale VD correction trials in obese patients may be required to consolidate research findings.

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Authors’ contributions

SK shared the research idea and conducted the clinical work and revised the last version of the manuscript. AF is the owner of the research idea, he conducted the clinical aspect of the research, wrote the first draft of the manuscript, and approved the last version of the manuscript. KKB was responsible for language editing and revision of the manuscript. YS conducted the laboratory and pharmaceutical part of the work and revised the last version of the manuscript. SA shared in research idea and manuscript writing and responsible for correspondence. All authors have read and approved the manuscript before it has been submitted to your journal.
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### Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

### Ethics approval and consent to participate
The study design was approved by King Abdullah Medical City Institutional Review Board (KAMC-IRB) and registered at the National BioMedical Ethics Committee, King Abdulaziz City for Science and Technology on 14-07-1433 (Registration no. H-02-K-001). IRB approval document is available.

### Consent for publication
Not applicable

### Competing interests
None of the authors has any financial and non-financial competing interests to declare.

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