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Original article

Is there a relationship between vitamin D nutritional status and metabolic syndrome in childhood acute lymphoblastic leukemia survivors? A PETALE study

E. Delvin [a, b, *], V. Marcil [a, c], N. Alos [a, d], C. Laverdière [a, d], D. Sinnett [a, d], M. Krajinovic [a, d], V. Bélanger [a, c], S. Drouin [a], C. Nyalendo [a, e], E. Levy [a, c, **]

[a] Sainte-Justine UHC Research Centre, Université de Montréal, Montréal, Canada
[b] Department of Biochemistry and Molecular Medicine, Université de Montréal, Montréal, Canada
[c] Department of Nutrition, Université de Montréal, Montréal, Canada
[d] Department of Pediatrics, Université de Montréal, Montréal, Canada
[e] Department of Clinical Biochemistry, Sainte-Justine UHC, Université de Montréal, Montréal, Canada

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SUMMARY

Background: Treatment of childhood acute lymphoblastic leukemia (cALL) has reached unprecedented success leading to survival rates reaching 90%. This is regrettably linked to increased risk of developing long-term health-related sequels into early adulthood.
Objective: This study aims at assessing the relationship between the vitamin D status and metabolic biomarkers in PETALE, a well-characterized cohort of cALL survivors.
Results: We demonstrate that 15.9% of the study participants exhibited 3 or more metabolic syndrome (MetS) risk factors. We also show a direct relationship between $s25OHD_3$ and plasma HDL-Cholesterol concentrations in female but not male participants.
Conclusion: Our data, from a metabolically well-described cohort, support a modest role for vitamin D in lipid metabolism in childhood leukemia survivors. The major outcome of this study is the strong association between HDL-Cholesterol concentration and $s25OHD_3$ only in female subjects, thereby conveying vitamin D a gender-specific cardio-protective effect. cALL survivors represent a population at higher risk for secondary diseases. For this reason thorough nutritional evaluation, including vitamin D should be part of the regular follow-up.
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1. Introduction

The advent of multimodal therapy has remarkably improved the long-term survival rate of childhood acute lymphoblastic leukemia (cALL) patients, which now reaches 90% [1,2]. This success story is however, associated with increased risk of health-related sequels, including several cardiometabolic complications [3–5]. Indeed cALL survivors display a higher cardiac mortality frequency than the general population, and a greater probability of developing cardiac disorders than their siblings [6,7]. Furthermore, our group and others have reported that insulin resistance, dyslipidemia and hypertension, all suggestive of premature cardiovascular disease, are more prevalent in cALL survivors [8–12]. We recently described the vitamin D status in the well-characterized PETALE cohort of cALL survivors, and showed that despite vitamin D intake below the Recommended Daily Intake (RDI) in 74% of the participants, the prevalence of vitamin D insufficiency and deficiency, assessed by serum 25-hydroxyvitamin D_3 ($25OHD_3$), was not different from the general population [13].

Although the universally accepted primary role of vitamin D relates to bone metabolism [14,15], its beneficial effects on glucose homeostasis, lipid metabolism and cardiovascular health remain a matter of debate. While observational studies support the relationship between a poor vitamin D status and a higher risk of cardiometabolic problems, systematic and meta-analyses of

* Corresponding author. GI-Nutrition Unit, Research Centre, CHU Sainte-Justine, 3175 Côte-Sainte-Catherine, Montreal, Quebec, H3T 1C5, Canada.
** Corresponding author. GI-Nutrition Unit, Research Centre, CHU Sainte-Justine, 3175 Côte-Sainte-Catherine, Montreal, H3T 1C5, Quebec, Canada.
E-mail addresses: delvine@sympatico.ca (E. Delvin), emile.levy@recherche-ste-justine.qc.ca (E. Levy).

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randomized clinical trials often come to opposing conclusions [16–21]. These prompted us to verify whether the vitamin D nutritional status is related to components of the metabolic syndrome (MetS) in a clinically and biochemically well-defined cohort of cALL surviving patients for whom such information is limited.

2. Methods

2.1. Patients and ethical issues

The PETALE cohort consisting of 251 French-Canadian cALL survivors of European origin, diagnosed and treated at the SJUHC (Montreal, Canada) between January 1989 and July 2005, has already been described [11,13]. For the purpose of the present study, full data were available for 239 patients [median age (inter-quartile range, IQR): 21.9 (16.8–26.2) years]. At the time of inclusion into the study, the median (IQR) time post-treatment was 12.9 (9.6–17.7) years. Although patients have undergone different Dana Farber Cancer Institute (DFCI) protocols depending upon the year of diagnosis, they all received asparaginase and vincristine/corticosteroids as backbone treatment [22]. Patients with high risk of relapse (45%) received increased cumulative corticosteroid doses. Given the higher cranial radiotherapy (CRT) in earlier protocols, a larger proportion of adult survivors versus pediatric-age survivors received CRT (69.8 vs 40%). The SJUHC Institutional Review Board of Sainte-Justine Hospital approved the study, and the investigations were carried out in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from study participants and/or parents/guardians.

2.2. Biochemical assays

Blood samples were collected after an overnight fast. Glucose (Gluc), total cholesterol (TChol), HDL-Cholesterol (HDL-C) and triglycerides (TG) were measured using an Architect *c*System (Abbott Diagnostics, Mississauga, ON, Canada). LDL-Cholesterol (LDL-C) was calculated employing the modified Friedewald equation [23]. Insulin was measured on an automated chemiluminescent immunoassay platform (Abbott Diagnostics). Supplemental Table S1 shows the respective intra- and inter-assay coefficient of variations obtained from the Internal Quality Control (QC) Scheme using Bio-Rad QC material [Bio-Rad Laboratories (Canada), Montreal, Quebec]. Supplemental Table S2 provides the results of the proficiency-testing scheme for the Oneworld Accuracy assessment program (Vancouver, Canada) for Gluc, TChol, HDL-C and TG and the Randox External International Quality Assessment Scheme (Crumlin, UK) for insulin. The homeostatic model assessment for insulin resistance (HOMA-IR) was calculated with the following equation: [Ins (mIU/l) X Gluc (mmol/l)]/22.5. The following cut-offs were selected for adolescent (>2.8) [24] and adult (2.5) [25] patients.

Quadrupole Time-of-Flight Mass Spectrometry (QTOF-MS) was used to measure serum 25-hydroxyvitamin D_3 ($s25OHD_3$) [26]. We have used the 2016 consensus report of experts to classify the vitamin D status based on $s25OHD_3$ concentrations necessary for preventing nutritional rickets in children: sufficiency: >50 nmol/l; insufficiency: ≥30-<50 nmol/l; and deficiency: <30 nmol/l [27]. It differs from the earlier guidelines of Misra et al. [28] giving a dichotomous threshold of >50 nmol/l for sufficiency and of <50 nmol/l for insufficiency.

2.3. Anthropometric measures

Blood pressure was measured by oscillometry (Dinamap XL, model CR9340, Critikon Company, FL, USA) in triplicate on the right arm after subjects rested for at least 5 min as already described [29]. Waist circumference (mid-distance between the last floating rib and the iliac crest at the end of a normal expiration) reflecting visceral fat deposition, associated with cardiometabolic risk [30], was measured to nearest 0.1 cm using a standard measuring tape [31].

2.4. Reference population

Reference intervals for anthropometric and biochemical variables were obtained from Cycle 3 (2012–2013) of the Canadian Health Measures Survey (CHMS) conducted by Statistics Canada, excluding participants ever diagnosed having cancer [32,33].

2.5. Metabolic syndrome risk factors

Supplemental Table S3 lists thresholds of the risk factors identifying the MetS 1) in adults according to the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP) criteria (systolic/diastolic blood pressure, waist circumference, fasting glucose, triglyceridemia and HDL-cholesterolemia or on therapy) above the given thresholds [34]; 2) in adolescents according to the International Diabetes Federation (IDF) standards (waist circumference above the cut-off value plus any two of the following factors: systolic/diastolic blood pressure, fasting glucose, triglyceridemia and HDL-cholesterolemia or on therapy) [35]. For children 10 to <16 years old, the MetS was defined with the following criteria: Waist circumference ≥90th percentile plus any two of high systolic diastolic pressure, fasting hyperglycemia, hypertriglyceridemia and low HDL-C.

As described above, the current MetS definition involves the presence of risk factors based on dichotomous decisions. However, the pathophysiology of the syndrome more likely follows a continuous pattern. Hence investigators have devised different continuous scores for evaluating MetS risk (cMetS score) [36–41]. Following this scheme, we calculated a cMetS score as the sum of the Z-scores adjusted for age and sex for waist circumference, systolic blood pressure, fasting glycemia, triglyceridemia, HDL-Cholesterolemia using the respective age and sex adjusted means and standard deviations obtained from the CHMS referent cohort. Since HDL-C is a protective factor, the Z-score was multiplied by −1.

2.6. Statistics

Descriptive statistics were used to report cALL survivors' anthropometric and metabolic characteristics. Results are expressed as mean ± standard deviation (SD) when data are normally distributed, or median and inter-quartile ranges (IQR) when not. ANOVA and the Kruskal–Wallis with the Dunn's multiple comparison test were used to verify the gender- and age-related difference between respectively normally- or not-normally distributed variables. Linear regression analysis was used to assess the association between $s25OHD_3$ on the one hand, and age, sex, exposition to CRT, year quarter, elevated BMI and waist circumference, on the other hand. The β coefficient refers to the degree of change in the outcome variable for every additional unit increase of $s25OHD_3$. A P value ≤0.05 was considered significant. Descriptive analyses were performed using GraphPad Prism 7.0a (GraphPad Software, La Jolla, CA, USA) and regression analyses with SPSS version 24.0 (IBM, Armonk, New York).

3. Results

Supplemental Table 4 lists the anthropometric and biochemical characteristics of the participants. As expected, there are age- and gender-related differences in the anthropometric and biochemical

Table 1
Number of metabolic syndrome risk factors, continuous metabolic syndrome scores and serum 25-hydroxyvitamin D_3.

dMetS factors	Number of subjects (%)	cMetS scores[a]	s25OHD$_3$ (nmol/l)[a]
0	72 (30.2)	1.09 (-0.22, 2.85)	61.0 (43.8, 73.8)
1	73 (30.5)	1.38 (0.58, 2.78)	64.0 (45.5, 80.0)
2	56 (23.4)	2.88 (1.55, 4.34)	58.0 (43.0, 74.0)
3–5	38 (15.9)	3.94 (1.23, 5.41)[b]	57.0 (38.0, 72.0)

For this analysis, the available data from the whole cohort was used (n = 239). dMetS: dichotomous Metabolic Syndrome risk factors; cMetS: continuous Metabolic Syndrome score; s25OHD$_3$: serum 25-hydroxyvitamin D_3.
[a] Median (IQR).
[b] Significantly different from 0 and 1 factor (p = 0.0015 and 0.0043 respectively).

variables. In terms of age-related variances, systolic and diastolic blood pressures, along with waist circumference were statistically lower in adolescents than in adults. Furthermore, whereas systolic blood pressure was higher in adolescent and adult males than in females, we observed no gender-related differences for diastolic pressure and waist circumference.

As for biochemical variables, the main observations are: 1) fasting glucose was significantly lower in adolescent females than in adult females and adolescent males; 2) triglycerides were lower in adolescent females than adult females; 3) adolescent and adult female HDL-cholesterol concentrations were higher than those observed for their male counterpart. Female adolescents, male adolescents and adults exhibited 36%, 11%, 28%, and 16% of HOMA-IR values, respectively, above cut-offs. (EDGARD, il y a 4 chiffres pour 3 nom relatifs: à verifier !

Table 1 shows the number and percentage of participants according to the increasing number of MetS components. 15.9% had 3 and more risk factors. We also observed a graded relationship between the number of unfavorable risk factors and the cMetS scores. The median and 95$^{\%}$ confidence interval (C.I.) cut-off point of the cMetS score for predicting the presence of the MetS (3 or more risk factors) was 3.94 (IQR: 1.23–5.41). Last, we could not demonstrate a relationship between the number of MetS components (either dichotomous or continuous) and serum 25OHD$_3$ concentrations.

Table 2 summarizes the relationship between the vitamin D status and specific metabolic risk factors. We detected no significant interaction between s25OHD$_3$ concentrations and MetS, glycemia, HOMA-IR or triglyceridemia before and after adjustment for age, period of the year for blood sampling, and exposition to cranial radiotherapy. There was no effect of gender. Last, s25OHD$_3$ was strongly and positively associated with HDL-cholesterol concentrations (p = 0.001) in the non-adjusted and adjusted regression analyses. Interestingly, this association was gender-dependent, remaining for female but not male participants.

4. Discussion

Our data, from a clinically and metabolically well-described cohort, show a modest role for vitamin D in the lipid profile. We demonstrate that 15.9% of the study participants exhibited 3 or more MetS risk factors (Table 1). This prevalence is similar to that reported by Saultier et al. [42] and van Waas et al. [43] for 2 distinct cohorts of cALL survivors; but strikingly lower than that reported by Nottage et al. [10] In the latter case, the age of the population studied could explain this disparity. Indeed the median age of their cohort (31.7 years) is higher than ours (21.7 years) and, therefore might likely have experienced higher cranial and craniospinal radiation during their therapy. The observation that, in our cohort, cranial radiotherapy exposure was a predictor of dyslipidemia supports this supposition [11].

Although the proposed thresholds for defining the MetS are derived from well-established guiding principle, the concept of a continuous score, as proposed in the Joint statement of the American Diabetes Association and the European Association study group on diabetes [44], is of interest as it theoretically offers a finer tuning of the risk evaluation. This however is valid on the *proviso* that reference values to calculate meaningful age- and gender-adjusted Z-scores are based on a representative population. The population-based Canadian Health Measure Survey (CHMS) [cycle 3] survey data [32,33] used in the present study fulfill this criterion. Founded on this basis, we show the direct relationship between the cMetS score and the number of risk factors present (Table 1). Shafiee et al. [38], in the CASPIAN population-based study, and Eisemann et al. [45] in physical activity intervention study reported a similar relationship.

Our data (Table 2) provides no evidence for an association between vitamin D nutritional status and either dMetS or cMetS score, glycemia, HOMA-IR or HOMA-IR Z-score and triglyceridemia.

Table 2
Relationship between specific metabolic risk factors and s25OHD$_3$.

Independent variables		All (n = 238)		Males (n = 116)		Females (n = 122)	
		β (95% CI)	*p*	β (95% CI)	*p*	β (95% CI)	*p*
Crude analysis	dMetS	−2.22 (−11.00–6.56)	0.62	3.93 (−7.11–14.98)	0.48	−8.13 (−21.70–5.45)	0.24
	cMetS	−0.73 (−1.89–0.44)	0.22	−0.36 (−1.86–1.14)	0.63	−1.28 (−3.06–0.49)	0.15
	Glycemia	−1.15 (−7.64–5.34)	0.73	2.57 (−8.26–13.41)	0.64	−0.49 (−9.08–8.09)	0.91
	HOMA-IR	−2.63 (−5.39–0.13)	0.06	−2.72 (−7.27–1.82)	0.24	−0.62 (−5.06–3.82)	0.78
	HOMA-IR Z-Score	0.28 (−0.09–0.65)	0.14	0.10 (−0.94–1.14)	0.84	0.01 (−0.58–0.58)	0.99
	Triglycerides	−2.24 (−8.30–3.82)	0.47	−4.05 (−12.12–4.02)	0.32	−1.32 (−10.23–7.59)	0.77
	HDL-C	17.18 (7.02–27.33)	0.001	3.94 (−12.98–20.86)	0.65	20.45 (6.36–34.54)	0.005
Model 1	dMetS	−2.77 (−11.48–5.94)	0.53	2.38 (−8.51–13.27)	0.67	−8.01 (−21.61–5.59)	0.25
	cMetS	−0.75 (−1.91–0.41)	0.20	−0.50 (−1.97–0.97)	0.50	−1.27 (−3.07–0.53)	0.16
	Glycemia	−1.67 (−8.24–4.90)	0.62	2.02 (−8.84–12.88)	0.71	−0.62 (−9.44–8.20)	0.89
	HOMA-IR	−2.50 (−5.28–0.29)	0.08	−2.79 (−7.28–1.69)	0.22	0.09 (−4.49–4.68)	0.97
	HOMA-IR Z-Score	0.35 (−0.05–0.75)	0.09	0.16 (−1.04–1.36)	0.79	−0.01 (−0.68–0.66)	0.97
	Triglycerides	−2.55 (−8.68–3.57)	0.41	−5.04 (−13.35–3.27)	0.23	−1.29 (−10.27–7.70)	0.78
	HDL-C	17.04 (6.92–27.17)	0.001	5.08 (−11.53–21.69)	0.55	19.43 (5.13–33.73)	0.008

Crude analysis: Tests for variation of metabolic risk factors to variation in s25OHD$_3$ without adjustment. Model 1: Tests for variation of metabolic risk factors to variation in s25OHD$_3$ after adjustment for age, period of the year and exposition to cranial radiotherapy as covariates. dMetS: Metabolic Syndrome based on dichotomous risk factors; cMetS: Metabolic Syndrome score based on the sum of z-scores for each component; s25OHD$_3$: serum 25-hydroxyvitamin D_3, HDL-C: high-density lipoprotein cholesterol; HOMA-IR: Homeostatic Model Assessment of Insulin Resistance. The associations between s25OHD$_3$ and continuous variables (cMetS, glycemia, Homa-IR, HOMA-IR Z-scores, triglycerides and HDL-C) were tested by univariate regression analysis. Chi-squared test was used for categorical classification (dMetS). The β coefficient refers to the change in the mean s25OHD$_3$ concentration per unit change for individual independent variables. A $p \leq 0.05$ is considered significant.

However it is worth noting that s25OHD$_3$ is directly associated with female but not male participants plasma HDL-C concentrations. Interestingly the concentration of this lipoprotein is distinctly higher in female participants (Table S4), a well-established fact [46]. Moreover, it is well-recognized that HDL plays a significant role in cholesterol efflux and reverse cholesterol in humans, a process highly beneficial for the prevention of cardiovascular diseases [47]. Given the positive relationship between vitamin D and HDL [48] and the possible interaction between vitamin D metabolism and oestrogens [49], it is understandable that gender-dependent pathways exert some influence on the HDL concentration. This study, as the other many prior studies, addresses the relationship between 25OHD$_3$, the nutritional beacon for vitamin D status. This metabolite is one step away from the active metabolite 1,25(OH)$_2$D$_3$ that acts through nuclear and membrane receptors [50,51]. This distance from the receptor-modulated mechanisms may explain the debate on action of vitamin D in extra-osseous tissues. Future studies should therefore also include the measure of 1,25(OH)$_2$D$_3$.

5. Conclusion

The major outcome of this study is the strong association between HDL-C concentration and s25OHD$_3$ only in female subjects, thereby conveying vitamin D a gender-specific cardio-protective effect. Although this observational study does not allow assigning a causal relationship, a relative pathway can be invoked. A link can however be invoked as HDL particles participate in the reverse cholesterol transport from macrophages, a protective mechanism, which function is in turn regulated by vitamin D [52]. cALL survivors represent a population at higher risk for secondary diseases. For this reason thorough nutritional evaluation, including vitamin D should be part of the regular follow-up.

Authors' contribution

Emile Levy, Caroline Laverdière, Nathalie Alos, Daniel Sinnett, Maja Krajinovik, Simon Drouin and Valérie Marcil conceptualized and initiated the study; Nathalie Alos and Caroline Laverdière recruited the cALL survivors and provided the clinical evaluations; Valérie Marcil collected all the nutritional data and with Véronique Bélanger contributed to their statistical analyses; Carine Nyalendo supervised the biochemical analyses; Edgard Delvin supervised the analysis of the vitamin D metabolites, analyzed the data and wrote the article. All authors revised and accepted the final version of the manuscript.

Conflicts of interest

The authors declare “Conflicts of interest: none”.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2019.03.006.

What is known?

Childhood ALL (cALL) surviving patients are at risk of developing secondary cardiometabolic disorders in late adolescence and early adulthood.

Conflicting findings characterize the relationship between vitamin D status and diverse cardiometabolic disorders.

What does this paper add?

Insight into cALL survivors' metabolic status.

Knowledge on cALL survivors metabolic profile.

Uncovering the relation between the vitamin D nutritional status in a clinically and biochemically well-defined cohort of cALL surviving patients and cardiometabolic risks.

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