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JUDUL ARTIKEL	Vitamin D level and early cow's milk protein exposure in type 1 diabetes mellitus
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Surabaya, 7 Agustus 2023

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March 10, 2021

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We would like to submit our original research article entitled " ***Vitamin D Level and Early Cow's Milk Protein Exposure in Type 1 Diabetes Mellitus*** " for publication in Archives of Hellenic Medicine.

Several studies reported that vitamin D deficiency enhanced T1DM progression. This is a case control study. Children with T1DM aged 4-18 years old and healthy controls were included in this study. Subjects grouped by level of vitamin D according to the 2011 guidelines of the Task Force: deficiency (≤20 ng/ml), insufficiency (>20–30 ng/ml), and sufficiency (>30 ng/ml). The history of cow's milk exposure was obtained. Statistics performed were independent t-test, Mann-Whitney and logistic regression with significance at $p < 0.05$.

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Nur Rochmah, M.D

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Title: Vitamin D Level and Early Cow's Milk Protein Exposure in Type 1 Diabetes Mellitus

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The corresponding author

(Nur Rochmah)

March 10, 2021

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Archives of Hellenic Medicine

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We warrant that the article is the Author's original work and the article is not under consideration for publication elsewhere. All authors agree to cede the copyrights to the Journal. We have no sources of funding and we declare that no conflict of interest. We attest to the fact that all authors listed on the title page have contributed significantly to the work, details are as follows: (1) Designed the experiments = S. (2) Performed the experiments = IWT, GW. (3) Analyzed the data = IWT, GW. (4) Contributed reagents / material / analysis tools = NR, MF. (5) Wrote the manuscript = NR, MF IWT, GW. (6) Data collection and data management = IWT, GW. (7) Statistical analyses and paper writing = IWT, GW, NR, MF. We suggest three reviewers for evaluating our paper; (1) Tatsuhiko Urakami, MD, PhD from Department of Pediatrics, Nihon University School of Medicine, 1-6 Kandasurugadai, Chiyodaku Tokyo. E-mail: urakami.tatsuhiko@nihon-u.ac.jp. (2) Prof Lee Yung Seng from Department of Paediatrics, Yong Loo Lin School of Medicine, National University of Singapore, Singapore. E-mail: paeleeys@nus.edu.sg (3) Prof. Dr. Irwanto dr.,SpA(K), from Department of Paediatrics, Airlangga University, Surabaya, Indonesia. Email: irwanto@fk.unair.ac.id. All authors have approved and read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to Archives of Hellenic Medicine.

We hope that this article could be considered for publication in Archives of Hellenic Medicine.

Sincerely yours,

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DETAIL OF SUBMITTED ARTICLE

Manuscript title	Vitamin D Level and Early Cow's Milk Protein Exposure in Type 1 Diabetes Mellitus
Running title	Vitamin D Level and Early Cow's Milk Protein in Type 1 Diabetes Mellitus
Keywords	Type 1 diabetes mellitus; children; vitamin D; cow's milk; risk factors.
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Type of manuscript	Original Article
Possible conflicts of interest	There is no conflicts of interest
Detail count	Word count for the abstract = 206 words Complete manuscript word count = 2250 words Number of references = 21 references Number of tables = two tables
Author contributions	Designed the experiments = AE, S. (2) Performed the experiments = IWT, GW. (3) Analyzed the data = IWT, GW. (4) Contributed reagents / material / analysis tools = NR, MF, AE, S. (5) Wrote the manuscript = NR, MF, AE, S. (6) Data collection and data management = IWT, GW. (7) Statistical analyses and paper writing = IWT, GW, NR, MF.
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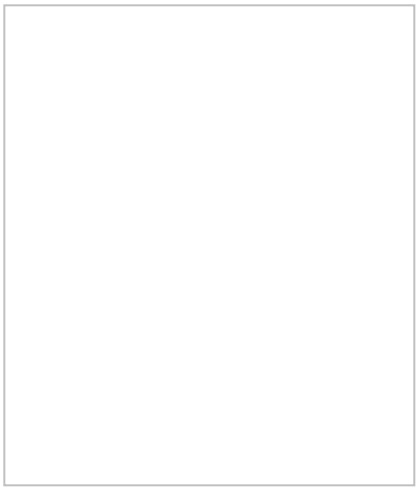

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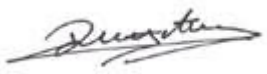

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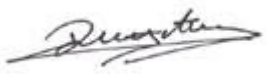

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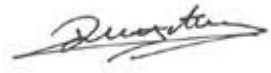

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Vitamin D level and early cow's milk protein exposure in type 1 diabetes mellitus

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Short title: Vit D and Cow's Milk Protein in Type 1 Diabetes

Corresponding author: N. Rochmah, ~~ORCID ID: 0000-0002-3308-1711~~
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ABSTRACT

OBJECTIVE To analyze the prevalence of vitamin D levels and cow's milk exposure in Type 1 Diabetes Mellitus (T1DM).**METHODS** This is a case control study. Children with T1DM aged 4-18 years old and healthy controls were included in this study. Subjects grouped by level of vitamin D according to the 2011 guidelines of the Task Force: deficiency (≤20 ng/ml), insufficiency (>20–30 ng/ml), and sufficiency (>30 ng/ml). The history of cow's milk exposure was obtained. Statistics performed were independent t-test, Mann-Whitney and logistic regression with significance at $p < 0.05$.**RESULTS** Thirty-one T1DM cases and 24 healthy controls were included. Four of 31 subjects with T1DM had vitamin D deficiency ($p < 0.001$). Vitamin D deficiency and insufficiency were detected in 77.41% T1DM cases and 25.0% controls ($p < 0.001$). The OR revealed that vitamin D deficiency and insufficiency were predictors of T1DM (OR = 3.09; $p < 0.001$). The number of subjects

exposed to cow's milk in the first 3 months was 51.16% T1DM cases and 50.0% controls (p = 1.000). Logistic regression test showed vitamin D significantly correlated with T1DM (p = 0.001). **CONCLUSION -** low vitamin D level correlate with T1DM, whereas early exposure to cow's milk is not.

Key words: Type 1 diabetes mellitus, children, vitamin D, cow's milk, risk factors

Type 1 diabetes mellitus (T1DM) mostly mediated by autoimmune process. Based on the International Diabetes Federation in 2017, the number of children with T1DM was 1,106,500 and 132,600 newly diagnosed cases each year globally.[1] The mortality rate for T1DM is 3–18 times higher than healthy children of the same age.[2]

There are risk factors for T1DM, such as genetics, microbial infections, and the environment factors, such as vitamin D and early cow's milk exposure.[1,3] Several studies reported that vitamin D deficiency enhanced T1DM progression.[4] Early exposure to cow's milk protein before 3 months old is suspected to associate with T1DM.[5] It may lead to antibodies formation that bind insulin and pancreatic β-cells. Furthermore, the autoimmune process induces beta cell apoptosis in T1DM.[6,7] The study on associations of vitamin D, early cow's milk exposure, and type 1 diabetes mellitus are still controversy.[8,9] This study aimed to analyze vitamin D levels and cow's milk exposure in children with T1DM.

METHODS

This case–control study was conducted at Dr. Soetomo General Hospital, Surabaya, Indonesia, from March to May 2019 which was approved by the Ethics Committee of Health Research, Dr. Soetomo General Hospital (Ethics No. 1020/KEPK/III/2019). Inclusion criteria in this study are children aged <18 years with T1DM (based on the International Society for Pediatric and Adolescent Diabetes protocol) and healthy controls whose informed consent was obtained from the parents. Subjects were children aged <18 years with T1DM (based on the International Society for Pediatric and Adolescent Diabetes protocol) and healthy controls. Patients who received any multivitamins and those with a renal disorder or clinical signs suggestive of vitamin D deficiency, including frontal bossing, pigeon chest, rachitic rosary, Harrison's sulcus, wrist widening, and double malleoli, were excluded from this study. Information about the early exposure to cow's milk before or at 3 months was obtained from the recall method of the breast milk and cow's milk exposure.

Samples of vitamin D were collected in heparinized amber-colored glass vials to prevent photodegradation. Plasma was extracted after centrifugation and then stored at −30°C for subsequent analyses. The levels of 25-hydroxyvitamin D in the serum were determined in patients with T1DM and healthy controls using an combination metode competitive enzyme immunoassay with enzym-linked flourescence assay (ELFA) from VIDAS. Subjects were grouped according to the vitamin D levels in serum as those with deficiency (≤20 ng/ml), insufficiency (>20–30 ng/ml), and sufficiency (>30 ng/ml), according to the 2011 guidelines of the Task Force of the Endocrine Society.

Data were analyzed using the Statistical Package for the Social Sciences version 16 (SPSS, Chicago, IL, USA). Comparisons between patients with T1DM and controls were evaluated by the independent t-test and the Mann–Whitney test. The odds ratio (OR) was calculated using the χ^2 test. For all statistical analyzes, $p < 0.05$ was considered statistically significant with the 95% confidence interval.

RESULTS

This study enrolled 31 children with T1DM (18 boys and 13 girls) and 24 healthy controls (10 boys and 14 girls). The median duration of consuming cow's milk was 12.0 (1.0–60.0) months in patients with T1DM and 6.0 (0–24.0) months in controls (p = 0.128). The median age at introduction to cow's milk was 3.0 (0–48.0) months in patients with T1DM and 2.0 (0–24.0) months in controls (p = 0.162). The median vitamin D levels were significantly lower in patients with T1DM than in controls [26.11 (13.95–52.11) vs. 34.39 (26.73–47.57) ng/ml; p < 0.001]. The baseline characteristics are shown in Table 1.

There are 12,9% children with T1DM had vitamin D deficiency, whereas no healthy controls had vitamin D deficiency (Table 2). The majority of subjects (54.54%), both in the T1DM group (77.41%) as well as in control group (25.0%), were either vitamin D deficient or insufficient. The risk of T1DM increased three times in patients with vitamin D deficiency or insufficiency (≤30 ng/ml), compared to >30 ng/ml (OR = 3.09; 95% CI = 1.51–6.35; p < 0.001). There wasn't any difference in the risk of developing T1DM in infants who first received cow's milk at ≤3 or >3 months of age (OR = 1.06; 95% CI = 0.36–3.09; p = 1.000; Table 2). Logistic regression test showed vitamin D significantly as risk factors of T1DM (p = 0.001).

DISCUSSION

This study found that most subjects with T1DM (77,41%) had either vitamin D deficiency or insufficiency, with median vitamin D levels of 26 ng/ml. Meanwhile, most control subjects (75%) had vitamin D sufficiency, with median vitamin D levels of 34 ng/ml. Several previous case–control studies also reported that children had lower serum vitamin D levels than the control group.[10-13] Our study has shown that the risk of T1DM was significantly increased in the deficient and insufficient groups compared to the sufficient group [OR = 3.09 for 25(OH)D ≤ 30 nmol/l; p < 0.001]. Based on the study of Franchi et al., low serum vitamin D levels seemed to increase the odds of developing T1DM [OR = 5.56 for 25(OH)D ≤ 50 nmol/l].[11] However, some literatures stated that serum vitamin D levels were lower in subjects with diabetes than in the controls.[14,15]

Our study showed that comparison of early cow's milk exposure between cases and controls were not significantly different (p = 1.000). However, several studies have investigated that early exposure to cow's milk protein (i.e., conventional infant formula) associated with the subsequent risk of β-cell autoimmunity and clinical disease.[16-18] Study from Lamb et al. stated that increased childhood cow's milk protein intake associated with risk of Islet Autoimmunity (IA).[19] Based on the study by Šipetic et al. in 2005, the early introduction of supplementary milk was associated with a higher risk of diabetes (OR = 5.75, 95% CI = 2.91–11.36). Meanwhile, some studies revealed that very early exposure to cow's milk did not affect the occurrence of T1DM.[20,21] A study by Rosenbauer et al. revealed that the introduction of cow's milk/formulas at age 7 weeks to 4 months had an OR (95% CI) of 0.85 (0.61–1.18) and *p* of 0.332.[20]

Limitation of the study is the small number of the subjects. Nevertheless, it would provide some information on low vitamin D status and early exposure to cow's milk protein before the first 3 months as the risk factors of T1DM. In conclusion, this study found that low vitamin D level correlate with T1DM, whereas early exposure to cow's milk is not.

Acknowledgments

The authors thank post graduate student faculty of medicine, Airlangga University, Dr. Soetomo General Hospital, Surabaya, Indonesia, the patients who participated in the study and the endocrine teams for the support.

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4. Khanh V, Lan T. The role of vitamin D in protecting type 1 diabetes mellitus. Diabetes Metab Res Rev 2005, 21:338-46.
5. Rewers M, Ludvigsson J. Type 1 diabetes environmental risk factors for type 1 diabetes. Lancet 2016, 387:2340-8.
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Table 1. Baseline characteristics.

Characteristics	T1DM (n = 31)	Control (n = 24)	*p*
Sex			
Male (n)	18	10	
Female (n)	13	14	
Age (years; mean ± SD)	11.22 ± 4.15	7.55 ± 3.18	0.309*
Weight [kg; median (min–max)]	30.0 (13.0–65.0)	26.0 (11.0–57.0)	0.465†
Height (cm; mean ± SD)	132.54 ± 19.49	122.08 ± 18.69	0.509*
BMI (mean ± SD)	17.35 ± 4.32	18.54 ± 5.23	0.160*
Duration of T1DM [years; median (min–max)]	1.0 (0–11.0)	-	
Race			
Javanese	29	22	
Madurese	1	1	
Chinese	1	-	

*Unpaired t-test.
†Mann–Whitney test.
T1DM : Type 1 Diabetes Mellitus
SD : Standard Deviation
BMI : Body Mass Index

Table 2. Vitamin D status and early exposure to cow's milk in T1DM and Control Group

	T1DM (n = 31)	Control (n = 24)	*p*	OR (95% CI)
Vitamin D status				
Deficiency	4	0	<0.001	
Insufficiency	20	6		
Sufficiency	7	18		
Deficiency + insufficiency	24	6	<0.001	3.09 (1.51–6.35)
Age at cow's milk introduction†				
≤3 months	16	12	1.000	1.06 (0.36–3.09)
>3 months	15	12		

OR : Odds Ratio

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WITH MY COMPLIMENTS!

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