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ORIGINAL ARTICLE

The relationship between serum vitamin D levels and intima-media thickness in term infants

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Abstract

Increasing epidemiologic evidence indicates that vitamin D deficiency is linked to a series of diseases, including cardiovascular disease. This prospective study was designed to determine the relationship between 25 hydroxyvitamin D (25(OH)D) level and aortic intima-media thickness (aIMT) and carotid intima-media thickness (cIMT) in term healthy neonates. A total of 135 term, healthy infants were included in the study. Ultrasonographic measurements were performed at 24–48 h after birth. Blood samples were obtained from the umbilical cord at birth. The neonates were divided into four groups according to serum 25(OH)D vitamin levels. For the entire cohort, the mean 25 hydroxyvitamin D level was found to be 15.17 ± 9.66 ng/mL. The mean values of cIMT and aIMT measurements were 0.386 ± 0.052 and 0.412 ± 0.076 mm, respectively. In group 4, mean and maximum aIMT measurements were significantly lower than the other groups ($p = <0.001$ and 0.001, respectively). We did not observe any significant difference between groups regarding cIMT measurements. Correlation was found between aIMT and 25 hydroxyvitamin D levels ($r = 0.295$ $p = < 0.001$).

Conclusion: We conclude that vitamin D deficiency may be associated with early relative intima-media thickening of the aorta already in the first week of life.

What is Known:
- *Vitamin D deficiency is linked to a series of diseases, including cardiovascular disease.*
- *Studies in adults and high-risk children have shown that the measurement of the intima-media thickness represents an excellent marker of subclinical atherosclerosis.*

What is New:
- *This is the first study evaluating the relationship between 25(OH)D vitamin level and intima-media thickness in term healthy neonates.*
- *Vitamin D deficiency in neonates may induce atherosclerosis early in life and the aortic intima-media thickness measurements may be used as an early marker for detection.*

Keywords Atherogenesis · Aortic intima-media thickness · Carotid intima-media thickness · 25 hydroxyvitamin D

Abbreviations

25(OH)D	25 hydroxyvitamin D
aIMT	Aortic intima-media thickness
cIMT	Carotid intima-media thickness

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Introduction

Increasing epidemiologic evidence indicates that vitamin D deficiency is linked to a series of diseases, including cardiovascular disease [10, 31, 37]. There is an increasing interest in the relationship between vitamin D deficiency and the pathogenesis of atherosclerotic cardiovascular diseases, especially in the early stage [14, 25].

The fetus is entirely dependent on maternal supplies for all nutrients. From the stage of placental formation to term, 25(OH)D readily diffuses across the placenta, and this is evident by the direct correlation between cord blood levels and the mother's serum concentrations [6]. Vitamin D downregulates inflammatory cytokine TNFα and IL-6 expression in placental trophoblasts [22] and suppresses thromboxane production which is one of the most potent vasoconstrictors for the vascular

system. This inhibitory effect on oxidative stress also provides further evidence of the beneficial effects of vitamin D on the placenta [32]. Wagih et al. [36], investigating the protective role of vitamin D in the development of atherosclerosis, concluded that vitamin D administration ameliorates aortic histopathological changes. In an atherosclerotic mouse model, it has been demonstrated that oral vitamin D reduces the formation of atherosclerotic plaques [33]. These studies emphasize that vitamin D levels may influence vascular wall thickness during fetal life and may be an important determinant of atherosclerotic changes. Besides that, vitamin D may have an additional protective role in atherosclerotic changes.

There have been a number of recent reports linking maternal vitamin D deficiency with pediatric cardiomyopathy and, in severe cases, heart failure [17, 19]. Experimental studies clearly show a role for vitamin D in the regulation of proliferation and differentiation of cardiomyocytes and exposure to vitamin D deficiency in utero and early life leads to hyperplastic cardiomyocyte growth [7].

The atherosclerotic process begins in childhood and develops inconspicuously for many decades before cardiovascular complications occur in middle and later ages [26]. These early changes include thickening of vessel walls and impairment of arterial vasodilatory function. Studies in adults have shown that the measurement of the cIMT represents an excellent marker of subclinical atherosclerosis [4]. Similarly in a study, comparing children with hypercholesterolemia and control group, cIMT was found to be increased in the study group [23]. Since autopsy studies have shown that the first atherosclerotic lesions actually begin to develop in the abdominal aorta [20], measuring aIMT might provide a better index of preclinical atherosclerosis in high-risk children than cIMT [13].

Because of the widespread prevalence of vitamin D deficiency, it becomes important to assess the relation between 25(OH)D levels and cardiovascular complications. There is lack of research about the relation between serum 25(OH)D levels and IMT in neonates. This prospective study was designed to determine the relationship between 25(OH)D levels and aIMT, cIMT in healthy term neonates.

Material methods

Subjects

This study was conducted at Ordu University Children's Education and Research Hospital between June 2017 and September 2017. A total of 135 term (37–42 weeks of gestation), healthy infants were included in the study group. Ultrasonographic measurements were performed at 24–48 h after birth. All of the infants in the study were singletons and appropriate for gestational age (appropriate for gestational age; defined as a birth weight within ± 2 standard deviations) [18]. Infants of mothers with diabetes, preeclampsia or high blood pressure, preterm premature rupture of the membranes (PPROM), obesity (body mass index > 30), and history of smoking were excluded from study. The study protocol was approved by the local committee. Informed parental consent was obtained for all infants.

Definitions

We evaluated gestational age by maternal dates and confirmed by the modified Ballard examination [2]. Serum 25(OH)D values lower than ≤ 10 ng/ml were considered as severe, values between 11 and 20 ng/ml were considered as moderate, and values between 21–29 ng/ml were considered as insufficiency (mild deficiency) and values above 30 ng/ml were considered sufficiency [11]. The neonates were classified into four groups according to serum 25(OH)D vitamin levels. Groups I, II, III, and IV were defined as severe, moderate, mild deficiency, and sufficiency, respectively.

Biochemical methods

Blood samples were obtained from the umbilical cord at birth. After centrifugation at 5000 rpm, serum samples were stored at − 40 °C before analysis. Serum 25(OH)D levels were measured with Architect immunoassay method (Abbott, IL, USA). Serum 25(OH)D level of ≤ 20 ng/mL is considered as vitamin D deficiency [21]. We could not evaluate the mother's 25(OH)D levels.

Ultrasonographic assessments

All the ultrasonographic studies were performed by a single experienced sonographer (ZC) who was blinded to the clinical and laboratory characteristics of infants (Toshiba Aplio 500 ultrasound, Toshiba Medical Systems, Tokyo, Japan). Ultrasonographic studies were performed with the neonates unsedated during quiet natural sleep in a supine position. Blood pressure was measured three times during the study, and the measurements were averaged. The abdominal aorta was first identified in the upper abdomen using a 7.5-MHz pediatric-phased array transducer, and it was then followed distally until the aortic bifurcation was reached. The images focused on the dorsal arterial wall (dorsal arterial wall of the most distal 15 mm of the abdominal aorta) and gain settings and high-resolution boxes were used to optimize image quality. The aortic intima-media thickness was measured in a straight, unbranched 1-cm longitudinal segment of the abdominal aorta using a 12-MHz linear transducer as previously described [28]. The dorsal arterial wall of the distal abdominal aorta which has shown to be the most lesion-prone site was chosen for the area of interest (Fig. 1) [20]. All images were taken at end-diastole, incident with the R-wave on a

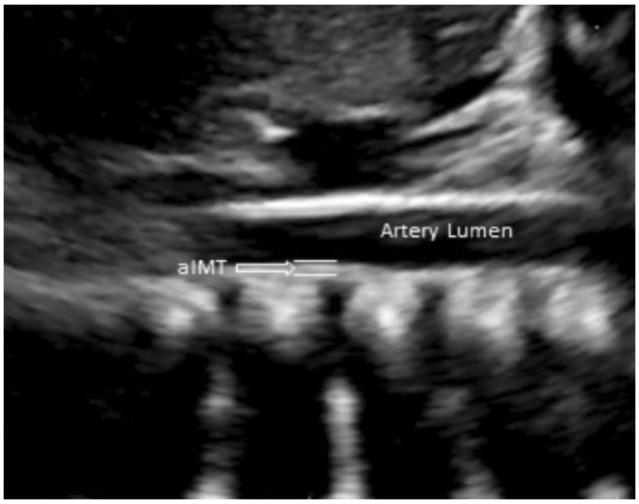

Fig. 1 Ultrasound image of posterior wall of aorta and measurement of intima-media thickness

continuously recorded electrocardiogram. Two images of the best quality were chosen for analysis in each study subject. Intima-media thickness was measured using ultrasonic calipers in each case by one blinded observer. At least four measurements covering the entire far wall segment of interest were taken for each image. All images were evaluated offline by two examiners (DA, ZC). All studies were done following a predetermined, standardized scanning protocol for the right and left carotid arteries [35]. The proximal part of the carotid bulb was identified, and the segment of the common carotid artery 1 to 2 cm proximal to the bulb was scanned. The image was focused on the posterior wall, and the resolution box function was used to magnify the arterial far wall. Two angles were used in each case: anterior oblique and lateral. All scans were digitally stored for subsequent offline analysis. Two end-diastolic frames were selected and analyzed for mean intima-media thickness, and the average measurement from these two frames was calculated for both right and left carotid arteries. The images were analyzed by two examiners (DA, ZC) and the average values were used in the analysis [13]. Intraobserver and interobserver reproducibilities for the analyses of aIMT and cIMT were determined in 25 randomly selected infants in a blinded manner. To assess interobserver reproducibility, both of the observers independently analyzed the data blinded to the other examiners' measurements. To assess intraobserver reproducibility, measurements were repeated by the same observer. The interobserver and intraobserver coefficient of variation for the evaluations of the records were calculated.

Statistical methods

Statistical analysis was performed using SPSS 25.0 software. The variables were investigated using visual (histogram, probability plots) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk's test) to determine whether or not they are normally distributed. Descriptive statistics were presented using medians and interquartile range (IQR) for the non-normally distributed variables. As the aIMT and cIMT measurements were not normally distributed, the Kruskal–Wallis tests were conducted to compare these parameters and vitamin D values. The Mann–Whitney *U* test was performed to test the significance of pairwise difference using Bonferroni correction to adjust multiple comparisons. An overall 5% type I error level was used to infer statistical significance. While investigating the associations between non-normally distributed variables, the correlation coefficients and their significance were calculated using the Spearman test. p values < 0.05 was considered as statistically significant.

Results

A total of 135 infants were eligible for this study. Demographic data is shown in Table 1.

There were no significant differences between groups regarding gestational age, maternal age, birth weight, systolic, diastolic blood pressure, and heart rate.

Aortic intima-media thickness

The mean and maximum values of aIMT measurements for the entire group were 0.412 ± 0.076 mm and 0.474 ± 0.079 mm respectively. While the mean aIMT values for groups I, II, III, and IV were 0.421 ± 0.008, 0.441 ± 0.020, 0.393 ± 0.014, and 0.357 ± 0.008; the maximum aIMT values for groups I, II, III, and IV were 0.481 ± 0.009, 0.505 ± 0.020, 0.442 ± 0.010, and 0.433 ± 0.007, respectively. Correlation was found between aIMT measurements and 25(OH)D vitamin levels ($r' = -0.295$ $p = < 0.001$) (Table 2). As shown in Fig. 2, groups classified according to 25(OH)D vitamin levels differ significantly in terms of aIMT max and aIMT mean values ($p = 0.001$, $p = < 0.001$, respectively). The neonates in

Table 1 Demographic data of the study group

	Mean ± SD ($n = 135$)
Gestational age, mean ± SD, wk	38.89 ± 0.72
Birth weight, mean ± SD, g	3334.1 ± 382
Maternal age, years	28.18 ± 5.6
Systolic BP, mmHg, mean ± SD	70.90 ± 4.86
Diastolic BP, mmHg, mean ± SD	39.01 ± 3.76
Mean BP, mmHg, mean ± SD	49.19 ± 3.64
Heart rate, bpm	138.61 ± 12.7
25(OH)D vitamin, ng/mL	15.17 ± 9.66

BP, blood pressure

Table 2 Correlation between intima-media thickness measurements and 25(OH)D vitamin levels

	25(OH)D vitamin ($n = 135$)	
	r'	p
aIMT max	− 0.270	*0.002**
aIMT mean	− 0.296	*< 0.001**
cIMT max	− 0.032	0.710
cIMT mean	− 0.088	0.309

aIMT max, maximum aortic intima thickness; *aIMT mean*, mean aortic intima thickness; *cIMT max*, maximum carotid intima thickness; *cIMT mean*, mean aortic intima thickness

*Significance: p < 0.05

group 4 had a significantly lower aIMT than the other groups (aIMT max, $p = 0.001$; aIMT mean, $p = < 0.001$).

Carotid intima-media thickness

The mean and maximum values of cIMT measurements were 0.386 ± 0.052 mm and 0.438 ± 0.060 mm, respectively. While the mean cIMT values for groups I, II, III, and IV were 0.398 ± 0.009, 0.384 ± 0.009, 0.373 ± 0.008, and 0.383 ± 0.006; the maximum cIMT values for groups I, II, III, and IV were 0.446 ± 0.009, 0.433 ± 0.010, 0.413 ± 0.07, and 0.444 ± 0.002, respectively. We did not observe any correlation between cIMT values and 25(OH)D vitamin levels ($cIMT_{mean}$ values $r' = -0032$ $p = 0.710$; $cIMT_{max}$ values $r' = 0.088$ $p = 0.309$) (Table 2). There was no difference in terms of cIMT between four groups (cIMT max, $p = 0.162$; cIMT mean, $p = 0.809$) (Fig. 2).

The intraobserver intersubject correlation coefficients for aIMT and cIMT were shown in Table 3. Intraclass correlation coefficient ranged from 0.90 to 0.82 (all $p < 0.001$) and

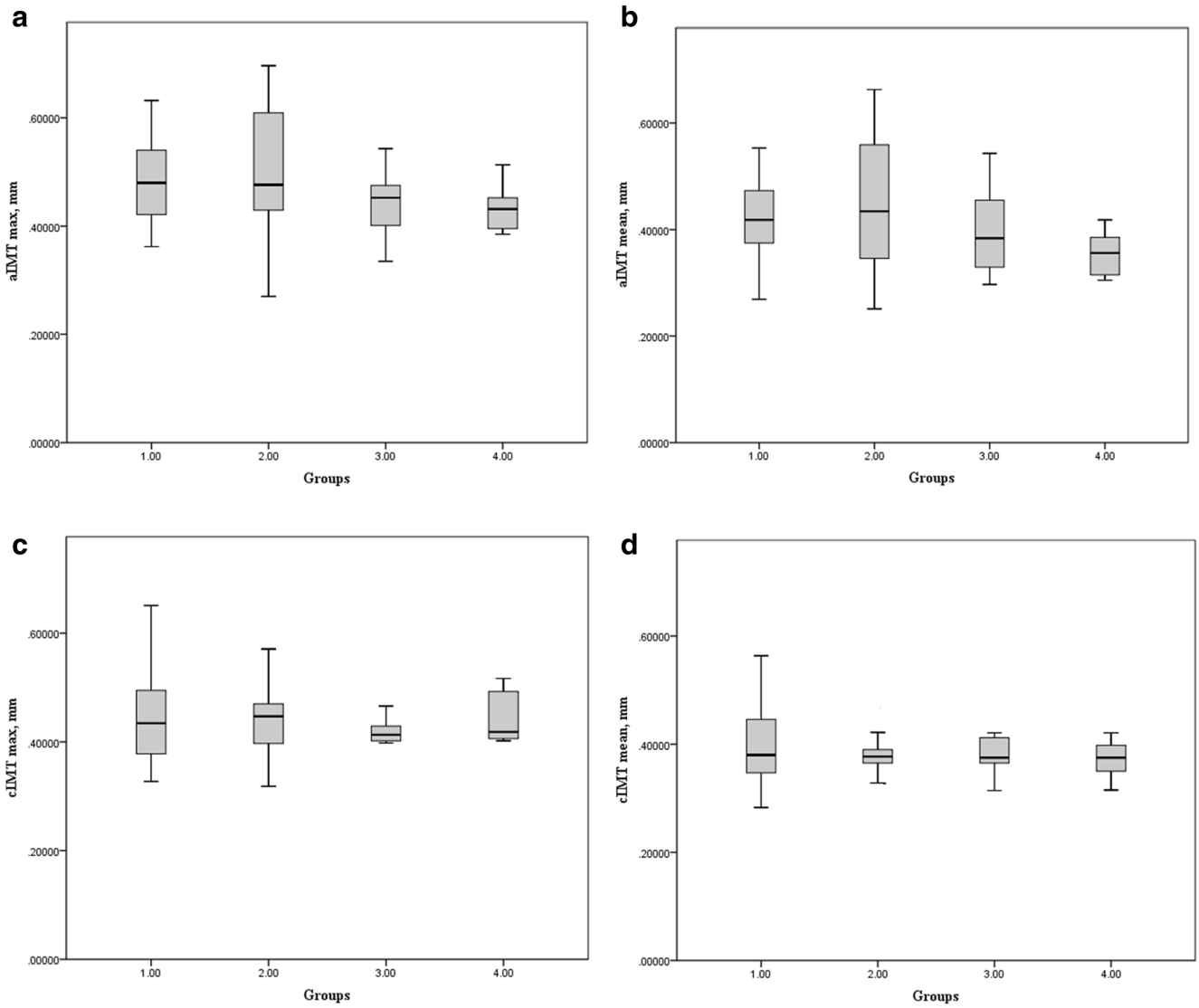

Fig. 2 **a** aIMT max values of infants in groups I, II, III, and IV. **b** aIMT mean values of infants in groups I, II, III, and IV. **c** cIMT max values of infants in groups I, II, III, and IV. **d** cIMT mean values of infants in groups I, II, III, IV

Table 3 Inter- and intraobserver reproducibilities in assessment of ultrasonographic parameters

	aIMT (m/s) mean ± SD	ICC[a]	*p*	cIMT (m/s) mean ± SD	ICC[a]	*p*
Observer 1 ($n = 25$)	0.410 ± 0.087	0.90[b]	< 0.001	0.370 ± 0.040	0.824[b]	< 0.001
Observer 2 ($n = 25$)	0.409 ± 0.074			0.375 ± 0.040		
Observer 1[c] ($n = 25$)	0.410 ± 0.087	0.96[e]	< 0.001	0.370 ± 0.040	0.860[e]	< 0.001
Observer 1[d] ($n = 25$)	0.408 ± 0.074			0.369 ± 0.038		

[a] Intraclass correlation coefficient

[b] Interobserver correlation coefficient

[c] First measurements of observer 1

[d] Second measurements of observer 1

[e] Intraobserver correlation coefficient

intraobserver correlation coefficient ranged from 0.96 to 0.86 (all $p < 0.001$).

Discussion

This study suggests that vitamin D deficiency may induce atherosclerotic changes in vascular structure in term healthy infants. Aortic intima-media thickness values were found to be higher in babies with vitamin D deficiency. Furthermore, correlation was found between aIMT measurements and 25(OH)D vitamin levels. We did not observe any significant difference or correlation between 25(OH)D vitamin levels and cIMT values. To the best of our knowledge, this is the first study evaluating the relationship between 25(OH)D level and aortic intima-media thickness and carotid intima-media thickness in term healthy neonates.

The concept that prenatal factors may affect the vascular wall and may contribute to the formation of atherosclerosis in early life has been well established [3]. Vitamin D has been shown to have anti-inflammatory effects and may modulate the excessive inflammatory response, arterial remodeling, and angiogenesis [5, 32]. Deficiency and insufficiency of vitamin D are associated with subclinical atherosclerosis [1, 24]. In some studies, increased intima-media thickness has been shown to be a good predictor of increased risk of cardiovascular disease and atherosclerosis [27, 34]. Aortic and carotid artery intima-media thickness have been widely used in adult population as a marker of atherogenesis. A few studies have evaluated aIMT and cIMT values in normal term newborns. In the study of Hondappanavar et al. [12], which evaluated aIMT and cIMT in 100 normal term newborns, mean aIMT and cIMT values were found to be 0.51 ± 0.041 mm and 0.37 ± 0.054 mm, respectively. Koklu et al. [15], determining aIMT values in newborns with different gestational ages, stated that abdominal aortic intima-media thickness can be reproducibly measured in neonates and the mean aIMT value was found to be 0.385 ± 0.019 mm (range, 0.34–0.42 mm) for gestational ages between 38 and 42 weeks. In this study, we found that the mean aIMT and cIMT values were 0.412 ± 0.076 mm and 0.386 ± 0.052 mm, respectively. The values were similar to the results of the previous studies.

Although the relationship between serum vitamin D levels and aIMT and cIMT measurements has been evaluated in adult studies and in animal models, this issue has not yet been thoroughly studied among neonates. In adults, Kalkan et al. showed that 25(OH)D vitamin levels are independently associated with the extent of IMT involvement of the thoracic aorta. In a previous study, it was shown that levels of 25(OH)D vitamin < 30 ng/ml were associated with a greater risk of myocardial infarction even after adjustment for risk factors [8]. In an animal study of diet-induced vitamin D deficiency, increased blood pressure and accelerated atherosclerosis was shown in all aortic segments and the proximal aorta was found to be the most severely affected part [38]. The study revealed that vitamin D deficiency increased atherosclerosis formation by modulating the macrophage phenotype within the atherosclerotic plaque through activation of endoplasmic reticulum stress. Several studies in high-risk children showed that low 25(OH)D vitamin level is associated with carotid atherosclerosis which was assessed with carotid IMT measurement [25]. On the other hand, Harrington et al. [9] reported that thoracic aortic IMT was considered as an earlier marker of preclinical atherosclerosis than carotid IMT in children with type I diabetes mellitus. In accordance with this study, we found correlation between aIMT and 25(OH)D vitamin levels. However, we could not find any correlation between cIMT and 25(OH)D vitamin levels. Since the aorta is the initially involved vascular area during atherogenesis, we proposed that longer period of time is needed for the carotid artery to get affected and develop atherosclerotic diversification on the ground of vitamin D deficiency.

While its prospective design and contribution to the literature with novel data constitutes the strengths of the study, relatively small sample size, lack of longitudinal data, and mother's vitamin D levels may be defined as the limitations.

Conclusion

Many researchers believe that the structural and functional cardiovascular derangements in response to endothelial dysfunction may be detectable soon after birth [16, 29, 30]. Nevertheless, due to its chronic nature and insidious progression, early diagnosis of atherosclerosis in infants and children is challenging. According to this study, we may suggest that vitamin D deficiency in neonates may be one of the determinants of atherosclerotic changes and aIMT measurements may be used as an early marker for detection. Randomized controlled studies with more participants and longitudinal data are required to provide additional data, enabling us to understand the pathophysiology better.

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Authors' contribution Design of the study, data analysis, preparation of the manuscript : DA

Performing ultrasonographic studies, data analysis : ZC

Compliance with ethical statements

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study protocol was approved by the local committee.

Informed consent Informed parental consent was obtained for all infants.

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