Graves' disease (GD) is an autoimmune disease caused by autoantibodies that stimulate thyroid stimulating hormone (TSH) receptors thereby increasing thyroid hormone synthesis and secretion. Many studies have also reported that vitamin D deficiency has an impact on cardiovascular namely cardiomyopathy and decreased left heart function. However, research on evaluation of 25-Hydroxyvitamin D (25(OH)D) levels and left ventricular systolic function in children with GD is still limited.

Methods: A cross-sectional, observational analytic study was conducted in 35 children with GD in the pediatric endocrinology division in Haji Adam Malik Hospital. The correlation of left ventricular systolic function and levels of 25(OH)D was analyzed by using Pearson correlation test.

Result: Of 35 children with GD, vitamin D deficiency accounted for all patients. The mean ejection fraction (EF) and fractional shortening (FS) were 65.9 ± 10.03% and 36.1 ± 6.3%, respectively. Increase of left ventricular systolic function was found in 6 children, whereas decrease of left ventricular systolic function was found in 4 children. Our study showed that levels of 25(OH)D were not correlated with EF and FS (r =0.134, P =0.443; r = -0.083; P =0.637, respectively).

Conclusion: Low level of 25(OH)D is prevalent in children with GD. However, vitamin D and impaired ventricular systolic function in patients with GD are not related. Children with GD have fewer heart complication than adults.

**KEY WORDS**

25-Hydroxyvitamin D levels, left ventricular systolic function, children with GD
To the knowledge of the researchers, there has not been any research on evaluating the correlation left ventricular systolic function and levels of 25(OH)D in children with GD. Therefore, there is a need to conduct a study to evaluate left ventricular systolic function and levels of 25(OH)D in children with GD.

METHODS

This research was a cross sectional study was conducted on children with GD admitted in the pediatric endocrinology clinic of H. Adam Malik General Hospital Medan, periods from May to August 2020. The sample size is calculated based on the sample size formula to test the hypothesis on a population using a correlation analysis design. The calculation was done by using a 95% confidence level with minimal sample size of 30 patients. All subjects will be asked for approval from parents after an explanation about the condition of the disease is made. Inclusion criteria were children from 1 month to 18 years old with GD. Exclusion criteria were patients with history of chronic heart disease, chronic kidney disease, chronic liver diseases, thalassemia and other endocrinological diseases were excluded.

History taking, physical examination, and recording of patient data are carried out according to the questionnaire on the subject under study. Laboratory test is carried out when patients come for treatment. Blood tests include TRab, TSH, fT4 and echocardiography was performed. Level of 25(OH)D range 21-29 ng/mL was classified as insufficient and < 20 ng/mL was classified as deficient. All data obtained was recorded, tabulated and analyzed. The study was conducted under the stipulations of the Health Ethics Committee from the Faculty of Medicine, University of North Sumatra (No: 43/KEP/USU-RSUP HAM/2020).
Results

Correlation of 25-Hydroxyvitamin D Levels and Left Ventricular Systolic Function

Research Flow Diagram

Research flow of this study shown in Figure 1.

Data Processing and Data Analysis

Univariate analysis was performed to determine the distribution of demographic and clinical characteristics of the sample in the study. Numerical data are displayed as means and standard deviations if they are normally distributed or median and maximum and minimum values if the data are not normally distributed. Categorical data are displayed in frequency and percentage. To determine the correlation between levels of 25(OH)D with EF and FS, Pearson correlation test was done with the alternative Spearman rank test if the sample was abnormally distributed.

Data processing was performed using the Statistical Package for Social Sciences (SPSS). The significance level was set at 0.05.

Results

In the research, there were 35 subjects were collected that met the study inclusion and exclusion criteria. The basic characteristic data showed that all subjects were female with age range between 9 to 17 years old with median of 13 years old. 14.3% of our patients were diagnosed with moderate whereas other 77.1% of patients were in normal nutritional status. All patients were included in this study suffering from vitamin D deficiency. All characteristic data from the research sample can be seen in Table 1.

The mean value of TRAb was 33.86 ± 10.7 IU/L with TSH levels range from 0.01 μIU/mL to 0.15 μIU/mL. Besides, the mean value of EF and FS in our subjects was 56.9 ± 10.03 % and 36.1 ± 6.3 % respectively with 17.1% patients showed increase of left ventricular systolic function and only 11.4% patients suffered from decrease of left ventricular (LV) systolic function. The mean value of 25(OH)D level was 13.38 ± 3.3 ng/ml with all subjects were categorized with vitamin D deficiency (listed in Table 2).

This study investigated the correlation between level of 25(OH)D and left ventricular systolic function in children with GD as presented in Table 3. Neither ejection fraction nor fractional shortening was correlated with levels of 25(OH)D in our study (r = -0.134, P = 0.443; r = -0.083, P = 0.637, respectively).

Discussion

Graves’ disease is an autoimmune disorder resulting from thyrotropin receptor stimulation by autoantibodies. Graves’ disease is characterized by thyrotoxicosis, hyperthyroidism and ophthalmopathy. Most patients present the classic symptoms and signs of hyperthyroidism. The early symptoms are often subtle, with changes in behavior, irritability, emotional lability, fatigue, nervousness, palpitations, tremor, sleep disturbance with insomnia, excessive perspiration, an increase in appetite accompanied by no weight gain or even weight loss, and diarrhea.

Graves’ disease is much more frequent in female than in male. It may occur at any age during childhood, but its frequency increases with age, peaking during adolescence. From this study, 35 patients with GD were all female with the median age of patients was 13 years old (9-17).

Graves’ disease is a multifactorial disease caused by a complex interaction between genetic and environmental factors that lead to the loss of immune tolerance to thyroid antigens, and therefore to the initiation of an immune reaction against the thyroid. A lack of vitamin D can increase the risk of GD. Vitamin D receptor (VDR) gene polymorphisms were found to be associated with the risk for GD.

We observed that 25(OH)D levels was low in patients with GD. The mean level of vitamin D was 13.3 ng/ml. The relationship between low vitamin D levels and GD has been previously reported. Vitamin D deficiency modulates Graves’ hyperthyroidism induced by thyrotropin receptor immunization in BALB/c mice. It is well known that Th1 chemokine CXCL10 plays an important role in the pathogenesis of GD, and that vitamin D analog inhibits CXCL10 in human thyroid cells. In addition, vitamin D analog inhibits inflammatory responses relating to autoimmune development in patients with GD.

Han et al. reported that the vitamin D level in the case group with GD was obviously lower than that in the control group (58.84 ± 8.01 ng/ml) which was much higher than in other studies. Xu and co-workers also evaluated the relationship between serum vitamin D levels and GD through a meta-analysis including 26 case control or cohort studies. Their results confirmed that subjects with GD were more frequently to be deficient in vitamin D than the control group (OR = 2.24, 95% CI 1.31-3.81, p < 0.001). But, in a recent metaanalysis, significant difference in the association of vitamin D levels and GD has been reported in African and Asian patients, while no significant difference was found in the European population. These differences might be related with the VDR polymorphisms among different ethnic populations.

In hyperthyroidism, heart failure may occur in the absence of underlying heart disease in the adult form. Hyperthyroidism is commonly due to hyperthyroidism decrease myocardial contractile reserve, precluding further increases in ejection fraction and cardiac output on exertion. Hemodynamic changes caused by excess thyroid hormone predispose the patient to heart failure.

In this study, mean of ejection fraction is 65.9% and fractional shortening is 36.1% in patients with GD. There are six patients with impaired left ventricular systolic function consisting of five with high cardiac output and one with low cardiac output. Childhood GD is not as common as the adult form and, moreover, the incidence of severe cardiac complications is also lower, being seen in only 1% of these patients. Measurement of thyroid hormone levels in GD showed an increase in T3 and T4, levels as well as a decrease in TSH. This may be affected with level hormone T3. Hormon T3 coordinates blood pressure and cardiac output. In vascular endothelial cells, T3 leads to activation of endothelial nitric oxide (eNOS). Acting together, in association with decreasing density of angiotensin receptors, vasodilatation effect becomes larger. This vascular dilatation effect contributes to maintain the homeostasis of systemic blood pressure. Smooth muscle cells isolated from a rat's aorta relax rapidly during T3 exposure. It leads to decreased arterial resistance and as a result decreased blood pressure and increased cardiac output.

Vitamin D has been hypothesized to play an important role in reduction of LV hypertrophy and function partly through modulation of the renin—angiotensin system (RAS), which plays a key role in the regulation of volume and blood pressure homeostasis. We analysed the relationship between vitamin D levels and impaired ventricular systolic function in patients with GD. There was no significant association between 25(OH)D levels and EF or FS in GD. Another study with Horn cohort where serum levels of 25(OH)D were reported as not being significantly associated with measures of LV geometry or function. Tova et al also reported all results from their longitudinal analyses relating circulating 25(OH)D to 5-year change in LV function and geometry were non-significant. Our result differ from Polat's research (2015) which found a positive association between 25(OH)D and LV geometric, LV fractional shortening, stroke volume, cardiac output, and cardiac index in the dilated cardiomyopathy patients. But, their results are not sufficient to prove a causal relationship between vitamin D deficiency and dilated cardiomyopathy. Considering the results of our study that most of the subject had normal EF and FS in GD, it can be the reason not related with 25(OH)D.

Our study has several limitations. First, calcium examination was not performed in this study. Some case reports indicated that the dilated cardiomyopathy can be associated with hypocalcaemia and vitamin D deficiency in the pediatric population. Regulation of intracellular Ca²⁺ is important for both normal systolic and diastolic function. Diastolic function of the heart is substantially influenced by the thyroid status. The speed of diastolic relaxation in the heart is markedly influenced by lowering of the Ca²⁺ levels. Besides, cardiac muscle cells posses a vitamin D receptor and a calcitriol-dependent Ca²⁺ binding protein. Moreover, a calcitriol mediated rapid activation of voltage-dependent Ca²⁺ channels exists in cardiac muscle cells. Therefore, it is important to perform calcium examination. Second, this study included either newly diagnosed or routine patients. Thyroid dysfunction with raised fT3 and fT4, had been present and untreated or partially treated for several weeks to months prior to presentation in all of them. Patients had substantial recovery of cardiac function after effective control of GD.

Conclusion

In conclusion this study, low level of vitamin D is prevalent in children with GD. But, vitamin D level and impaired ventricular systolic function was not related to GD. Children with Grave disease have fewer heart complication than adults.
CONFLICT OF INTEREST

None declared.

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REFERENCES