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Some biochemical tips in the etiopathogenesis of Pectus Excavatum

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Abstract

Pectus excavatum (PE) is the most common deformity among anterior chest wall abnormalities. Although many theories on the pathogenesis of PE have been described, the uncertainty is still going on whether it is a result of developmental, biochemical, or biomechanical reasons or their combination. The aim of this study was to evaluate the biochemical parameters that may cause or be associated with the development of PE between children with PE and their healthy peers.
A total of 33 patients' medical records were retrospectively analyzed who followed up because of pectus excavatum between 2019 and 2021. A control group was formed from 32 healthy children from the hospital records with similar age and gender profiles as the patient group. The data from both groups were collected and statistically analyzed in terms of gender, age, and laboratory tests, including hemogram, Vit B12, Parathormone (PTH), Vit.D, Alkaline phosphatase (ALP), and serum Calcium (Ca) and Phosphor (P) levels. Compared to the control group, statistically, significantly higher serum ALP, P, and PTH levels with low Vit.B12 levels were detected. The significant difference in the levels of ALP, PTH, P, and Vit B12, which have an important place in the construction and development of osteochondral structures, may impair the remodeling capacity of the costosternal structure with the contribution of thoracic biomechanics. When PE deformity is noticed, if appropriate medical treatment such as vitamin and mineral supplements and diet regulation is applied to children in the follow-up process, the process can be slowed down, and the deformity can be alleviated.

Keywords: Vitamin B12, phosphorus, pectus excavatum, children

Introduction

Anterior chest wall deformities are a rare medical problem, and pectus excavation is the most common deformity among anterior chest wall abnormalities [1,2]. There are several hypotheses regarding its pathogenesis; Hypertension of the diaphragm during embryonic development [3], thickened substernal ligament [4], muscle imbalance in the anterior portion of the diaphragm [5], defects in collagen formation [6], overgrowth and biomechanical weakness of the costosternal cartilage due to a metabolic defect [7], cartilaginous overgrowth [8] or premature cartilage aging in the costosternal cartilage [9] and abnormalities in the amount of trace elements in the costal cartilage [10]. Finally, two main hypotheses remain for the pathogenesis of PE, suggesting a developmental disorder or cartilage proliferation. A summary of all studies suggests that the changes in the amounts of trace elements in the cartilage structure or the disorders in collagen synthesis, and abnormalities in type-2 collagen structure leads to PE with abnormalities in cartilage and bone chemistry [11]. Although those extensive researches are interested in the etiopathogenesis of PE, no additional approaches other than surgical treatment are recommended in the management of PE. The aim of this study was to evaluate the biochemical parameters

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that may cause or be associated with the development of PE between children with PE and their healthy peers.

Material and Methods

A total of 33 patients' medical records were retrospectively analyzed who followed up because of pectus excavatum between 2019 and 2021. A control group was formed from 32 healthy children from the hospital records with similar age and gender profiles as the patient group. The data from both groups were collected and statistically analyzed in terms of gender, age, and laboratory tests, including hemogram, Vit B12, Parathormone, Vit.D, Alkaline phosphatase, and serum Calcium and Phosphor levels. Demographic information and clinical characteristics were recorded for all participants using a data list. Laboratory findings were obtained from the medical registry system of XXX Training and Research Hospital. Biochemical tests and hemograms were obtained through Abbott Architect c16000 (Illinois, USA) and Sysmex Corporation XN-10 (Kobe, Japan), respectively. This retrospective study was approved by the Institutional Ethics Review Board for Clinical Research (2022/214).

Statistical analysis

Data analyzes of the participants included in the study were carried out with the SPSS for Windows v.25 software (IBM, New York, USA). The normality assumption of the data was checked through a Kolmogorov-Smirnov Test. The significance level (p) for comparison tests was taken as 0.05. Since the variables did not have a normality assumption (p>0.05), the analysis was continued with non-parametric test methods. Because the assumption of normality was not provided, comparisons in independent pairs were carried out with the Mann-Whitney test. A chi-square ($\chi 2$) analysis was performed using cross tables for categorical data analysis. In the binary logistic regression analysis, the Hosmer-Lemeshow statistics were used to test the goodness of fit of the model. The model for binary logistic regression in patient and control groups' estimate of significant variables was constructed.

Results

Demographic characteristics of patients with pectus excavatum and the healthy control group

In this study, there were 8 (24.2%) girls and 25 (75.8%) boys in the PE group and 13(40.6%) girls, and 19 (59.4%) boys in the control group. Mean ages were 12.56±4.57 vs. 12.63 ± 4.17 in PE and control groups. There were no statistically significant differences regarding age between the groups. (Table 1).

Laboratory markers of pectus excavatum patients and healthy control group

A statistically significant difference was found between the groups according to the Alkaline phosphatase, Parathormone, Phosphorus, and vitamin B12. (p<0.05, Table 2).

Table 1. Comparison of the groups by gender and age distribution

Variable	Groups		Patients	Control	Total	p
Gender	Girl	n	8	13	21	0.004*[a]
		%	24.2%	40.6%	32.3%	
	Boy	n	25	19	34	
		%	75.8%	59.4%	52.3%	
	Total	n	33	32	65	
		%	100.0%	100.0%	100.0%	
Age	Mean±sd		12.56±4.57	12.63±4.17	12.55±4.71	0.057*[b]

n; frequency. %; percent. sd; standart deviation. M; Median. pa; Chi-Square Test value ($\chi 2$). pb; Mann Whitney Test Value. *; indicates statisticaly difference

Table 2. Measurements of blood parameters in both groups

Variables	Groups	Mean ± sd	M (Min-Max)	Test	p
Alkaline phosphatase U/L	patient	220 ± 51.17	212.5(115-336)	**177.000**	**0.001***
	control	137.63 ± 65.56	120(45-261)		
Phosphorus mg/dL	patient	5.09 ± 0.47	5.1(3.8-6)	**84.500**	**0.001***
	control	3.96 ± 0.64	4(2.7-5.6)		
Parathormone pg/mL	patient	37.81 ± 17.96	32.2(12.2-90.06)	**360.500**	**0.042***
	control	28.59 ± 10.68	25.8(9.21-50.6)		
Vitamin B12 pg/mL	patient	327.88 ± 130.57	298.5(124-605)	**327.500**	**0.009***
	control	427.59 ± 134.47	416.5(191-822)		
Calcium mg/dL	patient	9.67 ± 0.36	9.6(9.1-10.5)	397.000	0.084
	control	9.8 ± 0.31	9.75(9-10.5)		
Hemoglobin g/dL	patient	13.51 ± 1.37	13(11.2-17.1)	505.500	0.768
	control	13.44 ± 1.4	13.3(10.8-16.9)		
Ferritin ng/mL	patient	28.09 ± 17.54	27.6(5.99-97)	388.500	0.067
	control	40.82 ± 27.73	36(2.78-122)		
vitamin D	patient	17.58 ± 5.55	17(5.63-28.3)	490.500	0.773
	control	18.87 ± 7.44	17.7(6.81-36.1)		

sd; standard deviation, M; Median, Min; The smallest value taken, Max; the highest value taken, p; Mann Whitney Test Value, p value, *p<0.05; points a statistically significant difference between the groups

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Logistics regression analysis for groups

A Binary Logistic Regression model was established in which the dependent variables of the groups, ALP, phosphorus, parathormone, vitamin B12, age, and gender, were the independent variables. In the binary logistic regression analysis (Table 3), the Hosmer-Lemeshow statistics were used to test the goodness of fit of the model. In the established model, the groups of data (study-control) were predicted; The model established with Alkaline phosphatase, Phosphorus, Parathormone, Vitamin B12, age, and gender values was found to be a statistically sufficient model ($\chi 2$ = 9.188, degree of freedom= 8 p=0.327>0.05).

Table 3. Estimated Values of the Parameters in the Model

Variables	β	SE	W	df	p (sig)	Exp(β) (OR)	95% C.I.for EXP(β)	
							Min	Max
Alkaline phosphatase	-0.022	0.013	2.915	1	0.088	0.978	0.954	1.003
Phosphorus	**-3.989**	**1.540**	**6.710**	**1**	**0.010***	**0.019**	**0.001**	**0.379**
Vitamin B12	**0.017**	**0.007**	**6.144**	**1**	**0.013***	**1.017**	**1.104**	**1.231**
Parathormone	0.040	0.045	0.806	1	0.369	1.041	0.953	1.137
Age	-0.111	0.162	0.468	1	0.494	0.895	0.651	1.230
Gender	0.531	1.151	0.213	1	0.645	1.700	0.178	16.218
Constant	**17.487**	**7.351**	**5.659**	**1**	**0.017***	**4.469**		

β; parameter estimation, SE; standard error; W; Wald statistics, df; degrees of freedom, Exp (β); odds ratio, 95% CI; confidence interval.

Discussion

Although many theories on the pathogenesis of PE have been described [1-15], there has yet to be any reliable anatomical or radiological evidence. However, it is stated that structural abnormalities of costosternal cartilage are an important factor in the development of PE. As a main structural component of costal cartilage, the Type-2 collagen metabolism and its composition are of cardinal importance in the etiology and pathogenesis of PE [16]. Bone mineral density (BMD) and bone fragility are measured when assessing bone health. Decreased vitamin B12 levels have a negative effect on BMD [17], and high levels of homocysteine are an indicator of vitamin B12 deficiency. Homocysteine prevents the formation of collagen bonds by stimulating osteoclasts and increasing osteoclast formation [18]. Alkaline phosphatase activity and osteoblast growth are both directly influenced by vitamin B12 [19]. Vitamin B12 deficiency adversely affects the construction and destruction of bone. Therefore, supplementation with vitamin B12 is crucial to maintain healthy bone structure [20].

In healthy individuals, serum alkaline phosphatase levels change with age, and its level is higher during childhood and adolescence due to the maturation and growth of the bones [21,22]. However, we found a statistically significant increase in ALP values between PE and control cases. Mean ALP values were 220 ± 51.17 vs. 137.63±65.56 in PE and control groups, suggesting increased bone resorption in children with PE compared with their healthy peers. Indeed, ALP has been proposed as a novel predictor for high-turnover bone disease [13,23,24].

Maintaining serum phosphate levels within physiological limits for various biological processes is critical. An essential component of bones, nucleic acids, and cell membranes, phosphate is critical for cellular energy metabolism, intracellular protein phosphorylation, and hemoglobin oxygen release [25]. In this study, the serum phosphorus level was detected as higher in the PE group than in the control group. There was a statistically significant difference between mean phosphorus values in the PE group (5.09±0.47 mg/dL) versus (3.96±0.64 mg/dL) in the control group. Alkaline phosphatase level rises during early osteoblastic activity, and this increase provides local phosphate formation or its liberation in the presence of organic phosphates such as b-glycerophosphate, thus causing an increase in extracellular P concentration [26] . This situation explains the statistically significant high ALP and P values we found in the PE group. The effects of hyperphosphatemia on bone metabolism via the parathyroid gland are well known. Although vitamin D insufficiency results in PTH increase, which causes cortical thinning and, sometimes, marrow fibrosis [27], there was no significant difference in vitamin D levels between the groups in this study. However, there was a statistically significant difference in PTH levels between the PE and Control groups (Table 2).

Although the exact causes of PE are not known, the underlying mechanism may be related to corrupted collagen synthesis of costochondral structures, which may result in disrupted remodeling of ribs and sternum and, finally, the development of PE.

As a result, high phosphorus, alkaline phosphatase, parathormone, and low Vit B12 values, which are found with a statistically significant rate in PE cases compared to the control group, lead to disrupted bone and cartilage formation by complex mechanisms, possibly affecting the remodeling of the ribs and results with PE in slow progress.

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In this retrospective study, routine hematologic parameters of the PE patients, which were obtained during the first and follow-up examinations, were investigated. Its retrospective design and the lack of information on protein markers, minerals, and other vitamins and sex hormones are the limitations of this study. However, differences in some biochemical markers of bone and cartilage formation could be assumed to be related to the progression of deformity, together with unknown factors. Since PE generally progresses gradually until puberty when it is noticed earlier, the regulation of biochemical abnormalities may be useful to increase the remodeling capacity of the sternum and ribs and to prevent or slow the progression of the deformity. These limited results may be inspiring for prospective randomized trials.

Patient informed consent

Signed informed consent was gathered from the participants for this study.

Conflict of interests

The authors declare that there is no conflict of interest in the study.

Financial Disclosure

The authors declare that they have received no financial support for the study.

Ethical approval

This study was endorsed by Malatya Turgut Ozal University Non-Interventional Clinical Researches Ethics Committee (Decision Date: 13/12/2022, Meeting Number: 21, Decision Number: 2022/214).

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