**NJSC "Asfendiyarov Kazakh National Medical University"**

**Annotation to the dissertation**
for the degree
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# Clinical and diagnostic significance of fibroblast growth factor 23 (FGF-23) in children with chronic kidney disease

Specialty 6D110100 – "Medicine"

**BALMUKHANOVA ALTYNAY MAKSATOVNA**

**Scientific advisors:** DMedSc, Prof. Kabulbayev K.A.

DMedSc, Prof. Kanatbayeva A.B.

**Foreign scientific advisor:** MD, PhD, Prof. Harika Alpay

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# ANNOTATION

**for the dissertation by Balmukhanova Altynay Maksatovna on the topic «Clinical and diagnostic significance of fibroblast growth factor 23 (FGF-23) in children with chronic kidney disease» submitted for the degree of Philosophy Doctor (PhD) in specialty 6D110100 – "Medicine"**

**Relevance**

Chronic kidney disease (CKD) is a serious and complex medical and public health problem worldwide, ranking among the leading chronic noncommunicable diseases in terms of prevalence and mortality (Brück K., 2015; Bikbov B., 2020; Johansen K., 2021).

Various multicenter studies have found that the prevalence of CKD in the world among the adult population is 8-16%, while this indicator tends to gradually increase. (Brück K., 2015; Jha V, 2013). According to the ESPN / ERA-EDTA studies, the incidence of CKD stages 3-5 in children is approximately 11-12 cases, and the prevalence is about 55-60 per million children (2016). According to the results of a multicenter large-scale study, Global Burden of Disease, conducted in 2017, the prevalence of CKD in adults in Central Asia was 8.6 million people, of which about 1.8 million people in Kazakhstan (Bikbov B., 2020). In the Republic of Kazakhstan (RK), the incidence and prevalence of CKD among children and adolescents is higher than the world average (Kanatbayeva A., 2012).

CKD in children, in comparison with adults, despite similar pathophysiological mechanisms of formation, also has its own characteristics associated with childhood, which, in particular, affects growth and physical development, also leaving a significant mark in the psychosocial worldview of the child and his parents (Becherucci F., 2016).

It is known that CKD is a polymorphic symptom complex, and at advanced stages it has a number of complications from many organ systems, thereby determining the prognosis of the disease and affecting the patients' quality of life. One of the significant aspects of this problem is the early diagnosis of both the disease itself and its complications.

In this regard, the search for possible early markers of the development of CKD and its complications led to interest in the study of a new representative of the group of phosphatonins, fibroblast growth factor 23 (FGF-23). FGF-23 is a morphogenetic protein of bone origin, the main physiological role is to regulate the excretion of phosphate in the urine to maintain a stable level in serum (Iliin A., 2013; Milovanova L., 2017). This mechanism allows us to consider the new biomarker as a central regulator of bone mineral metabolism, the disturbance is accompanied by CKD.

At present, much of the European research on the role of FGF-23 in normality and pathology is focused only on adults (Plotnikova A., 2015; Milovanova L, 2017; Isakova T., 2011; Bouma-de Krijger A., 2020). Thus, according to the research of

Gutierrez O. and Isakova T., in CKD, the levels of circulating FGF-23 gradually increase with a decrease in renal function (Isakova T., 2011). In paediatrics, such research is scarce (Magnusson P., 2010; Sinha M., 2012; Liu D., 2017), moreover, the pre-clinical stages are neglected, which is crucial and key point in early diagnostics.

Thus, all of the above mentioned, namely, high incidence and prevalence of CKD among children and adolescents in the Republic of Kazakhstan, its clinical features in childhood, as well as such factors as late referral, delayed diagnosis and insufficient preventive measures make the present study of fibroblast growth factor 23 (FGF-23) relevant as an early prognostic marker.

**The aim of the research** is to determine the clinical-diagnostic significance of fibroblast growth factor 23 (FGF-23) in children with chronic kidney disease.

**Objectives:**

1. To study clinical features of chronic kidney disease in children.
2. To investigate the level of fibroblast growth factor 23 depending on the characteristics of the clinical course of chronic kidney disease in children.
3. To establish the relationship of fibroblast growth factor 23 with indicators of iron metabolism in children with chronic kidney disease.
4. To assess the relationship of fibroblast growth factor 23 with indicators of phosphorus-calcium metabolism in children with chronic kidney disease.
5. To develop a mathematical model for predicting an elevated level of fibroblast growth factor 23 in children with chronic kidney disease.

**Scientific novelty:**

1. For the first time in children with CKD, a comprehensive study was carried out to determine FGF-23 from early to terminal stages, and its increased level was detected already at the second stage.
2. The close correlation feedback of FGF-23 with the glomerular filtration rate (GFR) ($r = -0.826$, $p < 0.001$) was scientifically substantiated, significant differences were revealed depending on blood pressure (BP) ($p < 0.001$) and left ventricular hypertrophy (LVH) ($p < 0.001$). (Certificate of inclusion in the State register of rights to copyrighted objects №20359).
3. For the first time in children with CKD, an inverse relationship of FGF-23 with hemoglobin level ($r = -0.615$, $p < 0.001$), serum iron ($r = -0.493$, $p < 0.001$) and transferin saturation ($r=-0,331$, $p=0,004$). (Certificate of inclusion in the State register of rights to copyrighted objects №20459).
4. It was founded that FGF-23 is an early marker of changes in bone mineral metabolism; at the same time, the relationship of FGF-23 with indicators of phosphorus-calcium metabolism was revealed: positive - with parathyroid hormone ($r = 0.807$, $p < 0.001$) and phosphorus ($r = 0.473$, $p < 0.001$), inverse - with the levels of total ($r = -0.361$ , $p = 0.002$), and ionized calcium ($r = -0.305$,

p = 0.009) and 25 (OH) vitamin D (r = -0.332, p = 0.004). (Certificate of inclusion in the State register of rights to copyrighted objects №19182).

5. For the first time, we developed a mathematical predictive model for detecting an increased level of FGF-23 according to the principle of a decision tree based on the clinical and laboratory parameters available in practice. (Certificate of inclusion in the State register of rights to copyrighted objects №18925).

**Practical significance:**

1. Studies have shown the need to determine the level of FGF-23 at all stages, starting from the early.
2. The results of this research allow to consider FGF-23 as an early marker of complications of CKD in children (cardiovascular, bone mineral, hematological), and, therefore, to develop an adequate patient management tactics.
3. The developed prognostic mathematical model (decision tree) for the detection of an increased level of FGF-23 allows timely identification of the risk group for the early development of bone mineral disorders, cardiovascular complications in children with CKD.

**The main provisions for the defense:**

1. Fibroblast growth factor 23 (FGF-23) is a morphogenetic protein of bone origin (phosphatonin), the level of which progressively increases with a decrease in renal function, and depends on some features of the clinical course of CKD in children.
2. Fibroblast growth factor 23 (FGF-23) is associated with indicators of iron status, in particular hemoglobin, serum iron and transferrin saturation ratio.
3. Fibroblast growth factor 23 (FGF-23) is an early marker of bone mineral and cardiovascular disorders in children with CKD.
4. The developed mathematical prognostic model makes it possible timely identify an increased value of fibroblast growth factor 23 (FGF-23) to determine early the risk group for the development of mineral-bone and cardiovascular complications in children with CKD.

**Approbation of work.** The main provisions of the dissertation were reported and discussed at an extended interdepartmental meeting (Protocol No. 12 dated 06/10/2021).

The results of the research were reported to:

1. International scientific and practical conference for doctoral students, Master's degree students and residents: "Young researcher: challenges and prospects for the development of modern pediatrics and pediatric surgery" (Almaty, Kazakhstan, March 1, 2019). The theme of the report: Clinical predictors of chronic kidney disease.
2. The 56th ERA-EDTA Nephrology Congress (Budapest, Hungary, June 13-16, 2019). The features of birth weight in the development of hypertension.

3. Scientific and practical conference with international participation «Pediatric nephrology update» (Almaty, Kazakhstan, December 5-6 , 2019). The role of phosphatonins in CKD progression in children.
4. The 57th ERA-EDTA Congress (Milan, Italy, June 6-9, 2020). Biomarkers of CKD-MBD in children.
5. The 57th ERA-EDTA Virtual Congress (Milan, Italy, June 6-9, 2020). The role of FGF-23 in CKD progression in children.
6. The 58th ERA-EDTA Virtual Congress (Berlin, Germany, June 5-8, 2020). FGF-23 and low birth weight: is there any association?
7. 11 Uluslararası Katılımlı Çocuk Nefroloji E-Kongresi (Istanbul, Turkey, September 4-5, 2021). Association of fibroblast growth factor 23 with blood pressure and left ventricular hypertrophy in children with chronic kidney disease.

**Publications on the topic of the dissertation**

1. Balmukhanova A, Kabulbayev K, Alpay H, Kanatbayeva A, et al. FGF-23 and Phosphate in Children with Chronic Kidney Disease: A Cross-Sectional Study in Kazakhstan. Medicina. 2021; 57(1):15. https://doi.org/10.3390/medicina57010015. (Web of Science, **Q2**, **IF 2.430**, Scopus, **Q2, 59 перцентиль**).
2. Балмуханова А.М., Канатбаева А.Б., Кабулбаев К.А., и др. Низкий вес новорожденного как фактор развития хронической болезни почек у детей // Scientific and practical journal of the public association "Union of Pediatricians" of Kazakhstan "Pediatrics and Pediatric Surgery". №1(95). С.28-29. 2019г. (Recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan).
3. Балмуханова А.М., Канатбаева А.Б., Кабулбаев К.А., и др. Клинические предикторы развития хронической болезни почек // Scientific and practical journal of the public association "Union of Pediatricians" of Kazakhstan "Pediatrics and Pediatric Surgery". №1(95). С. 29-31. 2019г. (Recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan).
4. Балмуханова А.М., Канатбаева А.Б., Кабулбаев К.А., и др. Значение фактора роста фибробластов 23 (FGF-23) в организме человека // Medicine (Almaty). – 2020. – № 7-8 (217-218). – С. 37-43. DOI: 10.31082/1728-452X-2020-217- 218-7-8-37-43. (Recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan).
5. Балмуханова А.М., Кабулбаев К.А., Канатбаева А.Б. Фактор роста фибробластов 23 (FGF-23) и хроническая болезнь почек у детей. Medicine (Almaty). 2020;11- 12(221-222):43-48. DOI: 10.31082/1728-452X-2020-221-

222-11-12-43-48 (Recommended by the Committee for Quality Assurance in Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan).

6. Balmukhanova A, Kanatbayeva A, Kabulbayev K, et al. The features of birth weight in the development of hypertension // Nephrology Dialysis Transplantation, Volume 34, Issue Supplement_1, June 2019, gfz103.SP060, https://doi.org/10.1093/ndt/gfz103.SP060. (Web of Science, **Q1, IF 5.992**).
7. Balmukhanova A, Kanatbayeva A, Kabulbayev K, et al. The role of FGF-23 in CKD progression in children // Nephrology Dialysis Transplantation, Volume 35, Issue Supplement_3, June 2020, gfaa142.P1823, https://doi.org/10.1093/ndt/gfaa142.P1823. (Web of Science, **Q1, IF 5.992**).
8. Balmukhanova A, Kanatbayeva A, Kabulbayev K, et al. Biomarkers of CKD-MBD in children // Nephrology Dialysis Transplantation, Volume 35, Issue Supplement_3, June 2020, gfaa142.P0899, https://doi.org/10.1093/ndt/gfaa142.P0899 (Web of Science, **Q1, IF 5.992**).
9. Balmukhanova A, Kabulbayev K, Shepetov A, et al. FGF-23 and low birth weight: is there any association? Nephrology Dialysis Transplantation (Web of Science, **Q1, IF 5.992**).
10. Balmukhanova A. Certificate of entering information into the state register of rights to objects protected by copyright №18925, 23.06.2021г. Algorithm for predicting increased fibroblast growth factor 23 (FGF-23) as a marker of complications of chronic kidney disease in children.
11. Balmukhanova A., Kabulbayev K. Certificate of entering information into the state register of rights to objects protected by copyright №19182, 02.07.2021г. Mathematical determination of the level of fibroblast growth factor 23 (FGF-23) in blood serum based on parameters of phosphorus and parathyroid hormone.
12. Balmukhanova A., Kabulbayev K. Certificate of entering information into the state register of rights to objects protected by copyright №20359, 21.09.2021г. Fibroblast growth factor 23 (FGF-23) in the diagnosis of chronic kidney disease in children.
13. Balmukhanova A., Kabulbayev K. Certificate of entering information into the state register of rights to objects protected by copyright №20459, 24.09.2021г. Model for the determination of fibroblast growth factor 23 (FGF-23) in chronic kidney disease, taking into account the level of hemoglobin.

**Implementation of research results.** The main scientific provisions and conclusions of this study, as well as the prognostic model which was developed by us, have been incorporated into the work in the department of Nephrology and Extracorporeal Detoxification of “Aksai” University Clinic at NSC S.D. Asfendiyarov The Kazakh National Medical University, also in clinics and hospitals of the Republic of Kazakhstan. The materials of the dissertation are used in the

educational process at the Department of Nephrology of S.D. Asfendiyarov The Kazakh National Medical University.

**Structure and amount of work.** The thesis is composed of 123 pages of typewritten text and consists of a list of abbreviations and designations, introduction, literature review, description of materials and methods, results of own research, findings, conclusions and practical recommendations. References contain 190 titles in English and Russian. The scientific work is illustrated in 11 tables and 40 figures, and it contains 12 applications.

## MATERIAL AND RESEARCH METHODS

**General characteristics of the studies.** This study was carried out in the Department of Nephrology and Extracorporeal Detoxification of «Aksai» University Clinic, and also in polyclinics of Almaty. Laboratory diagnostic methods were carried out in the scientific clinical diagnostic laboratory at B. Atchabarov Scientific Research Institute of Fundamental and Applied Medicine.

The present work combined two consecutive stages of the study: analysis of children's medical records with the established diagnosis of CKD (chronic renal disease) 3-5 stages (cross-sectional study), which were on in-patient treatment in 2014-2018 and a prospective (cross-sectional) study in 2019-2020.

A total of 188 children participated in this study: 174 children with chronic kidney disease of 1-5 stage and 14 children had no evidence of kidney damage.

In the first stage, 101 patients who had been admitted to the clinic several times in 2014-2018 were chosen for justifying the relevance of the research problem (medical history of 572 patients).

The next stage was a one-time cross-sectional study. 73 patients with CKD aged from 2 to 18 who received inpatient and outpatient treatment in polyclinics of Almaty and «Aksai» Clinic, as well as healthy children comparable in age and sex. The material of the study included the data of physical, laboratory and instrumental examination of the groups of patients under investigation. *Inclusion criteria at this stage of the study* includes patient aged from 2 to 17 years and 11 months; with diagnosis of chronic kidney disease established according to diagnostic criteria of clinical protocol from MH of RK, 2016 and international clinical recommendations; written informed consent of the child's parents or other legal representatives. *Graduation criteria:* patient aged under 2 years and over 18 years; patients with primary diagnosis of tubulopathy; parathyroid pathology not associated with CKD; presence of an active infectious, inflammatory process, diseases of the osteo-articular system at the time of study; presence of oncological process; presence of kidney transplant; taking of glucocotrticochteroids for the last 6 months, calcium and vitamin D or derivatives for 1 month; lack of written informed consent of the child's parents or other legal representatives; refusal by parents and/or the child to undergo further research.

Thus, a total of 87 children with an average age of 9,64±0,5 years, 44 (50.6 per cent) boys and 43 (49.4 per cent) girls, participated in this phase of the study. In this study 73 patients with CKD of various degrees and 14 healthy children of comparable age and sex were the main participants in the study.

The distribution by stages of the disease was as follows: stage 1 - 19.2%, stage 2 - 20.5%, stage 3 - 17.8%, stage 4 - 19.2%, and stage 5 - 23.3%.

**Research Methods.**

The examination of patients was carried out taking into account the clinical protocols for diagnosis and treatment of diseases developed by the Ministry of Health of the Republic of Kazakhstan. Clinical, laboratory and instrumental methods were used to assess the condition of children. Laboratory tests were conducted on venous blood samples taken on an empty stomach.

We used a multimatrix enzyme immunoassay for the quantitative determination of human FGF23 in serum, EDTA plasma, heparinized plasma and citrated plasma, No. BI-20702, manufacturer - Biomedica Medizinprodukte GmbH, Austria to determine the level of fibroblast growth factor 23 (C-terminal) in the blood serum. The determination of fibroblast growth factor 23 was carried out by immunoforment analysis of type «sandwich» on automatic immunoforment and immunochemiluminescent analyzer ChemWell Fusion (Awareness Technology Inc., USA).

**Statistical methods.**

The collection, accumulation and systematization of basic information was carried out in the databases of MS Excel 2016. SPSS Statistics v.26 (IBM Corp., USA) provided further statistical processing and graphic representation of data. The first step in statistical processing was to check the data for the normal distribution using the Kolmogorov-Smirnov criterion, the W Shapiro-Wilk criterion. Next, descriptive statistical methods were applied. To test the difference in mean hypothesis, the t-criterion of Studenth was used for non-pair samples and the U criterion of Mann-Whitney which depends on the distribution. The statistical significance of differences in quantitative indicators with a normal distribution between several groups was assessed using one-way analysis of variance (ANOVA) with additional post-hoc tests if statistically significant differences were found between the groups. The Kruskal-Wallis test was used when comparing several quantitative samples with a different distribution from the normal which is followed by pairwise comparison of populations using the Bonferroni correction coefficient for statistical significance as p. Ratings were described with absolute values and percentages. The nominal data were compared by constructing the conjugacy tables and computing the chi-square criterion ($\chi 2$) of Pearson, as well as the exact Fisher criterion. The criterion $\varphi$ was used to assess the coupling force between the parameters being studied. The correlation analysis method Spearman was used to identify correlations between variables and their statistical significance. The mathematical predictive model is constructed on the principle of a decision tree.

The difference between the indicators was considered statistically significant at the error rate $p \leq 0,05$.

**RESEARCH RESULTS**

From the results of the first stage of study we have established the following indicators: the median age at which the first symptoms occur from birth, with a maximum age of 15 years; the median age of diagnosis was 6 years with a maximum age of 17 years; the median age for the onset of renal replacement therapy (RRT) was 9.5 years, from the first symptoms to the onset of RRT of 6 years. It is noted that children hospitalized in the ward had already greater extent complications of CKD such as mineral-bone disorders (MBD), renal anaemia, physical retardation and cardiovascular changes. Thus, 80.2 % of children had some form of mineral-bone exchange disorder requiring correction, and 82.2 % of them had renal and mixed genesis anaemia. 76.24 % of children with left ventricular hypertrophy (LVH) is also noted. Among 101 children, more than half - 55.45 % were already physically retarded at the time of their first hospitalization, while 19.8 % of them had skeletal deformity. A detailed study of the history of life, including perinatal history, revealed that 12.87 % of children had low birth weight and 43.56 % were born from mothers with one or another pathology of pregnancy. 10.89 % of children had heredity acute kidney problems, and in some cases the older siblings had similar symptoms or fatalities. According to the analysed medical records and prescribed epicryasis for this period of study, we have found that 9.9 % of children died from multiple organ failure, including cardiovascular failure. 15.85% of children underwent kidney allotransplantation, while 8.91 % of patients according to the age were treated at the adult care centres. At the end of the study period, 32.67 % of the children were still under observed treatment, and the same number had lost contact with the clinic and were no longer under observation.

According to the data of the second stage of the study we have established some clinical features of CKD in children, as well as their relationship with the level of phosphatonin - FGF-23 in the blood serum. In 69.86% of CKD development the data obtained confirm the leading position of congenital anomalies in the development of the urinary system and in children of any age category; in second place in terms of contribution to the development of CKD 17.81% of glomerular diseases are in children; relatively small percentages are on such groups of diseases as nephrolithiasis and nephrocalcinosis - 5.48%, hemolytic uremic syndrome - 4.11% and polycystic kidney disease - 2.74%.

Impairment of physical development is one of the clinical manifestations and complications of CKD in childhood which carries a medical social meaning. In our study population 32.88% of children had failure to develop, while there is a persistent increase in the number of children with impaired physical growth and development with the progression of the disease. So, at the $5^{th}$ stage 70.59% of children had a failure to develop, and the developmental disorders composed of half of all children

among multi-patient study. The largest deviations in height and weight (z-score) occur at stages 4 and 5 of the disease.

In 30.14% of children BP was determined above the target values with a maximum rise in BP up to 150/100 mm Hg. We also found that according to echocardiography 38.36% of the children had signs of LVH among multi-patient study, while the proportion of people with LVH increased from stage to stage of disease, and at the $5^{th}$ stage it was 94.12%. The results may indicate a high risk of death for cardiovascular causes in children with CKD.

In total, 50.68% of children with anemia of various origins, 41.1% with renal and mixed anemia, which occurs in some patients at the $3^{rd}$ and $4^{th}$ stage of the disease and fully detected at the 5th stage of the disease were studied. Also, we determined statistically significant differences in serum iron and TSAT levels in groups of patients with different stages of the disease ($p = 0.001$, $p = 0.002$, respectively).

Analysis of the data on phosphorus content at individual stages revealed that the differences in only patients with the $5^{th}$ stage of the disease were statistically significant compared to the $1^{st}$ and $2^{nd}$ stage of the disease ($p=0.004$, $p=0.019$, respectively), and a significant increase in PTH was observed in the $4^{th}$ of stage ($p<0.001$) which is a rather late diagnosis.

An analysis of the results in the laboratory blood sample tests to determine the FGF-23 concentration revealed a good variation in the levels of the test marker in different stages of children ($p<0.001$). Thus, a comparison of the groups among themselves revealed a significant increase of the $3^{rd}$ stage of the disease compared to the $1^{st}$ ($p\leq0,05$). The lack of differences between healthy children and patients with the $1^{st}$ stage of the disease was quite understandable, since the patients with the $1^{st}$ stage do not have a decrease in renal function and do not show any symptoms. At the same time, our analysis showed a significant increase of FGF-23 in 53.3% of patients with the $2^{nd}$ stage both healthy and children with the $1^{st}$ stage relatively ($p\leq0.05$). As a rule, considering that the $2^{nd}$ stage is also asymptomatic and can be clinically expressed only by symptoms that are characteristic of the pathology led to CKD, this fact allows us to regard FGF-23 as an earlier marker in the diagnosis of CKD and its complications. Moreover, we are witnessing a progressive increase in its concentration, reaching its apogee of the $5^{th}$ stage and far ahead of other indicators, which, in our view, goes beyond its clinical and diagnostic significance, but also the predictive ability to reflect the severity of the disease.

However, in the present study, the new marker was considered not only from the point of view of the stage of the disease, but also in close connection with the clinical manifestations of CKD in children.

As our study showed, the level of FGF-23 did not directly depend on the causes of CRD ($p>0.05$). Considering the high proportion of children with physical retardation, which may indicate late diagnosis, and also the fact that, in addition to growth hormone deficiency in children with CKD, the important risk factors for growth retardation are bone mineral disorders, anemia, electrolyte changes, etc. It is

of interest to consider the relationship of FGF-23 with the level of growth retardation. However, as our results shows, the level of physical development did not affect the concentration of FGF-23 in the blood serum ($p > 0.05$). Nevertheless, the presence of a statistically significant relationship between the marker and the standardized assessment of growth ($r = -0.256$, $p \leq 0.05$) suggests that there is a certain trend in the relationship between the child's growth and the level of phosphatonin in the blood serum.

It is noteworthy that there are statistically significant differences in the level of FGF-23 in groups of patients with high and normal BP rates ($p<0.001$), and a legitimate relation ($\varphi = 0.333$, $p=0.004$). Moreover, there is an increase in the level of FGF-23 with high BP by 4.2 times in comparison with the normotensive group ($p <0.001$).

It is known that LVH is one of the most common cardiovascular pathologies in CKD, including children, and reflects the processes of adaptation of the heart muscle to hemodynamic overload in arterial hypertension and may also be associated with preload increases which are often the case in patients with CKD of various origins. In this regard, it is relevant to search for a potential relationship between FGF-23 and the presence of LVH, which could contribute to the timely identification of patients from risk group and the search for possible ways of correction. Thus, in the group of children with LVH, absolutely everyone had high levels of FGF-23, while among patients without LVH, only 46.7%, and in 53.3% of cases, normal FGF-23. Moreover, we noted statistically significant differences in the level of phosphatonin between groups of patients ($p <0.001$), where the indicator in the group with LVH was 5.54 times higher than that in the group without LVH.

Further, we carried out a correlation analysis that allowed us to reveal a significant close inverse relationship between the level of hemoglobin and FGF-23 ($r = -0.615$, $p <0.001$), i.e. a lower hemoglobin value corresponded to a higher serum phosphatonin level. It should be noted that serum iron and TSAT were inversely correlated with the FGF-23 concentration index ($r = -0.493$, $p <0.001$; $r = -0.331$, $p = 0.004$, respectively).

Another significant aspect of our research has been the study of the characteristics of phosphorus-calcium metabolism and the identification FGF-23 role in MBD in CKD in children. Significant correlations were found with all parameters of bone mineral metabolism, with the exception of alkaline phosphatase, especially a high level of correlation was present between FGF-23 and PTH ($r = 0.807$, $p <0.001$). It is noteworthy that in some patients an isolated increase in FGF-23 was observed without changes in other indicators of phosphorus-calcium metabolism, especially in the early stages. Based on this, the FGF-23 marker can be considered as the earliest predictor of the course and progression of CKD, since it reflects not only the state of phosphorus-calcium metabolism, but also other clinical and laboratory changes that occur in children within the disease, regardless of the cause.

The culminating generalization of our obtained results during the research was the development of a mathematical predictive model that allows quickly and easily assume a high probability risk for a child in CKD having a high level of FGF-23 concentration, and, therefore, identify timely a number of disorders associated with an increase in this marker. Our predictive model indicated a high sensitivity of 98%, and the overall percentage of correctly predicted values was 82.2 ± 4.5% (Figure 1).

Thus, all of the above mentioned emphasizes the special role of fibroblast growth factor 23 in the course of CKD in children, its close relationship with clinical features (blood pressure, LVH), as well as the iron status, phosphorus-calcium metabolism. Our data indicate the clinical and diagnostic significance of FGF-23 in pediatric nephrology, making this marker attractive from the point of view of early diagnosis in number of complications that occur during the development of CKD in children.

Thus, in the course of the research, we scientifically substantiated the clinical and diagnostic significance of FGF-23 in children with CKD due to the implementations of all tasks and formulated following conclusions and practical recommendations.

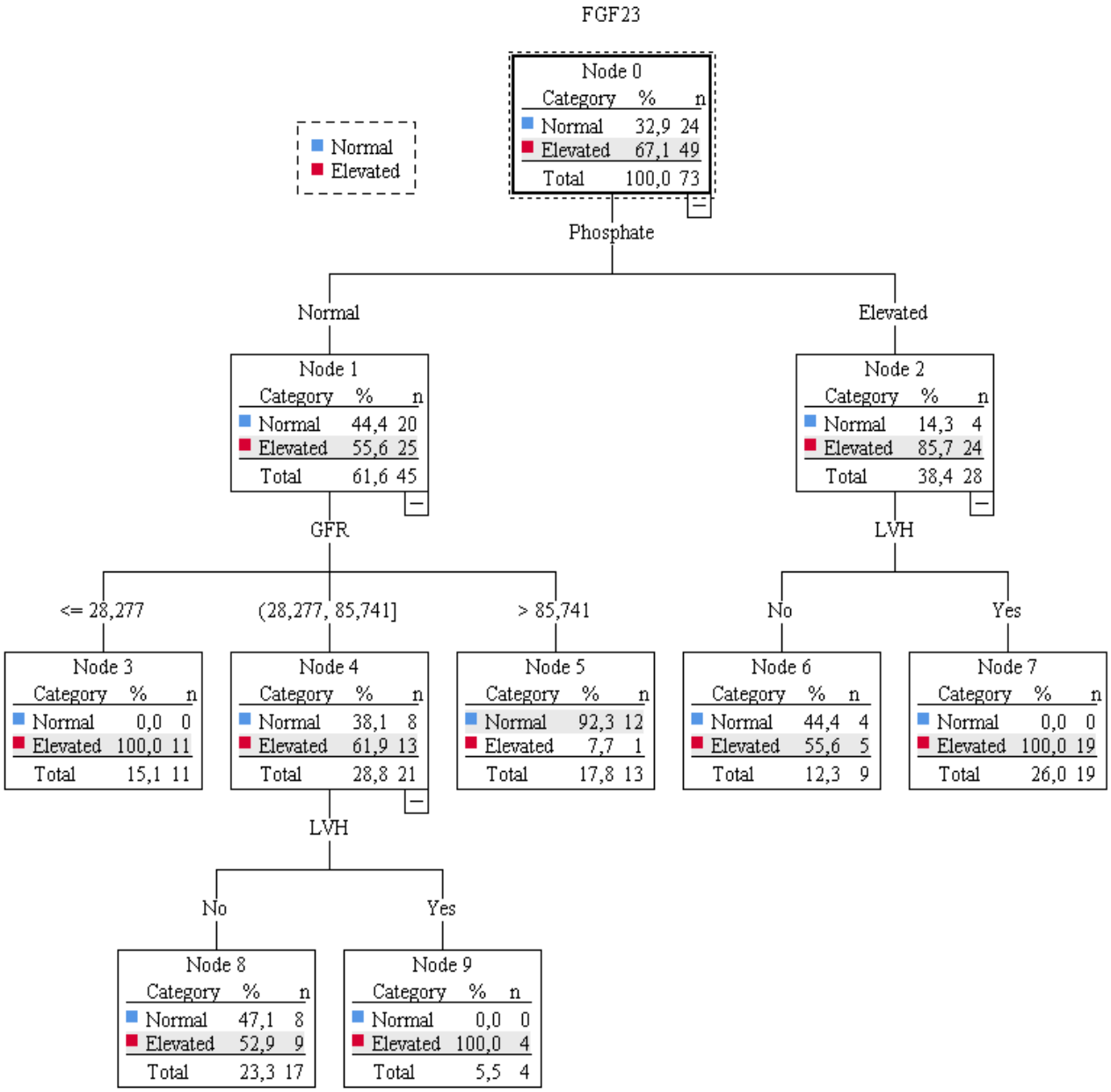


Figure 1 - Decision tree for determining the probability of high FGF-23 in children with CKD

**Based on obtained results, the following conclusions were drawn:**

1. The main reasons for the development of chronic kidney disease in children in Kazakhstan were identified: congenital anomalies in the development of the urinary system - 69.86%, glomerular diseases - 17.81%. The significant features of the clinical course were determined: impaired physical development - 32.88%; arterial hypertension syndrome - 30.14%; left ventricular hypertrophy - 38.36%; anemia - 50.68%; hyperphosphatemia - 38.36%; secondary hyperparathyroidism - 41.1%.
2. It was found that FGF-23 grows from stage to stage, while it is detected in 53.3% of children at the second stage, increasing by 1.7 times and reaching a maximum at the fifth stage, increasing by 14.7 times. There is an increase in the level of FGF-23 with high blood pressure by 4.2 times ($p < 0.001$), within left ventricle hypertrophy by 5.54 times ($p < 0.001$), there is a reliable inverse relationship between FGF-23 and the standardized assessment of the growth of children (z -score) ($r = -0.256$, $p = 0.029$).
3. It was revealed that a high level of FGF-23 is observed in 96.67% of cases in children with renal anemia; there is an inverse significant relationship of FGF-23 with hemoglobin ($r = -0.615$, $p < 0.001$), with the level of serum iron ($r = -0.493$, $p < 0.001$) and TSAT ($r = -0.331$, $p = 0.004$).
4. The relationship of FGF-23 with indicators of phosphorus-calcium metabolism was substantiated: parathyroid hormone ($r = 0.807$, $p < 0.001$), phosphorus ($r = 0.473$, $p < 0.001$), total calcium ($r = -0.361$, $p = 0.002$), ionized calcium ($r = -0.305$, $p = 0.009$) and 25 (OH) vitamin D ($r = -0.332$, $p = 0.004$).
5. A mathematical model has been developed for predicting an increased FGF-23 value by the decision tree method using available parameters. The sensitivity of the model was 98%, the total percentage of correctly predicted values was 82.2 $\pm$ 4.5%.

**PRACTICAL RECOMMENDATIONS**

1. It is recommended to study the level of fibroblast growth factor 23 (FGF-23) in the blood serum by ELISA of all children with CKD despite its stages.
2. To predict a high level of FGF-23 in children with CKD, it is recommended to use our algorithm in the form of a decision tree.
3. Children with left ventricular hypertrophy are recommended to be regarded as a risk group for high levels of FGF-23, and, therefore, all associated disorders in the body.
4. If a high level of FGF-23 is detected by laboratory means or by prediction, the patient should be considered as a high-risk group for anemia, bone mineral disorders, as well as the activity of the cardiovascular system.