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Białko Klotho i FGF23 – znani gracze w procesie starzenia, lecz niedoceniani w procesie rozwoju osobniczego i w wybranych chorobach dzieciństwa i adolescencji. Przegląd systematyczny

The Klotho protein and FGF23 as well-known players in the aging process but underestimated in the process of individual development and selected diseases of childhood and adolescence – a systematic review

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Streszczenie

Wprowadzenie i cel: Oś FGF23–Klotho nie tylko uczestniczy w procesach związanych ze starzeniem się organizmu, ale także w szlakach metabolicznych istotnych dla patofizjologii niektórych schorzeń wieku dziecięcego. Celem badania było przeprowadzenie przeglądu systematycznego dostępnej literatury na temat roli Klotho i FGF23 w populacji dziecięcej. **Materiał i metody:** Używając wyszukiwarek PubMed i Web of Science, zastosowano następujące terminy wyszukiwania: (klotho) AND (children) oraz (FGF23) AND (children). Przestrzegano wytycznych PRISMA, przeprowadzono ocenę jakości włączonych do przeglądu badań. **Wyniki:** W przeglądzie systematycznym uwzględniono 66 artykułów na temat Klotho i FGF23 w populacji dziecięcej. Wyniki analizowanych badań wskazują, że stężenia Klotho i FGF23 są zmienione u dzieci z różnymi zaburzeniami metabolicznymi (cukrzyca, niewydolność nerek), a także zaburzeniami wzrostu i szkieletowymi (skolioza, niedobór hormonu wzrostu, anoreksja, krzywice hipofosfatemiczne). Stężenia tych białek zmieniają się wraz z leczeniem niektórych z tych schorzeń. Zaburzenia stężeń FGF23 i Klotho korelują z ryzykiem sercowo-naczyniowym u dzieci z niewydolnością nerek. Stężenia Klotho były znacznie niższe u wcześniaków. Obniżone stężenia Klotho stwierdzono u wcześniaków z dysplazją oskrzelowo-płucną, a w wyniku wczesnej suplementacji białkiem Klotho w modelach zwierzęcych obserwowano złagodzenie negatywnych zmian w tkance płucnej i poprawę funkcji serca. Niskie stężenia Klotho w okresie okołooperacyjnym są u dzieci czynnikiem ryzyka powikłań po operacjach kardiochirurgicznych. **Wnioski:** Klotho i FGF-23 to obiecujące wczesne markery wielu zaburzeń metabolicznych w populacji dziecięcej i mogą stanowić przydatne narzędzie do oceny prawdopodobieństwa wystąpienia powikłań. Suplementacja Klotho może stać się jedną z metod leczenia niektórych schorzeń wieku dziecięcego, podczas gdy przeciwciało anty-FGF23 jest już ugruntowanym lekiem w leczeniu hipofosfatemii związanej z chromosomem X.

Słowa kluczowe: dzieci, Klotho, FGF-23, pediatria

Abstract

Introduction and objective: The FGF23–Klotho endocrine axis plays a pivotal role not only in processes associated with aging but also in metabolic pathways, with implications for paediatric disorders. The aim of this study was to systematically review the existing literature on Klotho and FGF23 in the paediatric population. **Materials and methods:** Based on the PubMed and Web of Science databases, we conducted a PRISMA-guided search using (klotho) AND (children); (FGF23) AND (children), adhering strictly to the PRISMA guidelines, and assessed evidence quality. **Results:** The systematic review included 66 studies. Altered Klotho and FGF23 serum levels were observed in paediatric metabolic conditions (chronic kidney disease, diabetes), cardiovascular, and growth and musculoskeletal disorders. In some of them, Klotho and FGF23 serum levels changed with disorder treatment. Elevated FGF23 and Klotho deficiency in renal failure adversely impacted the cardiovascular system.

Lower Klotho levels were found in preterm neonates, especially with bronchopulmonary dysplasia. Early Klotho supplementation in a bronchopulmonary dysplasia model mitigated lung tissue changes and improved the cardiac function. Children with lower Klotho levels undergoing cardiac surgeries faced a higher risk of postoperative complications, especially acute kidney injury. In X-linked hypophosphataemia, excess FGF23 led to musculoskeletal consequences. FGF23 serum levels aided the diagnosis of hypophosphataemic rickets, and anti-FGF23 antibody emerged as a common X-linked hypophosphataemia treatment. **Conclusions:** Klotho and FGF23 serve as promising early markers for paediatric metabolic disorders, offering a valuable tool for assessing complication risks. Klotho supplementation holds promise as a treatment method for specific paediatric disorders, while anti-FGF23 antibody is already established in X-linked hypophosphataemia treatment.

Keywords: children, Klotho, FGF-23, paediatrics

INTRODUCTION

There are a range of extremely dynamic and varied processes related to the development and formation of the human body from the beginning of foetal life until the end of adolescence. The normal course of these processes is determined by the interaction of various metabolic and signalling pathways. According to the most recent reports, the fibroblast growth factor-23 (FGF23)–Klotho endocrine axis, which is involved in the aging process, is also associated with the development, maturation and growth of the body from the earliest stages of life[1,2].
Klotho is a transmembrane and circulating protein whose expression is primarily observed in the kidneys, particularly in the distal tubules. To a lesser extent, it is also expressed in the endocrine organs, such as the parathyroid glands, testes, ovaries, adipose tissue, pituitary gland, and in the epithelial cells of the choroid plexus of the brain[3,4]. Secreted alpha-Klotho can be detected in the cerebrospinal fluid, blood, and urine[3,4]. Transmembrane Klotho acts as a co-receptor for FGF23[5–8], which is a potent phosphaturic factor and an inhibitor of vitamin D production in the kidneys[1,2]. FGF23 is mainly produced in bone cells. However, its expression also occurs in other organs, such as the brain, thymus, small intestine, heart, lung, liver, kidneys, thyroid, parathyroid glands, lymph nodes, skeletal muscle, spleen, skin, stomach, and testes[9]. The intact FGF23 assay enables the measurement of biologically active FGF23, while serum samples can also contain C-terminal fragments of FGF23, particularly in conditions characterised by excessive degradation of FGF23. In such cases, the ratio of intact FGF23 to C-terminal fragments (iFGF23:cFGF23) may provide valuable insights[10]. Circulating alpha-Klotho has an additional positive pleiotropic effect on the human body at the cellular level by inhibiting oxidative stress and free radical damage[11,12]. The discovery of the Klotho gene in 1997 initiated intensive research on the effect of the Klotho protein on the rate of aging of the human body (Fig. 1)[5,13–15]. At the same time, studies were conducted on the role of FGF23 in the processes for which the transmembrane form of Klotho is a co-receptor[6–8]. Over the past 25 years, the involvement of these proteins in calcium-phosphate metabolism, regulation of growth hormone and insulin secretion, and IGF-1-mediated pathways has been described in detail (Fig. 2)[14,16,17]. All these biological pathways affect not only the aging process but also the processes of growth and development of young organisms. Unfortunately, the number of studies on the roles of the Klotho protein and FGF23 in the paediatric population is limited. Therefore, the aim of our study was to conduct a systematic review of the literature in this field in the populations of healthy and unhealthy children.

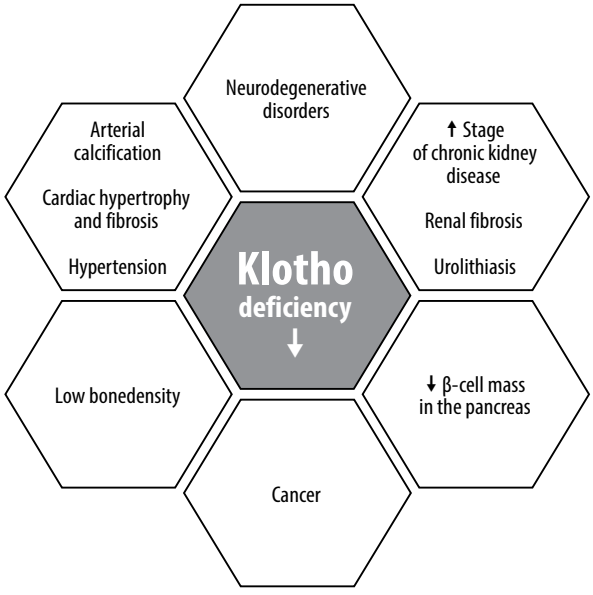

Fig. 1. Klotho deficiency is linked to many age-related diseases, including hyperphosphataemia, chronic kidney disease, cardiovascular conditions, neurodegenerative disorders, several types of cancer, low bone density, and reduced pancreatic β-cell mass in diabetes

MATERIALS AND METHODS

PubMed and Web of Science search engines were used for the systematic review. The following search terms were used: (klotho) AND (children); (FGF23) AND (children). No time restrictions were applied. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were strictly followed (http://www.prisma-statement.org/).

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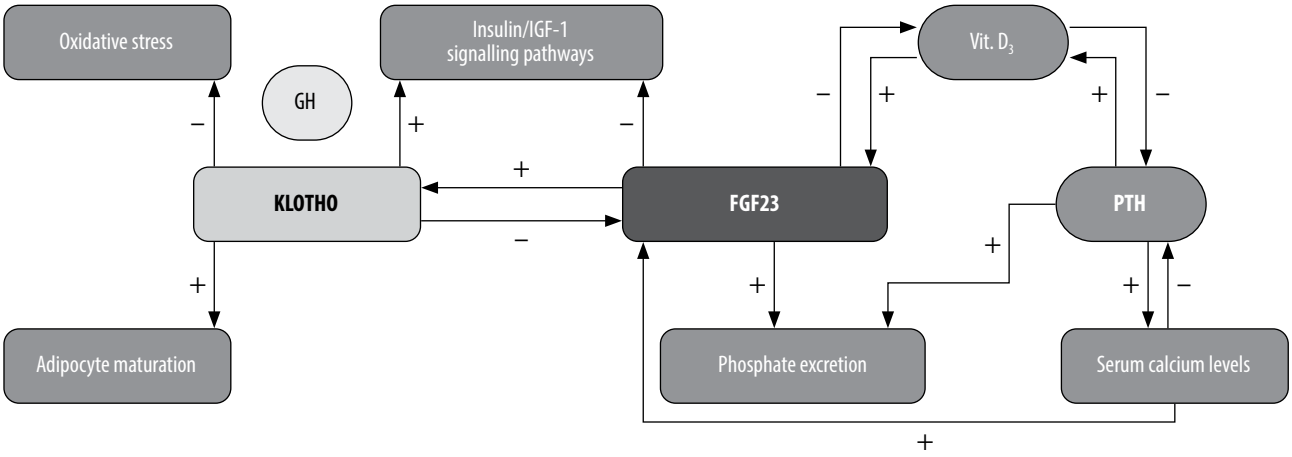

Fig. 2. Diagram depicting different actions and feedback loops involving Klotho and FGF23

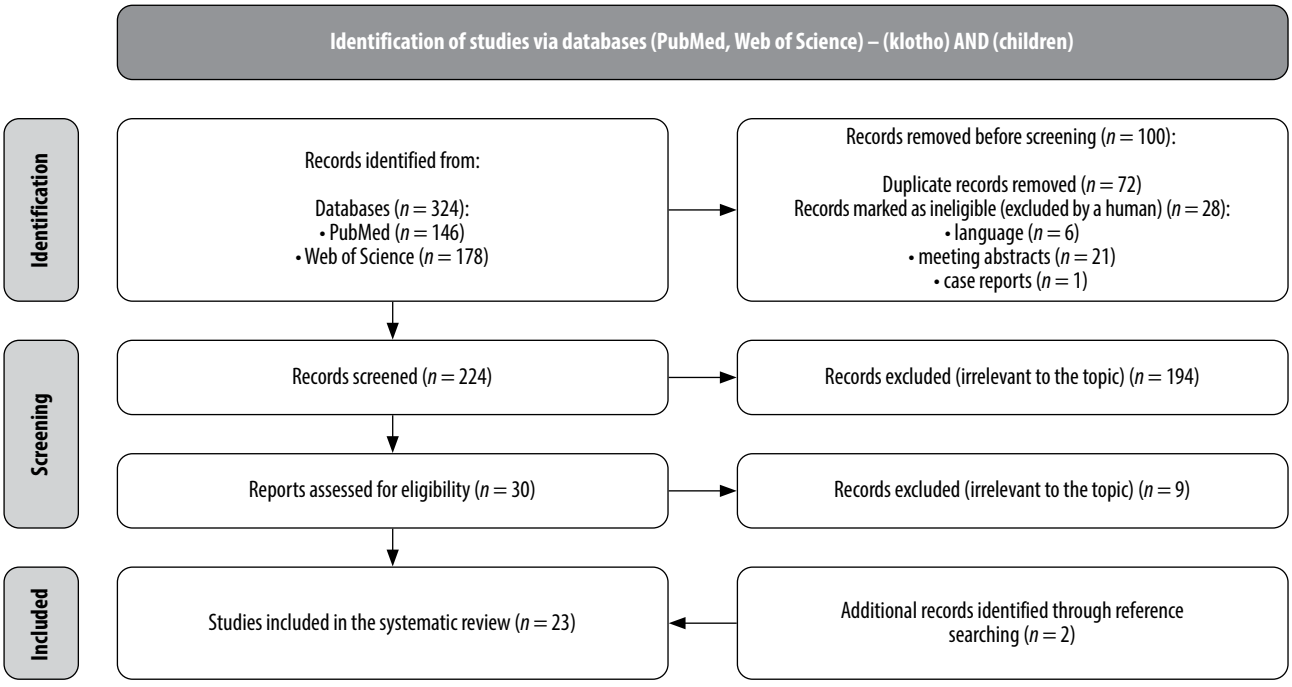

Fig. 3. PRISMA flow-chart showing the process of identifying and including papers in the systematic review; search terms: (klotho) AND (children)

The selection of papers for the systematic review was conducted independently by two members of the research team. Papers in languages other than English, reviews, meeting abstracts, case reports, and unrelated articles were excluded from the study. After an in-depth review of the identified articles, the papers that did not meet the inclusion criteria for the systematic review were rejected due to irrelevance to the topic. In case of disagreement among the investigators, the entire research team made the decision by consensus.

Finally, a total of 66 papers on alpha-Klotho and FGF23 proteins in the paediatric population were included in the systematic review (Figs. 3, 4). The quality of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach and rating scheme modified from the Oxford Centre for Evidence-based Medicine (Tab. 1). Based on the selected papers, a summary of the issues discussed was prepared.

RESULTS

Involvement of the FGF23–Klotho endocrine axis in the development and growth of the child's body

Healthy children

In light of previous studies on the Klotho protein in adults, it could be assumed that Klotho protein serum concentrations should be significantly higher in healthy children

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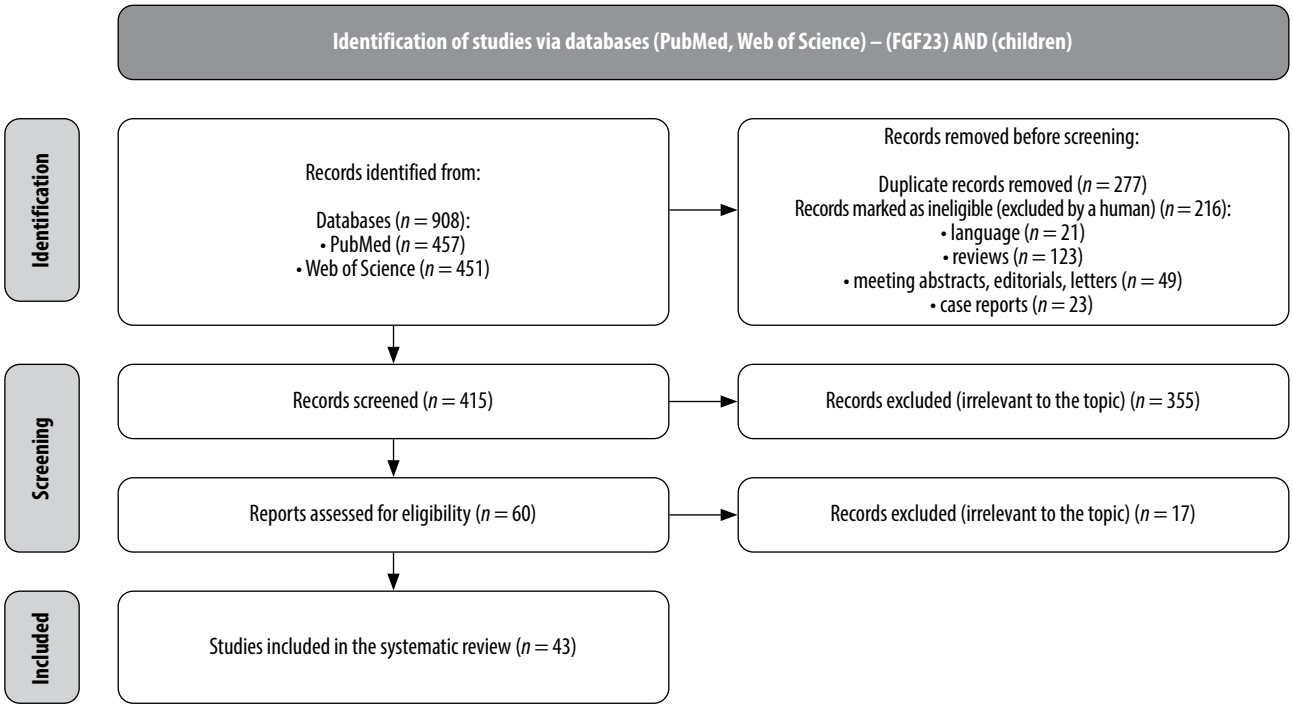

Fig. 4. PRISMA flow-chart showing the process of identifying and including papers in the systematic review; search terms: (FGF23) AND (children)

and decrease with age. However, data on alpha-Klotho and FGF23 serum concentrations in healthy children are limited. Only a few studies have been conducted on the subject, and their results are divergent. In their study on 39 patients, Yamazaki et al. showed that alpha-Klotho serum concentrations were significantly higher in children than in adults[18]. However, it is important to note that the observed differences in Klotho values between children and adults should be interpreted with caution due to the small size of the study group, which could have potentially affected the results. Another study, including 159 healthy children, showed no significant correlation between alpha-Klotho and FGF23 serum concentrations and the age of children. Significantly higher Klotho levels were observed in girls compared to boys, as well as in children during puberty compared to prepubertal children[9]. In both studies, high concentrations of alpha-Klotho and FGF23 correlated with phosphate and IGF-1 concentrations, which probably indicates an important role of Klotho in the growth process[9,18].

Currently, data on FGF23 age dependency is inconsistent overall. However, the study by Stanczyk et al. provides further support for the claim that the FGF23 serum level in the paediatric population is not age- or sex-dependent[19]. The study conducted exclusively on girls by Mitchell et al. further affirms these conclusions and demonstrates congruent results[20]. Conversely, the study by Holmlund-Suila et al. demonstrated that girls had higher serum levels of intact FGF23 compared to boys. However, C-terminal FGF23 did not vary between genders[21]. Further research is needed to clarify the disparity in serum concentrations of Klotho and FGF23 among healthy children, considering factors such as age, sex, and other potentially influential variables.

Growth hormone deficiency

Klotho and FGF23 are involved in calcium-phosphate metabolism, regulation of growth hormone and insulin secretion, and in IGF-1-mediated pathways[15,17,22,23]. They also directly affect adipocyte maturation[22–24]. These processes support normal growth and development of young organisms and the maintenance of the normal condition of bones, muscles, adipose tissue, and skin.

Studies on the paediatric population have shown that serum Klotho concentrations were significantly decreased in children with organic growth hormone deficiency (GHD) compared to children with idiopathic GHD and healthy children[25,26]. Of note, Klotho concentrations increased significantly in children after starting recombinant human growth hormone (rhGH) therapy[26,27]. By increasing serum phosphate concentrations after treatment initiation, the phosphaturic activity of the FGF23–Klotho axis also increased[27,28]. FGF23 rises during rhGH therapy, an anticipated observation given the role of FGF23 as a phosphaturic factor. GHD children have increased phosphate, associated with upregulation rather than with suppression of the phosphaturic FGF23[29]. Other authors did not find a direct correlation between Klotho and the growth hormone in children[30]. However, they all showed that decreased Klotho levels correlated with a low concentration of IGF-1, whose production in the liver is growth hormone-mediated. Therefore, according to researchers, Klotho could be a useful

Authors	Year	Country	Size of the study group	GRADE	Quality rating (1–5)*
Healthy children					
Yamazaki et al.	2010	Japan	39	Low	3
Gkentzi et al.	2014	Greece	159	Moderate	2
Holmlund-Suila et al.	2017	Finland	721	High	1
Mitchell et al.	2017	USA	90	Low	4
Stanczyk et al.	2021	Poland	121	Moderate	4
Growth hormone deficiency					
Wolf et al.	2014	Israel	99	Moderate	2
Guarnotta et al.	2022	Italy	58	Moderate	2
Efthymiadou et al.	2016	Greece	23	Moderate	2
Gardner et al.	2011	USA	23	Moderate	2
Meazza et al.	2017	Italy	20	Low	3
Delucchi et al.	2019	Chile	39	High	1
Belceanu et al.	2022	Romania	42	High	3
Hypophosphataemic rickets, bone mineral density, adolescent idiopathic scoliosis, anorexia nervosa					
El-Hodhod et al.	2012	Egypt	47	Moderate	3
Kubota et al.	2014	Japan	32	Moderate	2
Pekkinen et al.	2015	Finland + multi	183	Moderate	4
Wolf et al.	2016	Israel	19	Moderate	2
Brzęczek et al.	2019	Poland	35	Low	3
Imel et al.	2019	USA + multi	61	High	1
Giralt et al.	2021	Spain	18	Low	4
Batte et al.	2023	Uganda, USA	185	Moderate	2
Linglart et al.	2022	France + multi	52	High	1
Hartley et al.	2022	USA, Chile	434	High	2
Enlund-Cerullo et al.	2023	Finland, Sweden	622	High	1
Danielewicz et al.	2023	Poland	36	Low	4
Neonates (full-term and preterm)					
Ohata et al.	2011	Japan	23	Low	3
Siahanidou et al.	2012	Greece + multi	50	Moderate	2
Batlahally et al.	2020	USA	25 and animal model, cell culture	Moderate	3
Franklin et al.	2019	USA	54	Moderate	3
Askenazi et al.	2023	USA	20	Moderate	3
Central nervous system					
Kunert et al.	2017	Japan	39	Low	3
Bagińska et al.	2019	Poland	16	Low	2
Chronic kidney disease					
Cano et al.	2014	Chile, USA	31	Moderate	2
Portale et al.	2014	USA	464	High	2
Sinha et al.	2015	UK	83	Moderate	4
Portale et al.	2016	USA	419	High	2
Liu et al.	2017	Canada + multi	141	Low	4
Wan et al.	2013	UK	154	High	2
Leifheit-Nestler et al.	2016	Germany + multi	24	Moderate	3
Mitsnefes et al.	2018	USA	587	High	2
Gamrot et al.	2021	Poland	42	Moderate	2
Sawires et al.	2015	Egypt	124	High	2
Seifert et al.	2016	USA	31	Low	4
Tranæus Lindblad et al.	2018	Sweden	74	Moderate	2
Pukajło-Marczyk et al.	2019	Poland	70	Moderate	2
Okarska-Napierała et al.	2020	Poland	38	Low	2
Będzichowska et al.	2021	Poland	59	Moderate	2
Balmukhanova et al.	2020	Kazakhstan	73	Moderate	3
Palupi-Baroto et al.	2021	Indonesia	43	Low	4
Limm-Chan et al.	2021	USA	59	Low	4

Tab. 1. Characteristics of studies included in the review with quality assessment

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Authors	Year	Country	Size of the study group	GRADE	Quality rating (1–5)*
Singh et al.	2022	India	59	Low	4
Sharma et al.	2023	USA	29	Low	4
Karava et al.	2023	Greece	53	Moderate	4
Liu et al.	2023	China	21	Low	4
Kubota et al.	2023	Japan	24	Moderate	3
Primary hypertension, obesity					
Ali et al.	2014	USA	130	Moderate	4
Zając et al.	2015	Poland	42	Low	2
Lin et al.	2019	China	98	Moderate	4
Karampatsou et al.	2022	Greece	345	High	2
Type 1 diabetes					
Tarhani et al.	2020	Iran	46	Low	4
Zubkiewicz-Kucharska et al.	2021	Poland	80	Low	4
Cardiac surgery					
Isakova et al.	2013	USA	20	Low	4
Ali et al.	2013	USA	19	Moderate	3
Hanudel et al.	2016	USA	32	Moderate	2
Volovelsky et al.	2018	USA	83	Moderate	2
Pode Shakked et al.	2021	Israel	29	Moderate	2
Elzayat et al.	2023	Egypt	40	Low	4

* 1 – properly powered and conducted randomised clinical trial; systematic review with meta-analysis; 2 – well-designed controlled trial without randomisation; prospective comparative cohort trial; 3 – case-control study; retrospective cohort study; 4 – case series with or without intervention; cross-sectional study; 5 – opinion of respected authorities; case report.

Tab. 1. Characteristics of studies included in the review with quality assessment (cont.)

marker of IGF-1 activity in the body[30]. The association of FGF23 and Klotho with height and IGF1 could indicate complex interactions between both axes in promoting linear growth[29]. Remarkably, in a study involving kidney transplant recipients, glicocorticosteroid therapy was found to partially reduce longitudinal bone growth[31]. This occurs through the upregulation of FGF23 and FGFR3 expression. The findings suggest that targeting the FGF23–Klotho–FGFR3 axis at the growth plate could be a potential approach to manage growth impairments caused by glucocorticosteroid treatment in children[31]. Interestingly, normalisation of previously elevated Klotho and FGF23 concentrations was reported in adult patients with acromegaly after the removal of adenomas with excessive production of the growth hormone[32,33]. This finding confirms the close relationship between Klotho/FGF23 and growth hormone-mediated processes, which is of great interest for further studies.

Hypophosphataemic rickets

Hypophosphataemic rickets encompasses a range of rare disorders, including X-linked hypophosphataemia (XLH), vitamin D-deficient rickets (DR), and conditions associated with renal phosphate wasting such as Fanconi syndrome (FS)[34,35]. In XLH, excess FGF23 leads to hypophosphataemia and low calcitriol levels, resulting in musculoskeletal complications[34]. Treatment options for XLH include conventional oral phosphate with active vitamin D or burosumab, a monoclonal anti-FGF23 antibody approved for children and adults with XLH[34,36]. Clinical studies have demonstrated significant improvements in rickets severity, growth, and biochemical markers in children treated with burosumab compared to conventional therapy[36]. Measurement of serum FGF23 plays a critical role in diagnosing and distinguishing hypophosphataemic disorders[35]. Diagnostic cut-off levels for intact FGF23 (iFGF23) and C-terminal FGF23 (cFGF23) have been established to accurately differentiate between FGF23-mediated and FGF23-independent forms of hypophosphataemia[35,37]. Reliable serum FGF23 levels serve as a valuable marker in differentiating vitamin D-deficient rickets from hereditary hypophosphataemic rickets[38]. Additionally, FGF23 measurement aids in assessing the response to treatment in DR and guiding appropriate disease-specific therapies[38]. Overall, FGF23 plays a crucial role in the diagnosis, classification, and treatment of various hypophosphataemic disorders, providing valuable insights for personalised patient management.

Reduced bone mineral density

Multiple studies have shed light on the relationship between FGF23 and bone health in diverse populations. In a Finnish study focusing on healthy children and adolescents, FGF23 was found to be independently associated with total hip bone mineral density, which highlights its significance for skeletal health[39]. Another study from the same Finnish group, involving children aged 12 to 24 months, revealed that genetic variations in FGF23 had an impact on cFGF23 levels, phosphate metabolism, and bone strength[40].

Meanwhile, in paediatric inflammatory bowel disease (IBD), reduced bone mineral density has become a prominent concern. During flare-ups, patients with IBD exhibited

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significantly higher serum FGF23 levels compared to controls. Although there was improvement in FGF23 levels during remission, it did not reach the levels observed in the control group[41].

Furthermore, sickle cell anaemia (SCA) is also associated with mineral bone disorders. Increased FGF23, along with elevated osteopontin, was found to be linked to higher mortality rates in individuals with SCA. Additionally, FGF23 showed negative correlations with calcium and vitamin D levels, while displaying a positive correlation with parathyroid hormone levels[42].

Similar findings were reported in adolescent idiopathic scoliosis (AIS). The patients had low Klotho concentrations and high FGF23 levels, which correlated with abnormalities in other parameters of calcium-phosphate metabolism[43]. Brzęczek et al. found that not only the basic parameters of calcium-phosphate metabolism but also the Klotho-FGF23 axis could reflect impaired bone metabolism, thus affecting the development of scoliosis[43]. Study by Danielewicz et al. demonstrated normal phosphate-calcium and parathormone levels, but lower serum vitamin D levels and increased levels of FGF23 in AIS[44].

Anorexia is another disease in which the above metabolic pathways are disturbed and Klotho and FGF23 concentrations are abnormal[45]. Decreased bone density, atrophy of adipose tissue, and cachexia have also been reported. In patients in the acute phase of the disease, Klotho concentrations were significantly reduced, and they increased with hospitalisation, nutritional treatment, and regained body mass. Decreased Klotho concentrations correlated strongly with low bone mineral density and the formation of osteoporotic changes typical of patients with anorexia[45].

Prematurity and low birth weight

The group of neonates is interesting in terms of Klotho studies as, in general, circulating levels of soluble alpha-Klotho are markedly elevated in the human umbilical cord[46]. Innovative studies on Klotho and FGF23 have recently been performed on premature neonates[47–49]. The inspiration for conducting research in this group was the fact that the process of nephron formation can be significantly delayed in premature infants[47,50]. Nephrons are the main source of the Klotho protein and most of them are formed in the third trimester of pregnancy[50]. Therefore, nephrogenesis continues for several weeks after birth in premature infants[47]. In a study on 50 neonates (25 preterm, 25 full-term), Siahanidou et al. showed that circulating soluble alpha-Klotho concentrations were significantly lower in preterm compared to full-term neonates[47].

Acute kidney injury (AKI) is a prevalent condition with unfavourable clinical outcomes among premature neonates. The development and utilisation of urine biomarkers offer a promising approach to enhance our understanding and management of kidney disease in this population. Askenazi et al. demonstrated that extremely low gestational age newborns with early severe AKI had elevated concentrations of urine biomarkers, including cystatin C, creatinine, ghrelin, FGF23, tissue metalloproteinase 2 (TIMP2), and vascular endothelial growth factor A (VEGFa), compared to matched control subjects without AKI. This suggests that FGF23, a specific urine biomarker, may play a critical role in identifying and monitoring AKI in infants[51].

Another argument for further studies on Klotho and FGF23 in this group was the accelerated aging of lung tissue in premature infants diagnosed with bronchopulmonary dysplasia and pulmonary hypertension[49]. In the first studies on newborns, maternal serum levels of Klotho were examined. Intrauterine infections, smoking, and pre-eclampsia resulted in lower maternal serum Klotho concentrations, which caused decreased Klotho levels in the cord blood of the newborns[47,48]. Mothers of children with low Klotho concentrations in cord blood presented with increased histopathological changes suggestive of placental aging and vascular malperfusion, leading to intrauterine growth restriction[48].

In their innovative study, Batlahally et al. confirmed previous reports and showed that lower Klotho levels were found in cord blood in preterm infants with bronchopulmonary dysplasia with or without pulmonary hypertension[49]. More prolonged exposure to hyperoxia (14 or 21 days) significantly reduced lung Klotho gene and protein expression levels in an animal model of bronchopulmonary dysplasia (rat pups exposed to high oxygen concentrations)[49]. Early Klotho supplementation introduced to an animal model preserved lung alveolar and vascular structure, reduced pulmonary vascular remodelling and pulmonary fibrosis and improved cardiac function[49]. The *in vitro* study found that Klotho treatment of hyperoxia-exposed human pulmonary artery endothelial cells resulted in cell survival, proliferation and capillary tube formation[49]. These findings may support the thesis that Klotho deficiency in the perinatal period could increase the susceptibility to bronchopulmonary dysplasia in premature infants.

Furthermore, early Klotho supplementation could have a significant impact on distant outcomes in the youngest patients. Determining Klotho protein concentrations in other conditions that are complications of prematurity and result from tissue immaturity, such as necrotising enterocolitis (NEC), could be an interesting direction for further research. In this case, early Klotho supplementation could also have a positive effect on the proliferation of the intestinal vascular system and contribute to a less severe course of the disease.

Central nervous system

Studies conducted on adults have demonstrated a link between abnormal concentrations of Klotho and FGF23 and the development of neurodegenerative processes[52]. While these diseases are typically not associated with paediatric patients, investigating the effect of these proteins on the developing nervous system holds promise for research.

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Both soluble and transmembrane forms of Klotho and FGF23 have been found in the cerebrospinal fluid of children, indicating their potential impact on brain tissue[53]. Despite the low molecular weight of FGF23 and secreted Klotho, which enables their crossing of the blood–brain barrier, it has been shown that almost all of their synthesis occurs within the cerebrospinal fluid[53]. Notably, Klotho is predominantly produced by ependymal cells of the choroid plexus and hippocampal neurons in the brain[53]. Consequently, determining their influence on the central nervous system (CNS) and its functioning in diseases associated with elevated serum FGF23 levels, such as uraemia, presents a challenge. The roles of these proteins in CNS development and their effects on the CNS functioning in children, particularly in the context of disorders like myelomeningocele (MMC), have yet to be thoroughly examined. A prospective analysis conducted on 16 children with MMC has unveiled significant insights into the dysregulation of FGF23 in affected children, the potential of vitamin D replacement therapy in modulating FGF23 levels, and the common occurrence of vitamin D deficiency in these individuals[54]. It also suggests that the vitamin D requirements for children with MMC may differ from those for their healthy counterparts[54]. However, further studies are needed to elucidate the complex mechanisms underlying FGF23 regulation in MMC and to optimise management strategies for this paediatric patient population.

The role of the FGF23–Klotho axis in selected childhood metabolic and cardiovascular disorders

Chronic kidney disease

Most studies on FGF23 and Klotho in the paediatric population involved children with chronic kidney disease (CKD)[55–77]. Klotho deficiency in these patients was most likely caused by reduced active renal parenchyma and active nephrons[55]. Increasing FGF23 concentrations and decreasing Klotho levels with the progression of renal failure were found even in children with well-controlled phosphorus concentrations[56,62,66]. Due to the early increase in concentrations of these proteins and a progressive decline in eGFR even with normal serum phosphorus and parathyroid hormone values, these proteins could act as early and sensitive markers of renal failure[56,62,66]. Higher Klotho levels were found in younger patients with renal failure, and thus usually in those with a shorter disease duration. Klotho levels decreased with the disease duration, while FGF23 levels gradually increased[56]. FGF23 concentrations increased annually by an average of 5%, achieving even a sixfold increase in children with end-stage renal failure[56]. High serum FGF23 is an independent risk factor for CKD progression in children[63]. High FGF23 concentrations were accompanied by high calcium levels and vitamin D deficiency[56,64,66]. In turn, high Klotho concentrations were accompanied by normal vitamin D concentrations and low parathormone levels[56].

Significantly increased (20-fold) FGF23 concentrations and reduced (2.5-fold) Klotho concentrations were found in children treated with peritoneal dialysis[55]. High serum calcium levels were the strongest determinant of serum FGF23 concentrations, which can be clinically significant given the widespread use of calcium-containing phosphate-binding agents during dialysis[55]. Nevertheless, decreased Klotho levels in children with CKD were particularly evident in those on conservative treatment compared to those treated with dialysis[56]. Gradual improvement and normalisation of Klotho and FGF23 concentrations were found in patients after kidney transplantation[57,58,74]. Unfortunately, the process is long-lasting, and significant differences were observed compared to healthy children[57,58,74]. Klotho is now considered a promising marker of current graft function and graft survival[78]. The CKD–mineral bone disorder produces FGF-23 and related circulating pathogenic factors that are strongly associated with vascular injury and declining kidney function[75]. Similarly, chronic renal allograft injury (CRAI) is characterised by vascular injury and declining allograft function in transplant CKD. Higher FGF23 levels were found to be independently associated with biopsy-proven CRAI in 31 children[75]. Elevated FGF23 levels and Klotho deficiency in children with renal failure negatively affected the cardiovascular system, thus accelerating ventricular hypertrophy, atrial remodelling, and vascular calcification[56,59,61,65,68]. The mechanisms of this phenomenon are investigated in detail in animal models[79]. In these patients, abnormal Klotho and FGF23 levels were accompanied by abnormal values of the parameters indicating vascular stiffness, left ventricular hypertrophy, and decreased systolic function, which was related to a significant increase in cardiovascular risk despite their very young age[59–61,65,68]. However, there are two studies showing no correlation between FGF23 and cardiovascular parameters[67,69]. A retrospective case-control study on deceased patients with childhood-onset end-stage renal disease (ESRD) revealed enhanced expression levels of FGF23 and reduced Klotho in the myocardial autopsy samples of the left ventricle. These alterations were not observed in kidney transplant patients[76].

Studies investigating the role of FGF23 in anaemia among patients with CKD have consistently shown an inverse correlation between total FGF23 concentrations and haemoglobin levels[70]. This association remains significant even after adjusting for factors such as kidney function, iron parameters, erythropoietin (EPO), and inflammation[70]. The findings suggest that higher FGF23 levels are independently associated with prevalent and incident anaemia in both paediatric and adult CKD populations[70]. Iron deficiency and vitamin D deficiency may also contribute to increased FGF23 and anaemia in CKD patients[71].

In two separate studies, the significance of FGF23 levels in primary nephrotic syndrome (PNS) and its potential as an early marker to prevent progression to ESRD were examined[72,73]. In the study conducted by Liu et al., it was revealed that serum levels of FGF23 were significantly higher

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in both the PNS and ESRD groups compared to healthy controls[72]. Importantly, the study suggests that FGF23 may serve as a valuable tool for early detection of renal deterioration in PNS children, as its serum levels start to increase even before stage 1 CKD[72]. Furthermore, the other study on that topic confirmed those findings and indicated that FGF23 was significantly elevated in patients with glomerular hyperfiltration, suggesting its usefulness as a biomarker for the preclinical stage of renal disease[73]. Collectively, these findings highlight the potential of FGF23 as an early marker to identify renal disease progression, enabling timely interventions in PNS to prevent the development of ESRD[72,73]. Children with relapsing PNS treated with steroids have higher levels of sclerostin and FGF23, which can indicate a bone metabolism disorder[77].

Hypertension and obesity

Based on the findings of two studies, it has been observed that FGF23 may play a significant role in the development of primary hypertension in children and adolescents[80,81]. The first study, conducted by Zając et al., demonstrated that hypertensive individuals had higher levels of urine FGF23/creatinine compared to the reference group, with a positive correlation between urine FGF23/creatinine and systolic blood pressure. Additionally, FGF23 levels were found to correlate with various factors, such as serum calcium, serum 25(OH)D, urinary calcium, phosphorus, and magnesium, in hypertensive patients[80]. Similarly, the second study conducted by Lin et al. revealed that hypertensive children with abnormal cardiac geometry had elevated levels of FGF23 compared to those with normal cardiac geometry[81]. These findings emphasise the potential importance of FGF23 in the pathogenesis of primary hypertension in adolescents. However, further research is required to confirm the hypothesis and explore the possibility of reducing FGF23 levels to improve cardiac health in hypertensive children.

FGF23 plays a significant role in obese adolescents[82,83]. Based on the Ali et al. study, normotensive obese individuals exhibited higher levels of FGF23, which were associated with abnormal cardiac structure[82]. This suggests that FGF23 may serve as an early marker for cardiac injury in otherwise healthy obese individuals[82]. In the other study, a comprehensive lifestyle intervention program for children and adolescents with excess weight and obesity resulted in a significant decrease in body mass index (BMI) and FGF23 levels[83]. This indicates that lifestyle modifications can have a positive impact on FGF23 levels in obese individuals.

Type 1 diabetes

Another group of diseases in which Klotho and FGF23 play a special role comprises the disorders of carbohydrate metabolism, particularly diabetes[84,85]. Alpha-Klotho levels in children with type 1 diabetes were found to be significantly reduced compared to healthy children, which was especially evident in patients with poor glycaemic control, expressed as high glycated haemoglobin levels[84,85]. As opposed to renal failure, the duration of diabetes did not contribute to a decrease in Klotho levels, which may support the thesis that the loss of active nephrons is the main factor reducing Klotho production in the body[84,85]. Instead, it was found that in type 1 diabetes, decreased Klotho levels caused pancreatic beta-cell apoptosis[84].

Moreover, Klotho and FGF23 played an important role in maintaining glucose metabolism by suppressing insulin/IGF-1 signalling pathway and oxidative stress[84]. Abnormal Klotho concentrations also correlated with abnormal values of total cholesterol and its fractions[85]. Given these reports, gene therapy with the alpha-klotho gene carried in a viral vector could improve glucose tolerance, and inhibit pancreatic beta-cell apoptosis and the development of diabetic complications in these patients[84].

Congenital cardiovascular malformations

Cardiovascular malformations are the most common congenital defects in children[86]. They often require early surgical correction. In children undergoing such surgery with extracorporeal circulation, Klotho protein levels were assessed during the procedure[87]. Two hours after surgery, all children presented with a significant decrease in serum Klotho levels, which normalised about six hours postoperatively[87]. Children with low levels of Klotho in whom the return to normal values was longer were most at risk of developing postoperative complications, such as acute kidney injury, arrhythmia, atelectasis, pulmonary dysfunction, capillary leak syndrome, and seizures. None of the patients who developed complications required peritoneal dialysis or any other renal replacement therapy[87]. Several studies have further demonstrated that measuring FGF23 serum levels in children undergoing cardiac surgery can be a valuable tool for predicting the risk of postoperative complications, particularly acute kidney injury (AKI)[88–90]. In these studies, patients who developed AKI following cardiac surgery consistently exhibited elevated FGF23 serum levels both before and after the procedure[88–90]. It is important to consider that FGF23 may be generally elevated in patients with heart failure, particularly in association with diuretic use and the severity of heart failure[91,92].

Immune and coagulation disorders, generalised inflammatory response, and oxidative stress are the underlying pathophysiological basis of the complications of cardiac surgery with extracorporeal circulation[87]. In these patients, the pleiotropic effects of Klotho may have a protective function, and perioperative monitoring of Klotho levels could help identify children most at risk of developing postoperative complications in the future.

SUMMARY

The Klotho protein is not only a desirable "cure for old age", an endogenous protein slowing down the aging processes,

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but also an essential and still unrecognised factor in many processes involved in body development from the earliest stages. Thorough assessment of the roles of Klotho and FGF23 in paediatric patients is of great importance. Monitoring serum levels of these proteins can be an early marker for detecting many metabolic abnormalities, such as diabetes, kidney failure, and growth hormone-related disorders. Determination of these proteins can also be useful for estimating the risk of developing various complications in chronically ill paediatric patients. Additionally, possible therapy with Klotho supplementation or gene therapy with the Klotho gene could be part of the treatment in patients with chronic metabolic diseases, renal failure, in premature newborns, and even in patients in the perioperative period. The therapeutic properties of Klotho supplementation are being investigated in ongoing experiments in animal models and cell cultures.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript. We have no financial or personal relationships that could influence the content or interpretation of the research presented herein. This study was conducted with utmost objectivity and adherence to ethical standards. We affirm that no funding sources or sponsors have influenced the design, data collection, analysis, or decision to publish this work. All authors have contributed fairly to the study and writing of this manuscript without any potential conflicts of interest.

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Author contributions

Original concept of study: AW, LHK, TK. Collection, recording and/or compilation of data: AW, PB. Analysis and interpretation of data: AW, PB, MP. Writing of manuscript: AW, LHK, MP. Critical review of manuscript: LHK, GK, TK. Final approval of manuscript: LHK, GK, MP, TK.

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