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Fibroblast Growth Factor-23 (FGF-23) in Chronic Hemodialysis children

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Abstract:Background: Fibroblast growth factors are polypeptide growth factors essential for developmental processes like differentiation, cell proliferation, and migration. They are secreted into circulation through paracrine or autocrine mechanisms. Fibroblast growth factor-23 (FGF23), a circulating phosphaturic factor, regulates inorganic phosphate homeostasis. It binds to FGF receptors, likely requiring klotho for cell surface interaction. FGF23's most significant effects are on the kidney and parathyroid gland. In patients with chronic kidney disease (CKD), circulating FGF-23 levels are progressively elevated to compensate for persistent phosphate retention. In End-stage renal disease (ESRD), FGF-23 cannot reduce serum phosphate levels, and abnormally high FGF-23 concentration may exert unwarranted effects, including left ventricular hypertrophy, faster CKD progression, and premature mortality. Few data are available on FGF-23 metabolism in CKD children. ESRD is a leading cause of death for up to 40-50% of patients, primarily due to cardiovascular disease. Altered calcium, phosphorus, parathyroid hormone (PTH), and vitamin D levels in ESRD cause bone-like metabolism and mineralization in the vascular tunica media. FGF-23 levels also start rising early in patients with chronic kidney disease, which is implicated in cardiovascular and overall mortality of hemodialysis patients

Keywords:*Fibroblast Growth Factor-23, Hemodialysis, children*

Introduction

CKD is defined as an abnormality of kidney function, as determined by laboratory tests, urinalysis, or imaging tests, which have been present for at least 3 months. CKD has replaced “chronic renal failure” and “chronic renal insufficiency” as the globally accepted terminology for persistent renal dysfunction. This term, along with the CKD staging system, highlights the fact that there is a wide range in the magnitude of renal dysfunction, which occurs on a continuum **(1)**.

CKD is underdiagnosed and underreported worldwide, partly due to the asymptomatic nature of the disease. As a result, its prevalence may be underestimated. There exist geographical variations in the epidemiology of CKD, but no region of the world is untouched. The data from various national registries are limited. The epidemiological data from the "ItalKid Project," a prospective population-based registry, reported an incidence of CKD of 12.1 cases per million and a prevalence of 74.7 cases per million age-related population. Based on data from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) chronic renal insufficiency (CRI) database, 7,000 patients aged 2–17 years with an estimated GFR (eGFR) of less than 75 ml/min per 1.73 m^2 (1994–2008) have been entered into this voluntary registry**(2)**.

When GFR declines to less than 30 ml/min/1.73 m2, renal replacement therapy should be initiated with the child and family. Possible therapies include hemodialysis (HD), peritoneal dialysis (PD), and transplantation. A multidisciplinary team, including paediatric nephrologists, dieticians, psychologists, social workers, and transplant surgeons, is involved in the preparation process **(3)**.

PD is often preferred for younger children, as it can be performed at home without disrupting school attendance. However, parents may learn to manage medical interventions, which can lead to parental burnout. HD in children is typically performed in a paediatric nephrology center, but a nocturnal hemodialysis approach has little experience. Newer forms of dialysis are still under scrutiny in adults **(3)**.

Renal transplantation (RT) is the best management for children with stage 5 CKD, as it offers superior survival and reduced mortality compared to dialysis. Pre-emptive transplantation improves growth and development, while cadaveric transplant waiting lists are prioritized. Newer forms of transplantation, such as nonheart-beating donors and paired kidney exchange, are being used to increase the kidney donor pool. Living-related (LRD) transplantation provides shorter waiting times, convenience, and improved graft survival compared to cadaveric transplants **(4)**.

HD is a method used to purify blood for patients with acute or chronic renal failure by removing uremic toxins and providing buffer and electrolytes through a semipermeable membrane, developed in 1945, it has evolved to remove middle, protein-bound, and small water-soluble molecules. Purification of dialysis fluid is crucial to prevent contamination with endotoxin and bacterial DNA fragments **(5, 6).**

Classification of Dialysis Membranes

Dialysis membranes can be classified based on:

1) **Water flux or water permeability**: the flux of the dialyzer is defined by its ultrafiltration coefficient (Kuf). Clinically, the flux of the dialysis membrane is more frequently defined by its ability to remove middle molecules (often using β2-microglobulin as the marker). Low-flux dialyzers have small pores, which severely restrict the transport of β2-microglobulin; while high-flux dialyzers permit the transport of β2- microglobulin to various extents. Modified cellulosic membranes and synthetic membranes can both, either high-flux or low-flux dialyzers **(6).** This classification helps determine the suitability of dialyzers for different renal replacement therapy treatment modes. Water flux, expressed as the ultrafiltration coefficient KUF, is derived from in vitro tests and correlates with surface area. However, KUF and permeability for larger proteins may not necessarily correlate, depending on the membrane's pore morphology **(7, 8).**

Table 1 Classification of dialyzers based on dialysis membrane permeability **(9)**.

	Low-flux	**Mid-flux**	**High-flux**	**Super-flux (Protein-leaking)**
Ultrafiltration coefficient (K_{UF}) (ml/h/mm Hg)	<10	10–20	>20	>20
Instantaneous β_2-microglobulin plasma clearance (ml/min)	<10	10–20	>20	>20
Albumin loss per 4 h treatment (g)	0	0	<2	>2
Suitable treatment modality	HD	HD (HDF)	HD, HF, HDF	HD

2) **Biocompatibility**: refers to the effects of a membrane on complement system activation and transient leukopenia in blood during dialysis treatment. Three classes of biocompatibility can be defined according to the chemical composition of the dialysis membranes **(8):**
    - *Bioincompatible unsubstituted cellulose membranes:* the most commonly used polymer for dialysis membranes until the 1990s. However, unsubstituted cellulose membranes are impermeable for larger substances, only allowing small molecules like vitamin B12 to pass. Due to bioincompatibility, the use of unsubstituted cellulose membranes has become unpopular, and production is likely to cease in the near future**(10).**
    - *More biocompatible substituted/modified cellulosic membranes:* offer improved biocompatibility and mechanical strength, eg Hemophan® and SMC® which are low-flux hydrophobic membranes, and Polyethylene glycol (PEG) which used to create larger pore membrane and reduce permeability, also there are Cellulose acetate membranes which vary in permeabilities and thickness, but are sensitive to pH changes and can cause severe patient injuries **(11).**
    - *Biocompatible synthetic dialysis membranes* :since the mid-1990s, synthetic membranes have been widely used in dialysis, Polysulfone and polyethersulfone are the most widely used, highly biocompatible membranes, while others include DIAPES®, Polyamix®, Helixone®, PUREMA® H, PMMA, and EVAL **(12).**

Some reports suggest that increasing biocompatibility improves patient outcomes, while others find no differences in morbidity and mortality. However, the production of bioincompatible unsubstituted cellulose dialysis membranes is approaching an end, potentially affecting substituted cellulose **(13).**

- **High flux or Low flux membranes??**

The quality of life is one of the most consistent and powerful predictors of mortality and hospitalization in hemodialysis patients. The use of high-flux membranes can improve the adequacy of dialysis. These membranes can remove middle and large-size molecules, such as ß2 microglobulin, which has been shown to lower complications attributed to b2 microglobulin-mediated amyloidosis such as carpal tunnel syndrome, dialysis-associated arthropathy, and mortality **(14).**

Compared with low-flux cellulose, intermittent hemodialysis with a high-flux synthetic membrane had beneficial effects on the outcome (mortality, sepsis, and renal function) (***15).***

High-flux dialysis was associated with improvements in reducing serum ß2 microglobulin, and advanced oxidation protein products, this supports the adequacy of high-flux membranes in achieving optimal dialysis ***(16).***

Synthetic high-flux dialyzers were associated with improvements in neutrophil functions and plasma lipolytic activities, compared with low-flux cellulosic membranes. In addition, high-flux dialyzers were associated with lower rates of amyloidosis and death, compared with low-flux dialyzers. Since high-flux dialysis is so much more efficient, it can allow a significant reduction in dialysis times, often by 25 percent ***(17).***

The high-flux membranes were associated with reducing erythropoietin resistance, which might be related to a reduction in the level of PTH among patients with renal disease. High-flux filters with large pore sizes are efficient in the removal of toxins with medium weight but may also be markedly decreased ***(18).***

High-flux dialyzers can improve a patient's quality of life by improving general health, physical and mental health, physical functioning, symptoms, kidney disease effects, and social support ***(19).***

- **Potential benefits of high flux dialysis are summarized in this table 2 (20):**

- Higher clearance of small solutes, such as urea, compared with conventional dialysis without increase in treatment time
- Reduced morbidity and hospital admissions
- Potentially higher patient survival rates
- Reduced complement activation
- Decreased inflammation
- Decreased protein catabolism
- Reduced hypersensitivity reactions to dialyzer
- Improved neutrophil and lymphocyte function
- Reduced infection
- Improved nutritional status
- Improve neuropathy

- **Disadvantages of High Flux Dialysis:**

The major possible disadvantage of high flux dialysis regards pyrogen reactions. These reactions, characterized by high temperatures in patients during dialysis treatments, are caused by small pieces of dead bacteria that can be found in the dialysate. Although these reactions are not dangerous, they are uncomfortable for patients and typically require short hospitalizations for observation. Some nephrologists feel that because high-flux dialyzers have larger pores, the bacterial particles can pass more easily into the patient's bloodstream and that patients on high-flux dialysis have more frequent pyrogen reactions.Rapid solute shifts can cause dialysis disequilibrium syndrome in patients with high blood urea nitrogen concentration, especially during initial treatment **(21).**

It is important to note that adequacy of dialysis must be maintained, some patients may not be able to greatly shorten dialysis times when switching from conventional to high flux dialysis. Because treatment dose is affected by the combination of dialyzer clearance and time spent on the treatment modality, strict adherence to the recommended guidelines for urea clearance is essential for short hemodialysis to be safe and effective **(22).**

Any reduction in treatment time must be counterbalanced by a proportionate increase in the dialyzer clearance of low molecular weight substances to prevent under delivery of dialysis. To achieve this, blood flow rates should be maintained at 350 to 450 mL/min to optimize dialyzer performance. In addition, up to 10% more clearance can be obtained by increasing dialysate flow from 500 to 800 mL/min **(23).**

Another requirement for successful short hemodialysis is sufficient removal of interdialytic weight gain (IDWG) without causing cardiovascular instability or patient discomfort. Rapid ultrafiltration rates (UFRs) can be associated with hypotension and hemodynamic instability, especially if the UFR exceeds the rate of vascular refilling. A Dialysis Outcomes and Practice Patterns (DOPP) study analysis showed that UFRs of greater than 10 mL/hr/kg were associated with a 9% increased mortality risk**(24).**

The removal of fluid over a short period of 2-5 hours increases the risk of hypotension, particularly in patients with poor cardiac function or autonomic neuropathy. Short treatment times have a greater impact on the margin of safety compared to long treatment times. High blood flow rates may also predispose patients to vascular access damage **(25).**

Patients at particular risk for hemodynamic complications include those with underlying cardiac disease—namely, cardiac ischemia, arrhythmias, systolic or diastolic dysfunction—as well as those with autonomic dysfunction and persistent excessive IDWG. Therefore, educating about intradialytic weight gain is essential when utilizing short hemodialysis. Short hemodialysis is attractive because it offers the potential for reduced labor costs as well as patient and staff convenience**(26).**

However, the same requirements for adequacy must apply to these shortened treatments as with conventional hemodialysis: to ensure effective solute removal and volume control without compromising patient well-being. At present, most studies evaluating the adverse effects of shortened dialysis time on morbidity and mortality are limited by confounding issues such as the delivery of inadequate dialysis; inconsistencies among membrane characteristics concerning efficiency, flux, and biocompatibility, as well as lack of long-term follow-up **(27).**

Structure of FGF23

Human FGF23, a 32-kDa glycoprotein, is mainly produced by osteocytes and osteoblasts. However, low levels of FGF23 messenger RNA have been detected in the brain, thymus, spleen, small intestine, heart, and testis. FGF23 production has also been noted in response to trauma in liver, kidney, and heart. Intact FGF23 is cleaved by an unknown protease into inactive amino-terminal and carboxy-terminal fragments. During maturation, FGF23 is glycosylated at several sites which protects it from proteolysis and facilitates its secretion **(28, 29).**

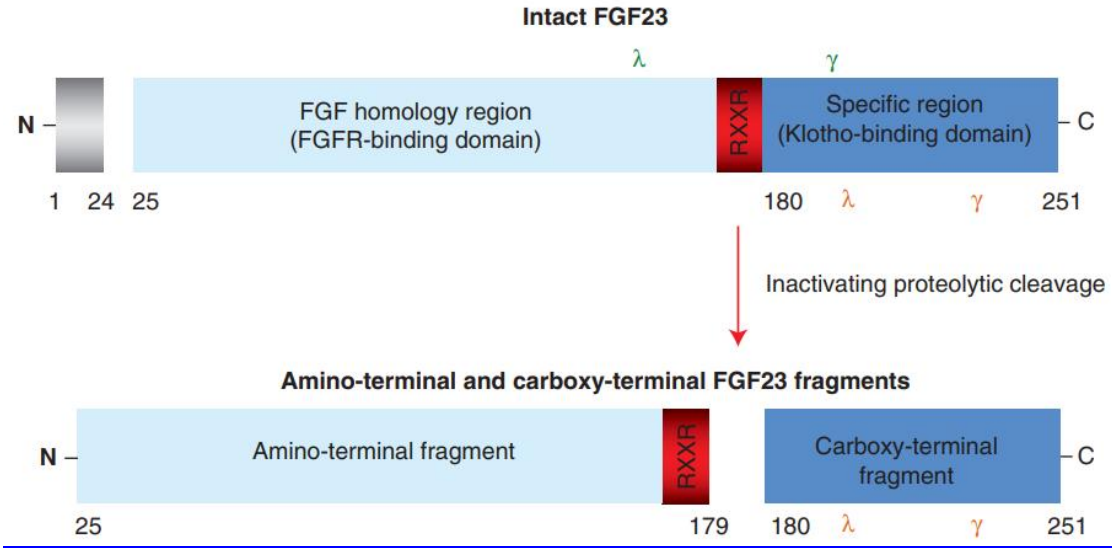


Figure 1. (Protein Structure of Fibroblast Growth Factor-23 (FGF-23)) **(30).**

FGF23 is a 32-kDa glycoprotein with 251 amino acid residues, including a signal sequence, amino-terminal FGF homology domain, and specific carboxy-terminal sequence. It can be secreted or cleaved into inactive fragments by a protease between aa 179 and 180 **(30).**

The plasma half-life of iFGF23 is estimated to be between 20 and 60 minutes, with rapid normalization after tumor removal. ELISA kits measure FGF23, with neutralizing antibodies showing αKlotho binding and FGFR binding **(31)**.

The FGF23 receptor, a homodimer of FGFR and αKlotho, regulates mineral ion homeostasis (phosphate and vitamin D) in kidney, parathyroid glands, osteoblasts, and osteocytes **(32, 33)**.

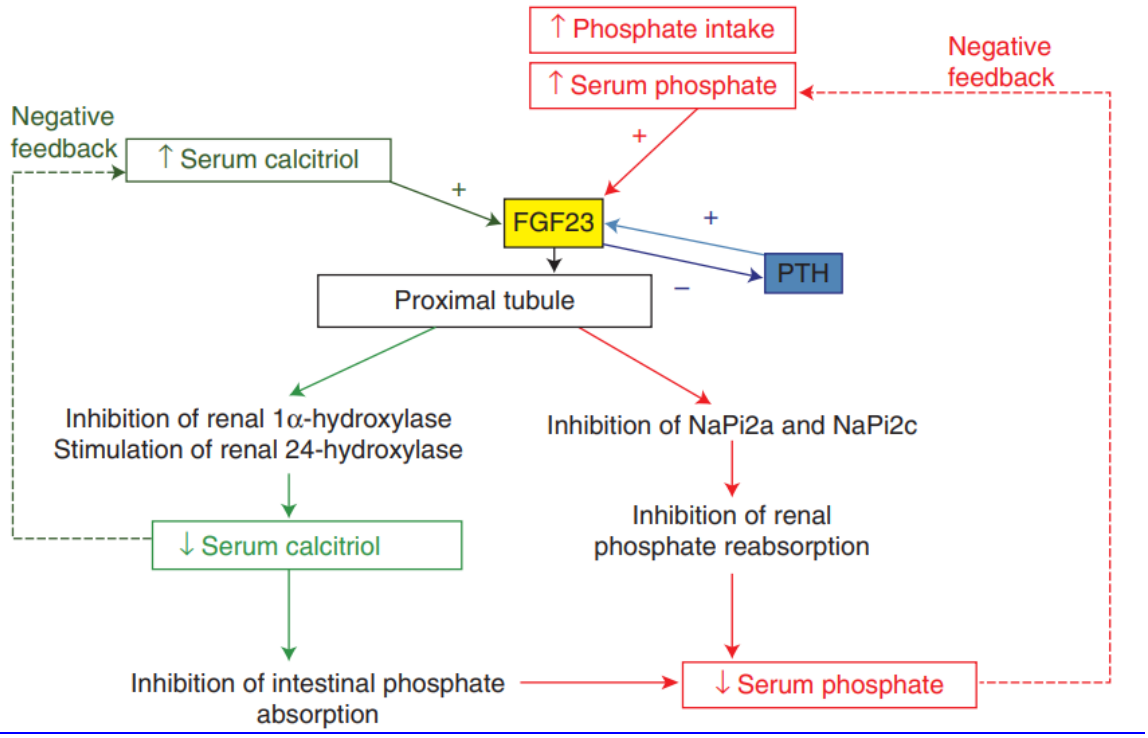
FGF23 Actions on the Kidney

FGF23 actions on the proximal tubule

The preservation of phosphate homeostasis is a complex interplay between bone, the gastrointestinal tract, and the kidneys and it is regulated by hormones including parathyroid hormone (PTH), 1, 25-hydroxy vitamin D, and FGF23. FGF23 acts on the renal proximal tubule to inhibit reabsorption and calcitriol production. FGF23 complexes with Klotho at FGFRs, which decreases proximal tubule expression of the

sodium phosphate, inducing phosphaturia. FGF23's phosphaturic action is mainly determined by the down-regulation of the apical membrane sodium phosphate **(34, 35).**

FGF23 decreases the conversion of 25-hydroxy vitamin D into its active form (1, 25-hydroxy vitamin D) in proximal tubular cells. It also increases catabolism of 1, 25-hydroxy vitamin D. These two effects lead to a decrease in circulating calcitriol levels and intestinal absorption of phosphate and calcium **(36, 37)**.



- **Figure 2.**(FGF23 actions on the proximal and the distal tubule)

FGF23 inhibits sodium/phosphate cotransporters, causing renal phosphate reabsorption. It stimulates renal 24-hydroxylase, reducing serum calcitriol and intestinal phosphate absorption. This leads to increased phosphate intake and FGF23 production. It also inhibits PTH synthesis and secretion, whereas PTH stimulates FGF23 production (**30)**.

FGF23 actions on the distal tubule

FGF23 increases calcium reabsorbtion, a process that correlates positively with serum calcium and negatively with urinary calcium/creatinine ratio in healthy individuals. FGF23 is therefore also a calcium conversing hormone. The parathyroid gland hyperplasia and the consequent increase in PTH secretion are responsible for hyperparathyroidism observed in ESRD, due to the incorrect control of PTH secretion, which occurs parallel to the parathyroid gland growth **(38).**

High levels of PTH directly inhibit the production of red blood cells and increase their fragility.Hyperparathyroidism can also cause bone marrow fibrosis, reducing the production of red blood cells. This is the explanation of reducing hemoglobin levels, anamia, in chronic kidney disease **(39).**

- **FGF-23 in Children With End Stage Renal Disease on Hemodialysis**

ESRD is a leading cause of death for up to 40-50% of patients, primarily due to cardiovascular disease. Altered calcium, phosphorus, parathyroid hormone, and vitamin D levels in ESRD cause bone-like metabolism and mineralization in the vascular tunica media. FGF-23 levels also start rising early in patients with chronic kidney disease, which is implicated in cardiovascular and overall mortality of hemodialysis patients **(40).**

In patients with CKD, circulating FGF-23 levels are progressively elevated to compensate for persistent phosphate retention. In late CKD, FGF-23 cannot reduce serum phosphate levels, and abnormally high FGF-23 concentration may exert unwarranted effects, including left ventricular hypertrophy, faster CKD progression, and premature mortality. Few data are available on FGF-23 metabolism in CKD children **(41)**.

Reduced renal function directly affects phosphorus reabsorption. The kidney becomes incapable of filtering enough phosphorus, and its high level in the blood directly stimulates the parathyroid gland, which in turn stimulates FGF-23 synthesis and secretion by the osteocytes. In ESRD, the kidney becomes no longer responsive to FGF-23 and reduces Klotho production by the kidney **(35)**.

High levels of FGF23 observed in CKD patients may contribute to the prevention of calcium loss, it is also involved in calcium regulation at the cellular level including atrial cells, which could be one of the explanations for the observation that higher FGF23 levels are associated with atrial fibrillation **(42, 43).**

FGF23 metabolism is influenced by iron deficiency and inflammation. Accelerated FGF23 production and cleavage during the acute phase of inflammation and iron deficiency increase the amount of cleaved C-terminal FGF23 compared with bioactive intact FGF23.The production and cleavage of FGF23 are diminished and seem to gradually stabilize during the chronic inflammatory phase, whereas levels of intact FGF23 become relatively increased compared with those in the acute phase **(44, 45).**

High FGF23 values, iron deficiency and inflammation are independently associated with increased mortality among patients with CKD. Thus, adequate management of FGF23 would help to improve the survival of such patients **(46, 47).**

- **The Effect of High Flux versus Low Flux Dialyzers on (FGF-23) Hemodialysis Children**

High-flux dialysis membranes are more permeable than low-flux membranes, allowing for the removal of larger molecules, including uremic toxins, which can improve dialysis therapy. This is particularly useful in complex cases like acute renal failure, multiorgan failure, and sepsis, where the removal of humoral mediators like proinflammatory cytokines, which are larger than 20,000 Da, can potentially modulate the course of the disease**(48).**

ESRD patients with altered calcium, phosphorus, PTH, and vitamin D levels are at higher risk of cardiovascular and overall mortality. High-flux dialyzers may be a potential treatment option for ESRD patients, as they may reduce the risk of cardiovascular and overall mortality **(49).**

Hypoalbuminemia is a common issue in patients with ESRD, which is caused by reduced synthesis and increased degradation of albumin. The altered albumin homeostasis in ESRD patients is linked to a systemic inflammatory state, which is closely related to mortality. The increase in serum albumin when using high-flux compared to low-flux dialyzer. This could be due to enhanced serum albumin and nutritional state with high-flux dialyzers, potentially due to improved dietary intake or removal of plasma substances that inhibit appetite. Leptin, a middle-sized uremic toxin, could be removed with high-flux dialyzer **(50).**

FGF-23 could represent a promising therapeutic target for improving the fatal prognosis of dialysis children with chronic renal failure in managing disordered phosphorus metabolism. Further research is needed to determine whether lowering FGF-23 levels improves outcomes in children on maintenance hemodialysis **(51).**

High flux dialysis better enhance removal of excess FGF23 than low flux dialysis, this cause better impact on regulation of inorganic phosphate homeostasis, PTH and other related substances with improvement of general health **(52, 53).**

References:

1. Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, Stevens PE, Caskey FJ, Farmer CK, Fuentes AF, Fukagawa M. Harmonizing acute and chronic kidney disease definition and classification: report of a

Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney international. 2021 Sep 1;100(3):516-26.

2. Wolf U, Ghadir H, Drewas L, Neef R. Underdiagnosed CKD in Geriatric Trauma Patients and Potent Prevention of Renal Impairment from Polypharmacy Risks through Individual Pharmacotherapy Management (IPM-III). Journal of Clinical Medicine. 2023 Jul 7;12(13):4545.
3. Zahr RS, Greenbaum LA, Schaefer F. The decision to initiate dialysis in children and adolescents. Pediatric Dialysis. 2021:115-29.
4. Stabouli S, Polderman N, Nelms CL, Paglialonga F, Oosterveld MJ, Greenbaum LA, Warady BA, Anderson C, Haffner D, Desloovere A, Qizalbash L. Assessment and management of obesity and metabolic syndrome in children with CKD stages 2–5 on dialysis and after kidney transplantation—clinical practice recommendations from the Pediatric Renal Nutrition Taskforce. Pediatric Nephrology. 2022 Jan;37(1):1-20.
5. Ragi N, Pallerla P, Babi Reddy Gari AR, Lingampelly SS, Ketavarapu V, Addipilli R, Chirra N, Kantevari S, Yadla M, Sripadi P. Assessment of uremic toxins in advanced chronic kidney disease patients on maintenance hemodialysis by LC-ESI-MS/MS. Metabolomics. 2023 Feb 24;19(3):14.
6. Lim JH, Park Y, Yook JM, Choi SY, Jung HY, Choi JY, Park SH, Kim CD, Kim YL, Cho JH. Randomized controlled trial of medium cut-off versus high-flux dialyzers on quality of life outcomes in maintenance hemodialysis patients. Scientific Reports. 2020 May 8;10(1):7780.
7. Eduok U, Abdelrasoul A, Shoker A, Doan H. Recent developments, current challenges and future perspectives on cellulosic hemodialysis membranes for highly efficient clearance of uremic toxins. Materials Today Communications. 2021 Jun 1;27:102183.
8. Sari FM, Aminah S. Effect of Ultra Filtration Rate (UFR) on Blood Sugar in Diabetes Mellitus Patients with Complications of Chronic Rental Failure Undergoing Hemodialysis. Jurnal Keperawatan Komprehensif (Comprehensive Nursing Journal). 2023 Jun 30;9(SpecialEdition).
9. Krieter DH, Wanner C. Membranes for dialysis and hemofiltration. Management of Acute Kidney Problems. 2010:491-505.
10. Kohlová M, Amorim CG, Araújo A, Santos-Silva A, Solich P, Montenegro MC. The biocompatibility and bioactivity of hemodialysis membranes: their impact in end-stage renal disease. Journal of Artificial Organs. 2019 Mar 15;22:14-28.
11. Patil D, Balivada S, Gorde S. Comprehensive Study of Cellulosic and Synthetic Membranes for Dialyzer. International Journal of Health Technology and Innovation. 2022 Dec 10;1(03):42-51.
12. Ran F, Nie S, Zhao W, Li J, Su B, Sun S, Zhao C. Biocompatibility of modified polyethersulfone membranes by blending an amphiphilic triblock co-polymer of poly (vinyl pyrrolidone)–b-poly (methyl methacrylate)–b-poly (vinyl pyrrolidone). Acta Biomaterialia. 2011 Sep 1;7(9):3370-81.
13. Krane V, Krieter DH, Olschewski M, März W, Mann JF, Ritz E, Wanner C, German Diabetes and Dialysis Study Investigators. Dialyzer membrane characteristics and outcome of patients with type 2 diabetes on maintenance hemodialysis. American journal of kidney diseases. 2007 Feb 1;49(2):267-75.
14. Yu S, Yang H, Chen W, Yuan H, Xiong X, Fu P et al. Middle-size molecule clearance as measured by β2-microglobulin in high-flux versus low-flux dialysis and hemodiafiltration: A prospective randomized controlled trial. Artificial Organs. 2023 Jan;47(1):38-46.
15. Raharjo Y, Zainol Abidin MN, Ismail AF, Fahmi MZ, Saiful, Elma M, Santoso D, Haula' H, Habibi AR. Dialysis membranes for acute kidney injury. Membranes. 2022 Mar 15;12(3):325.
16. Brunati CC, Gervasi F, Cabibbe M, Ravera F, Menegotto A, Querques M et al. Single session and weekly beta 2-microglobulin removal with different dialytic procedures: comparison between high-flux standard bicarbonate hemodialysis, post-dilution hemodiafiltration, short frequent hemodialysis with nxstage technology and automated peritoneal dialysis. Blood Purification. 2019 May 3;48(1):86-96.
17. Kanda E, Muenz D, Bieber B, Cases A, Locatelli F, Port FK, Pecoits-Filho R, Robinson BM, Perl J. Beta-2 microglobulin and all-cause mortality in the era of high-flux hemodialysis: results from the Dialysis Outcomes and Practice Patterns Study. Clinical kidney journal. 2021 May 1;14(5):1436-42.
18. Thammathiwat T, Tiranathanagul K, Limjariyakul M, Chariyavilaskul P, Takkavatakarn K, Susantitaphong P et al. Super high-flux hemodialysis provides comparable effectiveness with high-volume postdilution online hemodiafiltration in removing protein-bound and middle-molecule uremic toxins: A prospective cross-over randomized controlled trial. Therapeutic Apheresis and Dialysis. 2021 Feb;25(1):73-81.
19. Song W-J, Sohng K-Y. Effects of progressive resistance training on body composition, physical fitness and quality of life of patients on hemodialysis. J Korean Acad Nurs. 2012;42:947- 56.
20. Ambalavanan S, Rabetoy G, Cheung AK. High efficiency and high flux hemodialysis. Atlas of Diseases of the Kidney. 1999;5:1-0.
21. Shroff R, Hothi D, Symons J. Chronic Hemodialysis in Children. InPediatric Nephrology 2022 Sep 2 (pp. 1835-1868). Cham: Springer International Publishing.
22. Bharati J, Jha V. Achieving dialysis adequacy: A global perspective. InSeminars in Dialysis 2020 Nov (Vol. 33, No. 6, pp. 490-498).

23. Mohajerani F, Clark WR, Ronco C, Narsimhan V. Mass transport in high-flux hemodialysis: application of engineering principles to clinical prescription. Clinical Journal of the American Society of Nephrology: CJASN. 2022 May;17(5):749.

24. Lenggogeni DP, Malini H, Oktarina E, Chong MC, Sihombing PR. Post Hemodialysis Recovery Time Among End-stage Renal Disease'Patients Undergoing Hemodialysis. Malaysian Journal of Medicine & Health Sciences. 2022 Dec 2;18.

25. Kanbay M, Ertuglu LA, Afsar B, Ozdogan E, Siriopol D, Covic A, Basile C, Ortiz A. An update review of intradialytic hypotension: concept, risk factors, clinical implications and management. Clinical Kidney Journal. 2020 Dec;13(6):981-93.

26. Cheung AK, Levin NW, Greene T, Agodoa L, Bailey J, Beck G, Clark W, Levey AS, Leypoldt JK, Ornt DB, Rocco MV. Effects of high-flux hemodialysis on clinical outcomes: results of the HEMO study. Journal of the American Society of Nephrology. 2003 Dec 1;14(12):3251-63.

27. Abe M, Masakane I, Wada A, Nakai S, Nitta K, Nakamoto H. Super high-flux membrane dialyzers improve mortality in patients on hemodialysis: a 3-year nationwide cohort study. Clinical Kidney Journal. 2022 Mar;15(3):473-83.

28. Andrukhova O, Slavic S, Odörfer KI, Erben RG. Experimental myocardial infarction upregulates circulating fibroblast growth factor-23. Journal of bone and mineral research. 2015 Oct;30(10):1831-9.

29. Tagliabracci VS, Engel JL, Wiley SE, Xiao J, Gonzalez DJ, Nidumanda Appaiah H, Koller A, Nizet V, White KE, Dixon JE. Dynamic regulation of FGF23 by Fam20C phosphorylation, GalNAc-T3 glycosylation, and furin proteolysis. Proceedings of the National Academy of Sciences. 2014 Apr 15;111(15):5520-5.

30. Courbebaisse M, Lanske B. Biology of fibroblast growth factor 23: from physiology to pathology. Cold Spring Harbor Perspectives in Medicine. 2018 May;8(5).

31. Wolf M, White KE. Coupling FGF23 production and cleavage: iron deficiency, rickets and kidney disease. Current opinion in nephrology and hypertension. 2014 Jul;23(4):411.

32. Beenken A, Mohammadi M. The structural biology of the FGF19 subfamily. Endocrine FGFs and Klothos. 2012 Jan 1:1-24.

33. Nakatani T, Sarraj B, Ohnishi M, Densmore MJ, Taguchi T, Goetz R, Mohammadi M, Lanske B, Razzaque MS. In vivo genetic evidence for klotho-dependent, fibroblast growth factor 23 (Fgf23)-mediated regulation of systemic phosphate homeostasis. The FASEB Journal. 2009 Feb;23(2):433..

34. Tomoe Y, Segawa H, Shiozawa K, Kaneko I, Tominaga R, Hanabusa E, Aranami F, Furutani J, Kuwahara S, Tatsumi S, Matsumoto M. Phosphaturic action of fibroblast growth factor 23 in Npt2 null mice. American Journal of Physiology-Renal Physiology. 2010 Jun;298(6):F1341-50.

35. Andrukhova O, Zeitz U, Goetz R, Mohammadi M, Lanske B, Erben RG. FGF23 acts directly on renal proximal tubules to induce phosphaturia through activation of the ERK1/2–SGK1 signaling pathway. Bone. 2012 Sep 1;51(3):621-8.

36. Goetz R, Nakada Y, Hu MC, Kurosu H, Wang L, Nakatani T, Shi M, Eliseenkova AV, Razzaque MS, Moe OW, Kuro-o M. Isolated C-terminal tail of FGF23 alleviates hypophosphatemia by inhibiting FGF23-FGFR-Klotho complex formation. Proceedings of the National Academy of Sciences. 2010 Jan 5;107(1):407-12.

37. Razzaque MS, Sitara D, Taguchi T, St-Arnaud R, Lanske B. Premature aging-like phenotype in fibroblast growth factor 23 null mice is a vitamin D mediated process. The FASEB journal: official publication of the Federation of American Societies for Experimental Biology. 2006 Apr;20(6):720.

38. Sharaf IA, Helmy MH, Khalil ES, Badah MA. Assessment of Potential Role of Fibroblast Growth Factor 23 and Klotho Gene Polymorphism in Cardiovascular Calcification Associated with Chronic and End Stage Renal Diseases. Science Journal of Medicine and Clinical Trials. 2015;2015.

39. Ayuob NM, El-Said AM, Mohamed RR, El-deen AW. Clinical Relevance of Fibroblast Growth Factor-23 (Fgf-23) in Patients with End Stage Renal Diseases on Hemodialysis. Egyptian Journal of Medical Microbiology. 2014 Oct;23(4).

40. Anandh U, Mandavkar P, Das B, Rao S. Fibroblast growth factor-23 levels in maintenance hemodialysis patients in India. Indian journal of nephrology. 2017 Jan;27(1):9.

41. Mohamed EK, Al-Saeed A, Ahmed BK, Schaalan MF. Fibroblast Growth Factor 23 in Children With End Stage Renal Disease on Hemodialysis. Life Science Journal. 2012;9(2).

42. Koa YH, Chen YC, Lin YK et al. FGF-23 dysregulates calcium homeostasis and electrophysiological properties in HL-1 atrial cells. Eur J Clin Invest 2014; 44(8):795-801.

43. Nowak A, Friedrich B, Artunc F et al. Prognostic value and link to atrial fibrillation of soluble Klotho and FGF23 in hemodialysis patients. PLoS One 2014; 9(7):e100688.

44. Wolf M, White KE. Coupling FGF23 production and cleavage: iron deficiency, rickets and kidney disease. Current opinion in nephrology and hypertension. 2014 Jul;23(4):411.

45. David V, Martin A, Isakova T et al. Inflammation and functional iron deficiency regulate fibroblast growth factor 23 production. Kidney Int 2016; 89: 135–146.

46. Gutie´rrez OM, Mannstadt M, Isakova T et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. N Engl J Med 2008; 359: 584–592.

47. Munoz Mendoza J, Isakova T, Cai X et al. Inflammation and elevated levels of fibroblast growth factor 23 are independent risk factors for death in chronic kidney disease. Kidney Int 2017; 91: 711–719.
48. Sawires HK, Mohamed WA, Schaalan MF. High-flux and low-flux dialysis membranes and levels of intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in children with chronic kidney failure. Iranian journal of kidney diseases. 2012 Sep 1;6(5):366.
49. Geng X, Shi E, Wang S, Song Y. A comparative analysis of the efficacy and safety of paricalcitol versus other vitamin D receptor activators in patients undergoing hemodialysis: A systematic review and meta-analysis of 15 randomized controlled trials. Plos one. 2020 May 29;15(5):e0233705.
50. Ward RA, Beck W, Bernardo AA, Alves FC, Stenvinkel P, Lindholm B. Hypoalbuminemia: a price worth paying for improved dialytic removal of middle-molecular-weight uremic toxins?. Nephrology Dialysis Transplantation. 2019 Jun 1;34(6):901-7.
51. Raafat M, Madkour M, Metwaly A, Nasr FM, Mosbah O, El-Sheikh N. Clinical significance of FGF-23 in chronic kidney disease patients. Scholars Journal of Applied Medical Sciences. 2015;3:741-50.
52. Damasiewicz MJ, Lu ZX, Kerr PG, Polkinghorne KR. The stability and variability of serum and plasma fibroblast growth factor-23 levels in a haemodialysis cohort. BMC nephrology. 2018Dec; 19(1):1-7.
53. Bichari WA, Aabed MG, Abdelmobdy AH. The Effect of High Flux versus Low Flux Dialyzers on Serum Fibroblast Growth Factor-23 (FGF-23) and Its Cardiovascular Implications in Prevalent Hemodialysis Patients. The Egyptian Journal of Hospital Medicine. 2020; 79(1):481-8.