Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (9) Issue (7) (2024), (55- 60) **online: ISSN 2356–976x**
http://bjas.bu.edu.eg

Role of biomarkers in cardiac arrhythmia in children

Marwa M. Hegazy[1], Doaa R. Soliman[2], Eman G. Abd-El Rahman[2], Seham G. Ameen[3] and Ahmed N. El Shazly[2]
[1]Department of Pediatrics, Zagazig General Hospital
[2] Pediatrics Department, Faculty of Medicine, Banha University, Banha, Egypt
[3]Clinical and Chemical Pathology Department, Faculty of Medicine, Banha University, Banha, Egypt
E-mail: Marwahegazy417@gmail.com

Abstract

Background: The burden of pediatric cardiac arrhythmias is variable and can lead to morbidity and mortality. Many biomarkers are related to cardiovascular diseases. Fibroblast growth factor 23 (FGF-23) is an example for important biomarkers in arrhythmia. It is formed in bone and is related to mineral bone metabolism. Elevated levels of this factor were correlated with chronic renal disease and many cardiovascular diseases. Many studies correlated FGF-23 with arrhythmia particularly atrial fibrillation and revealed that it may be used as a prognostic biomarker in those patients. Knowledge of FGF-23 role in cardiovascular problems may be used to discover new methods in management of these disorders**.** Objective: The aim of this review is to shed light on pediatric cardiac arrhythmia and to study the importance of biomarkers in cardiovascular diseases particularly cardiac arrhythmia and study its relationship with prognosis and cardiac function.

Keywords: Fibroblast growth factor-23, Cardiac arrhythmia, Biomarkers, Atrial fibrillation.

Introduction

Cardiac arrhythmia in children occurs in about 55.1 out of every 100,000 visits to the pediatric emergency department (1). The most common type is sinus tachycardia, followed by supraventricular tachycardia (SVT) (2). Arrhythmia can worsen quality of life and cause stroke, heart failure, or even sudden cardiac arrest (3).

FGF-23 is mainly a bone-derived phosphaturic hormone that decreases 1, 25-dihydroxyvitamin D, aids in maintaining phosphate homeostasis. However, under stressful conditions, it can be produced by other tissues like the liver and heart (4). At first, it was connected to chronic kidney diseases but after that, it became related to other disorders including cardiovascular diseases (5). Its increased level was associated with cardiovascular conditions such as left ventricular enlargement, heart failure, cardiac dysfunction and arrhythmia (4). Many studies on animals found that FGF-23 can induce prolonged QT and ventricular arrhythmias (6). Numerous studies correlated high FGF-23 levels with atrial fibrillation (AF) (4). Knowledge of FGF-23 role in cardiovascular events can be used to provide new methods for management of these disorders (4).

1. Cardiac Arrhythmia

Cardiac arrhythmia is defined by any deviation from the normal pattern of myocardial activation. They can be classified according to their rate (tachycardia, bradycardia), mechanism (automaticity, re-entry, triggered) or site of origin. (3) The most frequently reported arrhythmia in pediatric age group is sinus tachycardia 50% then supraventricular tachycardia (SVT) 13%, bradycardia 6% and atrial fibrillation 4.6% (2).

- **Etiology**

Primary arrhythmias occur without underlying structural heart disease. Most of them are due to cardiac ion channelopathies caused by gene mutations (7). Secondary arrhythmia may be due to congenital cardiac anomalies, surgical repair, exposure to prolonged circulatory stress, electrolyte disturbance and acid-base imbalance (8)

- **Mechanisms of Arrhythmia**

A) Abnormal impulse formation

A.1) Abnormal Automaticity: Enhanced automaticity can speed up the discharge of action potentials by increasing the threshold potential, increasing the rate of phase 4 depolarization, and decreasing the maximum diastolic potential. While protected pacemaker (parasystole) occurs when the dominant pacemaker is surrounded by damaged tissues (infarcted or ischemic) that prevent action potentials from reaching the latent pacemaker (9).

A.2) **Triggered activity:** It happens as a result of one or more previous action potentials triggering afterdepolarizations that prematurely stimulate cardiac tissues. It is subdivided into early afterdepolarizations (EADs) in phase 2 or 3 of AP and delayed afterdepolarizations (DADs) in phase 4 of AP. (10).

B) Reentry:

B.1) Reentry involving an obstacle (circus-type): This happens when an action potential (AP) bypasses anatomical or functional obstacle and restimulate its original point (11).

B.2) Reentry not involving an obstacle: It may be reflection which explains the impulse that travels through the same pathway in both directions in a linear segment of tissue. (12). While phase 2 reentry results from a severe regional heterogeneity of repolarization,

and characterized by the loss of the spike-and-dome arrangement of AP characters at one site while it is preserved at another leading to reentry in APs without the dome (9).

- **Classification and Prevalence of Arrhythmia**

Tachyarrhythmias: There are 2 main categories;

A.1) Narrow QRS complex tachycardia (supraventricular tachycardia):

It means any fast heart rate greater than the normal value for age with a rapid ventricular depolarization represented by a QRS duration less than 120 milliseconds (ms) and begins above or at the bundle of His (13). It includes the following subtypes;

- **Atrioventricular re-entry tachycardia (AVRT):** It is the most popular SVT type in infancy. It resolves on its own by the end of infancy, however there may be late recurrences in 30% of children at the age of 7-8 years (14).
- **Atrioventricular nodal reentry tachycardia (AVNRT):** It makes up only 13–24% of all pediatric cases. This incidence increases with advancing age (15) representing 4% of in infants, 23% in the 1–5y age range, 34% in the 6–10y age range, and 20% in people beyond the age of 10 (16).
- **Atrial flutter (AFl):** Lone AFL that does not have a primary cardiac illness, is rare in children and more common in the newborn stage. After this time, AFL is mostly observed in children with congenital cardiac abnormalities, particularly following atrial cardiac surgery, or in cases of systemic illness accompanied by an immature heart conduction system (17).
- **Atrial fibrillation (AF):** It is very rare in infants and children but more common in adolescents, children with underlying structural heart disease and those who have had cardiac operation (18).
- **Sinus tachycardia:** It refers to a suitable rise in sinus rate above the normal range for age in response to a number of physiological, pathological, and/or pharmacologic triggers. A sustained elevation in the heart rate at rest that is not consistent with the degree of trigger is known as inappropriate sinus tachycardia (19).
- **Ectopic/ Focal atrial tachycardia:** It represents 11%-16% of SVTs in children and brought on by an aberrant, nonsinus atrial focus or foci with increased automaticity (14).

A.2) Wide QRS complex tachycardia:

It is characterised by a heart rhythm with a rate and QRS complex duration greater than the age-related measures (20). **It includes;**

- **Ventricular Arrhythmia:** It means a tachycardia emerging below the bundle of His (21). and subdivided into:
  - ***Premature ventricular Contractions (PVCs):*** PVCs are thought to be commonly seen in children with a variable incidence according to the age group. About 40% of children had PVCs visible on ECG and/or 24-hour ECG Holter monitoring. Isolated PVCs are found in 10-15% of newborns with anatomically normal hearts but fortunately are typically go away in the first three years of life. Conversely, 20–35% of healthy teenagers still have PVCs (22).
  - ***Ventricular tachycardia (VT):*** It refers to three or more consecutive beats (PVCs), at a rate more than 120 bpm or 20%–25% quicker than the baseline sinus rhythm. It is less prevalent having a pediatric occurance rate of 1/100000 (14).
  - ***Ventricular fibrillation (VF):*** VF-related cardiac arrest is uncommon in children, accounting for less than 10% of all pediatric out-of-hospital arrests (23).
- **Long QT syndrome (LQTS**): It is characterized by a disturbance in cardiac repolarization that results in a longer QT interval and irregular T waves with high probability of causing dangerous ventricular arrhythmias particularly torsades de pointes and cardiac arrest. It may be congenital or acquired (24). Congenital LQTS may occur in 1 /(2000- 2,500) of people and in untreated instances, There is a 20% chance of death after one year, but nearly 53% after fifteen. (14). Acquired LQTS is more common as frequent as 30% of intensive care units patients according to some studies (25).

A) **Bradyarrhythmias:** There are 2 main categories;

- **Sinus bradycardia and sinus node dysfunction:** Sinus bradycardia is a cardiac rhythm in which the sinus node initiates inadequate depolarization, resulting in a heartbeat of less than the normal values for age (26), while sick sinus syndrome results in a collection of aberrant rhythms due to pacemaker dysfunction and inappropriate impulse transmission (27).
- **AV conduction problems (heart block):** First-degree heart block denotes an expanding PR interval without loss of conduction and does not result in bradycardia or hemodynamic disturbances (28). Second-degree heart block means intermittent impairment of AV node conduction and is subdivided into Mobitz type I and II (29).

Third-degree AV block refers to a total loss of communication between the atria and ventricles, making the SA node unable to regulate heart rhythm and potentially lowering cardiac output (30).

2. Fibroblast Growth Factor 23

➢ **Origin**

FGF23 is with FGF19 and FGF21 in the endocrine subgroup of fibroblast growth factors (FGFs) superfamily (31). The primary producers of FGF23 are osteoblasts and osteocytes. Low quantities of FGF-23 messenger RNA (mRNA) have been found in the heart, testis, thymus, and spleen, in addition to the synthesis of FGF-23 in response to liver, heart and kidney damage (32).

➢ **Structure and Cleavage**

FGF-23 is a 32-kDa glycoprotein containing a proteolytic site. It is encoded by a 9386 nucleotide gene with three exons and two introns located on chromosome 12p13 (32). This glycoprotein is formed of 251 amino acids. The first 24 amino acids of this glycoprotein are the signal sequence, followed by 155 amino acids that make up the core FGF homology area, and the final 72 amino acids make up the C-terminal which is crucial for binding to Klotho while the FGFR binding area is located at the N-terminus (33).

The intact FGF-23 (iFGF-23) can be broken intracellularly at locations 176 and 179 before being released, preventing the physiologically active substance from reaching the bloodstream (34). This occurs at the Golgi-apparatus by subtilisin-like proprotein convertases (SPCs) (furin) (35). This cleavage produces inactive specific carboxy-terminal (C-terminal) and amino-terminal (N-terminal) fragments (32). The half-life of the biologically active iFGF23 is (~45–60) min in humans (34).

➢ **Physiological Basis**

The FGFR family consists of 4 members (FGFRs 1-4) which are individually encoded but highly similar (36). FGF-23 binds to FGFR1 in the kidneys with the help of the cofactor protein Klotho. However in the heart, FGF-23 binds to FGFR4 without Klotho's assistance.

(4). Interestingly, α Klotho can increase the binding affinity of FGF-23 to FGF receptor-1c (FGFR1c) by a factor of about 20. This FGFR1c is likely the most significant FGFR among the four FGFRs at least under physiological circumstances (37).

➢ **Functions of FGF-23**

- **FGF23 actions in the kidney:** FGF-23's primary function in the kidney is to down-regulate phosphate reabsorption and 1,25-dihydroxy vitamin D (1,25(OH)2D) synthesis in proximal renal tubules (37), in addition to stimulation of calcium and sodium uptake in distal renal tubules (38). Also, it can suppress angiotensin converting enzyme 2 transcription in the kidney (39).
- **FGF23 actions in bone:** The physiologically significant effects of FGF-23 in bone are related to downregulation of bone mineralization and Erythropoiesis (37).
- **FGF23 actions in parathyroid glands:** Many studies supposed that FGF-23 may have a significant physiological role in maintaining appropriate PTH signaling response in the kidney and bone (37).

➢ **Regulation of FGF23**

FGF23 is complexly regulated physiologically during the stages of gene expression, splitting, post-translational adjustments, and cellular discharge.

Additionally, Changes in α-Klotho quantity, inhibiting competition by FGF23-fragments, and changes in FGF receptor expression all affect the dynamic sensitivity of the receptor, which in turn affects the distant biological effect. The mechanism that controls FGF-23 metabolism involves a complex interaction involving local regulators, the hormonal system, minerals, and calciprotein particles that act in an autocrine or paracrine manner (35).

➢ **Significance of FGF-23 in Cardiovascular system**

At first there was a correlation between elevated plasma concentration of FGF-23 and cardiovascular complications of chronic kidney disease (CKD) in both dialysis and non-dialysis cases (40), (41). After that, FGF-23 moved beyond the nephrology to cardiology community because this correlation was also visible in patients with cardiac diseases without underlying renal impairment (42). Then it shifted from association to causality of cardiovascular diseases, specifically cardiomyopathy. The prognostic impact of FGF-23 on cardiovascular mortality has been explained by a number of theories, including the involvement of elevated FGF-23 in inflammation, stimulation of the renin-angiotensin system, endothelial dysfunction, vascular calcification, and left-ventricular hypertrophy (39).

- **FGF-23 and left ventricular hypertrophy (LVH):** FGF-23 has a cellular hypertrophic impact by increasing pro-hypertrophic genes, and it can cause cardiac fibrosis through the activation of β-catenin (4).
- **FGF-23 and heart Failure (HF):** Serum not intracardiac FGF-23 levels in HF patients were significantly greater than in healthy subjects (43). FGF-23 affects how calcium is handled by raising the phosphorylation of calmodulin kinase II (CaMKII) causing cardiomyocytes to exhibit contractile dysfunction (4).

- **FGF-23 and cardiac fibrosis:** FGF-23 can induce myocardial fibrosis via promoting β-catenin, a profibrotic factor that interacts with transforming growth factor-β1 (TGF-β1) signaling to induce fibroblasts chemotaxis and increase the production of fibronectin, collagen, and proteoglycans which mainly form the extracellular matrix (ECM) (4).

❖ **FGF-23 and Arrhythmia**

- **Mechanisms:**

FGF-23 in calcium handling: FGF-23 has acute arrhythmogenic effect on ventricular cardiomyocytes and chronic effect on atrial cells in addition to its effect on mice ventricular muscle strips. These findings revealed that FGF-23 can induce cellular arrhythmia and regulate the contraction and relaxation (4).

Fibrosis: Increased levels of FGF-23 contribute to both myocardial fibrosis and hypertrophy. Therefore, increased cardiomyocyte density, the development of fibrotic bands, and the disarray of muscle fibers make the myocardium more electrically unstable and make arrhythmias more likely to occur **(44).**

- **Types of Arrhythmia related to FGF-23**
  1) **QT Prolongation:** Recently, studies found that increased FGF23/FGFR4 signaling during CKD causes heart restructuring and lengthens QT (6).
  2) **Ventricular Arrhythmias:** FGF-23 injections resulted in ventricular arrhythmias such as PVCs or as transient bouts of ventricular tachycardia (45).
  3) **Atrial fibrillation (AF):** elevated levels of FGF-23 in plasma have been linked to AF in the overwhelming majority of clinical studies**. (45), (46), (4).**
- **FGF-23 and prognosis:** In a study on patients with acute heart failure episode, FGF-23 rose from admission to discharge, and patients with higher discharge FGF-23 had worse prognosis (47).

References

[1] Rohit, M., & Kasinadhuni, G. (2020). Management of Arrhythmias in Pediatric Emergency. Indian journal of pediatrics, 87(4), 295–304.

[2] Bobbo, M., Amoroso, S., Tamaro, G., Gesuete, V., D'agata Mottolese, B., Barbi, E., et al; (2019). Retrospective study showed that palpitations with tachycardia on admission to a paediatric emergency department were related to cardiac arrhythmias. Acta paediatrica (Oslo, Norway: 1992), 108(2), 328–332.

[3] Papadopoulos, C. H., Oikonomidis, D., Lazaris, E., & Nihoyannopoulos, P. (2018). Echocardiography and cardiac arrhythmias. Hellenic journal of cardiology: HJC = Hellenike kardiologike epitheorese, 59(3), 140–149.

[4] Vázquez-Sánchez, S., Poveda, J., Navarro-García, J. A., González-Lafuente, L., Rodríguez-Sánchez, E., Ruilope, L. M.; et al. (2021). An Overview of FGF-23 as a Novel Candidate Biomarker of Cardiovascular Risk. Frontiers in physiology, 12, 632260.

[5] Haffner, D., & Leifheit-Nestler, M. (2017). Extrarenal effects of FGF23. Pediatric nephrology (Berlin, Germany), 32(5), 753–765.

[6] Graves, J. M., Vallejo, J. A., Hamill, C. S., Wang, D., Ahuja, R., Patel, S., et al; (2021). Fibroblast growth factor 23 (FGF23) induces ventricular arrhythmias and prolongs QTc interval in mice in an FGF receptor 4-dependent manner. American journal of physiology. Heart and circulatory physiology, 320(6), H2283–H2294.

[7] Chockalingam, P., & Wilde, A. A. (2014).Inherited arrhythmia syndromes leading to sudden cardiac death in the young: a global update and an Indian perspective. Indian heart journal, 66 Suppl 1(Suppl 1), S49–S57.

[8] Brugada, J., Blom, N., Sarquella-Brugada, G., Blomstrom-Lundqvist, C., Deanfield, J., Janousek, J., et al; (2013). Pharmacological and non-pharmacological therapy for arrhythmias in the pediatric population: EHRA and AEPC-Arrhythmia Working Group joint consensus statement. Europace the European Society of Cardiology, 15(9), 1337–1382.

[9] Kistamás, K., Veress, R., Horváth, B., Bányász, T., Nánási, P. P., & Eisner, D. A.(2020). Calcium Handling Defects and Cardiac Arrhythmia Syndromes. Frontiers in pharmacology, 11, 72.

[10] Tsumoto, K., & Kurata, Y. (2022). Bifurcations and Proarrhythmic Behaviors in Cardiac Electrical Excitations. Biomolecules, 12(3), 459.

[11] Kaplan J, Kanwal A, Ahmed I, Lala V (2023). Reentrant Arrhythmias. In: StatPearls. Treasure Island (FL): StatPearls Publishing.

[12] Barrio-Lopez, T., Almendral, J. (2020). Mechanisms of Cardiac Arrhythmias. In: Martínez-Rubio, A., Tamargo, J., Dan, G. (eds) Antiarrhythmic Drugs. Current Cardiovascular Therapy. Springer, Cham.

[13] Shah, R. L., & Badhwar, N. (2020). Approach to narrow complex tachycardia: non-invasive guide to interpretation and management. Heart (British Cardiac Society), 106(10), 772–783

[14] Kafalı, H. C., & Ergül, Y. (2022). Common Supraventricular and Ventricular Arrhythmias in

Children. Turkish archives of pediatrics, 57(5), 476–488.
[15] Reddy, C. D., Silka, M. J., & Bar-Cohen, Y. (2015). A Comparison of AV Nodal Reentrant Tachycardia in Young Children and Adolescents: Electrophysiology, Ablation, and Outcomes. Pacing and clinical electrophysiology: 38(11), 1325–1332.
[16] Sekar R. P. (2008). Epidemiology of arrhythmias in children. Indian pacing and electrophysiology journal, 8(Suppl. 1), S8–S13.
[17] De Nigris, A., Arenella, M., Di Nardo, G., Marco, G. M. D., Mormile, A., Lauretta, D., et al; (2023). The diagnostic and therapeutic challenge of atrial flutter in children: a case report. Italian journal of pediatrics, 49(1), 137.
[18] Taylor, L. E., & Pflaumer, A. (2021). Review of atrial fibrillation for the general paediatrician. Journal of paediatrics and child health, 57(10), 1564–1571.
[19] Henning, A., & Krawiec, C. (2023). Sinus Tachycardia. In StatPearls. StatPearls Publishing.
[20] Katritsis, D. G., & Brugada, J. (2020). Differential Diagnosis of Wide QRS Tachycardias. Arrhythmia & electrophysiology review, 9(3), 155–160.
[21] Hanash, C. R., & Crosson, J. E. (2010). Emergency diagnosis and management of pediatric arrhythmias. Journal of emergencies, trauma, and shock, 3(3), 251–260.
[22] Cicenia, M., Silvetti, M. S., & Drago, F. (2021). When Should Premature Ventricular Contractions Be Considered as a Red Flag in Children with Cardiomyopathy? Journal of cardiovascular development and disease, 8(12), 176.
[23] Hylind, R. J., Chandler, S. F., Beausejour Ladouceur, V., Jamal, S. M., Alexander, M. E., Mah, D. Y., et al; (2020). Clinical and Genetic Findings in Children Presenting With Ventricular Fibrillation as the First Manifestation of Cardiovascular Disease. Journal of the American Heart Association, 9(10), e016322.
[24] Ponce-Balbuena, D., & Deschênes, I. (2021). Long QT syndrome - Bench to bedside. Heart rhythm O2, 2(1), 89–106.
[25] Uvelin, A., Pejaković, J., & Mijatović, V. (2017). Acquired prolongation of QT interval as a risk factor for torsade de pointes ventricular tachycardia: a narrative review for the anesthesiologist and intensivist. Journal of anesthesia, 31(3), 413–423.
[26] Hafeez, Y., & Grossman, S. A. (2023). Sinus Bradycardia. In StatPearls. StatPearls Publishing.
[27] Dakkak, W., & Doukky, R. (2023). Sick Sinus Syndrome. In StatPearls. StatPearls Publishing.
[28] Oldroyd, S. H., Quintanilla Rodriguez, B. S., & Makaryus, A. N. (2023). First-Degree Heart Block. In StatPearls. StatPearls Publishing.
[29] Mangi, M. A., Jones, W. M., Mansour, M. K., & Napier, L. (2023). Second-Degree Atrioventricular Block. In StatPearls. StatPearls Publishing.
[30] Knabben, V., Chhabra, L., & Slane, M. (2023). Third-Degree Atrioventricular Block. In StatPearls. StatPearls Publishing.
[31] Richter, B., & Faul, C. (2018). FGF23 Actions on Target Tissues-With and Without Klotho. Frontiers in endocrinology, 9, 189.
[32] Courbebaisse, M., & Lanske, B. (2018). Biology of Fibroblast Growth Factor 23: From Physiology to Pathology. Cold Spring Harbor perspectives in medicine, 8(5), a031260.
[33] Ratsma, D. M. A., Zillikens, M. C., & van der Eerden, B. C. J. (2021). Upstream Regulators of Fibroblast Growth Factor 23. Frontiers in endocrinology, 12, 588096.
[34] Czaya, B., & Faul, C. (2019). The Role of Fibroblast Growth Factor 23 in Inflammation and Anemia. International journal of molecular sciences, 20(17), 4195.
[35] Vervloet M. G. (2022). Shedding Light on the Complex Regulation of FGF23. Metabolites, 12(5), 401.
[36] Farrell, B., and Breeze, A. L. (2018). Structure, activation and dysregulation of fibroblast growth factor receptor kinases: perspectives for clinical targeting. Biochem. Soc. Trans. 46, 1753–1770.
[37] Erben R. G. (2018). Physiological Actions of Fibroblast Growth Factor-23. Frontiers in endocrinology, 9, 267.
[38] Murali, S. K., Roschger, P., Zeitz, U., Klaushofer, K., Andrukhova, O., & Erben, R. G. (2016). FGF23 Regulates Bone Mineralization in a 1,25(OH)2 D3 and Klotho-Independent Manner. Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research, 31(1), 129–142.
[39] Stöhr, R., Schuh, A., Heine, G. H., & Brandenburg, V. (2018). FGF23 in Cardiovascular Disease: Innocent Bystander or Active Mediator?. Frontiers in endocrinology, 9, 351.
[40] Gutiérrez, O. M., Mannstadt, M., Isakova, T., Rauh-Hain, J. A., Tamez, H., Shah, A., et al; (2008). Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. The New England journal of medicine, 359(6), 584–592.
[41] Seiler, S., Rogacev, K. S., Roth, H. J., Shafein, P., Emrich, I., Neuhaus, S., et al; (2014). Associations of FGF-23 and sKlotho with

cardiovascular outcomes among patients with CKD stages 2-4. Clinical journal of the American Society of Nephrology : CJASN, 9(6), 1049–1058.

[42] Souma, N., Isakova, T., Lipiszko, D., Sacco, R. L., Elkind, M. S., DeRosa, J. T., et al; (2016). Fibroblast Growth Factor 23 and Cause-Specific Mortality in the General Population: The Northern Manhattan Study. The Journal of clinical endocrinology and metabolism, 101(10), 3779–3786.

[43] Andersen, I. A., Huntley, B. K., Sandberg, S. S., Heublein, D. M., & Burnett, J. C., Jr (2016). Elevation of circulating but not myocardial FGF23 in human acute decompensated heart failure. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association, 31(5), 767–772.

[44] Bonato, F. O. B., & Canziani, M. E. F. (2017). Ventricular arrhythmia in chronic kidney disease patients. Jornal brasileiro de nefrologia, 39(2), 186–195.

[45] Dong, Q., Li, S., Wang, W., Han, L., Xia, Z., Wu, Y., et al; (2019). FGF23 regulates atrial fibrosis in atrial fibrillation by mediating the STAT3 and SMAD3 pathways. Journal of cellular physiology, 234(11), 19502–19510.

[46] Chua, W., Purmah, Y., Cardoso, V. R., Gkoutos, G. V., Tull, S. P., Neculau, G., et al; (2019). Data-driven discovery and validation of circulating blood-based biomarkers associated with prevalent atrial fibrillation. European heart journal, 40(16), 1268–1276.

[47] Vergaro, G., Aimo, A., Taurino, E., Del Franco, A., Fabiani, I., Prontera, C., et al; (2021). Discharge FGF23 level predicts one year outcome in patients admitted with acute heart failure. International journal of cardiology, 336, 98–104.