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# Correlation between Fibroblast Growth Factor 23 and Heart Failure in Children with Congenital Heart Disease

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***Abstract***

***Background:Congenital heart diseases (CHD) are lesions caused by abnormal development of the structure of the heart.heart failure(HF) is a common complication of CHD.Elevated Fibroblast growth factor 23 (FGF-23) levels were associated with increased risk of cardiovascular diseases (CVD) and mortality in general population.***

***Aim of the study: The aim of this study wasto assess serum FGF-23 levels among pediatric heart failure patients to demonstrate relationship between its levels and cardiac function and severity of the disease.***

***Patients and methods: In our study we have evaluated 60 children. They were divided into two groups: A case group: Included 30 patient with HF secondary to CHD and A control group: Included 30 age and sex matched apparently healthy children.The diagnosis of cases was established from the history, clinical examination investigation. All patients were subjected to full history taking, a complete clinical examination including Ross Score for detection of the degree of heart failure, Complete blood count ,kidney function tests, chest X ray, ECHO was performed and serum level of FGF-23was also measured.***

***Results:There were statistical significant decrease in Ejection fraction (EF) and Fractional Shortening (FS) of HF group compared to control group. There was significant increase in LVEDD, LVESD and ESPAP in HF group compared to control group. There was a statistical significant increase in serum FGF-23 level in HF group compared to healthy one. According to correlation analysis there was significant positive correlation between FGF-23 and Heart rate, respiratory rate, HB and Modified Ross score, also there was significant negative correlation between FGF-23 and FS, EF, while there was no significant correlation between FGF-23 and age, ESPAP, phosphorous and creatinine. The best cut-off value for FGF-23in HF patients was 141.5 ng/dl with sensitivity 88.3%, specificity 89.7%, positive predictive value 80.2%, negative predictive value 91.5%, accuracy 88% and area under curve 0.982. So, FGF-23 can be a good sensitive and specific marker for HF.***

***Conclusion:This study demonstrated that FGF23 is diagnostic for heart failure with good sensitivity and specificity and related to severity of heart failure and correlate significantly with left ventricular function.***

***Keywords:Fibroblast Growth Factor 23(FGF-23), congenital heart diseases (CHD), heart Failure (HF).***

## 1. Introduction:

Congenital heartdiseases (CHD) are lesions caused by abnormal development of the structure of the heart. This happens in the embryonic life due to environmental or unknown factors. Congenital heart diseases are classified into: congenital cyanotic heart diseases and congenital acyanotic heart diseases. Congenital heart disease is the most common cause of death in the first year of life, heart failure is a common complication of CHD **(1).**

Heart failure has been defined as an abnormality of cardiac structure or function leading to failure of the heart to deliver oxygen at a commensurate with the requirements of the metabolizing tissues, despite normal filling pressure **(2).**

Biomarkers of heart failure typically refer to proteins and /or other substances-measured in patients blood and these are different than the commonly used laboratory tests like sodium and albumin. Components of several pathways related to regulation of neurohormonal system, ventricular dysfunction, cardiac remodeling and myocardial injury are likely appear in circulation and their levels may alter with the progression of heart failure. The changes in the concentration of some of these components can be used as a potential biomarkers for diagnosing the progression of the disease**(3).**

Fibroblast growth factor 23 (FGF-23) is bone derived hormone that regulate mineral metabolism by promoting phosphaturia and decrease renal production of calcitriol **(4).**Dietary phosphate loading increase FGF 23 levels, whereas Dietary phosphate restriction has the opposite effect **(5).** Increase serum phosphate level had been reported to increase risk of cardiovascular diseases and mortality **(6).**

Elevated FGF-23 levels were associated with increased risk of cardiovascular diseases (CVD) and mortality in general population **(7).**Clinical studies show that FGF-23 play a role in chronic kidney diseases (CKD) and cardiovascular diseases via renal mineral metabolism axis**.**There is two studies in the adult heart failure population showing elevated FGF-23 levels used as a predictor of death **(8).**

We aimed in this study to assess serum FGF-23 levels among pediatric heart failure patients to demonstrate relationship between its levels and cardiac function and severity of the disease.

## 2. Patients and Methods:

**2.1.**The current study was conducted asprospective Case-control study.A total number of 60participants were included in the study. The study was carried out at cardiology unit of Pediatric Department and Clinical Pathology Department, Zagazig University Hospital, From February 2018 till November 2018after obtaining the approval of the institutional review board (IRB) of Zagazig University.

**Patients group:** 30 child with congenital heart diseases with heart failure who were 14 males (46.7%) and 16 Females (53.3%) their age ranged from (2-36) months. Twenty six of them were acyanotic CHD (86.7%) and four were cyanotic CHD (13.3%).

**Control group:** 30 apparently healthy children, sex and age matched to the patients were taken as control group who were18 males (60%) and 12 female (40%) their age ranged from (2-50) months**.**

**2.2**. A consent form approved by the committee of human rights in research in Zagazig University was obtained from parents of each case before the study initiation.

**2.3.**Patients who were included in this study; children with congenital heart disease cyanotic and acyanotic suffering from heart failure between the age of 1 month and 5 years.

**2.4.**All patients who had heart failure beginning before 1month and after the age of 6 years,patients with other cardiac causes of heart failure like cardiomyopathy, acute rheumatic carditis and infective endocarditis, patients with other non-cardiac causes of heart failure like renal failure, endocrinal diseases as hypothyroidism, and patients who had diseases affecting level of FGF-23 like renal failure, rickets were excluded from the study.

**2.5.**The patients who met the inclusion criteria and were suitable candidates for the study have been subjected to:

**A- Full history taking including**:

- **Personal history**: age, sex, presence of parental consanguinity, ethnicity.
- **History of the present illness**: including presence of:

**1**-Symptoms suggestive of pulmonary congestion: dyspnea, shortening of breathing (SOB), cough, recurrent chest infection, and expectoration.

**2**-Symptoms suggestive of systemic venous congestion: including Rthypochondrial pain, swelling (edema) of the LL or back, swelling of abdomen (ascitis) and genital swelling.

**3**-Symptoms of low COP: including exertional fatigue, blurring of vision, dizziness, giddiness, oliguria and chest pain.

**4**- Palpitation.

**5**-Syptoms suggestive of cardiomegaly: including wheeze and dysphagia.

**-Past history:** Previous admission, disease, drug intake and operation.

**-Family history:** Similar condition and consanguinity.

**B- Complete clinical examination:**

**General examination** to detect: pallor, cyanosis, orthopnea, clubbing, pulse, blood pressure and respiratory rate.

**Anthropometric measurements:** Including weight (kilogram) and height (centimeter) with plotting them into the standard growth charts. Z scores for weight for age (WAZ) were calculated using the Anthropometric calculator module of WHO (based on The 2006 WHO child growth standards) **(WHO, 2006).**

**Cardiac examination** to detect:-Pericordial bulge, cardiac pulsations, scar of previous operation, thrills, dullness and auscultation of the heart sounds and murmurs.

**Abdominal examination** for hepatomegally; liver size >2cm was considered hepatomegaly.

**Severity of heart failure** was established by Modified Ross classification for diagnosis and classification of HF.

**C- Laboratory investigations:**

**1-Complete blood count (CBC) :**( hemoglobin percentage, white blood cells count and platelets count) by automated cell counter **(Sysmex-K-21).**

**2-Serum Creatinine and serum phosphate level :(**cobas 8000).

**3-Serum fibroblast growth factor 23**: by ELISA technique **(SunRed, Shanghai, China).**

**D-Radiological finding:**

**1-Chest X-ray:** Postro-anterior view for detection of cardiomegally, pulmonary vasculature, and other cardiopulmonary diseases.

**2-Standard 12 Lead Electrocardiography (ECG):** for detection of ventricular enlargement (left, right or biventricular).

**3-Echocardiography:** all patients underwent echocardiographic examination using GE Vivid-7 multi-purpose system with various probe sizes. Each patient was examined inspected by suggestions of the American Society of Echocardiography **(9).**

Echocardiographic examination included M-mode, 2D, and Doppler echocardiography. The left ventricular end systolic diameter (LVESD), left ventricular end diastolic diameter (LVEDD); ejection fraction (EF) and fractional shortening (FS) were measured using M-mode echocardiography in the left para-sternal view.

*** Ejection Fraction (EF %)** identifies changes in the volume of the left ventricle (LV) with cardiovascular contraction. It is acquired from the following equation:

**Ejection fraction (EF %) =** (D)3 - (Ds)3 /(Dd)3 x100 =

$$\frac{\text{LV diastolic volume} - \text{LV systolic volume}}{\text{LV diastolic volume}}$$

**Where:** LV = left ventricle, diastolic is the relaxed state, systolic is the contracted state

*** Fractional Shortening (FS)** is determined from the following:

**Fractional shortening (FS %)** = Dd- Ds / Dd x100;6 =

$$\frac{\text{LV end-diastolic diameter} - \text{LV end-systolic diameter}}{\text{LV end-diastolic diameter}}$$

*** Estimated systolic pulmonary artery pressure (ESPAP**)was calculated through Doppler tracing of the peak velocity of the tricuspid regurgitation jet by using the Bernoulli formula: ESPAP=4(V) 2;+RAP **(10).**

Systolic pulmonary artery hypertension (PAH) is considered when systolic pulmonary artery pressure (PAP) > 36 mmhg.

**Serum fibroblast growth factor 23 was estimated by ELISA**

**2.6. Statistical analysis:**

The data were coded, entered and analyzed by SPSS program version 16 (statistical package for social sciences) (SPSS Inc. Released 2007.SPSS for windows, Version 16.0.0 Chicago. SPSS Inc.). Data were summarized as mean ± Standard deviation and percentage, median and range. T test was used for comparison of mean of the two groups of a data distributed normally .Chi square ($\chi 2$) test for comparison of qualitative date. Mann Whitney test was performed to compare two groups whose data were non parametric. Kruskal Wallis H test was performed to compare more

than two groups whose data were non parametric .Spearman's correlation was performed.
ROC curve: analysis was used to identify best cut-off values of FGF-23with maximum sensitivity and specificity for diagnosis of heart failure.
Cut off level:
P≤ 0.05= Significant (S), P≤ 0.001= highly significant (HS).

**3. Results:**

There was no significant difference between the studied groups as regard age and sex. There was a significant decrease in weight of cases with heart failure in comparison to control(median 4.8 vs 6.5) kgrespectively.There was a significant increase in number of children with underweight in cases with heart failure in comparison to control(53.3% vs 13.3% with P value <0.05)

Regarding the vital signs of cases, there was a high significant increase in temperature, heart rate and respiratory rate in cases with heart failure in comparison to control (37.7±0.8 vs 37.0±0.0°**C** , 171.7±10.9 vs 95.8±11.3beat/min, and 69.13±7.3 vs 28.15±2.6breath/minrespectively).

Regarding clinical features: the most prevalent pattern of breathing was retraction by 86.7%. Diaphoresis with head only was the most prevalent by 73.3%. Several times tachycardia was the most prevalent by 46.7%. Hepatomegally 2-3 cm was the most prevalent by 90%.Therewas a high significant increase in WBCs (11 vs 4)x$10^3$ and high significant decrease in HB (10.53±.053 vs 11.91 ±1.2)gm/dland platelet count in cases in comparison to control (236.2±35.4 vs 280.4±35.9)x$10^3$.

Our study showed that most oflungfield appearance by X-ray wasplethora by a percent of 76.7%.Left ventricular enlargement was predominant by percent of 60%. By ECG left and right ventricular hypertrophy were predominant by percent of 33.3% for each.

Regarding ECG of heart failure patients; left and biventricular hypertrophy were predominant by percent of 33.3% for each.

The most prevalent acyanotic cardiovascular lesion is ASD+VSD by percent of 30% and the most prevalent cyanotic cardiovascular lesion is transposition of great vessels by percent 10.0% **(Table 1).**

There was a significant increase in LVED and LVES in cases more than control and there is significant decrease in estimated ejection fraction and fraction shortening (significantly lower in cases more than control) and there is statistically significant increase in cases than control regarding estimated systolic pulmonary artery pressure (ESPAP) **(Table2)**.

Fibroblast growth factor 23 was significantly higher in cases group than in control group.There were no significantdifference between the studied groups as regard creatinine and phosphate level**(Table 3)**

There were statistically non-significant differences in FGF-23 level regarding pulmonary hypertension, type of CHD as obstructive lesions or not, and whether cyanotic oracyanotic lesion

in patients with HF(**Table 4).**

Our study showed that FGF-23 level was significantly elevated in each of class mild, moderate and severe Ross classification in comparison tocontrol. Moderate heart failure is predominant by a percent of 66.7%, mild heart failure was 20% and severe heart failure was 13.3%

Regarding the relation between FGF-23 level and ROSS classification among the studied patients; the difference was significant between control group and each of class A, B, and C ROSS classification but there was a non-significant difference between each class and other **(Table5).**

There was highly significant positive correlation between FGF-23 and Heart rate, respiratory rate,HB and Modified Ross score, also there are significant negative correlation between FGF-23 , FS, EF, and WBCs, While there are no significant correlation between FGF-23 ,age , Platelet count ,ESPAP, phosphate and creatinine **(Table 6)**.

The best cut off FGF-23 in prediction of heart failure is ≥141.5 ng/dl with area under curve0.982, with sensitivity 88.3%, specificity 89.7%, positive predictive value 80.2%, negative predictive value 91.5% and accuracy 88% (p<0.001) **(Table 7) (Figure 1)**.

**Table (1): Frequency of cardiovascular defects in CHD**

| | Number of cases | % |
|---|---|---|
| **Acyanotic** | **26** | **86.7** |
| **VSD** | **4** | **13.3** |
| **ASD (secondum)** | **3** | **10.0** |
| **PDA** | **1** | **3.3** |
| **ASD + VSD** | **9** | **30.0** |
| **VSD +ASD + PDA** | **4** | **13.3** |
| **Valvular pulmonary stenosis** | **3** | **10.0** |
| **Mitral stenosis with sever AS** | **2** | **6.7** |
| **Cyanotic** | **4** | **13.3** |
| **Double outlet right ventricle (DORV)** | **1** | **3.4** |
| **Transposition of great vessels** | **3** | **10.0** |
| **Total** | **30** | **100.0** |

**Table (2): Echocardiographic findings of the studied groups**

| Variable | Control group (N=30) | Case group (N =30) | t test | P value |
|---|---|---|---|---|
| **LVEDD(mm) Mean ± SD** | 28±3.4 | 32.1±1.1 | 6.28 | **<0.001** |

| | | | | |
|---|---|---|---|---|
| **Range** | 18-32 | 24-35 | | **(HS)** |
| **LVESD(mm)** | | | | |
| **Mean ± SD** | 14.1±1.2 | 18.2±2.3 | 8.65 | **<0.001** |
| **Range** | 12-22 | 14-25 | | **(HS)** |
| **EF %** | | | | |
| **Mean ± SD** | 84.23±5.54 | 57.9±2.26 | 24.084 | **<0.001** |
| **Range** | 74-95 | 55 - 65 | | **(HS)** |
| **FS %** | | | | |
| **Mean ± SD** | 33.13±4.77 | 21.97±2.26 | 12.427 | **<0.001** |
| **Range** | 28-44 | 20-24 | | **(HS)** |
| **ESPAP** | | | | |
| **Mean ± SD** | 25.13± 2.92 | 37.47±11.71 | -5.595 | **<0.001** |
| **Range** | 21 - 30 | 20 - 60 | | **(HS)** |

LVEDD: left ventricular end diastolic diameter
LVESD: left ventricular end systolic diameter
EF: ejection fraction
FS: fraction shortening
ESPAP:estimated systolic pulmonary artery pressure

**Table (3): FGF-23 in the studied groups**

| **FGF-23 (Ng/dl)** | **Control group (N=30)** | **Case group (N =30)** | **Ttest** | **P value** |
|---|---|---|---|---|
| **Mean ± SD** | **66.4±10.9** | **110.8±23.4** | **-9.42** | **<0.001** |
| **Range** | **59.1–92.7** | **78.4–187.1** | | **(HS)** |
| **Creatinine : mg/dl** | | | | |
| **Median** | **0.3** | **0.2** | **115** | **0.234** |
| **Range** | **0.2-0.6** | **0.1-0.6** | | |
| **Phosphate : mg/dl** | | | | |
| **Mean ± SD** | **4.31±0.31** | **4.39±0.31** | **0.999** | **0.321** |
| **Range** | **3-5** | **3.8-4.9** | | |

**Table (4): Relation between FGF-23 and gender, pulmonary artery pressure and type of CHD**

| **Variable** | **Male (N=32)** | **Female (N=28)** | **Mann Whitney test** | **p-value** |
|---|---|---|---|---|
| | **No.** | **No.** | | |
| **FGF-23: Ng/dl** | | | | |
| **Median** | 140 | 165 | 421 | 0.72 |
| **Range** | 30–1185 | 31– 972 | | (NS) |
| | **Pulmonary artery pressure** | | | |
| | **Normal (N=13)** | **PHP (N=17)** | | |
| **Mean ± SD** | **490.15± 308.2** | **315.06±205.95** | | |
| **Median** | **444** | **249** | -1.465 | 0.143 |
| **Range** | **149 - 1185** | **142 - 972** | | |
| | **Non obstructive** | **Obstructive** | | |

| | (N=25) | (N=5) | | |
|---|---|---|---|---|
| **Mean ± SD** | **373.24±273.25** | **479.4±226.83** | | |
| **Median** | **249** | **444** | -1.28 | 0.2 |
| **Range** | **142 -1185** | **193 - 790** | | |
| | **Acyanotic (N=26)** | **Cyanotic (N=4)** | | |
| **Mean ± SD** | **368.35±261** | **537.75±284.15** | | |
| **Median** | **254** | **585** | -1.037 | 0.3 |
| **Range** | **142 -1185** | **149 - 832** | | |

**Table (5): Relation between FGF-23 level and ROSS classification among the studied patients**

| **FGF-23**: Ng/dl | **ROSS classification** | | | | KW | p | Pairwise comparison |
|---|---|---|---|---|---|---|---|
| | **Control group (N=30)** | **Class A (N=6)** | **Class B (N=20)** | **Class C (N=4)** | | | |
| **Mean ± SD** | 90.4±49.79 | 423.27±282.16 | 351.9±259.7 | 537.75±284.15 | 41.8 | <0.001** | P1<0.001** |
| **Median** | 80.5 | 310 | 248.5 | 585 | | | P2<0.001** |
| **Range** | 30 - 280 | 244 – 972 | 142 - 1185 | 149 - 832 | | | P3<0.002* |
| | | | | | | | $P_{4-6} = 1$ |

P1 the difference between control group and Class A
P2 the difference between control group and Class B
P3 the difference between control group and Class C
P4 the difference between class A and B
P5 the difference between class A and C
P6 the difference between class B and C

**Table (6): The correlation betweenFGF-23 and different parameters among the heart failure studied group**

| | **FGF-23 level** | |
|---|---|---|
| **Variable** | **r** | **P** |
| **Age** | -0.038 | 0.77 (NS) |
| **Heart rate** | 0.787* | <0.001 (HS) |
| **Respiratory rate** | 0.807* | <0.001 (HS) |
| **S.creatinine** | -0.076 | 0.233 (NS) |
| **Hemoglobin** | 0.3* | 0.02 (S) |
| **Platelet count** | -0.23 | <0.073 (NS) |
| **WBCs** | -0.384* | 0.02 (S) |
| **Modified Ross score** | 0.808* | <0.001 (HS) |
| **EF** | -0.724 | <0.001 (HS) |
| **FS** | -0.768 | <0.001 (HS |
| **ESPAP** | -0.272 | 0.146(NS) |
| **Phosphate** | -0.32 | 0.073 (NS) |

**Table (7):Performance of FGF-23 in prediction of heart failure among the studied patients**

| Cutoff | Sensitivity % | Specificity % | PPV % | NPV % | Accuracy % | AUC | P value |
|---|---|---|---|---|---|---|---|
| ≥141.5 Ng/dl | 88.3 | 89.7 | 80.2 | 91.5 | 88 | 0.982 | <0.001** |

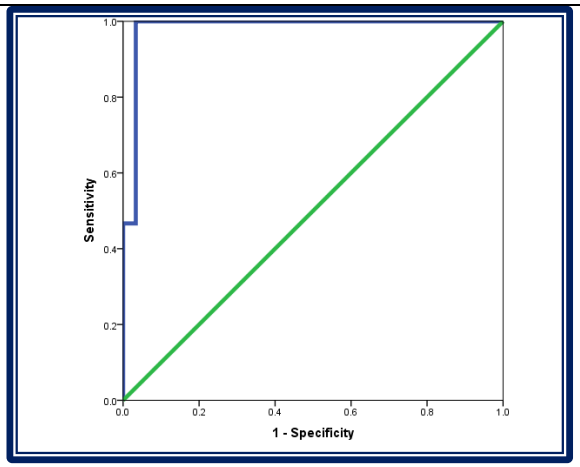


**Figure (1):ROC curve showing performance of FGF-23 in prediction of heart failure among thestudied patients**

**4. Discussion:**

Congenital heart diseases contribute significantly to the disease -related morbidity and mortality in children especially in the first year of life **(11).** It is estimated that 15% –25% of children with structural cardiac defects will develop HF, with defects causing left-to-right shunting **(12).** Over time, decreased cardiac output activates a cascade of compensatory responses that aimed directly or indirectly to restore normal perfusion to the body's organs and tissues such as adrenergic and renin–angiotensin system (RAS) that have long-term delirious effects **(13).**

Many biomarkers appear to provide important information regarding the pathogenesis of heart failure, one of these markers is Fibroblast growth factor 23 (FGF-23). There has been significant scientific interest in the potential systemic effects of FGF-23. Observational studies first suggested this possibility by reporting that elevated FGF-23 levels were associated with increased risks of cardiovascular disease events and mortality in the general population **(14).**

Two studies in the adult heart failure population have evaluated FGF-23 levels as a predictor of death **(8).** Comparable data in children with heart failure are not available. Therefore, we aimed to assess serum FGF-23 levels among pediatric heart failure patients, compared these with levels in healthy controls to demonstrate relationship between its levels and cardiac function and severity of the disease.

As regard the demographic data: Children with heart failure secondary to congenital heart diseases were 14 males(46.7%) and 16 Females(53.3%) their age range from (2-36) months. In control group; there were 18 males (60%) and 12 female (40%) their age range from (2-50) months.There was no statistical significant difference between patient and control as regard age, sex.

Studies have shown that patients with congenital heart disease have persistently low weight-for-

age z scores at 3 months of age **(15).**Chronic CHF and constant under-oxygenation in CHD weaken cellular metabolism and cell growth, while recurrent chest infections demand an increased metabolism **(16).**

Our results showed that there was a significant decrease of weight. This agreed with **El Amrousy and El-Mahdy(17)** they found that, weight was lower among cases than controls but without statistically significance .By plotting our cases into growth charts, the overall predominance of wasting (low WAZ) were fundamentally higher significantly in children with CHF(53.3%), compared with the healthy group(13.3%). This was in agreement with **Lissauer and carroll(18)** who stated that poor feeding is a common feature of symptoms of pediatric heart failure along with poor weight gain or faltering growth as a common sign. Our results were in agreement with the study done by **Hassan et al. (19)** that showed the overall prevalence of malnutrition reached 84.0% in cases compared to 20% for the control group.

Congenital heart diseases classified into; congenital acyanotic heart disease and congenital cyanotic heart diseases depending upon whether the patients exhibit cyanosis **(20).** In our study: congenital acyanotic heart diseases percentage was (86.7%) and congenital cyanotic heart disease percentage was (13.3%).

Our results show that the most prevalent acyanotic cardiovascular lesion was ASD + VSD by percent of 30%. This result was in disagree with **Bjornard et al. (21), Masarone et al. (22) and Lissauer and Carroll (18)** who showed that the most common type of heart defect is VSD.

There was a high significant increase in heart rate and respiratory rate in cases with heart failure in comparison to controls. This agreed with **Jayaprasad, (23)**who reported that tachycardia > 150/min, respiratory rate >50/min are features of HF in infants.

This agreed with **Hussain et al. (24)**who found clinically Cardiac Congestive Failure (CCF) is a syndrome of breathlessness and fatigue which commonly is associated with cardiac disease.

Our study showed hemoglobin level (HB) in our study there was significant statistical decrease in HB in HF group compared to healthy group. This agreed with **El Amrousy and El-Mahdy (17)**who found that HB level was significantly lower in children with HF than healthy control group.

Chest radiography is indicated in all children with suspected HF to assess heart size and to check for other signs of HF such as pulmonary edema, septal lines (or Kerley B lines), and pleural effusions. While electrocardiogram (ECG) findings show sinus tachycardia is common in acute HF. In chronic HF, an abnormal electrocardiogram increases the likelihood of decompensated HF **(22).** Our study showed that most of lung field appearance by X-ray was plethora by a percent of 76.7%.Left ventricular enlargement was predominant by percent of 60%. By ECG left and right ventricular hypertrophy were predominant by percent of 33.3% for each.

Echocardiographic finding in our study showed that there was significant increase in left ventricular end diastolic diameter (LVEDD) and left ventricular end systolic diameter (LVESD) in cases more than control and there was significant decrease in estimated ejection fraction (EF) and fraction shortening (FS) in comparison to control. This agreed with **Elsharawy et al. (25),** they detected significant differences between studied groups regarding LVEDD, LVESD ,EF ,FS and ESPAP, While, FS and EF were significantly lower in patient group than control group. Our study showed that levels of FGF-23 were higher in cyanotic cases in comparison to acyanotic cases but without significant difference .This may be due to small number of cyanotic cases. Similarly, obstructive lesion show non- significant high level of FGF-23 than non- obstructive lesion. FGF-

23 not differ regarding the presence of pulmonary hypertension or not and also there was no correlation between FGF-23 and levels of pulmonary artery pressure .This disagreed with **Isakova et al.** (**26)** showed a significant relationship between FGF-23 and echocardiographic measures of abnormal cardiac structure.
Regarding estimated systolic pulmonary artery pressure (ESPAP) in our study: there was statistically significant increase in cases than control. This agreed with a study done by **Ebrahim. (2019)** showed statistical significant increase in PAP level in CHF group comparing with control group.

Our study showed that FGF-23 was significantly higher in cases group than in control group. This agreed with a study of **Fischer et al. (2012)** that showed FGF23 is markedly higher incases than control. **Isakova et al. (26)** reported that the demonstration of nearly two fold higher FGF-23 levels in the pediatric heart failure population compared to healthy controls. **Andersen et al. (27)** confirmed the findings of prior studies showing that FGF-23 concentrations are elevated in adults with acute decompensated heart failure and that FGF-23 is expressed in human myocardial tissue. The mechanisms for elevated FGF-23 levels in heart failure are not known.Our study showed that there is no significant relation between sex and FGF-23.Its agreed with **Isakova et al. (26)** that there was no significant association between gender and FGF-23 level.

Our results detected non- significant difference between cases and control as regard creatinine levels denoting normal kidney function. Also, we did not detect association between FGF-23 and creatinine. Phosphate regulation is another factor that is important in FGF-23 regulation. Our study revealed that there was no significant difference between case and control groups as regard phosphate level. While, we did not detect correlation between FGF-23 and phosphate. This was agreed with **Mitchell and Jüppner (28)**showed that mean serum phosphate levels in the patients were within the reported reference range for healthy children.

Our study showed that FGF-23 level was significantly elevated in each of class mild, moderate and severe. Ross classification in comparison to control. Moderate heart failure is predominant by a percent of 66.7%, mild heart failure was 20% and severe heart failure was 13.3%.
Also our study showed that FGF-23 had a significant positive correlation with modified Ross score. **Isakova et al. (26**) found that FGF-23 levels were significantly higher in those patients treated with diuretics and in those with higher NYHA or Ross functional class.

Our results show that there was highly significant positive correlation between FGF-23, heart rate, respiratory rate, and HB. There was significant negative correlation between FGF-23, FS and EF. **Isakova et al. (26)** found non- significant correlation between FGF-23, EF and FS .Our data showed no significant correlation between FGF-23 and age. This run parallel to **Isakova et al. (26)** detected the same data.
According to ROC curve analysis of FGF-23 as a diagnostic marker of HF: The best cut-off value for FGF-23 in HF patients was ≥141.5ng/dl with sensitivity 88.3% , specificity 89.7% positive predictive value 80.2%, negative predictive value 91.5%, accuracy 88% and area under curve 0.982. So, FGF-23 can be a good sensitive and specific marker for HF.

**5. Conclusion:**

This study demonstrated that FGF23 is diagnostic for heart failure with good sensitivity and specificity.FGF23 level was related to severity of heart failure and correlate significantly with left ventricular function.

**Based on the results of this study, we recommend the following:**

Serum level of FGF-23 could be used as a marker for diagnosis of pediatric heart failure and assessment of its severity. Further studies to focus on FGF-23 role in different types of CHD with more number of cases with cyanotic lesions and also with obstructive lesions.Further studies to show role of FGF-23 in HF due to other causes other than CHD as cardiomyopathy.

**6. ConflictofInterest**: Noconflictofinterest.

**7. References**

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