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Serum Matrix Metalloproteinase 2 (MMP-2) Levels in Children with Pulmonary Hypertension Associated with Congenital Heart Disease

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Background: Pulmonary arterial hypertension (PAH) is a frequent consequence of untreated congenital heart disease (CHD). Elevated pulmonary pressure induces vascular remodeling and RV dysfunction through several mechanisms, culminating in a gradual elevation in pulmonary vascular resistance (PVR) and ultimately reversal of shunt with the progression of Eisenmenger syndrome.
Objectives: To analyze the role of matrix metalloproteinase 2 (MMP-2) in pulmonary hypertension (PH) due to CHD and also to investigate if this marker has a diagnostic or prognostic value.
Subjects and Methods: 25 subjects with PAH associated with CHD, 25 subjects with CHD without PH, and 25 healthy children as controls were included. Heart electrocardiography, Doppler and Two-dimensional, M-mode echocardiographic evaluation of CHD and pulmonary pressure were done. Blood specimens were collected from all subjects to assess serum MMP-2 levels by ELISA.
Results: The mean MMP-2 values significantly enhanced in PAH-CHD children as compared to CHD without PAH patients and controls ($P<0.05$). A significant correlation was found among MMP-

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2 and mean pulmonary artery pressure (mPAP) and echocardiographic parameters of RV diameter and function. Sensitivity of MMP-2 as a diagnostic marker was 52% and specificity was 96%.
Conclusion: Serum MMP-2 were significantly enhanced in PAH-CHD children and were correlated to severity of PH and to the echocardiographic measures of its assessment. MMP-2 could be used as an excellent diagnostic and predictive biomarker in PAH-CHD children, which could be beneficial in treatment of PH in children and prediction of their outcome.

Keywords: Pulmonary hypertension; congenital heart disease; serum matrix metalloproteinase 2; echocardiography.

1. INTRODUCTION

Congenital heart disease (CHD) occurs in around 8 per 1000 births and may present in a variety of ways. Left-to-right shunts, right-to-left shunts, and outflow tract blockages are the three major categories of congenital heart abnormalities [1].

The WHO indicates pulmonary arterial hypertension (PAH) as pre-capillary pulmonary hypertension (PH) with a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg [2]. PAH diagnosis in children is often linked with a pulmonary vascular resistance (PVR) > 3 wood units (WU) [3].

Post-capillary PH is represented by a mPAP 25 mmHg, a mean pulmonary artery wedge pressure (PAWP) > 15 mmHg, a diastolic pulmonary vascular pressure gradient (DPG) 7 mmHg, and/or a PVR 3 WU [4].

PH is a chronic illness brought on by vascular structural remodelling and increasing PVR, that result in a rise in intrapulmonary pressure, right ventricular (RV) failure, and mortality [5,6].

The pathogenesis of these changes seems to be multifactorial, caused by progressive endothelial dysfunction of the pulmonary arterial tree induced by flow and pressure overload [7].

Without early diagnosis and effective treatment, the survival rate of children with PAH and CHD is low [8]. Blood biomarker measurement may aid pediatric PAH care, as they give important knowledge on the detection, intensity, and progression of illness [9,10], like B-type natriuretic peptide (BNP), N-terminal pro-B-type natriuretic peptide (NT-proBNP) [11], and Matrix Metalloproteinases (MMPs), including (MMP-2, MMP-9, etc…) [12].

MMPs are a wide class of zinc-dependent proteases [13,14], together with their tissue blockers, are crucial for the stability of the extracellular matrix [15,16]. Essential functions are performed by these enzymes in matrix turnover, tissue remodeling, angiogenesis, and morphogenesis [17,18].

There is insufficient evidence linking the blood MMP-2 level in pediatric PH with CHD thus, this research objects to assess the serum values of MMP-2 in children with PH with CHD the diagnostic and prognostic value of MMP-2 in these patients, by correlation of its concentrations with clinical and echocardiographic data of PAH-CHD.

2. METERIALS AND METHODS

In this prospective case-control research, 50 children with CHD were involved as they asserted at the Pediatric Cardiology Unit, Pediatric Department, Tanta University Hospital.

They were classified into:

Group I: 25 children with PAH associated with CHD, **Group II:** 25 children with CHD with no PAH. 25 healthy children were included as a control group (group III). The degree of PH in group I patients were classified as mild (mPAP = 25-40 mmHg), moderate (mPAP = 41- 55 mmHg) and severe (mPAP > 55 mmHg).

2.1 Inclusion Criteria

Children in the pediatric age with CHD, with or without PAH.

2.2 Exclusion Criteria

Heart failure, Ischemic heart disease, Type 1 diabetes mellitus, Cancer, Acute or chronic illness, Obesity, Chronic liver disease, Bronchial asthma, Connective tissue diseases, eg. SLE.

All children underwent history taking, Thorough clinical assessment (heart rate (HR), respiratory

rate (RR), blood pressure and oxygen saturation) and cardiac investigation.

2.3 Echocardiographic Assessment

By Vivid 7 ultrasound (GE Medical System, Horten, Norway) with 7 and 4s MHz multi-frequency transducers. Doppler, two dimensional, and M mode echocardiography were utilized to evaluate the subsequent:

- Type of CHD.
- mPAP:

It was determined based on the peak pulmonary resurge (PR) Doppler signal; Using color Doppler, the PR signal is acquired in the view of parasternal short axis. Utilizing CW Doppler with 100 mm/s sweep speed, the peak PR velocity is measured. The Bernoulli equation measured peak pressure difference then it was added to the RAP [19].

It is possible to estimate the mean PAP from the peak PR Doppler signal by the subsequent formula: mPAP = 4(PR peak velocity)^2 + RAP [19].

- RV diameter [19].
- RV systolic function:
- RV fractional area change (FAC) was assessed using apical four chamber 2-D echocardiography [20].
- RV diastolic function: by pulsed trans-tricuspid Doppler [20]

2.4 Serum Level of Matrix Metalloproteinase 2 (MMP-2): [17]

Using ELISA, Blood sampling: 3.0 ml random venous blood sample under sterile condition was taken. The specimen was put into plain vacutainer tube and kept being clot for 30 minutes at room temperature and was centrifuged at 2000-3000 rpm for 15 minutes to isolate serum, that was kept at -20°c till the analysis time of MMP-2 measures. Estimation of serum MMP-2 by ELISA supplied by Sun Red Company, Catalogue number 201-12-0905.

2.5 Statistical Analysis

Data were inputted into the computer and analyzed utilizing IBM SPSS version 20.0 software programme. (Armonk, New York: IBM Corporation). Qualitative data were presented as number and percent. The Kolmogorov-Smirnov test was performed to confirm the normality of the data's distribution. Quantitative data with a normal distribution were presented by their range, mean, and standard deviation. The median and interquartile range were used to express quantitative data with an atypical distribution. Significance of the obtained results was judged at the 5% level.

3. RESULTS

There was no significant variance among the studied groups as regards age and sex while there was a significantly decreased weight in group I and II than group III ($P<0.05$). There is a significant elevation in HR, RR in group I than group II and III ($P<0.05$), but no significant variance in HR in group II than group III ($P>0.05$) and there is a significant decline in O_2 saturation in group I and II than group III ($P<0.05$), but no significant variance in O_2 saturation in group I than group II ($P>0.05$)). In group I with PAH the most common diagnosis was ASD + VSD (40%), whereas the most common diagnosis in group II was ASD (36%) (Table 1).

As regard to echocardiographic data of the studied group, there is a significant elevation in MPAP in group I than group II and III ($P<0.05$). As regard RV diameter; there is a significant increase in RV diameter in group I than group II and III and between group II and III ($P<0.05$).; there is a significant decline in RV FAC in group I than group II and III and between group II and III ($P<0.05$) there is a significant decline in RV E/A ratio in group I than group II and III ($P<0.05$), but no significant variance in RV E/A ratio in group II than group III ($P>0.05$) (Table 1).

As regard to mean MMP-2 concentration, there is a significant elevation in MMP-2 concentration in group I with PAH-CHD than group II and III ($P<0.05$) as shown in Table 2.

Also, there is a significant elevation in MMP-2 concentration in cases with severe PAH than moderate PAH and mild PAH ($P<0.05$) Table 3.

At follow-up, 8 of 25 cases with PAH-CHD had poor prognosis (dead patients). MMP-2 values were significantly elevated in cases with poor prognosis (dead patients) than those with good prognosis (survivors) ($P < 0.05$) (Table 4).

The best cutoff point of MMP-2 to differentiate cases in PAH-CHD group from CHD group without PH was ≥ 109.7 ng/ml, with sensitivity of

52%, specificity of 96%, PPV of 96 % and NPV of 52% as shown in Fig. 1.

There was a significant positive correlation among serum MMP-2 and mPAP and RV diameter in Group I (P<0.05), However, there was a significant negative correlation among serum MMP-2 and O2 saturation, RV FAC and RV E/A ratio in group I (P<0.05) (Table 5).

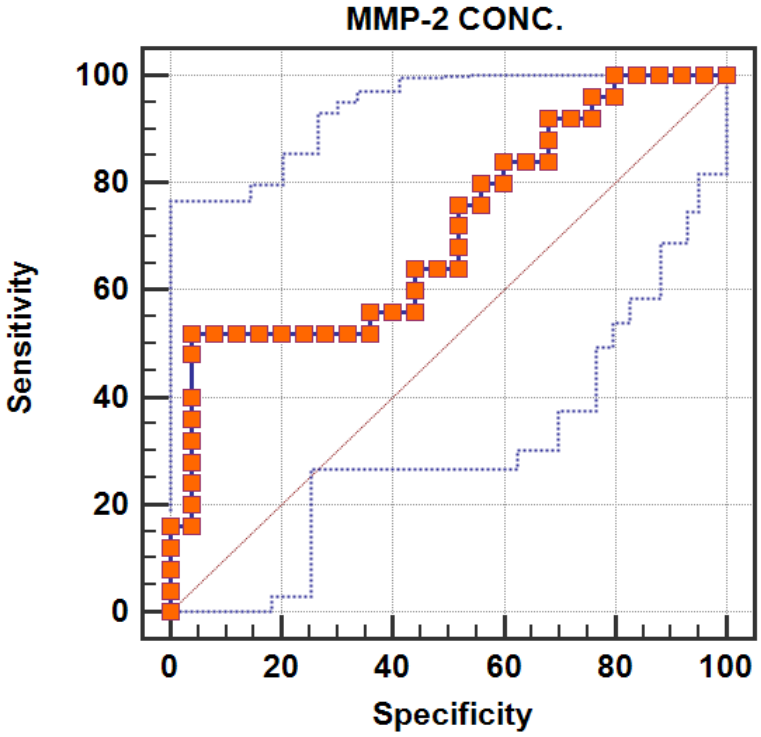

Fig. 1. ROC curve for MMP-2 concentration to discriminate group I (n = 25) from group II (n = 25)

Table 1. Demographic, clinical, and echocardiographic data of the studied groups

Variables	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P value
Age (months)	16.40 ± 41.61	15.70 ± 24.36	11.48 ± 21.10	NS
Sex (male:female)	10:15	15:10	10:15	NS
Weight (kg)	8.56 ± 12.29	7.73 ± 4.71	10.55 ± 4.50	< 0.001*
HR	142.6 ± 28.98	119.6 ± 27.10	103.1 ± 16.80	< 0.001*
RR	51.36 ± 16.47	41.80 ± 10.32	37.48 ± 4.34	< 0.001*
O_2 saturation%	93.32 ± 4.49	94.92 ± 3.08	97.32 ± 1.28	< 0.001*
MPAP (mmHg)	48.04 ± 14.66	17.96 ± 2.62	14.16 ± 2.13	< 0.001*
RV diameter(mm)	20.0 ± 6.26	15.26 ± 3.63	13.21 ± 2.19	< 0.001*
RV FAC (%)	32.92 ± 4.76	34.38 ± 8.13	38.52 ± 2.60	< 0.001*
RV E/A ratio	1.12 ± 0.23	1.31 ± 0.13	1.41 ± 0.15	< 0.001*

Table 2. Comparison between the three studied groups according to MMP-2 Concentration

MMP-2 Conc. (ng/ml)	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P
Mean ± SD	114.63 ± 73.99	64.85 ± 41.13	29.84 ± 12.04	<0.001*

Table 3. Relation between MMP-2 and various degrees of pulmonary hypertension in group I patients (n= 25)

MMP-2 Conc. (ng /ml)	MPAP (mmHg)			P
	Mild (25 – 40 mmHg) (n= 9)	Moderate (41 – 55 mmHg) (n= 9)	Severe (>55 mmHg) (n=7)	
Mean ± SD	54.49 ± 38.74	108.96 ± 52.25	199.26 ± 49.26	<0.001*

Table 4. Prognosis of patients in group I (PAH-CHD) (n= 25)

MMP-2 Conc. (ng /ml)	MPAP (mmHg)		P
	Survivors (25 – 55 mmHg) (n=18)	Died (>55 mmHg) (n= 7)	
Mean ± SD	81.72 ± 52.69	199.26 ± 49.26	<0.001*

Table 5. Correlation between MMP-2 and different parameters in each group of patients

	MMP-2 Conc	
	Group I P value	Group II P value
Age (months)	0.874	0.683
Weight (Kg)	0.825	0.829
MPAP (mmHg)	<0.001*	0.517
HR (b/min)	0.112	0.523
RR (cycle/min)	0.392	0.303
O2 saturation%	0.023*	0.940
RV diameter	0.031*	0.378
RV FAC	<0.001*	0.119
RV E/A ratio	<0.001*	0.915

MPAP =mean pulmonary arterial pressure, HR= heart rate, RR=respiratory rate, RV diameter= right ventricular diameter, RV FAC= right ventricular fractional area change

4. DISCUSSION

In the present research, there was a significant reduction in body weight in PH group than control group and also, a significant reduction in weight of CHD cases with normal pulmonary artery pressure than control group. Common causes of malnutrition in children with CHD, with or without PH, involve hypermetabolic condition, insufficient caloric intake, mal-absorption, hereditary variables, and fluid restriction as part of hemodynamic management [21,22].

These findings are in line with Chinawa et al. [23] who conducted that children with CHD have varied degrees of malnutrition that are worse than those of children without CHD.

In our study, there was a significant elevation in HR and RR in PH group than control cases and the non-PH group. Higher HR in our cases is explained by the increased RV afterload, which leads to an impaired RV stroke volume and sympathetic activation, resulting in a higher HR to maintain adequate oxygen delivery to the body, particularly during activity [24].

This is in agreement with another study on children conducted by Ploegstra and Berger who reported tachycardia in cases with PAH-CHD [25].

In our research, there was a significant decline in O2 saturation in PH group and CHD group without PH as compared to healthy control group. Hypoxemia in PAH is complex, with implications from mismatched ventilation and perfusion, decreased diffusing ability, mixed venous blood with low O_2 saturation in the context of reduced cardiac output, and intrapulmonary or intracardiac shunting [26, 27].

In the present research, there was a significant elevation in RV diameter and significant decrease in RV FAC and in RV E/A ratio in PAH-

CHD group than control group and the non-PH group. The increased RV volume is the outcome of chamber remodeling produced by the elevation in cardiac myocyte length because of recently manufactured sarcomeres resulting from the RV pressure overload generated by PAH [28].

In research by Marc et al. they reported the base diameter of the RV differed among PAH-CHD group and control group where it was larger in PH group [29].

Concerning the RV systolic function, represented by RV FAC, there was statistically significant decrease of RV FAC in PAH-CHD group than CHD and control group. The RV dilates due to an elevation in PAP and RV remodeling, which may impair the RV's systolic function. In cases with pulmonary illness and PAH, RV enlargement may predict death [30].

As regard the RV diastolic function, the RV E/A ratio was significantly decreased PAH-CHD group than CHD and control group, but not reaching diastolic RV dysfunction in our children with PAH-CHD, which may be due to their younger age. This is in line with the conclusions obtained by Elnoamany et al. [31] and Brėchot et al. [32] who exhibited that the rate of RV diastolic dysfunction was significantly increased in PAH cases.

In PAH-CHD cases, RV diastolic dysfunction is linked to RV mass and afterload. By lowering afterload, RV diastolic function enhance. The correlation among diastolic function and predictive factors demonstrated diastolic function is significantly decreased in cases with severe disease [33]. The major cause of RV adaptation and, eventually, failure in PAH is an increase in afterload [34].

In the current research, there was a significant elevation in serum MMP-2 in PAH-CHD children than CHD without PH group than controls, also there was positive relationship among serum level of MMP-2 and severity of PH in PAH-CHD group.

This is in line with Cheng et al. and by Schuman et al. [12,35] who reported a significant elevation in serum MMP-2 in CHD with PAH than control group.

Our outcomes are not in line with Marc et al. [29] who revealed plasma MMP-2 were improved in the PH group than control group, but the variance was not significant. In agreement with our results, according to WHO functional class of PH, the MMP-2 level was very considerably elevated. MMP-2 levels elevated in cases with very elevated SPAP [29].

Also, our outcomes are consistent with Hisazaki et al. [36] who demonstrated that significant positive correlations existed between PVR and serum MMP-2 levels.

In our study, there was significant elevation of MMP-2 in died cases with PAH-CHD (poor prognosis and outcome) as compared to survivors.

Arvidsson et al. [37] and Tiede et al. [38] revealed an increased risk of death among PH cases with MMP-2 concentrations above the median. This highlights the possible significance of MMP-2 as a prognostic indicator, as greater MMP-2 concentrations were related with a poor outcome in PAH.

Furthermore, Shirakabe et al. [39] reported that in the decompensated phase of heart failure, serum MMP-2 values were raised in cases with acute heart failure.

Also, Yamazaki et al. [40] reported that cases with severe heart failure had considerably greater blood levels of MMP-2 than cases with moderate heart failure.

The findings of the recent research showed that the best cutoff point of MMP-2 to differentiate cases in PAH-CHD group from CHD group without PH was ≥ 109.7 ng/ml, with sensitivity of 52 %, specificity of 96%, PPV of 96 % and NPV of 52 %, which are in line with Arvidsson et al. who revealed serum MMP-2 in PAH had sensitivity of 52% and specificity of 93% [37].

Our findings revealed that there was significant positive correlation among serum MMP-2 and mPAP and RV diameter in PAH-CHD cases, and there was significant negative correlation among serum MMP-2 and O2 saturation %, RV FAC and RV E/A ratio in these cases.

Our outcomes are in line with Marc et al. [29] who described MMP-2 values were significantly enhanced in cases with elevated WHO functional class of PH and with high SPAP. Also, this study showed positive correlation between MMP-2 levels and RV diameter.

Also, our outcomes are in line with Liu et al. [41] who stated MMP-2 levels enhanced significantly with declined oxygen saturation in PAH patients.

Moreover, Baggen et al. [42] demonstrated that MMP-2 values negatively correlated with O_2 saturation and positively correlated with RV diastolic dysfunction; represented by RV E/A ratio and with RV systolic Dysfunction; presented by RV FAC in PH patients.

Serum MMP-2 is a promising indicator which can be used to expect prognosis in children with PAH-CHD. Further studies on large groups of pediatric patients for a longer period, with variable causes and variable degrees of PH, are recommended to measure the diagnostic and prognostic value of MMP-2 in PAH-CHD cases. More research is required to comprehend the pathophysiology of elevated MMP-2 in children with PAH-CHD.

5. CONCLUSION

Serum MMP-2 was significantly improved in PAH-CHD children as than CHD children without PAH. Serum MMP-2 was correlated to severity and outcome of PH in PAH-CHD children and correlated to the echocardiographic parameters of its assessment. Serum MMP-2 could be utilized as a cardiac marker in PAH-CHD with good prognostic values, that might be effective in controlling PH in childhood and to predict outcome in PAH-CHD patients.

6. LIMITATION

Baseline evaluation and classification of small number of patient groups were done based on clinical assessment and echocardiographic finding. Follow-up information on a large number of patients would have enhanced the research. Importantly, MMP-2 status of the patient may change with time because of either the natural history of the disease, worsening of the condition, time of sampling after occurrence of PH or applied treatment.

CONSENT

Written informed consent was acquired from all cases, their parents or guardians.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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