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Dysregulation of MMP and TIMP in Congenital Heart Disease: A Non-Meta-Analysis Systematic Review of Molecular Pathology

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Abstract

Background: Matrix metalloproteinases (MMPs) include a group of factors responsible for cell proliferation, apoptosis, and angiogenesis. Changes in the level of this family are associated with the pathology of structural disorders such as Congenital Heart Disease (CHD). This systematic study assessed previous research to determine the therapeutic potential of MMPs in congenital heart disorders.

Method: This systematic review was written based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria, and the principle of nonbias was respected. All the articles from 2014-2024 were extracted from the Web of Science, PubMed and Scopus databases. The study investigated the role of MMPs in the pathology of cardiovascular structural disorders, as well as therapeutic and diagnostic effects of MMP and Tissue inhibitors of metalloproteinases (TIMP) levels.

Results: A total of studies15 were included in our analysis. MMP-1, MMP-2, MMP-3, MMP-8, MMP-10, MMP-13, TIMP-1, and TIMP-4 were found to be significantly elevated in patients with higher degrees of myocardial fibrosis and diastolic heart failure. MMP-2 and MMP-9 levels were significantly increased in hypertensive male patients with bicuspid aortic valve (BAV) and may be associated with an aneurysmal cellular phenotype. MMP-15 plays a critical role in the formation of endocardial cushions, while MMP-1 may serve as a biomarker for ventricular remodeling in patients who have undergone surgery for tetralogy of Fallot (TOF). Elevated levels of TIMP-1, MMP-7 and MMP-12 in patients with postoperative hypoxemia put these children at a higher risk for difficulty weaning off the mechanical ventilator.

Conclusion: Regulating of MMP levels during fetal and postnatal periods could lead to the prevention and treatment of CHD. MMP/TIMP homeostasis is considered the key to CHD treatment and is even an important diagnostic tool.

Key Words: Congenital heart disease; Diagnosis treatment; Matrix metalloproteinases; Systematic review; Tissue inhibitors of metalloproteinases.

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1- INTRODUCTION

Matrix metalloproteinases (MMPs) are important enzymes that remodel connective tissue by breaking down and reconstructing key components such as collagen, elastin, gelatin and casein, and their activity is balanced by Tissue inhibitors of metalloproteinases (TIMPs) (1, 2). The delicate balance between MMPs and TIMPs is critical because MMPs are capable of degrading various components of the extracellular matrix, and their imbalance can lead to cardiovascular disease, cancer and arthritis (3-6). MMPs also seem to be important for managing the process of epithelial-to-mesenchymal transition, including the endocardium mesenchymal transition (7), and influence the morphogenesis of the lower part of the heart and breakdown of the matrix in the dorsal mesocardium (8). This enzymatic activity is believed to play an important role in anatomical cardiac development (9). The interaction between MMPs and TIMPs has been demonstrated to influence processes such as vascular remodeling, the stability of atherosclerotic plaques, even reshaping of the left ventricle following a heart attack, and increased MMP levels in the blood are associated with larger left ventricular sizes (10-12). Changes in MMP and TIMP levels have been detected in the final stages of chronic heart failure (13).

Congenital Heart Diseases (CHDs) are significant cardiac diseases with a prevalence of 10 cases per 1,000 live births in the United States and considerable mortality and morbidity (14). Complications of CHDs, such as endocarditis, arrhythmias, pulmonary hypertension, and heart failure, are common and necessitate complex medical and surgical interventions (15, 16). Despite advances in medical science, the etiology of CHDs is not completely understood. MMPs are implicated in the pathophysiology of CHDs and exert different effects through various mechanisms.

Compared with those in healthy controls, there are higher levels of MMPs in CHD patients, especially in CHD patients with pulmonary hypertension and left-to-right shunts without pulmonary hypertension, and it seems that the presence of MMPs and their inhibitors in myocardial and vascular remodeling are associated with congenital heart defects, but the exact role is not clear (10, 17). This systematic review investigated existing studies on MMPs and TIMPs within the context of CHD. We hope to help these enzymes be potential biomarkers in the future and potentially enhance our understanding of the underlying mechanisms of CHD and may lead to the treatment of patients with CHD.

2- METHODS

2-1. Protocol and Registration

This systematic study was performed based on the accepted criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for answering investigative questions based on the PICO criteria. The study was registered on the Prospective Register of Systematic Reviews (PROSPERO) under the code CRD42024521485.

2-2. Eligibility Criteria and Search Strategy

We reviewed published studies from January 2014 to 2024 in databases such as Web of Science, PubMed and Scopus. To identify CHD, we included various structural disorders, including but not limited to the following:

- Aortic stenosis
- Atrial septal defect
- Atrioventricular septal defect
- Bicuspid aortic valve disorders

- Ebstein's anomaly
- Persistent truncus arteriosus
- Pulmonary atresia
- Tricuspid atresia
- Mitral atresia
- Ventricular septal defect
- Coarctation of the aorta
- Double aortic arch
- Patent ductus arteriosus
- Interrupted aortic arch
- Tetralogy of Fallot

A precise definition of CHD was necessary, so we referred to the definition based on the International Classification of Diseases 11th (ICD-11) criteria. Studies related to CHD were excluded. Studies with the following characteristics were also excluded:

- Studies investigating CHD or heart diseases related to complex syndromes like Marfan syndrome, Wolff–Parkinson–White syndrome, hypoplastic left and right heart syndrome or Down syndrome.
- Studies examining growth factors after surgery or uncongenial disorders.
- Studies focusing on growth factors in disorders (not structural), such as pulmonary arterial hypertension (PAH).
- Studies assessing the immunological aspects of CHD were excluded as they focused on heart disorders separately.
- Studies examining hematological disorders leading to heart disease, like leukemia or immune thrombocytopenia (ITP).

We excluded articles that assessed growth factors alongside other variables like obesity, immunochemical factors, and maternal disorders.

Review studies, case reports, and letters to the editor were excluded, and only original studies (including systematic reviews and meta-analyses) were included in this review. Studies without open access information were included if they provided basic information, at least according to the PRISMA criteria for summarizing articles.

The studies were arranged according to a timeline, older similar studies were replaced by new studies, and the comparison process based on the measurement protocol and the obtained result was carried out by two groups of authors separately and supervised by the responsible author.

We obtained our keywords by searching the Mesh database, which included:

- Matrix metalloproteinase
- Tissue inhibitor of metalloproteinase
- Congenital heart disease

2-3. Data Collection

The following information was extracted from articles by two separate groups:

The first author, main protocol (human or laboratory), main study aim, related immunity elements, main findings, side signaling pathway, investigation method, and inhibitors

An article extraction table was constructed based on the PRISMA checklist and the Cochrane handbook. The variables were determined based on the main points of the research question and were provided to both groups. The results tables of each group were checked under the supervision of the first author and coauthor to remove extraneous and meaningless data from the study.

2-4. Study Selection and Methodological Quality Assessment

Stem cells can reconstruct brain tissue by changing certain immune and tissue parameters. We first extracted these parameters and then investigated each parameter in the context of reported brain disorders. We used our studies based on Risk of Bias in a Randomized Trial 2 (RoB 2) for randomize and non-randomized Studies of intervention studies and product summary tables (18).

2-5. Synthesis

Two authors reviewed the studies separately, and all stages were conducted according to the PRISMA criteria. In case of disagreement in selecting a study, the coauthor resolved the issue. Two separate groups, each including two authors, reviewed the data extracted from the articles. The data were synthesized and revised by the supervision of the corresponding author and the first author. Finally, both groups reviewed the synthesized results so that they could be modified, if necessary, under the supervision of the responsible author.

3- RESULTS

After removing all types of review studies, case reports, and letters to the editor from the PubMed, Scopus, and Web of Science databases, duplicate titles were removed, and the summaries were screened. Studies with non-English full texts were removed after screening the full texts of the articles. Finally, 49 studies were obtained and independently reviewed by two groups of authors. Finally, 21 studies were fully assessed, and 15 were selected to answer our research question. After conducting our systematic review, we checked for similarities in the Cochrane Library database to ensure maximum differentiation. We did not find similar studies that reported similar results (Diagram 1). To ensure the replication of the results, we checked for similarities in the Cochrane Library database. We found almost no similar studies reporting our results, so our results were tracked in the Cochrane Library by the corresponding author and corresponding author.

These results are based on various studies that have examined the role of MMPs and related biomarkers in CHD and other pathological conditions. These proteins are involved in various biological processes, such as wound healing, inflammatory response, and angiogenesis, and can act both as disease factors and as part of homeostasis maintenance processes. The activities of the MMP family are correlated with cardiac development and the initiation, treatment and progression of congenital heart disease (such as aortopathy and TOF). etc.)(19-34).

3-1-1. The etiologies of congenital heart disease are related to the expression of tissue inhibitors of matrix metalloproteinases and the TMIPs.

According to a study by Hanadi, MMP-15 plays a crucial role in the formation of endocardial cushions. These findings confirm that MMP-15 is an important gene in human development, particularly cardiac development, and that its loss of function is likely to cause a severe disorder phenotype. Additionally, another study suggested that ECV is a potent marker for myocardial fibrosis, with specific MMPs and TIMPs (such as MMP-1, MMP-2, MMP-3, MMP-8, MMP-10, MMP-13, TIMP-1, and TIMP-4) being significantly elevated in patients with greater degrees of myocardial fibrosis and diastolic heart failure in Fontan circulatory insufficiency (Table 1).

3-1-2. Changes in aorta tissue growth under an increase in the MMP

MMPs, especially MMP-2, are associated with an enlarged aorta. The impaired elastic properties of the

ascending aorta are linked to elevated plasma MMP-2 levels in patients with bicuspid aortic valve (BAV), so AoD is significantly correlated with MMP-2. On the other hand, Shiho Naito reported a positive correlation between MMP-2 and an inverse correlation between TIMP-2 and BAV at the greater curvature of the aorta. Additionally, elevated WSS and greater MMP-2 expression are noted in the greater curvature region of the ascending morphotype. MMP-1 and MMP-3 show marked increases in the lesser curvature region of the ascending morphotype.

3-1-3. An increase in the MMP leads to degenerate valve and aorta elasticity

Based on a previous study, serum miRNA profiling and protein biomarkers may be useful for diagnosing ascending aortic dilatation in patients with BAV and TAV. MiR-34a and miR-125a may play a role in aortic wall diseases associated with BAV by regulating MMP-2 expression and extracellular matrix remodeling. BAV patients have larger aortas and greater stiffness but lower flexibility and strain. According to Yuntao's study, a surge in MMP-2 levels could have a degenerative effect on the ECM and ultimately lead to a decrease in the mechanical strength and elasticity of vascular walls, which are key events in the weakening of aortic walls in BAV patients. Yang Li showed that MMP-2 levels are significantly higher in BAV patients than in TAV patients.

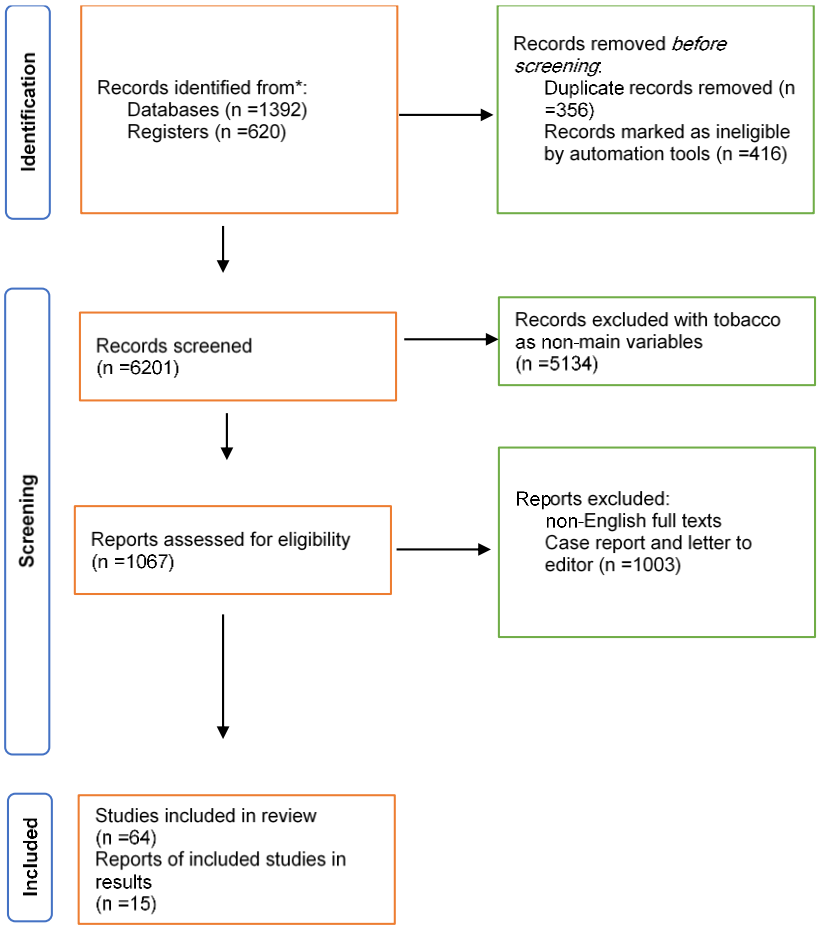

Diagram-1. PRISMA flow diagram for systematic reviews which included searches of databases and registers only.

Table-1. All related genes and factors, including the MMP and TIMP families, separately for each study.

First author/ publish date	MMP and TIMP family
Philip Kottmann (2023)	*MMP-9,* *TIMP-1,*
Karolina Borowie (2023)	*MMP-2, MMP-9,*
Alexandre Bergeron (2023)	*MMP9*
Yuntao LU (2022)	*MMP-2*
Michael P. DiLorenzo (2022)	*MMP1,* *MMP9 MMP2*
Alexandre Bergeron (2022)	
Hanadi A Abdelrahman (2022)	*MMP15*
Benjamin S Frank (2021)	*MMP 7, MMP 12, TIMP-1,*
Shiho Naito (2020)	*MMP2,* *TIMP1,* *TIMP2,*
Fei Li (2020)	*MMP1,* *MMP2,* *MMP3*
Yang Li (2020)	*MMP2,* *MMP9*
Tarek Alsaied (2020)	*MMP1,* *MMP2,* *MMP3,* *MMP8,* *MMP10,* *MMP13,* *TIMP1,* *TIMP4,*
Josephina Haunschild (2019)	*MMP-2,* *TIMP-2,*
Yiu-faiCheung (2019)	*MMP-2,* *MMP-9*
Alessia Gallo (2018)	*MMP-3, MMP-9,* *MMP-2,* TIMP-4, TIMP-1, TIMP-2, TIMP-3

Therefore, these findings indicate a link between endothelial function, aortic structural integrity, and the concentration. Of MMP-2 In contrast, Cheung reported no significant associations between indices of aortic circulating levels of MMP-2 and MMP-9 and elasticity. Additionally, Josephina Haunschild showed that MMP-2 is increased at the gene and protein levels in BAV patients and that MMP-2 activity is greater in aneurysms associated with BAV than in TAV controls.

MMP-2 and MMP-9 levels are significantly increased in hypertensive male BAV patients and are potentially associated with an aneurysmal cellular phenotype. In contrast, MMP-2 is significantly reduced in the ascending

aorta of female HT patients with BAV. Additionally, a study by Budbazar showed that a dramatic increase in aortic MMP-2 expression worsened TAA progression, leading to aortic rupture. Specific mutations in MMP-9 may be associated with diseases such as BAV. Snipas show that the role of MMP-9 in activating inflammatory mediators and/or modifying the connective tissue environment is consistent with the development of BAV.

3-1-4. MMP/TIMP as important parameters for heart remodeling

Neo intimal hyperplasia may play a role in the pathogenesis of increased risk for shunt obstruction in children with complex cyanotic heart disease. MMP-9 is mainly detected in the luminal region of PTFE material (systemic-to-pulmonary shunts) and has a ring-like structure. Therefore, MMP-9 is associated with neointimal hyperplasia in SP shunts in children with CCHD. Generally, these proteins may play a role in the pathogenesis that increases the risk for shunt obstruction. Similarly, Bergeron showed that reduced medial elastin content in pulmonary valve autografts is associated with increased protein levels of MMP-9. Thus, senescent VSMCs may represent the predominant cellular source of increased MMP-9 protein expression, which translates to maladaptive pulmonary valve autograft remodeling.

3-2-1.TOF Remodeling

MMP-1 may serve as a biomarker for ventricular remodeling in patients who undergo surgery for TOF. According to the DiLorenzo study, after TOF repair, patients had increased levels of MMP-1. On the other hand, patients with repaired TOF had significantly higher circulating levels of MMP-2 and MMP-9 than controls. These preliminary results revealed that MMP-1, MMP-2 and MMP-9 are possible biomarkers of ventricular remodeling and could be associated with fibrotic processes underlying RV remodeling, including dilation and hypertrophy.

3-2-2. TGA Remodeling

Postoperative levels of MMP-2 were significantly higher in patients who underwent TGA than in controls. Therefore, trials of therapies that target the MMP pathway for the management of aortopathy in congenital heart patients are warranted.

3-2-3.SVHD Remodeling

BENJAMIN showed that TIMP-1 and MMP-7 levels are higher in SVHD patients with greater morbidity, suggesting an important role for the regulation of extracellular matrix production because of the high levels of TIMP-1, MMP-7 and MMP-12 in patients with postoperative hypoxemia, which places those children at a higher risk of difficulty separating from the mechanical ventilator.

These findings highlight the complex roles of MMPs and related proteins in cardiovascular health and disease, emphasizing their potential as biomarkers and therapeutic targets. The intricate balance between these enzymes and their inhibitors plays a crucial role in maintaining the structural integrity of the cardiovascular system and in the pathogenesis of various cardiovascular conditions.

4- DISCUSSION

An increase in the level of the MMP family is associated with the occurrence of vascular and heart wall disorders. In contrast, a decrease in the level of TIMPs supports the possibility of occurrence. MMP-2 plays an effective role in TAV and BAV, although MMP-9 should be placed next to MMP-2. MMP-1

and MMP-3 play a role in increasing the curvature of cardiac wall surfaces, whileTIMP-1 and MMP-7 control the remodeling of the SVHD. Our results confirmed that disturbances in the homeostasis of MMP and the MMP/TIMP ratio are a pathology and cause of fetal CHD.

The MMP family includes 28 vital enzymes involved in angiogenesis, cellular immunity, cytokine activity, and especially cell proliferation (35). Embryo growth and the formation of primary tissues are stimulated by the expression of MMP, the regulation of the TIMP/MMP ratio and other factors, such as VEGF (36). As a result, cell formation and organ formation, especially in the cardiovascular system, are stimulated by a certain and regulated ratio of MMP. When MMP is lower than normal, the levels of cytokines and tissue factors are disrupted. If MMP increases, disorders such as preeclampsia or abnormal growth of organs can occur (35, 37), especially in the heart. Rabkin reported that aortic disorders, especially TAA, are the result of increased MMP-9 and decreased TIMP-1. His results showed a similar ratio in the BAV (38). Human studies did not contribute much, and patients with both TGA disorders and VSD showed lower levels of iNOS and MMP-2 than those with VSD alone. According to our results, MMP-2 has a positive correlation with BAV, and this ratio is inversely related to TIMP (39). Cheung did not observe a correlation between aortic elasticity and MMP-2 and MMP-9(40). An imbalance in the MMP and an increase in its expression, as well as a decrease in TIMP expression, are the key inhibitory factors of congenital heart disorders. Paying attention to MMP level regulation and MMP/TIMP homeostasis provides us with valuable therapeutic and diagnostic potential for fetal growth management. Jung introduced this family as a diagnostic tool for identifying inflammatory and structural disorders of valves in rats with CAVD (41). Suppression of the expression of MMP-8, MMP-13, and TIMP has been associated with improvements in cardiac and ventricular tissue regeneration in mice (42).

Disturbance of the MMP/TIMP balance during the fetal period and even during puberty and adulthood is associated with a decrease in the remodeling ability of cardiac cells and an increase in the incidence of cardiovascular disorders (10, 11). An increase in the serum level of MMP-1 indicates a decrease in the ability to regenerate vascular tissue in TOF, as a reduction in the MMP-3 level has been associated with the inability to effectively remodel COA. Our available studies showed that MMP-1, MMP-2 and MMP-9 play essential roles in the regeneration of ventricles and even in TGA.

TS patients with aortic coarctation have higher MMP-9 levels, and this ratio is also true for MMP-2 levels in patients with mitral and aortic regurgitation (43). However, no significant differences were found in the MMP-2, MMP-3, or MMP-9 levels between TS patients and controls. Heterotaxy syndrome mutations are associated with mutations in the MMP-21 gene, which affects the development of left–right asymmetry and plays an important role in cardiac rings (44).

Overall, changes in the levels of the MMP family during the fetal period are associated with many disorders, including CHD. Genetic disorders mainly affect the expression of genes in this family and cause regulatory disorders at the family level. The regulation of MMP expression, blood levels and MMP/TIMP homeostasis is considered an important therapeutic and diagnostic point in the course of CHD and overshadows both vascular disorders and cardiac disorders. Considering the role of MMPs in angiogenesis, it can be expected that this family will influence cell

regeneration in the lungs during the fetal period. In this systematic study, we investigated the therapeutic potential of MMPs and their ratio to TIMPs. Despite conflicting studies, the evidence confirms the role of this family in the occurrence of CHD, and few studies of this pathway for tissue regeneration in CHD patients have benefited.

5- CONCLUSION

MMPs and TIMPs, as a group of vital fetal proteins, have high therapeutic potential for the treatment of CHD in the fetal and postnatal periods. An increase in the levels of this group of proteins indicates a good prognosis for CHD patients. Based on our results, we confirmed that the homeostasis of MMPs and TIMPs in fetuses and newborns may be the key to the treatment of CHD. Considering that clinical studies have made few contributions, we suggest that future studies of treatments based on these factors are warranted.

6- ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All procedures performed in this systematic review involving human participants were conducted in accordance with the ethical standards of institutional and national research committees as well as the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The present study is a research project that was conducted under the nephrology department at Hormozgan of University Medical Sciences.

7- AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of this study can be requested from the corresponding author. They are not publicly available due to privacy or ethical restrictions

8- COMPETING INTERESTS

The authors declare that they have no competing interests.

9- FUNDING

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