Asian Journal of Pediatric Research

8(1): 34-40, 2022; Article no.AJPR.83218
ISSN: 2582-2950

Genetic Aspects in Congenital Heart Diseases in Infant of Diabetic Mother: A Review Article

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Authors' contributions

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

Article Information

DOI: 10.9734/AJPR/2022/v8i130236

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/83218

Review Article

Received 12 November 2021
Accepted 15 January 2022
Published 18 January 2022

ABSTRACT

Background: The pathogenesis and effects of maternal diabetes on their infants is still not entirely understood, but it's likely to have several teratogenic mechanisms. The fetal heart is anatomically and physiologically altered by diabetes mellitus. About 400 genes are thought to be involved in the etiology of congenital heart disease such as *DAW1, DNAI1,DRC1*, *PDE2A,CCDC39,TMEM67, and ICAM.* Endothelial cells and immune system cells exhibit the cell surface glycoprotein CD54, also known as intercellular adhesion mollecule-1 (ICAM-1), which is thought to contribute to atherogenesis by increasing monocyte accumulation within the artery intima. In adult individuals with unexplained cardiac dysfunction as well as animals with myocarditis, ICAM-1 expression has been seen on cardiac myocytes. So, the aim of our review is to explore variant genetic aspects implicated in development of congenital heart diseases (CHD) in infants of diabetic mothers and the possible effect of diabetes mellitus.
Conclusion: Genes that were highly enriched in cell adhesion molecules (CAMs) were found to be among the many differentially expressed genes (DEGs) in embryonic heart tissues from diabetic mothers, including ICAM-1, which had the greatest connection degree in the protein-protein interaction (PPI) of both upregulated DEGs and shared DEGs and are major determinants in development of CHD among infant born to diabetic mothers.

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Keywords: CHD; Genetic aspects; ICAM-1; DM.

1. INTRODUCTION

One in every 1,000 newborns is born with congenital heart disease (CHD), a type of birth defect [1]. Heart defects can be produced by a number of environmental teratogen exposures, but the high recurrence risk and familial forms of the illness, as well as the well-described link between CHD and chromosomal aberrations, strongly suggest a genetic basis for CHD [2-4].

1.1 Genes Implicated in Development of Congenital Heart Diseases

CHD etiology is thought to be connected with 400 genes at the most. Cell type cell type specification, differentiation, and patterning are all critical in the formation of the heart's structure and function, and they can all be disrupted by mutations in genes encoding transcription factors, cell signaling transducers, and chromatin modifiers. Disease may be linked to an extensive network of interactions between these genes' proteins since many of them operate together or are related by functional networks [5,6].

Mesodermal differentiation and heart development appeared to be disrupted in experimental models of maternal diabetes mellitus [7].

1.1.1 Intercellular adhesion molecule-1structure

Antibodies and T-cell receptors belong to the immunoglobulin superfamily, which also includes ICAM-1. It has a single transmembrane domain and a carboxy-terminus cytoplasmic domain with an amino-terminus extracellular domain and a single transmembrane domain. Disulfide bridges throughout the protein form many loops in the extracellular domain of ICAM-1, which is characterised by high glycosylation. The beta sheet is the protein's predominant secondary structure, prompting researchers to assume that ICAM-1 contains dimerization domains [8].

1.1.2 Intercellular adhesion molecule-1gene

The expression of certain gene variations has been linked to functional or quantitative changes in ICAM-1 protein in various diseases. Exons 4 and 6 of this gene have been shown to contain two single-base polymorphisms that affect codon 241 and 469. Both alter amino acids and may have various interactions with ICAM-1 ligands depending on how they are metabolized. Rheumatoid arthritis, inflammatory bowel illness, and giant cell arteritis, all have been linked to a variation in codon 241 [9-11]. Bechet's syndrome, chronic renal allograft failure, and multiple sclerosis have been linked to a codon 469 polymorphism [12-14].

1.1.3 Function of Intercellular adhesion molecule-1

In order to attach to the other cells or the extracellular matrix, cells need adhesion molecules [15,16]. In order for cells to engage and move, adhesion mechanisms are necessary. Embryonic development (cell contact and migration), immunology (leukocyte migration and activation) and hematopoiesis (the production of blood cells) are all affected by them (differentiation of hematopoietic cells). For immunology, three major classes of cell adhesion molecules have been identified [17].

Table 1. Genes and alleles implicated in CHD risk (31)

Gene Symbol (mouse)	Gene Symbol (human)	Mouse CDS (bp)	# Alleles Recovered
Daw1	DAW1	933	2
Dnai1	DNAI1	2,106	2
Drc1	DRC1	2,262	2
Pde2a	PDE2A	2,808	2
Ccdc39	CCDC39	2,814	3
Tmem67	TMEM67	2,988	2
Armc4	ARMC4	3,114	I[a]
Adamts6	ADAMTS6	3,351	I[b]
Pcsk5	PCSK5	5,634	2

Table 2. ICAM-1 and autoimmune diseases

References	Autoimmune diseases
Macchioni et al. [9]	ICAM-1 gene polymorphisms
Salvarani et al. [11]	ICAM-1 polymorphism and polymyalgia rheumatica/giant cell arteritis
Verity et al. [12]	ICAM-1 polymorphism and Behcet's disease
Braun et al. [10]	ICAM-1 polymorphism and Inflammatory bowel disease

Table 3. Functions of ICAM-1

References	Functions
Butcher [15]	Leukocyte-endothelial cell recognition
Takeichi et al. [16]	Cadherin cell adhesion receptors and morphogenetic regulator
Springer [17]	Immune system adhesion receptors

Antibody-like cell adhesion molecule (ICAM), which includes ICAM-1 (CD54), ICAM-2 and ICAM- 3 (CD50), as well as the neurons adhesion molecule (NCAM) and platelet/endothelial cell adhesion molecule (PECAM) [18-23]. ICAM-R and ICAM-3 are the same. There are three ICAMs (ICAM-I, II, and III) that share the same integrin receptor, as the leukocyte function associated antigen (LFA) 1 [24,25].

1.1.4 Intercellular adhesion molecule 1 and cardiogenesis

Protein-protein interaction (PPI) network of upregulated differentially expressed genes (DEGs) and PPI network of shared differentially expressed genes (DEGs) both showed ICAM1 to have the highest degree of connection. Endothelial cells and immune system cells usually express ICAM1 (CD54), a cell surface glycoprotein that is thought to have a role in atherosclerosis by encouraging monocyte accumulation in the artery intima [26,27].

Endothelial cells and circulating monocytes have been discovered to exhibit ICAM1, which may be essential for cell attachment to the vascular endothelium in earlier investigations [28]. Cardiac myocytes in both adults with unexplained cardiac failure and in animals with myocarditis have been shown to produce ICAM1[29-31].

Staphylococcus aureus infection, CAMs, and interferon-Gamma (γ) signalling are all associated with ICAM1 via enhancing inflammatory state [32]. Type 2 diabetes is believed to have a pathophysiology including inflammation [33]. The development of inflammatory reactions depends on the upregulation of adhesion molecules such as ICAM1 [34]. ICAM1 may also have a role in the formation of the heart in embryos because of the pathogenic cross-talk between the inflammatory and profibrotic pathways which may result in autoimmune related congenital heart block (CHB) [35].

2. EFFECT OF DIABETES MELLITUS ON CARDIOGENESIS

Glucose-induced abnormalities in left-right patterning, increased apoptosis as a result of oxidative stress, impairments in nitric oxide signaling, altered autophagy, and altered neural crest cell production and migration are all experimentally established pathways that may influence abnormal heart development [36-43].

Preliminary studies have shown that ex vivo models of heart development can serve as an accurate proxy for maternal diabetes because of the teratogenic propensity of glucose. It is yet to be determined how maternal glucose affects the development of cardiac metabolites such as beta-hydroyxbutyrate, but these metabolites are similarly impacted by maternal glucose fluctuations [44-46].

Mesodermal differentiation and heart development are two more areas where canonical signaling pathways have been demonstrated to be altered in experimental models of maternal diabetes mellitus. A variety of cell models and molecular pathways, none of which are mutually exclusive, must be used to better understand how gestational diabetes mellitus influences foetal heart development [7].

Table 4. ICAM-1 gene polymorphisms and disease risk

References	Diseases
Buraczynska et al. [26]	An ICAM-1 K469E mutation is seen in patients with advanced renal insufficiency.
Toyozaki et al. [29]	ICAM-1 and myocarditis
Chong et al. [30]	ICAM-1 and ICAM-2 expression upon Inflamed Pulmonary Epithelium
Lin et al. [32]	ICAM-1 gene polymorphism and congenital heart defects
Duan et al. [34]	ICAM-1 in HUVECs

Table 5. Cardiogenesis defects induced by diabetes mellitus during embryogenesis

References	Cardiogenesis defects
Helle et al. [36]	Children who are born to obese or diabetic mothers are more likely to have congenital heart disease.
Basu et al. [37]	Maternal hyperglycemia and the risk of congenital heart disease are linked to epigenetic mechanisms.
Engineer et al.[40]	Heart malformations associated with sapropterin therapy
Wang et al. [41]	High glucose-induced cardiac tube malformation is caused by autophagy.
Suzukietal. [42]	In vitro, rat cranial neural crest cells are prevented from migrating when glucose levels are severely elevated.
Basu et al. [7]	Fetal heart development and maternal hyperglycemia

2.1 Types of Congenital Heart Diseases in Infant of Diabetic Mother

Pregnant women with gestational diabetes mellitus (GDM) are more likely to give birth to children with heart defects with a percentage of 30%. Conotruncal abnormalities, such as transposition of the major arteries, chronic truncus arteriosus, visceral heterotaxia, and a single ventricle, account for almost half of all cardiovascular problems. These heart abnormalities are linked to high HbA levels in the first trimester. These findings point to an extremely early teratogenic influence on cardio genesis. Asymmetric septal hypertrophy, transient hypertrophic subaortic stenosis, and thicker myocardium are all possible complications ofType 1 and Type 2 diabetes-induced cardiomyopathy (IDMs) [47].

3. CONCLUSION

Maternal diabetes's teratogenic process is not yet entirely understood, and it is seems to be multifactorial. Diabetes mellitus affects the fetal heart both structurally and functionally. Genes that were highly enriched in cell adhesion molecules (CAMs) were found to be among the many differentially expressed genes (DEGs) in embryonic heart tissues from diabetic mothers, including ICAM-1, which had the greatest connection degree in the protein-protein interaction (PPI) of both upregulated DEGs and shared DEGs. We need more studies to explain the genetic aspects in congenital heart diseases.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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