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Fetal Aortic Dysmorphogenesis and Maternal Diabetes: Decoding the Molecular Signaling Pathways Towards New Therapeutic Targets

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Abstract

Morphogenesis in biology represent miraculous fact of our life on the planet. Decoding the mysteries of morphogenesis and the struggle to solve the complexity of the puzzle of creature started very late in human species time line. Deviation in the normal developmental steps of morphogenesis result in congenital anomalies which constitute leading cause of death in most world countries. The most common congenital anomaly is congenital malformation of the human heart. Until the moment, most of the causes of congenital heart diseases (CHDs) are still, obscure and unknown. CHD constitute major health ,social ,psychological and economic burden on individuals , families as well as world communities and nations. The most accurate illuminator to solve the puzzle of causes of diseases is epidemiology. Epidemiology must be the guiding force towards the different scientific directions to fight diseases. The study of the cellular and molecular pathogenesis of heart valve disease is an emerging area of research made possible by the availability of cultures of valve interstitial cells (VICs) and valve endothelial cells (VECs) and by the design and use of in vitro and in vivo experimental systems that model elements of valve biological and pathobiological activity. The wisdom derived from the up to date scientific literature dectate more gobal perspect of aortic valve disease. Congenital aortic valve stenosis most commonly due to bicuspid aortic valve stenosis(BCAS) and Calcific Aortic Valve Disease (CAVD) are continuum of one common stem of pathology. Towards the dream of aborting the process of cardiac dysmorphogenesis in human, we established a nation wide epidemiological project devoted to discover genetic and environmental risk factors of CHD. The philosophy of the project was to adopt etiological perspective based on collecting massive genetic and environmental data on each CHD subtype, followed by statistical management to establish statistical correlations towards investigating cause-effect relationship. Although, it is well known that maternal diabetes is very important risk factor for CHD in all world nations, the operating cellular and molecular signaling pathways ending up with BCAS are still elusive. *This paper is an atempt to explore the dynamics of cellular and molecular signaling involved with BCAS in maternal diabetes, toward the path of suggesting possible therapeutic as well as preventive measures of aortic valve disease in human species.*

Keywords: Aortic valve; Fetus; Cardiogenesis; Molecular signaling; Epidemiology; Risk factors; Metformin; Insulin

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Introduction

The orchestration of human cardiogenesis represents one of the most intricate and awe-inspiring phenomena in developmental biology, reflecting an evolutionary culmination of molecular precision, temporal fidelity, and spatial orchestration. Among the structural anomalies that disrupt this tightly regulated process, congenital heart diseases (CHDs) constitute a significant global health burden, with congenital malformations of the aortic valve—particularly bicuspid aortic valve stenosis (BCAS)—ranking among the most prevalent and clinically challenging phenotypes. Despite significant strides in the elucidation of cardiac developmental pathways, the precise etiopathogenic mechanisms that culminate in aortic valvulogenesis anomalies remain incompletely understood, particularly within the context of maternal metabolic derangements. Maternal diabetes mellitus, encompassing both pregestational and gestational subtypes, has emerged as a critical teratogenic milieu that perturbs embryonic signaling networks, epigenetic programming, and cellular energetics during critical windows of fetal development. Epidemiological meta-analyses chaired by us have substantiated the strong correlation between maternal hyperglycemia and increased incidence of CHDs, yet the molecular intermediaries that transduce these systemic metabolic cues into valvular dysmorphogenesis remain largely elusive. In response to this scientific imperative, we initiated a nation-wide, etiologically-driven epidemiological investigation in the Kingdom of Saudi Arabia, designed to comprehensively delineate the interplay between genetic susceptibilities and environmental exposures in the genesis of CHDs. This endeavor—unique in its scope, granularity, and methodological rigor—enabled the extraction of over 3 million statistical variables from 4491 affected individuals, thereby affording an unparalleled opportunity to statistically interrogate and biologically interpret associations with a high-resolution lens. This manuscript focuses specifically on the subset of patients diagnosed with isolated BCAS, exploring its epidemiological correlates with maternal diabetes and therapeutics, particularly oral hypoglycemic agents (OHAs) versus insulin therapy. In doing so, we aim to decode the epigenetic, inflammatory, and metabolic signaling cascades operative in fetal valvular morphogenesis. Our objective transcends mere association; rather, we endeavor to illuminate actionable molecular targets and identify modifiable maternal factors, potentially heralding a paradigm shift in the prevention and noninvasive therapeutic modulation of CHDs. Through this integrative investigation—anchored in clinical epidemiology and extrapolated into systems biology—we advance a novel, mechanistically grounded understanding of how maternal metabolic status interfaces with the fetal epigenome and valvular cell biology, charting a new path toward precision perinatal cardiology and regenerative valve therapeutics.

Materials and Method

Genetic and environmental risk factors of congenital heart defects (CHD) of the whole populated area of the Kingdom of Saudi Arabia were collected in the 60 month period. This experimental protocol was approved and funded by the government of Saudi Arabia represented by King Abdulaziz City for Science and Technology (https://kacst.gov.sa/), the principal governmental authority in charge of science, technology, and innovation as well as funding scientific research projects (11-Bio1840-19). The author of this paper is the principal investigator of the project. The project includes Hospitals, primary health care centers, pediatric cardiology centers concerned with care of CHD and the community. Congenital heart disease (CHD) is defined as a gross structural abnormality of the heart or intrathoracic great vessels that is actually or potentially of functional significance [1]. Participants in the project constitute a unique national sample of live born infants in the first year of life . The main objective of the project was to shed light on probable environmental and genetic risk factors implicated in the etiology of CHD. Cases were defined as infants born alive with CHD in the five years of the study period to parents who were residents of the study area. Disease status was defined as CHD present at birth (coded 1) else, it is absent (coded 0). Data sheets were designed to filter and encode the information from the questionnaires and qualitatively controlled (Figure 1).

CHD diagnosis is confirmed before 1 year of age by certified pediatric cardiologists, according to a hierarchical classification system (Figure 2). This hierarchy is divided to 49 morphogenetic land marks adopted to pinpoint the chronobiological timing of the embryogenic insult giving rise to the specific congenital heart disease subtype. One of the most important difficulties was the decision of the timing of the complex anomalies. For the purpose of purity of data trying as much as possible to hunt the cause or the risk factor under investigation, the decision in cases of more than one or more complex lesions, was to consider the diagnosis based on the timing of the first insult according to the hierarchy in Figure 2 [2]. Each subtype of the 4491 affected cases with congenital heart diseases received 412 questions and accordingly 412 statistical variables resulted, ending up with 1,850,292 potential risk factors for cases and 3,018,724 risk factors for the whole project.

Questionnaires were expanded to include a detailed inquiry about exposures to various environmental and genetic factors [3] (Abdullah Alabdulgader, Book, Congenital Heart Disease Project in the Kingdom of Saudi Arabia.Alahssa1427H. ISBN:1-2-901-56-9960.King Fahad National Library. Riyadh, Saudi Arabia.: 31061914; PMCID: PMC6488810). In addition to demographic data,it includes questions to the mother, detailed pregnancy history, detailed drug history,

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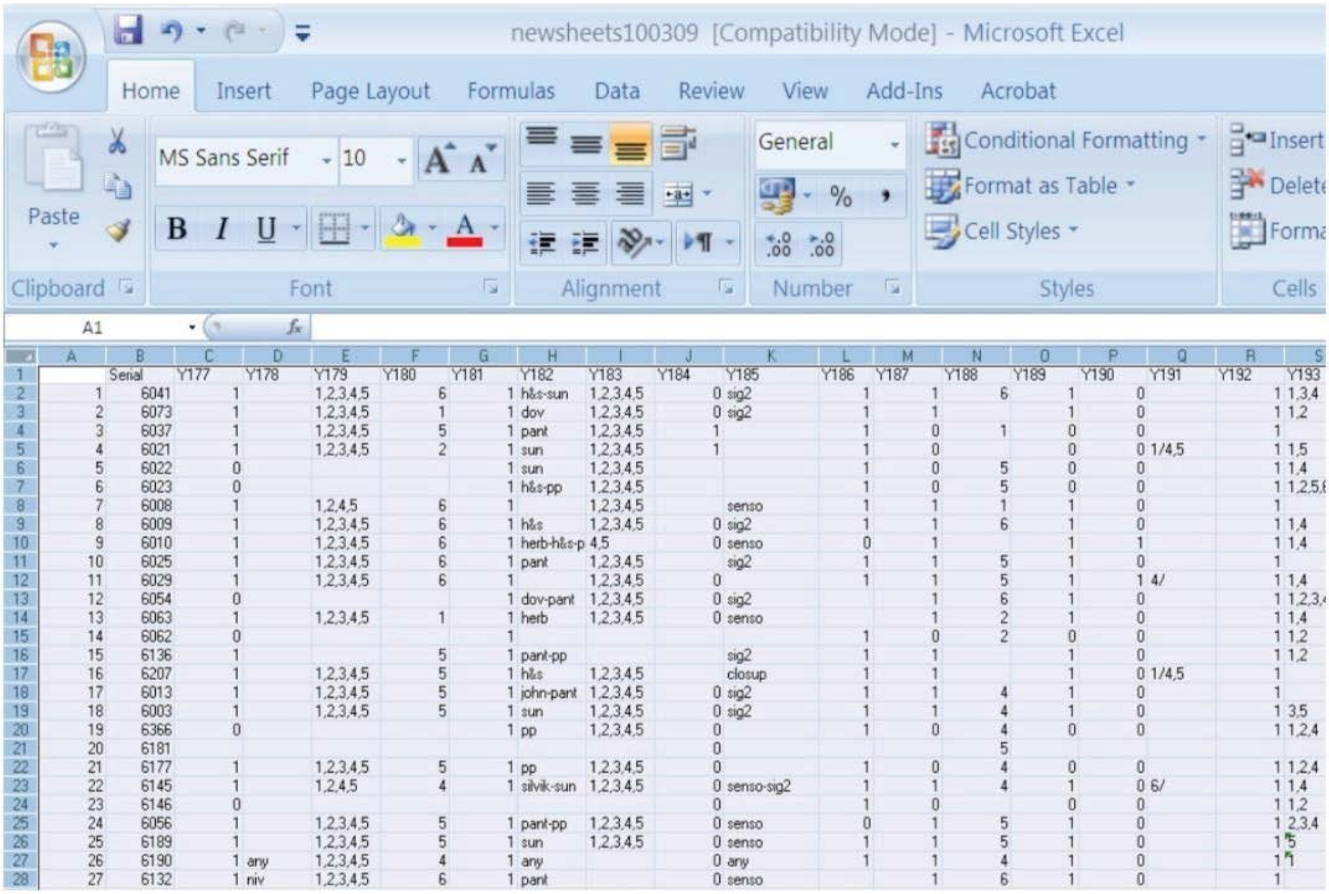
residence, income, mothers exposure and practice, fathers exposure and practice, as well as detailed nutritional questionnaire. The 7327 questionnaires for affected cases and controls were fulfilled by trained interviewer. 97 cases were isolated bicuspid aortic valve stenosis, constituting 2.6% of the whole affected population. Each single diagnosis was exposed to 412 question resulting in around 40,000 statistical variables related to BCAS which were exposed to extensive statistical analysis. All interviews were completed with physical confrontation with parents mainly mothers. Parents are interviewed about a wide range of genetic, physiological, medical and exposure to environmental factors that occurred during and before the pregnancy, assessing exposures at home, job and other sites. Vulnerability period in our project was defined as the six months period , three months before conception and three months post conception.



	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P	Q	R	S
1		Serial	Y177	Y178	Y179	Y180	Y181	Y182	Y183	Y184	Y185	Y186	Y187	Y188	Y189	Y190	Y191	Y192	Y193
2	1	6041	1		1,2,3,4,5	6	1	h&s-sun	1,2,3,4,5	0	sig2	1	1	6	1	0		1	1,3,4
3	2	6073	1		1,2,3,4,5	1	1	dov	1,2,3,4,5	0	sig2	1	1		1	0		1	1,2
4	3	6037	1		1,2,3,4,5	5	1	pant	1,2,3,4,5	1		1	0	1	0	0		1	
5	4	6021	1		1,2,3,4,5	2	1	sun	1,2,3,4,5	1		1	0		0	0	1/4,5	1	1,5
6	5	6022	0				1	sun	1,2,3,4,5			1	0	5	0	0		1	1,4
7	6	6023	0				1	h&s-pp	1,2,3,4,5			1	0	5	0	0		1	1,2,5,6
8	7	6008	1		1,2,4,5	6	1		1,2,3,4,5		senso	1	1	1	1	0		1	
9	8	6009	1		1,2,3,4,5	6	1	h&s	1,2,3,4,5	0	sig2	1	1	6	1	0		1	1,4
10	9	6010	1		1,2,3,4,5	6	1	herb-h&s-p	4,5	0	senso	0	1		1	1		1	1,4
11	10	6025	1		1,2,3,4,5	6	1	pant	1,2,3,4,5		sig2	1	1	5	1	0		1	
12	11	6029	1		1,2,3,4,5	6	1		1,2,3,4,5	0		1	1	5	1	1	4/	1	1,4
13	12	6054	0				1	dov-pant	1,2,3,4,5	0	sig2		1	6	1	0		1	1,2,3,4
14	13	6063	1		1,2,3,4,5	1	1	herb	1,2,3,4,5	0	senso		1	2	1	0		1	1,4
15	14	6062	0				1					1	0	2	0	0		1	1,2
16	15	6136	1			5	1	pant-pp			sig2	1	1		1	0		1	1,2
17	16	6207	1		1,2,3,4,5	5	1	h&s	1,2,3,4,5		closup	1	1		1	0	1/4,5	1	
18	17	6013	1		1,2,3,4,5	5	1	john-pant	1,2,3,4,5	0	sig2	1	1	4	1	0		1	
19	18	6003	1		1,2,3,4,5	5	1	sun	1,2,3,4,5	0	sig2	1	1	4	1	0		1	3,5
20	19	6366	0				1	pp	1,2,3,4,5	0		1	0	4	0	0		1	1,2,4
21	20	6181								0				5					
22	21	6177	1		1,2,3,4,5	5	1	pp	1,2,3,4,5	0		1	0	4	0	0		1	1,2,4
23	22	6145	1		1,2,4,5	4	1	silvik-sun	1,2,3,4,5	0	senso-sig2	1	1	4	1	0	6/	1	1,4
24	23	6146	0							0		1	0		0	0		1	1,2
25	24	6056	1		1,2,3,4,5	5	1	pant-pp	1,2,3,4,5	0	senso	0	1	5	1	0		1	2,3,4
26	25	6189	1		1,2,3,4,5	5	1	sun	1,2,3,4,5	0	senso	1	1	5	1	0		1	5
27	26	6190	1	any	1,2,3,4,5	4	1	any		0	any	1	1	4	1	0		1	1
28	27	6132	1	niv	1,2,3,4,5	6	1	pant		0	senso		1	6	1	0		1	

Figure 1: A sample of the data entry sheet was used to obtain 3,018,724 statistical variables of potential risk factors for congenital heart malformations.

Two cohort groups were derived from the study population.The first cohort consists of 1010 CHD affected subjects with 1010 control were studied specifically for extra cardiac anomalies association with valvular aortic stenosis and other CHD subtypes [4]. Another cohort composed of 2604 patients was studied for the proportion of each cardiac subtype in the four most populated regions of the country to overcome the referral bias to the central region where most cardiac centers are located [5]. Total of 3,018,724 statistical variables were collected for the whole study of all CHDs. Out of all, 2.16% of the whole study population were isolated aortic valve stenosis counting for 40,000 statistical variable.

Results

Isolated Bicuspid aortic valve stenosis(BCAS) was found in 97 cases out of the project 4491 cases constituting 2.16% of the total (Table 1).

Table 1: Cases of AS in 4491 subjects with CHD.

AS	Freq.	Percent	Cum.
No	4,394	97.84	97.84
Yes	97	2.16	100
Total	4,491	100	

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1. First fusion of epimyocardial layers of bilateral heart primordia	25. Upstream (proximal) division of bulbus with closure of interventricular foramen complete
2. Completion of fusion of primordia of bulbus cordis and primordia of ventricles	26. Appearance of intercalated swellings of semilunar valves
3. First appearance of myofibrils in myocardium	27. Semilunar valves achieve grossly mature form
4. First myocardial contractions	28. Atrioventricular valves achieve grossly mature form
5. Blood flow through heart begins	29. Aortic arches I definitive
6. Appearance of external atrioventricular and bulboventricular grooves or sulci	30. Dorsal aortas fuse
7. Earliest heart curvature apparent	31. Aortic arches I disappear
8. Achievement of S-shaped curve	32. Aortic arches II definitive
9. Expansion and ventromedial rotation of primordium of right ventricle	33. Aortic arches II disappear
10. Atrial septum primum appears	34. Aortic arches III definitive
11. Perforations (ostium secundum) in atrial septum first seen	35. Aortic arches IV definitive
12. Atrial septum secundum first definable	36. Dorsal aortas between arches III and IV disappear
13. Alignment of right atrial cavity with primordium of right ventricular cavity	37. Dorsal aorta (right or left) distal to arch IV disappears
14. Ventral and dorsal endocardial cushions first definable	38. Aortic arches VI definitive
15. Ostium primum closed by fusion of septum primum with endocardial cushions	39. Dorsal portion of one (right or left) aortic arch VI disappears
16. Ventral and dorsal endocardial cushions unite	40. Buds of main pulmonary vein projects from atrium
17. Cells first seen in cardiac jelly	41. Main pulmonary vein unites with pulmonary venous plexus
18. Trabeculations first seen in regions of ventricles	42. Buds of coronary veins from coronary sinus first definable
19. Muscular ventricular septum first definable	43. Buds of coronary arteries first definable
20. Aortic-pulmonary septum first definable	44. Left anterior cardinal vein obliterated
21. Internal division of aortic sac by aortic-pulmonary septum complete	45. Mesenteric portion of interior vena cava first definable
22. Rotation of downstream (distal) segment of bulbus cordis	46. Conduction system first definable histologically
23. Septa or ridges of bulbus cordis first definable	47. Main conduction system organized in its major form
24. Downstream (distal) division of bulbus cordis completed	48. Purkinje system can be identified
	49. Nervous tissue first definable histologically in heart or great arteries
From Sissman HJ. Developmental landmarks and cardiac morphogenesis: comparative chronology. Am J Cardiol 1970; 25:141.	

Figure 2: Developmental landmarks of the chronobiology of cardiogenesis. Land marks 24,25,26 and 27 are witnessing the formation of the aortic valve [2].

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Percentage of cardiac lesions in 2604 patients with congenital heart disease in the 4 most populated regions in Saudi Arabia is shown in Table 2.

VSD = ventricular septal defect; ASD = atrial septal defect; PS = pulmonary stenosis; PDA = patent ductus arteriosus; AVSD atrioventricular septal defect; TOF = tetralogy of Fallot; AS = aortic stenosis; COA = coarctation of aorta; D-TGA = dextro-transposition of great arteries

Percentage of congenital valvular aortic stenosis(VAS) in 9 different world countries is shown in Table 3.

Long term diabetes and Gestational diabetes using OHA (Metformin) increase ORs of BACS diagnosis by 2.09 and 4.8 respectively with 95% confidence interval of 0.6-7.4 and 0.9-26.9,respectively. Long-term diabetic mothers on insulin and gestational diabetes on insulin are showing protective effect manifested by odds ratio of 0.31 and 0.48 respectively with 95% confidence intervals of 0.6-1.6 and 0.13-1.7 respectively (Table 4).

Table 2: Distribution of congenital valvular aortic stenosis (VAS) and other most important CHD subtypes in the four most populated regions of the country.

Lesion	Al Hassa		South east		North central		West		Overall	
	No.	%	No.	%	No.	%	No.	%	No.	%
VSD	292	39.5	109	32.5	123	38.4	359	29.7	883	33.9
ASD	85	11.5	35	10.4	37	11.6	314	26	471	18.1
PS	66	8.9	34	10.1	29	9.1	195	16.1	324	12.4
PDA	64	8.6	53	15.8	25	7.8	159	13.2	301	11.6
AVSD	26	3.5	12	3.6	16	5	38	3.1	92	3.5
TOF	31	4.2	18	5.4	15	4.7	26	2.2	90	3.5
AS	26	3.5	9	2.7	9	2.8	20	1.6	64	2.5
COA	20	2.7	11	3.3	6	1.9	23	1.9	60	2.3
D-TGA	14	1.9	5	1.5	14	4.4	22	1.8	55	2.1
Other	116	15.7	49	14.6	46	14.4	53	4.4	264	10.1
Total	740	100	335	100	320	100	1209	100	2604	100

Table 3: Distribution of most frequent Congenital Heart Diseases in 9 countries.

Lesion	Saudi Arabia	Sweden[a]	USA[b]	Nigeria	Denmark	USA[c]	UK[d]	Canada[e]	Japan	Hungary
	% (n = 2604)	% (n = 369)	% (n= 163)	% (n = 635)	% (n = 5249)	% (n= 420)	% (n= 338)	% (n = 464)	% (n = 773)	% (n = 43)
VSD	33.9	27.1	31.3	35	24	32.1	28.1	31	60	20.9
ASD	18.1	4.3	6.1	7.5	9.4	7.4	8.3	11.2	5.3	10.4
PS	12.4	3.8	13.5	9	5.9	8.6	2.7	10.8	9.6	10.4
PDA	11.6	9.5	5.5	22	12.6	8.3	6.5	7.1	3.6	11.9
AVSD	3.5	3	3.7	-	2.6	3.6	7.4	-	1.8	4.5
TOF	3.5	4.1	3.7	10	5.8	5	8.6	8	5.8	4.5
AS	2.5	5.4	3.7	0.6	4.7	3.8	4.1	8.4	1	11
COA	2.3	9.8	5.5	2	7	6.7	5.6	3.4	2.7	6
D-TGA	2.1	6	3.7	4.5	4.8	2.6	5.6	2.6	2.2	4.5
Other	10.1	27	23.3	9.4	23.2	22	23.1	17.5	9.5	15.9

aGothenburg; bCalifornia; cMulti-centre; dBlackpool; eToronto. VSD = ventricular septal defect; ASD = atrial septal defect; PS = pulmonary stenosis; PDA = patent ductus arteriosus; AVSD = atrioventricular septal defect; TOF = tetralogy of Fallot; AS = aortic stenosis; COA =coarctation of aorta; D-TGA = dextro-transposition of great arteries. - = not measured

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Table 4: Odds ratio and 95% confidence intervals of known Diabetic and gestational Diabetic mothers on OHA. As well as known Diabetic and gestational Diabetic mothers on insulin.

BCAS	Odds ratio	Robust Std. error	z	P>|z|	[95% Conf.Interval]	
Kown Diabetic on OHA	2.098492	1.359447	1.14	0.253	0.5894962	7.470221
Gestational Diabetics on Hypoglycemics (OHA)	4.815838	4.224261	1.79	0.073	0.863042	26.87273
Known Diabetics on Insulin	0.3057426	0.2552816	-1.42	0.156	0.0595169	1.570622
Gestational Diabetics on insulin	0.4805834	0.3090597	-1.14	0.255	0.1362596	1.695003

Discussion

The process of cardiogenesis in the human species has remained as a mystery since the dawn of human history on earth. The explosive scientific developments in medicine and its subspecialties in the last 8 decades have increased our knowledge of the complexity of cardiogenesis. Solving the mysterys of the key questions in cardiogenesis require innovative, interdisciplinary approaches that integrate information from epidemiological, genetic, epigenetic,molecular biology, and bioengineering studies incorporating systems biology approach to identify the components of complex systems and to model their dynamic interactions on humans and animal models. Wisdom dictates that the holy mission can be achieved only through the science of epidemiology. We follow this wisdom pathway where an extensive questionnaire for cardiogenesis risk factors was established and published as a book for the use of the next generations of researchers in the field [4]. The vulnerability period expands for six-month periods, 3 months before conception reflecting the womb environment before conception, and 3 months after conception which coincides with organogenesis. This paper is devoted to Bicuspid Aortic Valve Stenosis (BCAS). Statistical significance for BCAS was documented with 7 genetic and environmental factors. Diabetes Millets was one of them. This paper will be devoted to investigate the mysterious pathways of fetal aortic dysmorphogenesis and maternal diabetes in an attempt to suggest new medical therapeutic measures for aortic valve stenosis in the human species.

According to WHO website at the time of publication about 830 million people worldwide have diabetes, the majority living in low-and middle-income countries. More than half of people living with diabetes are not receiving treatment. Both the number of people with diabetes and the number of people with untreated diabetes have been steadily increasing over the past decades (https://www.who.int/health-topics/diabetes#tab=tab_1). Pooled results of 24 studies (26 cohorts) suggested that maternal diabetes had a significant correlation with elevated CHD risk in offspring (OR 2.65, 95% CI 2.20–3.19). (6) Gestational Diabetes Miletus (GDM) reported one of the highest worldwide incidences in the study region(Saudi Arabia) and other Arab Gulf Cooperation Council Countries (GCC) (14.7%, 95% CI, 13.0–16.5%) [6]. In our population 2.16% of all CHD subjects were affected with BCAS which is reconfirming previous work for us with a similar percentage(2.5%) [7]. This percentage is considered to be low compared to most world countries but investigation in this direction is not the scope of this paper. *Women with diabetes at the time of conception are five times more likely to have infants with CHDs* [8]. Of great importance in our results is the risk of using oral hypoglycaemic agents(OHA) as well as insulin to treat diabetes during pregnancy. *The Oral Hypoglycaemic Agent (OHA), metformin, was found to exponentiate the risk of developing BCAV while insulin therapy was found to be protective*. The odds ratio for metformin was 4.8, the standard error was 4.2 and the 95% confidence interval was (.86-26.9). The odds ratio for insulin therapy was(0.30) , the standard error was (0.26) and 95% confidence interval was (0.6-1.6). Traditionally, the gold standard in the management of Type 2 diabetes in pregnancy and gestational diabetes is insulin. Implementation of (OHA) as an alternative to insulin therapy was practiced due to insulin-associated cost, pain at the injection site, need for refrigeration, need for multiple injections as well as need for skillful handling of the syringes [9]. Toward the exploration of cellular and molecular pathways, considering the complexity of Cardiac dysmorphology is a must. It is an intricate interplay of genetic as well as other factors like maternal environment, genetic predisposition, and epigenetic regulations. A new perspective on gene regulation has been expanding in recent years which brought us to a more integral perspective on the etiology of aortic stenosis from the time of conception until adult life. Hemodynamic abnormalities due to the bicuspid valve can not alone, explain the propensity of this type of valve for calcification and fibrosis but additional genetic, epigenetic, and tissue abnormalities are all operating. Bicuspid aortic valve stenosis represents most of the valvular aortic stenosis cases in adults and is characterized by representing the server proportion of the disease spectrum. We perceive bicuspid aortic valve stenosis in humans as a continuum process of morphogenetic events manifested as a bicuspid aortic valve in the newborn with genetic, histological, inflammatory, cellular responses, and hemodynamic predisposition for calcification and fibrosis in the adult life ending up with valvular aortic stenosis. Hyperglycemia alters gene

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expression at various stages of heart development including cardiac neural crest cell migration, outflow tract formation, and inflow tract formation [10,11]. Conditional DNA methyl transferase 3-B (DMT3B) knock-out is associated with congenital heart disease phenotypes like ventricular septal defects and endocardial cushion defects [12]. *Maternal hyperglycemia increases DNA methylation in several cardiac gene promoters and corresponds to differential expression* [13]. Other potential players that were linked to epigenetic reversible factors affecting aortic valve stenosis without hyperglycemia are posttranslational histone modification, ATP-dependent chromatin remodeling, and non- coding regulatory RNAs [14]. Promising and exciting understanding that might open the doors for future medical, noninvasive therapeutic interventions for aortic stenosis is the knowledge that *epigenetic marks are potentially reversible*. It was found that the methylation of Notch1 promoter mediates the osteogenesis differentiation in human aortic valve interstitial cells through Wnt/β-catenin signaling. Recently Crosstalk between Wnt and bone morphogenetic protein signaling during osteogenic differentiation was described [15]. Notch1 promoter methylation leads to a decreased Notch1 expression and subsequent decreased release of Notch1 intercellular domain(NICD) in the nucleus of human Aortic Valvular Interstitial Cells (hAVICs), therefore promoting the activation of Wnt/β-catenin signaling and the expression of osteogenesis differentiation factors, finally promoting the osteogenesis differentiation in hAVICs [16]. Pathogenic molecular alterations and the epigenetic regulatory mechanisms operating during fetal life may influence the adult phenotype, including an individual's susceptibility to cardiovascular diseases (CVD). As a matter of fact the late onset of CVDs may have its root linked to age related alterations of epigenetic marks [17,18,19,20,21]. *This level of knowledge might pave the way for DNA methylation to act as an important bridge to link epigenetic interaction and fetal BCAV development towards the way of aborting maternal hyperglycemia induced fetal aortic valve pathology ,and to adopt this knowledge in manipulation of similar pathologic pathways. It is promising to know that all known epigenetic marks are reversible, thus opening the possibility for prophylactic or therapeutic non invasive intervention and reprogramming of cells even in the early stages of disease progression in all human age spectrum from embryogenesis to adulthood.*

In contrast to finding *metformin exponentiating the risk of developing BCAV, insulin therapy on the other hand was found to be protective.* Endogenous insulin is well known to act as a growth factor for the fetus leading to storage of excessive amounts of glucose as glycogen and fat in the fetal body making these babies larger than the normal(macrosomia). Insulin signaling has been found to have some influence on heart development and valve formation during embryogenesis. Insulin, along with its associated signaling pathways, plays a role in regulating cell growth, differentiation, and survival, which are crucial processes in embryonic development. Based on the amino acid sequence, the molecular weight of insulin is 5734 daltons, which is equivalent to 5734 g/mol , so it does not pass through the placenta easily. Insulin can cross the placenta more easily if Insulin antibodies formed and increase its transfer to the fetus. The presence of insulin in fetal circulation can be also endogenous from the fetal pancreas. Insulin signaling has been implicated in regulating the proliferation and differentiation of valvular interstitial cells(VICs) and valve progenitor cells. Insulin promotes the expression of genes involved in valve development and extracellular matrix remodeling, which are essential for proper valve formation. Insulin molecules are relatively large. Exogenous insulin, if it passes the placenta, was found to produce significant effects in the form of structural and functional alterations of the placental as well as fetal and maternal outcomes [22]. VICs are susceptible to insulin by expressing insulin receptors and increasing proliferation activity under hyperinsulinemia. *Hyperinsulinemia was found to increased proliferation of the VICs, increased collagen type 1 and decreased α-smooth muscle actin expression* [23]. Those cellular changes might be beneficial but excess of which might be pathological. Increased VICs proliferation may be necessary for proper tissue growth and repair during development or following injury. But excessive VICs proliferation could lead to abnormal tissue growth or contribute to pathological conditions such as valve thickening or fibrosis. Collagen type 1 is a major component of the extracellular matrix (ECM) in heart valves. Increased collagen type 1 expression can contribute to ECM remodeling and tissue repair processes. However, excessive collagen deposition or remodeling can lead to stiffening and dysfunction of the valve, which can be detrimental. Decreased α-SMA expression in VICs may suggest a shift towards a more synthetic or myofibroblast-like phenotype. This phenotypic change can contribute to ECM remodeling but may also disrupt the normal balance of cell types within the valve and potentially impair its function. Another potential indirect mechanism is the role of insulin in inhibition of the neuronal damage through the Nrf2 signaling pathway, which regulates endogenous oxidant-antioxidant balance, therefore insulin may be a potential protective agent for the treatment of oxidative stress [24]. In adults, oxidative stress is associated with reduced antioxidant enzymes expression and Increased DNA damage in the early stage of CAVD [25]. Glycolytic capacity and mitochondrial function are activated by hyperinsulinemia leading to exaggerated metabolic activity. Potential protective mechanism of insulin in the context of fetal BCAV is that, insulin can increase glucose oxidation indirectly by enhancing glucose uptake and glycolysis. Insulin also directly stimulates mitochondrial

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glucose oxidation, independent of increasing glucose uptake or glycolysis, through activating mitochondrial pyruvate dehydrogenase (PDH). Direct insulin stimulation of glucose oxidation is associated with enhanced phosphorylation of mitochondrial Akt, GSK-3β and PKC-δ [26]. Mitochondrial glucose oxidation in fetal valvular interstitial cells(VICs) serves as a vital source of energy for its various cellular functions. VICs require energy to support their growth, proliferation, and maintenance of cellular homeostasis. The ATP generated through mitochondrial glucose oxidation fuels important cellular processes, including protein synthesis, transport of molecules, and maintenance of the extracellular matrix within the developing heart valves. Impaired mitochondrial function or disruptions in glucose metabolism can lead to reduced ATP production and altered cellular metabolism. These changes may affect cellular viability, impair normal cell functions, and potentially impact the proper development of the heart valves. *Under favorite circumstances, those mechanisms might explain the protective effect of insulin that we reported in our population against the anomalous embryogenetic pathways in the fetal VICs ending up with BCAV.*

The most commonly used oral hypoglycemic agents during the study period was metformin. Metformin is typically the first-line medication for the treatment of type 2 diabetes in our population. It works by reducing glucose production in the liver and improving insulin sensitivity in muscle and fat tissues. Sulfonylureas acts by stimulating the pancreas to produce more insulin. Examples include glyburide, glipizide, and glimepiride. Thiazolidinediones (TZDs), and Alpha-Glucosidase Inhibitors were not commonly prescribed during study period. Other diabetic medications such as Dipeptidyl Peptidase-4 (DPP-4) Inhibitors and Sodium-Glucose Cotransporter- 2 (SGLT2) Inhibitors were not approved (SGLT2 approved in 2013) at the time of the study period or approved during the study period(DPP-4 approved in 2006) but not reported to be used by any of our study mothers. Metformin in contrary to insulin, crosses the placenta [27]. Metformin, at physiological pH exists in the form of cationic species (>99.9%) [28]. Metformin intestinal absorption, tissue distribution, and renal elimination are mainly mediated by Na+-independent electrogenic channels located in plasma membranes named as organic cation transporters (OCTs). OCTs are broadly expressed in fetal and in placental tissues, resulting in fetal metformin concentrations that are equal to maternal levels [29,30] but its expression and functional plasma membrane localization is limited in embryos, which is reflected in minimal exposure to metformin at embryological stage (from conception to 12 weeks) [31]. Appearance of intercalated swellings of semilunar valves and achievement of semilunar valves maturity form are second trimester cardiomorphogenic events (land marks 24,25,26 and 27 in figure 2)are witnessing the formation of the aortic valve [2], which coincide with OCT broad expression [32]. Fine-tuned increase in OCT expression occur in the second trimester of pregnancy in order to maintain an adequate transport of nutrients to the growing fetus, but this developmental change may lead to a higher exposure to metformin [32,33]. Until the moment metformin is not considered as teratogenic, and studies investigating its use during pregnancy have been reassuring [34]. Exposure to metformin was not associated with increased risk of non-genetic congenital abnormalities in the EUROmediCAT population-based registry study but there was an alert signal of pulmonary valve atresia which was underestimated by the authors [35]. Recent literature documented that, metformin reduces activation of many inflammatory mediators which depends on the expression of nucleotide oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasome and contribute to the pathophysiology of placental-mediated diseases [36]. Inflammasomes are large intracellular multi-protein signalling complexes that are formed in the cytosolic compartment as an inflammatory immune response to endogenous danger signals. NLRP3 is a pattern recognition receptor (PRR). It is a crucial sensor of cardiovascular tissue damage which belongs to the NOD-like receptor (NLR) family . Diverse immune stimuli can activate NLRP3 and promotes the maturation of IL-1β and IL-18 in IL-1 family cytokines. IL-1β and IL-18 involve both innate and adaptive immune responses with critical contributions to the process of calcific aortic stenosis(CAS) as well as the inflammatory development of atherosclerosis, cardiomyopathy, abdominal aortic aneurysm, heart failure, and cardiovascular and cerebrovascular ischemic injury. Evidence shows that NLRP3 inflammasome not only boosts the cleavage and release of IL-1 family cytokines, but also leads to a distinct cell programmed death: pyroptosis [37]. While the vast majority of evidence points to inflammation as mediating pathological valve remodeling and eventual destruction, some studies suggest *inflammation may provide key signals guiding transient adaptive remodeling* [38]. It seems that the degree of inflammation being good or ugly is in delicate balance that is not well understood until the moment. While it is well appreciated that inflammation is a major driver of valve pathology in all age groups from embryological life until elderly, *recent evidence suggests that inflammatory cytokines are present in embryonic development and in remodeling valves, which suggests its presence may not be singularly negative* [38]. Inflammatory signaling may be a previously unrecognized ally in the quest for controlled rapid tissue remodeling, a key requirement for regenerative medicine approaches for heart valve disease in adults and tissue genesis during embryological life. *Complete cessation of inflammatory signaling may not be the best approach and might be of catastrophic outcome.* In addition, metformin

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reduction of NLRP3 based inflammation is not amenable for calibration. Based in our population result of high odds ratio of metformin use in pregnancy and BAVD and in view of the common pathways involved in the pathogenesis of both calcific aortic stenosis(CAS) and bicuspid aortic stenosis(BCAS) we might deduce that metformin with its documented effect on NLRP3 might contribute to the higher incidence of BCAS in our population. *This new knowledge might revolutionize the prospect to inflammation and inflammatory signaling as ,not only a common pathway for cascade of human diseases but also as critical remodeling and healing agent for heart endothelium and heart valves. Complete cessation of inflammatory signaling might be ctatstrophic.This might pave the way to regenerative medicine approaches for heart valve diseases at all ages.*

Another serious alarming concern of metformin exposure during embryological and fetal life is the development of B12 vitamin (cobalamin)) deficiency, due to intestinal malabsorption secondary to bacterial overgrowth and/or altered intrinsic factor secretion [39]. Long-term metformin exposure result in vitamin B12 malabsorption and deficiency, was documented in in 10–30% of people [40]. In addition, folic acid (vitamin B9)deficiency might be a consequence of long term metformin exposure [41]. Cobalamin as well as folic acid deficiencies have been linked to hyperhomocysteinemia. In adults, hyperhomocysteinemia has been linked to vascular disease, cancer, Alzheimer's disease, Parkinson's disease, dementia, diabetes, Down syndrome, megaloblastic anemia, osteoporosis, eye lens dislocation, end stage renal disease, insulin resistance, aneurysms, hypothyroidism, gastrointestinal and many other disorders [42] Vitamin B9 is vital for the synthesis of purine and pyrimidine bases, the fundamentals for all new RNA and DNA synthesis. Remethylating of methionine (by methionine synthase) from homocysteine requires folate(vitamin B9) and cobalamin (vitamin B12) as essential cofactors [42,43]. DNA methylation utilized methionine. Methionine is crucial for all fetal cell differentiation including valvular interstitial cells, development and maturation as it controls the regulation of gene expression and new protein production [44]. In addition, during fetal life, central nervous system begins to develop at three weeks gestation and continues through early childhood. Neural tube defects and other neurological disorders , such as spina bifida, anencephaly and other brain malformations has been well documented to be the result of maternal vitamin B12 and folic acid deficiencies [45]. It is crucial to alert medical communities that vitamin B12 can lead to a failure in central nervous system development, in the absence of hematological symptoms or any other symptoms leading to irreversible neurological damage [46]. *Bicuspid Aortic Valve Stenosis(BAVS) is not exemption as it may develop in asymptomatic mothers.This fact might create new indication to look for vitamin B12 as well as folate stores during pregnancy and advice for supplement especially for vulnerable mothers.* Metformin was found to increase incidence of BCAS in our population. Based in our results and and the other drawbacks like high failure rate to control gestational diabetes (40%), its antiproliferative HMGA1-mediated effect and interference with fetal reproductive system, vit B12 deficiency and others , *we do not advise to use metformin during pregnancy*.This new knowledge is heralding new era for intelligent Insights for noninvasive aortic valve stenosis therapeutics for human species [47].

Conclusion

The explosive developments in understanding the process of human cardiogenesis emphasise its extreme heterogeneity and intricacy. The role of epigenetic orchestration of cardiogenesis with its potential reversibility heralds a new era of optimism to provide medical therapies for structural congenital heart diseases toward the path of preventing CHDs in the human species. Molecular signaling pathways of adult calcific aortic valve stenosis(CAVS) and fetal bicuspid aortic stenosis (BCAS) are in common. For this reason, adult CAVS knowledge might be translated to the fetal BCAS. Diabetes Miletus and its variants, especially gestational diabetes constitute unquestionable risk factors for many subtypes of CHDs. We adopted an etiological perspective nationwide project of genetic and environmental risk factors of CHDs. Significant correlations were documented between maternal diabetes and fetal bicuspid aortic stenosis (BCAS).In depth examination to explain those correlations was discussed in an attempt to utilize this new knowledge for therapeutic and preventive measures of BCAS. Metformin, the most commonly used OHA, was found to correlate positively with the occurrence of BCAS while insulin therapy was found to be protective. Maternal hyperglycemia increases DNA methylation in several cardiac gene promoters and corresponds to differential expression. Methylation of Notch1 promoter mediates the osteogenesis differentiation in human aortic valve interstitial cells through Wnt/β-catenin signaling. Notch1 promoter methylation leads to a decreased Notch1 expression and subsequent decreased release of Notch1 intercellular domain(NICD) in the nucleus of human Aortic Valvular Interstitial Cells (hAVICs), therefore promoting the activation of Wnt/β-catenin signaling and the expression of osteogenesis differentiation factors, finally promoting the osteogenesis differentiation in hAVICs. Expression of osteogenesis differentiation factors, promote the later in life osteogenesis differentiation.On the other hand, insulin therapy was found to be protective. Exogenous insulin, if it passes the placenta, was found to produce significant effects in the form of structural and functional alterations of the placental as well as fetal and maternal outcomes . Insulin can

cross the placenta more easily if Insulin antibodies formed and increase its transfer to the fetus. Glycolytic capacity and mitochondrial function are activated by hyperinsulinemia leading to exaggerated metabolic activity. Hyperinsulinemia was found to increased proliferation of the Valvular Interstitstial Cells (VICs), increased collagen type 1 and decreased α-smooth muscle actin expression. Excessive VICs proliferation could lead to abnormal tissue growth and contribute to pathological conditions such as valve thickening or fibrosis. Excessive collagen deposition or remodeling can lead to stiffening and dysfunction of the valve, which can be detrimental. Decreased α-SMA expression in VICs may suggest a shift towards a more synthetic or myofibroblast-like phenotype. This phenotypic change can contribute to ECM remodeling but may also disrupt the normal balance of cell types within the valve and potentially impair its function. Insulin may be a potential protective agent for the treatment of oxidative stress through its inhibition of the neuronal damage through the Nrf2 signaling pathway. In addition,insulin can increase glucose oxidation indirectly by enhancing glucose uptake and glycolysis and directly stimulates mitochondrial glucose oxidation, through activating mitochondrial pyruvate dehydrogenase (PDH). Direct insulin stimulation of glucose oxidation is associated with enhanced phosphorylation of mitochondrial Akt, GSK-3β and PKC-δ. Mitochondrial glucose oxidation in fetal valvular interstitial cells(VICs) serves as a vital source of energy for its various cellular functions including VICs requirement for energy to support their growth, proliferation, and maintenance of cellular homeostasis. Impaired mitochondrial function or disruptions in glucose metabolism can lead to reduced ATP production and altered cellular metabolism. Metformin in contrary to insulin, crosses the placenta.Metformin intestinal absorption, tissue distribution, and renal elimination in fetal life are mainly mediated by organic cation transporters (OCTs) chanells. OCTs are broadly expressed in fetal and in placental tissues, resulting in fetal metformin concentrations that are equal to maternal levels. Recent literature documented that, metformin reduces activation of many inflammatory mediators which depends on the expression of nucleotide oligomerization domain-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasome and contribute to the pathophysiology of placental-mediated diseases. Inflammasomes are signalling complexes that are formed in the cytosolic compartment as an inflammatory immune response to endogenous danger signals which is a crucial sensor of cardiovascular tissue damage. Diverse immune stimuli can activate NLRP3 and promote the maturation of IL-1β and IL-18 in IL-1 family cytokines. NLRP3 inflammasome can lead to a pyroptosis which is distinct cell programmed death. Inflammation is not always pathological but may provide key signals guiding transient adaptive remodeling.Inflammatory cytokines are present in embryonic development and in remodeling valves, which suggests its presence may not be singularly negative. Complete cessation of inflammatory signaling may not be the best approach and might be of catastrophic outcome. In addition, metformin exposure during the vulnerable period might lead to the development of B12 vitamin deficiency and folic acid deficiency ending up with hyperhomocysteinemia. Vitamin B9 (folate) is vital for the synthesis of purine and pyrimidine bases, the fundamentals for all new RNA and DNA synthesis. Remethylating of methionine (by methionine synthase) from homocysteine requires folate and cobalamin (vitamin B12) as essential cofactors. DNA methylation utilized methionine. Methionine is crucial for all fetal cell differentiation (including valvular interstitial cells). For all those reasons *we do not advise to use metformin during pregnancy. This new knowledge of the role of hyperglycemia to induce DNA methylation, Insulin activation of mitochondrial glucose oxidation, and its effect on increased proliferation of the Valvular Interstitial Cells (VICs), increased collagen type 1 and decreased α-smooth muscle actin expression, and insulin role against oxidative stress as well as the role of metformin in suppression of many nucleotide oligomerization domains-, leucine-rich repeat-, and pyrin domain-containing protein 3 (NLRP3) inflammasome based inflammatory mediators and metformin related hyperhomocysteinemia, are all promises of new mercy to fight the agony CHDs created for individuals, families, communities and world populations.Those collective mechanisms herald a new era that might pave the way for prophylactic and/or therapeutic noninvasive intervention for aortic valve stenosis utilizing those new mechanisms for reprogramming of cells even in the early stages of disease progression in all human age spectrum from embryogenesis to adulthood.*

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