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Intelligent Insights for Noninvasive Aortic Valve Stenosis therapeutics

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ABSTRACT

Stagnation of therapeutic options is a prominent feature of valvular aortic stenosis (AS). Invasive therapeutic options in the form of open heart aortic valve surgery or transcatheter aortic valve implantation (TAVI) are still the only therapeutic options until the moment. Decoding the mystery of AS morphogenesis is a challenging endeavor. It is only possible by multidisciplinary approach emanating from epidemiological back ground. Eagle eye observations of clinical correlates as well as prudent research in the molecular, genetic and epigenetic arena targeting decoding the genesis involved in bicuspid aortic valve formation are critical demands to throw stone in the stagnant lake. Hybrid pharmaceutical therapies combined with effective physical therapies will pave the way for future breakthroughs targeting noninvasive therapeutic options for valvular aortic stenosis or even aborting the disease in human species.

Keywords: Bicuspid aortic stenosis (BCAS), Congenital Heart Disease(CHD), Abdominal Aortic Aneurysm (AAA), Diabetes Mellites (DM), Molecular Signaling Pathways, DNA methylation, Sexual Dimorphism.

1. Introduction

Malformation of the human heart, Congenital Heart Disease (CHD), is the most common organ malformation in human species. Most reported incidence in medical literature is around 1% of all life births. As a matter of fact the true incidence is 3-4% of all life birth. The under estimation comes from absence of reporting the true incidence of the most common CHD namely, Bicuspid Aortic Stenosis(BCAS).It represent most of Calcific Aortic Valve Disease (CAVD) cases and the most sever spectrum of left ventricular out flow tract obstruction(LVOTO) in adult life. Up till the moment treatment options are invasive, in the form of open heart aortic valve surgery or transcatheter aortic valve implantation (TAVI). Toward the dream of providing medical noninvasive therapy of aortic stenosis, secrets of organogenesis from the point of genetic, epigenetic and molecular signaling pathways must be elaborated. Sophisticated molecular signaling pathways will bring us closer to discover the Bicupid Aortic Stenois (BCAS) disease mechanism but also simple epidemiological as well as clinical observations my change the equation dramatically.

2. Sexual Dimorphism indicators of different risk factors associated with abdominal aortic aneurysm to support the research of valvular aortic stenosis

2.1 ABDOMINAL AORTIC ANEURYSM AND SMOKING RESEARCH

Cross talk and common pathomechanisms and molecular signaling pathways are in common between the aortic diseases like bicuspid aortic stenosis (BCAS), Calcific Aortic Valve Disease (CAVD) and abdominal aortic aneurysm (AAA).**Therefore, research and discoveries of aortic disease mechanisms and molecular signaling pathways peculiar to one diseases like abdominal aortic aneurysm (AAA), might be translated to aortic valve congenital and acquired diseases.** Smoking has a greater impact on the risk of aortic aneurysm rupture in males compared to females. Hormonal differences, variations in genetic susceptibility, and differences in arterial structure and remodeling between males and females have been suggested as potential factors contributing to this dimorphism. Nicotine, a major alkaloid in tobacco leaves and a primary component in cigarette smoke, can stimulate the Matrix metalloproteinases (MMPs) expression by vascular smooth muscle cells (SMCs), endothelial cells, and inflammatory cells in vascular wall and induce angiogenesis in the aneurysmal tissues. The effects of nicotine are probably dose dependent or associated with the exposure duration and may be partly exerted by its receptors—nicotinic acetylcholine receptors (nAChRs).[1] In addition, cigarette smoke can have a wide spectrum of effects on macrophages.[2] Macrophages also release matrix metalloproteases and cysteine endoproteases that lead to degradation of collagen and elastin in the aortic valve matrix ending up with disruption of the normal architecture.[3,4] Analyzing the secrets of the greater impact of the risk of aortic aneurysm rupture in males compared to females through those pathomechanisms might be future prospect to investigate and to be redirected toward disease prevention or at least amelioration.

2.2 ABDOMINAL AORTIC ANEURYSM AND SYSTEMIC HYPERTENSION RESEARCH

Hypertension with systolic BP > 160 mmHg, diastolic BP > 95 mmHg is associated with higher rupture risk in women.[5] Abdominal aortic aneurysm (AAA) as rupture risk associated fatal disease is linked to systolic blood pressure(SBP) but much stronger association between diastolic blood pressure (DBP) and AAA than for SBP was documented.[6] Scrutinizing the effect of certain risk factors with sexual dimorphism is adopted by us and others as intelligent future prospective toward discovery of preventive and therapeutic modalities. The male to female ratio of AAA is comparable to aortic stenosis and coarctation of the aorta 4:1 but

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characteristic tendency for AAA to rupture in women with smaller size of the rupture aneurysm is evident.[7] Sexually dimorphism as a biological variable to understand the molecular mechanisms of AAA based on sex chromosome studies and the hormonal influence of sex hormones in the degradation of the abdominal aorta collagen and elastin are promising directions toward future sex-based precision therapies for aortic valve and aorta diseases.[8] The common molecular signaling pathways of different aortic diseases might be the gate toward holding control over aortic diseases.

3. Abdominal aortic aneurysm and diabetes mellitus research

Paradoxes in epidemiological observations are blooming indicators to disclose diseases secretes. Diabetes, a well-defined risk factor for atherosclerosis and vasculopathy, has been shown to be protective against the AAAs. Oral Hypoglycemic Agents (OHA) were shown to be also protective against AAA.[9,10,11] The molecular pathways involved are in common with the molecular pathways of both genetic and acquired aortic valve stenosis. Aortic medial neovascularity has been shown to play a role in aneurysm pathogenesis via its close involvement with metalloproteinase (MMP) activation in the proteolytic degradation of the aortic wall. Hyperglycemia was shown to decrease neovessel density, macrophage infiltration and matrix metalloproteinase-9(MMP-9) levels. Rosiglitazone, a Dipeptidyl peptidase-4 (DPP-4) inhibitor, was observed to reduce risk of rupture in animal model of AAA to 23%. Administration of rosiglitazone in mice inhibited Ang-II-mediated activation of Jun N-terminal kinase (JNK) which is known to play critical role in extrinsic and intrinsic apoptotic pathways by activating apoptotic signals via proapoptotic genes, thereby reducing the formation of aneurysms.[12] Another way of rosiglitazone inhibition of Ang-II is through a key activator of the innate immune response which is the Toll-like receptor 4 (TLR4) pathway.[13] Another DPP-4 inhibitor , Alogliptin, showed suppression of reactive oxygen species (ROS) activity, as well as metalloproteinase 2(MMP-2) and metalloproteinase 9 (MMP-9).[14] Athird DPP-4, Sitagliptin showed lower MMP-2 and MMP-9 activity, reduced apoptosis in the aortic wall and significant reduction in the macrophage infiltration in the treated mouse. Metformin was found to pose a protective role against AAA formation through reduction in proinflammatory cytokine levels, indicating the protective role of metformin in the inflammation pathway. Metformin was found to decrease proinflammatory cells like B cells, macrophages, and CD4 and CD8 cells. Metformin treated mice was found to induce decrease in mural neovessel density, as well as a reduction in elastin degradation, smooth-muscle cell depletion and aortic inflammation.[15]

4. Maternal Hyperglycemia and cardiogenesis research

Maternal hyperglycemia is a very important epigenetic risk factor affect the process of cardiogenesis peculiar to aortic valve formation during land marks 24, 25, 26 of cardiogenesis in the second trimester of pregnancy. Maternal hyperglycemia alters gene expression at various stages of heart development including cardiac neural crest cell migration, outflow tract formation, and inflow tract formation.[16,17] Conditional DNA methyl transferase 3-B (DMT3B) knock-out is associated with congenital heart disease phenotypes like ventricular septal defects and endocardial cushion defects.[18] Maternal hyperglycemia increases DNA methylation in several cardiac gene promoters and corresponds to differential expression.[19] 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. Notch1 promoter methylation leads to a decreased Notch1

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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. Human Aortic Valvular Interstitial Cells (hAVICs) are the main precursor of the aortic valve formation. 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.[20] This level of knowledge might pave the way for DNA methylation to act as an important bridge to link epigenetic interaction and fetal bicuspid aortic valve 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 noninvasive intervention and reprogramming of cells even in the early stages of disease progression in all human age spectrum from embryogenesis to adulthood. To decode a complex and dynamic process like genesis of BCAS that is regulated by a multitude of environmental and genetic variables, implementation of bioinformatics might be necessary to discover the potential causative pathways.

5. Cardiac Derived stem cells and atherosclerosis research

The use of autologous cardiac derived stem cells for use as a therapeutic tool for BCAS is suggested by the evidence that cardiac mesenchymal stem cell-like cells derived from 21-year-old patient with BAVD disease were less metabolically active, less proliferative, had begun to show less 'stemness' characteristics and were prematurely aged compared with those of the 78-year-old patient with coronary artery disease.[21] Novel medical strategies to treat BCAS and Calcific Aortic Valve Disease (CAVD) might be deduced from the similarities between the pathogenesis of aortic stenosis and other aortic pathologies. Either positive or negative correlations are of advantage to propose therapeutic options. 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 cannot 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. Atherosclerosis pose many similarities to aortic stenosis as endothelial damage and angioneogenesis and inflammation.[22] Cholestrol incorporation in atherosclerosis which has been denied by our group[23,24,25,26,27,28] and others denied also for any significant reduction in in aortic valve calcium by using 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor administration.[29] Intensive lipid lowering with statin therapy did not affect aortic stenosis progression.[30,31,32] So time and efforts must be saved toward other directions of disease investigations other than the claim of cholesterol involvement.

6. Osteoporosis and Angiotensin-converting enzyme (ACE) inhibitors research

The role of angiotensin-converting enzyme (ACE) inhibitors in aortic stenosis progression is

controversial as different groups of investigators reported opposite results.[33,34] Increased incidence of aortic stenosis(AS) with rapid progression was observed in osteoporosis patients.[35] The 'Calcification paradox' which implies reduced bone mineral density or disturbed bone turnover, associated with vascular calcification is pathological manifestation of osteoporosis.**36** In addition to osteoporosis , calcification of the aorta and renal arteries was observed in osteoprotegerin (OPG) deficient mice , suggesting an important involvement of this pathway in both pathologies [37]. The association of bone resorption and artery calcification was confirmed as in vivo studies demonstrated that calcinosis-reducing drugs such as bisphosphonate administration leads to a reduction in the calcification of arteries and heart valves [38]. In addition, bisphosphonates are associated with in vivo inhibition of calcification of bioprosthetic porcine aortic valve cusps that showed calcification resistance in long-term implant studies in vivo [39]. Bisphosphonates and other drugs affecting calcinosis like denosumab and ACE inhibitors has been proposed as potential medical therapy for AS.[40,41] Ectonucleotidases which metabolize nucleotides into phosphate products was also proposed to inhibit progression of calcification in the aortic valve.[42]

7. Trans-thoracic ultrasound therapy research

revolutionary physical therapies away from pharmaceutical industry are creating new strategic options for humanity against diseases.[43] Recently, 40 symptomatic and high-risk patients were treated non-invasively with transthoracically delivered ultrasound therapy to soften the aortic cusps proved to be safe and feasible.[44] This treatment modality, might gain blooming success to treat or at least to ameliorate AS patients in all human age time line from fetal life to elderly. Hybrid prudent pharmaceutical therapies combined with effective physical therapies will pave the way for future breakthroughs targeting noninvasive therapeutic options for valvular aortic stenosis or even aborting the disease in human species.

8. Conclusion

In the current era, stagnation of therapeutic options is a prominent feature of valvular aortic stenosis(AS) management in all age groups. Up till the date, only invasive options are available. Prudent and comprehensive perspective with multidisciplinary integrated and holistic approach is highly needed incorporating the new knowledge to yield new wisdom. Sexual Dimorphism indicators observed of underlying mechanisms of different risk factors associated with abdominal aortic aneurysm like smoking and systemic hypertension might be intelligently translated to support the research of valvular aortic stenosis amelioration or even prevention. Hyperglycemia protective role against abdominal aortic rupture and its contribution to decrease neovessel density, macrophage infiltration and matrix metalloproteinase-9(MMP-9) levels, is a critical observation that must be translated to serve the common pathways diseases including valvular aortic stenosis. A relatively recent group of oral hypoglycemic agents (OHA), Dipeptidyl peptidase-4 (DPP-4) inhibitors were shown to affect multiple pathways and enzymes critical for AS progression in congenital and acquired AS. Rosiglitazone (a DDP-4 inhibitor), was observed to reduce risk of rupture in animal model of AAA through its role in inhibiting Ang-II-mediated activation of Jun N-terminal kinase (JNK) in a cascade of events ending up with reducing the formation of aneurysms. Another way of rosiglitazone inhibition of Ang-II is through a key activator of the innate immune response which is the Toll-like receptor 4 (TLR4) pathway. Another DPP-4 inhibitor, Alogliptin, showed suppression of reactive oxygen species (ROS) activity, as well as metalloproteinase 2(MMP-2) and metalloproteinase 9 (MMP-9). Athird DPP-4, Sitagliptin showed lower MMP-2 and MMP-9 activity, reduced apoptosis in the aortic wall and significant reduction in the macrophage infiltration in the treated mouse. The famous OHA,

Metformin, was found to pose a protective role against AAA formation through reduction in proinflammatory cytokine levels, indicating the protective role of metformin in the inflammation pathway. Metformin was found to decrease proinflammatory cells like B cells, macrophages, and CD4 , CD8 cells , induce decrease in mural neovessel density and to a reduce elastin degradation, smooth-muscle cell depletion and aortic inflammation. The strong association between, very important epigenetic teratogen, maternal hyperglycemia, and fetal bicuspid aortic valve was documented by us and others. Maternal hyperglycemia increases DNA methylation in several cardiac gene promoters corresponds to differential expression affecting molecular signaling pathways critical for promoting the osteogenesis differentiation of aortic valve formation. Methylation of Notch1 promoter mediates the osteogenesis differentiation in human aortic valve interstitial cells through Wnt/β-catenin signaling. In addition, autologous cardiac derived stem cells are intelligent future direction as therapeutic tool for BCAS. Atherosclerosis pose many similarities to aortic stenosis as endothelial damage, angioneogenesis and inflammation. Medical literature of atherosclerosis in those directions are expected to enrich noninvasive options to treat AS with the exemption of the false relationship of hypercholesterolemia to AS. The osteoporosis research is very promising field to be implemented in noninvasive options for AS. Bisphosphonates and other drugs affecting calcinosis like denosumab and ACE inhibitors has been proposed as potential medical therapy for AS. Ectonucleotidases which metabolize nucleotides into phosphate products was also proposed to inhibit progression of calcification in the aortic valve. Propitious and highly potential noninvasive therapeutic option for AS is the incorporation of transthoracically delivered ultrasound therapy to soften the aortic valve cusps. Hybrid prudent pharmaceutical therapies combined with effective physical therapies will pave the way for future breakthroughs targeting noninvasive therapeutic options for valvular aortic stenosis or even aborting the disease in human species.

Conflict of Interest:

None.

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