Molecular Linkage under the Bicuspid Aortic Valve with Dyslipidemia

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Abstract

Dyslipidemia is correlated with diverse cardiovascular problems, such as obesity, hypertension, and atherosclerosis, which are summarized as metabolic syndrome. Bicuspid aortic valve (BAV), as one of the congenital heart defects, is shown to influence approximately 2.2% of the general population worldwide, inducing the severe pathological development of aortic valve stenosis (AVS) or aortic valve regurgitation (AVR), and also to aortic dilatation. Notably, emerging evidence showed that BAV was correlated with not only the aortic valve and wall diseases but also the dyslipidemic related cardiovascular disorders. Recent results also proposed that multiple potential molecular mechanisms inducing the progression of dyslipidemia played important roles in BAV and the progression of AVS. Several altered serum biomarkers under dyslipidemic condition, including higher low-density lipoprotein cholesterol (LDL-C), higher lipoprotein (a) [Lp(a)], lower high-density lipoprotein cholesterol (HDL-C), and different pro-inflammatory signaling pathways, have proposed to embrace a vital function in the development of BAV correlated cardiovascular diseases. In this review, different molecular mechanisms which embrace an important role in personalized prognosis in the subjects with BAV was summarized. The illustration of those mechanisms might facilitate an accurate follow-up for patients with BAV and give new pharmacological strategies to improve development of dyslipidemia and BAV.

Keywords: bicuspid aortic valve; dyslipidemia; aortic valve stenosis; aortic valve regurgitation; inflammatory pathways

1. Introduction

Dyslipidemia, characterized by high levels of total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and low levels of high-density lipoprotein cholesterol (HDL-C), is closely correlated with diverse cardiovascular problems, such as obesity, hypertension, and atherosclerosis, which are summarized as cardio-metabolic disorder diseases [1,2]. Notably, for some different instances, several diverse cardio-metabolic disorder diseases might be sequentially or simultaneously correlated within the same individual, resuitantly proposing the potential physiological inter-relationships of different cardiovascular diseases [3,4].

Bicuspid aortic valve (BAV), as one of the most common congenital heart defect diseases, is shown to affect approximately 2.2% of the general population worldwide, playing an important role in inducing the pathological development of aortic valve stenosis (AVS) or aortic valve regurgitation (AVR) [5,6]. Importantly, the subjects with BAV are inclined to suffer from the AVS which occurs at a relatively younger age compared to those individuals with a tricuspid aortic valve who might suffer from AVS after the age of 65 years [7,8]. On the other hand, such pathological alterations in the individuals with BAV could be identified as the results of disrupts circulating hemodynamics which is peculiar compared with the individuals with tricuspid aortic valve [9]. Concerning on this notion, recent evidence has proposed that in the subjects with BAV, the pathological development of AVS is correlated with aortic dilatation or aortic dissection which could be pathologically correlated to the risk of dyslipidemia, indicating a potential relationship between the risk of dyslipidemia and the pathological development of AVS in patient with BAV [10,11]. Nevertheless, the prevalence of dyslipidemia in subjects with BAV, the potential mechanism, and the prognostic significance of BAV-related dyslipidemia are still not elucidated [12,13].

In this review, emerging evidence on the potential relationship between BAV with the atherosclerotic related disease is well summarized. Furthermore, different molecular mechanisms which promote the personalized prognosis in patients with BAV are also elucidated. The illustration of those mechanisms might facilitate an accurate follow-up for patients with BAV and give new pharmacological strategies to improve development of dyslipidemia and BAV.

2. Epidemiological Relationship between BAV and Dyslipidemia

The epidemiological relationship between BAV and the prevalence of dyslipidemia is given attention during the past several decades by several cohorts in diverse countries. As demonstrated by USA national statistics, the prevalence of dyslipidemic related cardiovascular disease which needs percutaneous transluminal coronary intervention (PCI) or coronary artery bypass grafting (CABG) in subjects with BAV is significantly increased compared to those in the
healthy control individuals with consistent age [10]. Otherwise, in the patients undergoing the primary cardiovascular prevention, the risk of dyslipidemia and subclinical vascular disorder are evaluated by detecting the serum lipid profiles and assessing the vascular status by angiography, respectively [14,15]. Importantly, aberrant serum lipid profiles of disrupt metabolism of lipids, especially those involving in serum LDL and triglyceride (TG) metabolism, are undisputed essential promoters for the development of dyslipidemia and the formation of atherosclerotic plaques which are causally correlated with several cardio-metabolic diseases [16].

It is worth noting that emerging results indicated the pathological relationship between BAV with the development of dyslipidemia. As a general observation, the individuals with BAV present relatively higher serum concentrations of TC, LDL-C, and high sensitive C-reactive protein (hs-CRP), all of which could be reversedly correlated with valvar calcification by diverse severity [17]. Consistently, the patients undergoing aortic valve replacement, with or without BAV, is shown to exhibit higher circulating levels of TC and LDL-C compared with those individuals underwent isolated valve replacement [18]. Nevertheless, in the younger individuals with BAV, especially 5 to 15 years-old, no serum atherosclerotic lipid markers altered compared with the control individuals [19]. Via detecting the relationship between dyslipidemia with the risk of aortopathies in Japanese individuals with either BAV, the authors confirmed that those patients presented a relatively larger maximal diameter of ascending aorta in a larger proportion compared to the individuals with normal aortic valve. Notably, the patients with BAV exhibited higher serum contents of TC, LDL-C, TG, and reduced serum contents of HDL-C. In these patients, the increased LDL-C and TC concentrations were found in patients with AVS, whereas TG were found to be elevated in patients with AVS and AVR [20,21]. Similar with these results, a recent epidemiological case-control study conducted by Gracia et al. [22] which included 102 patients and 221 healthy control individuals, found that the certain cardiovascular risk factors associated with severe symptomatic AVS were hypercholesterolemia, hypertension, and lower serum concentrations of HDL-C, indicating that dyslipidemia was one of the certain cardiovascular risk factors with a greater risk of AVS. Mundal et al. [23] also explored the relationship between serum LDL-C with the risk of AVS in familial hypercholesterolemia (FH) in the total Norwegian population of about 5 million individuals. After analysis, the authors demonstrated a remarkable increased prevalence of AVS in the patients with FH.

Another clinical study enrolling 95 individuals with BAV and severe AVS undergoing the surgery for aortic valve replacement, approximately 26% presented CABG owing to a relevant greater than 75% of at least one coronary artery [24]. In this cohort, 26 patients with BAV underwent CABG with concomitant surgery for thoracic aorta aneurysm, suggesting a significantly pathological correlation between AVS, dyslipidemia, and thoracic aortic aneurysm. Concerning on these results, it is speculated that several risk factors involved in progression of dyslipidemia might also facilitate the severity of AVS in the individuals with BAV. Interestingly, the authors also demonstrated that dyslipidemia was frequent in the individuals with tricuspid aortic valve, proposing that in patients with BAV and AVS, the initially pathological factor might be the anatomic alteration [24]. Nevertheless, due to the lack of literatures, the relationship between serum factors involving in lipid metabolism and severity of aortopathy in the individuals with BAV is not elucidated. Recently, a research demonstrated no significantly relationship between TC, LDL-C, and TG with the cross-sectional aortic diameters in the individuals who underwent aortic valve replacement with BAV [13]. A potential explanation for these discordances resided in the fact which a simple detection of serum lipids might not reflect the pro-dyslipidemia of diverse exposure time to increased serum LDL-C levels. Additionally, several limitations are also reported, since other research which contained relatively small cohorts or showed a relatively weak significance [13].

The individuals with BAV is also shown to be inclined to suffer from the genetic disorder syndromes, such as Turner syndrome, with increased prevalence of early-onset ascending aortic dissection. Importantly, ascending aortic dissection is promoted by arterial hypertension and by the development of dyslipidemia and atherosclerotic related cardiovascular diseases [25]. Taken together, these findings induced the clinicians conducting a comprehensive assessment of the risk of dyslipidemia in daily clinical practice. Nonetheless, it should be noticed that all the clinical trials mentioned above are cross-sectional design study. Thereby, it is necessary to conduct other longitudinal measurements of dyslipidemia to further confirm the contribution of serum LDL-C contents to the pathological development of abdominal aortic aneurysm in the subjects with BAV.

3. Mechanic Linkage between the Risk of Dyslipidemia with BAV

According to the previous reports, in the patients with BAV, the severity of AVS is correlated with the development of ascending aortic dissection, which is confirmed to be associated with the increased serum levels of pro-atherogenic lipid profile [26–29]. Recent results showed the potential mechanism of aortic dissection contains a complex biological pathogenesis. Among several mechanisms, remodeling and degeneration of extracellular matrix (ECM) is confirmed as the leading mechanism in facilitating the ascending aorta dissection in patients with BAV [30,31]. With in-depth investigation, it is shown that the pathological development could be induced by the changed
biosynthesis of collagen and by aberrant gene expression levels of lysyl-hydroxylase (PLOD1) or reduced activity of the corresponding enzyme [32]. Concerning on the abdominal aorta, the altered metabolism of ECM is shown to be more interlinked with inflammatory response and dyslipidemia condition [33]. Under both states, the excessive stimulation of matrix metalloproteinases (MMPs) is involved in inducing dyslipidemia and inflammatory response in patients with BAV [34–36].

The diameter of aortic root and ascending aorta were associated with TC, LDL-C, and the atherosclerotic lipids in the individuals with BAV, such as apolipoprotein B (ApoB) and its lipoprotein components [37]. Notably, in these clinical trials, the serum levels of LDL-C and ApoB were identified as novel biomarkers in predicting aortic root diameter; whereas only the circulating concentrations of ApoB could predict the ascending aorta diameter, suggesting a relationship between serum lipid profiles with the risk of valve disease. By analyzing the data from abdominal aortic aneurysm mouse models induced by angiotensin-II (Ang-II), multiple important dyslipidemic biomarkers, especially LDL-C, TC, and proprotein convertase subtilisin/kexin type 9 (PCSK9), exhibited a vital effect in modulating the pathological progression of abdominal aortic disease [27,38]. Additionally, the authors also demonstrated that increased concentrations of TC and LDL-C could induce the storage of macrophages, which promotes the cascading inflammatory response and results in aneurysm progression under the intervention by Ang-II [39]. Consistently, the early stage of macrophage-related innate immune response is shown to excessively release multiple pro-inflammatory cytokines during aneurysm progression and is partly triggered by oxidized LDL. As a consequence, these findings were recognized as the mechanisms correlated with vascular endothelium impairment [40–42]. Recent reports also demonstrated that elevated LDL-C concentration could be considered as a potent inflammatory factor which facilitated the recruitment of macrophages and the stimulation of multiple proteins, including serine proteases, MMPs, and cysteine [43,44]. Aside from the classical circulating pro-inflammatory biomarkers, the dysfunction of several other pro-inflammatory cytokines, such as smooth muscle cells (SMCs), are shown to activate the Toll-like receptor-3 (TLR-3) signaling pathway and subsequently facilitates the inflammatory response [45]. These results proposed that BAV and its related aortopathies are associated with multiple molecular events involving in the progression of dyslipidemia.

The association between serum PCSK9 concentrations and the progression of abdominal aortic aneurysm also presented a clinical translation since the increased PCSK9 concentrations could reduce the hepatic LDL receptor (LDLR), resultant causing the higher LDL-C and further promoted the progression of hyperlipidemia [46,47]. Furthermore, the inflammatory response and dyslipidemia were correlated due to the risk of dyslipidemic related cardio-metabolic diseases could be also induced by low-grade inflammatory response via the stimulation of the NLRP3 inflammasome and other pro-inflammatory signaling pathways [48,49]. The early involvement of the macrophage-induced innate immune response promotes the production of various pro-inflammatory cytokines during the pathological development of aneurysm which is partly triggered by excessive storage of LDL-C, especially ox-LDL. Therefore, the process is currently identified as a potential mechanism involved in the injury of vascular endothelium [43,50]. Conclusively, since the macrophage-induced cholesterol reverse transportation plays a vital function in modulating dyslipidemia, the results also indicates the relationship between dyslipidemia and aortic disease.

4. Relationship between Lipoprotein (a) and BAV

The important role of Lipoprotein (a) [Lp(a)] in modulating the progression of BAV to AVS has begun to gain appreciation since the Lp(a) plays a vital role in dyslipidemia and its related cardiovascular diseases. As shown in several previous studies, a correlation between increased Lp(a) contents and aortic valve disease has been demonstrated [51,52]. For instance, Glader et al. [51] enrolled 41 women and 60 men with significant AVS who underwent aortic valve replacement and demonstrated that the increased serum Lp(a) concentration, as greater than 480 mg/L, could be identified as a risk marker for AVS. Furthermore, a strong synergism between Lp(a) and C. pneumoniae IgG anti-bodies in circulating immune complexes was found, indicating that higher serum Lp(a) concentrations could influence and aggravate AVS via the formation of circulating immune complexes. Similar relationship could also be found in the reports provided by another two independent clinical trials conducted by Gotoh et al. [53] and Stewart et al. [54]. More recently, Nordestgaard et al. [55] conducted a comprehensive systemic review and meta-analysis to elucidate the relationship between serum Lp(a) concentrations with the incidence of calcified valvar disease. As shown, the serum Lp(a) levels greater than 50 mg/dL were significantly associated with an approximately 2.0-fold increased risk of calcified valvar disease, indicating that increased serum Lp(a) concentrations are significantly associated with elevated prevalence of calcified valvar disease.

With in-depth investigation, it has been shown that Lp(a) is a cholesterol-abundant particle containing a molecule of ApoB-100 covalently linked with a molecule of Apo(a) [55]. As a consequence, the serum levels of Lp(a) is currently recognized as a risk factor for atherosclerotic related disease [56] and pro-thrombotic status [57]. Due to BAV induced-AVS could be promoted by oxidized development, consequently elevated serum Lp(a) concentrations
might be found in aortic valve disease, predominantly by high mechanical stress, where Lp(a) is retained [58]. Actually, serum Lp(a) has been demonstrated to be storage during the pathological development of AVS and to co-localize with calcium deposition [59,60]. It is also worthy to notice that the serum Lp(a) levels are determined by variation in the quantity of kringle IV type 2 (KIV-2) repeats at its gene locus, encoding the Apo(a) which plays a vital function in promoting calcified related diseases [61]. Notably, one single nucleotide polymorphism (SNP) in the lipoprotein (a) gene locus, as identified as rs-10455872, was confirmed to be strongly correlated with both serum Lp(a) levels and the prevalence of atherosclerotic related diseases [62]. Importantly, this SNP was firmly reported to reach genome-wide significance for the risk and the development of aortic valve calcification especially in populations from diverse countries, such as Hispanic-American and African-American [63]. In the individuals with BAV, the relationship between serum Lp(a) levels with the presence of aortic valve stenosis has been assessed by Sticchi et al. [64] via enrolling the Italian population. Though the authors found no significant relationship between serum levels of Lp(a) with the KIV-2 repeat quantity and BAV, it was shown significantly increased serum Lp(a) concentrations according to the calcification degree. By contrast, it has also been found that lower KIV-2 repeat quantity in the individuals with more severe calcification degree were found. Moreover, higher levels of Lp(a) were observed in the individuals with BAV who suffered from AVS [64]. Consequently, these findings revealed that serum Lp(a) concentrations might be identified as a risk factor useful to stratify the severity of valvar calcifications and AVS among the individuals with BAV.

Taken together, the results mentioned above supported that in the subjects with BAV, the existence of a causal association between Lp(a) and the progression of calcific aortic valve disease, especially AVS, which revealed genetic variation at the Lp(a) gene locus in the pathological development. Concerning on this notion, the elevated circulating Lp(a) could also be identified as a potential therapeutic target to AVS or AVR in individuals with BAV.

5. Potential Linkage between Valve Calcification, Dyslipidemia, and Inflammatory Response

Due to the technological advances, several novel serum biomarkers were shown to potentially be involved in linking dyslipidemia and inflammatory response in the patients with BAV. Emerging results have provided by multivariate analysis which indicated emanative protein expression finger prints in patients with tricuspid aortic valve compared to those in patients with BAV [64,65]. Notably, these findings also suggested that aortic aneurysm dilatation in the individuals with BAV could be partly correlated with tissue repair capacity induced by disrupted fibronectin and enhanced vascular permeability.

Increasing results proposed that diverse risk factors, which modulate the pathological development for atherosclerotic related diseases, are associated with the progression of aortic calcification and AVS [66]. For instance, the elevated blood pressure detected on the left side of the heart is involved in valve calcium formation, whereas this phenomenon detected on the right side of the heart is rarely observed by analyzing the results from two independent research [7,67,68]. On the other hand, the features of aortic flow and aortic wall in BAV could affect the predisposition of patients to dyslipidemia. In details, an important and initial cardiovascular event in the progression of AVS is endothelial dysfunction owing to the enhanced mechanical stress, as also observed in patients with BAV by decreased flow-mediated dilatation [69]. With in-depth investigation, this process induced serum lipid profiles to enter into the impaired endothelium, indicating a potential relationship between dyslipidemia and AVS in patients with BAV [70]. Furthermore, via the progression of LDL oxidation, which is identified as an important inflammatory progression induced by excessive storage of T lymphocyte, monocytes, and CD3(+) leukocytes, the authors found that disrupted LDL-oxidation promoted the development of AVS [71,72]. The underlying mechanisms, which contained a mineralizing progression, were confirmed via several experimental data and indicated that dyslipidemic-related AVS could be facilitated by two important potential mechanisms, as one is an endothelial-mesenchymal oxidative stress and the other one is a signal abnormal forces in the dyslipidemic micro-environment, which subsequently induced the enhanced expression of LDL-receptor (LDLR) to further facilitate the myo-fibroblast cell to form the calcified tissue in humans [73].

Recently, it was shown that inflammatory response could importantly stimulate the process of angiogenesis which subsequently induced the rupture of small fragile vessels and released the intra-leaflet hemorrhage. Notably, this process could promote the progression of valve stenosis [74]. Via this inflammatory response, the fibroblast like-cells, also be considered as the valve interstitial cells, is shown to facilitate the formation process within the fibrous tissue. It is worth noting that several valve interstitial cells could further differentiate into the myo-fibroblasts which reversely differentiate into the osteoblasts and induce the progression of calcification. On the other hand, it is also proposed a genetic predisposition to aortic calcification is associated with diverse serum level of Lp(a) and the gene expression levels of Lp(a). Furthermore, the Lp(a) is correlated with varying degrees of valve calcification and AVS [63]. Notably, the vital function of lipoprotein (a) has been well described in previous paragraph of this review.
6. Molecular Relationship between Dyslipidemia and BAV-Induced Diseases

Multiple research has provided the resulted and suggestions for the aortic valve replacement, no matter by transcatheter active valve replacement (TAVR) or aortic valve surgery, is necessary and effective in the treatment for BAV and its related AVS. Nonetheless, the results of follow-up observation trial in terms of dyslipidemia and its impact on AVS could not fully elucidate the molecular relationship between dyslipidemia and BAV-induced diseases [75]. Due to the apparent relationship between the hypercholesterolemia, characterized by increased serum levels of LDL-C and TC, with the pathological development of the AVS in patients with BAV, it is reasonable to make a speculation about the potential advantage of specific medicine treatment. Among several lipid-lowering medicines in daily clinical practice, statins are one of the most widely used medicines specifically suppressing the serum 3-hydroxy 3-methylglutaryl coenzyme A reductase (HMG-CoA), which resultanty lowers the serum LDL-C and TC concentrations. Moreover, the prevalence of cardio-metabolic disorder diseases is also reduced significantly by using the lipid-lowering therapy [76]. Interestingly, two independent research suggested that statins could, at least partly, influence the aorta through inhibiting the biological activity of serum inflammatory factors, such as IL-6 and TNF-α, and modulate the expression of other factors such as angiotensin-II [77,78]. Similar with these results, in a retrospective observational clinical trial, which enrolled 174 patients with BAV and moderate calcific AVS, demonstrated that approximately 18% patients undergoing the statin-induced lipid lowering therapy presented a significantly decreased pathological development of AVS compared with those who were not treated with statins [79]. In addition, another in-depth observational clinical trial also showed that the statin-treated individuals with BAV and AVS exhibited a relatively smaller ascending aortic size compared to those who were not treated with statins [80]. In a more recent study, the statin-treated patients with BAV who underwent the aortic valve surgery presented a relatively smaller proximal aortic diameter (approximately 40.2 mm) only when at target for serum HDL-C concentrations, compared with the individuals who were not at target for serum HDL-C concentration (approximately 46 mm); however, all the enrolled individuals who were not treated with statin exhibited a relatively larger diameter independently of serum HDL-C concentrations [81]. Taken together, this clinical trial shed light on that the common problems of lipid-lowering treatment, especially by statins are widely observed in the individuals with BAV.

On the other hand, it has also been suggested that the advantage of using lipid-lowering therapy, such as using statins or ezetimibe, in the individuals with BAV is probably induced by significantly reduced serum levels of lipid profiles, especially LDL-C and TC, in the early pathologi-cal stages of AVS before the severe calcification could take place by the lesions [82,83]. However, in a randomized study which enrolled the individuals with BAV and without BAV, the authors found that in the patients without clinical indications for lipid lowering, using rosuvastatin could not improve the pathological development of mild or moderate AVS [84,85]. Concerning on this notion, it could not make a conclusion to elucidate the most appropriate BAV-related therapeutic strategy.

Interestingly, recent notion showed that the paradigm of dyslipidemia plus stimulation of Ang-II-induced mechanisms as pathogenic triggers of the pathological development of abdominal aortic aneurysm could propose that the multi-medicine combinations, such as statin and agents blocking angiotensin, could embrace an important modulatory function in the risk of aortic disease in the individuals with BAV [86]. Otherwise, the clinical administration the stimulation of diverse pro-inflammatory cytokines, including the NLRP3 inflammasome, TNF-α, and IL-6, are still needed to be deeply elucidate by further research whose results might be promising and eye-catching.

7. Conclusions and Future Perspectives

As summarized in our review, BAV has currently been identified as a syndrome containing several aortic valve diseases and important aortic wall disruption including rupture, dissection, and dilatation with aortic lesion. Additionally, such diseases could be promoted to contain, aside from AVS and ascending aorta aneurysm, also dyslipidemia and its related cardiovascular diseases. Emerging recent research mentioned in the current article proposed that multiple diverse potential mechanisms could significantly facilitate the development of dyslipidemia in the individuals with BAV which is also involved the promotion from AVS. Concerning on this notion, the future basic experiment and clinical trials should focus on a more accurate pathway to elucidate the modulatory function of dyslipidemic related serum biomarkers in the development of AVS in the individuals with BAV, for a relatively personalized diagnosis and follow-up period. Notably, those research should also take into consideration the diverse aspects which have been neglected such as the influence of sex and race in regulating the risk of dyslipidemia in patients with BAV. Through this effort, it could provide several potential and novel therapeutic treatment for the diseases in daily clinical practice.

Abbreviations

BAV, Bicuspid aortic valve; AVS, aortic valve stenosis; AVR, aortic valve regurgitation; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); HDL-C, high-density lipoprotein cholesterol; TLR-4, Toll-like receptor 4; PCI, percutaneous transluminal coronary intervention; CABG, coronary artery bypass grafting; TG, triglyceride; ECM, extracellular matrix; ApoB-100, apolipoprotein B-100; Apo(a), apolipoprotein (a).
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XS, YC, and BW contributed to the study design; PW, HK, and YV wrote the manuscript. All authors reviewed drafts and approved the final version of the manuscript.

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Conflict of Interest
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References


Clare R, Peden JF, Hopewell JC, Kyriakou T, Goel A, Heath


