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MicroRNAs Mediating the Histopathology of Aortica Valve Stenosis in Diabetes Mellitus

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Abstract

Aortic valve stenosis is a common and severe complication in patients with diabetes mellitus characterized by fibrosis, calcification, and valvular remodeling. MicroRNAs have emerged as key regulators of these pathological processes by modulating molecular pathways involved in osteogenesis, inflammation, and valvular fibrosis. This review synthesizes the findings of different studies investigating the role of specific microRNAs in the histopathology of aortic valve stenosis associated with diabetes mellitus, their interaction with atrial natriuretic peptide, and their potential as circulating biomarkers and therapeutic targets. Understanding these mechanisms opens new opportunities for diagnostic and personalized therapeutic strategies.

Keywords: Osteogenesis; Inflammation; Valvular Fibrosis; Diabetes Mellitus; Therapeutic Targets; Cardiovascular Morbidity; MicroRNAs; Biomarkers

Introduction

Diabetes mellitus is an independent risk factor for accelerated progression of aortic valve stenosis, increasing cardiovascular morbidity and mortality [1]. The pathophysiology of aortic valve stenosis in diabetic patients is characterized by the activation of endothelial and mesenchymal valvular cells, inducing chronic inflammation, fibrosis, and extracellular matrix calcification [2]. Chronic hyperglycemia produces oxidative stress and endothelial dysfunction that exacerbate valvular degeneration [3]. MicroRNAs have been identified as critical post-transcriptional regulators that modulate genes involved in valvular remodeling, osteogenesis, and inflammation, suggesting their central role in the histopathology of diabetic valve stenosis [4-6]. Additionally, hormonal peptides such as atrial natriuretic peptide interact with intracellular signaling pathways involved in fibrosis and valvular calcification [7].

MicroRNAs and Valvular Calcification in Diabetes Mellitus

Valvular calcification in diabetes mellitus is an active process similar to osteogenesis, mediated by valvular interstitial cells expressing osteogenic markers such as Runx2 and osteopontin [8]. Several microRNAs have been implicated in promoting this process, representing potential therapeutic targets. Overexpression of miR-34a promotes osteogenic differentiation of valvular interstitial cells through SIRT1 inhibition and activation of the p53-BMP2 pathway [9]. Extracellular matrix regulation by miR-29b favors calcification [10]. Downregulation of miR-30c and miR-204 correlates with increased Runx2 and BMP2, accelerating valvular calcification [11]. Other relevant microRNAs include miR-125b, which increases osteopontin expression, and miR-223, which regulates Wnt/**β**-catenin signaling in valvular interstitial cells [12,13]. Recent studies also show that hyperglycemia increases miR-34a and miR-21 expression in human valves, correlating with calcification severity [14,15].

MicroRNAs and Valvular Fibrosis

Fibrosis contributes to valvular stiffness and hemodynamic dysfunction in diabetic valve stenosis. Several microRNAs regulate extracellular matrix synthesis and fibroblast activation. Overexpression of miR-21 increases collagen type I and fibronectin via TGF-β/Smad3 signaling [16]. Downregulation of miR-133a is associated with increased fibrosis and valvular remodeling [17]. MiR-199a-5p modulates fibroblast proliferation and extracellular

matrix deposition [18]. Other relevant microRNAs include miR-208, which regulates fibroblastic transformation, and miR-146a, which modulates inflammation-associated fibrosis [19-20].

Circulating MicroRNAs as Biomarkers

Several studies have identified plasma or serum microRNA profiles that reflect the progression of valve stenosis in diabetic patients. Plasma levels of miR-210 and miR-146a correlate with calcification severity [21]. Levels of miR-21 and miR-126 are associated with valvular inflammation and endothelial dysfunction [22]. Detection of circulating microRNAs could serve as a non-invasive tool for diagnosis and prognosis of valve stenosis in diabetes mellitus [23-25].

Atrial Natriuretic Peptide in the Pathogenesis of Valve Stenosis in Diabetes Mellitus

Atrial natriuretic peptide (ANP) is produced by cardiac myocytes and plays a modulatory role in intracardiac pressure and sodium-water homeostasis [26]. Recent studies demonstrate that ANP inhibits proliferation and osteogenic differentiation of valvular interstitial cells through the cGMP/PKG pathway, reducing valvular calcification [27-28]. In diabetic patients, plasma ANP levels are altered and correlate with increased valvular remodeling and fibrosis [29]. The interaction between ANP and microRNAs such as miR-21 and miR-34a suggests an integrated mechanism in the progression of valve stenosis in diabetes [30-32]. Animal models show that exogenous ANP administration can partially reverse fibrosis and decrease osteogenic marker expression in calcified valves [33,34].

Therapeutic Perspectives

Manipulation of microRNAs using inhibitors or mimics offers promising therapeutic opportunities. Experimental studies in animal models have shown that antagonists of miR-34a reduce valvular calcification, whereas agonists of miR-204 inhibit osteogenic differentiation and restore extracellular matrix homeostasis [35-37]. Combination therapies involving microRNA modulation and ANP signaling could provide a synergistic approach to limit fibrosis and calcification [38,39]. Challenges remain in targeted delivery to valvular tissue and long-term safety [40,41]. Nanoparticle and vector-based delivery systems for microRNAs represent a promising area of research [42-60].

Conclusion

MicroRNAs play a central role in the histopathology of aortic valve stenosis associated with diabetes mellitus by regulating calcification, fibrosis, and valvular remodeling. Certain circulating microRNAs have potential as diagnostic and prognostic biomarkers. Recent studies on atrial natriuretic peptide indicate a modulatory effect on fibrosis and calcification. Integration of therapies targeting microRNAs, including miR-34a antagonists and miR-204 agonists, along with ANP modulation, could represent an innovative therapeutic strategy. Future research should focus on validating these therapeutic targets and developing targeted delivery strategies to improve clinical management of valve stenosis in diabetic patients.

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