Syndecan-1: New Perspectives of Risk and Prognostic Assessment in Heart Failure

Radu Stefan Miftode¹, Viviana Aursulesei¹*, Larisa Miftode¹,², Amalia Stefana Darie¹, Ana Maria Buburuz¹, Adriana Ion¹, Alexandru Dan Costache¹, and Irina Iuliana Costache¹

¹Department of Cardiology, Grigore T. Popa University of Medicine and Pharmacy, Romania
²Department of Infectious Diseases, Grigore T. Popa University of Medicine and Pharmacy, Romania

EDITORIAL

Heart failure (HF) represents an important cause of hospitalization throughout the world, with limited therapeutical options and high mortality rates [1]. Frequently, HF is a consequence of myocardial injury of various etiologies, fibrosis and subsequent remodellisation further affecting the cardiac function.

The lumenal side of the endothelial cells is covered by glycocalyx, which is a complex structure of proteoglycans and other macromolecules. Recent studies have demonstrated that syndecan-1 is a main component of the glycocalyx, a high blood concentration of syndecan-1 indicating a serious degradation of glycocalyx and a various degree of endothelial dysfunction [2,3]. Other experimental studies on animals have shown that syndecan-1 was involved in both inflammation and fibrosis after myocardial injury [4,5].

In patients with ischemic heart disease or heart failure, elevation of serum syndecan-1 has been associated with a degradation not only of cardiac, but also renal function, justifying further studies on this molecule [3,6]. Also, one study revealed that syndecan-1 was associated with poor prognosis in HF patients with preserved ejection fraction, suggesting the future use of syndecan-1 as a possible marker of cardiac fibrosis [6].

The importance of glycocalyx is based on its antiadhesive and anticoagulant properties, maintaining the integrity of the endothelium and an efficient vascular barrier function. Also, glycocalyx is essential in mediating the production and depositing of various mediators (eg, nitric oxide), enzymes (eg, superoxide dismutase) or coagulation inhibitors, like protein C or antithrombin [2,7].

Syndecan-1 is a type-I transmembrane heparan sulfate proteoglycan and is a member of the syndecan proteoglycan family, which consists of four transmembrane heparan sulfate proteoglycans mainly present on the cell surface, mediating cell adhesion, cell signaling, endocytosis and the structural layout of the cytoskeleton [2,8].

The structure of syndecan-1 is based on a 310 amino acids long core protein, with an extracellular domain with glycosaminoglycans chains, a transmembrane domain, and also a cytoplasmic domain [8]. Given the ability of syndecan-type molecules to bind to different growth-factors, syndecan-1 has been associated with the development of cardiac fibrosis and a poor outcome in patients with HF, by representing a target for transforming growth factor-β [2].

Even if there is scarce data about the role of syndecan-1 in patients with HF, Tromp et al., conducted a study with 567 patients and revealed that higher serum levels of syndecan-1 were more often associated with lower blood pressures, a lower left ventricle ejection fraction, and more previous HF-related hospitalizations [6]. In addition, patients with high syndecan-1 levels had also elevated serum NT-proBNP, fibrosis markers, and a worse renal function, but without elevated inflammatory markers [6]. Thereby, the study highlighted a positive correlation between syndecan-1 and fibrosis and remodeling factors (P<0.001), and a negative correlation with renal function (P=0.009). Male sex was also a predictor of a high serum syndecan-1 in patients with HF (P=0.029). No correlation was found between syndecan-1 levels and inflammatory markers (P=0.635). Interestingly, an increase in syndecan-1 levels represented a much stronger increase in risk and poor clinical outcome for patients with preserved ejection fraction (EF<40%) than in patients with reduced ejection fraction (EF<40%) [6].

In both HF and renal disease, there is endothelial dysfunction, which appears to have a bidirectional relationship in both conditions [9,10]. In 2015, the results of a study conducted by Oliveira-Neves et al. further confirmed the connection between an increased serum syndecan-1 and a poor renal function in patients with acute decompensated HF (P<0.001). However, these findings apply only to patients who developed acute kidney injury (AKI) during their hospitalization, revealing no significant difference in syndecan-1 levels between patients with stable chronic kidney disease and those with normal renal function [3].
Also, elevated syndecan-1 was observed more often in patients with pre-hospitalization NYHA III/IV than those classified as NYHA I/II (P=0.002), but no significant correlation was found between syndecan-1 and a high BNP (p=0.281) [3].

Syndecan-1 has proven to be a reliable predictor of both in-hospital (P<0.001) and long-term mortality (P=0.007) in patients with HF, by using a cut-off value of 125 ng/mL [3].

It is also worth-mentioning that syndecan-1 can be elevated in patients with chronic pathologies, like diabetes [11], or with acute dysfunctions (septic shock, ischemic-reperfusion syndrome or other conditions associated with inflammation or adrenergic activation) [7,12]. Thus, when assessing the role of syndecan-1 in patients with HF, it is important to exclude other conditions associated with an increased syndecan-1, which can alter the results.

Syndecan-1 may also represent an early biomarker of AKI, especially in patients with acute HF, being suggested that high levels of syndecan-1 are not related to decreased creatinine clearance, but to continuous damage to the glycocalyx [13]. This theory is based on the pre-existence of an increased serum syndecan-1, even at the admission for HF, before the installation of AKI and the subsequent drop in creatinine clearance. One study even revealed the superiority of dosing the syndecan-1 in patients with HF and AKI, compared to KIM-1 and N-GAL, suggesting that the prevention of glycocalyx damage in these patients may be a possible intervention for avoiding AKI [3].

One study reported the implication of syndecan-1 in atherosclerosis progression [14], while another highlighted the significant elevation of serum syndecan-1 in patients with acute coronary syndrome, suggesting that endothelial glycocalyx damage increases the vulnerability of the atherosclerotic plaque [15].

Many studies suggested that endothelial dysfunction is associated with HF progression and long-term mortality [2,16,17], but only a few confirmed the role of increased syndecan-1 via glycocalyx damage in the pathophysiology of HF [2,3,6], also opening new perspectives in the study of cardiac renal syndrome.

In conclusion, these findings offer a solid base for further research of syndecan-1 molecule and its role not only in preserving endothelial architecture, but also for a more practical approach in the prevention and early diagnosis of some life-threatening conditions associated with HF (eg. AKI) [18].

REFERENCES


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